Therapeutic Drug Monitoring of Antibiotics in Critically Ill Patients: Current Practice and Future Perspectives With a Focus on Clinical Outcome

Birgit C. P. Koch, PharmD, PhD, Anouk E. Muller, MD, PhD,†‡ Nicole G. M. Hunfeld, PharmD, PhD,*§ Brenda C.M. de Winter, PharmD, PhD,* Tim M. J. Ewoldt, MD,*§ Alan Abdulla, PharmD,* and Henrik Endeman, MD, PhD§*

Purpose: Early initiation of antibiotics is essential for ameliorating infections in critically ill patients. The correct dosage of antibiotics is imperative to ensure their adequate exposure. Critically ill patients have altered pharmacokinetic parameters and are often infected by less susceptible microorganisms. Differences in drug disposition are not considered with standard doses of antibiotics. This can lead to suboptimal antibiotic exposure in critically ill patients. To overcome this problem of suboptimal dosing, therapeutic drug monitoring (TDM) is a strategy commonly used to support individualized dosing of antibiotics. It is routinely used for vancomycin and aminoglycosides in clinical practice. In recent years, it has become apparent that TDM may also be used in other antibiotics.

Methods: This review summarizes the evidence for TDM of antibiotics in critically ill patients, focuses on clinical outcomes, and summarizes possibilities for optimized TDM in the future.

Results and Conclusion: After reviewing the literature, we can conclude that general TDM implementation is advised for glycopeptides and aminoglycosides, as evidence of the relationship between TDM and clinical outcome is present. For antibiotics, such as beta-lactams, fluoroquinolones, and linezolid, it seems rational to perform TDM in specific patient cases. TDM involving other antibiotics is supported by individual cases, specifically to decrease toxicity. When focusing on future possibilities to improve TDM of antibiotics in critically ill patients, implementation of model-informed precision dosing should be investigated because it can potentially streamline the TDM process. The logistics of TDM, such as turnaround time and available equipment, are challenging but may be overcome by rapid bioanalytical techniques or real-time monitoring of drug concentrations through biosensors in the future. Education, clinical information on targets, and clinical outcome studies are other important factors that facilitate TDM implementation.

Key Words: target attainment, clinical outcome, intensive care, pharmacokinetics/pharmacodynamics, model-informed precision dosing

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INTRODUCTION

Severe sepsis and septic shock are life-threatening conditions in critically ill patients. Early antibiotic therapy is the first key step for improving survival.[1,2] The second is to choose the right antibiotic, and the third is the correct dose. The correct dosage of the antibiotic is essential to maximize therapeutic success and prolong the clinical lifespan of currently available antibiotics by limiting the emergence of resistance.[3] However, dosing regimens are often derived from studies in healthy volunteers, although critically ill patients have altered pharmacokinetic (PK) parameters.[4] These differences in drug disposition are not considered in the standard dosing of antibiotics, which can lead to suboptimal antibiotic exposure in critically ill patients.[5–7]

To overcome the problem of suboptimal dosing, therapeutic drug monitoring (TDM) is a commonly used strategy to minimize toxicity and maximize the efficacy of drugs. The goal of TDM is to reach a pharmacodynamic target (PDT) in an individual patient. In clinical practice, the TDM approach is routinely used for antibiotics with a narrow therapeutic window, such as vancomycin and aminoglycosides, to increase effectiveness and decrease toxicity.[8,9] In recent years, it has become apparent that TDM may also be used to increase efficacy by ensuring adequate exposure to other antibiotics. Therefore, for other antibiotics, such as beta-lactams and fluoroquinolones, interest in TDM is increasing.[10] TDM of beta-lactams and fluoroquinolones is only applied in specific cases and a limited number of hospitals. This is due to a lack of methodology to determine antibiotic concentrations (free fraction included), lack of software to use these concentration data to predict concentration profiles, and knowledge about optimal doses for individual patients. In addition, research on the relationship between TDM and clinical outcomes is limited. This review presents a summary of TDM and clinical outcomes of antibiotics used in critically ill patients. In addition, a brief background on drug characteristics, PK, and target attainment are provided.

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From the *Department of Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, the Netherlands; †Department of Medical Microbiology, Haaglanden Medical Center, The Hague, the Netherlands; ‡Department of Medical Microbiology & Infectious Diseases, Erasmus MC, University Medical Center Rotterdam, the Netherlands; and §Department of Adult Intensive Care, Erasmus MC, University Medical Center Rotterdam, the Netherlands.

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Correspondence: Birgit C. P. Koch, PharmD, PhD, Hospital Pharmacist-Clinical Pharmacologist, Hospital Pharmacy, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands (e-mail: b.koch@erasmusmc.nl).

PHARMACOKINETICS IN THE CRITICALLY ILL PATIENTS

Generally, PKs in critically ill patients can be different from that in non-ICU patients.[3,11] Rapid dynamic changes in physiological function, including augmented clearance, renal or hepatic dysfunction, or increased volume of distribution, can lead to unpredictable PK alterations that significantly affect antibiotic exposure.[12] In addition, organ supportive techniques allow far larger changes in organ function: for instance, using supportive extracorporeal therapies, such as continuous renal replacement therapy, including the different filters used nowadays and extracorporeal membrane oxygenation (ECMO).[13] Furthermore, these techniques also have an effect on drug disposition.

In addition to changes in physiological function in critically ill patients, which lead to different clearances and volumes of distribution, there might also be changes in protein binding.[14] Because only the free fraction of the antibiotic is clinically effective, changes in protein binding might also have an effect on actual exposure to the active drug. In particular, for antibiotics with high protein binding, such as ceftriaxone or flucloxacillin, a decrease in protein binding due to lower plasma albumin concentration in critically ill patients[14] might result in a clinically relevant increase in the exposure to unbound drug.[15,16] Furthermore, multiple drug interactions may also play a role in drug exposure.

ANTIBIOTICS

To optimize the dosage of antibiotics, knowledge of the minimal exposure required for an antibacterial effect is needed. Exposure can be calculated in different ways, such as the C_{max}/minimum inhibitory concentration (MIC) or area under the curve (AUC)/MIC. These are the PK/PD indices, and usually, one of them is best correlated with efficacy. Most of these PK/PD indices are determined in preclinical studies, performed in animal models, in vitro PK models, and volunteer studies, although some have been performed on patients.[17]

For certain classes of antibiotics, the major lethal effect on an organism is produced by either the time or the concentration of the drug at the binding site. The inhibitory effect can be effective because its concentration exceeds the MIC of the microorganism. Hence, these antibiotics are referred to as time-dependent antibiotics. For time-dependent drugs, the PK/PD index is the percentage of time of the dosing interval (T > MIC or %*f*T > MIC). To explain these terms, *f* is the free fraction and T is the time.[18]

For instance, for antibiotics with time-dependent killing, antibacterial responses occur when the time that the drug remains above the MIC is equal to or greater than a percentage of the dosing interval; for instance, 45% *f*T > MIC in patients with ceftazidime and nosocomial pneumonia[17] or 100% *f*T > MIC in critically ill patients.[5]

Other classes of antibiotics, such as aminoglycosides and quinolones, have high concentrations at the binding site, which eradicates the microorganism, and hence, these drugs are considered to have a different type of bacterial killing, named concentration-dependent killing. For concentration-dependent agents, the PK/PD parameter is the *f*peak/MIC ratio or *f*AUC/MIC ratio. Peak or fC_{max}/MIC represents the maximum concentration divided by the MIC. Antibiotics whose efficacy is best correlated with fC_{max}/MIC will have an additional antibacterial effect when fC_{max}/MIC increases and most often benefit from a once-daily dosing regimen. The AUC and the PK/PD index are divided by the MIC. For those antibiotics that are best correlated with *f*AUC/MIC, the antibacterial effect increases with exposure to the unbound drug, and their effectiveness is independent of the dosing frequency.

Some antibiotics have concentration- and time-dependent characteristics, depending on their mode of action. Fosfomycin seems to have both characteristics depending on the microorganism researched.[19]

With regard to MIC, the pathogen is often not known when empirical antibiotic therapy is initiated. Furthermore, due to the variability in MIC (measurement), it has become apparent to rely more on the epidemiological cutoff values (ECOFF),[20] the upper value of the wild-type distribution, assigned by the European Committee on Antimicrobial Susceptibility Testing, based on epidemiological data of bacteria and resistance information.[21]

Aminoglycosides

Aminoglycoside antibiotics used to treat systemic gram-negative infections include gentamicin, tobramycin, and amikacin. Aminoglycosides are used in septic shock as a single or limited number of dosages in patients who do not respond fast enough to first-line antibiotic therapy. The magnitude of the PK/PD index to have sufficient antibacterial efficacy of aminoglycosides is a C_{max}/MIC ratio exceeding 8–10, which was initially developed for every 8 hours or every 12 hours dosing intervals.[22] However, a recent reassessment of the literature suggests that for once-daily dosing regimens, an AUC0-24/MIC of ≥110 mg·h/L may be targeted, as only navigating on the C_{max}/MIC target would result in too low exposure.[3]

Previous studies have reported that for up to 30%–40% of critically ill patients, aminoglycoside concentrations were lower than the targeted peak concentrations using standard dosing regimens,[23–26] although all these studies were carried out with amikacin. Trough concentrations of aminoglycosides (<1 mg/L for tobramycin and gentamicin and <5 mg/L for amikacin) have been reported as thresholds to minimize ototoxicity and nephrotoxicity.[3] From a mechanistic point of view, a saturation of uptake transporters at higher plasma concentrations supports extended interval dosing: lower aminoglycoside concentrations were observed in renal tubular epithelial cells with extended interval dosing. For ototoxicity, genetic factors can be involved in the reduction in the toxicity threshold.[27] Another reason to support once daily aminoglycosides is the decreased risk of adaptive resistance.[28]

Several studies have been published on TDM-based interventions and clinical outcomes. In critically ill patients, only one study showed that TDM can significantly reduce the duration of therapy, hospital stay, and nephrotoxicity.[8]

In a recent study,[29] however, no relationship was found between PK/PD target attainment and clinical outcome in

critically ill patients with short courses of high aminoglycoside doses. This finding was probably due to several factors, such as the heterogeneity of the patients, the use of combination therapy, the large proportion of patients (67%) not reaching the PK/PD target, and the small TDM group in the cohort, and probably an inadequate start dose.

In a study by Duszynska et al,[30] TDM resulted in the adjustment of amikacin therapy in most patients with sepsis, with a significant relationship found between clinical cure and increased C_{max}/MIC.

In general, standard TDM of aminoglycosides in critically ill patients is advised, both for toxicity and efficacy.

Glycopeptides

Glycopeptides are used to treat infections caused by gram-positive microorganisms. They display high PK variability and a narrow therapeutic window. Glycopeptide TDM is the most common in standard patient populations and in critically ill patients. Teicoplanin has high protein binding (>90%).[3] With regard to vancomycin, protein binding is approximately 50%, but considerable variability surrounds this estimate.[31]

Vancomycin

The target for vancomycin is often set at an AUC0-24/MIC of 400–600 mg/L × h to achieve effective therapy.[32] As AUC sampling is often not feasible, trough concentrations are used as a proxy for the AUC. Trough reference levels for susceptible microorganisms are targeted from 10 to 15 mg/L (intermittent therapy) and 15–20 mg/L for more virulent bacteria such as *Staphylococcus aureus*. However, for many pathogens, the required exposure is unknown. In specific patients, such as pediatric oncology patients, the AUC0-24/MIC target may sometimes allow for the use of lower dosages in some patients, especially given an infective species with epidemiological cut-off value (ECOFF) of <1 mg/L. In clinical practice, if a high dose does not result in adequate trough levels, a second non-trough level is measured to calculate the AUC.

A systematic review and meta-analysis concluded that vancomycin TDM significantly increases the rate of efficacy and decreases the rate of nephrotoxicity in patients.[9] In a small study by Cardile et al,[33] it was found that TDM of vancomycin resulted in faster target concentration attainment, more rapid discharge from the hospital, clinical stability, and shorter courses of vancomycin. This study was performed using TDM based on the trough levels. In another recent study, it was found that peak-trough–based TDM was significantly associated with a higher therapeutic cure rate than trough-only–based TDM. This difference was not observed with regard to all-cause mortality, neutropenia, or nephrotoxicity.[34] TDM with Bayesian forecasting has also been shown to be cost-effective when reducing nephrotoxicity was taken into account.[35]

Neely et al showed that AUC- versus trough-based TDM was superior with regard to the reduction in nephrotoxicity (<1% versus 8%) and shorter therapy time (4.7–5.4 versus 8.2 days).[36] Nonetheless, more research is required to potentially further optimize the AUC target for vancomycin because a recent systematic meta-analysis found that the vancomycin AUC/MIC performance is modest and inconsistent with regard to positive clinical outcomes.[37]

Larger studies are needed to investigate the difference between only trough levels or AUC or peak-trough TDM with regard to the effects on clinical outcomes. Meanwhile, using trough levels is easy to implement and use in clinical settings. In addition, more hospitals are changing to continuous vancomycin regimens in critically ill patients.[38] Continuous regimens have been associated with less nephrotoxicity than intermittent regimens.[39,40] With continuous infusion, only one sample was needed as an advantage. Other studies are needed to confirm the beneficial effects of continuous vancomycin infusion on clinical outcomes.

Teicoplanin

Although the literature on TDM of teicoplanin is more difficult to obtain than for vancomycin, TDM is recommended for critically ill patients, although this is mostly based on the variability in teicoplanin exposure in critically ill patients, retrospective analysis[41,42] and not on TDM prospective studies. For uncomplicated infections, a C_{min} of ≥10–20 mg/L has been suggested. A retrospective study found that achieving a trough level of >20 mg/L can improve clinical outcomes and decrease adverse effects, and this threshold has also been recommended for severe staphylococcal infections.[43] In MRSA infections, AUC/MIC of >900 has been associated with bacteriological responses.[44,45] Unpublished studies have reported that a level of >60 mg/L increases the likelihood of nephrotoxicity. An elaborate overview of teicoplanin reference levels is provided in Kucers' The Use of Antibiotics.[46] In general, standard TDM of glycopeptides in critically ill patients is advised, both for toxicity and efficacy.

Fluoroquinolones

Quinolones are an important group of antibiotics for both community-acquired and hospital-acquired infections. Bacterial resistance to quinolones is an increasing problem; optimal dosing of these antibiotics is an essential part of preventing this phenomenon. In this review, we focused only on fluoroquinolones. Fluoroquinolones are lipophilic antibiotics, most of which have moderate to low protein binding and are mostly renally cleared. The most frequently used fluoroquinolone is ciprofloxacin, which has a protein binding rate of approximately 30%. The ratio of the area under the drug serum concentration–time curve over 24 hours at a steady state and the minimal inhibitory concentration (AUC0-24/MIC) is a good predictor of ciprofloxacin efficacy. The PDT for the optimal outcome for ciprofloxacin is AUC0-24/MIC ≥125, or ≥100 for the unbound (free) drug concentration (ƒAUC0-24/MIC).[47] The probabilities of a microbiological and clinical cure for ciprofloxacin AUC0-24/MIC <125 were poor (26% and 42%, respectively) compared with AUC0-24/MIC ≥125, where the probabilities were 80% ($P < 0.005$) and 82% ($P < 0.001$), respectively.[47,48] In addition, a C_{max}/MIC ratio of 8–10 is suggested to be particularly important to prevent the emergence of resistance.[49]

In a recent study, we found that in standard dosing, the proportion of patients achieving the target ƒAUC0–24/MIC of ≥100 was 61.9% and 16.7%, respectively, with MICs of 0.25 and 0.5 mg/L, respectively.[47]

Although increasing reports of fluoroquinolone-associated seizures have emerged,[50] no toxicity threshold has been established and causality is unclear.[51] None of these reports contained ciprofloxacin. No TDM outcome studies have been performed, and one multicenter randomized controlled trial is currently ongoing to investigate the effect of TDM of beta-lactams and fluoroquinolones on clinical outcomes in critically ill patients (the DOLPHIN trial).[10] In critically ill patients with a very heterogeneous PK, antibiotic resistance emergence, and bacterial species with a high ECOFF, individual TDM can be indicated.[47]

Lipopeptides

Colistin

Colistin is administered parenterally as a prodrug, colistin methane sulfonate. Both had a small distribution volume. Colistin protein binding can be between 59% and 74% and is concentration-dependent. Elimination occurs via several routes, although renal elimination plays an important role, and dosing needs to be adjusted in patients with renal failure. The free AUC/MIC seems to best predict activity, although in noncystic fibrosis patients, only a trough level is often measured. A total trough level above 2.4 mg/L is associated with nephrotoxicity.[52] The therapeutic window for colistin is narrow, and the trough levels of colistin are suggested to be approximately 2 mg/L as an optimum between efficacy and nephrotoxicity.[53,54]

In a recent review,[55] 7 manuscripts described TDM and clinical efficacy and/or nephrotoxicity. The results are contradictory, although a relationship between high levels and nephrotoxicity seems to exist.[56,57] More research is needed to link efficacy to TDM in colistin therapy.

Polymyxine B

In some countries, polymyxin B is used for intensive care. It is a mixture of polypeptides and polymyxins B1 and B2. Polymyxin B has a low distribution volume and is mostly cleared by nonrenal elimination. Protein binding is reported to be approximately 58%–98.4%.[3] A steady state of AUC0-24 of 100 mg × h/L has been proposed as the nephrotoxicity threshold.[58] It exhibits concentration-dependent killing characteristics. A fAUC0-24/MIC ratio of 3.7–28 correlated best with *Klebsiella pneumoniae* killing.[59] No TDM and clinical outcome studies have been performed with regard to polymyxin B.

Daptomycin

The distribution volume of daptomycin is low. It is mostly cleared by the kidneys and is highly protein bound (>92%). AUC/MIC above 666 mg × h/L has been described for daptomycin efficacy in critically ill patients.[60] In addition, a trough level below 3.2 mg/L may lead to poor clinical outcomes in patients with gram-positive infections.[61] If the trough level is above 24.3 mg/L, patients are more at risk at elevations of creatinine phosphokinase.[62] In a recent review,[63] 16 articles were found, including TDM, antibiotic resistance, side effects, and therapeutic success. It was concluded that TDM seems relevant for daptomycin, although there are no studies proving the added benefit of TDM on clinical outcomes. Analytical methods are sparse, and TDM is only possible in some hospitals.

Co-trimoxazole

Co-trimoxazole is a combination of sulfamethoxazole and trimethoprim. Both drugs are primarily renally excreted and, only to a small extent, protein-bound. The PK data of co-trimoxazole are limited. In general, TDM is performed only in the higher dosing used in PJP/*Stenotrophomonas* infections due to the renal toxicity caused by the metabolite of sulfamethoxazole, and higher C_{max} or higher AUC/MIC are indicated.[3] A target sulfamethoxazole peak serum concentration of 100–150 mg/L has been advocated to maximize therapeutic efficacy.[64] In 279 patients, no relationship was found between sulfamethoxazole levels and toxicity.[65] In individual cases in which higher dosing is indicated and therapeutic failure or toxicity may play a role, sulfamethoxazole levels may be analyzed. With regard to the metabolite, >75 mg/L seems to be related to toxicity, and concentrations between 50 and 75 mg/L seem to be good if diuresis is adequate. Preferably, metabolite levels are below 50 mg/L.[66]

Beta-lactams

Beta-lactams are the cornerstones of anti-infective therapy for sepsis. They are most often used as first-line treatment. Therefore, dose optimization should be performed as soon as possible. Beta-lactam generally has low to moderate protein binding, although some agents exhibit high protein binding (eg, ceftriaxone and flucloxacillin). Owing to the high variability in free fractions in critically ill patients, it is recommended to measure unbound concentrations of beta-lactams, especially for highly bound beta-lactams (>70%).[14]

Beta-lactams are often categorized into 3 groups: carbapenems, cephalosporins, and penicillins. Beta-lactams are commonly administered using a traditional fixed-dosing scheme. TDM is frequently not performed due to logistics, assay unavailability, and the assumption that there is no need for TDM of beta-lactams: they generally display a wide therapeutic range and favorable safety profile. Recently, several studies have shown that TDM of beta-lactams may also be useful in maximizing efficacy, especially in critically ill patients who are prone to inadequate exposure to beta-lactams.[4,5] TDM of beta-lactams can also be useful in populations with altered PK, such as obese, elderly, pregnant, or burn patients, and patients with difficult-to-treat bone infections.[3] In a recent review, male sex, younger age, and augmented clearance were shown to be significant predictors for target nonattainment of beta-lactams in critically ill patients.[67]

Beta-lactams are time-dependent antibiotics and their PDT is commonly described as the percentage of a period in which free (f) concentrations exceed the MIC (% fT > MIC). The % fT > MIC required for optimal activity of beta-lactams depends on the specific drug class and the microorganism. Dosing regimens are typically designed to cover at least

40% fT > MIC of the presumed MIC of the pathogen to have a bacteriostatic effect.[68] However, in general, a 1 − log reduction is preferred over stasis. In immunocompromised and critically ill patient populations, 100% fT > MIC is often suggested as a prudent target for beta-lactams.[6] There are also guidelines reporting 100% fT > 2–5 × MIC, but these are only based on 3 clinical observational studies: one in meropenem and lower respiratory tract infections, showing better clinical outcomes if 5 × MIC is used,[69] cefepime and gram-negative infections with better microbiological outcomes if 3.6 × MIC,[70] and cefepime and clinical failure in gram-negative pneumonia.[71] Only a few clinical studies have described significantly better bacteriological eradication and clinical cure rates when fT > MIC was 100%.[4,72] More research is needed to determine whether the target should be increased from 100% fT > MIC to 100% fT > 4 × MIC. In this discussion, the variability in the MIC measurements should also be taken into account because this may in part explain the need for a target that includes a factor multiplied by the MIC.[20]

With regard to clinical outcome and TDM, in a retrospective study on imipenem in 300 patients, a trend was observed between increased clinical failure and C_{min} of <2 mg/L.[73] In a small prospective study on piperacillin in hematological malignancies, no relationship was found between the duration of fever, days to recovery from neutropenia, and achievement of PK/PD targets.[74]

Regarding toxicity, cefepime plasma trough concentrations of >35 mg/L were related to neurotoxicity, and it has even been suggested that for intermittent infusions, trough concentrations of >20 mg/L should be avoided.[75] However, in general, cefepime is considered more toxic than other beta-lactams. As beta-lactams are considered "time-dependent" antibiotics, continuous or prolonged infusion is increasingly used in place of intermittent therapy. In continuous therapy, even in continuous infusion studies, target attainment is sometimes difficult.[76] A meta-analysis showed mixed effects for continuous infusion.[77] A large international trial is currently being conducted to investigate the effect of continuous infusion of beta-lactams.[78] Randomized clinical trials are warranted to assess the value of beta-lactam TDM and dose individualization regarding clinical outcome; randomized clinical trials are warranted and currently conducted.[10] Currently, TDM of beta-lactams for efficacy in critically ill patients can be advised in individual cases with risk factors for target nonattainment.[67]

Linezolid (Oxazolidinones)

Linezolid is lipophilic and has low protein binding (31%). Elimination occurs via renal excretion (35%) or enzymatic pathways. Elimination has been associated with nonlinear PK; therefore, PK is difficult to predict and presents a challenge to linezolid dosing.

The PDT of linezolid to yield effective therapy has been described as AUC/MIC values of 85–164 for different severe gram-positive infections. T > MIC seemed to be linearly correlated with AUC/MIC (<120 mg × h/L), and targets of T > MIC of 82%–99% have been related to clinical outcomes, whereby concentrations ideally exceed the MIC throughout the entire dosing interval.[79] Linezolid TDM is mostly performed on trough levels, mostly due to its practicality. Various studies have shown a linear trough level-AUC correlation and an adequate prediction of AUC using trough levels.[79] High linezolid concentrations (C_{min} = 6.3–35.6 mg/L) resulted in toxicity including myelosuppression, often thrombocytopenia, lactic acidosis, or neuropathy.

Underexposure and lack of efficacy are often observed in obesity, critical illness [eg, augmented renal clearance (ARC), renal replacement therapy, or ECMO], burns, or cystic fibrosis.[80,81] To decrease adverse events or lack of efficacy, TDM can be advised, particularly in high-risk populations and prolonged treatment. Evidence for the benefit of linezolid TDM (eg, improved therapeutic exposure or recovery from thrombocytopenia) has emerged from retrospective analyses.[80] Linezolid TDM is not often performed but can be deployed in specific patients, such as patients with augmented clearance or renal replacement therapy.

Other antibiotics, such as doxycycline, metronidazole, and rifampicin, are used in intensive care. However, TDM has never been requested for metronidazole and doxycycline, and literature on this subject is nonexistent, and therefore, these antibiotics have not been described in this article. For rifampicin, TDM is most often performed in patients with tuberculosis. As this is a different patient category with different characteristics, rifampicin was excluded from this review.

FUTURE PERSPECTIVES

In this paragraph, we will discuss which steps are essential for the optimal implementation of TDM for all antibiotics in critically ill patients.

Depending on the background, several aspects need to be addressed to better relate TDM to clinical outcomes and to implement TDM and model-informed precision dosing (MIPD) in clinical practice.

Model-Informed Precision Dosing

TDM typically covers the assessment of PK parameters and concurrent dose adaptation after initial standard dosing and drug concentration analysis. However, although TDM offers the possibility to adjust doses based on exposure, this may be too late in critically ill patients treated with antibiotics. When using MIPD, personalized dosing can be given right from the start of treatment based on population PK parameters and patient-specific covariates.[79] The advantage of MIPD is that it captures drug, disease, and patient characteristics in modeling approaches and can be used to perform Bayesian forecasting and dose optimization. Ideally, MIPD should be used at the start of therapy to tailor the dose to the individual patient because optimal exposure is essential in patients with severe infections.[79] The added value and clinical benefits of MIPD are yet to be established. However, remarkable efforts have been made over the past decade in the development of easy-to-use and secure MIPD software tools.[82] In addition, there has been a significant increase in the number of MIPD software tools with electronic health record integration capability to minimize the data entry burden.

Practical Issues

Timely initiation of adequate treatment is essential for critically ill patients. The rapidly changing PK in these patients makes most PK data, often obtained from less severely ill populations, less useful. Laboratory equipment and services should be suited to report a TDM analysis and advise within several hours. Additionally, easy withdrawal schedules and instructions are essential. The use of rest material (scavenged sampling to perform TDM) or limited sampling with MIPD needs to be developed more intensely in the coming years. In addition, not all hospitals have LC-MS/MS equipment to quantify their concentrations. Development of analytical assays for antibiotics that can be used more easily with less expensive equipment will be important; for example, immunoassays for beta-lactams.

Biosensor development is at its starting point, and hopefully, can be introduced. Biosensors are analytical devices that combine a biological component with a physicochemical detector and are used for the detection of chemical substances. The first report on its application is on its way.[83,84] The goal would be to directly measure the antibiotic concentration at the bedside of critically ill patients: real-time monitoring of drugs.

Education and Knowledge on Pharmacology

A great amount of information on PK/PD, modeling, MIPD, and TDM can be found in databases such as Medline. The crucial part is to what extent data can be used in patients, for example, if the same filters are used with regards to renal replacement therapy or the same tubes in ECMO. To interpret these data correctly, knowledge of the pharmacology and equipment of critically ill patients is essential. In addition to renal replacement therapy and other equipment information, more education is needed on the physiology of critically ill patients. A specialized pharmacist-pharmacologist is essential because they have specific knowledge of critically ill patients and their physiology.

Multiple research topics should be covered in the next couple of years to move toward precision dosing of antibiotics in critically ill patients. First, ARC is observed in critically ill subpopulations. ARC is defined as an increased creatinine clearance of >130 $mL \cdot min^{-1} \cdot 1.73^{-1} \cdot m^{-2}$ measured using an 8- to 24-hour urine collection and refers to the enhanced renal elimination of circulating solute (such as metabolic waste and drugs).[85] 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.[3] Identifying patients with ARC is challenging because these patients may have elevated renal function despite normal serum creatinine concentrations; importantly, commonly used glomerular filtration rate mathematical estimates are unlikely to be as reliable as urinary creatinine clearance data.[86] More research is needed on ARC, and the effect on the PK of drugs is warranted.

Second, there is a need for more clinical benefit studies, which are lacking for most antibiotics and TDM. This shortage also applies to most drugs. Although it has been shown in clinical patients that with increased exposure, the probability of clinical cure increases as well, the added value of TDM with regard to clinical outcome needs to be confirmed in antibiotics, as can also be observed in the earlier paragraphs. In addition, identifying patients who are prone to not reaching the target and who may also be at risk of resistance using clinical rules can be the next step. Other possible research topics include the added value of biomarkers and the role of inflammation in PK in a clinical setting.

Microbiology

As mentioned above, information on PK/PD targets is derived most often from animal/preclinical studies. The currently used breakpoints, on which laboratory results are based, are designed for a limited range of patients, excluding extremes, such as critically ill or morbidly obese patients. More research is needed on target site concentration and (variability in) MICs, PK/PD targets, and dose–response relationships in patients. In addition, knowledge of the protein binding of drugs in relation to target attainment is needed. Furthermore, a dosing regimen that prevents the selection of resistance and the relationship between targets, concentration, and the risks of tolerance or resistance needs to be unraveled.

Conclusions

Although more research on clinical outcomes is needed, the TDM of antibiotics is essential in critically ill patients. TDM is often performed for glycopeptides and aminoglycosides because most research is performed with these antibiotics, and on outcomes, and assay availability is good. For other antibiotics, TDM can be of added value, but mainly because of practical issues, assay problems, or simply because less research is available on outcomes, it is not advisable in the standard workflow. However, in critically ill patients, TDM of beta-lactams, fluoroquinolones, and linezolid can be indicated in specific patients. For other antibiotics, individual cases support TDM, however, results are contradictory, and most relationships are found between TDM and decrease in toxicity.

Integration of MIPD can potentially streamline the TDM process. PK/PD models of antibiotics must include (more) biomarkers, treatment response, and clinical outcome parameters, which might further advance the implementation of TDM and MIPD. Rapid bioanalytical techniques or real-time monitoring of drug concentrations through biosensor knowledge, education, and clinical information on targets are other important factors for TDM implementation in clinical practice.

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