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From Therapeutic Drug Monitoring to Model-Informed Precision Dosing for Antibiotics

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Therapeutic drug monitoring (TDM) and model-informed precision dosing (MIPD) have evolved as important tools to inform rational dosing of antibiotics in individual patients with infections. In particular, critically ill patients display altered, highly variable pharmacokinetics and often suffer from infections caused by less susceptible bacteria. Consequently, TDM has been used to individualize dosing in this patient group for many years. More recently, there has been increasing research on the use of MIPD software to streamline the TDM process, which can increase the flexibility and precision of dose individualization but also requires adequate model validation and re-evaluation of existing workflows. In parallel, new minimally invasive and noninvasive technologies such as microneedle-based sensors are being developed, which—together with MIPD software—have the potential to revolutionize how patients are dosed with antibiotics. Nonetheless, carefully designed clinical trials to evaluate the benefit of TDM and MIPD approaches are still sparse, but are critically needed to justify the implementation of TDM and MIPD in clinical practice. The present review summarizes the clinical pharmacology of antibiotics, conventional TDM and MIPD approaches, and evidence of the value of TDM/MIPD for aminoglycosides, beta-lactams, glycopeptides, and linezolid, for which precision dosing approaches have been recommended.

Success or failure of antibacterial therapy is driven by three determinants: the patient, the bacterium, and the antibiotic. These factors determine the required dose of an antibiotic that successfully eradicates the infection and at the same time does no harm to the patient. In particular, in the case of severe infections in special patient populations such as critically ill patients, therapeutic drug monitoring (TDM) is desirable to ascertain that the exposure of the drug is optimal to achieve these aims. Model-informed precision dosing (MIPD) is an emerging term, representing approaches to integrate different sources of information into a mathematical framework that has the potential to streamline the TDM process and maximize the success of antibacterial therapy.

The present review aims at providing a concise summary of the clinical pharmacology of antibiotic therapy with regard to pharmacokinetic (PK) and pharmacodynamic (PD) factors and circumstances that may favor the use of TDM. Moreover, it discusses technological advancements in bioanalysis, biomarkers, pharmacometric models, and MIPD algorithms to foster the use of precision dosing approaches in clinical practice. Lastly, we intend to provide a summary of the clinical pharmacology and evidence of the value of TDM for selected antibiotic classes and drugs, including aminoglycosides, beta-lactams, glycopeptides, and linezolid, for which precision dosing approaches have been recommended.[1]

CLINICAL PHARMACOLOGY OF ANTIBIOTICS

PK alterations in critically ill patients

Illness, and particularly critical illness, has been associated with vastly variable pharmacokinetics (i.e., drug concentration-time profiles in the body), making adequate dosing a challenging endeavor. Pathophysiological disturbances in intensive care patients resulting from acute or chronic disease processes and treatment interventions may affect all major pharmacokinetic processes, leading to altered and highly variable PK and thus making TDM advisable.

The rate and/or extent of absorption may highly vary between and within patients, both following enteral and other routes of administration, such as inhalation, subcutaneous, intramuscular, and rectal administration.[2] Changes in gastric pH (often caused by frequently used proton pump inhibitors), gastric emptying and local perfusion due to vasopressors or shock, and formula feeding and timing thereof, as well as adherence to feeding tubes may impair or delay drug absorption, although evidence is scarce for

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antibiotics.[2,3] Hence, oral antibiotics are infrequently used in critically ill patients.

Cardiovascular disorders and fluid shifts particularly affect the volume of distribution (V_d), which is critical for initial antibiotic dosing. Systemic inflammation can promote endothelial dysfunction, consequently leading to capillary permeability and plasma leakage into the interstitial space, which can further be aggravated by therapeutic intravenous fluid administration. This clinical scenario can prompt an increased V_d especially for hydrophilic antibiotics such as beta-lactams, glycopeptides, or aminoglycosides, and can require a loading dose.[4] For highly protein-bound antibiotics, increased V_d may further be caused by reduced plasma albumin and protein binding, which may potentially also increase the drug clearance for renally eliminated highly bound antibiotics such as daptomycin, ceftriaxone, and ertapenem.[5]

Altered metabolism in critically ill patients may arise from changes in hepatic blood flow in states of shock, or altered enzyme activity and protein binding, which have been reported in connection with acute kidney injury and hepatic dysfunction.[5,6] Consequently, variable first pass effects and thus bioavailability or decreased drug clearance may occur.[5] Furthermore, drug–drug interactions substantially affect drug metabolism and eventually clearance and may put patients at risk of antibiotic overexposure and underexposure.[7]

Organ impairment may detrimentally reduce the clearance of hepatically and renally eliminated antibiotics and thus require lower-than-standard maintenance doses and/or prolonged dosing intervals. Acute kidney injury as an abrupt deterioration of kidney function is frequently observed in intensive care patients.[6] In contrast, augmented renal clearance (creatinine clearance > 130 mL/min/1.73 m^2) triggers underexposure and is commonly encountered in young patients with hyperdynamic circulation, enhanced cardiac output and organ perfusion, and/or undertreatment interventions involving fluid resuscitation.[8] Last, machine-based life support with the ability to contribute to drug clearance like renal replacement therapy, extracorporeal membrane oxygenation, or molecular adsorbent recirculation system therapy further complicates antibiotic dosing in the critically ill.[5,9,10]

Pharmacodynamics: MIC

Antibiotic pharmacodynamics describes the effect of an antibiotic on its target bacteria. Bacterial susceptibility towards an antibiotic, i.e., antibacterial activity, is routinely reported as the minimum inhibitory concentration (MIC). It is defined *in vitro* as the lowest concentration of an antimicrobial agent that inhibits the visible growth of a defined bacterial inoculum following overnight incubation (16–20 hours) in a standard growth medium.[11] Usually, test concentrations differ by twofold increments (e.g., 0.25/0.5/1/2 mg/L). Apart from this broth dilution method, further techniques, including agar diffusion methods such as the E-test, are available, which may lead to different results.[12]

Independent of the method of determination, the MIC concept bears limitations: MIC values are based on unphysiologically static concentrations and mirror only a snapshot of antibiotic activity at one timepoint, i.e., they reflect merely the result of a previous dynamic time course of bacterial killing.[12] As the MIC represents a threshold value distinguishing solely between visible growth or suppression of visible growth, a routinely available continuous variable for the antibiotic effect might be preferable. Furthermore, limited accuracy and reproducibility, assay variations, and ultimately MIC variability are critical and need to be considered together with wild-type distributions and European Committee on Antimicrobial Susceptibility Testing (EUCAST) or Clinical and Laboratory Standards Institute (CLSI) MIC breakpoints when informing dosing decisions by MIC values, particularly if repeated MIC determinations are not possible or if the MIC value is not available and only susceptible/intermediate/resistant categories are reported.[13] Hence, the MIC can be used in precision dosing, but fine-scale interpretation of the MIC is not possible, and for dosing calculations a worse case such as using the twofold value of the reported MIC could be a prudent approach. In case of missing MIC values, the local MIC distribution can inform about the likely susceptibility pattern of the target organism.

Pharmacokinetic/pharmacodynamic indices

To evaluate and determine dosing regimens, the pharmacokinetic behavior of a drug in the patient's body needs to be placed in context with its pharmacodynamic characteristics. PK/PD indices relate summary measures of drug exposure (total or free (f) concentrations) to the bacterial MIC and categorize antibiotics according to the highest correlation between index and antibiotic efficacy. The PK/PD indices fAUC/MIC (area under the concentration-time curve / MIC) and fC_{max}/MIC (maximum concentration / MIC) mirror "concentration-dependent" bactericidal killing and/or prolonged persistent effects, while $fT_{>MIC}$ (cumulative percentage of time that concentrations exceed MIC) reflects "time-dependent" bactericidal killing and minor persistence.[14] Notably, PK/PD indices used as targets for dose optimization reflect the steady-state situation. Optimal dosing regimens for an antibiotic depend on the PK/PD index driving its efficacy. For example, prolonged infusion durations rather improve $T_{>MIC}$ than AUC/MIC. Like the MIC, PK/PD indices represent simplifications and lack information about dynamic antibiotic effects. Target values of PK/PD indices resulting in a specific effect such as bacterial decrease or eradication predominantly stem from *in vitro* and animal studies.[12] Of note, PK/PD targets might vary depending on the type of outcome, time of determination, patient population, extent of tissue distribution, infection/target site, pathogen susceptibility, or combination therapy. Targets for individual patients must additionally consider their specific clinical condition, immune system functionality, concomitant disorders, comedication affecting pharmacodynamics (synergy, antagonism), and initiation of therapy.[12]

Pharmacokinetics/toxicity relationships

Different surrogate markers of drug exposure are utilized to link PK to toxicity, including the trough concentration (C_{min}), the C_{max}, or the AUC.[15] Similar to efficacy, the underlying mechanisms determine which surrogate marker might correlate best with toxicity. Ideally, when performing TDM, the PK/toxicity thresholds predict toxicity before its occurrence.

Acute, concentration-dependent toxicity might correlate best with C_{max}.[15] As an example, neurotoxicity mediated by some beta-lactam antibiotics, such as cefepime, might correlate better with C_{max} than C_{min} given the hypothesized concentration-dependent gamma-aminobutyric acid antagonism triggering neurotoxicity.[16] Yet, studies are required to corroborate such relationships. When interpreting C_{max} values, it needs to be considered that the achieved value depends on the length of the infusion. For oral but even intravenous administration, sampling precisely at C_{max} is practically almost impossible, and model-based approaches help to approximate the "true" C_{max}.

Nonacute toxicity, developing in the long term, might best correlate with the AUC as a cumulative measure of drug exposure.[15] Indeed, AUC is a frequently utilized PK surrogate to minimize the toxicity of antibiotics, e.g., vancomycin nephrotoxicity.[17] C_{min} is frequently applied as a surrogate for the AUC (see limitations below), but it can also provide distinct information. For example, when toxicity is dependent on saturable transporter-mediated drug uptake as observed for nephrotoxicity due to aminoglycosides,[18] C_{min} might be a superior marker to minimize toxicity compared with AUC, as the contribution of drug concentrations above the drug concentration producing 50% inhibition of the transporter to drug uptake is disproportionately low. Nonetheless, further research is required to better understand mechanisms of drug toxicity and its correlation with drug exposure.

Biomarkers: quantitative information about treatment response and toxicity

Feedback individualization of dosing is not necessarily restricted to drug concentrations. Biomarkers may early identify the onset of an infection, evaluate the response, and define when to stop treatment.[19] For example, repeated measurements of endogenous substances, or signs of adverse effects, have the potential to guide individual dose adjustments in a more rational and precise way than drug concentrations. One such endogenous substance measured routinely in infected patients is C-reactive protein (CRP). CRP is today primarily used to track the occurrence of an inflammation. In conjunction with other biomarkers like procalcitonin it is also studied to discriminate a bacterial from a viral infection. Ramos-Martin and colleagues developed a PKPD model describing the reduction in CRP based on teicoplanin concentrations.[20] Although this model could be a step towards individualization based on CRP measurements, the large interindividual variability in the pharmacodynamic parameters potentially due to host factors, infection type, and infection site, among others, may have limitations for its predictive value. Moreover, CRP has a relatively slow onset and turnover rate and may therefore not be an ideal marker to guide individualization of antibiotic treatment.

Cytokines that rise earlier during the infection, such as interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha), may find wider application, at least for supporting the initiation of antibiotic treatment as in the case of hospital-acquired infections. For example, in patients exposed to myelosuppressive chemotherapy, it was shown that the IL-6 peak occurred ~ 2 days before the CRP peak, which coincided with the diagnosis of febrile neutropenia.[21] A rise in IL-6 may hence suggest initiation of antibiotic treatment, i.e., before the infection has manifested and becomes life-threatening in immune-suppressed patients. TNF-alpha appears to be an even earlier biomarker indicating immune response to a pathogen.[22] Other immune response biomarkers that have been suggested to guide treatment include immune cell response, IL-8, IL-10, and procalcitonin.[19] Procalcitonin indeed appears to be one of the most promising host-response biomarkers given that it reflects the disease progression fairly well; i.e., when an antibiotic treatment is efficient, the procalcitonin concentrations decrease relatively rapidly, indicating that treatment can be stopped.[23] Given the complexity in the interplay between these factors it follows, however, that the relationships need to be characterized in mathematical models, considering different sources of variability, before their full potential for individual dose adjustments can be evaluated, and before biomarkers can be used in clinical practice. Other promising measurements, more specific to the infection, that may indicate the disease state include the quantification of bacterial DNA or RNA, where increased possibilities to apply polymerase chain reaction and matrix assisted laser desorption/ionization technologies can facilitate their use in precision dosing. Yet, while certainly attractive, the cost and time associated with measuring infection-related biomarkers is still substantial and many institutions may not (yet) have the capacity to implement these measurements in-house and in real time.

Biomarkers can also inform about drug-induced toxicity. Thrombocytopenia under linezolid therapy is one of the well-studied examples for this: Tsuji and colleagues have developed a semimechanistic PK/toxicity model which describes thrombocyte concentrations over time under linezolid exposure and could be used in MIPD software.[24] Hence, biomarkers represent an interesting opportunity to be included into a holistic MIPD framework; yet, further research is required to test such models in clinical practice and to define their potential therapeutic value. Also, novel biomarkers for nephrotoxicity including kidney-specific proteins or urinary micro RNA are being researched. These may provide advantages over the classic criteria for acute kidney injury such as elevated serum creatinine in association with oliguria and increased blood urea nitrogen, which are not sensitive enough to detect early signs of kidney injury and often indicate only irreversible kidney damage.[25]

Under which conditions is TDM with individualized dosing of antibiotics useful?

Individualized dosing informed by TDM measurements is the method of choice if the observed variability in PK/PD measures exceeds the acceptable variability in safety and efficacy after flat or covariate-based dosing,[26] i.e., if the variability in PK and response leads to therapy failure or toxicity in a part of the population. As outlined above, increased PK variability in conjunction with less susceptible target pathogens as frequently observed in hospital-acquired infections calls for individualized dosing to maximize efficacy and safety for different antibiotics. In a recent position paper presenting current evidence, individualized antibiotic dosing was explicitly recommended for aminoglycosides, beta-lactams, linezolid, teicoplanin, and vancomycin in critically ill patients.[1]

THE MEASURED DRUG CONCENTRATION AS INPUT TO TDM AND MIPD: MOVING BEYOND PLASMA

Determining the concentration of drugs in biological matrices can be accomplished with a range of bioanalytical methods like immunoassays, high-performance liquid chromatography (HPLC) with fluorescence or ultraviolet detection, and liquid chromatography with single tandem mass spectrometry detection (LC-MS/MS). Immunoassays are based on antibodies against the drug of interest and are operated on automated analyzers. The turnaround time is short and costs per test are generally low. Currently, few tests are available for antimicrobial drugs such as aminoglycosides and vancomycin. Since the introduction of HPLC with ultraviolet detection, a wide variety of in-house assays have been developed, but the introduction of LC-MS/MS, with more specific, sensitive, and faster assay turnaround times, best facilitates real-time TDM, with results returned to the physician on the same day. Due to high procurement costs, facility requirements, and the need for highly trained analytical scientists, the implementation of LC-MS/MS is often not feasible in smaller and less resourced settings. HPLC and LC-MS/MS might be more accurate and precise than immunoassays, and display less/no cross-reactivity. This is also reflected in the less strict acceptance criteria for a successful validation for immunoassays (accuracy within ± 20% of the nominal value, imprecision < 20% CV (coefficient of variation)) vs. LC-based techniques (accuracy within ± 15% of the nominal value, imprecision < 15% CV).[27]

Plasma and serum are the most widely used specimens when measuring drug concentrations, as most reference values for TDM have been established for these matrices. Although most assays measure total drug concentrations (protein-bound and unbound), only the free, unbound antibiotic is able to reach peripheral infection sites like tissues, and unbound concentrations determine both its efficacy and toxicity.[28] Thus, free concentrations are increasingly determined using procedures like ultrafiltration. As these methods are more time-consuming, expensive, and difficult to validate, routine implementation is limited to specific drugs and specific settings, such as for highly protein-bound drugs in the intensive care unit (ICU) setting.[29]

Dried blood spot (DBS) and dried plasma spot techniques facilitate minimally invasive microsampling in remote or home settings. DBS samples do not need to be frozen, as drug stability is usually much higher in the DBS as compared with a plasma sample. Recently, the International Association of Therapeutic Drug Monitoring and Clinical Toxicology published a guideline on the development and validation of DBS methods.[30] Despite the above-mentioned advantages of DBS, hematocrit, blood droplet size, and environmental factors like humidity can pose a challenge for assay development and validation.[30] Implementation of DBS requires clinical validation in which paired plasma-to-serum samples are compared with results obtained from the DBS.[30,31] When predefined criteria are met, suitability for routine use has been proven.[30]

Saliva has been introduced as a patient-friendly alternative matrix to determine drug concentrations.[32] Depending on the interpatient and intrapatient variability in the saliva/plasma ratio, saliva monitoring can be applied as semiquantitative (screening) or quantitative assays.[33] When using saliva sampling, salivary flow, pH, and protein binding can cause variability and must be considered.[33]

Interstitial space fluid (ISF) has emerged as a matrix with high potential to measure drug concentrations, as it is considered to better reflect drug exposure at the site of infection.[34] Different microneedle technologies to measure ISF concentrations have been proposed, ranging from continuous monitoring devices to hydrogel-forming microneedles.[34] The main challenges associated with microneedle technologies are related to the different stages between sample extraction and analysis, which can lead to drug concentrations below the limit of quantitation and measurement variability.[34]

Microdialysis constitutes the method of choice to measure antibiotic ISF concentrations in relevant target tissues.[35] It enables measuring unbound drug concentrations, as only unbound drug is able to move through the membrane of the catheter.[36] A recent study proposed that an intravenous microdialysis catheter used to measure lactate and glucose concentrations in the ICU could also be used to determine antimicrobial drug concentrations (e.g., of vancomycin and gentamicin).[36] The microdialysis catheter enables clinicians to semicontinuously monitor drug concentrations, thus allowing more rapid interventions using target-controlled infusions. Such automated applications may be the future, especially for ICU patients, in whom the PK can change rapidly.[37]

FROM THERAPEUTIC DRUG MONITORING TO MODEL-INFORMED PRECISION DOSING

Approaches to interpret TDM data

Traditional TDM. In traditional TDM, therapeutic exposure ranges are defined, within which a drug is expected to be effective and safe. Usually, the measured drug concentration arising from the TDM itself is interpreted in relation to the therapeutic range. Advantages of the traditional TDM approach include its straightforward implementation, the simple interpretation of TDM data, and that dose adjustments can be performed on the mathematical "rule of three" by changing either the maintenance dose or the dosing interval (also known as the Dettli rules) to keep the drug concentration in the therapeutic range. An extension of such traditional therapeutic ranges are dosing nomograms that can be used to guide adjustment of the maintenance dose or dosing intervals.

Several limitations are associated with this traditional TDM approach: First, sampling needs to be performed at steady state. For drugs with a reasonably long half-life, this leads to the practice that TDM is usually performed on day 2 or 3 of therapy and means that the sample is commonly available for interpretation on the subsequent day. While such a time frame might be acceptable for other indications, PK/PD targets should be attained as early as possible in the case of infections. In line therewith, doses of antibiotics with nonlinear PK such as rifampicin cannot be adjusted by the rule of three, as the PK is concentration dependent and/or time dependent. Second, a single drug concentration such as the trough sample is a suboptimal surrogate

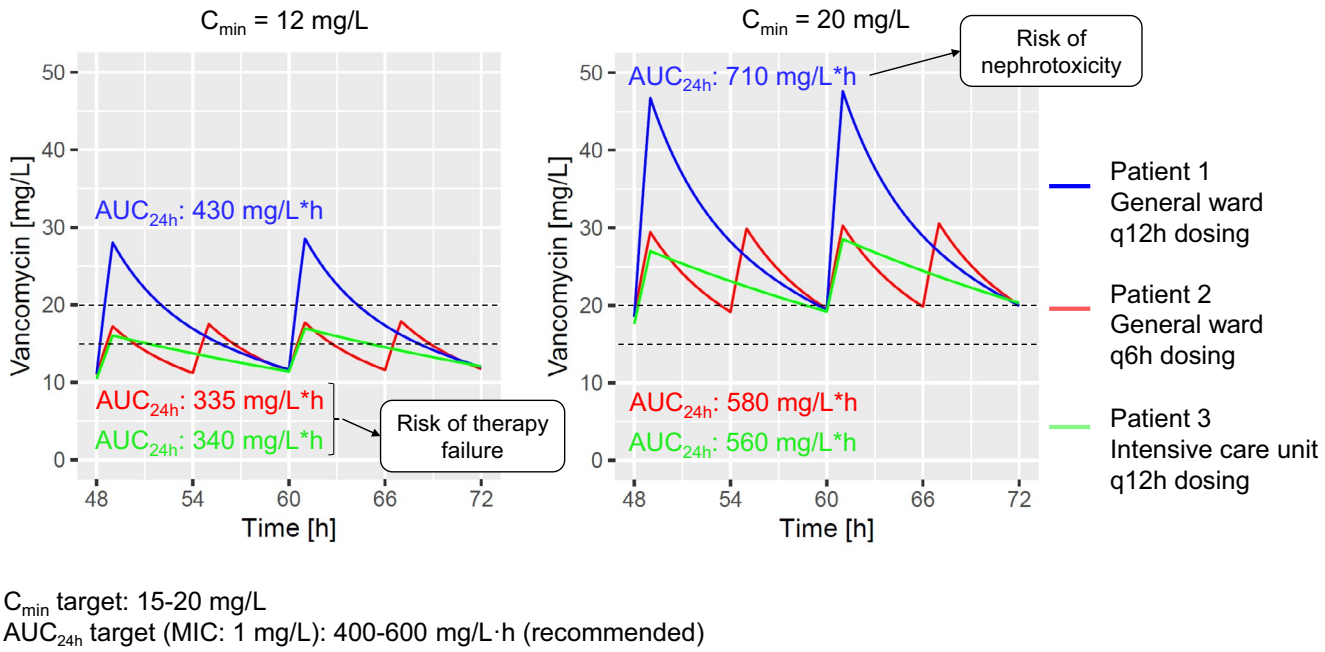

Figure 1 Comparison of AUC_{24h} and trough concentration to exemplify that trough concentrations can be misleading and are a suboptimal surrogate for AUC in the case of different dosing intervals or altered PK. Vancomycin serves as a case example for a general ward patient with unaltered PK receiving vancomycin at Q12H (blue) or Q6H (red) or a critically ill patient with altered PK (increased V_d) receiving Q12H dosing (green). Dashed lines, C_{min} target range from 15–20 mg/L. Left, although C_{min} of 12 mg/L would indicate underexposure for all three patient examples, patient 1 (blue) displays exposure in the AUC_{24h} target range. Right, C_{min} of 20 mg/L would indicate that all patients are in the target range. However, the AUC_{24h} of patient 1 (blue) is outside of the AUC_{24h} target range and suggests a higher risk of developing nephrotoxicity. AUC_{24h}, area under the concentration-time curve over 24 hours; C_{min}, trough concentration; h, hours; MIC, minimum inhibitory concentration; PK, pharmacokinetics; Q6H, every 6 hours; Q12H, every 12 hours; V_d, volume of distribution.

of overall drug exposure. While there is a relationship between the trough concentration and the AUC, this relationship is only conserved for the same dosing interval and in the absence of PK changes such as increased V_d in critically ill patients.[38] As outlined in **Figure 1** using the example of vancomycin, various PK profiles can lead to the exact same trough concentration for every 6 hours (Q6H) or every 12 hours (Q12H) dosing or in the presence of PK alterations. Third, timing is crucial: If the sample or the dose is taken outside of a predefined acceptable time window, it cannot be interpreted accurately. Fourth, traditional TDM is a rather passive approach by monitoring and accepting the measured drug concentration as "therapeutic" whenever inside the (sometimes quite wide) therapeutic range, potentially leading to suboptimal attainment of the PK/PD target.[39] The passive nature of TDM has been criticized, and the concept of target concentration intervention has been introduced. This concept uses a defined target (instead of range) and pharmacological principles for dose calculation, and defines an intervention in the individual patient's therapy.[40]

Model-informed precision dosing (MIPD)

MIPD is an emerging, integrative term that summarizes the use of mathematical models to predict personalized dosing beyond a specific approach or technique. In MIPD, a mathematical model is used to interpret the measured drug concentration. These models, so-called population models, contain several components: (i) a structural model describing the typical PK, i.e., concentration-time profile, of the antibiotic in a (patient) population, (ii) a covariate submodel defining the relationship between the PK parameters and patient-specific covariates such as body weight, age, organ function markers, or co-medication, and (iii) a mathematical representation of the interindividual and intraindividual variability of the PK parameters and residual variability around the individually predicted drug concentration-time profiles accounting for differences to observed concentrations. To interpret the residual variability, knowledge about the assay parameters is key: For a good model, the magnitude of the residual error should lie within the margin of the analytical error. To account for interindividual variability, both parametric[41] and nonparametric approaches[42] are used. The main difference is the use of a defined distribution of PK parameters in the case of the parametric approaches, whereas in the case of nonparametric approaches so-called support points are estimated from the clinical data, which do not make distribution assumptions. For a detailed review of either approach, the reader is referred to two comprehensive reviews.[41,42] More research, beyond simulation studies, is necessary to compare the predictive performance of both approaches in real-world data when future drug exposure is predicted in the context of MIPD.

Harvesting the power of the population model, the MIPD workflow is substantially different as compared with traditional TDM. First, the population model can be utilized before the administration of the first dose to predict a dosing regimen that maximizes the chance to meet the PK/PD/toxicity targets. Such

an approach can consider multiple covariates at the same time and is thus more flexible than dosing nomograms or tables that typically consider only one or two factors at best. Together with the patient covariates, the interindividual variability in PK can be considered and probability of target attainment for the PK/PD/toxicity target can be calculated and optimized *a priori*. Second, when measured drug concentrations become available, these can be used to derive the individual PK parameters—even from one single sample—using Bayesian estimation. This individual PK parameter estimate is also referred to as the maximum *a posteriori* (MAP) Bayesian estimate. If not only the mode of the PK parameter distribution (i.e., the MAP estimate), but also the entire posterior distribution shall be quantified, more advanced data assimilation techniques are required, as recently described comprehensively by Maier *et al*.[43] Any timed sample, even from the first dosing interval before reaching steady state, can be considered for MIPD and the precision of the individual PK parameter estimates determined for a patient typically increases as more drug concentration samples are added. Third, using the individual PK parameters, simulations can be performed to determine a dosing regimen that maximizes the attainment of the PK/PD/toxicity target. A workflow outlining the steps of TDM and how MIPD can enhance this process is presented in **Figure 2**. Lastly, it can be anticipated that the development of electronic health record systems, in which MIPD tools are directly implemented, and which thus eliminate the need for time-consuming and error-prone manual data entry into an MIPD software, will enhance the broader clinical uptake of MIPD approaches.[44]

The need for model selection and qualification in MIPD

Particularly for antibiotics, a plethora of population models is frequently available for one drug. Hence, the model used to adjust dosing in a patient needs to be carefully chosen with respect to factors likes matching age groups (e.g., pediatric, adult, etc.), indication, disease status (e.g., general ward, critically ill), body

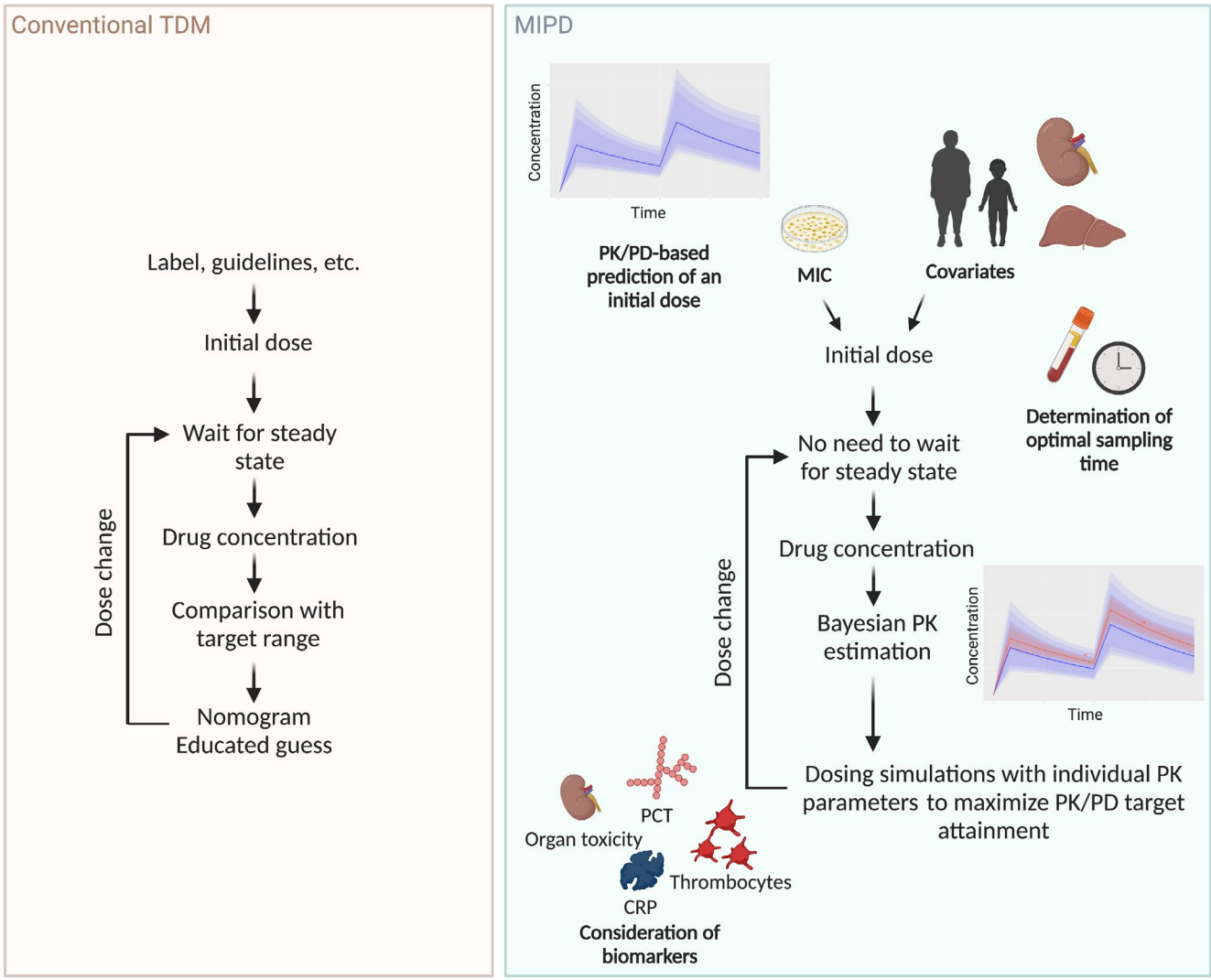

Figure 2 Comparison of (left) the conventional TDM workflow and (right) the MIPD workflow. CRP, C-reactive protein; MIC, minimum inhibitory concentration; MIPD, model-informed precision dosing; PCT, procalcitonin; PD, pharmacodynamic; PK, pharmacokinetic; TDM, therapeutic drug monitoring.

composition (e.g., normal, obese, cachectic), genetic status, studied dose levels and covariate ranges, and employed analytical methods.[45] Ideally, the chosen model and the target population are a perfect match.

Yet, even if the population model and the target population for MIPD match, it has to be acknowledged that population models often have not been developed with the intention to be used in MIPD. Therefore, usually a fit-for-purpose evaluation of the models is required that evaluates their predictive performance in the MIPD setting. Different aspects of the model should be evaluated, including the performance regarding the *a priori* prediction, the correct depiction of PK variability components by simulation-based diagnostics, and, importantly, the performance in Bayesian forecasting. For this purpose, retrospective TDM data sets with several measured drug concentrations can be utilized, in which parts of a data set are blinded to the models and predicted by the models using earlier measured concentrations in the data set, thus mimicking the TDM process retrospectively. Of note, in a recent systematic review on the external evaluation of population models for MIPD with antibiotics, only 8 of 35 external evaluation studies assessed the performance in Bayesian forecasting in such a way.[46] When evaluating the performance metrics, not only bias and imprecision of the forecasted concentrations should be evaluated, but also their impact on the calculated PK/PD target attainment and the subsequently derived dosing decisions.[46] For example, in a recent study by Broeker *et al.*, the predictive performance of 31 population models for vancomycin was systematically evaluated in a general ward population.[47] The predictive performance was very heterogenous across the evaluated models, and the calculated PK/PD target attainment—here the calculated area under the concentration-time curve over 24 hours (AUC_{24h}) (required for AUC_{24h}/MIC calculation)—differed by more than threefold across models, which would drastically impact dosing decisions. While some of the observed differences in the predictive performance could be attributed to nonmatching population models, further factors were identified that influenced the predictive performance: (i) Models built upon larger populations tended to perform better than models built from smaller collectives, and (ii) Biased sampling designs (e.g., trough-only sampling) for data used for model building can lead to mis-specified population models with biased predictions.[47] Moreover, population models are often built based upon clinical routine data. Accurate documentation, particularly of dosing and sampling time, is highly important if the derived models should be used for MIPD, as inaccurate documentation can inflate the residual variability and thus decrease the weight of the measured drug concentration sample in Bayesian forecasting, leading to shrinkage of the PK parameters towards the population mean, i.e., all in all a less accurate prediction of the individual PK.[48]

New algorithms for MIPD

To overcome some of the issues with model selection and associated fit-for-purpose model validation, new approaches are needed to streamline this process and enable widespread implementation of MIPD in clinical practice. Hughes and colleagues introduced a continuous learning approach to adapt a population model to a local environment, which re-estimates the population parameters based on local TDM data in several cycles as data is becoming available.[49] As a prerequisite, input data of adequate quality needs to be available for this learning approach. Using the example of vancomycin dosing in a pediatric ICU population, the authors demonstrate that such an approach can reduce the prediction error significantly by up to 13% compared with the original model. Uster and colleagues proposed an automated model averaging/selection approach.[50] This algorithm uses a number of candidate models, some of which may be mis-specified for a specific patient. The algorithm selects the best-fitting model (model selection) or a combination of models (model averaging) for an individual patient when TDM data become available in the course of therapy. When using this approach for heterogenous data sets for vancomycin in general ward and ICU populations,[47,51] the predictive performance was better after model averaging than for the best single model in previous external evaluations.[47,50,51]

Another challenge for the use of population models in MIPD is that the PK in patients might not be stable over the entire course of therapy, and the most recent measured drug concentration usually carries the most information for Bayesian forecasting.[47] If this variability is random and the study from which it is derived has monitored the PK across several dosing intervals, it can be quantified using an additional variability component, the so-called interoccasion variability.[52] Abrantes and colleagues have shown in a simulation study that interoccasion variability should be adequately implemented as simple inclusion and omission can lead to imprecise Bayesian forecasting.[53] In case the individual PK parameters follow a trend, the adaptive MAP approach[54] or model predictive control[55] have been proposed, whereby the population prior is adjusted towards the individual PK parameters each time new TDM data become available, improving the predictive performance of a vancomycin population model in ICU patients.[54] For nonparametric models, unstable patients can be handled using the "interacting multiple model" approach, in which different support points from the nonparametric distribution can be chosen when new TDM data become available.[56]

Optimized sampling strategies

To date, trough samples are most commonly used for TDM. For aminoglycosides (Q8H), a postinfusion concentration (30 minutes after the infusion, in many cases termed "C_{max}," but not C_{max} from a PK perspective) is commonly also sampled. Using peak and trough concentrations, the AUC can be derived using a log-linear regression approach, for example through the Sawchuk-Zaske method[57] or variants thereof, which intrinsically assume a one-compartment model and linear PK. These methods are sometimes also called "two-point" methods. More robust approaches include limited sampling strategies (LSSs), which use regression techniques and do not make intrinsic assumptions of compartmental models. LSSs are developed using regression techniques by correlating timed drug concentration samples with AUC values determined by rich sampling. For example, Kamp and colleagues developed an LSS for linezolid that could determine linezolid

AUC with a bias of 4.6% and a r^2 (coefficient of determination) of 0.97 from a trough and 1-hour sample.[58] Limitations of log-linear regression and LSSs include that the sampling scheme needs to be strictly followed and the prediction might be unreliable in case of altered PK, e.g., in critically ill patients.

For MIPD, the accuracy of determined primary or derived PK parameters is less sensitive to the sampling time in relation to the dose as compared with conventional approaches.[59] Bayesian estimation of the PK parameters can be performed with any timed plasma sample as long as the sampling time is accurately documented.[48] This makes MIPD attractive particularly for the clinical setting, as even for vancomycin, for which TDM is well established, 61.5% of trough samples are "wrongly" taken, requiring additional sampling, or causing delayed or wrong dose adjustment.[60] A study on tobramycin in cystic fibrosis patients demonstrated that AUC values determined using Bayesian forecasting can be more precise and less biased than the two-point method if both samples are used, or as precise when only one single sample is used.[61] To determine the AUC in MIPD, using samples early after drug administration rather than the trough sample seems advantageous for aminoglycosides and vancomycin.[59,62] However, more research is required to elucidate whether this is generalizable, as the choice of the population model also has an impact on which sampling times perform best.[62]

Lastly, the optimization of the sampling time can also be performed on an individual level by using optimal design techniques to calculate a minimum number of individually optimized sampling timepoints as implemented for vancomycin[63] or beta-lactam antibiotics.[64]

Mechanism-based models and their prospective role for MIPD

Mechanism-based PKPD models may be integrated in a decision support tool to guide the dosing for individual patients.

In contrast to the PK/PD indices, where summary measures of drug exposure are linked to a single timepoint evaluation of efficacy, the aim of mechanism-based PKPD models is to describe the full time courses of both the drug concentration (PK) and its effects on the bacteria (PD). Such models could be used to tailor the dose to the individual patient. Mechanism-based PK/PD models typically consist of three parts: (i) a bacterial model describing the rate of growth and natural killing of bacteria, (ii) a drug model describing the change in drug concentration over time, and (iii) equations describing the effects the antibiotics have on the growth and/or killing of the bacteria.[12] These models are generally developed based on data from *in vitro* time-kill curve experiments, with quantification of the change in bacterial count over time when exposed either to a constant (static) drug concentration or a dynamic drug concentration profile mimicking the PK profile of a patient population of interest.[12]

A benefit of using a mechanism-based modeling approach is that the dynamic nature of the data is reflected in the analysis. Avoiding the use of summary measures of drug exposure will improve the translational properties, especially in the case of large differences in PK characteristics, e.g., when results observed in small animals are utilized to guide dosing in humans.[65] Furthermore, when taking the time aspect into account, the link between the drug exposure and resistance development may be integrated in the analysis, and thus also in the dose optimization process.[66] Moreover, inclusion of combination data and their PD interactions in the mechanism-based PKPD models might be advantageous to optimize the dose of combination therapy regimens.[67,68] Another benefit of model-based analysis is that it allows for data from different sources to be jointly analyzed. Even though *in vitro* time-kill curve experiments are highly informative of the interaction between the antibiotic and the bacteria and often form the basis for the PKPD modeling, other factors, such as the hosts' immune defense, might be better studied *in vivo*. Within a modeling framework, both *in vitro* and *in vivo* data may be combined, allowing the translational properties to be evaluated and used to individualize the dose.[69]

Several studies have shown that mechanism-based models developed based on *in vitro* data are able to adequately replicate the PK/PD index results obtained using dose-fractionation studies in the neutropenic mouse model.[65] A direct comparison to clinical data is challenging, e.g., due to difficulties in exploring a wide range of dosing regimens and assessing efficacy in patients, and due to large heterogeneity in patient populations, infecting organisms, and infection sites. Thus, the clinical evidence confirming the *in vitro* and animal targets are still limited, and an important focus area for future research. Typically, PKPD models are developed for a specific antibiotic and bacterium combination. To maximize the use of a PKPD model at the bedside, early knowledge on the maximum rate of killing, the potency (half maximal effective concentration) and the fitness (growth rate) may be possible to define based on limited data and an available model for the bacterial species and antibiotic at hand.

ANTI-INFECTIVES FOR WHICH PRECISION DOSING IMPROVES OUTCOMES

Aminoglycosides

Aminoglycoside antibiotics to treat systemic infections comprise gentamicin, tobramycin, and amikacin. Aminoglycosides display a low volume of distribution (~ 0.3 L/kg), and the clearance is highly correlated with renal function. Hence, PK is often altered in critically ill patients.

The traditional surrogate PK marker to assure sufficient antibacterial efficacy of aminoglycosides is a C_{max}/MIC ratio exceeding 8–10, which was developed for Q8H or Q12H dosing intervals.[70] As critically ill patients can display altered fluid balance affecting the V_D of hydrophilic aminoglycosides, monitoring of C_{max} can be performed 30 minutes after the end of the intravenous infusion (with common durations 15–30 minutes). However, for once-daily dosing regimens, an AUC_{24h}/MIC of ≥ 110 mg·hour/L should be targeted, as the exposure achieved with the C_{max}/MIC target would be too low in this setting.[1]

Trough concentrations of aminoglycosides (< 1 mg/L for tobramycin and gentamicin, < 5 mg/L for amikacin) have been reported as surrogate markers to minimize ototoxicity and nephrotoxicity.[1] The time until the C_{min} target is reached is highly dependent on the renal function. C_{min} might be a superior target for toxicity to AUC: Aminoglycoside toxicity was not different for three-times-daily vs. once-daily dosing with similar trough concentrations, despite much higher peak concentrations in the once-daily

regimen.[71] Mechanistically, saturation of uptake transporters at higher plasma concentrations supports extended interval dosing,[18] and lower aminoglycoside concentrations were observed in renal tubular epithelial cells with extended interval dosing.[72] For ototoxicity, genetic factors might reduce the toxicity threshold.[73] Hence, pharmacogenomic testing might be of interest particularly when treatment courses can be planned and repeated such as in cystic fibrosis patients, but might be difficult to realize in an acute setting.

Conventional TDM of aminoglycosides can be supported by the use of dosing nomograms or log-linear regression, which allow straightforward adjustment of the dosing interval with timed drug concentration samples,[74] but have been criticized for leading to overexposure or underexposure.[75] The use of MIPD software for aminoglycoside dosing was found to be more precise regarding accurate determination of the AUC and less susceptible to the choice of the sampling timepoint as compared with log-linear regression.[59,75] For single sample AUC determination of tobramycin in cystic fibrosis patients using MIPD software, a sample at 70 minutes after start of the (30-minute) infusion was found to be most precise, although the bias of any other timed sample was also clinically acceptable and resulted in estimated AUC values within ± 15% of the true AUC. Instead, to use log-linear regression, two samples were required and incorrectly timed samples led to imprecision of up to ± 25%; only strict adherence to the sampling time of 100 and 520 minutes led to unbiased AUC estimates for the log-linear regression technique.

TDM-based dosing interventions for aminoglycosides have been evaluated in prospective and retrospective studies, which found that TDM can significantly reduce the duration of therapy and hospital stay as well as nephrotoxicity (**Table S1**).

Glycopeptides

Glycopeptide antibiotics are hydrophilic molecules displaying a volume of distribution of 0.8 L/kg (vancomycin) up to 1.4 L/kg (teicoplanin). The high PK variability and the narrow therapeutic index suggest TDM for glycopeptides, which is deemed especially useful in the case of PK alterations in special patient populations like critically ill, obese, or geriatric patients.[76] Also, patients with organ support and renal insufficiency require TDM to ascertain adequate target attainment.

For vancomycin, an AUC_{24h}/MIC target of 400–600 has been recommended with the goal of an effective yet non-nephrotoxic therapy.[77] Conventionally, trough concentrations are sampled as a proxy for AUC and trough ranges of 10–15 mg/L (intermittent therapy) for susceptible microorganisms and 15–20 mg/L for more difficult bacteria such as *Staphylococcus aureus* are targeted. Notably, the trough target does not consider the MIC of the pathogen. In contrast, the AUC_{24h} /MIC target may specifically allow for the use of lower dosages in some patients—especially given an infective organism with MIC < 1 mg/L—and consequently actual AUC values below 400 mg/L·hour. Vancomycin likely represents the antibiotic for which TDM is most commonly performed, and for which TDM and outcomes have been researched most extensively. A systematic review and meta-analysis concluded that vancomycin TDM significantly increases the rate of efficacy and decreases the rate of nephrotoxicity in patients.[78]

As the trough concentration depends on the dosing interval and might not fully reflect altered PK, it has been criticized as a suboptimal proxy for the AUC[38] (also illustrated in **Figure 1**), and international guidelines recommend performing TDM based on the AUC rather than the trough concentration.[77] To determine the AUC in a clinical setting, either a peak and trough sample or Bayesian forecasting using a single sample has been recommended.[77] A recent study found that considering both peak and trough levels showed better therapeutic cure rates compared with only trough levels, although this result requires confirmation in larger studies.[79] Neely and colleagues showed that AUC-based vs. trough-based TDM was superior with regard to reduction of nephrotoxicity (<1% vs. 8%), and shorter therapy time (4.7–5.4 vs. 8.2 days).[63] Nonetheless, more research is required to potentially further optimize the AUC target for vancomycin, as a recent systematic meta-analysis found that the sensitivity and specificity was 0.77 (95% confidence interval (CI), 0.67–0.84) and 0.62 (95% CI, 0.52–0.71), respectively, for the primary outcome variable mortality.[80] Clinical studies showing the value of TDM and precision dosing approaches for glycopeptides are summarized in **Table S1**.

For children, several publications showed that to achieve an AUC target of 400, trough levels lower than 10–15 mg/L, namely 7–10 mg/L seemed sufficient,[81,82] which also indicates that AUC monitoring using a pediatric population model seems beneficial. However, pediatric data for MIPD of vancomycin (and other antibiotics) are limited due to the common difficulty of obtaining extra blood samples. Furthermore, low mortality rates in the pediatric population necessitate different outcomes or biomarkers to be studied to assess the value of TDM or MIPD-guided dose individualization.

With regard to teicoplanin, literature is sparser. TDM has been recommended for critically ill patients.[1] For uncomplicated infections, C_{min} ≥ 10–20 mg/L has been suggested.[1] A retrospective study found that achieving a trough level of > 20 mg/L can improve clinical outcome and decrease adverse effects, and this threshold has also been recommended for severe staphylococcal infections.[1,83] In methicillin-resistant *Staphylococcus aureus* infections, AUC/MIC > 900 has been associated with bacteriological response.[84]

Beta-Lactams

Beta-lactam antibiotics are the cornerstones of anti-infective therapy and display very small distribution volumes (~0.2 L/kg) and are mainly excreted renally. Beta-lactam antibiotics are commonly dosed in 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, which generally display a wide therapeutic range and favorable safety profile. However, evidence is mounting that TDM of beta-lactams can be useful also to maximize efficacy, especially in critically ill patients[85] who are prone to inadequate exposure of beta-lactams. The importance of TDM in maximizing antimicrobial effectiveness and decreasing adverse events has been emphasized also for additional populations with altered PK, e.g., obese, elderly, pregnant, or burns patients, as well as patients with difficult-to-treat bone infections.[76,86]

Optimal exposure of beta-lactam antibiotics is commonly determined as the percentage of a period of time that free concentrations exceed the MIC (% $fT_{>MIC}$). It is recommended to measure unbound concentrations of beta-lactams, especially for highly bound beta-lactams (>30–50%).[87] For most gram-negative infections, dosing regimens are typically designed to cover at least 40% $fT_{>MIC}$ of the presumed MIC of the pathogen, yielding a bacteriostatic effect.[88] For severe infections, higher targets like $fT_{>MIC}$ = 100 up to $fT_{>4\times MIC}$ = 100 or even higher have been proposed, at which maximal killing has been observed and the emergence of resistant subpopulations is suppressed.[89] Using conventional TDM, the trough concentration is sampled, and if it exceeds the MIC (or, e.g., 4× MIC), target attainment is assumed. If the sample concentration is below the MIC, the % $fT_{>MIC}$ can be accurately determined using MIPD software.

First examples of evidence supporting beta-lactam TDM are presented in **Table S1** and are available particularly for critically ill patients. In a retrospective study on imipenem in 300 patients, a trend was observed between increased clinical failure and C_{min} < 2 mg/L.[90] In a small prospective study on piperacillin in hematological malignancies, no relationship was found between duration of fever, days to recovery from neutropenia, and achievement of PK/PD targets.[91] Regarding toxicity, cefepime plasma trough concentrations > 35 mg/L were related to neurotoxicity,[92,93] and it has even been suggested that for intermittent infusions trough concentrations > 20 mg/L should be avoided.[93] To assess the value of beta-lactam TDM and dose individualization regarding clinical outcome, randomized clinical trials are warranted and currently being conducted.[94]

As beta-lactams are considered "time-dependent" antibiotics, continuous therapy is increasingly used in place of intermittent therapy. In continuous therapy, TDM helps to ensure that concentrations are constantly above the MIC.[1]

Linezolid

Linezolid exhibits moderate lipophilicity, complete bioavailability, overall good tissue penetration, a volume of distribution approximating total body water (40–50 L), and low protein binding (31%). Elimination occurs via renal excretion (35%) and nonrenal, presumably nonenzymatic pathways, which have been associated with nonlinear pharmacokinetics and are difficult to predict, thus challenging linezolid dosing.[95] Linezolid represents a vital treatment option for gram-positive infections impervious to other antimicrobials. Linezolid is employed for approved indications including nosocomial and community-acquired pneumonia or skin/soft tissue infections,[95] but also to treat off-label infections like osteomyelitis, nocardiosis, or drug-resistant tuberculosis, often as long-term therapy (>28 days).[96]

The clinical efficacy of linezolid has been associated with AUC/MIC values of 85–164 for different severe *gram-positive* infections. $T_{>MIC}$ appeared linearly correlated with AUC/MIC (<120) and targets of $T_{>MIC}$ = 82–99% have been related to clinical outcome, whereby concentrations ideally exceed the MIC throughout the entire dosing interval.[97] For tuberculosis, drivers of efficacy (AUC/MIC,[98,99] trough concentrations[100]) have so far been established in *pre*clinical studies.

Linezolid TDM still heavily relies on C_{min} rather than PK/PD indices, mostly due to reasons of practicality. Various studies have shown a linear C_{min}-AUC correlation and adequate prediction of AUC using C_{min}.[101–103] Due to the use of a usually fixed Q12H dosing interval for linezolid, C_{min} might be an acceptable surrogate for the AUC in contrast to vancomycin for which several dosing intervals are commonly used interchangeably, which complicates the interpretation of the C_{min}-AUC relationship. Efficacy thresholds of C_{min} depend on the susceptibility of the target pathogen and have frequently been set to MIC_{90} values.[104] On the other side of the therapeutic window, excessive linezolid concentrations (C_{min} = 6.3–35.6 mg/L[104,105]) prompt toxicity, including myelosuppression (often thrombocytopenia), lactic acidosis, or neuropathy.[95] A lower threshold (C_{min} < 2 mg/L) has been suggested for long-term treatment of chronic tuberculosis.[106]

Staggering variability with a tendency towards overexposure and toxicity has been observed following standard dosing (600 mg Q12H intravenous or by mouth for labeled indications), particularly prompted by long-term treatment, age, and renal or hepatic dysfunction.[107–109] In contrast, patients most prone to underexposure and lack of efficacy often display obesity, critical illness (±augmented renal clearance, renal replacement therapy, or extracorporeal membrane oxygenation), burns, or cystic fibrosis.[96,107,110,111] Furthermore, drug–drug-interactions with P-glycoprotein modulators (e.g., rifampicin, clarithromycin, levothyroxine, and proton pump inhibitors), sympathomimetic agents, amiodarone, phenobarbital or amlodipine may trigger subtherapeutic or supratherapeutic concentrations.[7,96,107,112]

To prevent or reverse adverse events or lack of efficacy, experts endorse TDM, particularly in high-risk populations and prolonged treatment, and alternative dosing regimens involving a loading dose or continuous infusions.[1,7,113] Evidence for a benefit of linezolid TDM, e.g., improved therapeutic exposure or recovery from thrombocytopenia, has emerged foremost from retrospective analyses.[7,112] A recent encouraging prospective study showed thrombocytopenia in 10.5% vs. 75% of patients with no/transient (n = 57) vs. persistent (n = 4) overexposure of linezolid during TDM (**Table S1**).[114]

Limited intraindividual variability of linezolid and less invasive sampling techniques (e.g., dried blood spot or saliva sampling) support the feasibility of linezolid TDM.[31,113,115] A shift from empirical dose adjustment—assuming dose–exposure linearity—towards MIPD seems promising for linezolid, as it facilitates considering nonlinear PK and more complex targets like AUC/MIC.

MORE EVIDENCE FOR THE VALUE OF PRECISION DOSING NEEDED: CLINICAL TRIAL DESIGN IMPLICATIONS

To justify the implementation of TDM and MIPD in clinical practice, well-designed clinical trials are required to evaluate the improvement in clinical and pharmacoeconomic outcomes that TDM may provide. Preliminary information on PK/PD relationships and targets, drug exposure, efficacy, and toxicity aids the decision on appropriate end points for a clinical study.[116] End points for studies with TDM as an intervention can range from specific PK/PD index values, biomarker response like reduction

in procalcitonin or galactomannan after start of treatment, to all-cause mortality—although the latter can be challenging to show in TDM studies.[116]

Observational studies can be the first step to exploring pharmacokinetic variability, to obtaining hints towards the potential benefit of TDM and to calculating the sample size for a randomized controlled trial (RCT). These studies do not require as much funding and/or time investment as RCTs or intense PK sampling studies and are, as part of operational activities, often more feasible. Importantly, observational studies are meant to inform future trial design and not to provide evidence, as commonly a control group is not included.

A step forward from observational studies are quasi-experimental studies, which require less funding than RCTs and can be performed next to clinical care.[117] This type could be illustrated by a study which describes the effect of a TDM service on clinical care by comparing clinical outcome before and after the TDM implementation.[117,118] It is important to note that for quasi-experimental studies specific statistical considerations are required, for example regarding the number of data points before and after the intervention.[117,119]

To date, RCTs investigating the TDM of antimicrobials have not been widely available, and the existing studies are highly heterogenous (**Table S1**). The few available RCTs studying the effect of TDM are open-label, as blinding of TDM is a very complex and therefore expensive procedure. One must keep in mind that a substantial proportion of the patients may achieve a favorable outcome of treatment also without TDM, making it more difficult to detect significant differences in clinical response. TDM will benefit mainly those patients with either too-low or too-high exposure, for whom the initial dose cannot be well predicted based on covariates and dosages need to be adjusted to achieve concentrations within the therapeutic window. To show a benefit on mortality requires a very large sample size when the general, heterogenous population is targeted. With a more selective approach, i.e., selecting patients at risk for failure using standard doses, a smaller sample size would suffice. For a more detailed overview on trial design for TDM we refer to a recently published review.[116]

CONCLUSION AND PERSPECTIVES

TDM can serve as a suitable approach for dose adjustment in relevant patient populations such as the critically ill and should be implemented in clinical practice particularly for aminoglycosides, glycopeptides, beta-lactams, and linezolid. Likely, many more antibiotics might benefit from precision dosing approaches, but more research is required to justify their implementation in clinical practice. Wherever possible, MIPD approaches should be used, as they entail several advantages and have the potential to streamline the TDM process. In the future, it can be expected that PKPD models become more mechanistic and will include biomarkers for toxicity and treatment response, which might further advance the role of MIPD tools in clinical decision support. The challenge for implementation, beyond interpretation of the TDM data, lies at the moment in the availability and access to rapid bioanalytical techniques, but novel sampling techniques such as DBS, noninvasive sampling, or even real-time monitoring of drug concentrations through wearable sensors might help to overcome such limitations in the future. At present, a lot of information on the potential benefit of TDM is generated from retrospective and/or small clinical trials. Well-designed prospective clinical trials are required to determine the benefit of precision dosing and will be crucial to put the effort of TDM into a pharmacoeconomic perspective. Ideally, to better achieve this in the future, evaluation of the potential benefit and need for precision dosing approaches should be evaluated early during drug development.

SUPPORTING INFORMATION

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CONFLICT OF INTEREST

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