

Review Article

Therapeutic Drug Monitoring (TDM): A Necessity in Critical Care and Transplant Settings

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ABSTRACT

Therapeutic drug monitoring (TDM) personalizes dosage by quantifying plasma concentrations to enhance treatment effectiveness and reduce toxicity. In critically sick patients and transplant recipients, pathophysiological alterations, restricted therapeutic indices, and organ support measures frequently result in unexpected pharmacokinetics (PK). This study emphasizes TDM's significance in critical care and transplantation, concentrating on antimicrobials such as vancomycin, β -lactams, antifungals, and immunosuppressants like tacrolimus, cyclosporine, and mycophenolic acid, substantiated by PubMed-cited literature.

Key words: TDM, critical illness, transplantation, vancomycin, β -lactams, antifungals, immunosuppressants

Therapeutic drug monitoring (TDM) is the practice of adjusting a patient's medication dosage to maintain drug concentrations within a specified therapeutic range in the bloodstream [1]. TDM employs a comprehensive analysis of pharmaceuticals, pharmacokinetics, and pharmacodynamics to assess the safety and efficacy of a medication across many clinical contexts. For therapeutic drug monitoring (TDM) to be effective, the concentration of a medication must be assessed in several physiological fluids. A depiction of these concentrations in relation to significant clinical considerations is provided [2].

In the last ten years, the theory, practice, and clinical relevance of therapeutic drug monitoring (TDM) have significantly evolved due to the advent of widely accessible and technically proficient modelling, simulation, and dosing software tools [3].

Consequently, TDM, once a peripheral area of clinical chemistry, has evolved into a multidisciplinary domain of clinical medicine, enabling laboratory and pharmacometrics experts to provide extremely pertinent clinical information to support pharmacotherapy management. The emerging field is termed "model-informed precision dosing" and is poised to revolutionize medicine through enhancements in performance and usefulness facilitated by machine learning and artificial intelligence technologies. The ultimate objective of the revolution in model-informed precision dosage is to establish individualized, patient-centric therapies [4].

TDM-guided therapy is particularly beneficial for individuals exhibiting significant susceptibility and unique pharmacokinetic characteristics regarding the supplied medicines. Examples encompass cancer patients, seriously ill individuals, organ transplant recipients, and people who have undergone significant surgical procedures. Moreover, specific groups, like children and those with obesity, should be regarded as subjects for specialized dosage procedures. Individuals that possess abnormal biological characteristics, such as pharmacogenomic mutations or liver diseases, need personalized therapy strategies [5].

Critical illness alters absorption, distribution, metabolism, and excretion of drugs, making fixed dosing strategies inadequate [6]. Post-transplant, maintaining immunosuppressant levels is crucial to prevent rejection while avoiding toxicity. TDM enables dose individualization based on plasma concentrations, integrating PK/pharmacodynamic (PD) principles to optimize therapy [7].

Consequently, in both critical care and transplant medicine, the clinical significance of therapeutic drug monitoring (TDM) is highlighted by the administration of medications with a narrow therapeutic index, including aminoglycosides, vancomycin, tacrolimus, and cyclosporine [8]. Insufficient exposure in these patients may lead to therapeutic failure, the development of antimicrobial resistance, and graft rejection, while concentrations exceeding the sub-therapeutic threshold are linked to severe toxicities, including nephrotoxicity, hepatotoxicity, and neurotoxicity,

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culminating in end-stage organ failure [9]. The significant inter- and intra-patient pharmacokinetic heterogeneity in these groups is affected by variables including organ failure, sepsis, polypharmacy, drug-drug and drug-disease interactions, and genetic variants that influence drug metabolism. As a result, personalized concentration-guided treatment is becoming acknowledged as a fundamental aspect of precision medicine in many contexts [10].

By sustaining medication concentrations within specified therapeutic ranges, therapeutic drug monitoring (TDM) boosts clinical efficacy, mitigates adverse drug reactions, shortens hospital stays, and improves overall cost-effectiveness [11]. Therefore, incorporating TDM into standard clinical practice is essential for enhancing patient outcomes in critically sick and transplant groups.

I. TDM in Critical Care

In the intensive care unit (ICU), where patients frequently undergo significant physiological alterations, therapeutic drug monitoring (TDM) plays a crucial role in directing pharmacotherapy. Critical illness is linked to hemodynamic instability, hypoalbuminemia, disrupted fluid balance, increased renal clearance, and organ failure, all of which affect pharmacokinetics (PK) and pharmacodynamics (PD) [12]. These alterations render traditional dosage techniques insufficient, necessitating individualized dosing informed by therapeutic drug monitoring as a crucial element of critical care treatment.

The ICU population is particularly susceptible owing to the severity of illnesses, the frequent administration of life-sustaining treatments, and the prevalence of polypharmacy [13]. Extracorporeal techniques, including continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO), significantly modify medication distribution and clearance, resulting in sub-therapeutic exposure or drug toxicity when traditional dosing protocols are utilized [14].

TDM facilitates precise dosage by guaranteeing goal attainment, particularly for medications with narrow therapeutic indices or those necessitating specific pharmacokinetic/pharmacodynamic thresholds for effectiveness [15]. This is especially pertinent for antimicrobials, since under-dosing can lead to therapeutic failure and antimicrobial resistance, whilst overdoing heightens toxicity concerns [16].

a. Antimicrobial TDM

β -lactams are the most extensively researched antimicrobials in critical care environments. These time-dependent medicines exhibit significant interpatient variability in critically sick patients; therapeutic drug monitoring (TDM) paired with longer or continuous infusions has demonstrated enhancement in pharmacokinetic/pharmacodynamic (PK/PD) goal achievement and perhaps improved clinical outcomes

[17]. Similarly, vancomycin, aminoglycosides, and colistin necessitate vigilant monitoring owing to their limited therapeutic ranges and possible nephrotoxicity [18]. Antifungals like voriconazole and posaconazole benefit from therapeutic drug monitoring due to their variable bioavailability and considerable inter-individual variability [19].

Evidence increasingly advocates for the widespread application of antimicrobial therapeutic drug monitoring (TDM) in intensive care unit (ICU) treatment, bolstered by recent consensus recommendations from the European Society of Intensive Care Medicine (ESICM) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), which offer practical frameworks for implementation [20].

b. Non-antimicrobial applications

In addition to managing infectious diseases, therapeutic drug monitoring (TDM) plays a vital role in optimizing treatment with anticonvulsants, immunosuppressants, and cardiovascular medications in intensive care unit (ICU) patients. Agents like phenytoin and valproic acid demonstrate modified protein binding in hypo-albuminemic conditions, requiring the assessment of free drug concentrations to inform dosage [21]. Similarly, immunosuppressants like tacrolimus and cyclosporine necessitate monitoring to equilibrate rejection risk with toxicity, especially in post-transplant patients in the ICU. Digoxin, a cardiac glycoside characterized by a narrow therapeutic index, necessitates meticulous monitoring in critically sick patients with variable renal function. These instances demonstrate the extensive applicability of TDM beyond antimicrobials, underscoring its significance as a fundamental component of personalized medication in critical care [22].

II. TDM in Transplant settings

TDM is crucial in managing transplant patients, since it is vital to maintain a delicate equilibrium between sufficient immunosuppression and the prevention of drug-related toxicity. Post-transplant patients need prolonged use of immunosuppressive medications, including calcineurin inhibitors (cyclosporine, tacrolimus), mTOR inhibitors (sirolimus, everolimus), mycophenolate mofetil, and corticosteroids [23]. Drugs such as tacrolimus and cyclosporine exhibit a narrow therapeutic index, considerable inter-individual pharmacokinetic variability, and a substantial risk for drug-drug and drug-food interactions. TDM is essential for personalizing treatment, reducing the likelihood of graft rejection, and preventing side effects such as nephrotoxicity, neurotoxicity, and infections [24].

The pharmacokinetics of immunosuppressants in transplant recipients is affected by various patient-specific and procedural factors, including age, weight, genetic polymorphisms (particularly CYP3A5 variants impacting

tacrolimus metabolism), organ function, concomitant medications, and the type of transplanted organ. Additionally, the post-operative phase frequently exhibits erratic absorption and metabolism resulting from hemodynamic instability, polypharmacy, and fluctuating gastrointestinal motility. Thus, conventional dosage protocols may not consistently forecast drug exposure, rendering personalized TDM-guided modifications crucial for best results [25].

In clinical practice, trough concentrations (C₀) are the predominant monitoring metric for calcineurin inhibitors and mTOR inhibitors in clinical practice, owing to their simplicity and robust connection with clinical success. Nevertheless, several studies indicate that monitoring the area under the concentration-time curve (AUC) may offer a more precise assessment of drug exposure, especially for mycophenolate mofetil, as trough levels may not reliably forecast therapeutic effectiveness. Advancements in Bayesian forecasting and population pharmacokinetic models have facilitated limited sampling tactics for more reliable AUC estimation, therefore alleviating patient burden and enhancing accuracy [26].

The application of TDM in transplantation transcends effectiveness and safety, incorporating long-term graft survival. Evidence indicates that insufficient immunosuppressant exposure is a primary factor in acute rejection, but chronic overexposure correlates with growing nephrotoxicity and metabolic problems. Incorporating TDM into standard post-transplant treatment enables doctors to proactively manage inter-individual variability and customize regimens according to patients' changing clinical conditions. Moreover, the integration of pharmacogenomic testing with therapeutic drug monitoring (TDM) presents an opportunity to enhance dosing regimens, advancing the concept of precision medicine in transplantation [27].

Overall, TDM in the transplant context is an emerging yet essential instrument. Current investigations into innovative biomarkers, non-invasive monitoring techniques, and model-informed precision dosage aim to improve its efficacy, guaranteeing that transplant recipients have the most effective and safest immunosuppressive protocols for sustained graft function.

Table 1- List of drugs requiring TDM in critical care and Transplant settings

Drug / Class / Context	TDM Target / Metric	When to Sample	Clinical Rationale & ICU/Transplant Notes	Key References
Vancomycin	AUC/MIC 400–600 (or trough 15–20 mg/L)	Trough before 4th dose or steady-state	AKI risk ↑ with high troughs; AUC-based dosing preferred over trough-only methods	[4], [18], [29]
Aminoglycosides (Amikacin, Gentamicin)	Peak/MIC ≥8–10; Trough <1–2 mg/L	Peak: 30 min post-infusion; Trough: before dose	Nephrotoxicity, ototoxicity risk; altered PK in sepsis, ECMO, CRRT	[6], [30]
β-lactams (Pip-Tazo, Meropenem, etc.)	Time > MIC: 100% for critically ill	Random / steady-state sampling	ARC, CRRT, ECMO → altered PK; continuous/prolonged infusion often needed	[16], [17], [31–33]
Linezolid	Trough 2–8 mg/L	Pre-dose trough	Toxicity risk if >10 mg/L; thrombocytopenia, lactic acidosis concerns	[34]
Azoles (Voriconazole, Posaconazole)	Voriconazole: 2–5.5 mg/L; Posaconazole: >1 mg/L	Trough after ≥5 days of therapy	CYP2C19 polymorphism affects voriconazole levels; toxicity >5.5 mg/L (neurotoxicity)	[19], [35], [36]
Flucytosine	Peak 30–80 µg/mL; Trough <25–50 µg/mL	Peak 2h post-dose; trough before next dose	Myelotoxicity risk if >100 µg/mL; dose adjustment in renal failure	[19], [37]
Tacrolimus (Calcineurin inhibitor)	Trough 5–15 ng/mL (organ/time-specific)	12-h trough (C ₀)	Narrow TI; CYP3A5 polymorphism affects metabolism; toxicity: nephro/neurotoxicity, infections	[22–27], [38]
Cyclosporine (Calcineurin inhibitor)	Trough 100–400 ng/mL; some centers use C2 sampling	Trough (C ₀) or 2-h post-dose (C2)	AUC-based dosing may improve outcomes; multiple interactions with drugs/food	[39], [43]
Sirolimus (mTOR inhibitor)	Trough 5–15 ng/mL	24-h trough	Long half-life; cytopenias, hyperlipidemia; erratic absorption post-transplant	[40]
Everolimus (mTOR inhibitor)	Trough 3–8 ng/mL	24-h trough	Renal-sparing protocols; post-op PK variability	[41]
Mycophenolate mofetil (MMF)	AUC _{0–12} >30–60 mg·h/L	Bayesian AUC or limited sampling	Trough not reliable for efficacy; AUC-based monitoring increasingly used	[42]
Corticosteroids	No standard TDM	Clinical + biomarker endpoints only	PK variability post-op; risk of metabolic & infectious complications	[7], [23–27]
Precision Medicine & TDM Advances	Bayesian modeling, pharmacogenomics (CYP3A5)	Limited sampling + model-informed dosing	Enables individualized regimens, reduced toxicity, improved graft survival	[4], [10], [26–27]

Challenges and Future Direction

Notwithstanding its acknowledged advantages, therapeutic drug monitoring in the intensive care unit encounters several obstacles. The restricted availability of tests for novel pharmaceuticals, inconsistencies in laboratory turnaround times, and the absence of standardized dosage algorithms impede its regular implementation. Furthermore, the interpretation of therapeutic drug monitoring necessitates the amalgamation of pharmacokinetic and pharmacodynamic principles with the evolving clinical situation, rather than dependence on fixed reference ranges. Improvements in bedside tests, population pharmacokinetic modelling, and Bayesian dosing software are expected to increase the accessibility and clinical applicability of therapeutic drug monitoring in real time. Subsequent research must prioritize the validation of TDM-guided methods through extensive randomized controlled trials to enhance the evidence base and optimize dose recommendations for various ICU populations.

CONCLUSION

In conclusion, TDM in critical care serves as an essential instrument for precise dosage in patients exhibiting variable pharmacokinetics and a heightened risk of therapeutic failure or toxicity. Its use in antimicrobials, anticonvulsants, immunosuppressants and cardiovascular medications underscores its extensive significance within the ICU domain. Despite ongoing logistical and interpretative obstacles, the incorporation of TDM into clinical workflows—bolstered by technology advancements and global consensus guidelines—provides a pathway to safer, more effective, and personalized medication administration for critically sick patients.

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