Therapeutic Drug Monitoring: Fundamentals, And Optimization.

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Abstract

Therapeutic drug monitoring (TDM) is a teamwork clinical pharmacokinetic services aimed to optimize pharmacotherapy of certain drugs such as those with a narrow therapeutic range, complicated pharmacokinetics. It involves the determination of drug level in blood samples taken at the appropriate time. Interpretation of results requires integration of pharmacokinetics, the pharmacodynamics of the drug and the patient's clinical profile. To be cost-effective the service should be optimized. This review was written by experts from three different developing countries to highlight the fundamentals of the service and provide suggestions for its optimization. These cover the rationale of requesting drug level, design of request form, optimal sampling, and analytical tools. guidelines for appropriate interpretation of drug levels; completeness of the roles of the qualified medical team; continuing education and skills development; involve the patients in improving the service, conducting relevant research; use PK software and integration of TDM with pharmacogenomics.

Keywords: Therapeutic drug monitoring, Clinical pharmacokinetics, optimal dosing, drugs with the narrow therapeutic range

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1. OVERVIEW

Therapeutic drug monitoring (TDM) is a clinical service aimed to optimize pharmacotherapy of drugs with a narrow therapeutic window or complicated pharmacokinetics   It supports the design of dosing regimens on an individual basis. It comprises the following1- Measurement of serum or blood drugs level (SDC) in samples taken at an appropriate time after drug administration   2- Knowledge of the pharmacological profile of the administered drugs 3- Reviewing relevant patient's profile (demographic data, clinical status s certain lab and other investigations) 4- Interpretation of SDC given all of the above to enable the optimal dosage to be tailored according to the need of the individual patient (Marshall et al., 2014)   All these components should be considered as a network and deficit in any part will lead to halting the entire system.

TDM when used properly it ensures efficacy and minimizes adverse drug events   (Marshall et al., 2014). The benefits of therapeutic drug monitoring include significant cost saving because hospitalization will be shortened for the patient and avoidance of expensive diagnosis and treatment of an adverse drug event(Dasgupta, 2012). TDM data assists clinicians in making the best clinical decisions. For example, it allows for a more personalized approach to epilepsy treatment, with dosage changes dependent on drug doses assessed to improve clinical outcomes. (Patsalos et al., 2018). An organ transplant is often accompanied by lifelong immunosuppressive treatment to ensure the organ's longevity in the recipient. Immunosuppressive medications must be used to save the graft and, ultimately, the patient's life. TDM is highly recommended for these medications to tailor the appropriate dosage for each patient and prevent rejection. (Zhang and Zhang, 2018b). TDM   has been utilized for optimizing the use t of aminoglycosides(Boyer et al., 2013) and vancomycin. (Rybak et al., 2009). Moreover, more patients in critical care with higher levels of illness severity and immunosuppression, obesity, elderly and neonates, the risk of suboptimal antibiotic exposure is rising. As a result, TDM's value continues to rise.   especially   for   beta-lactams

antibiotic(Mabilat et al., 2020, Wicha et al., 2021). TDM service is expanding to include *the* newer antiepileptic drugs(Jacob and Nair, 2016), systemic antifungal agents(John et al., 2019), atypical antipsychotics (Urban and Cubała, 2017), Kinase Inhibitors in Oncology(Verheijen et al., 2017), infliximab in spondyloarthritis (Fobelo Lozano et al., 2019) Ustekinumabl, Vedolizumab and other biologics in Inflammatory Bowel Disease (Franca et al., 2019, Hoseyni et al., 2018, Papamichael et al., 2019, Restellini et al., 2018, Sparrow et al., 2020), immuno-modulating drugs in systemic lupus erythematosus (Mok, 2017),. Biopharmaceuticals in Psoriasis Patients(Hermans et al., 2017) and monoclonal antibodies(Imamura, 2019). Recently TDM was used to monitor antiviral drugs serum level in COVID-19, for example, remdesiviar (Pasupuleti et al., 2021), TDM was also suggested to improve the clinical outcome of Hyroxycloroquine in COVID-19 patients admitted to ICU. (Tecen-Yucel et al., 2021)

2. Optimization of TDM service:

Now TDM became slandered in clinical practice. However, like other clinical services it showed be optimized to ensure the best outcomes. The following represents the road map to achieving this desired goal.

. 2.1 Clear indication for determination of serum drug concentration (SDC)

Rational indication of SDC determination include suspected toxicity, assessment of patient compliance., etc.; common indications are summarized in table 1& commonly monitored drugs are shown in table 2. (Dasgupta, 2012, Marshall et al., 2014, AHMED S. ALI et al., 2016)

Table 1; Common indications for drug monitoring	
Examples	Indication
Lithium, phenytoin, digoxin	Drugs with a narrow therapeutic index
phenytoin	Drugs with complex pharmacokinetics
immunosuppressant drugs. & antibiotics	Drugs, their efficacy is difficult to clinically predicate.
Digoxin, aminoglycosides	Drugs are prescribed to patients who have impaired renal function
drugs are taken chronically for prophylaxis	To identify non-compliant patients
Lithium, digoxin, paracetamol	In case of suspected toxicity
Co-administering of an enzyme inducer and Cyclosporine A	To adjust the drug regimen due to drug-drug interaction
resistance to vancomycin or aminoglycosides	In case of suspected therapeutic failure

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Table 2 *List of candidate drugs for drug monitoring*	
I-COMMONLY MONITORED DRUGS	
-Cardio active drugs	Digoxin; (amiodarone,)
Antibiotics:	gentamycin, amikacin; tobramycin; vancomycin
Antiepileptic drugs:	Phenytoin, Phenobarbitone, Valproic Acid, Carbamazepine (Ethosuximide), Clonazepam.
Bronchodilators	Theophylline
Immunosuppressives	Cyclosporine; FK 506
Cancer chemotherapy	Methotrexate
Analgesic	Acetaminophen; Aspirin
antipsychotic: Antidepressants &	Lithium & Tricyclic Antidepressants
II- EXPANDING LIST OF OTHER DRUGS **(Fobelo Lozano et al., 2019, Franca et al., 2019, Hermans et al., 2017, Hoseyni et al., 2018, Imamura, 2019, Jacob and Nair, 2016, John et al., 2019, Mok, 2017, Papamichael et al., 2019, Restellini et al., 2018, Sparrow et al., 2020, Urban and Cubała, 2017, Verheijen et al., 2017)**	
Anti-TB drugs	Isoniazid, Rifampicin
Biologics for inflammatory bowel disease	Infliximab, Adalimumab
Immuno-modulating drugs in systemic lupus erythematosus;	Hydroxychloroquine (HCQ), Mycophenolate Mofetil (MMF)
Systemic antifungal agents	Flucytosine, Itraconazole, Voriconazole, and Posaconazole
Atypical antipsychotics	Iloperidone, Asenapine and Lurasidone
Newer antiepileptic	Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate, Brivaracetam, Zonisamide, Pregabalin
Antiretroviral Drugs in the Management of HIV	**Raltegravir & Maraviroc**

2.2 Design of an appropriate request form

It is essential to design a request form specific for TDM to accurately interpret results, the request form must contain all relevant information. Table 2. (AHMED S. ALI et al., 2016)

Table 2: Data that must be available in the request form for drug analysis
1. Date, the patient hospital no, sample identification code, unit etc.
2. Indications for testing (e.g. toxicity, non-compliance)
3. Time sample collected.
4. Time dose is given. (last dose)
5. Dosage regimen (dose, duration, dosage form)
6. Patient demographics (age/sex) & weight.
7. Other medications
8. Other relevant co-morbidities (e.g., renal/liver disease)
9. Any additional note: e.g., pregnancy.

2.3. Optimal sampling

2.3.1 Sampling time

In most cases, blood samples should not be collected until concentrations have reached a steady state. For most drugs, this is achieved after 4–5 half-lives. An essential requirement for some drugs is to take the sample at a specified time after the last dose as shown below. (AHMED S. ALI et al., 2016, Wong et al., 2014, Burton, 2006, Zhao and Jacqz-Aigrain, 2011).

1. Peak, trough or at specified time post-dose: Aminoglycosides (Fig. 1)

2. 2 h post-dose: Cyclosporine A (good correlation with AUC and hence efficacy. (Fig. 2).

3. At least 6 h post-dose: Digoxin (avoid sampling during distribution phase)

4. Specified timed post-dose: Acetaminophen (suspected toxicity)

5. Specified timed post-dose: Methotrexate. (24, 48, 72 h)

2.3.2. The Sample types

Most assays for drug levels allow serum or plasma. TDM guidelines usually recommend avoiding serum-separator tubes because these may lower drug concentrations by adsorbing drug into the matrix. For cyclosporine A some methods request collecting whole blood. Some analytical methods are affected by the temperature of the sample (standardize all variables (AHMED S. ALI et al., 2016). Several studies demonstrated the use of dry blood spot for analysis of immunosuppressant drugs; anti-epileptic drugs; anti TB, Anticancer Drugs and antipsychotic drugs. (Capiau et al., 2019, Iacuzzi et al., 2021, Klak et al., 2019, Martial et al., 2017, Min et al., 2019, Vu et al., 2011).

Volumetric absorptive microsampling (VAMS) was proposed as a sampling alternative for TDM and clinical trials during the COVID-19 pandemic. VAMS involve a simple sampling procedure, which can be done at home, minimally invasive sample volume, and storage and distribution at ambient temperature. VAMS can also absorb a fixed volume, enhance the precision and of analytical methods and reduce the effect of hematocrit (Harahap et al., 2020)
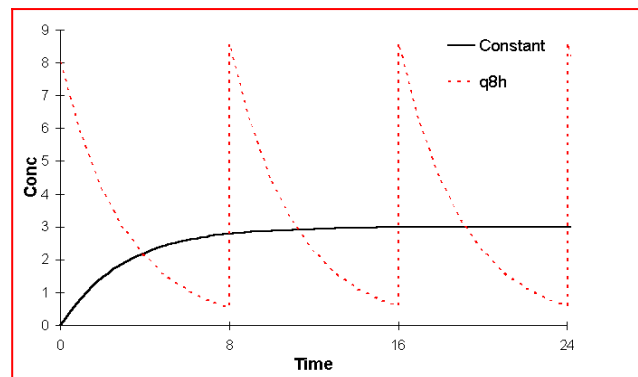
Fig 1: peak & trough le
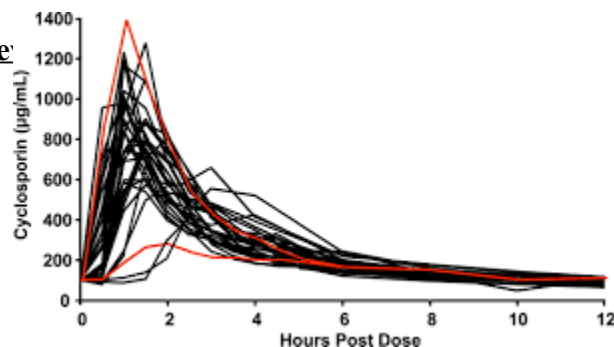
Fig2: Variable bioavailability of cyclosporine A after oral administration

2.4. Optimal analytical tools.

2.4.1 Analytical methods

The methods of analysis of drugs should be rapid so that TDM services are appropriate for emergencies. The analytical method should be sensitive, precise. accurate, and specific. All these parameters should be documented and assessed regularly. Using the least possible sample size e.g. 30 ul serum or less is an important requirement to make drug analysis suitable for samples from neonates. For these reasons immunoassay such as fluorescence polarization immunoassay (FPIA), enzyme immunoassay (EMIT), and enzyme-linked immunosorbent assay (ELISA) are the most widely used procedures. The lab personnel should be aware that cross-reactivity with the drug's metabolites, endogenous compounds or drugs with similar structures, may occur and results in false results. (Kang and Lee, 2009). HPLC-MS/MS is considered superior to immunoassays for some drugs such as immunosuppressants and techniques represent the major analytical tool to measure drugs in dry blood spots, (Dasgupta and Datta, 2008, Cui et al., 2020, Min et al., 2019, Seger and Salzmann, 2020, Tuzimski and Petruczynik, 2020, van Nuland et al., 2020, Vogeser and Seger, 2008, Zhang and Zhang, 2018a, Zheng and Wang, 2019).

2.4.2 Quality control

The laboratory must ensure that appropriate quality control is undertaken. The lab technologist should be aware of analytical interference and artefacts. For some drugs e.g. cyclosporine A the lab must report the method used for analysis (The reference range depends on the method used) (Patsalos et al., 2008, Xu and Madden, 2011).

2.5. *Optimal Cost*

In general, drug analysis is expensive relative to other routine biochemical analysis. Efforts should be done to provide a good service at a reasonable cost. The following key points may be considered: To run samples on batches whenever possible., to select analytical tools that suitable to the workload; rational use the service. (AHMED S. ALI et al., 2016). There are numbers of criteria to be considered to make TDM cost-effective, including providing clinical information to allow the interpretation of results; appropriate analytic techniques are available to determine the drug and its metabolite among others detailed in these references. (Nwobodo, 2014, Touw et al., 2005, Vithanachchi et al., 2021)

2.6. Appropriate interpretation of results

2.6.1 Variables affecting SDC.

... The following is a brief review of the most important key variables (AHMED S. ALI et al., 2016, Aarnoutse et al., 2003, Winter et al., 2004, Ghiculescu, 2008)

ACTIVE METABOLITE:

Some monitored drugs are biotransformed into pharmacologically active compounds. When evaluating the therapeutic effect of such drugs, the relative contributions of all active substances present in the serum must be integrated e.g., carbamazepine is biotransformed to the active metabolite carbamazepine– 10,11 epoxides. Other examples include active metabolites of *psychotropic drugs and methotrexate*.(Hendset et al., 2006, Jacob and Nair, 2016, Karami et al., 2019)

DISEASE STATES:

Some acute or chronic disease are known to alter drug clearance patterns., e.g., severe liver disease, renal impairment, and cardiac failure. Patients with severe renal impairment have lower albumin level and hence high free level of strongly bound drugs.(Ghiculescu, 2008)

AGE: Variability in PK parameters and clinical response to drugs occurs at extremes of age. e.g., neonates during the 1st weeks of the show a higher volume of distribution of aminoglycoside and long half-life compared to children. They also showed an altered

metabolic pathway of theophylline; neonates subjected to birth asphyxia showed a marked reduction in phenobarbital clearance. Renal function is known to be reduced at an advanced age.(Ghiculescu, 2008)

PREGNANCY An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. However, postpartum restoration of the original dosage will probably be indicated. Pregnant women have a higher volume of distribution of hydrophilic drugs. (Feghali et al., 2015)

Miscellaneous variables: Smoking, stress, and drug formulation (generic versus trade name); drug-drug or drug-food interaction; environmental factors; the circadian effect can alter pharmacokinetic properties of the drug being measures. (Mayor, 2017)

2.6.2. Practical Guide

Serum drug level without interpretation is usually useless and could be misleading. Drug concentration determinations must always be interpreted in the context of the clinical data.

A. Reviewing relevant clinical & lab investigation & diagnosis e.g. renal, liver function; certain biochemical values, examples are shown in table 3 &4. (AHMED S. ALI et al., 2016, Ghiculescu, 2008)

B. The reference range must be used as a guide rather than absolute values (AHMED S. ALI et al., 2016). The target peak of gentamicin depends on the severity, site of infection, immune status. (Krause et al., 2016). Sometimes the reference range of the drug depends on its indication (e.g carbamazepine indicated for epilepsy and off label for neuropathic pain)(Ghiculescu, 2008). Drug concentrations within the usual therapeutic range do not rule out drug toxicity in all patients. Example: digoxin, where other physiologic variables (egg, hypokalemia) affect drug toxicity.(Grześk et al., 2018) We should also recognize that many adverse effects are dose-independent e.g., gum hyperplasia after the use of phenytoin, aplastic anemia produced by carbamazepine. (Gajjar et al., 2016)

Many factors alter the effect of a drug concentration at the site of action,(DiPiro, 2010) e.g., level serum concentration of phenytoin that is within therapeutic range may be associated with dose-related adverse effects in patients with very low albumin level. (Wu and Lim,

2013). We should consider the synergism additive effect of drugs for example consider lower carbamazepine range when used with some other antiepileptic(Panday et al., 2017). In certain life-threatening condition high than normal level may be allowed or even recommended example Phenobarbital SDC of 200 umol/L (refrence 40-170). maybe acceptable in severe seizures in neonates. (Byun et al., 2015)

Table 3 Example of Important investigations & clinical observations	
Comment	Investigation
Signs of adverse effects e.g., antiepileptic drugs phenytoin	skin, hair, gum, eye
To ensure proper selection of the antibiotic; design an optimal regimen	Culture M.o, MIC
Markers for the efficacy of bronchodilators; theophylline	Forced expiratory volume in one second (FEV1); -Peak expiratory flow rate, (PEFR), Arterial blood gas (ABG)
Digoxin toxicity	ECG abnormality, nausea, vomiting, headache

Table 4: examples of important biochemical & hematological parameters		
Comment	drug	Biochemical/hematological parameter
Toxicity or reduced elimination	Gentamicin. Vancomycin	Elevated: S Cr
Marker for Liver toxicity	Valproic acid &Acetaminophen	AST
Enhance cardiac toxicity of digoxin	Digoxin	Low K
Marker for aplastic anemia	Carbamazepine	CBC: Abnormal progressive low RBC?
Altered response in case of hypo or hyperthyroidism	Digoxin	T3 & T4

C. Recognize abnormal results.

Abnormal or confusing results are not uncommon in TDM clinical practice. For example, suddenly high gentamicin trough level in a patient with normal renal; Vancomycin peak level in a patient who receives a normal dose, very high digoxin level in a patient with normal renal function while previous digoxin levels are normal; Etc.(AHMED S. ALI et al., 2016)

The most common causes of unexpected serum concentrations are.

1. Sampling time error common for antibiotics

2. Wrong request, (peak/ trough) common for antibiotics e.g., gentamicin

3. Contaminated sample (abnormal high SDC) *

4- Other possible reasons; inappropriate dosage, change in the generic product; poor bioavailability, drug or food interactions, acute hepatic or renal dysfunction altered protein binding and genetic factors.

D. Knowledge of appropriate procedure for the management of overdose and toxicity

For example, estimation of the appropriate dose of Fab digoxin in case of severe digoxin toxicity. (Hassan and Goyal, 2020). Appropriate decision to administer N-acetyl cysteine in case of documented acetaminophen poisoning. (Agrawal and Khazaeni, 2020)

2.7.- Completeness of the roles of the qualified medical team.

An optimal TDM service requires an analyst with appropriate experience in drug analysis Clinical pharmacist with experience in interpretation of results Consultant with extensive experience in TDM is highly recommended to ensure overall good service through updating reference range, sampling guideline, audit of service and supervise relevant continuous education & research. Measurement of SDC without appropriate interpretation may be useless or misleading. An effective TDM process requires a collaborative, multidisciplinary approach with input from doctors, nurses, and clinical pharmacists. Physicians will determine the initial dose of the drug. Clinical Pharmacists assist by providing essential information about the drug and revise the initial regimen and provide a plan for SDC. A nurse or phlebotomist collects the specimen by venipuncture documenting the time of the draw, the nurses usually document essential information and clinical response. Clinical laboratory scientists, perform drug assays. Clinical pharmacists have a vital role to play in TDM they are the co-coordinator in the team and support interpretation of the results obtained. recommending an appropriate drug regimen considering dose, dosage interval and route, based on several patient-specific factors such as age, weight, and renal function (Almohammde et al., 2021). Pharmacists can also use their expertise to examine possible causes of unusual TDM results, which may arise from problems with

bioavailability, drug interactions, non-compliance or medication errors (Kang and Lee, 2009, Clarke, 2016).

2.8. - Continuing education and skills development.

Continuous education program regarding TDM relevant issues is important to make health staff aware of basic principles and ensure effective implementation of service in a clinical setting. (Khairi et al., 2020). Strategies for physician education regarding optimal use of TDM. include Traditional and non-traditional education approaches have been applied in general, most traditional educational approaches are effective at changing physician behaviors in the short term, but the problem has been that these approaches are labor-intensive, and their effect has waned with time.   Computer added learning was suggested as superior to traditional teaching (Hussain et al., 2020)

We suggest including basic principles of TDM in undergraduate courses for medical, nursing, medical technology students as an effective tool for optimization of TDM service in developing countries.(AHMED S. ALI et al., 2016)

2.9. Involve the patient in adherence to guidelines of dosing and monitoring of medications .

Patient education improves the adherence to medications (Allison, 2012, Mathes et al., 2017) : Patients should be educated on the importance of complying with their physician's orders for medications and should be told to report any complications or side effects they may experience. Regarding TDM Patients should also be told about the frequency of their drug monitoring tests, and why keeping their appointment is important. Patients' education can support the accuracy of sampling time for example sampling 2 h post-dose for peak cyclosporine A level.

2.10. Conducting relevant research & use PK software

Research in TDM improves the utilization of service in clinical practice. Relevant research covers several aspects including example optimization of TDM in a certain population or clinical situation e.g., preterm neonates, children, transplant patients. (Ali et al., 2012, Ali et al., 2018, Islam, 2008, Al-Nasser et al., 2016). Many PK programs are now available to support utilizing serum drug level to generate dosing regimen on an individual basis (Fuchs et al., 2013) (Drennan et al., 2018).

2.11 Integration of TDM and pharmacogenomics

To individualize dosing regimens, optimize drug effectiveness, and improve drug safety for certain drugs such as immunosuppressant drugs, certain population e.g., antidepressants in older people. TDM of parent drugs and metabolites, in combination with available pharmacogenetic tests, may provide the best clinical outcome. (Albers and Ozdemir, 2004, de Leon, 2020, Doki, 2018, Jaquenoud Sirot et al., 2006, Owusu Obeng et al., 2014, Plesničar and Plesničar, 2014, Stieffenhofer and Hiemke, 2010).

REFERENCES

AARNOUTSE, R. E., SCHAPIRO, J. M., BOUCHER, C. A., HEKSTER, Y. A. & BURGER, D. M. 2003. Therapeutic drug monitoring. *Drugs,* 63**,** 741-753.

AGRAWAL, S. & KHAZAENI, B. 2020. Acetaminophen toxicity. *Statpearls [internet]*.

AHMED S. ALI , HMED, M. S., RAHMAN, A. F. A. & SOLIMAN, M. I. 2016. *Therapeutic drug monitoring practical guide.*, Scientific publishing centre, KAU,.

AL-NASSER, M., ALI, A., SATTAR, M., ABDULFATTAH, E. & KHAN, L. 2016. Therapeutic drug monitoring of tacrolimus in Saudi Kidney transplant patients. *J Nephrol Ther,* 6**,** 2161-0959.1000264.

ALBERS, L. J. & OZDEMIR, V. 2004. Pharmacogenomic-guided rational therapeutic drug monitoring: conceptual framework and application platforms for atypical antipsychotics. *Curr Med Chem,* 11**,** 297-312.

ALI, A. S., AL-NASSER, M. S., SATTAR, M. A. A., ALKREATHY, H. M., AL-AMMA, M. N., ALSULAIMANI, R. A. & ABDULFATTAH, E. H. 2018. Major Adverse Effects Associated with Tacrolimus (Fk506) Based Regimen among Saudi Kidney Transplant Patients. *Journal of Pharmaceutical Research International***,** 1-8.

ALI, A. S., FAROUQ, M. F. & AL-FAIFY, K. A. 2012. Pharmacokinetic approach for optimizing gentamicin use in neonates during the first week of life. *Indian journal of pharmacology,* 44**,** 36.

ALLISON, K. 2012. Adherence through education: a call to clinicians to educate all patients on medication use. *Mental Health Clinician,* 2**,** 83-85.

ALMOHAMMDE, S., ALHODIAN, H., ALMOFAREH, S., ALSHEHRI, S., ALMASRI, D. M. & GHONEIM, R. H. 2021. A survey of therapeutic drug monitoring in a teaching hospital. *Saudi Journal of Biological Sciences,* 28**,** 744-747.

BOYER, A., GRUSON, D., BOUCHET, S., CLOUZEAU, B., HOANG-NAM, B., VARGAS, F., GILLES, H., MOLIMARD, M., ROGUES, A.-M. & MOORE, N. 2013. Aminoglycosides in septic shock. *Drug safety,* 36**,** 217-230.

BURTON, M. E. 2006. *Applied pharmacokinetics & pharmacodynamics: principles of therapeutic drug monitoring*, Lippincott Williams & Wilkins.

BYUN, J. I., CHU, K., SUNWOO, J. S., MOON, J., KIM, T. J., LIM, J. A., JUN, J. S., LEE, H. S., LEE, W. J. & LEE, D. Y. 2015. Mega‐dose phenobarbital therapy for super‐refractory status epilepticus. *Epileptic Disorders,* 17**,** 444-452.

CAPIAU, S., VEENHOF, H., KOSTER, R. A., BERGQVIST, Y., BOETTCHER, M., HALMINGH, O., KEEVIL, B. G., KOCH, B. C. P., LINDEN, R., PISTOS, C., STOLK, L. M., TOUW, D. J., STOVE, C. P. & ALFFENAAR, J. C. 2019. Official International Association for Therapeutic Drug Monitoring and Clinical Toxicology Guideline: Development and Validation of Dried Blood Spot-Based Methods for Therapeutic Drug Monitoring. *Ther Drug Monit,* 41**,** 409-430.

CLARKE, W. 2016. Overview of therapeutic drug monitoring. *Clinical Challenges in Therapeutic Drug Monitoring.* Elsevier.

CUI, J. J., WANG, L. Y., TAN, Z. R., ZHOU, H. H., ZHAN, X. & YIN, J. Y. 2020. MASS SPECTROMETRY-BASED PERSONALIZED DRUG THERAPY. *Mass Spectrom Rev,* 39**,** 523-552.

DASGUPTA, A. 2012. Chapter 1 - Introduction to Therapeutic Drug Monitoring: Frequently and Less Frequently Monitored Drugs. *In:* DASGUPTA, A. (ed.) *Therapeutic Drug Monitoring.* Boston: Academic Press.

DASGUPTA, A. & DATTA, P. 2008. Analytical techniques for measuring concentrations of therapeutic drugs in biological fluids. *Handbook of Drug Monitoring Methods.* Springer.

DE LEON, J. 2020. Personalizing dosing of risperidone, paliperidone and clozapine using therapeutic drug monitoring and pharmacogenetics. *Neuropharmacology,* 168**,** 107656.

DIPIRO, J. T. 2010. *Concepts in clinical pharmacokinetics*, ASHP.

DOKI, K. 2018. [Use of Pharmacogenetic Information for Therapeutic Drug Monitoring of an Antiarrhythmic Drug]. *Yakugaku Zasshi,* 138**,** 1145-1150.

DRENNAN, P., DOOGUE, M., VAN HAL, S. J. & CHIN, P. 2018. Bayesian therapeutic drug monitoring software: past, present and future. Future Science.

FEGHALI, M., VENKATARAMANAN, R. & CARITIS, S. Pharmacokinetics of drugs in pregnancy. Seminars in perinatology, 2015. Elsevier, 512-519.

FOBELO LOZANO, M. J., SERRANO GIMÉNEZ, R. & SÁNCHEZ FIDALGO, S. 2019. Therapeutic drug monitoring of infliximab in spondyloarthritis. A review of the literature. *Br J Clin Pharmacol,* 85**,** 2264-2279.

FRANCA, R., CURCI, D., LUCAFÒ, M., DECORTI, G. & STOCCO, G. 2019. Therapeutic drug monitoring to improve outcome of anti-TNF drugs in pediatric inflammatory bowel disease. *Expert Opin Drug Metab Toxicol,* 15**,** 527-539.

FUCHS, A., CSAJKA, C., THOMA, Y., BUCLIN, T. & WIDMER, N. 2013. Benchmarking therapeutic drug monitoring software: a review of available computer tools. *Clinical pharmacokinetics,* 52**,** 9-22.

GAJJAR, B. M., SHAH, A. M. & PATEL, P. M. 2016. The pattern of adverse drug events to antiepileptic drugs: A cross-sectional study at a tertiary care teaching hospital. *National Journal of Physiology, Pharmacy and Pharmacology,* 6**,** 616-621.

GHICULESCU, R. 2008. Therapeutic drug monitoring: which drugs, why, when and how to do it.

GRZEŚK, G., STOLAREK, W., KASPRZAK, M., KRZYŻANOWSKI, M., SZADUJKIS-SZADURSKA, K., WICIŃSKI, M. & GRZEŚK, E. 2018. Therapeutic drug monitoring of digoxin–20 years of experience. *Pharmacological Reports,* 70**,** 184-189.

HASSAN, S. A. & GOYAL, A. 2020. Digoxin Immune Fab. *StatPearls [Internet]*.

HENDSET, M., HASLEMO, T., RUDBERG, I., REFSUM, H. & MOLDEN, E. 2006. The complexity of active metabolites in therapeutic drug monitoring of psychotropic drugs. *Pharmacopsychiatry,* 39**,** 121-7.

HERMANS, C., HERRANZ, P., SEGAERT, S. & GILS, A. 2017. Current Practice of Therapeutic Drug Monitoring of Biopharmaceuticals in Psoriasis Patients. *Ther Drug Monit,* 39**,** 356-359.

HOSEYNI, H., XU, Y. & ZHOU, H. 2018. Therapeutic Drug Monitoring of Biologics for Inflammatory Bowel Disease: An Answer to Optimized Treatment? *J Clin Pharmacol,* 58**,** 864-876.

HUSSAIN, M., SAHUDIN, S. & YUSSOF, I. 2020. Exploring the Use of Computer-aided Learning Modules (CAL) to Enhance the Teaching and Learning of Pharmacokinetics to Pharmacy Students. *Journal of Young Pharmacists,* 12**,** 354.

IACUZZI, V., POSOCCO, B., ZANCHETTA, M., GAGNO, S., POETTO, A. S., GUARDASCIONE, M. & TOFFOLI, G. 2021. Dried Blood Spot Technique Applied in Therapeutic Drug Monitoring of Anticancer Drugs: a Review on Conversion Methods to Correlate Plasma and Dried Blood Spot Concentrations. *Pharm Res*.

IMAMURA, C. K. 2019. Therapeutic drug monitoring of monoclonal antibodies: Applicability based on their pharmacokinetic properties. *Drug Metab Pharmacokinet,* 34**,** 14-18.

ISLAM, S. I. 2008. Pharmacogenomics and therapeutic drug monitoring: The challenge in drug safety. *Int. J. Integr. Biol,* 4**,** 62-66.

JACOB, S. & NAIR, A. B. 2016. An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs. *Drugs R D,* 16**,** 303-316.

JAQUENOUD SIROT, E., VAN DER VELDEN, J. W., RENTSCH, K., EAP, C. B. & BAUMANN, P. 2006. Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. *Drug Saf,* 29**,** 735-68.

JOHN, J., LOO, A., MAZUR, S. & WALSH, T. J. 2019. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. *Expert Opin Drug Metab Toxicol,* 15**,** 881-895.

KANG, J.-S. & LEE, M.-H. 2009. Overview of therapeutic drug monitoring. *The Korean journal of internal medicine,* 24**,** 1.

KARAMI, F., RANJBAR, S., GHASEMI, Y. & NEGAHDARIPOUR, M. 2019. Analytical methodologies for determination of methotrexate and its metabolites in pharmaceutical, biological and environmental samples. *J Pharm Anal,* 9**,** 373-391.

KHAIRI, L. N. H. M., AHMAD, F. S., ANUAR, A. S. M., OMAR, N. A. W., MUHAMMAD, N. N., JAMAL, N. A. & ZAINUDDIN, M. 2020. IMPROVING THE APPROPRIATENESS OF THERAPEUTIC DRUG MONITORING SAMPLING IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU. *Q Bulletin,* 1**,** 28-35.

KLAK, A., PAUWELS, S. & VERMEERSCH, P. 2019. Preanalytical considerations in therapeutic drug monitoring of immunosuppressants with dried blood spots. *Diagnosis (Berl),* 6**,** 57-68.

KRAUSE, K. M., SERIO, A. W., KANE, T. R. & CONNOLLY, L. E. 2016. Aminoglycosides: an overview. *Cold Spring Harbor perspectives in medicine,* 6**,** a027029.

MABILAT, C., GROS, M. F., NICOLAU, D., MOUTON, J. W., TEXTORIS, J., ROBERTS, J. A., COTTA, M. O., VAN BELKUM, A. & CANIAUX, I. 2020. Diagnostic and medical needs for therapeutic drug monitoring of antibiotics. *European Journal of Clinical Microbiology & Infectious Diseases,* 39**,** 791-797.

MARSHALL, W. J., LAPSLEY, M., DAY, A. & AYLING, R. 2014. *Clinical Biochemistry E-Book: Metabolic and Clinical Aspects*, Elsevier Health Sciences.

MARTIAL, L. C., AARNOUTSE, R. E., MULDER, M., SCHELLEKENS, A., BRÜGGEMANN, R. J. M., BURGER, D. M., SCHENE, A. H. & BATALLA, A. 2017. Dried Blood Spot sampling in psychiatry: Perspectives for improving therapeutic drug monitoring. *Eur Neuropsychopharmacol,* 27**,** 205-216.

MATHES, T., GROßPIETSCH, K., NEUGEBAUER, E. A. & PIEPER, D. 2017. Interventions to increase adherence in patients taking immunosuppressive drugs after kidney transplantation: a systematic review of controlled trials. *Systematic reviews,* 6**,** 1-14.

MAYOR, S. 2017. Pharmacokinetics: optimising safe and effective prescribing. *Prescriber,* 28**,** 45-48.

MIN, K. L., RYU, J. Y. & CHANG, M. J. 2019. Development and clinical applications of the dried blood spot method for therapeutic drug monitoring of anti-epileptic drugs. *Basic Clin Pharmacol Toxicol,* 125**,** 215-236.

MOK, C. C. 2017. Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus. *Expert Rev Clin Immunol,* 13**,** 35-41.

NWOBODO, N. 2014. Therapeutic drug monitoring in a developing nation: a clinical guide. *JRSM Open,* 5**,** 2054270414531121.

OWUSU OBENG, A., EGELUND, E. F., ALSULTAN, A., PELOQUIN, C. A. & JOHNSON, J. A. 2014. CYP2C19 polymorphisms and therapeutic drug monitoring of voriconazole: are we ready for clinical implementation of pharmacogenomics? *Pharmacotherapy,* 34**,** 703-18.

PANDAY, D., PANDAY, K., BASNET, M., KAFLE, S., SHAH, B. & RAUNIAR, G. 2017. Therapeutic drug monitoring of carbamazepine. *Int J Neurorehabilitation Eng,* 4**,** 2376-0281.1000245.

PAPAMICHAEL, K., VOGELZANG, E. H., LAMBERT, J., WOLBINK, G. & CHEIFETZ, A. S. 2019. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. *Expert Rev Clin Immunol,* 15**,** 837-848.

PASUPULETI, R. R., TSAI, P.-C., PONNUSAMY, V. K. & PUGAZHENDHI, A. 2021. Rapid determination of remdesivir (SARS-CoV-2 drug) in human plasma for therapeutic drug monitoring in COVID-19-Patients. *Process Biochemistry,* 102**,** 150-156.

PATSALOS, P. N., BERRY, D. J., BOURGEOIS, B. F., CLOYD, J. C., GLAUSER, T. A., JOHANNESSEN, S. I., LEPPIK, I. E., TOMSON, T. & PERUCCA, E. 2008. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia,* 49**,** 1239-1276.

PATSALOS, P. N., SPENCER, E. P. & BERRY, D. J. 2018. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: a 2018 update. *Therapeutic drug monitoring,* 40**,** 526-548.

PLESNIČAR, B. K. & PLESNIČAR, A. 2014. Therapeutic drug monitoring and pharmacogenetics--is this a way towards creative psychopharmacotherapy? *Psychiatr Danub,* 26**,** 96-9.

RESTELLINI, S., KHANNA, R. & AFIF, W. 2018. Therapeutic Drug Monitoring With Ustekinumab and Vedolizumab in Inflammatory Bowel Disease. *Inflamm Bowel Dis,* 24**,** 2165-2172.

RYBAK, M. J., LOMAESTRO, B. M., ROTSCAHFER, J. C., MOELLERING JR, R. C., CRAIG, W. A., BILLETER, M., DALOVISIO, J. R. & LEVINE, D. P. 2009. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clinical infectious diseases,* 49**,** 325-327.

SEGER, C. & SALZMANN, L. 2020. After another decade: LC-MS/MS became routine in clinical diagnostics. *Clin Biochem,* 82**,** 2-11.

SPARROW, M. P., PAPAMICHAEL, K., WARD, M. G., RIVIERE, P., LAHARIE, D., PAUL, S. & ROBLIN, X. 2020. Therapeutic Drug Monitoring of Biologics During Induction to Prevent Primary Non-Response. *J Crohns Colitis,* 14**,** 542-556.

STIEFFENHOFER, V. & HIEMKE, C. 2010. [Pharmacogenetics, therapeutic drug monitoring and non compliance]. *Ther Umsch,* 67**,** 309-15.

TECEN-YUCEL, K., ARAS-ATIK, E. & BAYRAKTAR-EKINCIOGLU, A. 2021. Does therapeutic drug monitoring of hydroxychloroquine improve treatment outcome in intensive care unit patients with COVID-19? *International Journal of Clinical Practice,* 75**,** e13894.

TOUW, D. J., NEEF, C., THOMSON, A. H. & VINKS, A. A. 2005. Cost-effectiveness of therapeutic drug monitoring: a systematic review. *Ther Drug Monit,* 27**,** 10-7.

TUZIMSKI, T. & PETRUCZYNIK, A. 2020. Review of Chromatographic Methods Coupled with Modern Detection Techniques Applied in the Therapeutic Drugs Monitoring (TDM). *Molecules,* 25.

URBAN, A. E. & CUBAŁA, W. J. 2017. Therapeutic drug monitoring of atypical antipsychotics. *Psychiatr Pol,* 51**,** 1059-1077.

VAN NULAND, M., ROSING, H., SCHELLENS, J. H. M. & BEIJNEN, J. H. 2020. Bioanalytical LC-MS/MS validation of therapeutic drug monitoring assays in oncology. *Biomed Chromatogr,* 34**,** e4623.

VERHEIJEN, R. B., YU, H., SCHELLENS, J. H. M., BEIJNEN, J. H., STEEGHS, N. & HUITEMA, A. D. R. 2017. Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. *Clin Pharmacol Ther,* 102**,** 765-776.

VITHANACHCHI, D. T., MAUJEAN, A., DOWNES, M. J. & SCUFFHAM, P. 2021. A comprehensive review of economic evaluations of therapeutic drug monitoring interventions for cancer treatments. *Br J Clin Pharmacol,* 87**,** 271-283.

VOGESER, M. & SEGER, C. 2008. A decade of HPLC-MS/MS in the routine clinical laboratory--goals for further developments. *Clin Biochem,* 41**,** 649-62.

VU, D. H., ALFFENAAR, J. W., EDELBROEK, P. M., BROUWERS, J. R. & UGES, D. R. 2011. Dried blood spots: a new tool for tuberculosis treatment optimization. *Curr Pharm Des,* 17**,** 2931-9.

WICHA, S. G., MÄRTSON, A. G., NIELSEN, E. I., KOCH, B. C., FRIBERG, L. E., ALFFENAAR, J. W., MINICHMAYR, I. K. & INTERNATIONAL SOCIETY OF ANTI−INFECTIVE PHARMACOLOGY , T. P. P. S. G. O. T. E. S. O. C. M., INFECTIOUS DISEASES 2021. From Therapeutic Drug Monitoring to Model−Informed Precision Dosing for Antibiotics. *Clinical Pharmacology & Therapeutics,* 109**,** 928-941.

WINTER, M. E., KATCHER, B. S. & KODA-KIMBLE, M. A. 2004. *Basic clinical pharmacokinetics*, Lippincott Williams & Wilkins Philadelphia.

WONG, G., SIME, F. B., LIPMAN, J. & ROBERTS, J. A. 2014. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? *BMC Infectious Diseases,* 14**,** 288.

WU, M. F. & LIM, W. H. 2013. Phenytoin: A guide to therapeutic drug monitoring. *Proceedings of Singapore Healthcare,* 22**,** 198-202.

XU, Q. A. & MADDEN, T. L. 2011. *Analytical methods for therapeutic drug monitoring and toxicology*, Wiley Online Library.

ZHANG, Y. & ZHANG, R. 2018a. Recent advances in analytical methods for the therapeutic drug monitoring of immunosuppressive drugs. *Drug Test Anal,* 10**,** 81-94.

ZHANG, Y. & ZHANG, R. 2018b. Recent advances in analytical methods for the therapeutic drug monitoring of immunosuppressive drugs. *Drug testing and analysis,* 10**,** 81-94.

ZHAO, W. & JACQZ-AIGRAIN, E. 2011. Principles of therapeutic drug monitoring. *Pediatric Clinical Pharmacology.* Springer.

ZHENG, Y. Z. & WANG, S. 2019. Advances in antifungal drug measurement by liquid chromatography-mass spectrometry. *Clin Chim Acta,* 491**,** 132-145.