

MEMORANDUM

From: Secretary of SAGE IVD **To:** Secretary of the Expert Committee on Selection and Use of Essential Medicines **Date:** 3 March 2021

Our ref: **Attention:**

Your ref: FM/nm **Through:** Director, HPS

Originator: **Subject:** REQUEST FOR ADVICE FROM THE EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES ON PRIORITIZATION OF MEDICINES REQUIRING THERAPEUTIC DRUG MONITORING

After the development of the first WHO Essential In Vitro Diagnostics List (EDL) in 2018, the EDL Secretariat commissioned a report evaluating therapeutic drug monitoring (TDM) assays. The objective was to identify a priority list of medicines in the WHO Model List of Essential Medicines that require TDM, which would inform the requirements for in vitro diagnostics for TDM that should be considered for inclusion on the EDL by the Strategic Group of Experts on In Vitro Diagnostics (SAGE IVD).

Following critical review of the evidence about TDM for a proposed list of drugs (amikacin, carbamazepine, cyclosporin, digoxin, gentamicin, lithium, methotrexate, phenobarbital, phenytoin, valproic acid and vancomycin), the following prioritization of the value of monitoring was proposed in the report.

Priority	Medicines
High (most authors consider TDM useful even for non-critically ill patients)	Amikacin Gentamicin Lithium Phenytoin
Moderate (TDM considered useful in patients with co-treatments or concomitant clinical complications (e.g. impaired renal function))	Cyclosporin Methotrexate Vancomycin
Low (careful clinical assessment is enough for most cases, or there is evidence that there are no differences between patients with and without TDM)	Carbamazepine Digoxin Phenobarbital Sodium valproate

The full report is provided in Attachment.

The report was considered by the SAGE IVD at its meeting in March 2019. The SAGE IVD requested the report to be presented to the Expert Committee on Selection and Use of Essential Medicines (EML) for endorsement or modification of the prioritized list of medicines. Following the advice of the EML Expert Committee, the EDL Secretariat will invite submissions for the relevant in vitro diagnostic tests for consideration by the SAGE IVD at its next meeting. Full details of the SAGE IVD's recommendations are included in the Technical Report of the meeting available at: <https://apps.who.int/iris/handle/10665/329527>

Therefore, the EML Expert Committee is requested to consider the attached report and provide its advice to the SAGE IVD.

Please do not hesitate to contact Dr Francis Moussy, Secretary of SAGE IVD, for further information. Thank you for your kind attention to this request.

Dr Francis Moussy

ENCL. As stated

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**Review of the evidence to include TDM in the Essential in vitro Diagnostics List and
prioritization of medicines to be monitored**

REPORT

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Fundació Institut Català de Farmacologia

Version February 18th, 2019

EXECUTIVE SUMMARY

Monitoring the results of the treatment is an important part of the rational prescribing process. In most cases, the clinical assessment of patients will provide information on their clinical improvement and possible adverse drug reactions. However, a few medicines with well-known pharmacological characteristics (e.g., narrow therapeutic window, marked pharmacokinetic variability, desired therapeutic effect difficult to monitor) benefit from therapeutic drug monitoring (TDM).

In the last decades, TDM has evolved considerably. New laboratory methods and plasma concentration reference data for new medicines have been used, both for clinical and research purposes. Within this framework, to decide whether TDM for a specific drug is essential or not, requires a clear approach based on evidences.

First, it is important to remember that:

- TDM is just a tool to help in the complex prescribing process; TDM without a clinical approach is useless.
- TDM is a three step process including: (1) the precise and reliable measure of the plasma concentration of a specific medicine; (2) the interpretation of the obtained concentration value according to the knowledge on the concentration-effect relationship, and (3) the calculation and proposal of an individual dose adjustment for that specific patient.

There are many published observations of:

- Unnecessary use of TDM as a laboratory test.
- Differences or inaccuracies in the measured plasma concentration values due to inadequate sampling.
- Lack of knowledge for the necessary interpretation of the plasma concentration value taking into account the clinical characteristics of the individual patient and his/her concomitant treatments.

After a careful and critical review of the evidences about TDM for a proposed list of drugs (amikacin, carbamazepine, cyclosporin, digoxin, gentamicin, lithium, methotrexate, phenobarbital, phenytoin, valproic acid and vancomycin), the following prioritization of the value of monitoring is proposed:

High (most authors consider TDM useful even for noncritically ill patients):

amikacin, gentamicin, phenytoin, lithium

Moderate (TDM useful in patients with co-treatments or concomitant clinical complications [e.g., impaired renal function]):

vancomycin, methotrexate, cyclosporin

Low (careful clinical assessment is enough for most cases, or there are evidences that there are no differences between patients with and without TDM):

digoxin, phenobarbital, carbamazepine, valproate

AGREEMENT FOR PERFORMANCE OF WORK (APW)

The present report is the result of an APW to perform a comprehensive review of the evidence to include therapeutic drug monitoring (TDM) in the list of Essential in vitro Diagnostics (EDL), prioritize those that should be used and make full submissions for those selected.

PREMISE

Following the first meeting of the Strategic Advisory Group of Experts on In vitro diagnostics (SAGE IVD) last April 2018, WHO published the first ever EDL. In preparation of the second edition of the EDL, the secretariat is commissioning the evaluation of therapeutic drug monitoring assays.

The **objective** is identifying the *in vitro* diagnostics that could help monitoring the use and effect of the drugs listed in the Essential Medicine's List (EML), evaluating the effects and the cost at all economical level specially LMICs.

The supplier will establish a list of priorities, review and recommend TDMs for submission for SAGE IVD consideration and do the full submissions of those TDMs, while providing the necessary evidence, to be published ahead of the next SAGE IVD meeting in March 18-22, 2019.

WORK TO BE PERFORMED

Objective 1: Establish a priority list for drugs that should have therapeutic drug monitoring (TDM);

Output 1.1: Perform a comprehensive review of the available evidence appeared in the last five years on TDM lists (including the 11 drugs provided on Lee Schroeder's Clin. Chem. 64(8):1148-1157 (2018) publication) and establish a prioritization;

Objective 2: Prioritize the list and make recommendation to SAGE IVD and secretariat;

Output 2.1: Prioritization list with analysis and recommendations;

Objective 3: Submit for SAGE IVD consideration;

Output 3.1: file pre- submission and full submission of the selected IVDs for SAGE IVD consideration during the March meeting.

1. GENERAL CONSIDERATIONS

Despite being well-known, it is important to remember some basic aspects of treating patients and using medicines before identifying drugs suitable of being monitored and establish a prioritization.

The prescribing process does not end after writing a recipe; in fact, **monitoring the results of the treatment is an important part of the rational prescribing process** [1]; this means that clinicians should assess patients' clinical evolution, expected outcomes and potential adverse effects of the prescribed medicines periodically.

For most medicines, the benefits could be easily observed and measured, so it is possible to know if the administered dose is appropriate for that patient or if some dose adjustments are required either to avoid toxic effects or to obtain the desired benefit. Notwithstanding this, for a few specific medicines, this is not the case.

When there is a large inter-individual variation between dose and effect individualising drug dosage is difficult. This is particularly relevant for drugs with a narrow target range or concentration-dependent pharmacokinetics. Additionally, drug concentration at the site of action cannot be routinely measured, but the desired or adverse effects may correlate better with plasma or blood concentrations than they do with dose. So, for these drugs, concentration measurements are a valuable surrogate of drug exposure, particularly if there is no simple or sensitive measure of effect [2].

1.1. Therapeutic drug monitoring

Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window) [3]. TDM is useful when the following criteria are met [4]:

- (1) A good correlation exists between the pharmacologic response and plasma concentration. An increase in drug concentration in the biological matrix, for example plasma, is related to an increase in efficacy and/or toxicity related to the drug.
- (2) Drug concentrations cannot be predicted from a given dose, as result of inter-individual variability.
- (3) The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
- (4) The pharmacological effects of the drug cannot be monitored easily (e.g., monitoring blood pressure for antihypertensives) or the adverse effects cannot be easily differentiated from lack of efficacy of a drug.

The characteristics of drugs which make them suitable for, or make them require, therapeutic drug monitoring are:

- marked pharmacokinetic variability
- concentration related therapeutic and adverse effects

- narrow therapeutic index
- defined therapeutic (target) concentration range
- desired therapeutic effect difficult to monitor

If the clinical effect can be readily measured (e.g. heart rate, blood pressure), it is obviously better to adjust the dose on the basis of response. Where this cannot be done, therapeutic drug monitoring is used in two major situations [3]:

- drugs used prophylactically to maintain the absence of a condition such as seizures, cardiac arrhythmias, depressive or manic episodes, asthma relapses or organ rejection
- to avoid serious toxicity as with the aminoglycoside antibiotics which, unlike most antibiotics, have a narrow therapeutic range.

The appropriate indications for TDM include [2]:

- toxicity: diagnosing toxicity when the clinical syndrome is undifferentiated (e.g., unexplained nausea in a patient taking digoxin) or avoiding toxicity (e.g., when using aminoglycosides, cyclosporin)
- dosing: after dose adjustment (usually after reaching a steady state); assessment of adequate loading dose (after starting phenytoin treatment), or dose forecasting to help predict a patient's dose requirements (aminoglycosides)
- monitoring: assessing compliance (e.g., anticonvulsant concentrations in patients having frequent seizures); diagnosing under treatment (particularly important for prophylactic drugs such as anticonvulsants, immunosuppressants), and diagnosing failed therapy (TDM can help distinguish between ineffective drug treatment, non-compliance and adverse effects that mimic the underlying disease).

An important aspect of TDM that should be highlighted is the fact that TDM is the measurement of plasma or blood concentrations of a medication **to assist the management of patients**. This is, the drug concentration levels facilitated by the laboratory is subsequently interpreted to individualise and optimise a patient's dosage regimen and therapeutic outcomes by maintaining drug concentrations within a target therapeutic window.

For the majority of drugs, routine monitoring is not supported and should only occur if it can be accurately interpreted and subsequently contribute to patient management. Resources should not be expended on monitoring drug concentrations if they are unable to be interpreted and subsequently do not contribute to patient management.[5]

For example, the target concentration may depend on the indication; so, the recommended concentration for digoxin depends on whether it is being used to treat atrial fibrillation or congestive heart failure [2]. Similarly, sources of pharmacokinetic variability in a patient's response to drugs include age, gender, organ function, drug interactions and drug metabolising capacity [5]. Drug concentrations need to be interpreted in the context of the individual patient without rigid adherence to a target range. This requires knowledge of the pharmacokinetics, sampling time, drug history and the patient's clinical condition [2].

In fact, therapeutic drug measuring after obtaining a blood sample and sending it to the laboratory is only one part of TDM which provides expert clinical interpretation as well as the concentration. Nevertheless expert interpretation of a drug concentration measurement is essential to ensure full clinical benefit [6]. Only clinically meaningful tests should be performed and limited funds should not be wasted on measurements which cannot be interpreted and do not assist patient management.

Similarly, the method of analysis must be robust, standardized, and validated, and less time consuming, to allow quick reporting of results. Additionally, it is important to pay attention to the sample collection process and the moment when they are collected [4].

The drug concentration is complementary to and not a substitute for clinical judgement so it is important to treat the individual patient and not the laboratory value [6]. Expert clinical interpretation of the concentration measurements is invaluable in order to derive any meaningful clinical benefit from the procedure [7]. It is important to note that therapeutic ranges are mere recommendations based on the clinical response of a small group of patients taking the drug. Because therapeutic ranges are predominantly derived from small studies, there will be individuals for whom lower concentrations are adequate and those who experience adverse events, even within the published therapeutic range. Hence it is important to interpret drug concentrations in the patient's clinical context [5].

So, TDM is not limited to have laboratory facilities able to determine blood concentration levels of different drugs. **TDM is a tool which can help in the rational prescribing process, and should be required: (i) when it is necessary to help in clinical decisions, and (ii) when the results can be clearly interpreted.**

1.2. TDM as a helpful tool in therapeutics

Routine monitoring is not advocated for most drugs. Only clinically meaningful tests should be performed. Drug assays are costly, so the reason for monitoring and the additional information to be gained (if any) should be carefully considered. So, regular monitoring of many drugs is not required in a clinically stable patient [2, 6].

Different authors suggest: **“treat the patient and not the level”**. There are additional considerations. For example, with lithium the reference range is a true target range, but with many other drugs the range of plasma concentrations associated with optimal therapeutic benefit is much less clearly defined, and interpretation of results has to be made in context [9]. This approach is an important point of view when considering TDM. For example, if a patient has an anticonvulsant drug concentration just below the target range, but is not having seizures, an increase in dose is probably not required. Before making dose adjustments, it is important to consider if the sample was taken at the correct time with respect to the last dose, if a steady state has been reached and whether the patient has adhered to their treatment. There are other considerations, for example, the serum potassium should be noted when interpreting digoxin concentrations as toxicity can occur at a therapeutic concentration if there is hypokalaemia [2].

In addition to these characteristics associated with each individual patient, when considering TDM, other aspects should be taken into account. The most important are the published evidences to support therapeutic ranges for specific drugs, and also the effectiveness of measuring blood concentrations for different medicines.

Recently, Cooney *et al.* conducted an interesting analysis of the published evidences on therapeutic ranges [8]. Ten systematic reviews that investigated the correlation between serum concentrations and clinical outcomes encompassing a variety of medicines and indications were assessed. There were significant variations in the methodologies used (including the search terms used, data extraction methods, assessment of bias, and statistical analyses undertaken). Current systematic reviews investigating therapeutic ranges have highly variable methodologies and there is no consensus of best practice when undertaking systematic reviews in this field. Therapeutic ranges should be population and indication specific and based on clinically relevant outcomes.

Only a limited number of articles have been published which demonstrate the cost-effectiveness of therapeutic drug monitoring, and there continues to be debate as to whether these services make a cost-effective contribution to patient care [6]. Additionally, the level of evidence of the different studies is not the same. The French group *Suivi thérapeutique pharmacologique* of the *Société Française de Pharmacologie et Thérapeutique* lead by Le Guellec has proposed a model for the TDM recommendations for different medicines, according to the scientific quality of the different published studies supporting the need for therapeutic drug monitoring for each individual drug. So, this team associates a recommendation level to each TDM indication, according to different criteria (see Table 1.2.) [10].

Table 1.2. – Evidence level classification for the TDM recommendations according to the *Groupe pour la suivi thérapeutique pharmacologique* [10].

RECOMMENDATION LEVEL	JUSTIFICATION
Essential	Using that drug depends on the TDM result. TDM appears in the product leaflet or SPC document.
Strongly recommended	Randomised clinical trials show benefits in efficacy and/or toxicity. Pharmacoeconomic studies show the benefits of TDM.
Recommended	Non-randomised studies have shown some advantages on efficacy and/or toxicity.
Occasionally useful	The drug shows a great pharmacokinetic variability, and a link between an exposure parameter and pharmacological response has been shown in certain situations.
Not evaluated	Pharmacokinetic variability is important, but the concentration/response link has not been established, usually with a therapeutic margin reasonably wide.

Despite the differences in the evidence level to support TDM recommendations for the different medicines, clinicians continue to order drug concentrations. In an ideal environment drug levels would only be requested when there is an appropriate indication. In a large hospital with a high staff turnover, continuing education by the members of the TDM team about the criteria for rational drug level requests is required [6].

According to McCudden [11], “an essential element of TDM is the provision of accurate and clinically relevant reference intervals, but unlike most laboratory reference intervals, which are derived from a healthy population, TDM reference intervals need to relate to clinical outcomes in the form of efficacy and toxicity. This makes TDM inherently more difficult to develop as healthy individuals are not on therapy, so there is no ‘normal value’. In addition,

many of the aforementioned drugs are old and much of the information regarding reference intervals is based on small trials using methods that have changed. Furthermore, individuals have different pharmacokinetics and drug responses, particularly in the context of combined therapies, which exacerbates the challenge of universal TDM targets". So, all these factors should be taken into account before deciding to use TDM.

It is important to assess carefully the published evidences supporting benefits of TDM with each medicine before establishing recommendations, especially when expertise to interpret laboratory results are not ensured and when performing unnecessary or routine TDM analyses can represent useless expenditure.

1.3. Essential diagnostics

The present report analyses evidences supporting TDM for a list of drugs included in the WHO Essential Medicines List with the aim of being considered as part of the Essential Diagnostics List (EDL). The first EDL thus encompasses a minimum set of IVDs that should be made available in primary care, hospitals and reference laboratories, with a focus on common diseases with public health importance and the WHO defined priority infectious diseases [11].

As defined by WHO, *Essential diagnostics* are: "Diagnostics that satisfy the priority health care needs of the population and are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and accuracy, and comparative cost-effectiveness; similar to the definition of an essential medicine".

The basis for the present analysis are the suggestions appearing in the article published by Schroeder *et al.* in 2018 [12]. TDM is suggested for: amikacin, carbamazepine, cyclosporin, digoxin, gentamicin, lithium, methotrexate, phenobarbital, phenytoin, valproic acid and vancomycin (see **Table 1.3.**).

1.4. Methods

In order to review that list of 11 medicines and propose a prioritization, a comprehensive PubMed search has been conducted by using the keywords "therapeutic drug monitoring" or "TDM" and limiting the search to "reviews" and the period to Jan 1st 2014 to December 20th, 2018.

During those five years, 589 articles have been included in the PubMed database. A first title and abstract reading allowed to exclude 429 articles (case descriptions, editorial comments, studies on pharmacogenetics or personalised medicine, animal studies, etc.). Up to 42 articles described TDM in medicines not included in the initial list. Additionally, 24 studies described different technical aspects of TDM. Finally, 15 articles had been discarded because they were written in Japanese, Russian, German or Czech. So, 79 articles have been taken into

Table 1.3. Therapeutic drug monitoring. List of medicines suggested by Schroeder, *et al.* and WHO EML recommendations.

WHO EML group	Drug		WHO EML indications
Antibacterials	Aminoglycoside	amikacin	Injection: 250 mg (as sulfate)/mL in 2- mL vial FIRST CHOICE -pyelonephritis or prostatitis (severe) SECOND CHOICE - high-risk febrile neutropenia - sepsis in neonates and children [c]
		gentamicin	Injection: 10 mg; 40 mg (as sulfate)/ mL in 2- mL vial. FIRST CHOICE - community acquired pneumonia (severe) [c] - complicated severe acute malnutrition [c] - sepsis in neonates and children [c] SECOND CHOICE - <i>Neisseria gonorrhoeae</i>
	Glycopeptide	vancomycin	Capsule: 125 mg; 250 mg (as hydrochloride). SECOND CHOICE - <i>C. difficile</i> infection Powder for injection: 250 mg (as hydrochloride) in vial. SECOND CHOICE -high-risk febrile neutropenia
Anticonvulsants/ Antiepileptics Medicines used in bipolar disorders	Carbamazepine		Oral liquid: 100 mg/5 mL. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg
	Phenobarbital		Injection: 200 mg/ mL (sodium). Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg.
	Phenytoin		Injection: 50 mg/ mL in 5- mL vial (sodium salt). Oral liquid: 25 mg to 30 mg/5 mL. * Solid oral dosage form: 25 mg; 50 mg; 100 mg (sodium salt). Tablet (chewable): 50 mg. * The presence of both 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
	Valproic acid		Oral liquid: 200 mg/5 mL. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate). Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).
Medicines used in bipolar disorders	Lithium carbonate		Solid oral dosage form: 300 mg
Cytotoxic and adjuvant medicines	Methotrexate		Powder for injection: 50 mg (as sodium salt) in vial. Tablet: 2.5 mg (as sodium salt). <ul style="list-style-type: none"> • Early stage breast cancer • Gestational trophoblastic neoplasia • Osteosarcoma • Acute lymphoblastic leukaemia • Acute promyelocytic leukaemia
Antiarrhythmic medicines Medicines used in heart failure	Digoxin		Injection: 250 micrograms/ mL in 2- mL ampoule. Oral liquid: 50 micrograms/ mL. Tablet: 62.5 micrograms; 250 micrograms.
Immunosuppressive medicines	Cyclosporin		Complementary List. Capsule: 25 mg. Concentrate for injection: 50 mg/ mL in 1- mL ampoule for organ transplantation

consideration, as well as a number of articles identified among the list of references of these studies. The following considerations have been written after the review of these publications, and the most relevant references supporting the prioritization proposal are listed at the end of the present document.

Criteria for prioritization

TDM is a tool to help clinicians to improve the prescribing process when certain medicines are being administered. As any tool, it should be used when patients receiving one of the listed TDM drugs require a measurement of their blood concentration. **In most cases, however, the decision to ask for TDM is not so much related to specific drugs, as to factors related with the patient who is being treated with them.** Concomitant treatments and potential drug-drug interactions, special conditions (e.g., pregnancy, neonates, obesity) or comorbidities (e.g., liver or kidney failure), as well as being admitted to especial units (e.g., intensive care units), are situations which advise TDM for medicines that, in other situations (e.g., non-complicated patients in primary health care) probably do not require TDM because a close clinical follow-up is enough to anticipate potential dosage problems.

Taking into account these considerations, the prioritization suggested in the next section is based on non-complicated patients. A three-category scale is being proposed, after a simplification of the French scale [10]: “high”, “moderate” and “low” TDM recommendation, where “low” is for those drugs with published evidences of the useless value of TDM in clinical practice, and “high” is for drugs with a really narrow therapeutic window with published evidences of the clinical benefits of TDM. For those included in the “high” TDM recommendation, TDM is useful even for noncritically ill patients.

2. SPECIFIC MEDICINES

2.1. Antibacterial drugs

It is well-known that most antimicrobial agents are well tolerated and TDM is not required. Most authors highlight several exceptions; among the medicines included in the WHO Essential medicines List, the aminoglycoside antibiotics amikacin and gentamicin, and the glycopeptide vancomycin are relevant exceptions. The current recommendations for these three drugs are being revised in this section.

Aminoglycosides (amikacin, gentamicin)

TDM of aminoglycoside antibiotics such as gentamicin has been well-established for many years, and its interpretation is best provided in conjunction with microbiology laboratories [9].

In a detailed revision published in 2014, Hallworth explained the relative simple pharmacokinetics of aminoglycoside antibiotics [14]. This author highlights different aspects:

“The drug concentration at which bactericidal effects are achieved (the minimum inhibitory concentration, MIC) is relatively easy to determine in vitro but often has little relevance in vivo, owing to variable penetrance of the drug to the site of infection and differing conditions at the infection site. Aminoglycosides also show a marked post-antibiotic effect – suppression of bacterial growth persists for some time after the drug is no longer present in the plasma. This makes definition of target plasma concentrations difficult, and this difficulty has been compounded in recent years by changes in the ways in which aminoglycosides are administered.

Since mid-1990, it has become clearer that less frequent dosing (every 24 h or more) produces higher peak concentrations, which enhance bacterial kill, and lower trough concentrations, which reduce the systemic toxicity. Such regimens are more convenient, less toxic, reduce adaptive resistance and are generally more suitable in patients with normal renal function. The approach was originally devised as once daily dosing, but a more accurate term is probably ‘extended dosing interval’, in which a plasma concentration measurement is used to design an individual dosing interval which reflects the patient’s needs and renal function”.

And recommends following the dosage recommendations found in local clinical guidelines.

Hallworth concludes that the value of monitoring of aminoglycosides is high: “Monitoring is essential to achieve effective therapy while avoiding toxicity, particularly in infants, the elderly, the obese and patients with cystic fibrosis, if high doses are being used or if renal function is impaired [14], special condition that will be further commented below. Ghiculescu [2] also includes TDM of aminoglycosides as clinically meaningful tests to avoid toxicity.

McCudden [11] adds that the combination of MIC requirements and toxicity risk is the basis for aminoglycoside TDM. “The combined need to achieve a minimum drug concentration

and avoid toxicity necessitates measurement of both minimum and maximum concentrations. Thus, with conventional dosing of aminoglycosides, both peak and trough levels are typically measured. However, there are recommendations that suggest a peak and random timed collection would be more effective for dose adjustments”.

Several nomograms and algorithms have been proposed and tested. This means that, in addition to the laboratory facilities, TDM of aminoglycosides require capacity for antimicrobial testing to measure MIC, and also knowledge about these nomograms and algorithms.

In general, there is some evidence that patients who achieve target concentrations have better outcomes, but McCudden [11] adds:

“However, aminoglycosides typically lack evidence-based outcome measures for TDM targets. Despite extensive anecdotal information, case reports and small trials in selected patient groups, there is a lack of randomized control trials and limited support for optimal TDM targets. Collectively, the evidence for TDM target concentrations for aminoglycosides is complex and varied, making concise universal recommendations difficult”.

And this author repeats a sentence which has also been highlighted by different authors, regarding the importance of the involvement of clinical pharmacology, assurance of accurate data (e.g. time of collection and dosing) and recognition of risk factors (e.g. renal impairment) for aminoglycoside TDM.

Despite the general recommendation for TDM of gentamicin and amikacin for patients having treatments longer than 5 days, the results of a systematic review of amikacin use and TDM in adults published by Jenkins, et al. in 2016 [15] should be referenced here. The authors analysed 17 studies (including randomized controlled trials, controlled clinical trials and interrupted time series trials) involving amikacin TDM and dose adjustment. Among their results, the authors found that 15 studies reported rates of nephrotoxicity, and auditory and vestibular toxicities were reported in 12 and 8 studies, respectively.

They conclude: “This systematic review found little published evidence to support an optimal dosage regimen or TDM targets for amikacin therapy. **The use of alternative approaches, such as consensus opinion and a review of current practice, will be required to develop guidelines to maximize therapeutic outcomes and minimize toxicity with amikacin**”.

There are some recommendations for an empirical therapy in noncritically ill patients without requiring TDM. Dosing commences with a dose of 4 - 5 mg/kg iv for adults, independent of renal function. If renal function is normal then two additional doses are given

24 h apart and dosing ceases. As creatinine clearance decreases the dosing interval lengthens (every 36 hours for two doses only if creatinine clearance between 60 and 40 ml/min, and one dose only if creatinine clearance less than 30 ml/min) [47].

Glycopeptides (vancomycin)

Hallworth [14] also revised TDM for the glycopeptide vancomycin, a reserve antibiotic used either intravenously (for example in patients with endocarditis and other serious infections caused by Gram-positive cocci including multi-resistant Staphylococci) or orally in the treatment of pseudomembranous colitis. This author concludes that the value of monitoring vancomycin blood concentrations is moderated: “like the aminoglycosides, the glycopeptides are poorly absorbed, not metabolized, excreted renally and are potentially nephrotoxic and ototoxic. Indications for monitoring have been controversial, but there is definitely a role for monitoring in patients with poor renal function to achieve maximum effect with minimal toxicity”.

In a chapter on TDM of antimicrobials published in a specialized book of Clinical Chemistry, Dasgupta concluded [16]: “TDM of aminoglycosides and vancomycin is essential in order to avoid drug toxicity especially nephrotoxicity and irreversible ototoxicity”. For vancomycin, this author explains that TDM can be performed in clinical laboratories using immunoassays, but chromatographic methods are also available for this drug, although he adds:

“Because of complex nature of chromatographic techniques, small- to medium-size laboratories do not have the capability of using such methods, and only reference laboratories and larger medical centres as well as academic medical centres offer such testing. This is a limitation because a patient experiences an unexpected toxicity from an antibiotic may be benefitted if serum drug level result is available to the clinician within hours of ordering, and only patients in large medical centres and academic centres can get the benefit of in-house offering of therapeutic drug monitoring of uncommon antibiotics. For a patient in a small- or medium-size hospital, the clinician must wait for few days up to a week for the result to come back from a reference laboratory”.

McCudden [11] refers to joint guidelines for TDM targets for vancomycin published in 2009, thus remembering the dynamics of TDM concepts and recommendations according to new evidences and the experience of use of medicines. For example, this author wrote:

“According to the joint 2009 guidelines, the older recommendation of 5–10 mg/L is too low to reach the MICs for many types of infection. The guidelines recommend that trough vancomycin concentrations should be higher than 10 mg/L to reduce development of resistance. (...) This reflects the time-dependent kinetics of vancomycin on bacterial killing, where cure rates are independent of peak concentration”.

Many aspects regarding how vancomycin is used and also the characteristics of patients (e.g., conditions such as renal instability) influence on the interpretation of concentration values. Also, this author alerts on inter-assay consistency: “Vancomycin results differ from 9 to 29% depending on the concentration. The Institute for Quality Management in Healthcare (IQMH) proficiency testing program allows for up to a 2-mg/L difference at concentrations below 10 mg/L and up to 20% at concentrations above 10 mg/L, which equate to a lower cutoff of 8–12 and an upper cutoff of 16–24 mg/L. Clinical users of vancomycin should be aware of these ranges and the limitations of the assay when monitoring patients”.

More recently, Elbarbry published a critical evaluation of the current vancomycin guidelines. [17]. This author states that the current practice of vancomycin dosing is not efficient to achieve and maintain therapeutic levels, especially in the critically ill patients. To improve the efficiency of vancomycin dosing while avoiding the risk of nephrotoxicity and minimizing the cost of therapeutic drug monitoring, two user-friendly and scientifically based dosing strategies are proposed. Although Elbarbry explains that continuous infusion is considered a preferred dosing method for vancomycin, he describes an intermittent infusion dosing strategy that is based on deriving patient specific pharmacokinetic parameters. This author recommends:

“revising the dosing method (intermittent infusion versus continuous versus), dosing approach (weight-based versus AUC-based), and the pharmacodynamic end point (trough versus AUC)”.

Additionally, two user-friendly nomograms based on creatinine clearance estimates are proposed to help in calculating vancomycin dosing by both intermittent and continuous infusion methods. “These nomograms are expected to improve the therapeutic efficacy while minimizing the risk of toxicity and cost of vancomycin dosing”.

Notwithstanding this, in non-complicated patients, the recommendation for TDM of vancomycin could be considered ‘moderate’, according to Hallworth [14], and also to Ye, et al. [18]. These authors concluded: “Despite the availability of clinical practice guidelines for TDM of vancomycin, vancomycin serum concentrations still do not reach therapeutic concentrations in many patients. The specific recommendations for vancomycin TDM were moderately consistent and guidelines varied in trough concentration monitoring, frequency of TDM, and serum concentration targets. **As the overall guideline quality for vancomycin TDM is not optimal, efforts are needed to improve guideline quality, especially in the domain of rigor of development and stakeholder involvement**”.

Phillips *et al.* suggested: “Significant resources are invested during the development of such guidelines; however, there is often little or no information about how such guidelines or other vancomycin practice improvement initiatives should be implemented” [19].

Special conditions

Different articles describing TDM of aminoglycosides and vancomycin in specific situations have been identified. In general, these authors agree that “a TDM-guided approach could be particularly useful in critically ill patients in whom achieving target concentrations is more difficult, such as obese patients, immunocompromised patients, those infected by highly

resistant bacterial strains, patients with augmented renal clearance, and those undergoing extracorporeal support techniques” [20].

Obesity is one of such conditions. It is well-known that physiologic alterations seen in obesity commonly impact the pharmacokinetics of medicines in general and antibiotics in particular. Meng et al. published a critical review of the available data regarding pharmacokinetics and dosing issues for 34 antimicrobials based on 121 articles of the 2336 identified by the search strategy. Regarding the antimicrobials of interest in the present report, these authors concluded [21]: “For gentamicin and amikacin: Consider ABW0.4 as the dosing weight scalar to limit risks of toxicity. For vancomycin, doses do not appear to scale linearly with body weight; it requires decreases in weight-based doses. Two point measurements (peak and trough) would increase accuracy of AUC estimates, as would single levels if using software capable of Bayesian analysis”. Caution in dose calculations is also recommended by other authors [22].

There are different special situations which require dose adjustments and possibly careful TDM for aminoglycosides and vancomycin. This is the case of patients admitted in intensive care units (ICU). Some authors suggest TDM with adaptive feedback [23]: “It is likely to be the most robust approach to optimize dosing for individual patients”. But these authors recognize that although the scope of TDM is broadening from the traditional focus on prevention of toxicity, to include optimization of antibiotic exposure thereby improving patient outcomes, “the evidence relating TDM practice with improved clinical outcome remains limited”.

If the ICU patient is a neonate, then the situation can be even more complicated. “Current antibiotic regimens for critically ill neonate and pediatric patients are frequently suboptimal due to a poor understanding of altered pharmacokinetic properties. An assessment of the suitability of microsampling in neonate and pediatric patients is suggested, although additional studies are recommended before wider use of this technique [24]. Other authors are trying to validate a stepwise approach to define dosing regimens for neonates [25].

The future of TDM

As many clinical laboratory approaches, TDM is dynamic and techniques are evolving quickly. These advances affect aminoglycosides and vancomycin, but also other antimicrobials. It is well known that antimicrobial resistance is one of the worrying situations involving antimicrobials, so, approaches to try to use the most appropriate dose as a way to minimize the risk of resistance are on study as part of the antibiotic stewardship concept [12].

On the other hand, different initiatives are being studied to try to reduce the risks, burden, and costs of blood-based therapeutic drug monitoring; salivary TDM is one of these approached, and it is being tested with antituberculosis drugs [26]. This could be an interesting advance, although more studies and validations are needed.

Additionally, new data analyses, such as big data approaches are being tested to try to optimize antibiotic dosing [27]. Probably, TDM will change in the next years.

2.2. Digoxin

Digoxin, together with some antiepileptics drugs and antibiotics such as aminoglycosides, has been traditionally in the list of medicines which require TDM. Notwithstanding this, a careful analysis of the published evidences associated with TDM of digoxin in daily clinical practise in non-complicated patients allow to minimise previous recommendations.

Most authors agree on the fact that the risk of digoxin toxicity is potentiated in elderly patients and in those with renal impairment (as digoxin is predominantly renally cleared), electrolyte disturbances (e.g., hypokalaemia, hypomagnesaemia, hypercalcaemia), acidosis, hypoxia, hypothyroidism or co-administered P-glycoprotein inhibitors [5]. In general, it is well-known that loading doses of digoxin should be halved in the elderly and in patients with renal impairment (creatinine clearance <60 mL/min); on the other hand, maintenance doses of digoxin should be halved in the elderly and may be as low as 62.5 µg on alternate days in patients with severe renal impairment [5].

Notwithstanding this, analyses of aliquots from 261 routine digoxin samples by accredited laboratories using commercially available immunoassays showed that the reproducibility of the digoxin assay is such that through the course of digoxin therapy, patient samples analysed by different laboratories and medical practitioners may be unacceptably inconsistent [28]. According to the authors of this study, such variation may arise because of substances in a patient's blood that interact with the antibody used in various commercial digoxin immunoassays. The authors concluded that **this extensive variation in digoxin monitoring has significant implications, as it makes drug concentrations difficult to interpret.**

According to a review by Benlmouden and Billaud [29], "the clinical relevance of digoxin therapeutic monitoring is also proved but the serum digoxin concentrations required for optimal clinical efficacy and acceptable toxicity remains controversial". Literature reviews conducted by these authors identified considerable variation in the routine monitoring of digoxin, which makes TDM difficult to interpret and complicates clinical management when treating physicians are endeavoring to avoid toxicity and optimize dosing. And concluded: "The appropriate therapeutic range for digoxin in chronic heart failure patients continues to be debated. The target serum digoxin concentration should be 0.5 to 1.0 ng/mL (0.6 to 1.3 nmol/L). Evidence rating is at B level (inconsistent or limited-quality patient-oriented evidence)" based on three previous studies [30-32].

Thus, clinical monitoring of heart rate and adverse effects may be more helpful than TDM [5, 28]. Flanagan states that "TDM of digoxin is well established; although its clinical relevance is often obscure" [9], based on the conclusions of a study conducted in a New Zealand hospital [33].

This New Zealand study assessed one hundred consecutive requests for digoxin concentrations in Christchurch Hospital inpatients. The case notes and hospital medication records were reviewed to determine the indication for testing, the appropriateness of the sampling time and of the subsequent alteration to dosing. The authors found that in 53% of requests no clear indication for digoxin TDM could be determined. In the remainder, 'suspected toxicity' accounted for 31% and 'therapeutic failure' for 16%. Samples were

inappropriately taken within eight hours post-dose in 32% of requests. In 19% of cases, the samples did not reflect steady-state conditions. In 5% of occasions, the subsequent decision regarding dose adjustment was felt to be clearly inappropriate, and there was uncertainty regarding appropriateness in some other cases. Overall, in only 29% of requests was TDM performed appropriately with regard to indication, sampling and subsequent dose alteration. So, the authors concluded that at Christchurch Hospital, the practice of TDM for digoxin is often inappropriate. It would seem that medical staff education is required to improve this practice [33].

Taking into account all these published evidences, for non-complicated patients receiving digoxin, it seems that close clinical control can be enough in most cases, and routine TDM seems unnecessary. The recommendation for TDM can be categorized as 'low' because of these inconsistencies.

2.3. Antiepileptics

Medicines used to treat epilepsy, especially the classical antiepileptics (phenytoin, phenobarbital, carbamazepine and valproate) are among the most commonly monitored drugs. Notwithstanding that, it seems that there is little evidence that monitoring concentrations of anticonvulsants improves clinical outcomes when the drugs are used to treat mood disorders [2].

In their concise recommendations, Lucas and Donovan explain that there is reasonable evidence for monitoring phenytoin, carbamazepine and sodium valproate [5]. These authors add that there is little evidence regarding the application of therapeutic ranges for epilepsy when anti-epileptic drugs are used for other indications (e.g., migraine prophylaxis, mood disorders), although carbamazepine's anti-epileptic therapeutic range can be used to help avoid toxicity [5]. Despite this, refer to the complexity of adjusting doses for sodium valproate and phenytoin, as these drugs display nonlinear kinetics.

One of the best analysis of the TDM recommendations for the traditional antiepileptics drugs published until this moment is the Cochrane review conducted by Tomson *et al* [34]. Regarding phenytoin, these authors wrote:

“Phenytoin was the drug of choice for most seizure types when drug level measurements were introduced in the 1960s and it was found to exhibit particularly complex dose-dependent pharmacokinetics. Studies carried out in the 1960s and 1970s demonstrated a correlation between the concentration of phenytoin in serum and its therapeutic and toxic effects, thus measuring the serum concentration of phenytoin was soon established as a guide to individualised dosing. Since then, drug level monitoring (therapeutic drug monitoring) has been established as a routine aid to optimising treatment with other antiepileptic drugs. The goal of therapeutic drug monitoring is to optimise a patient's clinical outcome by managing the medication regimen, assisted by the measurement of drug concentrations”.

Thomson and his colleagues also explained highlighted that the concept of therapeutic drug monitoring rests on the assumption that drug concentration correlates better with clinical effects than dose; later, they describe: “however, comparatively few studies have been designed specifically to explore the relationship between serum concentrations and effects of antiepileptic drugs, and the documentation in this respect for many of the drugs is scarce” [35]. Additionally, these authors have identified several studies showing that TDM services may vary in its methods (as drug concentrations can be measured in specimens other than serum, such as saliva, while analytical methods with varying specificities), as well as in ways in which the results of the analysis are presented to the treating physician [34].

According to a classical paper published by Chadwick in 1987, “given the heterogeneity in the concept of TDM and in the pharmacological characteristics of antiepileptic drugs, it is not surprising that the use of therapeutic drug monitoring varies markedly and that we lack consensus concerning the value of its application in epilepsy [36].

The Cochrane review performed by Tomson *et al.* in 2007 [34] only found one study that met the inclusion criteria for the review. It was an open study including 180 patients with newly-diagnosed, untreated epilepsy were randomised to treatment with the antiepileptic drug selected by their physician either with or without therapeutic drug serum level monitoring as an aid to dosage adjustments. The antiepileptic drugs used were carbamazepine, valproate, phenytoin, phenobarbital and primidone. A 12-month remission from seizures was achieved by 60% of the patients randomised to therapeutic drug monitoring (intervention group) and by 61% in the control group [37]. So, based on this clinical trial, Tomson *et al.* found **no clear evidence to support routine antiepileptic drug serum concentration measurement with the aim of reaching predefined target ranges for the optimisation of treatment of patients with newly-diagnosed epilepsy with antiepileptic drug monotherapy** [34], although these authors added: “However, this does not exclude the possible usefulness of therapeutic drug monitoring of specific antiepileptic drugs during polytherapy, in special situations or in selected patients, although evidence is lacking”.

Notwithstanding this, it should be noted that most patients included in the trial received carbamazepine; less patients received phenobarbital and valproate, and just one patient received phenytoin. So, no conclusions can be taken for phenytoin, as the authors recognise: “Because phenytoin was used in only a small minority of cases, these results may not be applicable to the subgroup treated with this drug, for which TDM is likely to be most useful due to its dose dependent kinetics”. [37]

Flanagan *et al.* [9] also follow the recommendations made by Tomson in the sense that: “in newly-diagnosed patients there is no clear evidence to support the use of TDM with the aim of reaching predefined target ranges in dose optimization with anticonvulsant monotherapy, although this does not reflect clinical practice with phenytoin especially”. It should also be highlighted that carbamazepine and valproate can also be used in bipolar disorder, and valproate is also used in acute mania when the plasma concentrations associated with efficacy may be somewhat higher than when the drug is used as an anticonvulsant [38].

In the case of sodium valproate, other authors concluded: “Several studies show a concentration-effect relationship, but two interventional trials ended in the lack of interest of the TDM, although it is of current practice. However, numerous drug interactions may modify the plasma concentrations of valproate. The level of proof of the interest of the TDM for this

molecule was estimated in: recommended, although systematic TDM is not recommended, except in specific cases, such as pregnancy, concomitant treatments or suspected non-compliance [39].

As it was explained before, in the case on antibiotics, TDM of antiepileptic drugs, including phenobarbital, carbamazepine or valproate can be useful in complex physiological or clinical conditions such as pregnancy, elderly patients or those admitted in intensive care units [40-42].

According to the previous evidences, TDM for carbamazepine, phenobarbital and valproate in uncomplicated patients could be considered of “low” priority, while TDM of phenytoin could be classified as “high” priority (mainly because of the lack of evidence against this consideration).

2.4. Lithium

Less controversy exists regarding TDM of lithium. Lithium has a narrow therapeutic index, so its serum concentration should be carefully monitored and patients should be warned to report symptoms that might indicate their lithium dose requires reduction, such as unsteadiness, confusion, nausea, diarrhea or worsening tremor [5].

Recommendations from the Australian guidelines are that serum lithium concentration should be measured at least every 3–6 months after achieving a stable therapeutic concentration [5], although higher frequency is recommended by other authors [9].

2.5. Methotrexate

Methotrexate is an anti-cancer drug used to treat several malignancies including paediatric acute lymphoblastic leukaemia and choriocarcinoma, which remains a mainstay of therapy since its discovery in the early second half of the previous century, despite many therapeutic advances in oncology. Additionally, low-dose methotrexate is a gold standard antirheumatic drug in the treatment of rheumatoid arthritis, psoriasis, systemic scleroderma and other autoimmune disorders.

In their review, Flanagan *et al.* conclude that plasma concentration-effect relationships have been established for chemotherapy/immunosuppressant agents such as 5-fluorouracil (at a dose of 1 g m⁻² d⁻¹), 6-mercaptopurine, and methotrexate. In this section, the focus is methotrexate, and Flanagan wrote: “Interpretation is complicated by the use of different agents simultaneously” [9].

A brief review conducted by Silva *et al.* [43] concluded: “Because of the existence of a relationship between drug therapeutic outcome and its systemic concentration, TDM may ensure the effectiveness and safety of methotrexate use.

On the other hand, Le Guellec *et al.* [44] highlighted the documented toxicity associated with methotrexate and classified TDM of methotrexate as “recommended” according to the TDM classification of the Société Française de Pharmacologie et de Thérapeutique [10].

On the other hand, as it seems that there is no rationale for methotrexate TDM in the setting of low-dose toxicity [45], our proposal would be to consider it ‘moderate’ priority.

2.6. Cyclosporin

In their review, Flanagan *et al.* conclude that TDM of cyclosporin is well established, although they remark: “All is not straightforward, however, as some patients experience acute rejection episodes or post-operative complications despite blood concentrations within the reference range” [9].

Starting doses of cyclosporin are typically chosen on a calculated mg/kg bodyweight basis and, after initiation of treatment, doses are adjusted with TDM. Several authors provide dosing algorithms for adult and children patients, although they conclude: “Whether or not implementation of such algorithms will improve clinical outcome remains to be demonstrated” [46].

Taking into account the indications of use of cyclosporin, as well as the complexity of patients suitable to be treated with this drug, the recommendation for TDM of cyclosporin could be “moderate”.

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3. RECCOMENDATIONS

TDM should be considered a therapeutic tool. Although more indicated in several narrow therapeutic window medicines, more than associated with specific medicines, TDM should be considered within the framework of the rational prescribing process, in those patients that could benefit from it because of their physiological or clinical conditions, the presence of co-treatments which could produce drug-drug interactions, etc.

So, although it is possible to prioritize which medicines require TDM, the best option would be to recommend TDM for those patients that really would benefit from the results of monitoring its blood concentration. It is also very important to highlight that TDM is not just having a laboratory with the necessary tools to obtain plasma concentrations, but also to have specialists with enough expertise to interpret these results in the clinical context of each patient, as well as to have clinicians with expertise to adapt dosages to the results of TDM measures.

A review of the evidences published during the last five years for the 11 active ingredients proposed, showed the results described in the previous text and summarized in Table 3.1. below.

Table 3.1.- Summary of the TDM recommendation for each of the 11 proposed active ingredients.

WHO EML group	Drug		TDM?	Reference
Antibacterials	Aminoglycoside	amikacin	Monitoring is essential to achieve effective therapy while avoiding toxicity, particularly in infants, the elderly, the obese and patients with cystic fibrosis, if high doses are being used, for treatments longer than 5 days or if renal function is impaired. Value of monitoring: high	14, 47
		gentamicin		
	Glycopeptide	vancomycin	Indications for monitoring have been controversial, but there is definitely a role for monitoring in patients with poor renal function to achieve maximum effect with minimal toxicity, for treatments longer than 5 days. Value of monitoring: moderate	14
Anticonvulsants/ Antiepileptics Medicines used in bipolar disorders	Carbamazepine		Newly diagnosed epilepsy receiving monotherapy can be optimally treated without need for monitoring serum AED drug levels. Value of monitoring: low	2, 34, 37
	Phenobarbital		Newly diagnosed epilepsy receiving monotherapy can be optimally treated without need for monitoring serum AED drug levels. Value of monitoring: low	2, 34, 37
	Phenytoin		Value of monitoring: high	37
	Valproic acid		Newly diagnosed epilepsy receiving monotherapy can be optimally treated without need for monitoring serum AED drug levels. Value of monitoring: low	2, 34, 37
Medicines used in bipolar disorders	Lithium carbonate		Serum lithium concentration should be measured at least every 3–6 months after achieving a stable therapeutic concentration. Value of monitoring: high	5
Cytotoxic and adjuvant medicines	Methotrexate		Value of monitoring: moderate	9, 44, 45
Antiarrhythmic medicines Medicines used in heart failure	Digoxin		Clinical monitoring of heart rate and adverse effects may be more helpful than TDM. For some drugs, clinical monitoring may be more helpful than TDM and in all cases, it is imperative that drug concentrations are interpreted in the patient's clinical context. Value of monitoring: low	5
Immunosuppressive medicines	Cyclosporin		Value of monitoring: moderate	9, 46

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