

# Cost-effectiveness of therapeutic drug monitoring: an update

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## ABSTRACT

**Background:** There are a number of effective but highly toxic drugs that exhibit a narrow therapeutic index and marked inter-patient pharmacokinetic variability. Individualised therapy with such drugs requires therapeutic drug monitoring (TDM) in order to obtain the desired clinical effects safely. Cost-effectiveness analysis in health care is still at an early stage of development, especially for TDM.

**Study objectives:** To carry out a systematic review documenting studies which have addressed the cost-effectiveness of TDM.

**Methods:** The Cochrane database and Medline were searched. References identified by this approach were then searched manually for relevant articles.

**Results:** Very few studies have been performed that document the cost-effectiveness of TDM. Indeed TDM has only been demonstrated to be cost-effective for aminoglycosides and to a lesser extent for vancomycin, anti-epileptics and immunosuppressants. For the other classes of drugs that are monitored, there is a rationale behind the application of TDM but appropriate prospective cost-effectiveness analyses have not been performed.

**Conclusion:** Because there would be an increased risk of under- or overdosing if certain drugs are prescribed without the support of TDM, emphasis should not be placed solely on cost-effectiveness, but rather on how such interventions can be applied in the most cost-effective and clinically relevant manner.

## KEYWORDS

TDM, cost-effectiveness analysis, cost-benefit analysis

## INTRODUCTION

TDM, the measurement and interpretation of drug concentration measurements, has been used to individualise drug therapy since the early 1970s. In addition, application of pharmacokinetic principles – as part of TDM – has been used to assess drug behaviour. The aim of TDM is to opti-

mise pharmacotherapy by maximising therapeutic efficacy, while minimising adverse events, in those instances where the blood concentration of the drug is a better predictor of the desired effect(s) than the dose. The reasons why these principles have gained wide acceptance include:

- A better relationship, although imperfect, often exists between the effect of a given drug and its concentration in the blood, than between the dose of the drug and the effect.
- A recognition that inter-patient variability in the pharmacokinetic processes of drug absorption, distribution, metabolism and excretion results in a need for dosage individualisation.
- The development of reliable and relatively easy-to-use drug monitoring assays.

In addition, TDM can aid in diagnosis and management in cases in which compliance is in question. These cases are where:

- It is not clear if the right drug is being taken.
- Dosage adjustment is required because of drug-drug or drug-food interactions.
- Unintentional overdose is suspected.

TDM is more than simply the analysis of a single drug concentration in the blood of a patient and a report of this number. It also comprises interpretation of the value measured

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using the mathematical (pharmacokinetic) principles mentioned above, drawing the appropriate conclusions about the result and advising the physician who ordered the test how to optimise treatment. It is important to apply a uniform definition of TDM here, because different definitions have previously been used in cost-effectiveness studies and reviews of TDM. Consequently, comparisons have been made based on different approaches, which can influence the results. The International Association for Therapeutic Drug Monitoring and Clinical Toxicology has adopted the following definition: *Therapeutic drug monitoring is defined as the measurement made in the laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures. Commonly, the measurement is in a biological matrix of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as replacement therapy in an individual who is physiologically or pathologically deficient in that compound* [1].

Besides a definition of TDM, clear definitions of cost-effectiveness must be presented, because most of the older studies are driven by financial considerations. Useful definitions are:

**Cost-benefit analysis:** costs and benefits measured simultaneously in monetary units.

**Cost-effectiveness analysis:** costs and benefits measured simultaneously to obtain a specified objective, and in monetary units.

**Cost-utility analysis:** benefits measured in terms of quality of life, willingness to pay, and patient preference for one intervention over another.

**Cost-minimisation analysis:** costs analysed and compared when two or more interventions have been shown, or assumed, to be equivalent in terms of outcomes.

In recent years, TDM has developed a much more patient-oriented focus to include all the processes around drug therapy (patient response, adverse events, dosing information, timing of the taking of blood, pharmacokinetic behaviour, drug analysis, interpretation and dose adjustment). The pharmaceutical industry, in general, is not in favour of TDM because it is felt that it increases therapeutic complexity and drug-associated costs thereby raising barriers for the use of their drug. However, in some cases, well-conducted cost-effectiveness studies have shown the opposite. TDM is not a goal in itself, but aims to contribute to the therapeutic drug management process, in other words, patient safety. A change from the passive “monitoring” in the TDM acronym into (pro)active “management” has been advocated (Charles Pippingier, Department of Laboratory Medicine,

The Cleveland Clinic Foundation, Cleveland, Ohio, USA, personal communication).

There are several approaches to the evaluation of cost-effectiveness. In 1966, Donabedian proposed the structure – process – outcome-oriented method for the evaluation of the quality of health care [2]. Schumacher and Barr translated this method to TDM [3]. The structure component includes the total of laboratory facilities and personnel; the process component comprises the process of proper sampling, interpretation and intervention based on the results; and the outcome component comprises the clinical effect of the TDM intervention, including speed of recovery, number of adverse events, morbidity and mortality, as well as cost-savings of TDM. Schumacher and Barr identified the following categories for TDM cost-effectiveness analysis [3]:

- patient oriented
  - what percentage of patients treated with TDM did not experience adverse events?
- process oriented
  - what percentage of TDM blood samples was correctly drawn?
  - what percentage of TDM patients had serum concentrations that were within a predefined “therapeutic or target range”?

It is obvious that patient-oriented studies are to be preferred over process-oriented studies. In process-oriented studies, surrogate endpoints are used because of the lack of well defined and measurable clinical parameters.

An important factor in carrying out a cost-effectiveness analysis is the question of which costs and benefits are to be included in the model. Are only the direct costs calculated (e.g. human resources, materials, equipment, energy costs, maintenance) or are indirect costs included (i.e. costs associated with loss of productivity of the patient, the costs borne by relatives in supporting the patient, and healthcare costs associated with a longer life)? Benefits of TDM can be assessed in several ways. Differences in mortality, morbidity, duration of the hospital stay, duration of drug therapy, number of drug dosages and number of serum concentrations ordered can be costed and compared. Benefits can also be costed in natural units (e.g. costs per life year gained) or in qualys (quality-adjusted life years). With this latter technique, each year that is gained is also corrected for the quality of that extended life. It is evident that well-conducted cost-effectiveness studies need thorough pharmaco-economic expert support.

Most of the published cost-effectiveness research in TDM is process oriented, and many of these studies have been

summarised and discussed in an excellent review by Ensom and co-workers [4]. Recently, a paper has been published on behalf of the Cost-effectiveness Committee from the International Association for Therapeutic Drug Monitoring and Clinical Toxicology where cost effectiveness studies in TDM were reviewed and recommendations made [5]. From this paper and other reviews [4] it is clear that the majority of TDM cost-analysis studies have focused on the aminoglycoside antibiotics.

This review aims to update the existing information on the rationale and cost-effectiveness of TDM for different classes of drugs by using the method of a systematic review. For each class of drugs, information from the previous systematic review is summarised (for details and discussion on the evidence, please refer to our previous paper) [5] and new information is added if available.

## METHODS

The medical literature was searched (MedLine) for the indexed terms “cost-effectiveness” or “cost-benefit” or “pharmacoeconomics” and “therapeutic drug monitoring” or “drug analysis”. Studies found were selected for the categories “patient oriented” and “process oriented”. Reference lists of review articles were searched by hand for studies that were missed using the search terms.

Reviews and studies were rated according to the Canadian Task Force rating system [6]:

- A1. Systematic review containing several studies of A2 level and with consistent outcomes
- A2. Prospective randomised clinical trials of good quality
- B. Randomised clinical trials of moderate quality (e.g. too few patients), or other comparative trials (e.g. not randomised, cohort studies, case-control studies)
- C. Non-comparative trials
- D. Experts’ opinions (e.g. according to the authors)

A clinical trial was rated “good” if the study included the following components: a clear hypothesis, the presence of blinding, analysis of confounders, statistical power and sample size calculation, summary of patient characteristics, specification of data analysis methods and identification of sources of bias such as the number of patients lost for follow-up. In addition, a level of recommendation was assigned according to:

- 1. One systematic review (A1) or at least two independent trials of level A2
- 2. At least two independent studies of level B
- 3. One study of level A2, B or C
- 4. Experts’ opinions, e.g. according to the authors

For each drug class the review paragraph is summarised by a conclusion and a recommendation.

## Aminoglycosides

The success and continuing use of the aminoglycosides can be attributed to various factors, including a rapid concentration-dependent bactericidal effect, clinical efficacy, synergism with  $\beta$ -lactam antibiotics, a low rate of true resistance and low costs. Aminoglycosides are the prototype drugs for TDM. Since the publication of our paper [5], Bond and Raehl published a paper on clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy [7]. The study was part of a National Clinical Pharmacy Services study [8]. In hospitals that did not have pharmacist-managed aminoglycoside or vancomycin therapy, death rates were 6.7% higher, length of stay was 12.3% higher, total charges were 6.3% higher, hearing loss was 46.4% higher, renal impairment was 34.0% higher and the death rate in patients who developed complications was 10.2% higher than in hospitals with pharmacists managing these drugs. All differences were statistically significant. These data are consistent with a Dutch cost-effectiveness study comparing standard of care with a population model-based TDM approach for aminoglycoside dosing that showed both cost-effectiveness and reduced mortality [9]. Panel 1 shows a summary of our findings indicating that TDM of aminoglycosides is proven cost-effective.

### Panel 1: Conclusion and recommendation on cost-effectiveness with respect to aminoglycosides

Conclusion (level 1): TDM of aminoglycosides leads to a reduction of side effects (A2) [9], (A2) [10], (B) [7].

Conclusion (level 2): TDM of aminoglycosides leads to a reduction of mortality (A2) [9], (B) [7], (B) [11].

Conclusion (level 1): TDM of aminoglycosides is cost-effective (B) [7], (B) [11], (B) [12], (A2) [13], (A2) [9].

Recommendation: it is recommended that aminoglycoside therapy is guided by TDM.

Note: All cost-effectiveness studies reviewed here have been performed before the introduction of extended interval dosing.

## Vancomycin

Vancomycin is considered to be less nephrotoxic than the aminoglycosides. Nevertheless, a relationship seems to exist between serum concentrations and both toxicity and efficacy [14]. Since the systematic review of Touw et al. [5], Bond and Raehl published their study on the clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy [7]. A limitation of this study is that aminoglycosides and vancomycin were analysed together, which is not

logical because of the different efficacy and safety profile of vancomycin. Consequently, no separate conclusions for vancomycin can be drawn except those for the group as a whole. Panel 2 shows a summary of our findings indicating that for some populations, TDM of vancomycin is proven cost-effective.

#### Panel 2: Conclusion and recommendation on cost-effectiveness with respect to vancomycin

Conclusion (level 2): TDM of vancomycin results in reduced nephrotoxicity (B) [7], (A2) [15].

Conclusion (level 2): TDM is cost-effective in selected patient populations: oncology patients; intensive care unit patients and patients treated with other nephrotoxic drugs (A2) [14], (B) [16], (B) [7].

Recommendation: it is recommended that vancomycin therapy is guided by TDM in patient populations at risk, such as ICU patients, oncology patients and patients receiving concomitant nephrotoxic medicines.

#### Classical anti-epileptic drugs

Since the 1960s, therapy with classical anti-epileptic drugs (phenobarbital, phenytoin, carbamazepine, primidone, valproic acid) has been guided by TDM in Europe and in the US. However, well-conducted, patient-oriented studies on the cost-effectiveness of TDM for anti-epileptic drugs are lacking. In addition, there are conflicting views on the need to use TDM to optimise therapy. The need to monitor phenytoin, phenobarbital and carbamazepine seems clear for pharmacokinetic reasons, but there is less support for the routine monitoring of valproic acid and primidone. For the modern anti-epileptic drugs (oxcarbazepine, gabapentin, lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide), there are no studies that have investigated the rationale for or cost-effectiveness of TDM. Concentration-effect studies are scarce and concentration-effect relationships that have been described were established in retrospective studies [16]. Nevertheless, for a number of new anti-epileptic drugs, pharmacokinetic parameters differ greatly between individuals and analysis of the serum concentration can be helpful if a patient is difficult to control, to document at what drug concentration a patient responds, or where there are drug-drug interactions [16]. Recently, Bond and Raehl analysed data from the 1995 National Clinical Pharmacy Services Study [8] where they investigated associations between pharmacist-managed anti-epileptic therapy (including ordering drug concentration measurements and adjusting the dose based on interpretation of that measurement) and outcomes such as death rate, length of

hospital stay, medical charges, drug charges, laboratory charges, complications and adverse drug reactions [17]. In hospitals without pharmacist-managed anti-epileptic drug therapy, death rates were 121% higher, length of stay was 14.7% higher, medical and laboratory charges were higher and aspiration pneumonia rate was higher. These differences were all statistically significant. No differences were investigated between the types of anti-epileptic drug that were monitored. Because this pharmacist management is largely supported by TDM of anti-epileptic drugs, one may conclude that TDM is beneficial. Moreover, this study clearly demonstrates the advantages of integrated therapy management. Panel 3 shows a summary of our findings.

#### Panel 3: Conclusion and recommendation on cost-effectiveness with respect to anti-epileptic drugs

Conclusion (level 2): TDM of anti-epileptic drugs leads to better control of epileptic patients with fewer side effects (B) [18], (B) [17].  
Conclusion (level 2): TDM of the anti-epileptic drugs can be cost-effective (B) [18], (B) [17].

Recommendation: it is preferable that therapy with anti-epileptic drugs is guided by TDM.

#### Theophylline

Theophylline used to have an important place in the treatment of asthma in the western world. At present, it is used principally in the treatment of chronic obstructive pulmonary disease. There are no published studies on the cost-effectiveness of TDM of theophylline. However, there is a clear relationship between theophylline concentrations and therapeutic and toxic effects [19, 20]. In addition, its pharmacokinetics show large inter-individual variability, and theophylline is very sensitive to drug-drug interactions mediated by CYP1A2, its main metabolic pathway. Based on these considerations, TDM of theophylline is rational. Panel 4 shows a summary of our findings.

#### Panel 4: Conclusion and recommendation on cost-effectiveness with respect to theophylline

Conclusion (level 3): in view of the large inter-individual variability in theophylline pharmacokinetics, TDM is of help in optimising treatment (B) [21], (D) [authors' opinions].  
Conclusion (level 4): TDM of theophylline can be cost-effective (D) [21].

Recommendation: TDM of theophylline therapy can be helpful.

#### Caffeine

Caffeine is used in neonates with apnoea associated with

bradycardia and/or decreased oxygen saturation. Although caffeine is frequently monitored, there are no studies that have investigated the cost-effectiveness of routine caffeine monitoring in neonates. In an attempt to establish an association between caffeine serum concentrations and clinical efficacy, Keijer et al. retrospectively studied the number of apnoea attacks in relation to caffeine TDM results [22]. No straightforward relationship between caffeine serum concentrations and the number of apnoea events could be demonstrated. However, the authors commented that the retrospective nature of the study had probably had a negative influence on the registration of apnoeic periods. A recent study, conducted by Natarajan et al., demonstrated no difference in median and interquartile concentrations of caffeine in neonates who responded to therapy and those who did not respond to therapy when treated for apnoea [23]. To conclude, from retrospective analyses carried out so far, there is no strong evidence for a straightforward concentration-effect relationship of caffeine in neonates with apnoea. One may thus argue that TDM will be of limited value. Panel 5 shows a summary of our findings.

**Panel 5: Conclusion and recommendation on cost-effectiveness with respect to caffeine**

Conclusion: based on the present data, the rationale for caffeine TDM cannot be established in neonates with apnoea.

Recommendation: more studies are needed before a conclusion can be drawn on the rationale for TDM in neonates with apnoea.

**Digoxin**

Digoxin is predominantly used in the treatment of atrial fibrillation but there are no published studies that document the cost-effectiveness of TDM of digoxin in this condition. Criteria for ordering a digoxin serum concentration have been published recently [24]. For use in atrial fibrillation, digoxin can be titrated until sinus rhythm is achieved and the serum level (or as some authors say, the peripheral compartment level [25]) serves as the concentration at which the individual patient responds to therapy. In cardiac failure, a post-hoc analysis of the DIG study [26] demonstrated a positive effect of digoxin on mortality in males with serum concentrations ranging from 0.5-0.8 mcg/L [27]. If this observation can be confirmed in a prospective study, then TDM of digoxin is warranted because of its very narrow target range, large inter-

individual variability in pharmacokinetics and potential for drug-drug interactions. Panel 6 shows a summary of our findings.

**Panel 6: Conclusion and recommendation on cost-effectiveness with respect to digoxin**

Conclusion (level 4): in atrial fibrillation, TDM of digoxin may be of use (D) [authors' opinions].

Conclusion (level 3): in cardiac failure, TDM of digoxin is useful (B) [27].

Recommendation 1: in atrial fibrillation it can be clinically useful to document the digoxin serum concentration after titrating the patient with digoxin until the heart rate is controlled.

Recommendation 2: when digoxin is used in cardiac failure, it can be useful to use serum concentration measurements to guide digoxin therapy.

**Immunosuppressants**

Immunosuppressants are used to prevent acute and chronic organ rejection following transplantation. For ciclosporin, tacrolimus and sirolimus, blood concentration ranges have been established that give the least chance of rejection with acceptable side-effect profiles [28]. Current immunosuppressants all exhibit large inter- and intra-patient variability in pharmacokinetics and in several concentration-controlled trials it has been demonstrated that the blood concentration is a better predictor of clinical efficacy than dose [29]. From this perspective, the immunosuppressants are ideal candidates for TDM. As it has been clearly established that TDM increases the chance of one-year survival of a transplanted kidney from 60% to 95% [29], a randomised study that investigates

**Panel 7: Conclusion and recommendation on cost-effectiveness with respect to immunosuppressants**

Conclusion (level 4): because of a shortage of donor organs and costs associated with rejection of a transplant, immunosuppressants must be monitored. There is a wide inter-individual pharmacokinetic variability and risk of drug-drug interactions, therefore TDM of immunosuppressants is required (D) [authors' opinion].

Conclusion (level 2): TDM of immunosuppressants is cost-effective (B) [30], (B) [31].

Recommendation: therapy with immunosuppressants must be guided by TDM.

the cost-effectiveness of TDM versus no monitoring in transplant patients would be ethically unacceptable. Recent studies have indicated that C2 monitoring leads to a further reduction of acute rejection and graft loss compared with trough level monitoring alone, and model studies have demonstrated that C2 monitoring is more cost-effective than trough level monitoring [30, 31]. The next step should be to establish the cost-effectiveness of abbreviated AUC (area under the curve) measurements that are currently gaining popularity. Studies that investigate the superiority of abbreviated AUC monitoring over the traditional TDM are ongoing. Panel 7 shows a summary of our findings.

### Psychiatric drugs

There are no published studies on the cost-effectiveness of TDM for psychiatric drugs. Only for a few psychiatric drugs (lithium, imipramine, desipramine, nortriptyline, haloperidol and clozapine) has a relationship been described between serum concentration and efficacy or toxicity [32-35]. Many psychiatric drugs are substrates for CYP2D6, CYP2C9 and/or CYP2C19, resulting in highly variable pharmacokinetics because of genotype. Furthermore, drug-drug interactions are most likely. It is recommended that the serum concentration associated with a patient's best response is documented so that if drug-drug interactions occur, the dose can be titrated accordingly.

A recent study demonstrates that the metabolic ratio of desmethylsertraline/sertraline (DSER/SER) can be used to identify noncompliance over a larger time window than the assay of a serum concentration of the parent drug alone [36]. The reason for this is that desmethylsertraline has a longer half-life than sertraline. The inter- as well as intra-individual variability of the ratio of DSER/SER is remarkably low

and ratios outside the mean  $\pm 2$  standard deviation could be regarded as non-compliance. This extra information from a serum concentration assay can be used as a discussion point with the patient when non-compliance is suspected. In principle, the same methodology could be applied with other antidepressants with metabolites, such as amitriptyline, nortriptyline, venlafaxine. Panel 8 shows a summary of our findings.

### Anti-retroviral drugs

With the introduction of the protease inhibitors and nucleoside and non-nucleoside reverse transcriptase inhibitors, the prognosis of HIV-positive patients has improved dramatically. Because poor compliance is the main cause of failure with HIV therapy, TDM can contribute to a greater chance of success in the long term. In 2003, Gerber and Acosta published their review on TDM in the treatment of HIV infection [38]. They reviewed four prospective randomised clinical trials investigating the effect of concentration-targeted HIV therapy versus fixed dose. The trials reviewed were the ATHENA trial, investigating nelfinavir and indinavir, the PharmAdapt trial, investigating protease inhibitors, the trial by Fletcher et al. investigating zidovudine, lamivudine and indinavir, and the GENOPHAR trial, investigating protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Their conclusion was that "...TDM may be useful in specific situations (not specified which situations) and may eventually play a prominent role, but currently there are not enough data to broadly recommend its use ...". For monitoring of HIV drugs, not only the concentration of the drug is interesting, but the genotypic inhibitory quotient (GIQ), which integrates drug resistance and drug concentration, can be useful. In addition, Valer et al. published a study on the impact of amprenavir drug level monitoring and the virological response in amprenavir/ritonavir fixed-dose-based salvage regimens [39]. They measured amprenavir trough levels and calculated GIQ. Patients with viral response had

#### Panel 8: Conclusion and recommendation on cost-effectiveness with respect to psychiatric drugs

Conclusion (level 1): TDM is clinically useful for lithium, nortriptyline, desipramine, imipramine, haloperidol and clozapine (A1) [32], (C) [35], (C) [37].

Conclusion (level 3): TDM of sertraline can be of use in questions of compliance and drug-drug interactions (B) [36].

Conclusion (level 4): for the other psychiatric drugs, TDM can be of use in questions of compliance and drug-drug interactions (D) [authors' opinions].

Recommendation: although cost-effectiveness has not been proven, therapy with lithium, nortriptyline, desipramine, imipramine, haloperidol and clozapine should be guided using TDM.

#### Panel 9: Conclusion and recommendations on cost-effectiveness with respect to HIV drugs

Conclusion (level 3): TDM of nelfinavir is useful (A2) [40].

Conclusion (level 3): TDM of the other protease inhibitors and non-nucleoside reverse transcriptase inhibitors can be useful (C) [41], (C) [42].

Recommendation 1: nelfinavir therapy must be guided by TDM.  
Recommendation 2: TDM can be useful to guide therapy of the other protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

higher values of GIQ than non-responders, although the difference was not significant. They conclude that HIV genotyping but not drug levels could be helpful to predict which patients would benefit from amprenavir/ritonavir rescue therapy. It would have been interesting, when they had increased the dose based on GIC, if they had examined its effect on viral response. Panel 9 shows a summary of our findings.

### Antimycotic drugs

Antimycotic drugs can be divided into the polyene antimycotics, echinocandins, antimetabolites and azole antimycotics. The polyenes, flucytosine and the azole antimycotics will be discussed.

Amphotericin B is a most lipophilic polyene drug with broad-spectrum antifungal activity. It has been used for decades as the treatment of choice for invasive candidiasis. Unfortunately, it is poorly tolerated. No studies are known that relate efficacy to clinical effect or toxicity. Nephrotoxicity is related to male gender, body weight >90 kg, chronic renal disease, simultaneous use of other nephrotoxic drugs and dose [43].

The systemically-used azole antimycotics at present comprise fluconazole, itraconazole, voriconazole and posaconazole. Fluconazole is well absorbed with a high bioavailability. Oral doses should be halved in patients with creatinine clearance less than 50 mL/min and reduced by 75% if clearance is less than 20 mL/min because high concentrations of fluconazole are associated with neurological side effects [44]. Given the highly predictable pharmacokinetics, TDM of fluconazole is not usually necessary. In contrast, itraconazole is poorly absorbed with a bioavailability that is highly dependent on food. Furthermore, its pharmacokinetics vary with co-administration of enzyme-inducing and enzyme-inhibiting drugs. A relationship between total blood concentrations above 0.5 mg/L and antifungal efficacy was demonstrated in post-marketing data analysis which supports the monitoring of blood levels during therapy [45]. It is even better to target free concentrations above the minimum inhibitory concentration for a substantial time of the dosing interval [46, 47]. Voriconazole has an oral bioavailability of 60-100% and is hepatically metabolised by CYP2C19, an isoenzyme that displays genetic polymorphism with poor and ultra-rapid metabolisers. Metabolism is further affected by enzyme-inducing and enzyme-inhibiting co-administered drugs. There are many retrospective studies that suggest that low levels of voriconazole are associated with a higher failure rate and high levels of voriconazole are associated with neurological and ocular adverse events [48-50]. Given the high

variability of systemic availability together with potential for drug-drug interactions, monitoring can be helpful in life-threatening situations. Cost-effectiveness, however, has not been assessed. Posaconazole is a new azole with broad-spectrum activity. The hepatic pathway differs from itraconazole and voriconazole: glucuronidation plays a major role in its elimination whereas enzymes of the CYP system are insignificant. Oral bioavailability may vary but increases with food. At present, there are no data to support the use of TDM to guide therapy. Panel 10 shows a summary of our findings.

#### Panel 10: Conclusion and recommendations on cost-effectiveness with respect to antimycotic drugs

Conclusion: there is no evidence that TDM of amphotericin B is useful.

Conclusion (level 3): TDM of voriconazole is useful (C) [46], (C) [47], (C) [48].

Conclusion (level 3): TDM of itraconazole can be useful (C) [45].

Recommendation 1: voriconazole therapy must be guided by TDM.

Recommendation 2: TDM can be useful to guide therapy of itraconazole.

### CONCLUSIONS

There is still a paucity of well-conducted studies investigating the added value and cost-effectiveness of TDM. The importance and cost-effectiveness of TDM is well described for aminoglycosides and to a lesser extent for vancomycin, anti-epileptic drugs and immunosuppressant drugs.

For therapy with theophylline, digoxin, psychiatric and some antifungal drugs, TDM is considered as a standard of care despite the lack of formal cost-effectiveness data. Without TDM, many of these drugs could not be used effectively and there would be risks of either underdosing or serious toxicity. Antiretroviral agents and antifungals have been identified as new areas for TDM with a proven positive effect when TDM is used for some of these drugs.

The clinical efficacy of TDM is strongly associated with appropriate pharmacokinetic interpretation and is reflected in individualised dosing recommendations being provided to the clinicians who order the drug concentration tests. "Numbers only" TDM services that provide test results without appropriate interpretation and recommendations can be misleading and do not use what we already know about drug concentration-time profiles and behaviour. Such TDM

services will predominantly generate costs without gaining great clinical benefits. With the incorporation of sound recommendations to clinicians ordering drug assays, TDM has already proved its added value in well-conducted studies.

A recent US survey of outpatients receiving long-term therapy with drugs having a narrow therapeutic index demonstrated that 50% or more of patients receiving digoxin, theo-

phylline, procainamide, quinidine or primidone were not monitored, and 25-50% of patients receiving valproic acid, carbamazepine, phenobarbital, phenytoin or tacrolimus were not monitored [51]. Regarding the benefits that can be gained in terms of reduction of mortality, morbidity and increase in medication safety, one should question whether money should be spent on either proving the cost-effectiveness of TDM or on increasing the effectiveness of TDM.

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