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Therapeutic drug monitoring of antimicrobials

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Optimizing the prescription of antimicrobials is required to improve clinical outcome from infections and to reduce the development of antimicrobial resistance. One such method to improve antimicrobial dosing in individual patients is through application of therapeutic drug monitoring (TDM). The aim of this manuscript is to review the place of TDM in the dosing of antimicrobial agents, specifically the importance of pharmacokinetics (PK) and pharmacodynamics (PD) to define the antimicrobial exposures necessary for maximizing killing or inhibition of bacterial growth. In this context, there are robust data for some antimicrobials, including the ratio of a PK parameter (e.g. peak concentration) to the minimal inhibitory concentration of the bacteria associated with maximal antimicrobial effect. Blood sampling of an individual patient can then further define the relevant PK parameter value in that patient and, if necessary, antimicrobial dosing can be adjusted to enable achievement of the target PK/PD ratio. To date, the clinical outcome benefits of a systematic TDM programme for antimicrobials have only been demonstrated for aminoglycosides, although the decreasing susceptibility of bacteria to available antimicrobials and the increasing costs of pharmaceuticals, as well as emerging data on pharmacokinetic variability, suggest that benefits are likely.

Introduction

Maximizing the effectiveness whilst minimizing the toxicity of antimicrobial agents is an essential step in the treatment of infections. Adequate control of the source of infection is also important. However, maximizing efficacy and minimizing toxicity requires an understanding of the pharmacokinetics (PK) of the prescribed antimicrobial and the susceptibility of the causative bacterial pathogen [1]. In the context of high morbidity and mortality associated with some patient populations [2–4], as well as escalating resistance to antimicrobials [5] and increased cost of pharmaceuticals, methods to optimize antimicrobial use should be considered. The aim of this manuscript is to review the place of therapeutic drug monitoring (TDM) in the use of antimicrobial agents and discuss the issues regarding analysis of these drug concentrations. We will focus on the role of TDM in optimizing antimicrobial dosing for patient populations with variable pharmacokinetics, such as the critically ill and obese. Discussion of the role of TDM of antifungals, antiparasitics and antiviral agents is beyond the scope of this paper, although other reviews for these agents are available [6, 7].

Therapeutic drug monitoring can be used to both maximize the efficacy and minimize the toxicity of antimicrobial therapy for individual patients. In this context, TDM is used to personalize dosing to attain antimicrobial exposures associated with a high probability of therapeutic success, and suitably low probabilities of toxicity and generation of antimicrobial resistance [8, 9]. Whilst most commonly employed for drugs with a narrow therapeutic range, the desire to use TDM is increasing because of the increasing number of patients in groups for whom PK has not been clearly studied (e.g. critically ill, significant comorbidities, elderly and extremes of body size), as well as the decreasing susceptibility of pathogens, which may require higher antimicrobial doses to maximize effect [9, 10].

Over the last 30 years, a significant body of research has emerged to inform researchers and clinicians about the concentration–effect relations for antimicrobials [11, 12].

Table 1
Pharmacodynamic index correlated with maximal efficacy of selected antimicrobials

Pharmacodynamic index	$f\,T_{>MIC}$	C_{max}/MIC	AUC_{0-24}/MIC
Antimicrobials	β-Lactams	Aminoglycosides	Fluoroquinolones
	Carbapenems	Metronidazole	Aminoglycosides
	Linezolid	Fluoroquinolones	Azithromycin
	Erythromycin	Telithromycin	Tetracyclines
	Clarithromycin	Daptomycin	Glycopeptides
	Lincosamides		Tigecycline
			Linezolid

$f\,T_{>MIC}$, time dependent antimicrobials; C_{max}/MIC, concentration-dependent antimicrobials; AUC_{0-24}/MIC, concentration-dependent antimicrobials with time dependence.

Reproducing these concentrations in patients should lead to optimized antimicrobial effect. An understanding of the relevance of antimicrobial concentrations is thus helpful in the interpretation of these concentrations obtained as part of a TDM process.

To be appropriate for TDM, a drug must ideally satisfy the following factors.

- Drug factors (must have all of these): large between-subject variability; small therapeutic index; an established concentration–effect (or toxicity) relationship (or both); and where the therapeutic response is not obvious.
- Patient factors (any of these): suspected drug interactions; suspected drug adverse effects/toxicity; suspected drug abuse; unexplained failure of therapy; and suspected noncompliance.

For antimicrobials generally, the increasing understanding of the concentration–effect relationship [11] has meant that TDM can be used not only to minimize potential toxicities, but also to increase the effectiveness of treatment. However, considering the factors listed above, benefits of TDM will manifest mostly for drugs with large PK variability. For antimicrobials not typically associated with TDM, e.g. β-lactams, TDM is most likely to be beneficial in patient populations with profound PK variability.

Pharmacokinetics and pharmacodynamics of antimicrobials

Pharmacokinetics is the study of the relationship between dose administered and concentration observed in body fluids and tissues. Pharmacodynamics, in contrast, is the study of the relationship between concentration and effect or, in the case of antimicrobials, the ability to kill or inhibit bacterial growth. It follows that PK/PD is the study of the relation between dose and effect, with concentration as an important variable [11].

Antimicrobials can be classified by various PK/PD indices that describe their efficacy. These include: (i) time-dependent antimicrobials, whose efficacy is related to the time for which the free, or unbound, antimicrobial concentration is maintained above a certain threshold, typically the minimum inhibitory concentration (MIC; $f\,T_{>MIC}$); (ii) concentration-dependent antimicrobials, whose efficacy is related to the ratio of the peak concentration during a dosing interval and the MIC (C_{max}/MIC); and (iii) concentration-dependent antimicrobials with time dependence, whose efficacy is related to the ratio of the area under the concentration–time curve (AUC) of the unbound drug from 0–24 h and the MIC (AUC_{0-24}/MIC). Examples of antimicrobials in these classes are shown in Table 1.

Therapeutic drug monitoring or target concentration intervention?

Target concentration intervention has been proposed as an alternative strategy to TDM. Target concentration intervention is suggested to enable more accurate dose adjustment because it uses all relevant data on the patient and disease [13]. Such an approach would certainly provide the aforesaid advantages over TDM, although data quantifying the microbiological killing effects of a range of concentrations of an antimicrobial are not available at present, which limits the potential of such an approach. Furthermore, as is the case for Bayesian-based TDM software, many centres appear not to have the infrastructure or expertise to maximize use of this promising concept. More research is suggested so that the potential advantages of target concentration intervention over TDM can be measured. We recommend readers to review the work of Holford and others on this area [13, 14].

Therapeutic drug monitoring: the importance of PK

For many antimicrobials, patient populations will have 'predictable' PK, whereby an antimicrobial dose recommended by the product information will reliably achieve a target

concentration range. However, some patients, such as the critically ill, may have pathology that results in physiological changes and therefore in altered PK behaviour. This topic has previously been discussed in detail elsewhere [15, 16]. Suffice to say that increased or decreased drug clearances [17–20], as well as altered volumes of distributions [21], are common in some patient groups, making drug exposure difficult to predict. It follows that for a clinician working with such patients, choosing an antimicrobial dose that will confidently achieve a target drug exposure is challenging.

Therapeutic drug monitoring: the importance of the MIC

The MIC is a central component of the PK/PD of antimicrobials. As defined in each of the PK/PD indices, the MIC is the denominator and therefore defines the PK exposure required to achieve the target PK/PD ratio. The importance of increasing the PK exposure relative to the MIC of the pathogen is illustrated by the fact that MICs are reported in multiplication factors of two and therefore with each level of decreased susceptibility (e.g. MIC increase from 1 to 2 mg l^{-1}), a doubling of the PK component is required to maintain the target PK/PD ratio. For example, when prescribing gentamicin, a target C_{max}/MIC ratio of 8–10 is suggested [11]. Therefore, if a bacterial pathogen is isolated and determined to have a MIC of 0.5 mg l^{-1}, then a C_{max} of 5 is suggested. However, if the MIC is determined to be 1 mg l^{-1}, then a C_{max} of 10 mg l^{-1} is suggested to achieve the optimal PK/PD ratio. The consequences of this effect of decreasing susceptibility on the likelihood that a different dosing strategy will achieve a PK/PD target are often presented in the form of 'probability of target attainment' graphs.

Therapeutic drug monitoring: the relevance of antimicrobial toxicity

An enduring and highly relevant utility of TDM is to ensure that dosing does not result in high drug exposures likely to result in patient harm through drug toxicity. Therapeutic drug monitoring allows dose decreases when unnecessarily high exposures are measured, minimizing the likelihood of adverse effects (e.g. β-lactams and seizures). The following sections provide a discussion on TDM for specific antimicrobial classes, listing the targets associated with efficacy, as well as the toxicities that may be minimized with use of TDM.

Antimicrobial classes

Aminoglycosides

Therapeutic drug monitoring of aminoglycosides (e.g. gentamicin, tobramycin and amikacin) has become standard clinical practice. Whilst the purpose of this was initially to minimize toxicities, increasingly the dosing regimens and TDM targets are specified to maximize efficacy.

Aminoglycosides are small, hydrophilic molecules with a volume of distribution similar to extracellular fluid volume and clearance proportional to glomerular filtration rate [22]. Alterations in volume of distribution can be very large in conditions leading to unstable or unknown fluid balances (e.g. sepsis of burn injuries), resulting in a reduced peak concentration if the dose is unchanged [23]. With concentration-dependent antimicrobials, an increased volume of distribution will reduce the ability of a prescribed dose to achieve a target C_{max}. To confirm that a larger dose does achieve the optimal target, TDM can be performed by sampling 30 min after the end of the intravenous infusion [24]. A C_{max}/MIC ratio of 8–10 should be targeted, with the precise C_{max} guided by known MIC data or by local antibiogram data.

Many unwell patients have impaired renal function. If the dose is not adjusted, reduced aminoglycoside clearance will predispose to toxicities (e.g. nephrotoxicity or ototoxicity). In such cases, an extension of the dosing frequency is suggested. Other patients, e.g. burns patients, may develop augmented renal clearances and enhanced aminoglycoside clearances, which may suggest the need for an incrementally shortened dosing frequency [1, 20]. In any event, the dosing interval should seek to maximize use of the aminoglycoside postantimicrobial effect [24].

How to monitor aminoglycoside antimicrobials The widespread use of once-daily dosing of aminoglycosides means that monitoring of C_{max} has become redundant because most once-daily doses will achieve therapeutic targets. Monitoring of C_{max} would only be necessary where the patient has a volume of distribution that is significantly different from 'normal' patients. Therefore, C_{max} monitoring of critically ill, obese and burns patients might be reasonable.

To ensure that reasonable clearance is occurring, it has been suggested that concentrations are taken anywhere from 6 h postdose to trough concentrations. For once-daily dosing, trough concentration monitoring may not be useful in some patients, who may have undetectable concentrations. For dosing every 36 or 48 h in renal dysfunction, trough concentration monitoring is suggested to ensure that redosing does not risk toxicities. Various nomograms have been developed to aid dosing, including the Sawchuk and Zaske [25], MacGowan and Reeves [26], Begg [27] and Nicolau [28] nomograms. The relative merits of these approaches are discussed by Begg and Barclay [29]. However, it is noted that some patients are underdosed with the Begg and the Australian Therapeutic Guidelines nomogram [30, 31] and others potentially overdosed (Nicolau nomogram) [32, 33]. As a result of this, and the fact that computer facilities are available at many institutions, use of freely available Bayesian adaptive feedback software

(e.g. http://www.tciworks.info) has been recommended where skilled clinical pharmacists or pharmacologists are available [34]. Such software can facilitate achievement of C_{max}/MIC ratios of 8–10 and AUC_{0-24} targets of 70–120 mg h l^{-1}, which have been proposed by some authors [35, 36]. Bayesian software includes a population pharmacokinetic model describing the covariates descriptive of altered pharmacokinetic parameters in patients. As TDM data from the individual patient are included, the software is able to confirm the likely parameters in the individual patient and therefore provide accurate dosing recommendations that can achieve therapeutic PK/PD targets.

The impact of aminoglycoside TDM, however, is best noted in its improvement in health outcomes. The clinical relevance of aminoglycoside TDM has been investigated in a comparative multicentre study of a 'standard' TDM strategy *vs.* an 'active' TDM strategy in 232 hospitalized patients [37]. The 'active' TDM strategy used PK dosage optimization at the start of treatment, subsequent Bayesian adaptive control and ongoing patient follow-up. The 'standard' TDM strategy used attending physician dosing and utilized TDM on request only. The results of this study showed that the 'active' TDM strategy resulted in shorter hospitalization and reduced nephrotoxicity. Although the authors could not describe statistical significance for reduced mortality ('active' group 9% *vs.* 'standard' group 14%), a strong trend was present.

Assaying aminoglycosides Assays supporting TDM of the aminoglycosides are well established and are the subject of limited, if any, contention in the scientific literature. Current immunoassay methods for the aminoglycosides remain highly appropriate [38].

Glycopeptides

The glycopeptide class of antimicrobials includes vancomycin and teicoplanin. Vancomycin, in particular, is widely used, and TDM is commonly employed. Teicoplanin is used less and is also subject to TDM less frequently, probably because there are fewer data correlating concentration with improved outcome.

The data correlating vancomycin exposure with clinical outcome are strong. In a retrospective evaluation of hospitalized patients, Moise-Broder *et al*. [39] evaluated the relation between AUC_{0-24}/MIC and outcomes in patients with meticillin-resistant *Staphylococcus aureus* pneumonia and suggested that an AUC_{0-24}/MIC ratio >400 was associated with improved clinical outcomes and correlated with more rapid eradication of the bacteria. This target is also endorsed by professional societies [40, 41]. Although AUC_{0-24} is not routinely monitored in clinical practice, Jeffres *et al*. [42] have shown that trough concentrations are well correlated with AUC_{0-24} and thus are regarded as an appropriate surrogate measure and a more practical method to monitor vancomycin dosing [40, 43]. Many authors have shown the difficulty of achieving these target concentrations using twice-daily dosing in critically ill patients [44, 45]. Furthermore, it has been suggested that commencing therapy with a standard 1 g daily may not be appropriate and that loading doses up to 35 mg (kg bodyweight)$^{-1}$ should be considered for rapidly achieving concentration targets [41, 46].

An alternative method for administering vancomycin is by continuous infusion [47], with most data suggesting equivalence with intermittent dosing [48], and only one study showing a trend to improved clinical outcome with continuous infusion [49].

How to monitor glycopeptides Monitoring of vancomycin peak concentration is no longer considered necessary given the strong correlation between trough concentrations and AUC_{0-24}/MIC. For intermittent dosing, a trough concentration of 15 mg l^{-1} will result in an AUC_{0-24} >400 mg h l^{-1} and is therefore a suitable target for vancomycin-susceptible meticillin-resistant *Staphylococcus aureus*, which commonly has an MIC of ~1 mg l^{-1}. For continuous infusion, a steady-state concentration of ~17–20 mg l^{-1} has an AUC_{0-24} of 400–480 mg h l^{-1}. Each of these approaches will achieve optimal vancomycin exposures in blood, although the poor penetration of vancomycin into some tissue sites (e.g. lung or cerebrospinal fluid) means that higher concentrations may be empirically targeted as a method to potentially maximize penetration [50]. The most rigorous method for optimizing dosing would be to use Bayesian software as previously described [51]. Finally, where vancomycin concentrations are not available in a timely manner, creatinine clearance data can be used with nomograms as a surrogate dose-adjustment method [52–54]. Although vancomycin-induced nephrotoxicity is reported to occur in only 5% of patients and is reversible, increasing target concentrations may mean that TDM can serve to minimize such toxicity [55–57].

Although less research has been conducted into teicoplanin TDM, the present approach is to monitor concentrations to ensure patients achieve therapeutic trough concentrations (defined as >10 mg l^{-1}, or 15–20 mg l^{-1} for endocarditis) [58]. A retrospective analysis of a large database from Harding and colleagues suggests that achieving target trough concentrations >10 mg l^{-1} is likely to result in improved clinical outcomes [59]. Importantly, aggressive loading dosing of teicoplanin is required in critically ill patients, with 6 mg kg^{-1} loading doses every 12 h for 36–48 h recommended to ensure rapid achievement of therapeutic concentration [60, 61]. Toxicity is considered less likely with teicoplanin than vancomycin [58].

Assaying vancomycin Both immunoassay and high-performance liquid chromatography (HPLC) methods have been reported for vancomycin. Immunoassay provides the advantage of enabling a faster reporting of results, which may be advantageous in some clinical scenarios [62, 63].

Assaying teicoplanin Several reports compare various methods (e.g. microbiological assay [64], solid phase enzyme receptor assay [64], fluorescence polarization immunoassay [65] and HPLC), resulting in a somewhat confusing picture. In this context, each method displays good correlations, which are interpreted as acceptable irrespective of slope and standard error values, which may suggest that the assays are not optimal. Our suggestion is that use of a reference method such as HPLC should probably be preferred.

β-Lactams

β-Lactam TDM has not been widely investigated because of the wide therapeutic window associated with these antimicrobials. However, PK variability can be huge with this family, a fact that has been well described in critically ill, obese, burns and febrile neutropaenic patients, as well as in those with renal dysfunction. Unless poorly susceptible organisms are present, then these are the only populations likely to benefit from TDM.

The targets for β-lactam TDM remain unresolved [9]. *In vitro* and animal *in vivo* data support a PD target of between 40 and 70% for the time that the free (or unbound) antimicrobial concentration should be maintained above the MIC ($fT_{>MIC}$) [11, 12]. This contrasts with data from recent retrospective evaluations, which support maintenance of a longer $fT_{>MIC}$ in critically ill patients [66–69]. Given that in most situations bacterial regrowth will occur as soon as the β-lactam concentration falls below the MIC [70–74], and that maximal bactericidal activity is reported to occur at concentrations four to five times the MIC [75–79] a pharmacodynamic target of 50–100% $fT_{>4–5\times MIC}$ (trough concentrations at four to five times the the MIC of the known or suspected pathogen) could be chosen in patients with severe infections or perceived poor antimicrobial penetration into infected tissues [79, 80]. Otherwise, 40–100% $fT_{>MIC}$ is likely to be sufficient. Toxicities of β-lactams that may be minimized with TDM include cholestasis, interstitial nephritis and seizures.

Few studies have reported the results of a β-lactam TDM programme [80–82]. Trough concentration data have been shown to be effective to adjust dosing to a high PK/PD target of 100% $fT_{>4–5\times MIC}$ in an intensive care unit [80]. The authors found that 73% of patients fell outside the desired PK/PD range and suggested that β-lactam TDM could therefore be useful in critically ill patients. However, until the effect of β-lactam TDM on clinical outcomes and the development of bacterial resistance is quantified, the role of TDM for these antimicrobials remains equivocal. Another innovative TDM programme was recently published by Connor and colleagues using antibiotic concentrations determined in dialysis effluent, and this approach may indeed be useful in patients receiving renal replacement therapy [83].

How to monitor β-lactam antimicrobials Whilst Bayesian adaptive feedback software would be the preferred method of dose adjustment for β-lactams, such facilities may not be available. Instead, monitoring of trough concentrations for the target selected by the clinician (100% $fT_{>MIC}$ or 100% $fT_{>4–5\times MIC}$) would appear safe and appropriate. Where continuous infusions are prescribed, 100% $fT_{>4–5\times MIC}$ would be an appropriate target [82].

Assaying β-lactams β-Lactams have historically been assayed only by HPLC, with 90% of assays using reversed phase chromatography with C18 columns [84]. A review by Samanidou *et al*. of over 80 reports showed that 76% of assays used ultraviolet detection [84]. The most promising assay for rapid measurement of multiple β-lactams is one that can measure 12 drugs concurrently with a 7 min runtime by monitoring three different wavelengths simultaneously [85]. This type of assay lends itself ideally to use in a systematic TDM programme [9].

Linezolid

There are few data describing the potential role for TDM of linezolid [86, 87], despite variable PK in patient populations and defined robust PK/PD targets [88]. Whilst toxicities such as bone marrow suppression, peripheral neuropathy and lactic acidosis have been identified with linezolid use, there are no reports of TDM minimizing the frequency of these.

The PD of linezolid was characterized by Rayner *et al*. [88] in a retrospective analysis of data from skin and skin structure infections and lower respiratory tract infections. The authors found that achievement of a PK/PD index of $AUC_{0–24}$/MIC 80–120 was highly indicative of clinical efficacy. In addition to this index, the authors found that 80% $T_{>MIC}$ was correlated with clinical success for treatment of bacteraemia, lower respiratory tract infections and skin and skin structure infections. If a clinician elects to use TDM to guide linezolid dosing, interpretation of trough concentrations appears possible because of a strong correlation between $\%T_{>MIC}$ and $AUC_{0–24}$/MIC [86, 88].

A retrospective observational study reported the frequency of linezolid dose adjustment from a single-centre TDM programme in 92 patients [87]. Here 60–70% of patients achieved the stated therapeutic targets ($C_{min} \geq 2$ mg l^{-1} and/or $AUC_{0–24}$/MIC >80), with 12% of patients recording potentially toxic concentrations ($C_{min} \geq 10$ mg l^{-1}). Toxic concentrations were significantly associated with cotreatment with omeprazole, amlodipine and amiodarone.

How to monitor linezolid Given the difficulty of measuring multiple samples to calculate $AUC_{0–24}$/MIC, use of trough concentrations is recommended [87]. Incremental dose adjustment is practically difficult, however, because of the strength of the available formulations and the reality that the $AUC_{0–24}$ for a 300 mg dose is ~2.3-fold smaller than

from a 600 mg dose [86]. The patient populations likely to benefit most from TDM of linezolid include patients with cystic fibrosis or end-stage renal disease, neonates, burn-injured patients, patients with pathogens that have MIC values ≥ 2 mg l^{-1} and those receiving cotreatment with potentially interacting medications [87, 89].

Assaying linezolid The assay of linezolid has been performed predominantly using HPLC with ultraviolet detection (HPLC-UV assays). Although liquid chromatography tandem mass spectrometry methods have been investigated, it is likely that HPLC-UV assays with automated sample preparation may lend themselves better to routine application [90, 91].

Other antimicrobials

Few other antimicrobials have been subject to TDM, although many have variable PK and may be candidates. Few papers discussing quinolone TDM are available; however, the PK/PD indices for the various quinolones against many bacteria have been accurately described [92] and therefore dose adjustment to meet these targets may become more common given the problems with subtherapeutic dosing and the development of resistance [93]. In a report of a local PK/PD programme by Scaglione [81], TDM of ciprofloxacin was performed and used a target of a C_{max}/MIC of 10. No ciprofloxacin-specific clinical outcome data were provided in this paper. Another paper by Pea and colleagues [94] used similar end-points. The authors in this study were also able to show that doses of ciprofloxacin as low as 200 or 400 mg every 12 h can only be used for very susceptible organisms (MIC <0.3 mg l^{-1}). Given the decreasing susceptibility to quinolones, we would advocate use of higher doses [95]. In our institution, TDM of ciprofloxacin is rarely performed. It is performed most frequently in obese patients and patients with significant burn injuries to ensure adequate dosing. Given that the PD index associated with optimal activity for this antimicrobial is AUC_{0-24}/MIC, high intermittent doses that achieve a trough concentration that matches the MIC of the known or presumed pathogen are suggested to achieve maximal AUC_{0-24}. Clinical data on this topic are needed.

Assaying quinolones The lesser demand for rapidly available quinolone assays means that the predominant method for analysis is HPLC, with some reported methods using capillary electrophoresis [96, 97].

Therapeutic drug monitoring of antituberculosis therapy has been the subject of various publications. Some papers have shown significant pharmacokinetic variability of these drugs, supporting the use of TDM. For example, measured concentrations of isoniazid and rifampicin were found to be outside the therapeutic range in 77 and 48% of patients, respectively, in one study [98]. The data supporting the therapeutic ranges for these drugs remain sparse, and more research on this area is suggested. However, the work of Peloquin in this area is significant, and excellent reviews are available [99, 100].

Is TDM likely to improve patient outcomes?

To date, there are no randomized controlled trials that conclusively demonstrate a reduction in mortality from antimicrobial TDM. As discussed above, data from van Lent-Evers *et al*. have demonstrated system cost savings from reduced hospital stay and reduced toxicities [37]. A trend towards reduced mortality in the active TDM group was present, although not statistically significant. For other antibiotics, well-designed randomized controlled trials have not been performed to determine what benefits exist. However, clear relationship between antibiotic exposure and effect have been demonstrated for many drugs. This, in combination with data describing a failure in some patient populations to achieve predefined therapeutic exposures, suggests that an active TDM programme is likely to result in significant patient benefits. This advantage is even more likely in the setting of decreasing susceptibility of pathogens globally.

Conclusions

Therapeutic drug monitoring serves as an accurate method for dose adjustment for particular antimicrobials in relevant patient populations. Where possible, Bayesian approaches to dose adjustment should be used, but not all hospitals will have access to such facilities, and indeed suitable population PK models may not be available. To date, the clinical outcome benefits of a systematic TDM programme for antimicrobials have only been demonstrated for aminoglycosides, although the decreasing susceptibility of bacteria to available antimicrobials, as well as emerging data on pharmacokinetic variability, suggest that benefits are likely. The challenge for institutions seeking to develop such programmes lies not only in the interpretation of TDM data, but also in the development of rapid-throughput assays that can accurately determine antimicrobial concentrations in blood or other biological matrices and the clear correlation with patient benefit. Investment by clinical institutions for clinically relevant outcome research in TDM needs to be undertaken so that attempts can be made to improve efficacy, reduce resistance and toxicity and reduce costs associated with antimicrobial use.

Competing Interests

DP has received speaking fees or consulting fees from Merck, AstraZeneca, Cubist, Novartis and Pfizer.

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