



Optimizing dosing of antibiotics in critically ill patients

Suzanne L. Parker^a, Fekade B. Sime^a, and Jason A. Roberts^{a,b,c}

Purpose of review

Recent studies suggest that contemporary antibiotic dosing is unlikely to achieve best outcomes for critically ill patients because of extensive pharmacokinetic variability and altered pharmacodynamics. Dose adaptation is considered quite challenging because of unpredictable dose–exposure relationships. Consequently, individualization of antibiotic dosing has been advocated. Herein, we describe recent developments in the optimization of antibiotic dosing in the critically ill.

Recent findings

Conventional doses of many antibiotics frequently result in sub or supratherapeutic exposures in the critically ill. Clinical studies continue to illustrate that dose–exposure relationships are highly variable in severely ill patients. Dose optimization based on pharmacokinetic/pharmacodynamic principles can effectively improve antibiotic exposure. Therapeutic drug monitoring (TDM) with adaptive feedback is likely to be the most robust approach to optimize dosing for individual patients. This more accurate approach to dosing is made possible with the user-friendly dosing software that is emerging.

Summary

The scope of TDM is broadening from the traditional focus on prevention of toxicity, to include optimization of antibiotic exposure thereby improving patient outcomes. However, the evidence relating TDM practice with improved clinical outcome remains limited. Well designed, multicentre, randomized controlled studies are warranted.

Keywords

antibiotics, critically ill, pharmacokinetics, therapeutic drug monitoring

INTRODUCTION

Critically ill patients with severe infections are at a high risk of death, with mortality rates two-fold higher in infected patients versus noninfected patients [1]. Inappropriate initial antibiotic therapy, due to infection by multidrug-resistant pathogens, has been identified as an important determinant in hospital mortality. [2]. Delayed identification of severe sepsis and septic shock with delayed commencement of antibiotic treatment is further associated with an increased risk of mortality [3].

Critically ill patients provide a substantial challenge to critical care physicians and pharmacists, as these patients experience alterations in their pathophysiology as a consequence of life-saving medical interventions or the natural course of critical illness [4,5]. Furthermore, common antibiotic dosing recommendations have been devised in patients who are not critically ill and thus may be unsuitable [6]. Knowledge of the impact of these patient changes on antibiotic dosing is essential to

ensure effective treatment aimed at maximizing clinical outcomes and, where possible, suppress the emergence of bacterial resistance [5].

In this review, we describe recent findings in pharmacokinetic variability encountered within the critically ill population and the consequent impact on dosing strategies, including the effect of patient-specific issues.

^aBurns, Trauma and Critical Care Research Centre, The University of Queensland, ^bDepartment of Intensive Care Medicine and ^cDepartment of Pharmacy, Royal Brisbane Hospital, Brisbane, Australia

Correspondence to Prof. Jason A. Roberts, Burns Trauma and Critical Care Research Centre, The University of Queensland, Level 3 Ned Hanlon Building, Royal Brisbane and Women's Hospital, Butterfield St, Brisbane, Queensland 4029, Australia. Tel: +617 3646 4108; fax: +617 3636 3542; e-mail: j.roberts2@uq.edu.au

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KEY POINTS

- Altered pharmacokinetic properties of antibiotics in the critically ill necessitate dose adaptation to ensure maximal patient outcomes.
- Dose adaptation in the critically ill is challenging because of significant pharmacokinetic variability between patients.
- Dose individualization through TDM may be necessary to attain optimal antibiotic exposure.
- TDM feedback combined with Bayesian dosing software enables a precise prediction of dosing requirements for an individual patient.
- Although clinical studies illustrate that the TDM-guided interventional dose adjustment improves antibiotic exposure, a positive impact on clinical outcomes is yet to be demonstrated.

THE EFFECT OF PHARMACOKINETICS AND PATIENT PATHOPHYSIOLOGY ON DOSING REQUIREMENTS

The changes to the pathophysiology in critically ill patients can alter the pharmacokinetic profile of a drug within the patient because of the patients' altered ability to absorb, metabolize, distribute, and eliminate antibiotics. The distribution characteristics of an antibiotic help determine the likelihood of the drug to reach the site of infection. These drug characteristics can be described by the pharmacokinetic parameter of volume of distribution, which from a dosing perspective, mostly relates to the initial phase of antibiotic dosing. The elimination of an antibiotic is described with the pharmacokinetic parameter of clearance. Clearance helps define maintenance dosing requirements [7]. Pharmacokinetic studies are highly valuable because they define these important pharmacokinetic parameters and can confirm or redefine dosing regimens that can result in more effective antibiotic exposure. However, the volume of distribution and clearance in critically ill patients are highly variable [8–10], making a singular dose for critically ill patients less likely to succeed and therefore an individualized approach to patient antibiotic dosing may be preferable [6].

The capacity of an antibiotic to distribute to the site of infection (e.g. interstitial fluid of soft tissue infections, epithelial lining fluid in pneumonia, and cerebrospinal fluid in central nervous system infections) is related to molecular size, solubility, hydrophilicity, and protein binding. These physicochemical properties determine concentrations in tissues outside the vascular system and therefore

can affect antibiotic effectiveness. Lipophilic antibiotics have a high volume of distribution and tend to have good intracellular penetration, and predominantly undergo hepatic clearance. Examples of lipophilic antibiotics include quinolones and lincosamides. Conversely, hydrophilic antibiotics primarily distribute into the extracellular space (low intracellular penetration), have a low volume of distribution, and predominantly undergo renal elimination. Examples of hydrophilic antibiotics include beta-lactams and aminoglycosides [11]. The level of protein binding can be used to predict the concentration of the unbound antibiotic, which is both the pharmacologically active component as well as the fraction available for elimination.

The potency of an antibiotic to kill or inhibit the growth of a pathogen is described by the minimum inhibitory concentration (MIC) and is specific to both the antibiotic and the pathogen. The interrelationship between antibiotic concentrations and therapeutic effects is termed pharmacodynamics and is an essential consideration in antibiotic dosing. Not only does pharmacodynamics quantify antibiotic exposures necessary to maximize pathogen killing, but also exposures that can suppress the emergence of antibiotic resistance [12].

ANTIBIOTIC VARIATION IN CRITICALLY ILL PATIENT SUBPOPULATIONS

Increasing data from clinical pharmacokinetic studies have described significant pharmacokinetic variability among different critically ill patient subpopulations and have clearly refuted the assumption that standardized dosing of antibiotic is sufficient in these patients [6]. Pharmacokinetic alterations are driven by complex pathophysiologic processes such as the systemic inflammation response syndrome (SIRS). The influence of SIRS on the pharmacokinetics of antibiotics has been well described in a recent review by Blot *et al.* [13]. In brief, activation of a diverse set of inflammatory mediators during SIRS can result in hyperdynamic effects on the cardiovascular system, augmented renal clearance (ARC) [14], enhanced capillary permeability, and possibly end-organ damage such as acute kidney injury (AKI). Particularly, for hydrophilic antibiotics, these pathophysiologic changes give rise to unpredictable changes in volume of distribution and clearance. Often volume of distribution is elevated and clearance may be increased, decreased, or unchanged [6].

Augmented renal clearance versus acute kidney injury

ARC (enhanced clearance of circulating drug, generally defined as clearance ≥ 130 ml/min/1.73 m²)

appears to be a significant risk factor for treatment failure in infected adult intensive care patients. One observational study observed that treatment failure was 27.3% in the ARC patients versus 12.9% in the patients without ARC [15]. A mechanistic investigation illustrated that possibly both elevated glomerular filtration rate and active tubular secretion contribute to ARC, resulting in subtherapeutic plasma concentrations [14]. A recent study by Udy *et al.* [16] in intensive care unit (ICU) patients with sepsis and without significant renal impairment found that ARC is associated with lower trough plasma piperacillin concentrations, and standard intermittent dosing is unlikely to achieve optimal piperacillin exposures. Similarly, a study by Huttner *et al.* [17] of 100 critically ill patients with ARC and receiving beta-lactam antibiotics (which undergo predominant renal elimination) found that there was a strong association with ARC and reduced beta-lactam antibiotic concentrations, with only 13 patients having trough concentrations above the desired pharmacodynamic threshold. However, in this relatively small heterogeneous cohort, there was no link between low trough concentrations and clinical failure. Further research is required in both the clinical implications of subthreshold concentrations and the ecological consequences for antibiotic resistance [18].

AKI is defined as an abrupt reduction in kidney function, defined by increasing serum creatinine concentrations or a reduction in urine output [19]. Initiating renal replacement therapy (RRT) is a common ICU intervention for patients with AKI and these patients have very high mortality rates (approximately 49% [20]). Total antibiotic clearance during RRT is the sum of residual renal clearance, nonrenal clearance, and extracorporeal clearance by the machines, all of which may be highly variable. RRT procedures are not consistent from institution to institution with regard to the different modalities, operational settings, and filter types used, whereas the conventional doses of antibiotics are more or less similar across institutions [21]. Consequently, antibiotic exposures in patients receiving RRT are inconsistent because of the significant variability in clearance, as illustrated in a recent multicentre study by Roberts *et al.* [22].

Normal weight versus obese critically ill patients

Pharmacokinetic alterations have been observed in obese patients and have been characterized by changes in total body weight, lean body weight, and/or body mass index [23,24]. Obesity increases volume of distribution, especially for lipophilic

antibiotics, and can lead to lower than expected plasma antibiotic concentrations [25]. Compared with nonobese patients, clearance was found to be significantly higher for both piperacillin (13.2 versus 9.8 l/h) and tazobactam (13.5 versus 7.8 l/h), and volume of distribution has been shown to be significantly larger for both piperacillin (32.5 versus 24.5 l) and tazobactam (51.2 versus 24.9) in obese patients [23]. Similarly, clearance (11.7 versus 8.1 l/h) was found to be significantly higher, and volume of distribution (corrected for total body weight; 0.18 versus 0.13 l/kg) was significantly larger for doripenem in obese patients compared with nonobese patients [24].

HOW DO WE MEET INDIVIDUAL DOSING REQUIREMENTS IN THE CRITICALLY ILL?

To date, the evidence from clinical pharmacokinetic/pharmacodynamic (PK/PD) studies has underscored that achieving optimal antibiotic exposure in every critically ill patient is not possible without making significant changes to dosing regimens for individual patients. Clinical studies have described different dose optimization strategies (Table 1). Two general approaches may be considered to individualize dosing regimens. The first approach involves the use of dosing nomograms based on patient-specific clinical covariates (e.g. weight or renal function), and the second involves dose modifications to target a PK/PD index using therapeutic drug monitoring (TDM) with adaptive feedback. The use of nomograms is limited as they may frequently result in inappropriate dosing recommendations [43], consequently many of the recent developments focus on TDM-based dose optimization approaches.

ALTERED DOSING STRATEGIES: PROLONGED INFUSIONS AND THERAPEUTIC DRUG MONITORING

In clinical practice, dose adjustments are commonly informed by guidelines which may be based on interpretations of measured TDM concentrations. The dose adjustment strategies depend on the pharmacokinetic properties and the specific PK/PD index of the antibiotic. Generally, **for antibiotics with concentration-dependent activity where the goal is to achieve a target peak concentration (C_{max}) to MIC ratio (C_{max}/MIC) or target ratio of the area under the concentration-versus-time curve (AUC) to the MIC (AUC/MIC), adjustment of the magnitude of the dose may be adequate;** whereas for time-dependent antibiotics, like the beta-lactams, adjusting the frequency or mode of administration (prolonged infusion in preference to intermittent

Table 1. Summary of recent studies providing relevant data on optimization of antibiotic dosing in critically ill patients

Authors	Title	Patient subgroup	Antibiotic	Dosing recommendation
Jamal <i>et al.</i> [26]	Pharmacokinetics of piperacillin in critically ill patients receiving continuous venovenous haemofiltration: an RCT of continuous infusion versus intermittent bolus administration	Receiving continuous venovenous haemofiltration	Piperacillin	Continuous infusion administration may improve PK/PD target attainment
De Waele <i>et al.</i> [27]	Extended versus bolus infusion of meropenem and piperacillin: a pharmacokinetic analysis	Without renal dysfunction	Meropenem and piperacillin	Extended infusion results in improved PK/PD target attainment
Carlier <i>et al.</i> [28]	Population pharmacokinetics and dosing simulations of cefuroxime in critically ill patients: nonstandard dosing approaches are required to achieve therapeutic exposures	Creatinine clearance ranged from 10 to 304 ml/min	Cefuroxime	High-dose continuous infusion is more likely to reach PK/PD targets. Patients with creatinine clearance of 300 ml/min may not achieve PK/PD targets for a MIC of 8 mg/l
Cousson <i>et al.</i> [29]	Lung concentrations of ceftazidime administered by continuous versus intermittent infusion in patients with ventilator-associated pneumonia	Ventilator-assisted pneumonia	Ceftazidime	Continuous infusion presents PK/PD advantages and predictable efficacy
Laterre <i>et al.</i> [30]	Temocillin (6g daily) in critically ill patients: continuous infusion versus three times daily administration	Intra-abdominal or lower respiratory tract infections caused by <i>Enterobacteriaceae</i>	Temocillin	Temocillin (6g daily) given by continuous infusion increases PK/PD target attainment for infections caused by <i>Enterobacteriaceae</i> with an MIC of 16 mg/l
Tafelski <i>et al.</i> [31]	Observational clinical study on the effects of different dosing regimens on vancomycin target levels in critically ill patients: continuous versus intermittent application	Postoperative ICU	Vancomycin	Continuous administration of vancomycin allowed more rapid PK/PD target attainment with fewer subtherapeutic concentrations observed
Lin <i>et al.</i> [32]	Vancomycin continuous infusion versus intermittent infusion during continuous venovenous haemofiltration: slow and steady may win the race	Patient receiving continuous venovenous haemofiltration, no residual renal function	Vancomycin	Continuous infusion achieved PK/PD targets faster than intermittent infusion and consistently kept the vancomycin concentrations within target range
Brunetti <i>et al.</i> [33 [■]]	Clinical and economic impact of empirical extended-infusion piperacillin-tazobactam in a community medical centre	Patients receiving piperacillin/tazobactam >48 h	Piperacillin/tazobactam	Extended infusion of piperacillin/tazobactam is well tolerated and not associated with a reduction in mortality or length of stay
Cutro <i>et al.</i> [34]	Extended-infusion versus standard-infusion piperacillin-tazobactam for sepsis syndromes at a tertiary medical centre	ICU patients	Piperacillin/tazobactam	Patients with urinary or intra-abdominal infections had lower mortality and clinical failure rates when receiving extended infusions. No significant differences in inpatient mortality rates, length of stay, or clinical failure rates. Patients receiving extended infusion treatment had a shorter duration of therapy
Dulhunty <i>et al.</i> [35 ^{■●}]	A multicentre randomized trial of continuous versus intermittent beta-lactam infusion in severe sepsis	ICU patients with severe sepsis	Piperacillin/tazobactam, meropenem, and ticarcillin/clavulanate	Continuous administration of beta-lactam antibiotics improves PK/PD target attainment, with an improvement in clinical cure

Table 1 (Continued)

Authors	Title	Patient subgroup	Antibiotic	Dosing recommendation
De Waele <i>et al.</i> [36]	Therapeutic drug monitoring-based dose optimization of piperacillin and meropenem: an RCT	Patients with normal kidney function	Meropenem and piperacillin	Dose adaptation based on daily TDM led to an increase in PK/PD target attainment compared with conventional dosing
Sime <i>et al.</i> [37]	Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? An RCT	Febrile, neutropenic patients	Piperacillin/tazobactam	Conventional doses of piperacillin/tazobactam may not achieve PK/PD targets. TDM provides useful feedback of dosing adequacy to guide dose optimization
Fournier <i>et al.</i> [38]	Impact of the introduction of real-time TDM on empirical doses of carbapenems in critically ill burn patients	Burn patients	Carbapenems	Real-time carbapenem TDM availability significantly altered the empirical daily dosage of imipenem/cilastatin
Neely <i>et al.</i> [39 ^{***}]	Are vancomycin trough concentrations adequate for optimal dosing?	Adult patients with <i>Staphylococcus aureus</i> infections	Vancomycin	Adjustment of vancomycin doses on the basis of trough concentrations without a Bayesian tool results in poor achievement of PK/PD targets
Cardile <i>et al.</i> [40]	Optimization of time to initial vancomycin target trough improves clinical outcomes	Adult patients in TDM programme	Vancomycin	Interventions designed to decrease the time to reach initial target vancomycin troughs can improve clinical outcomes in Gram-positive infections, including MRSA infections
Felton <i>et al.</i> [41]	Individualization of piperacillin dosing for critically ill patients: dosing software to optimize antimicrobial therapy	Patients with nosocomial infections	Piperacillin-tazobactam	Individualized piperacillin regimens delivering a target serum piperacillin concentration is achievable
Nezic <i>et al.</i> [42]	TDM of once daily aminoglycoside dosing: comparison of two methods and investigation of the optimal blood sampling strategy	Patients receiving once daily aminoglycoside therapy	Amino-glycosides : tobramycin, gentamicin, amikacin	The ideal time-points for TDM of once daily administered aminoglycosides are 1 h after start of a 30-min infusion for the first time-point and 8–10 h after start of the infusion for the second time-point

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PK/PD, pharmacokinetics/pharmacodynamics; RCT, randomized controlled trial; TDM, therapeutic drug monitoring.

bolus administration) is the best approach to maximize the time the free drug concentration remains above the MIC ($fT_{>MIC}$) [26–30]. The glycopeptide vancomycin, having both time and concentration-dependent activities, may achieve favourable exposure with prolonged infusions [31,32].

Prolonged infusions

Studies have demonstrated that wide clinical application of prolonged infusions is feasible with contemporary infusion pump technologies, and is probably cost-effective, particularly if the potentially

improved patient outcomes are included in this analysis [33[•],44,45].

However, the evidence for clinical outcome benefit from prolonged infusions of beta-lactam antibiotics is still inconsistently reported, and is yet to be established [34,46]. Meta-analyses of published studies support benefits of reduced length of ICU stay, improved clinical cure rate, [47,48] and/or reduced toxicity [49] with prolonged infusions. However, a recent large multicentre randomized study [45] reported no difference in patient outcomes when comparing continuous versus intermittent infusion of three beta-lactams in 420 patients

with severe sepsis. The study included a high proportion of patients receiving RRT and these patients are less likely to benefit from continuous infusion, thereby reducing the number of patients that the intervention may have benefitted. Also, this study did not confirm appropriateness of dosing regimens through TDM. Therefore, the ultimate outcome benefits of dose optimization through prolonged infusions are yet to be conclusively addressed [47,35²²].

Therapeutic drug monitoring

So far, outcome benefits of TDM are better demonstrated for antibiotics with a narrow therapeutic index, particularly the aminoglycosides and to some extent vancomycin [50,51]. The traditional focus of TDM for these antibiotics was mainly avoidance of toxicity. However, the recent developments in TDM for other antibiotics with a wider therapeutic index suggest a valid use for TDM with a primary aim to optimize treatment of infections [52,53]. Beta-lactams, quinolones, linezolid, daptomycin, and colistin are among the antibiotics subject to TDM in recent studies, with relatively more recent data on beta-lactam TDM [53]. Given the lack of explicitly defined and objective clinical endpoints to assess clinical outcomes of antibiotic therapy, most of the studies demonstrated the benefits of TDM using PK/PD target attainment as a surrogate indicator of outcome. Recently, a partially blinded randomized controlled trial (RCT) by De Waele *et al.* [36] investigated the role of TDM-guided interventional dose adjustment in optimizing target exposure for piperacillin and meropenem. The study showed a distinct PK/PD advantage in target attainment with TDM-guided dosing. Similarly, a PK/PD advantage of interventional TDM for a beta-lactam antibiotic was demonstrated in another recent RCT by Sime *et al.* [37]. Although real-time TDM for beta-lactams is not yet widely practiced, data from such studies have influenced the adaptation of routinely used empiric dosing regimens [37,38].

An important limitation of TDM-guided dose adaptation based on predefined algorithms is that, although attempts are made to individualize the dose based on the measured TDM concentration, no additional consideration is made specific to the individual patient. Consequently, inappropriate exposure may be observed even after TDM-guided dose adjustment, as was documented in recent RCTs [36,37]. A similar limitation of inappropriate exposures has been recently described by Neely *et al.* [39²²] for the widely endorsed vancomycin TDM consensus guidelines, although the guidelines are generally helpful to rapidly achieve PK/PD

targets thereby improving clinical outcomes [40]. A recent systemic review by Ye *et al.* [54] also challenges the rigor of development processes that defined the consensus guidelines, highlighting the limitation of dose individualization based on predefined criteria.

APPLICATION OF PHARMACOMETRICS TO THERAPEUTIC DRUG MONITORING-GUIDED DOSE INDIVIDUALIZATION

A better prediction of individual dosing requirements is possible through pharmacokinetic analysis based on TDM concentrations. Pharmacokinetic analysis methods from simple linear regression to advanced mathematical modelling tools are available, with much of the recent development being in the latter. Although the involvement of sophisticated computer software for the pharmacokinetic analysis has been a significant drawback as compared with the simplistic dosing guidelines, improved user-friendly computer software tools for bedside use are emerging [6]. These software programs use population pharmacokinetic models coupled with Bayesian forecasting to precisely predict individual dosing requirements. The population pharmacokinetic models provide mathematical equations that can help estimate dosing for an individual patient based on his/her unique characteristics described by clinical covariates, such as creatinine clearance, weight, and sex. In the Bayesian approach of estimation, incorporating the additional information obtained from measured TDM concentrations enhances the precision of individualized dose prediction by the selected population pharmacokinetic model. The TDM concentrations will provide input on the actual dose–exposure relationship in the patient, which will be used to develop the ‘individual-specific pharmacokinetic model’ together with prior information contained in the population pharmacokinetic model. The software then uses the ‘patient-specific model’ with the patient’s specific clinical covariates for a more precise prediction of dosing requirements [39²²,41,55].

Recent clinical studies have demonstrated the utility of the Bayesian approach of estimation. Neely *et al.* [39²²] showed that prediction of vancomycin therapeutic exposure by the Bayesian approach is more precise compared with the traditional TDM based on the consensus guidelines (3 versus 25% error). Felton *et al.* [41] also described the feasibility of using Bayesian dosing software for individualized dosing of piperacillin in the critically ill. The study by Nezic *et al.* [42] compared Bayesian dosing software with the traditional peak–trough-based TDM approach of aminoglycosides. Although the study failed to highlight previously reported [56]

advantages of Bayesian forecasting, it is important to note that the precision of Bayesian estimation is highly dependent on the quality of the *a priori* population pharmacokinetic model and the degree of relevance to the patient. Therefore, the various population pharmacokinetic models available need to be validated in clinical studies to minimize imprecision of the dosing software. Overall, the clinical application of Bayesian dosing software appears to be the most accurate approach for dose individualization.

THE ROLE OF THERAPEUTIC DRUG MONITORING IN COMBINATION ANTIBIOTIC THERAPY

The outcome benefit of combination versus monotherapy continues to be controversial, although a review of the collective literature suggests a potential benefit for empiric therapy, rather than for directed therapy [57]. Unfortunately, most of the comparative outcome trials did not monitor the appropriateness of dosing while comparing outcomes of combination versus monotherapy. Given the extensive evidence that antibiotic pharmacokinetics is highly variable in the critically ill, inappropriate exposures are perhaps an important confounder that contribute to the conflicting results from clinical studies. TDM would be helpful not only to optimize the efficacy of monotherapy, hence avoiding the unnecessary use of combination regimens, but also to maximize the benefit of combination regimens when clinically warranted. Advanced PK/PD modelling studies illustrate that synergy in combination regimens is dependent on the pharmacokinetic profile or relative exposure of each antibiotic in the combination [58[•],59]. Thus, optimization of exposure to individual antibiotics through TDM would be instrumental to ensure the theoretical benefit of synergy from combination regimens.

CONCLUSION

Clinical studies continue to highlight the presence of altered antibiotic pharmacokinetics in the critically ill and the importance of innovative dosing strategies to ensure optimal antibiotic exposures. Unfortunately, dose guidelines are unable to meet the altered dosing needs in the critically ill and their unpredictable pharmacokinetic variability. These characteristics necessitate a patient-specific approach to dose optimization. TDM feedback is invaluable not only to confirm the appropriateness of dosing in an individual patient, but also to guide dose adjustment. Although TDM-based approaches

have been shown to improve antibiotic exposure, the evidence of clinical outcome benefit from multicentre RCTs is still outstanding.

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Conflicts of interest

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