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An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units

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Objectives: Emerging evidence supports the use of therapeutic drug monitoring (TDM) of β-lactams for intensive care unit (ICU) patients to optimize drug exposure, although limited detail is available on how sites run this service in practice. This multicentre survey study was performed to describe the various approaches used for β-lactam TDM in ICUs.

Methods: A questionnaire survey was developed to describe various aspects relating to the conduct of β-lactam TDM in an ICU setting. Data sought included: β-lactams chosen for TDM, inclusion criteria for selecting patients, blood sampling strategy, analytical methods, pharmacokinetic (PK)/pharmacodynamic (PD) targets and dose adjustment strategies.

Results: Nine ICUs were included in this survey. Respondents were either ICU or infectious disease physicians, pharmacists or clinical pharmacologists. Piperacillin (co-formulated with tazobactam) and meropenem (100% of units surveyed) were the β-lactams most commonly subject to TDM, followed by ceftazidime (78%), ceftriaxone (43%) and cefazolin (43%). Different chromatographic and microbiological methods were used for assay of β-lactam concentrations in blood and other biological fluids (e.g. CSF). There was significant variation in the PK/PD targets (100% $fT_{>MIC}$ up to 100% $fT_{>4\times MIC}$) and dose adjustment strategies used by each of the sites.

Conclusions: Large variations were found in the type of β-lactams tested, the patients selected for TDM and drug assay methods. Significant variation observed in the PK/PD targets and dose adjustment strategies used supports the need for further studies that robustly define PK/PD targets for ICU patients to ensure a greater consistency of practice for dose adjustment strategies for optimizing β-lactam dosing with TDM.

Keywords: dosing, antimicrobial, TDM, critical care, pharmacokinetics

Introduction

Therapeutic drug monitoring (TDM) is a commonly utilized dosing strategy to minimize toxicity and maximize the efficacy of drugs with a narrow therapeutic index. It is most commonly used when the pharmacokinetics (PK) and therefore the optimal dose of a drug for an individual patient are difficult to predict. In clinical practice, the approach has been routinely used for many years

for vancomycin and aminoglycosides, selected anticonvulsants, anticoagulants and antipsychotics.[1]

β-Lactams are a family of antibiotics frequently prescribed in the setting of severe infection in intensive care units (ICUs). The indication may be for either empirical or directed therapy. In the setting of the dynamic physiological changes that patients may undergo secondary to disease processes and clinical interventions, significantly altered β-lactam PK is common.[2–7] Specifically, increases in volume of distribution (*V*) and dramatic fluctuations in drug clearance are common in critically ill patients, leading to sub-therapeutic or toxic concentrations in a large proportion of ICU patients when standard dosing strategies are used.[8,9] In view of the difficult-to-predict PK and the importance of early and appropriate antibiotic therapy in reducing mortality rates,[10–14] TDM of β-lactam antibiotics is increasingly being reported in critically ill patients.[9,15,16] The aim of β-lactam TDM is to provide doses of antibiotic that maintain unbound β-lactam concentrations above bacterial MICs over a desired percentage of the dosing period (% $fT_{>MIC}$).[17–19]

The feasibility of performing β-lactam TDM as a part of routine care in ICUs has been reported by various ICUs.[9,15,16] Despite emerging evidence of the value of β-lactam TDM as a dose optimization strategy in ICUs, there is limited information on how it is actually performed in the clinic.[9,19–22] The aim of this paper is to describe in detail the various approaches used for β-lactam TDM in ICUs.

Methods

A questionnaire survey was developed to describe various aspects relating to the conduct of β-lactam TDM in an ICU setting. The protocol items associated with practical implementation of β-lactam TDM are listed in Table 1. Contributing ICUs (or TDM units that perform TDM hospital-wide, including ICUs) were identified by a literature review of publications on β-lactam TDM and from ICUs known by the investigators to be using TDM for β-lactams in ICU patients. Approval to conduct this low- and negligible-risk study was obtained from the Human Research Ethics Committee at the Royal Brisbane and Women's Hospital, Australia (reference HREC/13/QRBW/243).

Statistical analysis

Data were subject to descriptive statistical analysis and are presented as the proportion of ICUs (%), mean (SD) or median (IQR) as appropriate.

Results

Response rate and ICU demographics

Nine of the 11 ICUs that were approached responded to the survey. The survey was completed by ICU physicians ($n=3$), infectious disease physicians ($n=1$), clinical pharmacologists ($n=1$) and clinical pharmacists ($n=4$). The characteristics and locations of the participating ICUs included are listed in Table 2. The majority of the ICUs were located in European countries (66.7%).

Logistics of TDM programmes

The TDM programmes were primarily managed by ICU physicians ($n=6$), pharmacists ($n=5$), infectious disease physicians ($n=3$) and clinical pharmacologists ($n=1$), in conjunction with microbiologists and clinical biochemists depending on the nature of the clinical cases. The median number of days per week when TDM was available was 5 (IQR 4–5). The median number of patients subject to TDM per day and per week ranged from 1 to 4 and from 1 to 15, respectively.

β-Lactams subject to TDM

The 21 β-lactam antibiotics subject to TDM across the various ICUs are shown in Figure 1. The number of β-lactams monitored by a single centre ranged between 3 and 12 (mean 7). All ICUs

Table 1. β-Lactam TDM practice information collected in the survey

β-Lactam TDM practice item surveyed	Rationale
Number of ICU beds and ICU type	Demographic characteristics of ICUs that perform β-lactam TDM
Median number of TDMs per day and per week	
Personnel who manage TDM programme	
Names of β-lactams subject to TDM	
Inclusion and exclusion criteria	Criteria each ICU uses to select patients that will be subject to TDM
Blood sample timing	Timing of blood samples during a dosing interval for measurement of β-lactam concentrations
Sampling of body fluids other than blood	Whether fluids other than blood are sampled for TDM
β-Lactam assay method	Determine whether published methods are used to measure β-lactam concentrations and whether total or free concentrations are measured
Measurement of bacterial pathogen susceptibility	How and under which circumstances MICs are determined (e.g. published susceptibility breakpoints, Vitek 2 and/or Etest)
Time delay between sampling and availability of results to treating clinician	
PK/PD targets for dose adjustment	(i) What therapeutic target is used? i.e. which % $fT_{>MIC}$ is used? (ii) What is the PK/PD threshold of toxicity?
Dose adjustment methods	What strategies are used to adjust doses when concentrations are deemed too low or too high?

% $fT_{>MIC}$, percentage of the dosing period during which the free concentration of drug remains above the MIC for the pathogen.

Table 2. Details of the participating ICUs

	n or median (IQR)
Country	
Australia	2
Belgium	2
France	1
Germany	1
Italy	1
Switzerland	1
USA	1
ICU bed numbers	30 (15–35)
ICU type	
medical–surgical only	6
medical–surgical, with burns unit and/or other subspecialty units	3

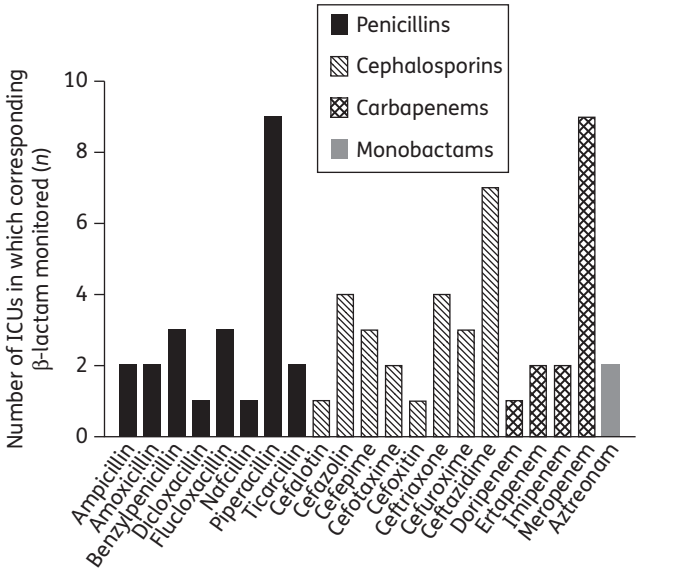

Figure 1. Frequency with which β-lactam antibiotics were included as part of a TDM programme in surveyed ICUs.

included piperacillin (administered co-formulated with tazobactam) and meropenem for TDM. As shown in Figure 1, various cephalosporins were also frequently subject to TDM.

Inclusion and exclusion criteria

There was significant heterogeneity across the protocols for choosing which patients would be subject to β-lactam TDM. The majority of the ICUs ($n=5$) specifically targeted TDM to patients with severe sepsis or septic shock. Other inclusion criteria were: specific types of serious bacterial infection requiring prolonged antibiotic treatment (e.g. brain abscess, endocarditis, meningitis); impaired organ function [e.g. renal impairment, assumed augmented renal clearance (ARC);[5,23] liver failure/cirrhosis]; and patients undergoing renal replacement therapy (RRT) and/or extracorporeal membrane oxygenation (ECMO). Other patient factors included immunosuppression, organ transplantation, severe burn injury and patient weight (underweight or obese). Some ICUs performed TDM in the presence of multidrug-resistant pathogens, suspected β-lactam toxicity and/or when β-lactams were administered by continuous infusion.

Three facilities also performed β-lactam TDM in non-ICU patients who met one or more of the above criteria. Exclusion criteria included: (i) paediatric patients (age <18 years) ($n=7$); (ii) patients whose β-lactam antibiotic treatment was expected to be ceased within 24 ($n=2$) or 72 h ($n=1$) of sampling; (iii) prophylactic antibiotic use ($n=1$); and (iv) concomitant antimicrobials with activity against the indicator organism of the microbiological assay (*Staphylococcus epidermidis*, *Clostridium perfringens* or *Klebsiella pneumoniae* depending on the assay) ($n=1$).

PK sampling timing

All protocols sampled trough concentrations of β-lactams at assumed PK steady state when administered by intermittent dosing (steady state was mostly defined as having been reached after four doses or 24–48 h after onset of treatment). Sampling was performed at PK steady state when the antibiotic was given by a continuous infusion (frequently defined as four to five half-lives after commencement of therapy or after a dose change). One ICU obtained an additional sample at 30% of the dosing interval. Multiple samples [immediately after dosing, then 30% (or 40%), 50% and 70% of the dosing interval] were taken in two units for research purposes but not for dose adjustment calculations. Six ICUs also performed TDM in body fluids other than blood. Samples that could be subject to TDM included CSF ($n=5$), peritoneal fluid ($n=4$), RRT dialysate, urine and, rarely, pleural effusion, bronchoalveolar lavage fluid, bile and joint aspirate.

β-Lactam assay methods

Microbiological assays were used in two units and chromatographic methods elsewhere. Among the facilities that used chromatography, two units measured total and/or unbound β-lactam concentrations for TDM, while other ICUs measured total concentrations only. The majority of the assay protocols were published ($n=9$; Table 3). Those that were not published were in-house protocols that had been validated by Valistat 2.0 (Arvecon, Germany) or according to local regulatory guidelines.[24,25] HPLC with ultraviolet detection (HPLC/UV) was the predominant analytical system used ($n=4$); other systems used were ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) and liquid chromatography–tandem mass spectrometry (LC–MS/MS). Generally, antibiotic concentration results were available to treating clinicians within 6–12 h from sampling time (when samples were received by the laboratories within scheduled hours) and up to 24–48 h in some facilities.

Determination of bacterial susceptibility

Two ICUs measured bacterial MICs routinely for TDM by the microdilution broth method and the Phoenix Automated Microbiology System (BD Diagnostic Systems, Sparks, MD), respectively. For

Table 3. Published β-lactam assay methods used by the surveyed facilities

Analytical system	Antibiotics	Calibration curve range, precision and accuracy	Interval between sampling and availability of results[a]	Reference
Microbiological assay	amoxicillin/clavulanic acid, cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, doripenem, ertapenem, imipenem, meropenem, piperacillin/tazobactam, ticarcillin	calibration curve ranges chosen depending on antibiotics and test organism precision: ±10%–15%	24–48 h	Kitzis[26]
HPLC/UV	aztreonam, cefepime, ceftazidime, cefuroxime, meropenem, piperacillin	2–200 mg/L precision: CV <11% accuracy: ±30%	12 h (or 3 days over weekend)	Wolff *et al.*[27]
	ampicillin, benzylpenicillin, cefalotin, cefazolin, ceftazidime, ceftriaxone, dicloxacillin, ertapenem, flucloxacillin, meropenem, piperacillin, ticarcillin	1–500 mg/L (except meropenem 1–250 mg/L) precision: CV <10% accuracy: ±6%	within 12 h	McWhinney *et al.*[28]
	ampicillin, benzylpenicillin, cefalotin, cefazolin, ceftriaxone, dicloxacillin, ertapenem, flucloxacillin, meropenem, piperacillin	unbound antibiotics:[b] 0.1–50 mg/L (except piperacillin 0.1–100 mg/L) precision: CV <9.4% accuracy: ±15%	within 12 h	Briscoe *et al.*[29]
	meropenem	3–50 mg/L	6 h	Bias *et al.*[30]
	ceftazidime	1–200 mg/L precision: CV <6.2% accuracy: 97.5%–105.5%	within 6 h	Hanes *et al.*[31]
HPLC	meropenem	10–70 mg/L LOQ: 12.85 μg/L precision: CV <0.85% accuracy: 99.1%–100.1%	within 6 h	Mendez *et al.*[32]
UPLC–MS/MS	amoxicillin, ampicillin, cefazolin, cefuroxime, ceftazidime, clavulanic acid, meropenem, piperacillin, tazobactam	0.5–100 mg/L (except piperacillin 1.5–100 mg/L) precision: 10%–20% at LOQ and 3%–15% at higher levels accuracy: 86.8%–101.5%	6 h	Carlier *et al.*[33]
LC–MS/MS	ampicillin, cefazolin, cefepime, cefmetazole, cefotaxime, doripenem, meropenem, piperacillin	0.1–50 mg/L (except doripenem 0.5–50 mg/L) precision: CV <14.6% accuracy: 86.4%–112.3%	within 6 h	Ohmori *et al.*[34]

CV, coefficient of variation.
[a]Limited to samples received by the laboratories before scheduled cut-off times on days that TDM was available.
[b]Concentrations of unbound (free) β-lactam antibiotics were measured directly.

others, MICs were measured by the disc method, Etest (bioMérieux, France) or the micro-dilution broth method only when the pathogen was determined to be intermediately susceptible to the antibiotic or where resistance to the prescribed antibiotic was demonstrated with the Vitek 2 system (bioMérieux, France). Surveyed ICUs adopted EUCAST ($n=8$) or CLSI ($n=1$) breakpoints to determine PK/pharmacodynamic (PD) targets when MICs were not measured. Two of the ICUs also reported using local hospital antibiogram data to describe likely pathogen susceptibility.

PK/PD targets for dose adjustment

A minimum of 100% $fT_{>MIC}$ was adopted as the PK/PD target for dose increase by six of the ICUs. Dose reduction was undertaken mostly on a case-by-case basis by all units when toxicity (especially neurological) was suspected or concentrations were above locally defined threshold concentrations for potential toxicity. Six other targets for dose increase were described, as shown in Table 4. Only four units would reduce the dose if concentrations were above the recommended PK/PD targets for efficacy.

Method of dose adjustment

All ICUs adjusted the dose as soon as results became available. Only two ICUs determined a new dosage by calculation of the individual patient's drug clearance from measured β-lactam concentrations. Other ICUs adopted more generalized dose adjustment methods, as summarized in Table 5. All except one of the

Table 4. List of PK/PD targets for dose adjustment adopted by selected ICUs

	PK/PD targets	Specific conditions
For dose increase	100% $fT_{>MIC}$ ($n=5$)	
	100% $fT_{2-4\times MIC}$ ($n=1$)	
	50% $fT_{>4\times MIC}$ ($n=1$)	intermittent bolus dosing
	100% $fT_{>4\times MIC}$ ($n=2$)	continuous infusion
	40% $fT_{>4\times MIC}$ ($n=1$)	for meropenem
	50% $fT_{>4\times MIC}$ ($n=1$)	for piperacillin, aztreonam and cefuroxime
	70% $fT_{>4\times MIC}$ ($n=1$)	for cefepime and ceftazidime
Threshold of potential toxicity for dose reduction	100% $fT_{10\times MIC}$ ($n=4$)	
	100% $fT_{8\times MIC}$ ($n=1$)	MIC for *Pseudomonas aeruginosa* of the antibiotic
	100% $fT_{6\times MIC}$ ($n=1$)	continuous infusion
	100% $fT_{4-5\times MIC}$ ($n=1$)	in the presence of susceptible pathogens
	steady-state concentration exceeding 2 × maximum exposure expected in general population; e.g. piperacillin >100 mg/L (>32 g/24 h in normal patients), meropenem >32 mg/L (>12 g/24 h in normal patients) ($n=1$)	continuous infusion

% $fT_{>x\times MIC}$, percentage of the dosing period during which the free (unbound) concentration was *x* times the MIC for targeted pathogen.

ICUs increased the dose based on β-lactam concentrations, susceptibility of the clinical isolate and the nature of infection, without a definite maximum dose per day for any specified antibiotic. Eight units performed follow-up TDM. This was done regularly after dose adaptation (generally every 24–48 h), after dose changes or if changes in a patient's characteristics were anticipated to alter β-lactam PK.

Discussion

This is the first multicentre survey to describe the clinical practice of β-lactam TDM in an international selection of ICUs that currently use TDM for clinical purposes. This report demonstrates the variation in β-lactam TDM practice, especially in selection of β-lactams and the patient population for TDM, drug assay methods, PK/PD targets and dose adjustment strategies. Despite quite significant variations in practice, the general steps that pertain to β-lactam TDM can be summarized as illustrated in Figure 2.

The list of β-lactam antibiotics for TDM in each ICU varied, likely due to differences in the availability of β-lactams in different countries, the hospital formulary, prescribing habits, the case mix of patients and the pattern of bacterial susceptibility.[35–41] Piperacillin, meropenem, ceftazidime, ceftriaxone and cefazolin were subject to TDM in the majority of the ICUs surveyed. This finding is consistent with their high prevalence of usage[36,38,42] and the variable PK that has previously been published in critically ill patients.[21,43–50] Despite an increasing amount of PK data in critically ill patients, the variability in the inclusion criteria for TDM may reflect the lack of robust dosing data.

A range of validated chromatographic β-lactam assays were most commonly used for TDM. All assays were reported to meet regulatory limits of accuracy and precision, with calibration curve concentration ranges that are clinically appropriate. However, some assays have a relatively high limit of quantification (LOQ) (3 and 10 mg/L for meropenem). Although a high LOQ will not cause under-dosing in practice, it may result in unnecessarily high antibiotic exposures in some patients infected by highly susceptible bacteria. Of note, only two ICUs directly measured the unbound concentrations of β-lactams. Given that the unbound concentration of β-lactams is responsible for bacterial killing and that hypoalbuminaemia occurs in ∼40% of critically ill patients,[51,52] measuring total concentrations only may lead to under- or over-estimation of the unbound concentrations and may jeopardize the accuracy of the method, especially for highly protein-bound antibiotics.[53] Most assays are efficient and provide a same-day turn-around for results; however, the availability of TDM was still limited to certain hours and days of the week in some facilities. The chromatography technique used is associated with high equipment and personnel costs, which might theoretically affect the cost–effectiveness of β-lactam TDM. Microbiological assays performed by some units are an alternative to chromatography with comparable precision and robustness that could overcome the disadvantages of chromatography in terms of costs.[26] However, its processing time is comparatively much longer. Interference of concomitant antibiotics with indicator bacteria also limits the use of bioassay in clinical practice.

Only two of the ICUs surveyed routinely measured bacterial MICs for β-lactam TDM. Although other units reported measuring MICs by Etest or Vitek 2 where deemed necessary, the majority of ICUs used local antibiograms or EUCAST breakpoints to determine MICs for PK/PD targets for most patients. Whilst useful for most clinical situations, the reporting of EUCAST breakpoints by microbiology laboratories is mostly categorical (susceptible, intermediate or resistant), only providing the upper MIC threshold for each category, leading to a high target dose that is unnecessary for more susceptible pathogens. In addition, factors used for determination of breakpoints are dynamic, and the predictive value of breakpoints might not hold when the bacterial epidemiology changes or a new resistance mechanism emerges.

Although the majority of ICUs adopted 100% $fT_{>MIC}$ as a PK/PD threshold for dose increase, targets for β-lactam TDM remain

Table 5. Methods for dose adjustment based on initial mode of drug administration

	Dose adjustment strategy
Dose increase	increase dose administration frequency by 25%–50%
	25%–50% increased dose with same frequency
	change to extended infusion (if concentration within 20% of target)
	change to continuous infusion (if at maximum daily dose according to product information)
Dose reduction	decrease frequency of administration at the same dose
	25%–50% decrease in dose with same dosing frequency
	withhold therapy for 1 day

diverse. *In vitro* and animal studies demonstrated that the PK/PD targets of $fT_{>MIC}$ of 35%–40%, 30% and 20% are bacteriostatic for cephalosporins, penicillins and carbapenems, respectively, whilst 40% $fT_{>MIC}$ for carbapenems, 50% for penicillins and monobactams, and 60%–70% for cephalosporins are required for maximum bactericidal effect.[54–57] However, more aggressive PK/PD targets have also been suggested. In a study of critically ill patients with bacteraemia and sepsis treated with cefepime and ceftazidime, 100% $fT_{>MIC}$ was associated with significantly greater clinical cure and bacteriological eradication compared with $fT_{>MIC}$ <100%.[18] Similar data were found by Tam *et al.*,[58] except for a higher PK/PD target with cefepime. The most significant predictor of successful clinical and microbiological responses was determined to be the fC_{min}/MIC ratio of 5 in a study of meropenem PD in patients with lower respiratory tract infections.[59] A similar target was suggested in an *in vitro* PK model of ceftazidime against *Pseudomonas aeruginosa* by Mouton and den Hollander comparing the effectiveness of intermittent and continuous β-lactam infusion.[60] In view of the varied information available in the literature, the variation in clinical practice we observed is not unexpected, although PK/PD targets selected by individual ICUs all cited published literature, albeit different literature. Similar uncertainty in defining a potential toxicity threshold was observed, which is consistent with the scarcity of published data on this topic.[61–63] These observations also support the need for further studies that robustly define PK/PD targets for β-lactam TDM.

Apart from two ICUs that calculated individual PK parameters for each new dosing regimen, the strategies for dose adjustment reported were quite non-specific. Other approaches to dose adjustment were not necessarily widely used or available. The availability of nomograms for β-lactam dosing is limited.[64] PK software could also be applied to more accurately define therapeutic doses, although such software has not been widely tested or validated.[65] In addition to rapid achievement of therapeutic concentrations, accuracy and appropriateness of dose adjustment are needed to maximize the advantages that β-lactam TDM could provide, as is the case when TDM is applied to any antibiotic.[66–68]

Limitation of the study

The differences in clinical environment and antibiotic usage strategy between institutions and the small sample of ICU populations limit the generalizability of our findings. Data collection by convenience sampling may also have introduced a selection bias, although the response rate was high and we are unaware of other centres also performing β-lactam TDM at the time of the survey. Nevertheless, such a bias is probably unavoidable with a limited number of centres around the world known to be performing TDM routinely, and this study is the largest representation of ICUs adopting this strategy in β-lactam antibiotic dosing.

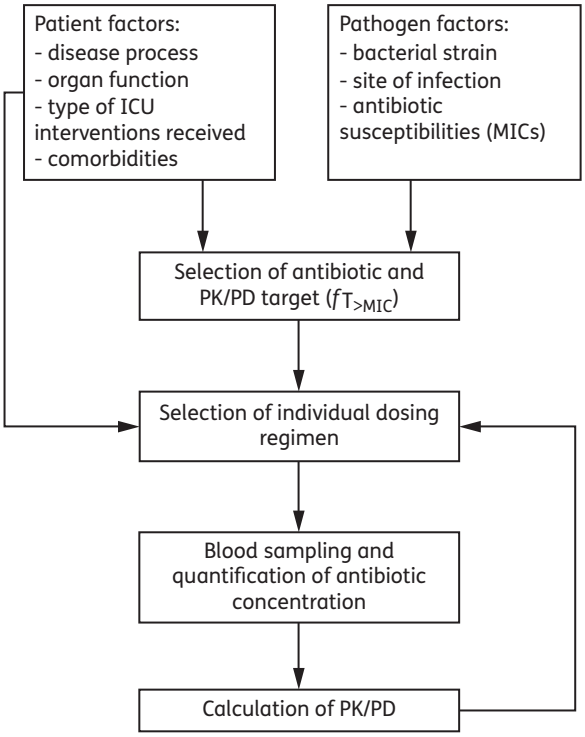

Figure 2. General process used among participating sites for application of β-lactam TDM.

Conclusions

This is the first paper describing the practice strategies used by ICUs that perform β-lactam antibiotic TDM as part of routine clinical care. We found large variations in the β-lactams tested as well as the patients selected for TDM, drug assay methods and dose adjustment strategies. In particular, this survey highlights the controversies that apparently exist relating to the question of which PK/PD targets should be used in critically ill patients. We await robustly designed randomized controlled trials to address this gap in the literature.

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Transparency declarations

None to declare.

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