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Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial

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Take home message: TDM based optimization of antibiotic therapy increases pharmacokinetic target attainment in critically ill patients with normal kidney function receiving meropenem or piperacillin tazobactam.

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Abstract *Purpose:* There is variability in the pharmacokinetics (PK) of antibiotics (AB) in critically ill patients. Therapeutic drug monitoring (TDM) could overcome this variability and increase PK target attainment. The objective of this study was to analyse the effect of a dose-adaption strategy based on daily TDM on target attainment. *Methods:* This was a prospective, partially blinded, and randomised controlled trial in patients with normal kidney function treated with meropenem (MEM) or piperacillin/tazobactam (PTZ). The intervention group underwent daily TDM, with dose adjustment when necessary. The predefined PK/pharmacodynamic (PK/PD) target was 100 % $fT_{>4MIC}$ [percentage of time during a dosing interval that the free (*f*) drug concentration exceeded 4 times the MIC]. The control group received conventional treatment. The primary endpoint was the proportion of patients that reached 100 % $fT_{>4MIC}$ and 100 % $fT_{>MIC}$ at 72 h. *Results:* Forty-one patients (median age 56 years) were included in the study. Pneumonia was the primary infectious diagnosis. At baseline, 100 % $fT_{>4MIC}$ was achieved in 21 % of the PTZ patients and in none of the MEM patients; 100 % $fT_{>MIC}$ was achieved in 71 % of the PTZ patients and 46 % of the MEM patients. Of the patients in the intervention group, 76 % needed dose adaptation, and five required an additional increase. At 72 h, target attainment rates for 100 % $fT_{>4MIC}$ and 100 % $fT_{>MIC}$ were higher in the intervention group: 58 vs. 16 %, $p = 0.007$ and 95 vs. 68 %, $p = 0.045$, respectively. *Conclusions:* Among critically ill patients with normal kidney function, a strategy of dose adaptation based on daily TDM led to an increase in PK/PD target attainment compared to conventional dosing.

Keywords β-Lactam antibiotics · Pharmacokinetics · Pharmacodynamics · Therapeutic drug monitoring · Critical care

Introduction

Infection is an important problem in critically ill patients and an important source of morbidity and mortality in intensive care units (ICUs) [1]. Antimicrobial therapy has emerged as one of the most crucial elements in the treatment of severe infections and has been studied extensively in recent years [2, 3]. Timely initiation of the antimicrobial agent as well as the selection of an antimicrobial agent with the appropriate spectrum have shown to be important

determinants of clinical success. Antimicrobial therapy in ICU patients most often is based on standard dosing protocols, with little or no attention to the baseline characteristics (e.g. weight) or the altered physiology of the patient that results in changes in pharmacokinetics (PK) [4].

Numerous studies [5–9] have demonstrated that antibiotic plasma concentrations—especially those of hydrophilic antibiotics, such as β-lactams—are variable and unpredictable in ICU patients. Increased volume of distribution, changes in protein binding and in the elimination rate from the circulation through the kidney or the use of extracorporeal circuits contribute to this phenomenon, which has important implications [10–12]. A significant number of patients therefore do not reach the pharmacokinetic/pharmacodynamic (PK/PD) target required for the treatment of severe infection [13, 14].

Several strategies have been proposed to overcome this problem, such as continuous or extended infusion [5, 15]. Recently published studies have demonstrated higher PK/PD target attainment [16] as well as improved outcomes [17] when extended or continuous infusion strategies are used, and the results of a randomised controlled trial (RCT) comparing intermittent with continuous infusion demonstrated both better antibiotic exposure and improved clinical cure in the continuous infusion group [18]. However, while continuous infusion may be an improvement over intermittent dosing, in some patients even higher doses may be required.

There have been multiple reports of patients with augmented renal clearance (ARC) in whom standard dosing is not adequate [19, 20]. Some patients required up to fourfold increases in dosing for the treatment of severe infection—and often therapeutic drug monitoring (TDM) was used to guide treatment [20–22]. PK studies also confirmed that some patients may require higher doses of β-lactam antibiotics or glycopeptides, especially when aiming for higher PK/PD targets [23–26].

A more individualised approach using TDM-guided antimicrobial therapy with dosing tailored to the altered PK of the patient may be a proper strategy to overcome this variability and the problem of underdosing [27]. Therefore, we designed a RCT using a TDM-based dose-adaptation strategy in patients with normal kidney function at risk of underdosing who required therapy with piperacillin/tazobactam (PTZ) and meropenem (MEM). We hypothesise that a TDM-based approach will result in the higher attainment of PK/PD targets.

Methods

Study design

Between April 2011 and February 2012 we conducted a prospective, partially blinded RCT at the medical and surgical ICU of Ghent University Hospital. Criteria for inclusion were the need for antibiotic treatment with PTZ and/or MEM, age of ≥18 years, and the presence of an arterial catheter. Patients were excluded in the case of pregnancy and/or lactation, allergy to the administered medication, impaired renal function {estimated glomerular filtration rate as assessed by the CKD–EPI equation of <80 mL/min [28]}, hemoglobin of <7 g/dL, or do-not-resuscitate orders or if the patient was expected not to survive the first 48 h.

Patients were randomly assigned to the control group, receiving conventional dosing, or the intervention group, subjected to TDM-guided dosing which consisted of daily monitoring of the antibiotic plasma concentration, followed by dosing adjustment if the concentration did not meet the predefined target. In the control group, antimicrobial concentration was also measured daily, but the treating physician was blinded to the results, and the data were used for comparison only. Total duration of the study was 7 days. Patients were followed up until hospital discharge.

All antibiotics were administered according to the extended infusion protocol used at Ghent University Hospital: patients received a loading dose (1 g MEM or 4 g PTZ) administered over 30 min, followed immediately by the first extended infusion dose of either antibiotic (1 g MEM or 4 g PTZ) at 6-h (PTZ) or 8-h (MEM) intervals. Extended infusion doses were administered over 3 h using a syringe pump. All antibiotics were administered via a central venous catheter.

Target concentrations in the intervention group were in line with those reported previously using TDM in critically ill patients. It is traditionally accepted that maintaining concentrations above the minimal inhibitory concentration (MIC) of the causative organisms during 40–70 % of the time is adequate. However, recent studies suggest that higher targets are needed in critically ill patients. Given the fact that concentrations four to fivefold greater than the MIC are associated with maximal bactericidal activity [29–31], the PK/PD target in this study was set at 100 % $fT_{>4MIC}$ [percentage of time during a dosing interval that the free (*f*) drug concentration exceeded 4 times the MIC] as in previous studies [20, 32].

Based on actual antibiotic concentrations, dosing of intervention patients then followed a pre-established algorithm (Fig. 1). Until the MIC of the causative microorganism was known, the epidemiological cutoff of wild-type *Pseudomonas* spp. (16 mg/L for PTZ and 2 mg/L for MEM) was targeted, and this MIC was used for all calculations in the study as we only investigated the effect of dose adaptation in the first 72 h—the time it would usually take to determine a MIC of the actual infecting organism. Target trough concentrations were therefore >64 mg/L for PTZ and >8 mg/L for MEM, respectively (>4× MIC). In the case of lower concentrations, dosing frequency was increased as a first step in the intervention (4 g/0.5 g every 4 h for PTZ and 1 g

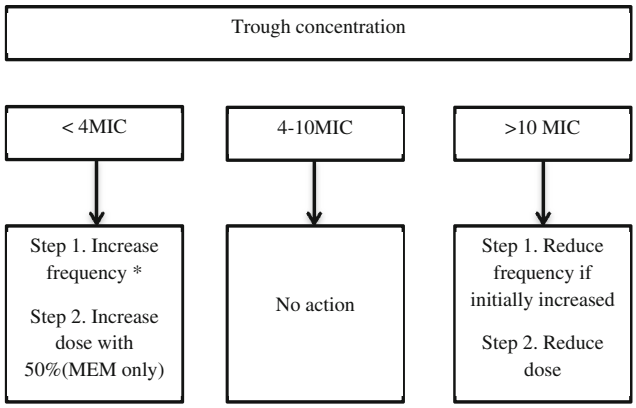

Fig. 1 Therapeutic drug monitoring (TDM)-based dose adaptation strategy. *MIC* Minimal inhibitory concentration, *MEM* meropenem. *Asterisk* see text for details

every 6 h for MEM). If MEM concentrations remained below the target, the dose was increased by 50 %. If these adjustments failed to reach the targets, no further actions were taken. In patients with trough concentrations of >10× MIC, the antibiotic dose was decreased by 50 % or the dosing frequency reduced if this had been increased in an earlier step.

Endpoints

Target attainment defined as 100 % $fT_{>MIC}$ and 100 % $fT_{>4MIC}$ within the first 72 h of treatment were the primary endpoints. The $fT_{>MIC}$ and $fT_{>4MIC}$ at 72 h were compared between the intervention and control groups, as well as between baseline and at 72 h after initiation of treatment. Although fourfold the MIC was the target of the intervention, we also wanted to study the effect of the intervention on a more conservative PK target, hence 100 % $fT_{>MIC}$ was also used as an endpoint.

Secondary endpoints were absolute values of $fT_{>MIC}$ and $fT_{>4MIC}$.

Clinical response at the end of the study (day 7) was evaluated by two of the authors. Resolution was defined as the disappearance of all signs and symptoms related to infection, improvement was defined as a marked or moderate reduction in the severity and/or number of signs and symptoms of infection and failure was defined as insufficient lessening of the signs and symptoms of infection to qualify as improvement, including death. Response to therapy was also evaluated by bacterial persistence at day 7.

Patient data collection

Relevant data were retrieved from the hospital's Electronic Patient File and the unit's Patient Data Management System and included demographic parameters (gender, age), weight, length, date of hospital/ICU admission and discharge, start and end date of the antibiotic treatment with PTZ/MEM, comorbidities, admission diagnosis, type of infection, Acute Physiology And Chronic Health Evaluation (APACHE)-II score, daily Sequential Organ Failure Assessment (SOFA) score, daily body temperature, urinary output and outcome (survival or death) including cause of death. The following laboratory results were recorded: white blood cell count, platelet count, fibrinogen, C-reactive protein, serum creatinine, urinary creatinine and microbiological data.

Study samples

Blood samples were collected daily; during the first 3 days mid-dose (i.e. halfway the dosing interval) and trough samples were obtained and during the last 4 days of the study only trough concentrations were determined. On the first study day, the first sample (baseline concentration) was drawn after at least three completed infusions of the antibiotic. Twenty-four-hour urinary creatinine clearance was measured throughout the study period. The calculated creatinine clearance was corrected for the body surface area.

Sample analysis

The TDM samples were analysed at the Department of Laboratory Medicine of Ghent University Hospital. PTZ and MEM concentrations were assayed by validated ultra-high performance liquid chromatography–tandem mass spectrometry using oxacillin as an internal standard [33].

Sample preparation consisted of protein precipitation using acetonitrile and subsequent dilution. A 5-μL sample was injected onto a BEH C_{18} column (1.7 μm, 100 mm × 2.1 mm) (Waters Corp., Milford, MA), kept at 50 °C. The mobile phase consisted of 0.1 % formic acid in water and 0.1 % formic acid in acetonitrile at a flow rate of 0.350 mL/min. Separated compounds were detected with the Waters® TQD mass spectrometer, which operated in positive electrospray ionisation, using a compound-specific multiple reaction monitoring method. The run time was 5.5 min. The method was linear between 4 and 250 mg/L for PTZ and between 2 and 80 mg/L for MEM. Imprecision and inaccuracy were found to be <15 % at high, medium and low concentrations. Concentrations considered to be below the linear range were reported as <4 mg/L for PTZ and as <2 mg/L for MEM. System performance was monitored by analysing three internal quality control samples at low, medium and high concentrations in each run.

PK and PD calculations

One concentration (C_1) was taken halfway through the dosing interval; the second sample was a trough concentration (C_2). Using these two concentrations, it is possible to calculate the elimination constant (Eq. 1).

$$C_2 = C_1 - \mathrm{ek} \cdot t. \quad (1)$$

Assuming one-compartmental first-order kinetics, these data are sufficient to calculate the time within the dosing interval when the concentration drops beneath a certain threshold (1 or 4× MIC).

Power analysis

The power analysis computed a required sample size of 16 patients per study group, taking into account a one-sided test with $\alpha = 0.05$, $\beta = 0.20$ and an expected increase of target attainment (with trough concentrations of at least 4× MIC as a target) from 50 to 90 % of the patients. Taking into account a dropout rate of 20 %, 20 patients per group were projected.

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics ver. 19.0 (SPSS Inc., Chicago, IL). Data for continuous variables are expressed as median values with interquartile ranges (IQR), and those for categorical variables as numbers and percentages. The Mann–Whitney *U* test for comparison of median values and the Friedman test or the Wilcoxon matched-pairs signed-ranks test were used where appropriate. Proportions were compared using 2 × 2 tables and the χ^2-test or Fisher's exact test as appropriate. A *p* value of ≤ 0.05 was considered to be statistically significant.

Ethics

The study was approved by the Ethics Committee of the Ghent University Hospital (registration number 2010/814) and approved by the Belgian regulatory agency (B67021020250). Written informed consent was obtained from the patient or his/her legal representative.

Results

A total of 41 patients were included in the study—21 in the intervention group and 20 in the control group. Twenty-eight patients received PTZ (15 in the intervention group, 13 in the control group) and 13 patients received MEM (6 in the intervention group, 7 in the control group).

The majority of the patients were male ($n = 35$, 85 %). Characteristics of the intervention and control patients were comparable and are summarised in Table 1. Most patients were treated for pneumonia (78 %); other diagnoses included tracheobronchitis, peritonitis and blood stream infection (Table 1); one patient received antibiotics due to febrile neutropenia.

Forty-three causative microorganisms were cultured from 27 patients; the isolates included *Escherichia coli*

Table 1 Patient characteristics of the study population

Characteristics	All patients ($n = 41$)	Intervention ($n = 21$)	Control ($n = 20$)	*p* value
Age (years)	56 (46–69)	57 (42–76)	56 (48–64)	0.804
Weight (kg)	76 (67–88)	77 (69–89)	75 (66–88)	0.657
Body mass index (kg/m^2)	25 (22–27)	25 (22–28)	24 (22–25)	0.705
APACHE II score	18 (13–24)	19 (12–24)	17 (13–23)	0.557
Day 1 SOFA score	5 (2–6)	5 (3–6)	5 (2–6)	0.711
Day 1 creatinine clearance (mL/min)	99 (80–135)	130 (92–177)	108 (88–145)	0.291
Day 2 creatinine clearance (mL/min)	115 (82–170)	129 (100–167)	106 (74–175)	0.461
Day 3 creatinine clearance (mL/min)	131 (90–172)	155 (83–182)	110 (90–165)	0.697
Infection characteristics				
Pneumonia	32 (78 %)	16 (80 %)	16 (76 %)	
Tracheobronchitis	2 (%)	1 (5 %)	1 (5 %)	
Peritonitis	5 (12 %)	3 (15 %)	2 (10 %)	
Blood stream infection	1 (2 %)	0 (0 %)	1 (5 %)	
Febrile neutropenia	1 (2 %)	0 (0 %)	1 (5 %)	
Community-acquired infection	3 (7 %)	2 (10 %)	1 (5 %)	
Hospital-acquired infection	38 (93 %)	18 (90 %)	20 (95 %)	

Data are presented as the median with the interquartile range in parenthesis, or as a number (of patients) with the percentage in parenthesis, as appropriate

APACHE Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *ICU* Intensive care unit, *IQR* Interquartile range

($n = 7$), *Klebsiella pneumoniae* ($n = 7$), *Pseudomonas aeruginosa* ($n = 6$), *Enterobacter cloacae* ($n = 4$), *Staphylococcus aureus* ($n = 4$), *Klebsiella oxytoca* ($n = 2$), *Acinetobacter baumanii* ($n = 2$), *Enterococcus faecalis* ($n = 2$), *Prevotella spp.* ($n = 2$), *Citrobacter* spp. ($n = 2$), *Morganella morganii* ($n = 2$), *Serratia marcescens* ($n = 2$), *Enterobacter aerogenes* ($n = 1$) and *Streptococcus viridans* ($n = 1$). The median MIC was 2 (IQR 1.5–8) mg/L for PTZ and 0.125 (IQR 0.125–0.690) mg/L for MEM.

Median antibiotic concentrations before randomisation were 30 (IQR 18–56) mg/L for PTZ and <2 (IQR <2–4) mg/L for MEM.

Baseline target attainment was as follows: 100 % $fT_{>4MIC}$ was achieved in 21.4 % of the PTZ patients and in none of the MEM patients; 100 % $fT_{>MIC}$ was achieved in 71.4 % of the PTZ patients and 46.2 % of the MEM patients. The median $fT_{>4MIC}$ at baseline was comparable for both antibiotics, with 46.5 % for PTZ (IQR 18–86.25) and 56.5 % for MEM (IQR 15–65). Median baseline $fT_{>MIC}$ was much higher at 100 % for both PTZ and MEM.

Patients in the intervention group had numerically lower baseline median concentrations than the controls (PTZ 26 vs. 40 mg/L; MEM <2 vs. 2 mg/L, respectively). As a consequence, at baseline fewer intervention patients achieved 100 % $fT_{>4MIC}$ (9.5 vs. 20 %, respectively), and their $fT_{>4MIC}$ was lower (44.5 vs. 58 %, respectively).

In the intervention group, dose adaptation was necessary in 16 patients (76 %); the initial step of increasing the frequency was enough to reach the target of 4× the MIC in 69 % (11/16) of these patients.

Three patients did not complete the study protocol and, consequently, target attainment at day 3 could not be calculated for these patients. In the remaining 38 patients, the use of a TDM-based dose adaptation protocol significantly increased the proportion of patients reaching the PK/PD target within the first 72 h of treatment: 94.7 % of the intervention patients reached 100 % $fT_{>MIC}$ in contrast to 68.4 % of the control patients ($p = 0.045$). Also for the target of 100 % $fT_{>4MIC}$, attainment rates were higher in the intervention group (57.9 vs. 15.8 %, $p = 0.007$) (Figs. 2, 3). No adverse events occurred.

The intervention significantly increased the median $fT_{>4MIC}$ from 44.5 to 86 % and 90 % on days 2 and 3, respectively ($p = 0.012$) (Fig. 4).

Clinical failure was present in four and two patients in the control and intervention groups, respectively ($p = 0.41$); bacterial persistence at day 7 was present in five and one patients in the control and intervention groups, respectively ($p = 0.09$).

The recovery of organ function during the study was evaluated using the SOFA score in patients who completed the 7-day study protocol ($n = 15$). The median SOFA score changed from 5.5 to 3 in the intervention patients ($p = 0.093$) and from 5 to 4 in the control group ($p = 0.575$).

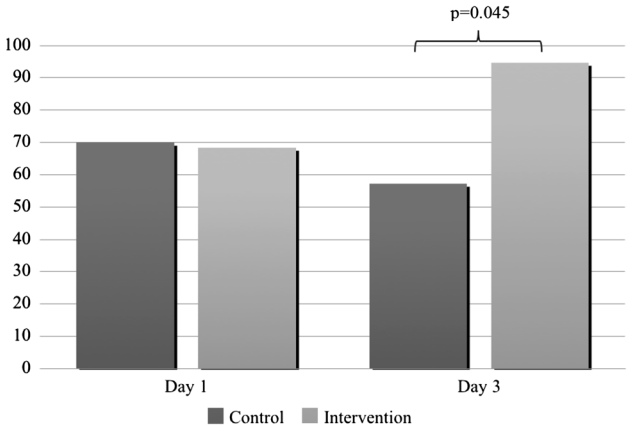

Fig. 2 Percentage of control and intervention patients reaching 100 % $fT_{>MIC}$ at baseline and on day 3. $fT_{>MIC}$ Cumulative percentage of a 24-h period that the free (*f*) drug concentrationexceeded the MIC under steady-state pharmacokinetic conditions

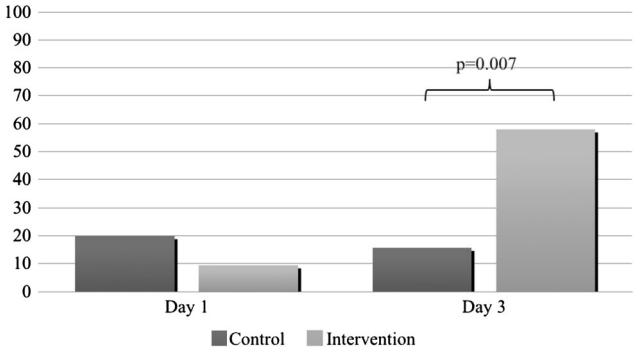

Fig. 3 Percentage of control and intervention patients reaching 100 % $fT_{>4MIC}$ at baseline and on day 3. *>4MIC* Fourfold the MIC

Five patients died in the ICU [4 control patients (20 %) and 1 intervention patient (4.8 %); $p = 0.18$]. Hospital and 28-day mortality were also not significantly different, with five deaths in the control group and three in the intervention group (25 vs. 14.3 %, respectively; $p = 0.45$).

Discussion

In this study we found that daily TDM with dose adaptation resulted in a higher median $fT_{>4MIC}$, and a higher proportion of patients attaining both the 100 % $fT_{>MIC}$ and 100 % $fT_{>4MIC}$ target in patients with normal kidney function. This attainment of the target level required doses that were 33–100 % higher than those used in standard dosing regimens.

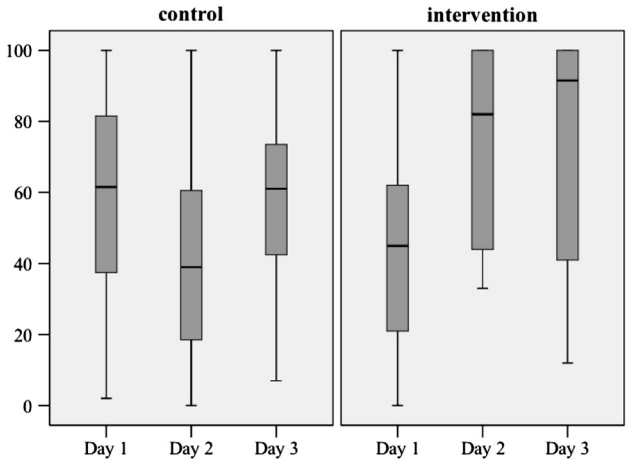

Fig. 4 Boxplots of time above the 4× MIC ($fT_{>4MIC}$) during the first 3 days of treatment in control and intervention patients. *Top, bottom of box* 25 and 75 % percentile, respectively, *dark horizontal line in box* median, *whiskers* minimum and maximum, respectively

We also demonstrated that standard dosing—even using extended infusion—does not reach target antibiotic concentrations in all patients, either the 100 % $fT_{>MIC}$ or 100 % $fT_{>4MIC}$ target. Both the extended and continuous infusion of β-lactam antibiotics have been found to increase exposure of the microorganism to the antibiotic, which in the case of time-dependent antibiotics, such as piperacillin and MEM, should theoretically lead to a more efficient antibiotic effect, faster control of the infection and improved outcomes. There is an abundance of simulation data in the literature—most often based on studies in healthy or non-critically ill patients but all consistently demonstrating that extended or continuous infusion results in improved target attainment rates. Small-scale clinical studies have confirmed this for both piperacillin and MEM [5, 25]. However, extended infusion may not be sufficient to overcome the changed physiology of the patient, notably when higher PK targets are used or (borderline) resistant microorganisms are involved but also in more common settings, such as ARC. Taccone et al. [23] recently reported a patient infected with a highly resistant microorganism who needed a daily dose of 12 g MEM to treat the infection.

The question remains if our findings apply to all patients in the ICU. This study was performed in patients considered to be at the highest risk of underdosing, i.e. patients with apparent normal renal function. ARC is a frequent finding in this population [34], and for many antibiotics, including piperacillin and MEM, drug clearance is largely determined by renal clearance [11]. ARC has been linked to inadequate antibiotic concentrations [20] and will also have played a role in our study. It is possible that ARC patients are the best candidates for a TDM-based approach to optimise antibiotic exposure. However, other patient categories may be at risk of underdosing. Hites et al. [35] recently reported that obese critically ill patients treated with carbapenems had lower concentrations than non-obese patients.

This study has a number of limitations. First, the study was performed in selected ICU patients and patients with impaired renal function or on renal replacement therapy (RRT) were excluded. Patients on RRT are at particular risk of underdosing when package insert dosing recommendations are followed, and they may indeed also benefit from a TDM-based antibiotic dosing approach. Secondly, we only measured total antibiotic concentrations, and not free antibiotic concentrations. Protein binding is limited for piperacillin and almost nil for MEM [36], and therefore the potential effect of changes in protein binding is expected to be limited. Furthermore, the study was not designed or powered to detect any difference in clinical outcome parameters. Finally, we did not include a second step of dose increase in those patients who had inadequate piperacillin concentrations. This would have increased the daily dose to 36 g piperacillin and 4.5 g of tazobactam, a very high dose of which the PK has never been investigated. As the PK of both compounds are not completely alike, administration of a high dose of PTZ could potentially lead to accumulation of tazobactam and related toxicity.

The potential benefits of a TDM-based approach include a better outcome because of more appropriate antibiotic concentrations, but also less resistance development and avoidance of toxicity. Although considered safe, β-lactam antibiotics have a number of adverse effects, including neurotoxicity, liver damage and bone marrow suppression, and some of these are dose-dependent. TDM may thus not only be helpful to increase efficacy but also to reduce toxicity.

Although TDM was able to increase target attainment, it should be noted that underdosing remains frequent in the initial phase; TDM may be useful to correct initial underdosing, but alternative strategies remain warranted to avoid underdosing in the first 24 h of therapy. Dose predictions based on PK modeling may offer a solution to counter this.

The literature on the TDM-based approach for β-lactam dosing is limited [37], and the use of TDM in clinical practice remains controversial [38]. Roberts et al. [32] demonstrated that 74 % of 236 patients treated with β-lactam antibiotics did not reach adequate concentrations and therefore needed dose adjustment. However, the effect of the latter was not systematically evaluated; only 21 % of the patients were re-sampled, and only 43 % of these reached adequate concentrations, confirming our findings. TDM has also proved beneficial in specific populations, such as burn patients. Patel et al. [39] found that TDM was able to detect underdosing in up to 60 % of the patients. Several case reports have shown that in difficult situations, either patients with a complex physiology or microorganisms with increased resistance to an antibiotic, TDM may indeed be useful to guide therapy [19, 21–23]. Our

study is, however, the first to pharmacokinetically confirm that dose adaptation results in better target attainment.

In conclusion, TDM-based dose adaptation of β-lactam antibiotic therapy improves antibiotic exposure in critically ill patients with normal renal function. Whether this approach leads to improved outcomes remains to be determined.

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Conflicts of interest The authors declare that they have no conflict of interest.

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Monitoring-based antibiotic dose optimisation

Therapeutic drug monitoring (TDM)-based dose adjustment of piperacillin/tazobactam and meropenem is associated with improved antibiotic exposure in critically ill patients with normal renal function.
Level of evidence: 1B (CEBM, RCT of good quality)

Appraised by: B Spooner and T Whitehouse

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Three-part clinical question:
Patients: Critical care patients with normal renal function who were receiving piperacillin/tazobactam and/or meropenem.
Intervention: Therapeutic drug monitoring (TDM)-based dose adjustment of piperacillin/tazobactam and meropenem.
Outcomes: The primary outcome was the percentage of time the plasma antibiotic concentration exceeded four times the minimum inhibitory concentration (MIC) of the causative organism (or if unknown, the MIC used was the epidemiological cut-off of wild-type *Pseudomonas* species of 16 mg/L for piperacillin/tazobactam and 2 mg/L for meropenem) during a dosing interval, over the first 72 h of treatment (% $fT_{>4MIC}$). The target was 100%.

Secondary outcomes were the percentage of time the plasma antibiotic concentration exceeded the MIC during a dosing interval over the first 72 h of treatment (% $fT_{>MIC}$) and absolute values for the $fT_{>4MIC}$ and $fT_{>MIC}$. Clinical response was also evaluated at day 7. ICU, hospital and 28-day mortality were recorded.

Search terms: B-lactam antibiotics, pharmacokinetics, pharmacodynamics, therapeutic drug monitoring (TDM), critical care

Study design: Single-centre, prospective, partially blinded, randomised controlled trial.

The study patients:
Eligible: Patients over 18 years old, receiving piperacillin/tazobactam and/or meropenem on ICU, with an arterial catheter (for blood sampling).
Included: 41 patients from the ICU at Ghent University Hospital, Belgium between April 2011 and February 2012.
Exclusion criteria: Pregnancy, lactation, allergy to administered drugs, impaired renal function (eGFR < 80), haemoglobin <7 g/dL, do not resuscitate order or if the patient was not expected to survive 48 h.

Control group: (20 patients) Antibiotics were delivered according to standard hospital extended infusion protocols (30 min loading infusion followed by infusion over 3 h). The infusion was then repeated at 6 hourly (piperacillin/tazobactam) or 8 hourly (meropenem) intervals. Antibiotic levels were taken at predefined times throughout the study.

Therapeutic drug monitoring dose adjustment group: (21 patients) As per control group except the dosing frequency (and dose for meropenem) was increased or decreased according to a pre-defined algorithm based on the actual antibiotic levels.

The evidence:

	Group		
	Dose adaptation	**Control**	***p***
Primary outcome			
% time when plasma levels above target [target = 100% $fT_{>4MIC}$]	57.9%	15.8%	0.007
Secondary outcomes			
% time when plasma levels above target [target = 100% $fT_{>1MIC}$]	94.7%	68.4%	0.045
Treatment failure	9.5%	20%	0.41
Bacterial presence on day 7	4.8%	25%	0.09
Death on ICU	4.8%	20%	0.18
Death at 28 days	14.3%	25%	0.45

Key % $fT_{>4MIC}$: percentage of time the plasma antibiotic concentration exceeded four times the minimum inhibitory concentration (MIC) of the causative organism over the first 72 h of treatment. % $fT_{>1MIC}$: percentage of time the plasma antibiotic concentration exceeded the minimum inhibitory concentration (MIC) of the causative organism over the first 72 h of treatment.

- Significantly more patients achieved target antibiotic plasma levels in the intervention group.
- The intervention significantly increased the median time the antibiotic levels were more than four times MIC (44.5% to 86% on day 2 and 60% to 90% on day 3; $p = 0.012$).
- There were no adverse events relating to antibiotics in either group.

EBM questions:

1. *Do the methods allow accurate testing of the hypothesis?* **Yes.** This study was well designed to detect whether dose adjustment (based on daily therapeutic drug monitoring) could achieve better pharmacokinetic target attainments than with standard dosing. It was a single-centre, prospective, partially blinded, randomised controlled trial. The main outcomes were blinded. Some of the secondary clinical outcomes (clinical response at day 7) were only partially blinded making observer bias unlikely; however, this does not weaken the main pharmacokinetic outcomes of the study.
2. *Do the statistical tests correctly test the results to allow differentiation of statistically significant results?* **Yes**, although this is the first work of its kind and powering the study was impossible.
3. *Are the conclusions valid in light of the results?* **Yes.** They are that:
   - TDM-based dose adaptation of beta-lactam antibiotic therapy improves antibiotic exposure in critically ill patients with normal renal function.
   - Standard dosing does not achieve target concentrations in all patients even with conservative plasma targets.
   - Whether TDM-based dose adaptation leads to improved patient outcomes remains to be determined.
4. *Did results get omitted and why?* **Yes.**
   - Three patients did not complete the study protocol and target attainment at day 3 could not be calculated for these patients.
5. *Did they suggest areas of future research?* **Yes.** It suggests TDM could be studied in patients at risk of under-dosing (obese patients and patients on renal replacement therapy). The paper also acknowledges it was not powered to detect clinical outcome differences and this requires further study.
6. *Did they make recommendations based on the results and were they appropriate?* **No.**
7. *Is the study relevant to my clinical practice?* **Yes.** The study shows many (up to 85%) patients with normal renal function may not be receiving adequate doses of piperacillin/tazobactam or meropenem. This could explain treatment failure on ICU and contribute to unnecessary morbidity and mortality; this may also add to selection pressures and compound antibiotic resistance. TDM is a strategy to address this shortfall in antibiotic delivery.
8. *What level of evidence does this study represent?* ***1B*** (Well-conducted single-centre, blinded, randomised controlled trial)
9. *What grade of recommendation can I make on this result alone?* **B.**
10. *What grade of recommendation can I make when this study is considered along with other available evidence?* **B.** There are other studies (not randomised controlled trials and with limitations) about TDM with beta-lactams but they mainly highlight the issue of insufficient plasma levels.
11. *Should I change my practice because of these results?* **No**.
    - Although it is likely that there are patients with normal renal function on critical care who are receiving insufficient levels of meropenem and piperacillin, TDM is not available in most hospitals and therefore wide-scale implementation is currently not possible.
12. *Should I audit my current practice because of these results?* ***Yes, if possible***, where TDM is available.

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