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Impact of β-lactam antibiotic therapeutic drug monitoring on dose adjustments in critically ill patients undergoing continuous renal replacement therapy

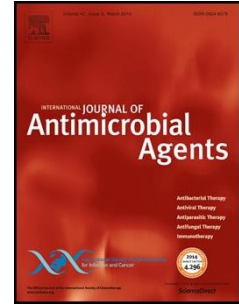Caleb J.P. Economou [a,b], Gloria Wong [a], Brett McWhinney [c], Jacobus P.J. Ungerer [c], Jeffrey Lipman [a,d], Jason A. Roberts [a,d,e,f,*]

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Highlights

- Antibiotic dosing in continuous renal replacement therapy in ICU patients is highly challenging.

- Over one-third of patients had concentrations outside the therapeutic range.

- 24% of therapeutic drug monitoring (TDM) results manifested unnecessarily high antibiotic concentrations.

- TDM is useful for ensuring optimised dosing.

- Hospital-acquired pneumonia patients had the highest rates of excessive antibiotic concentrations.

ABSTRACT

The objective of this study was to describe the effect of therapeutic drug monitoring (TDM) and dose adjustments of β-lactam antibiotics administered to critically ill patients undergoing continuous renal replacement therapy (CRRT) in a 30-bed tertiary intensive care unit (ICU). β-Lactam TDM data in our tertiary referral ICU were retrospectively reviewed. Clinical, demographic and dosing data were collected for patients administered β-lactam antibiotics while undergoing CRRT. The target trough concentration range was 1–10× the minimum inhibitory concentration (MIC). A total of 111 TDM samples from 76 patients (46 male) with a mean ± standard deviation age of 56.6 ± 15.9 years and weight of 89.1 ± 25.8 kg were identified. The duration of antibiotic therapy was between 2 days and 42 days. TDM identified a need for dose modification of β-lactam antibiotics in 39 (35%) instances; in 27 (24%) samples, TDM values resulted in decreasing the prescribed dose of β-lactam antibiotic whereas an increase in the prescribed dose occurred in 12 (11%) cases. In patients

treated for hospital-acquired pneumonia and primary or secondary bacteraemia, the dose was required to be decreased in 10/25 (40%) and 7/46 (15%) cases, respectively, to attain target concentrations. β-Lactam TDM is a useful tool for guiding drug dosing in complex patients such as those receiving CRRT. Although over one-third of patients manifested concentrations outside the therapeutic range, most of these CRRT patients had excessive β-lactam concentrations.

1. Introduction

Antibiotic dosing in critically ill patients has been increasingly studied in recent years as many antibiotics display severely altered pharmacokinetics in this patient population [1]. Drug and patient factors associated with altered pharmacokinetics in critically ill patients include the hydrophilicity of the antibiotic, use of invasive procedures and devices in the intensive care unit (ICU), organ dysfunction and fluctuating fluid balance [1]. Antibiotics are commonly prescribed in the critical care setting [2] for the treatment or prophylaxis of infection. There is currently a dearth of information available for dosing antibiotics in critically ill patients given the extreme heterogeneity of this patient population. Therefore, prescribers are often required to extrapolate data from existing studies when selecting an antibiotic dosing regimen for individual critically ill patients. The number of factors that need to be considered for potential effects on antibiotic dosing in critically ill patients receiving renal replacement therapy (RRT) further increases. Indeed, RRT is indicated for a variety of conditions in critically ill patients, such as acute kidney injury, fluid overload, metabolic acidosis, electrolyte disturbances and drug overdose. RRT introduces a largely unquantified effect on β-lactam concentrations.

Therapeutic drug monitoring (TDM) of β-lactam antibiotics has been proposed as an intervention to optimise dosing, particularly in critically ill patients. TDM that measures the unbound concentration of the β-lactam can guide dose adjustment which can ensure free (unbound) concentrations above the minimum inhibitory concentration (MIC) of the causative pathogen. Indeed, maximum bactericidal activity is believed to occur when β-lactam antibiotic concentrations are maintained

above the MIC for a specified amount of time; the percentage of time required ($\%fT_{>MIC}$) for this to occur is 40%, 50% and 60–70% for carbapenems, penicillins and cephalosporins, respectively [3]. The clinical rationale of TDM is to minimise the incidence of subtherapeutic and supratherapeutic drug concentrations with the aim of improving treatment success and minimising drug toxicity, respectively.

The aim of this study was to describe the effect of TDM and dose adjustments of β-lactam antibiotics administered to critically ill patients undergoing continuous RRT (CRRT).

2. Materials and methods

2.1. Patients

Patients prescribed β-lactam antibiotics in our unit are routinely sampled up to four times weekly as part of the β-lactam TDM programme. Therefore, data were prospectively collected in consecutive patients requiring β-lactam antibiotic treatment in our 30-bed non-cardiac tertiary adult ICU. From February 2009 until December 2011, data from all patients aged ≥18 years undergoing CRRT in whom TDM samples were obtained for piperacillin/tazobactam (TZP), meropenem, benzylpenicillin, ampicillin, flucloxacillin and ceftriaxone were reviewed. Patients were evaluated regardless of antibiotic indication but must have been undergoing CRRT at the time of antibiotic administration and were expected to remain on CRRT for the following 48 h. Exclusion criteria included expected antibiotic cessation within 24 h of identification of expected sampling. Ethical approval for data collection was granted by the Ethics Committee of Royal Brisbane and Women's Hospital

(Brisbane, QLD, Australia), and the need for informed consent was waived in view of the retrospective nature of the data analysis of the prospectively completed database.

2.2. Sampling

Blood samples were taken immediately before re-dosing to determine trough concentrations of the antibiotic at steady-state, defined as prior administration of four consecutive doses. Steady-state samples were collected to avoid incorrect interpretation of results in which the distribution kinetics of the antibiotic may have provided a misleadingly low concentration. Total blood concentrations and free unbound drug concentrations were measured by the hospital Pathology Department and were made available for clinical review within 8 h of collection as previously described [4]. Determination of unbound β-lactam antibiotic concentrations, including the chromatographic system, solutions and sample preparation used at our institution, have been previously described in a report by Briscoe et al. [5].

2.3. Therapeutic drug monitoring targets

The pharmacodynamic targets for β-lactam antibiotics have been defined in in vitro and animal models to be unbound concentrations above the MIC of the infective bacteria for 40–70% of the dosing interval [6]. For convenience and to increase feasibility, an unbound drug concentration above the MIC for 100% of the dosing interval is the most common target of treatment for β-lactam TDM programmes and is also used in our institution [7]. Dose decreases were performed when the unbound trough concentration was >10× MIC.

2.4. Continuous renal replacement therapy

Continuous venovenous haemodiafiltration (CVVHDF) is the most commonly applied form of CRRT in our ICU. During the data collection period, CRRT was initiated as a standard of care using an Aquarius (Edward Life Sciences, Sydney, NSW, Australia) RRT machine. Vascular access was achieved using a double-lumen catheter in the internal jugular or femoral vein. The haemodiafilter was a hollow-fibre high-flux AN69 Nephral ST 200 (Gambro Lundia AB, Lund, Sweden) polyacrylonitrile and sodium methallyl sulfonate copolymer filter with a surface area of 1.05 m^2. The dialysate and replacement fluid used was lactate-free Hemosol BO (Gambro Lundia AB). The CRRT circuit was anticoagulated with unfractionated heparin or regional sodium citrate.

2.5. Susceptibility data

β-Lactam concentrations were compared with the susceptibility of the known or suspected pathogen. Where identified, the MIC of the pathogen was provided as determined using VITEK®2 (bioMérieux, Durham, NC). Where the MIC for an individual pathogen was not available, susceptibility breakpoints were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST). If no organism was isolated for a patient, the susceptibility of the potential pathogen was based on local bacterial epidemiology, and the highest MIC in the susceptible range was selected as the dosing target. Patients admitted for >48 h prior to developing symptoms indicative of a bacterial infection were deemed to have nosocomial infection.

2.6. Statistical analysis

Various data relating to demographics, clinical characteristics, microbiology, CRRT and clinical outcome were collected. Descriptive statistics were used to describe the patient sample, with data presented as the mean ± standard deviation and range. Where appropriate, percentages are used to describe the data.

3. Results

3.1. Patients

A total of 76 patients met the inclusion criteria for this study (30 female and 46 male), with 111 TDM samples collected. The mean age of the patients was 56.6 ± 15.9 years (range 21–86 years) with a mean weight of 89.1 ± 25.8 kg (range 36–175 kg). The mean serum creatinine concentration was 205.2 ± 120.3 μmol/L and the mean duration of antibiotic therapy was 7 ± 6 days (range 2–42 days). The demographic data of the patients are listed in Table 1. Two patients received multiple drug dose changes, one patient received two consecutive dose decreases, whilst another patient received three consecutive dose increases following TDM. In the study population, 38% (29/76) of patients had bacteraemia as the source of infection, with hospital-acquired pneumonia (29%; 22/76), abdominal sepsis (13%; 10/76) and urosepsis (8%; 6/76) being the other most common indications for therapy. Modification of the antibiotic dose based on indication is presented in Table 2. The antibiotic dose from which the TDM concentration was measured and the need for subsequent dose adjustment is shown in Table 3. The mortality data of patients who died during treatment with the study antibiotics and the number of micro-organisms

identified and not identified based on clinical diagnosis are presented in Table 4 and Table 5, respectively. There were no documented adverse events during the course of this retrospective study.

3.2. Continuous renal replacement therapy

TDM samples were collected during 111 episodes of CVVHDF. In four of these episodes the CRRT settings were changed during treatment, with the patients undergoing periods of continuous venovenous haemofiltration (CVVH). Post-dilution was the primary fluid replacement setting used during study data collection, accounting for 107 (96%) episodes, whilst pre-dilution was used in 9 (8%) episodes and 5 (5%) treatments used both pre- and post-dilution. The CRRT modes and settings reported in Table 1 show the standard CVVHDF settings during TDM sampling used a blood flow rate of 200 mL/min, a dialysis flow rate of 1000 mL/h, an ultrafiltration rate of 150 mL/h, a post-dilution rate of 1000 mL/h and, when used, a pre-dilution rate of 1000 mL/h.

3.3. Dose adjustment data

Over the data collection period, TDM values required 27 (24%) dose decreases, 12 (11%) dose increases and maintenance of the current antibiotic dosing regimen in 72 patients (65%). Table 3 displays the antibiotic dosing regimen administered to the patient and the subsequent dose adjustment upon availability of the TDM result.

When considering antibiotic dosing regimens by indication for therapy, for bacteraemia, abdominal sepsis and skin and soft -tissue infections no dose

adjustment was required based on the majority of TDM samples obtained. In contrast, TDM targets demonstrated the need to increase the antibiotic dose in hospital-acquired pneumonia in 5 (20%) cases whilst decreasing the antibiotic dose in 10 (40%) of that same patient population.

3.4. β-Lactam treatment failures

Eighteen deaths occurred in this cohort of patients during treatment with the prescribed antibiotics (Table 5). The duration of β-lactam therapy in this patient group ranged from 2–10 days. Of note, the admission diagnosis for the majority of these patients was not due to an infectious aetiology but was the result of an acute or chronic deteriorating health condition with an associated progressive morbidity.

4. Discussion

In this study, we found that antibiotic dose adjustment was indicated in 39 (35%) patients presumed to be at pharmacokinetic 'steady-state'. Indeed, this is a significant proportion of patients in this single-centre study and supports the further need, first, to describe innovative individualised approaches to antibiotic dosing that can improve the achievement of therapeutic concentrations. Second, this study also supports the conduct of clinical studies that evaluating whether dose optimisation of β-lactams to achieve target concentrations results in improved patient outcomes.

β-Lactam antibiotics display time-dependent characteristics in which optimal bacterial killing occurs when the free drug concentration remains above the MIC ($fT_{>MIC}$) of the bacteria at the site of infection throughout the dosing interval [8]. Some

clinical data support even higher exposures of concentrations that are 4–5× MIC. In the current study, 72 TDM samples (65%) achieved the pre-defined pharmacokinetic targets, suggesting that the same dose could be maintained until subsequent TDM sampling or patient monitoring showed otherwise. Interestingly, almost one-quarter of TDM values reported (27/111; 24%) required a decrease of the β-lactam antibiotic dose; 14 (52%) of those dose decreases occurred for TZP when dosed at 4.0/0.5 g every 6 h or 4.0/0.5 g every 8 h. TZP in these cases was indicated to treat infection with *Pseudomonas aeruginosa* or an Enterobacteriaceae with MICs of 16 mg/L or 8 mg/L, respectively. Despite the relatively high MICs, TZP dramatically exceeded the target concentration. Beumier et al. described the differences in β-lactam antibiotic concentrations during the later treatment phase during CRRT in which β-lactam antibiotics demonstrated higher TDM concentrations in their study [9]. Furthermore, TDM values reported for drugs with high protein binding (flucloxacillin and ceftriaxone) suggested the need to decrease or increase the dose in three episodes (21%) (Table 3). The pharmacokinetics of these antibiotics in critically ill hypoalbuminaemic patients have been described elsewhere [10,11]. A review by Jamal et al. concluded that clearance of piperacillin, meropenem and vancomycin positively correlated with effluent flow rate [12]. Whilst highly protein bound antibiotics were not included in the review by Jamal et al., it is plausible that the nature of the chemical interactions that facilitate protein–antibiotic binding may affect the amount of bound drug that is removed during RRT, as described by other researchers [12,13].

Dosing of β-lactam antibiotics in critically ill patients poses many challenges as both the volume of distribution and clearance of hydrophilic drugs, including β-lactams,

may be affected. Critically ill patients undergoing CVVHDF provide further challenges in dosing owing to the paucity of information available as well as variability in CVVHDF settings, membrane filter material and filter size. The fluid volume status of the patient further complicates this, as CVVHDF in many cases is aimed at removing excess fluid from the patient thereby decreasing the volume of fluid in which hydrophilic drugs are distributed. As euvolaemia is restored in hypervolaemic patients, the volume in which β-lactam antibiotics disperse may be reduced thereby potentially raising the plasma concentration of the drug. The rate at which CRRT corrects fluid volumes in relation to time and the subsequent effect on antibiotic pharmacokinetics remains largely unknown. This concept is also problematic when prescribing β-lactam antibiotics in RRT other than CRRT. The CVVHDF settings in our patient group displayed some variation in which flow rates of dialysis, ultrafiltrate and post-dilution were modified during a patient's treatment to meet the clinical need. In a retrospective analysis of TDM in ICU patients undergoing CRRT, Beumier et al. showed that β-lactam drug clearance was positively correlated with intensity (mL/kg/h) of CRRT, and the $T_{>MIC}$ was lower in patients with high CRRT intensity [9]. These authors also showed that antibiotic concentrations were also higher at >5 days of therapy compared with those at 2 days, which may in part support the hypothesis of higher concentrations with fluid removal over time.

Trotman et al. suggested dosing meropenem at 1 g every 12 h during CVVH or CVVHDF [14]. A previous study by Seyler et al. found that this dose was inadequate in reaching target their chosen pharmacodynamic targets for bacteria with an MIC > 1 mg/L in critically ill patients [15]. Only three of our patients received this dose, with most receiving 500 mg every 8 h. Indeed, this smaller but more frequent dose of

meropenem very consistently achieved our chosen pharmacodynamic targets, which was specific to an MIC of 2 mg/L.

Patients receiving TZP provided the largest number of TDM samples (53/111; 48%), and when TZP was dosed at 4.0/0.5 g every 8 h no patients required a dose increase. These results are similar to those described by Awissi et al. in which TZP was administered as a 4-h infusion in 20 critically ill patients receiving CVVHDF [16]. The authors of that study found piperacillin $fT_{>MIC}$ for *P. aeruginosa* (MIC of 64 mg/L) occurred in 18 patients for $\geq$50% of the dosing interval. This result contrasts with that from Seyler et al. who reported failure to attain concentrations for higher MICs with TZP doses 4.0/0.5 g every 6 h in critically ill patients undergoing CRRT [15]. The differences in observations between studies may be attributed to differences in the critically ill patient population and demographics [17], residual renal function, method of drug administration, fluid status, CRRT settings, membrane material and size, indication for antibiotic and CRRT, and study size.

This study has limitations. First, the prescription of CVVHDF was suited to meet the clinical needs of the individual patient. This included changes in the flow rates of the blood, ultrafiltrate, dialysate and pre/post-dilution fluid. It follows that pharmacokinetic variability of antibiotics may exist due to the heterogeneity of critically ill patients and CRRT settings, although this is the scenario clinically. Second, in patients in whom an infective organism was not identified, the target concentrations were based on the susceptibility of the most likely infective pathogen. The target MIC was therefore based on information from the local antibiogram for the institution and as such higher target concentrations than may have actually been necessary were used. Third,

TDM values were reported up to 8 h following blood collection. This occurs as the chromatography method used to determine β-lactam concentrations is more time consuming compared with the immunoassay methods used to measure aminoglycoside and glycopeptide concentrations. Despite the delay, we consider this timing for data interpretation and potential dose adaptation rarely exceeded one dosing interval. Fourth, blood samples provide a surrogate marker for β-lactam antibiotics and may differ from concentrations of the antibiotic at the site of infection. Blood samples, however, are readily analysable and the unbound concentration of the antibiotic is likely to correlate with similar concentrations at the site of infection in most patients [4].

Given that β-lactam antibiotics have no 'end of needle' effect where no immediate clinical effect of therapy is readily observable, TDM appears to be attractive as a tool to determine whether current dosing is achieving therapeutic concentrations and provide subsequent dosing guidance. We were able to determine from TDM values reported in our CRRT patient group the need to maintain, increase or decrease β-lactam antibiotic levels in 72 (65%), 12 (11%) and 27 (24%) doses, respectively. When available, TDM should be used to titrate β-lactam antibiotic therapy in critically ill patients in an effort to improve patient outcomes. A definitive study of the clinical outcomes benefits of β-lactam TDM is required.

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Ethical approval: Ethical approval for data collection was granted by the Ethics

Committee of Royal Brisbane and Women's Hospital (Brisbane, QLD, Australia); no

approval number is provided for low-risk ethics applications. The need for informed

consent was waived.

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Table 1. Demographic data and continuous venovenous haemodiafiltration (CVVHDF) settings of 76 patients

	Mean ± S.D. [a]	Range
Male/female (*n*)	46/30	
Age (years)	56.6 ± 15.9	21–86
Weight (kg)	89.1 ± 25.8	36–175
SCr (μmol/L)	205.2 ± 120	36–711
Duration of antibiotic therapy (days)	7 ± 6	2–42
CVVHDF settings		
Q_b (mL/min)	192 ± 22	150–250
Q_d (mL/h)	1346 ± 524	1000–3000
Q_f (mL/h)	144 ± 110	0–1000
Post-dilution rate (mL/h)	1532 ± 739	50–3375
Pre-dilution rate (mL/h)	1222 ± 441	1000–2000

S.D., standard deviation; SCr, serum creatinine; Q_b, blood flow rate; Q_d, dialysate flow rate; Q_f, ultrafiltrate flow rate.

[a] Data are mean ± S.D. unless otherwise stated.

Table 2. Effect of indication for antibiotic therapy on the need for β-lactam antibiotic dose adjustment at the first therapeutic drug monitoring (TDM) level

Indication for antibiotic therapy	TDM samples	Dose maintained	Dose increased	Dose decreased
Primary or secondary bacteraemia	46 (41%)	35 (76%)	4 (9%)	7 (15%)
Hospital-acquired pneumonia	25 (23%)	10 (40%)	5 (20%)	10 (40%)
Community-acquired pneumonia	1 (1%)	0 (0%)	0 (0%)	1 (100%)
Wound prophylaxis post-trauma or post-operative	4 (4%)	1 (25%)	0 (0%)	3 (75%)
Meningitis	2 (2%)	1 (50%)	1 (50%)	0 (0%)
Skin and soft-tissue infection	4 (4%)	3 (75%)	0 (0%)	1 (25%)
Abdominal sepsis	18 (16%)	16 (89%)	0 (0%)	2 (11%)
Neutropenic sepsis	3 (3%)	3 (100%)	0 (0%)	0 (0%)
Urosepsis	8 (7%)	3 (38%)	2 (25%)	3 (38%)
Total	111 (100%)	72 (65%)	12 (11%)	27 (24%)

Table 3. β-Lactam dose adjustments based on therapeutic drug monitoring (TDM) value for individual drugs in critically ill patients (*n* = 76) during continuous venovenous haemodiafiltration

Antibiotic	Standard initiation dose	TDM samples	Dose maintained	Dose increased [a]	Dose decreased [b]
TZP	4.5 g q6h	9	2 (22%)	1 (11%)	6 (67%)
	4.5 g q8h	37	29 (78%)	–	8 (22%)
	4.5 g q12h	7	4 (57%)	2 (29%)	1 (14%)
Ampicillin	1 g q6h	1	–	–	1 (100%)
Meropenem	0.5 g q6h	5	5 (100%)	–	–
	0.5 g q8h	17	13 (76%)	1 (6%)	3 (18%)
	0.5 g q12h	1	–	1 (100%)	–
	1 g q6h	2	1 (50%)	1 (50%)	–
	1 g q8h	10	5 (50%)	2 (20%)	3 (30%)
	1 g q12h	3	1 (33%)	1 (33%)	1 (33%)
Penicillin G	1.2 g q4h	1	–	–	1 (100%)
	1.8 g q4h	2	–	1 (50%)	1 (50%)
	1.8 g q6h	2	1 (50%)	–	1 (50%)
Flucloxacillin	1 g q4h	1	–	1 (100%)	–
	1 g q8h	1	–	1 (100%)	–
	2 g q6h	7	7 (100%)	–	–
Ceftriaxone	1 g q12h	4	4 (100%)	–	–

2 g q12h	1	–	–	1 (100%)
Total	111	72 (65%)	12 (11%)	27 (24%)

TZP, piperacillin/tazobactam; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q4h, every 4 h.

[a] Includes increased dosing frequency or increased dose.

[b] Dose adjustment for TZP was based on piperacillin concentrations only.

Table 4. Mortality data for patients (n = 18) who died during β-lactam therapeutic drug monitoring (TDM)

Patient	Sex	Age (years)	Weight (kg)	SCr (mg/L)	Duration of therapy (days)	Admission diagnosis/reason for antibiotic	TDM details
1	F	29	61	31	3	GvHD with respiratory, skin and GIT involvement; respiratory failure	Meropenem for MSSA (MIC = 2mg/L), fC$_{min}$ = 3× MIC
2	M	68	91	354	7	Hypoxic brain injury secondary to pulseless electrical activity following cardiac arrest; VAP	TZP for Enterobacteriaceae (MIC = 8 mg/L), fC$_{min}$ = 5× MIC
3	M	70	153	172	4	Pulmonary embolism with DVT; intra-abdominal sepsis with MODS	Meropenem for *Pseudomonas aeruginosa* (MIC = 2 mg/L), fC$_{min}$ = 6× MIC
4	M	86	116	104	2	Multi-organ failure in the context of abdominal sepsis	Meropenem for Enterobacteriaceae (MIC = 2 mg/L), fC$_{min}$ = 8× MIC
5	F	44	60	160	2	Acute liver failure secondary to paracetamol overdose; VAP	TZP for *P. aeruginosa* (MIC = 8 mg/L), fC$_{min}$ >10× MIC

6	F	58	80	<30	5	Cholecystitis, Wilson's haemolytic crisis; acute liver failure, AKI, rapid AF; sepsis	Meropenem for Enterobacteriaceae, fC_{min} = $6\times$ MIC
7	F	32	36	76	8	Sepsis; cardiac failure secondary to cardiac infiltrates in the setting of AML	Meropenem for empirical therapy (MIC = 2 mg/L), fC_{min} >$10\times$ MIC
8	M	70	120	209	3	Multi-organ failure and aortic graft infection in context of ruptured abdominal aortic aneurysm	Meropenem for Enterobacteriaceae (MIC = 2 mg/L), fC_{min} = $5\times$ MIC
9	M	48	105	138	3	MODS secondary to MSSA sepsis	Flucloxacillin for MSSA (MIC = 1 mg/L), fC_{min} >$10\times$ MIC
10	M	66	80	108	2.5	Multi-trauma; circulatory shock secondary to LV dysfunction	TZP for empirical therapy (MIC = 16 mg/L), fC_{min} = $4\times$ MIC
11	M	47	80	92	2	Acute liver dysfunction, MODS secondary to upper GIT bleed in the context of chronic alcoholic liver disease	TZP for Enterobacteriaceae (MIC = 8 mg/L), fC_{min} >$10\times$ MIC
12	F	49	79	82	10	Respiratory failure, fluid overload; MODS secondary to streptococcal sepsis in the context of bone marrow failure post-transplantation for aplastic anaemia	TZP for *Streptococcus salivarius* (MIC = 0.5 mg/L), fC_{min} >$10\times$ MIC

13	M	68	80	59	3	Burns; MODS secondary to *P. aeruginosa* septic shock	TZP for *P. aeruginosa*, fC_{min} = 6× MIC
14	M	77	95	133	6	MODS; ESRF, type II diabetes mellitus, cerebellar stroke	Meropenem for *P. aeruginosa* (MIC = 4 mg/L), fC_{min} = 3× MIC
15	M	33	61	502	5	CAP (MSSA) and ARDS; bone marrow transplant GvHD	TZP for MSSA (MIC = 2 mg/L), fC_{min} >10× MIC
16	F	64	40	164	6	VAP, ESRF, COAD	Meropenem for *P. aeruginosa* (MIC = 2 mg/L), fC_{min} >10× MIC
17	M	24	86	349	5	VAP, IVDU, hypoxic brain injury	TZP for Enterobacteriaceae (MIC = 8 mg/L), fC_{min} = 1× MIC
18	F	60	65	78	3	MODS secondary to *Escherichia coli* UTI sepsis in the background of chronic alcoholic liver disease; decompensated hepatic failure	TZP for Enterobacteriaceae (MIC = 8 mg/L), fC_{min} >10× MIC

SCr, serum creatinine; GvHD, graft-versus-host disease; GIT, gastrointestinal tract; MSSA, methicillin-sensitive *Staphylococcus aureus*; MIC, minimum inhibitory concentration (known or presumed); fC_{min}, free (unbound) minimum (trough) concentration in a dosing interval; VAP, ventilator-associated pneumonia; TZP, piperacillin/tazobactam; DVT, deep vein thrombosis; MODS, multiple

organ dysfunction syndrome; AKI, acute kidney injury; AF, atrial fibrillation; AML, acute myeloid leukaemia; LV, left ventricular;

ESRF, end-stage renal failure; CAP, community-acquired pneumonia; ARDS, acute respiratory distress syndrome; COAD, chronic

obstructive airways disease; IVDU, intravenous drug user; UTI, urinary tract infection.

Table 5. Number of micro-organisms identified and not identified based on clinical diagnosis

Clinical diagnosis	Organisms isolated
Primary or secondary bacteraemia	MSSA (7)
	Klebsiella pneumoniae (6)
	Escherichia coli (5)
	Enterobacter cloacae (3)
	Other organism (13)
	Unidentified (12)
Hospital-acquired pneumonia	MSSA (3)
	Pseudomonas aeruginosa (3)
	Other organism (10)
	Unidentified (9)
Community-acquired pneumonia	MSSA (1)
Meningitis	*Streptococcus anginosus* (1)
	Unidentified (1)
Wound prophylaxis post-trauma or post-operative	*Serratia marcescens* (1)
	Morganella morganii (1)
	Enterobacter aerogenes (1)
	Streptococcus pyogenes (1)
Skin and soft-tissue infection	*S. marcescens* (1)
	E. coli (2)
	K. pneumoniae (1)
Abdominal sepsis	*Enterococcus faecalis* (4)
	E. coli (3)
	Salmonella Typhimurium (1)
	Other organism (6)
	Unidentified (4)
Neutropenic sepsis	Unidentified (3)
Urosepsis	*E. coli* (4)
	Other organism (3)
	Unidentified (1)
Total organisms identified	81 (73%)

Total organisms not identified	30 (27%)

MSSA, methicillin-sensitive *Staphylococcus aureus*.