

Article

Personalized Piperacillin Dosing for the Critically Ill: A Retrospective Analysis of Clinical Experience with Dosing Software and Therapeutic Drug Monitoring to Optimize Antimicrobial Dosing

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Abstract: Optimization of antibiotic dosing is a treatment intervention that is likely to improve outcomes in severe infections. The aim of this retrospective study was to describe the therapeutic exposure of steady state piperacillin concentrations (c_{PIP}) and clinical outcome in critically ill patients with sepsis or septic shock who received continuous infusion of piperacillin with dosing personalized through software-guided empiric dosing and therapeutic drug monitoring (TDM). Therapeutic drug exposure was defined as c_{PIP} of 32–64 mg/L (2–4× the ‘MIC breakpoint’ of *Pseudomonas aeruginosa*). Of the 1544 patients screened, we included 179 patients (335 serum concentrations), of whom 89% achieved the minimum therapeutic exposure of >32 mg/L and 12% achieved potentially harmful c_{PIP} > 96 mg/L within the first 48 h. Therapeutic exposure was achieved in 40% of the patients. Subsequent TDM-guided dose adjustments significantly enhanced therapeutic exposure to 65%, and significantly reduced c_{PIP} > 96 mg/L to 5%. Mortality in patients with c_{PIP} > 96 mg/L (13/21; 62%) (OR 5.257, 95% CI 1.867–14.802, $p = 0.001$) or 64–96 mg/L (30/76; 45%) (OR 2.696, 95% CI 1.301–5.586, $p = 0.007$) was significantly higher compared to patients with therapeutic exposure (17/72; 24%). Given the observed variability in critically ill patients, combining the application of dosing software and consecutive TDM increases therapeutic drug exposure of piperacillin in patients with sepsis and septic shock.

Keywords: piperacillin; continuous infusion; therapeutic drug monitoring; dosing software; PK/PD

1. Introduction

Empirical antimicrobial therapy needs to be administered in a timely manner to critically ill patients with sepsis and septic shock to reduce mortality [1,2]. Furthermore,

achievement of effective serum concentrations is important within the first 24–48 h of treatment [3]. However, optimal drug exposure is a difficult to achieve target and requires an understanding of both the pharmacokinetic (PK) changes that can occur in septic patients [4–7], and the antimicrobial pharmacodynamics (PD) [8] of the antimicrobial agent prescribed. Using the standard dosing regimen according to the Product Information is considered to have limited value in critical care as patients with sepsis and septic shock are likely to exhibit profound PK changes [9]. There is a strong body of evidence demonstrating that standard dosing approaches are concomitant with suboptimal plasma concentrations [9,10] leading to either inadequate antimicrobial exposure at the site of infection [11,12] or toxic serum concentrations [13–16] in a large fraction of critically ill patients. Therefore, antibiotic dosing in critically ill patients is very challenging, but should be considered a key intervention to further improve infection-related outcomes in patients with sepsis [17]. To this end, a more personalized approach to drug dosing, which understands PK in the individual patient and pathogen susceptibility (minimal inhibitory concentration (MIC); epidemiological cutoff (ECOFF)), should be further investigated [18].

In the case of β -lactams, prolonged infusion is advantageous as it produces and maintains higher β -lactam concentrations above the MIC, while intermittent infusion leads to unnecessary high peaks followed by low concentrations for a considerable part of the dosing interval [19–21]. Recent clinical data demonstrated that critically ill patients benefit from considerably higher (e.g., 1–4 \times MIC) and longer (e.g., 100% $fT_{>MIC}$) β -lactam exposures [22,23] than those described in earlier preclinical infection models [8]. Therapeutic drug monitoring (TDM) provides a robust method to ensure optimal exposures [24,25]. The use of dosing nomograms or dosing software [5,26,27] with respect to pathophysiological changes that occur in severe infections, sepsis and septic shock, respectively (i.e., renal function, renal replacement therapies (RRT) [28]) enables individual empiric dosing already in the early phase of treatment. Therefore, combining prolonged/continuous infusion with personalized empiric dosing and TDM is expected to be the safest and most effective way to ensure therapeutic drug exposure in critically ill patients [3,29,30].

The aim of this study was to describe the therapeutic exposure of piperacillin concentrations (c_{PIP}) and clinical outcome in critically ill patients with a personalized dosing strategy including dosing software and TDM.

2. Results

In total, 1544 patients were admitted to the intensive care unit (ICU), of which 179 patients received empirical piperacillin/tazobactam treatment and were included. Moreover, in total, 335 piperacillin concentrations were available with each patient contributing 1 to 6 observations. Detailed demographic characteristics are summarized in Tables 1 and 2. Diagnosis and bacterial pathogen distributions are presented in Table S1 in the supplement. Briefly, the study population was relatively old (median age 75 years) with moderate renal function (median 47 CrCL mL/minute) on admission. Overall, 33 (19%) patients received RRT. Of these patients, 18 (11%) were treated with continuous renal replacement therapy (CRRT) and 15 (8%) were treated with intermittent hemodialysis (iHD). The median (IQR) piperacillin daily dose was 8000 (7000) mg (software-guided empiric daily dose: 8000 (6750) mg, TDM-guided daily dose: 7000 (6675) mg), and thus less than the predicted median (IQR) piperacillin standard daily dose in these patients (12,000 (8000) mg). The median (IQR) c_{PIP} was 54 (34) mg/L (c_{PIP} after software-guided empiric daily dosing: 64 (38) mg/L, c_{PIP} after TDM-guided daily dosing: 49 (26) mg/L).

2.1. Therapeutic Exposure

With software-guided empiric dosing, the minimum therapeutic exposure of >32 mg/L was overall realized in 89% of patients after empiric dosing including 22 patients (12%) with potentially harmful concentrations ($c_{PIP} > 96$ mg/L). Therapeutic exposure of 32–64 mg/L was observed in 72 patients (40%) within 48 h after onset of treatment. Subsequent TDM-guided dose adjustments significantly enhanced the target exposure of piperacillin concen-

trations to 65%, and significantly reduced $c_{PIP} > 96$ mg/L to 5%. With standard dosing, therapeutic exposure would have been realized in 76 patients (23%) whereas 125 patients (38%) would have shown $c_{PIP} > 96$ mg/L. The effect of personalized empiric dosing on therapeutic exposure is shown in Table 3. Data describing the distribution of c_{PIP} for all concentrations are shown in the supplement in Table S2 and for concentrations under CRRT in Table S3.

Table 1. Patient characteristics.

	Median (IQR), <i>n</i> (%)
Age, years	75 (15)
Weight, kg	78 (18)
Height, cm	170 (13)
BMI, kg/m ²	26 (7)
Sex male	115 (64%)
Creatinine, mg/dL	1.18 (1.13)
CrCL, mL/min	47 (50)
RRT	33 (19%)
CRRT	18 (10%)
iHD	15 (8%)
Mechanical ventilation	105 (59%)
SOFA	6 (6)
SAPS	37 (18)
APACHE II *	22 (14)
ICU mortality	56 (31%)
Hospital mortality	64 (36%)
Length of hospital stay, days	17 (18)
Antimicrobial treatment, days	6 (4)

BMI: Body mass index; CrCL: Creatinine clearance; CRRT: Continuous renal replacement therapy; iHD: Intermittent hemodialysis; ICU: Intensive care unit; RRT: Renal replacement therapy; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment. * On day of inclusion.

Table 2. Diagnosis.

Diagnosis	<i>n</i> (%)
Sepsis/Severe sepsis	126 (70%)
Septic shock	53 (30%)
Site of infection	
Pneumonia	96 (54%)
Abdominal infection, peritonitis	37 (23%)
Soft tissue/bone infection	10 (6%)
Urinary tract infection	11 (7%)
Endocarditis, blood stream infection	7 (4%)
Cholecystitis, cholangitis	6 (4%)
Diverse	10 (6%)

Values are given in absolute numbers (*n*) and relative incidence (%).

Table 3. Effect of personalized empiric dosing on therapeutic exposure. Distribution of piperacillin concentrations (c_{PIP}) in 179 critically ill patients with a continuous infusion personalized by the dosing software ($=c_{PIP}$ observed based on software-guided empiric dosing) compared to a continuous infusion of standard doses according to national guidelines (NAK; National committee on antimicrobial susceptibility testing in Germany) ($=c_{PIP}$ predicted based on standard dosing) within 48 h after the onset of treatment.

c_{PIP} (mg/L)	<16	16–32	32–64	64–96	>96
Predicted based on standard dosing	0 (0%)	3 (1.7%)	35 (19.6%)	63 (35.2%)	78 (43.6%)
Software-guided empiric dosing	1 (0.6%)	18 (10.1%)	72 (40.2%)	66 (36.9%)	22 (12.3%)

Values are given in absolute number (*n*) and relative incidence (%). c_{PIP} : Piperacillin concentration; TDM: Therapeutic drug monitoring.

2.2. Predictors for Clinical Outcome

The binary logistic regression revealed a high sequential organ failure assessment (SOFA) score (OR 3.533, 95% CI 1.993–6.262, $p = 0.001$), low creatinine clearance (CrCL) (OR 0.533, 95% CI 0.296–0.961, $p = 0.036$), and reduced piperacillin clearance (CL_{PIP}) (OR 0.336, 95% CI 0.116–0.974, $p = 0.045$) to significantly increase the odds for hospital mortality within this study. There was no significant association with c_{PIP} , age or BMI. Furthermore, mortality in patients with a $c_{PIP} > 96$ mg/L (13/21; 62%) (OR 5.257, 95% CI 1.867–14.802, $p = 0.001$) or in patients with c_{PIP} of 64–96 mg/L (30/76; 45%) (OR 2.696, 95% CI 1.301–5.586, $p = 0.007$) was significantly higher compared to patients with a piperacillin concentration of 32–64 mg/L (17/72; 24%). Mortality in patients with $c_{PIP} \leq 32$ mg/L (4/19; 22%) (OR 1.159, 95% CI 0.339–3.965, $p = 0.814$) and patients with c_{PIP} of 32–64 mg/L (17/72; 24%) did not significantly differ (Table 4, Figure 1). Differences in median SOFA score and median simplified acute physiology score (SAPS) were not significant between patients with therapeutic drug exposure and patients with $c_{PIP} > 64$ mg/L (Table 4).

Table 4. Cross table depicting the distribution of clinical parameters in different piperacillin concentration (c_{PIP}) groups.

c_{PIP} (mg/L)	<16	16–32	32–64	64–96	>96
Hospital mortality (%)	0%	22%	24%	45% *	62% *
Median SOFA score (IQR)	2 (1) *	3 (7) *	6 (6)	7 (8)	6 (5)
Median SAPS (IQR)	26 (7) *	30 (23) *	37 (19)	38 (20)	37 (7)
Median CL_{PIP} (L/h) (IQR)	11.5 (8.8)	12.8 (10.6)	6.9 (5.0) *	5.0 (3.2) *	2.8 (1.7) *
Median CrCL (mL/min) (IQR)	71.6 (12.6)	88.5 (91.4)	42.1 (54.1) *	38.7 (38.8) *	23.2 (19.1) *
Median age (years) (IQR)	77 (0)	61 (24)	72 (16)	77(13)	79 (11)
Median BMI (kg/m ²) (IQR)	30 (0)	29 (8)	27 (7)	25 (7)	25 (5)

* $p < 0.05$. Values are given as median (IQR) or relative incidence (%). CrCL: Creatinine clearance; CL_{PIP} : Observed piperacillin clearance; SAPS: Simplified acute physiology score; SOFA: Sequential organ failure assessment.

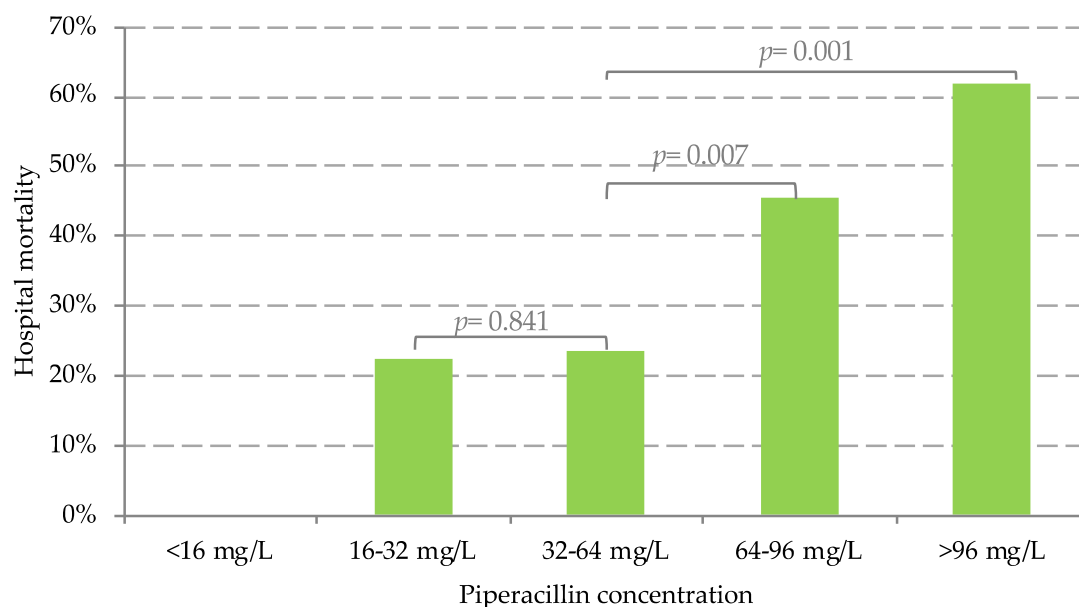


Figure 1. Distribution of hospital mortality rates. Hospital mortality rates over piperacillin concentration within 48 h after onset of treatment. Statistical analysis was performed using the chi-square test. Significant levels were considered as $p \leq 0.05$.

The median observed piperacillin clearance (CL_{PIP}) was 6.7 (5.4) L/h (Figure 2). In the first 48 h, no augmented clearance was observed (Figure 2). The median piperacillin clearance predicted by CADDy (CL_{CADDy}) was higher compared to the observed clearance (CL_{PIP48}) in the first 48 h (CL_{CADDy} 8.3 (5.0) L/h vs. CL_{PIP48} 6.4 (5.3) L/h). The predictive capacity of CADDy was assessed by comparing the predicted with the observed clearance (Figure 3). The estimates of bias and imprecisions were also acceptable (0.30 and 1.30).

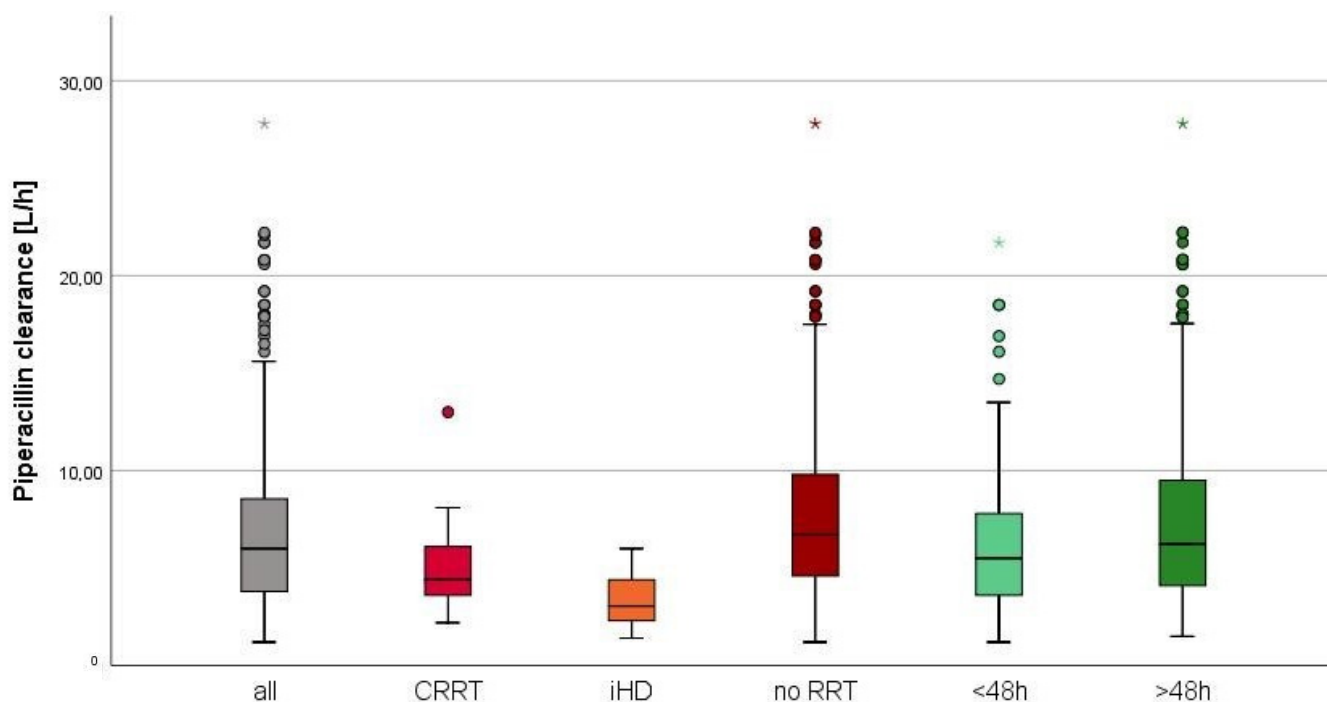


Figure 2. Observed piperacillin clearance. Distribution of the observed piperacillin clearance given in L/h of all patients ($n = 335$), patients with CRRT ($n = 35$), patients with iHD ($n = 42$), patients without RRT ($n = 258$), in the first 48 h ($n = 179$) and after 48 h ($n = 156$).

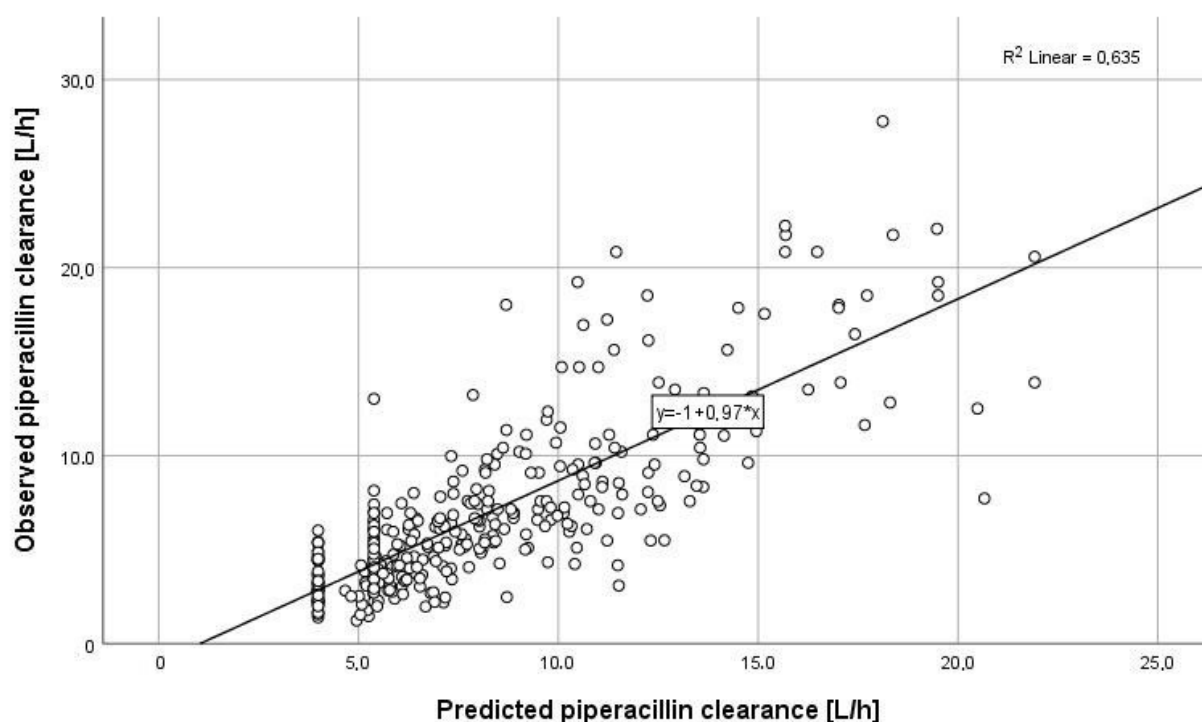


Figure 3. Piperacillin clearance predicted by CADDy versus observed piperacillin clearance within the first 48 h ($r^2 = 0.635$). The solid black line shows the linear regression line of fit. The estimates of bias and precisions were also acceptable (0.30 and 1.30).

3. Discussion

The present retrospective study evaluated the therapeutic exposure of piperacillin concentrations using a personalized dosing strategy including dosing software and consecutive TDM as recommended in the current guidelines [3,29,31,32]. Therapeutic exposure

of piperacillin was high with a personalized dosing strategy. Already with empiric dosing guided by the Calculator to Approximate Drug-Dosing in Dialysis (CADDy) software the minimum therapeutic exposure of >32 mg/L was realized in 89% of the study population in the first 48 h. We identified 12% of the patients with potentially harmful $c_{PIP} > 96$ mg/L, which were reduced by 63% through subsequent TDM-guided dose adjustment. Furthermore, mortality in patients $c_{PIP} > 64$ mg/L was significantly higher compared to patients with therapeutic exposure. Our data do not support previous findings of insufficiently low serum concentrations associated with continuous infusion of β -lactams [9,13].

Sepsis and septic shock continue to be associated with high mortality [33,34]. The SOFA score and SAPS are established to predict the clinical outcomes in these patients [35,36]. The observed hospital mortality of sepsis (36%) and severe sepsis/septic shock (43%) is comparable to other findings in European ICUs reporting a mortality rate between 36.3 and 42.8% [37–39]. Critically ill patients with severe sepsis/septic shock in a large, prospective multicenter study in German ICUs also showed a hospital mortality rate of 40% [34].

From a PK point of view, a positive clinical outcome in critically ill patients is associated with increasing 100% $fT_{>MIC}$ ratios [3]. Traditional antibiotic dosing repeatedly failed to attain this PK target recommendation in previous studies with critically ill patients. In the DALI trial, a prospective multinational study that included 361 critically ill patients who were treated with a β -lactam, only 30 and 67% of the patients achieved 100% $fT_{>4 \times MIC}$ and 100% $fT_{>MIC}$, respectively [9]. These findings were recently confirmed in the EXPAT study by Abdulla et al. [10]. Abdulla et al. found, that 37 and 63% of the patients with intermittent bolus application of β -lactams achieved 100% $fT_{>4 \times MIC}$ and 100% $fT_{>MIC}$, respectively [10]. It is of utmost importance to interpret the DALI and EXPAT data in the setting of the antibiotic application mode, since most patients in the DALI study and all patients in the EXPAT trial received an intermittent bolus application. With a personalized dosing approach including continuous infusion in this study, 49 and 99% of the patients achieved 100% $fT_{>4 \times MIC}$ and 100% $fT_{>MIC}$, respectively, within the first 48 h after onset of treatment. Only 10% of the patients demonstrated piperacillin concentrations below therapeutic exposure, 1% of the patients demonstrated piperacillin concentrations below the ECOFF of *Pseudomonas aeruginosa*.

Using software-guided empiric dosing in the patients of this study demonstrated that an unnecessary high c_{PIP} (>96 mg/L) in only 12% of patients within the first 48 h after onset of treatment compared to 44% of patients would have exhibited $c_{PIP} > 96$ mg/L in the case of standard doses administered as continuous infusion. Compared to these findings, a previous retrospective study from Richter et al. [14] found a very high number of patients receiving continuous infusion of piperacillin with potentially harmful concentrations. About 30% of the patients demonstrated $c_{PIP} > 100$ mg/L within the first 48 h [14]. A possible explanation might be the implementation of empiric dose adjustment according to renal function rather than standard doses before the concentration measurement to avoid a high concentration either to high doses or decreased drug clearance. Harmful effects potentially related to excessively high serum concentrations (>96 mg/L) have been reported. Quinton et al. [15] observed neurotoxicity in about 40% of critically ill patients treated with a median daily dose of 12,000 mg (range 8000–12,000 mg) piperacillin administered by continuous infusion. The median serum concentration after 48 h was significantly higher compared to patients without neurotoxic symptoms (157 [95–236] mg/L vs. 91 [69–127] mg/L). Moreover, patients with neurotoxic c_{PIP} showed a remarkable reduction in CrCL within 48 h (46%).

Due to the fact that β -lactam antibiotics have the potential to precipitate antibiotic-induced toxicity is increasingly apparent [16], but likely remains underestimated in the clinical practice of sepsis therapy [16]. Dose-induced toxicity may manifest in the form of neurological deterioration and acute kidney injury (AKI). Acute kidney injury is a known major complication of vancomycin treatment, especially when it is co-administered with other nephrotoxins. A combination therapy of vancomycin with piperacillin/tazobactam is associated with higher acute kidney injury rates than its parallel use with meropenem or cefepime [40,41]. In a recent clinical study, Dhaese et al. identified a significantly higher

mortality in critically ill patients with piperacillin concentrations of 64–160 mg/L [13]. Scharf et al. found no benefit for patients who reached the highest target of 100% $fT_{>4x\text{ MIC}}$, but a significant higher mortality rate [23]. Although confounding factors such as worse liver function, higher APACHE II, and SOFA scores must be considered, the authors recommended a PK target of 100% $fT_{>1x\text{ MIC}<4x\text{ MIC}}$ for critically ill patients. In our study, hospital mortality was significantly higher in patients with concentrations above therapeutic exposure. In patients with $c_{\text{PIP}} > 96$ mg/L (corresponding 4–6x ECOFF *Pseudomonas aeruginosa*) hospital mortality was 5 times higher compared to patients with therapeutic exposure, despite the fact that the SOFA and SAPS scores were not significantly different in these patients. However, from these data it cannot be concluded that high levels are harmful or whether they are a prognostic factor. On the other hand, the benefit of high concentrations is debatable. There is only one in vitro infection model with piperacillin/tazobactam that reported a relationship between bacterial kill and % $fT_{>\text{MIC}}$ with significant thresholds of 27% for bacteriostasis and 75% for bactericidal activity [42].

Considering the association of potentially toxic serum concentration ($fT_{>4x\text{ MIC}}$) and a higher mortality [13,14,23], this study strongly supports the present recommendations on personalized antibiotic dosing [3,18,31,43] including continuous application of β -lactams [20,21,31,32] in critically ill patients with sepsis and septic shock. Hydrophilic β -lactam antibiotics demonstrate a foremost renal elimination. Consequently, renal function is the most relevant covariate for individualization of β -lactam dosing to achieve therapeutic exposure [44]. In patients with impaired renal function, the relationship between decreased piperacillin clearance and increased concentration, more specifically decreased drug amount, may not come as a surprise as previous studies have already demonstrated the correlation between CrCL and clearance of β -lactam antibiotics [9,18,24,45]. In line with previous studies, we identified pathophysiological changes presented as reduced piperacillin clearance compared to non-critically ill patients [14]. Piperacillin clearance demonstrated a high variability. However, previous findings frequently postulated a normal β -lactam clearance independent of the renal function in critically ill patients in the beginning of the infection resulting in underdosing within the first 48 h after onset of treatment [13,15]. Our data do not support these considerations and suggest a dose adjustment according to renal function from the beginning to avoid very high piperacillin concentrations. With a median age of 75 years and a compromised renal function (median CrCL 47 mL/min) by the time of admission the investigated study cohort resembles a realistic cross section of patients treated in interdisciplinary ICUs [34].

Therefore, an optimal dosing scheme that is worthy of implementation into clinical practice as an optimal renal dose adjustment should balance the probability of achieving therapeutic exposure against the risks of toxicity and the emergence of antimicrobial resistance [46,47]. Given the observed variability in critically ill patients, the dose adjustment according to renal function using, for example, the dosing software might help avoid potentially harmful effects of very high β -lactam concentrations, in particular in patients with compromised renal function [18,43]. Further data on the benefit of TDM-based dose optimization in septic patients with piperacillin treatment are expected soon in the already completed TARGET trial [48].

The present study has several limitations. First, the study was a single center study which may have hampered robust estimates of the extent of PK variability. Second, CrCL was estimated using the Cockcroft-Gault equation since the CrCL measurement is not performed in routine clinical care and the β -lactam clearance and Cockcroft-Gault equation show a good overall correlation ($r = 0.57$) [14,49].

Third, non-renal clearance and organ dysfunctions (other than renal) might be relevant but are not considered in the CADDy calculation. Active metabolites that might influence drug clearance, efficacy, and toxicity cannot be estimated by the algorithm. Although, the observed piperacillin clearance shows a good correlation to the CADDy-predicted piperacillin clearance. Finally, this was a retrospective analysis of serum concentrations measured as total drug concentrations. Therefore, drawing causal relations from retrospec-

tive data is hardly possible and mortality data should be interpreted carefully as biasing factors might be present. However, a retrospective analysis of serum concentrations has the advantage of considering all patients, even those with low survival rates and might show a more realistic picture compared to prospective approaches.

4. Material and Methods

4.1. Study Design and Population

This was a retrospective observational study at a German academic teaching hospital in 2013. Ethical approval was waived by the Ethics Commission of the University of Ulm, Germany (project number 137/19). All critically ill patients admitted to the ICU were screened and patients > 18 years of age, with sepsis, severe sepsis or septic shock (according to the meanwhile revised Surviving Sepsis Campaign (SSC) definition [50]) and empiric piperacillin/tazobactam treatment administered by continuous infusion were included in the study. Patients were excluded if they were <18 years of age or treated with piperacillin administered by intermittent infusion.

4.2. Study Procedures

All patients received initial antibiotic treatment within the first 3 h after diagnosis according to the effective Surviving Sepsis Campaign (SSC) guideline of 2013 [50]. Piperacillin was administered by TDM-guided continuous infusion in all patients according to our standard operating procedure [51]. This approach consisted of a loading dose (2000 mg, 15 min infusion) followed by immediate continuous infusion with an empiric dose using the calculator to approximate drug-dosing in dialysis (CADDy) and subsequently adjusted by TDM within the first 24–48 h (Figure 4). The CADDy program (www.thecaddy.de accessed on 1 January 2013; Dr. Otto Frey, Klinikum Heidenheim) was used to predict piperacillin clearance (CL_{CADDy}) as well as piperacillin doses in patients considering the CrCL evaluated by the Cockcroft-Gault equation, and if applicable dialysis settings [5]. TDM-guided dose adjustments and consecutive TDMs were advised and supervised by trained clinical pharmacists. Piperacillin concentration was measured, using a validated high-performance liquid chromatography assay (HPLC) [52].

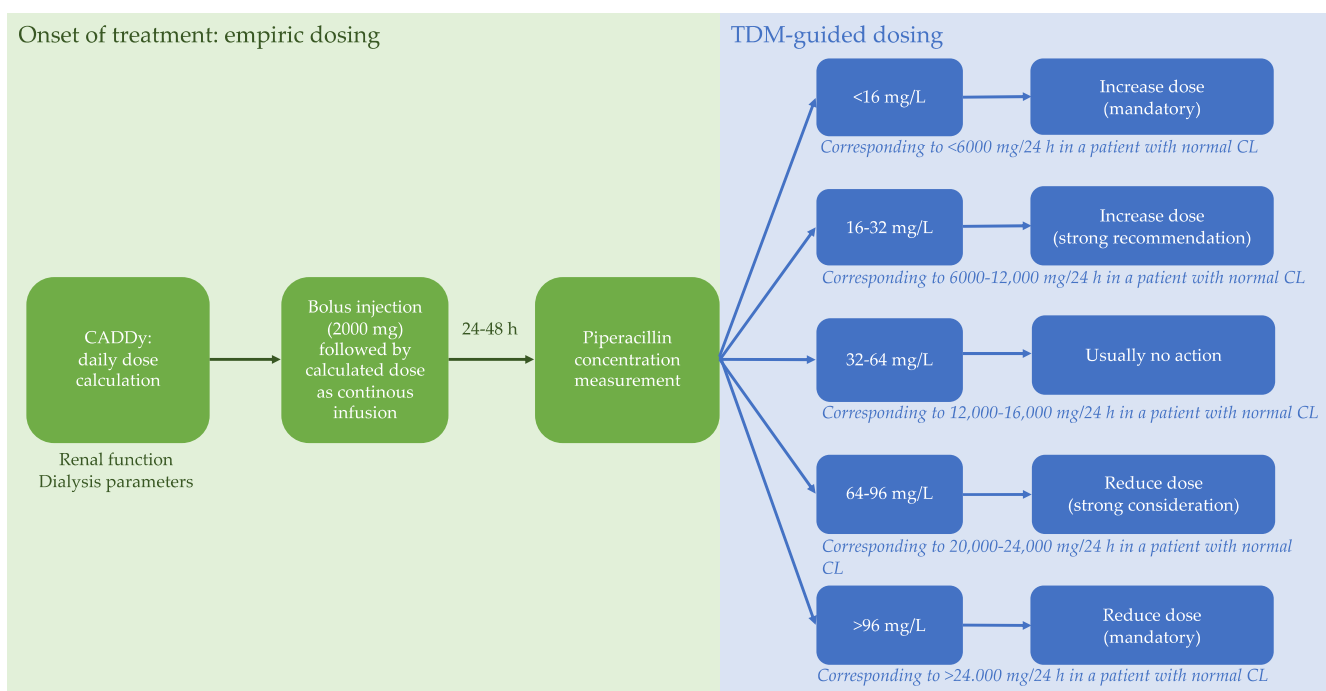


Figure 4. Dosing procedures. Therapeutic drug monitoring (TDM)-based dose adaptation strategy for continuous infusion. CADDy Calculator to Approximate Drug-Dosing in Dialysis; CL piperacillin clearance; TDM Therapeutic drug monitoring.

4.3. Assessment of Therapeutic Drug Exposure

A therapeutic drug exposure was defined as c_{PIP} of 32–64 mg/L corresponding to two to four times the ‘MIC breakpoint’ of *Pseudomonas aeruginosa* (http://www.eucast.org/clinical_breakpoints: Piperacillin 16 mg/L, accessed on 1 January 2013) as a rational compromise between effective bacterial killing and possible harmful concentrations. Piperacillin concentrations of 64–96 mg/L were defined as moderately high. To assess the suitability of empiric dosing considering individual pharmacokinetics, concentration was stratified by the time of observation and prediction was evaluated. In addition, empiric dosing was compared to a continuous infusion of standard doses according to the national committee on antimicrobial susceptibility testing in Germany (NAK). Concentrations were predicted by the observed CL_{PIP} . A one-compartment model was used to perform PK analyses since piperacillin has a small volume of distribution, low protein binding, and is essentially excreted by the kidneys. CL_{PIP} was calculated using the following equation:

$$CL_{PIP} [L/h] = \frac{\text{dose} [mg]}{24h} \cdot c_{PIP}^{-1} [mg/L].$$

Distribution of clinical parameters was assessed in relation to c_{PIP} and factors likely to contribute to clinical outcome were analyzed for association based on clinical relevancy or previously described relationships [53–55]. These included patient characteristics (age, BMI), illness severity scores (SOFA), c_{PIP} , serum creatinine, eGFR, and CL_{PIP} .

4.4. Statistical Analysis

All calculations and statistical analysis were performed using IBM SPSS Statistics version 26 software (IBM, Armonk, NY, USA). Discrete variables are expressed as counts (percentage) and continuous variables as means \pm standard deviation (SD) or median with the interquartile range (IQR). We used the logistic regression analysis to evaluate the association of clinical outcomes with patient characteristics. Differences between groups were assessed for statistical significance using the Kruskal–Wallis test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Significant levels were considered as $p \leq 0.05$.

For pharmacokinetic analysis, we evaluated the predicted clearance against the observed clearance using the ratio of predicted and observed piperacillin concentrations (relative error). Bias was assessed by calculating the median of the relative errors of all observations and subtracting 1. Precision was assessed from the magnitude of the relative error. We chose to report median errors, as they were not normally distributed, according to the alternative method of Sheiner and Beal [56].

5. Conclusions

Our data strongly support the use of dosing interventions including the application of dosing software, CI, and TDM to ensure sufficient therapeutic drug exposure in septic patients with an *a priori* high mortality rate. Personalized dosing strategies lead to therapeutic drug exposure within the first 48 h of treatment as well as throughout the treatment course, while avoiding critically low piperacillin concentrations and minimizing potentially harmful piperacillin concentrations at the same time. CADDy reliably predicts the piperacillin clearance (empiric dosing) in critically ill patients. However, further validation of the dosing software in a clinical trial is required.

Key Messages

- Piperacillin clearance in critically ill patients with septic patients shows high variability;
- Recommended personalized dosing strategy of piperacillin, including dosing software and TDM, ensures adequate serum concentrations;
- CADDy is a useful and reliable dosing software for empiric dose calculations.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/antibiotics10060667/s1>, Table S1: Distribution of pathogens; Table S2: Piperacillin concentrations stratified by the time of observation; Table S3: Piperacillin concentrations under continuous renal replacement therapy.

Author Contributions: U.C. and D.C.R. analyzed and interpreted patient data and drafted the manuscript; O.R.F. was responsible for acquisition of data, interpretation of results, measured and interpreted β -lactam concentrations; A.C.R. was responsible for acquisition of data, measured and interpreted β -lactam concentrations; S.H. (Sophia Helbig) was responsible for acquisition of data, measured and interpreted β -lactam concentrations; J.P. was responsible for acquisition of data, measured and interpreted β -lactam concentrations; S.H. (Stefan Hagel) interpreted the results and helped draft the manuscript; J.A.R. interpreted the results and helped draft the manuscript; M.A.W. interpreted the results and helped draft the manuscript; A.B. was responsible for acquisition of data, interpretation of the results, and helped draft the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Commission of the University of Ulm, Germany (project number 137/19).

Informed Consent Statement: Patient consent was waived for several reasons. First, given the retrospective analysis without any intervention, the research project did not pose a risk for patients. Secondly, the database was established in 2013 and data were already anonymized and safeguarded. Obtaining retrospective consents would have been a time-consuming endeavor with most likely substantial data loss (e.g., deceased patients, incorrect addresses and phone numbers) and a critical delay in publishing relevant data with actual clinical impact for critically ill patients. Institutional measures encompassing data handling at the University Hospital Heidelberg and at Heidenheim Hospital ensured that proper safeguards were in place throughout the whole process to prevent accidental disclosure of sensitive data. Weighing the hypothetical risk of loss of confidentiality against the advantages of conducting a study with a waiver of consent, we agreed on waiving consents.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Bloos, F.; Ruddel, H.; Thomas-Ruddel, D.; Schwarzkopf, D.; Pausch, C.; Harbarth, S.; Schreiber, T.; Grundling, M.; Marshall, J.; Simon, P.; et al. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: A cluster randomized trial. *Intensive Care Med.* **2017**, *43*, 1602–1612. [[CrossRef](#)] [[PubMed](#)]
2. Ferrer, R.; Martin-Loeches, I.; Phillips, G.; Osborn, T.M.; Townsend, S.; Dellinger, R.P.; Artigas, A.; Schorr, C.; Levy, M.M. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: Results from a guideline-based performance improvement program. *Crit. Care Med.* **2014**, *42*, 1749–1755. [[CrossRef](#)]
3. Abdul-Aziz, M.H.; Alffenaar, J.C.; Bassetti, M.; Bracht, H.; Dimopoulos, G.; Marriott, D.; Neely, M.N.; Paiva, J.A.; Pea, F.; Sjøvall, F.; et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: A Position Paper. *Intensive Care Med.* **2020**, *46*, 1127–1153. [[CrossRef](#)] [[PubMed](#)]

4. Roberts, J.A.; Lipman, J. Antibacterial dosing in intensive care: Pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin. Pharm.* **2006**, *45*, 755–773. [[CrossRef](#)] [[PubMed](#)]
5. Roberts, J.A.; Abdul-Aziz, M.H.; Lipman, J.; Mouton, J.W.; Vinks, A.A.; Felton, T.W.; Hope, W.W.; Farkas, A.; Neely, M.N.; Schentag, J.J.; et al. Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. *Lancet Infect. Dis.* **2014**, *14*, 498–509. [[CrossRef](#)]
6. Brinkmann, A.; Röhr, A.C.; Köberer, A.; Fuchs, T.; Preisenberger, J.; Krüger, W.A.; Frey, O.R. Therapeutic drug monitoring and individual dosing of antibiotics during sepsis: Modern or just “trendy”? *Med. Klin. Intensivmed. Notf.* **2018**, *113*, 82–93. [[CrossRef](#)] [[PubMed](#)]
7. Sukarnjanaset, W.; Jaruratanasirikul, S.; Wattanavijitkul, T. Population pharmacokinetics and pharmacodynamics of piperacillin in critically ill patients during the early phase of sepsis. *J. Pharmacokinetic. Pharm.* **2019**, *46*, 251–261. [[CrossRef](#)]
8. Drusano, G.L. Antimicrobial pharmacodynamics: Critical interactions of ‘bug and drug’. *Nat. Rev. Microbiol.* **2004**, *2*, 289–300. [[CrossRef](#)]
9. Roberts, J.A.; Paul, S.K.; Akova, M.; Bassetti, M.; De Waele, J.J.; Dimopoulos, G.; Kaukonen, K.M.; Koulenti, D.; Martin, C.; Montravers, P.; et al. DALI: Defining Antibiotic Levels in Intensive care unit patients: Are current beta-lactam antibiotic doses sufficient for critically ill patients? *Clin. Infect. Dis.* **2014**, *58*, 1072–1083. [[CrossRef](#)]
10. Abdulla, A.; Dijkstra, A.; Hunfeld, N.G.M.; Endeman, H.; Bahmany, S.; Ewoldt, T.M.J.; Muller, A.E.; van, G.T.; Gommers, D.; Koch, B.C.P. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: A two-center prospective study (EXPAT). *Crit. Care* **2020**, *24*, 1–12. [[CrossRef](#)]
11. Felton, T.W.; Ogungbenro, K.; Boselli, E.; Hope, W.W.; Rodvold, K.A. Comparison of piperacillin exposure in the lungs of critically ill patients and healthy volunteers. *J. Antimicrob. Chemother.* **2018**, *73*, 1340–1347. [[CrossRef](#)] [[PubMed](#)]
12. Felton, T.W.; McCalman, K.; Malagon, I.; Isalska, B.; Whalley, S.; Goodwin, J.; Bentley, A.M.; Hope, W.W. Pulmonary penetration of piperacillin and tazobactam in critically ill patients. *Clin. Pharm.* **2014**, *96*, 438–448. [[CrossRef](#)] [[PubMed](#)]
13. Dhaese, S.A.M.; Thooft, A.D.J.; Farkas, A.; Lipman, J.; Verstraete, A.G.; Stove, V.; Roberts, J.A.; De Waele, J.J. Early target attainment of continuous infusion piperacillin/tazobactam and meropenem in critically ill patients: A prospective observational study. *J. Crit. Care* **2019**, *52*, 75–79. [[CrossRef](#)]
14. Richter, D.C.; Frey, O.; Röhr, A.; Roberts, J.A.; Köberer, A.; Fuchs, T.; Papadimas, N.; Heinzl-Gutenbrunner, M.; Brenner, T.; Lichtenstern, C.; et al. Therapeutic drug monitoring-guided continuous infusion of piperacillin/tazobactam significantly improves pharmacokinetic target attainment in critically ill patients: A retrospective analysis of four years of clinical experience. *Infection* **2019**, *47*, 1001–1011. [[CrossRef](#)] [[PubMed](#)]
15. Quinton, M.C.; Bodeau, S.; Kontar, L.; Zerbib, Y.; Maizel, J.; Slama, M.; Masmoudi, K.; Lemaire-Hurtel, A.S.; Bennis, Y. Neurotoxic Concentration of Piperacillin during Continuous Infusion in Critically Ill Patients. *Antimicrob. Agents Chemother.* **2017**, *61*, e0065417. [[CrossRef](#)]
16. Imani, S.; Buscher, H.; Marriott, D.; Gentili, S.; Sandaradura, I. Too much of a good thing: A retrospective study of beta-lactam concentration-toxicity relationships. *J. Antimicrob. Chemother.* **2017**, *72*, 2891–2897. [[CrossRef](#)] [[PubMed](#)]
17. Drusano, G.L.; Lodise, T.P. Saving lives with optimal antimicrobial chemotherapy. *Clin. Infect. Dis.* **2013**, *56*, 245–247. [[CrossRef](#)]
18. Roberts, J.A.; Roger, C.; De Waele, J.J. Personalized antibiotic dosing for the critically ill. *Intensive Care Med.* **2019**, *45*, 715–718. [[CrossRef](#)]
19. Aardema, H.; Bult, W.; van Hateren, K.; Dieperink, W.; Touw, D.J.; Alffenaar, J.C.; Zijlstra, J.G. Continuous versus intermittent infusion of cefotaxime in critically ill patients: A randomized controlled trial comparing plasma concentrations. *J. Antimicrob. Chemother.* **2020**, *75*, 441–448. [[CrossRef](#)]
20. Rhodes, N.J.; Liu, J.; O’Donnell, J.N.; Dulhunty, J.M.; Abdul-Aziz, M.H.; Berko, P.Y.; Nadler, B.; Lipman, J.; Roberts, J.A. Prolonged Infusion Piperacillin-Tazobactam Decreases Mortality and Improves Outcomes in Severely Ill Patients: Results of a Systematic Review and Meta-Analysis. *Crit. Care Med.* **2018**, *46*, 236–243. [[CrossRef](#)]
21. Roberts, J.A.; Abdul-Aziz, M.H.; Davis, J.S.; Dulhunty, J.M.; Cotta, M.O.; Myburgh, J.; Bellomo, R.; Lipman, J. Continuous versus Intermittent beta-Lactam Infusion in Severe Sepsis. A Meta-analysis of Individual Patient Data from Randomized Trials. *Am. J. Respir. Crit. Care Med.* **2016**, *194*, 681–691. [[CrossRef](#)] [[PubMed](#)]
22. Wong, G.; Taccone, F.; Villosio, P.; Scheetz, M.H.; Rhodes, N.J.; Briscoe, S.; McWhinney, B.; Nunez-Nunez, M.; Ungerer, J.; Lipman, J.; et al. beta-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill. *J. Antimicrob. Chemother.* **2020**, *75*, 429–433. [[PubMed](#)]
23. Scharf, C.; Liebchen, U.; Paal, M.; Taubert, M.; Vogeser, M.; Irlbeck, M.; Zoller, M.; Schröder, I. The higher the better? Defining the optimal beta-lactam target for critically ill patients to reach infection resolution and improve outcome. *J. Intensive Care* **2020**, *8*, 1–10. [[CrossRef](#)]
24. Wong, G.; Brinkmann, A.; Benefield, R.J.; Carlier, M.; De Waele, J.J.; El, H.N.; Frey, O.; Harbarth, S.; Huttner, A.; McWhinney, B.; et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J. Antimicrob. Chemother.* **2014**, *69*, 1416–1423. [[CrossRef](#)] [[PubMed](#)]
25. Wong, G.; Briscoe, S.; McWhinney, B.; Ally, M.; Ungerer, J.; Lipman, J.; Roberts, J.A. Therapeutic drug monitoring of beta-lactam antibiotics in the critically ill: Direct measurement of unbound drug concentrations to achieve appropriate drug exposures. *J. Antimicrob. Chemother.* **2018**, *73*, 3087–3094. [[CrossRef](#)]

26. Williams, P.; Beall, G.; Cotta, M.O.; Roberts, J.A. Antimicrobial dosing in critical care: A pragmatic adult dosing nomogram. *Int. J. Antimicrob. Agents* **2020**, *55*, 105837. [[CrossRef](#)]
27. Minichmayr, I.K.; Roberts, J.A.; Frey, O.R.; Röhr, A.C.; Kloft, C.; Brinkmann, A. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. *J. Antimicrob. Chemother.* **2018**, *73*, 1330–1339. [[CrossRef](#)]
28. Roberts, J.A.; Joynt, G.; Lee, A.; Choi, G.; Bellomo, R.; Kanji, S.; Mudaliar, M.Y.; Peake, S.L.; Stephens, D.; Taccone, F.S.; et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: Data from the multinational SMART Study. *Clin. Infect. Dis.* **2020**, *72*, 1369–1378. [[CrossRef](#)] [[PubMed](#)]
29. Guilhaumou, R.; Benaboud, S.; Bennis, Y.; hyot-Fizelier, C.; Dailly, E.; Gandia, P.; Goutelle, S.; Lefeuvre, S.; Mongardon, N.; Roger, C.; et al. Optimization of the treatment with beta-lactam antibiotics in critically ill patients-guidelines from the French Society of Pharmacology and Therapeutics (Societe Francaise de Pharmacologie et Therapeutique-SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Societe Francaise d’Anesthesie et Reanimation-SFAR). *Crit. Care* **2019**, *23*, 1–10.
30. Liebchen, U.; Paal, M.; Scharf, C.; Schröder, I.; Grabein, B.; Zander, J.; Siebers, C.; Zoller, M. The ONTAI study—A survey on antimicrobial dosing and the practice of therapeutic drug monitoring in German intensive care units. *J. Crit. Care* **2020**, *60*, 260–266. [[CrossRef](#)]
31. Brinkmann, A.; Röhr, A.C.; Frey, O.R.; Krüger, W.A.; Brenner, T.; Richter, D.C.; Bodmann, K.F.; Kresken, M.; Grabein, B. S2k-Leitlinie der PEG zur kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen Fokussierte Zusammenfassung und ergänzende Informationen zur Antibiotikatherapie kritisch kranker Patienten [S2k guidelines of the PEG on calculated parenteral initial treatment of bacterial diseases in adults: Focussed summary and supplementary information on antibiotic treatment of critically ill patients]. *Anaesthesist* **2018**, *67*, 936–949.
32. Derendorf, H.; Heinrichs, T.; Reimers, T.; Lebert, C.; Brinkmann, A. Calculated initial parenteral treatment of bacterial infections: Pharmacokinetics and pharmacodynamics. *GMS Infect. Dis.* **2020**, *8*. [[CrossRef](#)]
33. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit. Care Med.* **2017**, *45*, 486–552. [[CrossRef](#)] [[PubMed](#)]
34. Marx, G.; SepNet Critical Care Trials, G.; Brinkmann, A. Incidence of severe sepsis and septic shock in German intensive care units: The prospective, multicentre INSEP study. *Intensive Care Med.* **2016**, *42*, 1980–1989. [[CrossRef](#)] [[PubMed](#)]
35. Le Gall, J.R.; Lemeshow, S.; Saulnier, F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* **1993**, *270*, 2957–2963. [[CrossRef](#)] [[PubMed](#)]
36. Moreno, R.; Vincent, J.L.; Matos, R.; Mendonca, A.; Cantraine, F.; Thijs, L.; Takala, J.; Sprung, C.; Antonelli, M.; Bruining, H.; et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. *Intensive Care Med.* **1999**, *25*, 686–696. [[CrossRef](#)] [[PubMed](#)]
37. Fleischmann, C.; Thomas-Rueddel, D.O.; Hartmann, M.; Hartog, C.S.; Welte, T.; Heublein, S.; Heublein, S.; Dennler, U.; Reinhart, K. Hospital Incidence and Mortality Rates of Sepsis. *Dtsch. Arztebl Int.* **2016**, *113*, 159–166.
38. Levy, M.M.; Artigas, A.; Phillips, G.S.; Rhodes, A.; Beale, R.; Osborn, T.; Vincent, J.L.; Townsend, S.; Lemeshow, S.; Dellinger, R.P. Outcomes of the Surviving Sepsis Campaign in intensive care units in the USA and Europe: A prospective cohort study. *Lancet Infect. Dis.* **2012**, *12*, 919–924. [[CrossRef](#)]
39. Beale, R.; Janes, J.M.; Brunkhorst, F.M.; Dobb, G.; Levy, M.M.; Martin, G.S.; Ramsay, G.; Silva, E.; Sprung, C.L.; Vallet, B.; et al. Global utilization of low-dose corticosteroids in severe sepsis and septic shock: A report from the PROGRESS registry. *Crit. Care* **2010**, *14*, R102. [[CrossRef](#)]
40. Bellos, I.; Karageorgiou, V.; Pergialiotis, V.; Perrea, D.N. Acute kidney injury following the concurrent administration of antipseudomonal beta-lactams and vancomycin: A network meta-analysis. *Clin. Microbiol. Infect.* **2020**, *26*, 696–705. [[CrossRef](#)]
41. Kadomura, S.; Takekuma, Y.; Sato, Y.; Sumi, M.; Kawamoto, K.; Itoh, T.; Sugawara, M. Higher incidence of acute kidney injury in patients treated with piperacillin/tazobactam than in patients treated with cefepime: A single-center retrospective cohort study. *J. Pharm. Health Care Sci.* **2019**, *5*, 1–8. [[CrossRef](#)]
42. Zelenitsky, S.; Nash, J.; Weber, Z.; Iacovides, H.; Ariano, R. Targeted benefits of prolonged-infusion piperacillin-tazobactam in an in vitro infection model of *Pseudomonas aeruginosa*. *J. Chemother.* **2016**, *28*, 390–394. [[CrossRef](#)]
43. Leone, M.; Roberts, J.A.; Bassetti, M.; Bougle, A.; Lavigne, J.P.; Legrand, M.; Neely, M.; Paiva, J.A.; Payen, D.; Rello, J.; et al. Update in Antibiotic Therapy in Intensive Care Unit Report from the 2019 Nimes International Symposium. *Anaesth. Crit. Care Pain Med.* **2019**, *38*, 647–656. [[CrossRef](#)]
44. Crass, R.L.; Williams, P.; Roberts, J.A. The challenge of quantifying and managing pharmacokinetic variability of beta-lactams in the critically ill. *Anaesth. Crit. Care Pain Med.* **2020**, *39*, 27–29. [[CrossRef](#)] [[PubMed](#)]
45. Carlier, M.; Carrette, S.; Stove, V.; Verstraete, A.G.; De Waele, J.J. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course. *Int. J. Antimicrob. Agents* **2014**, *43*, 470–473. [[CrossRef](#)] [[PubMed](#)]
46. Patel, N.; Scheetz, M.H.; Drusano, G.L.; Lodise, T.P. Determination of antibiotic dosage adjustments in patients with renal impairment: Elements for success. *J. Antimicrob. Chemother.* **2010**, *65*, 2285–2290. [[CrossRef](#)] [[PubMed](#)]

47. Patel, N.; Scheetz, M.H.; Drusano, G.L.; Lodise, T.P. Identification of optimal renal dosage adjustments for traditional and extended-infusion piperacillin-tazobactam dosing regimens in hospitalized patients. *Antimicrob. Agents Chemother.* **2010**, *54*, 460–465. [[CrossRef](#)]
48. Hagel, S.; Fiedler, S.; Hohn, A.; Brinkmann, A.; Frey, O.R.; Hoyer, H.; Schlattmann, P.; Kiehntopf, M.; Roberts, J.A.; Pletz, M.W. Therapeutic drug monitoring-based dose optimisation of piperacillin/tazobactam to improve outcome in patients with sepsis (TARGET): A prospective, multi-centre, randomised controlled trial. *Trials* **2019**, *20*, 1–10. [[CrossRef](#)]
49. Udy, A.A.; Lipman, J.; Jarrett, P.; Klein, K.; Wallis, S.C.; Patel, K.; Kirkpatrick, C.M.; Krüger, P.S.; Paterson, D.L.; Roberts, M.S.; et al. Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? *Crit. Care* **2015**, *19*, 1–9. [[CrossRef](#)]
50. Dillinger, R.P.; Levy, M.M.; Rhodes, A.; Annane, D.; Gerlach, H.; Opal, S.M.; Sevransky, J.E.; Sprung, C.L.; Douglas, I.S.; Jaeschke, R.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med.* **2013**, *39*, 165–228. [[CrossRef](#)]
51. Röhr, A.C.; Köberer, A.; Fuchs, T.; von Freyberg, P.; Frey, O.R.; Brinkmann, A. Individuelle Dosierung und Applikation von Antiinfektiva auf der Intensivstation. *Intensive Up2date* **2018**, *14*, 238–243.
52. Röhr, A.C.; Frey, O.R.; Köberer, A.; Fuchs, T.; Roberts, J.A.; Brinkmann, A. Anti-infective drugs during continuous hemodialysis—Using the bench to learn what to do at the bedside. *Int. J. Artif. Organs* **2015**, *38*, 17–22. [[CrossRef](#)]
53. De Waele, J.J.; Lipman, J.; Akova, M.; Bassetti, M.; Dimopoulos, G.; Kaukonen, M.; Koulenti, D.; Martin, C.; Montravers, P.; Rello, J.; et al. Risk factors for target non-attainment during empirical treatment with β -lactam antibiotics in critically ill patients. *Intensive Care Med.* **2014**, *40*, 1340–1351. [[CrossRef](#)]
54. Imani, S.; Buscher, H.; Day, R.; Gentili, S.; Jones, G.R.D.; Marriott, D.; Norris, R.; Sandaradura, I. An evaluation of risk factors to predict target concentration non-attainment in critically ill patients prior to empiric β -lactam therapy. *Eur. J. Clin. Microbiol. Infect. Dis.* **2018**, *37*, 2171–2175. [[CrossRef](#)] [[PubMed](#)]
55. Woksepp, H.; Hällgren, A.; Borgström, S.; Kullberg, F.; Wimmerstedt, A.; Oscarsson, A.; Nordlund, P.; Lindholm, M.L.; Bonnedahl, J.; Brudin, L.; et al. High target attainment for β -lactam antibiotics in intensive care unit patients when actual minimum inhibitory concentrations are applied. *Eur. J. Clin. Microbiol. Infect. Dis.* **2017**, *36*, 553–563. [[CrossRef](#)]
56. Sheiner, L.B.; Beal, S.L. Some suggestions for measuring predictive performance. *J. Pharmacokinetic. Biopharm.* **1981**, *9*, 503–512. [[CrossRef](#)] [[PubMed](#)]