



# Time above the MIC of Piperacillin-Tazobactam as a Predictor of Outcome in *Pseudomonas aeruginosa* Bacteremia

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**ABSTRACT** *Pseudomonas aeruginosa* bacteremia is an infection associated with a high mortality rate. Piperacillin-tazobactam is a  $\beta$ -lactam- $\beta$ -lactamase inhibitor combination that is frequently used for the management of *Pseudomonas aeruginosa* infections. The pharmacokinetic-pharmacodynamic index associated with *in vitro* maximal bacterial killing for piperacillin-tazobactam is the percentage of the time between doses at which the free fraction concentration remains above the MIC ( $\%fT_{>MIC}$ ). However, the precise  $\%fT_{>MIC}$  target associated with improved clinical outcomes is unknown. The aim of this study was to investigate the correlation between the survival of patients with *Pseudomonas aeruginosa* bacteremia and the threshold of the piperacillin-tazobactam  $\%fT_{>MIC}$ . This retrospective study included all adult patients hospitalized over an 82-month period with *Pseudomonas aeruginosa* bacteremia and treated with piperacillin-tazobactam. Patients with a polymicrobial infection or those who died within 72 h of the time of collection of a sample for culture were excluded. The  $\%fT_{>MIC}$  of piperacillin-tazobactam associated with in-hospital survival was derived using classification and regression tree analysis. After screening 270 patients, 78 were eligible for inclusion in the study; 18% died during hospitalization. Classification and regression tree analysis identified a  $\%fT_{>MIC}$  of  $>60.68\%$  to be associated with improved survival, and this remained statistically significant after controlling for clinical covariates (odds ratio = 7.74, 95% confidence interval = 1.32 to 45.2). In conclusion, the findings recommend dosing of piperacillin-tazobactam with the aim of achieving a pharmacodynamic target  $\%fT_{>MIC}$  of at least 60% in these patients.

*Pseudomonas aeruginosa* bacteremia is a common hospital-acquired infection (1) associated with an increased rate of mortality ranging from 18 to 61% (2). Early appropriate antimicrobial therapy is associated with improved survival (3–8).

Piperacillin and the combination of piperacillin and tazobactam (TZP) are extensively used in the treatment of infectious diseases in critically ill patients, specifically, when *P. aeruginosa* is the causative pathogen (8). Protein binding for piperacillin ranges from 20 to 30%, and for tazobactam it is approximately 30% (9, 10). Various population pharmacokinetic (PK) studies have suggested that the main covariates influencing the volume of distribution and the clearance of TZP are weight and creatinine clearance, respectively (11–16). The usual dose of TZP is 4.5 g three times daily for most infections and may be increased to 4.5 g four times daily in severe health care-acquired infections (17) and in *P. aeruginosa* infections, as recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards

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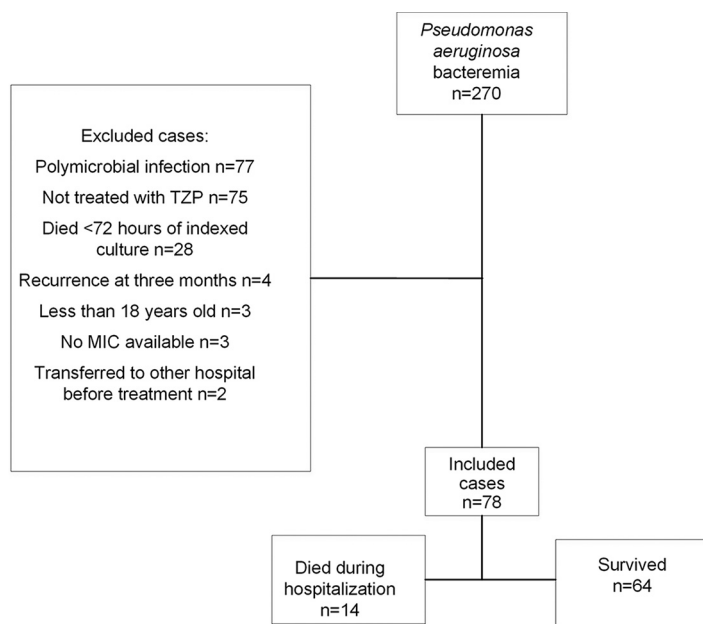


FIG 1 Study flow chart.

Institute (CLSI). Dose adjustments for renal impairment vary widely between sources (9, 17, 18). There are no sufficient data regarding dosing regimens that achieve pharmacokinetic and pharmacodynamic (PD) targets that are correlated with improved clinical outcomes.

Piperacillin, like other  $\beta$ -lactams, exhibits time-dependent bactericidal activity. *In vitro* and animal studies suggest that the PK-PD parameter for  $\beta$ -lactams that is most predictive of microbiological efficacy is the percentage of time between doses at which the free fraction concentration remains above the MIC ( $\%fT_{>MIC}$ ) (19). For piperacillin, a PK-PD target of a  $\%fT_{>MIC}$  of 50% is often cited based on studies of other penicillins (20), for example, ticarcillin (21, 22). There is only one study that reported a relationship between bacterial killing and  $\%fT_{>MIC}$ , with significant thresholds of 27% for bacteriostasis and 75% for bactericidal activity (23).

Very few studies have tried to correlate  $\%fT_{>MIC}$  with clinical outcomes. Among them is the DALI trial, a prospective multinational study that included 361 critically ill patients who were treated with a  $\beta$ -lactam (24). This study concluded that for all  $\beta$ -lactams a  $\%fT_{>MIC}$  of  $>50\%$  is associated with better outcomes. Other studies dealt specifically with meropenem and neutropenic patients (25) and cephalosporins (26, 27).

Moreover, the need for a clinically driven  $\%fT_{>MIC}$  target is augmented by the fact that  $\beta$ -lactams display indirect antimicrobial properties. These properties cannot be identified by standard *in vivo* susceptibility testing and include synergy with cationic host defense peptides and action as immune adjuvants (28). The use of an *in vitro*-derived PK-PD target for any antimicrobial without clinical validation is highly problematic (29). This observation is especially true in the case of  $\beta$ -lactams.

The aim of this study was to investigate the correlation between the concentration-time profile of TZP and clinical outcomes in patients with *P. aeruginosa* bacteremia. Additionally, the study aimed to find if there is a threshold of  $\%fT_{>MIC}$  that is associated with improved survival at 30 days.

## RESULTS

A total of 270 patients with *P. aeruginosa* bacteremia were screened for this retrospective study from January 2012 to October 2018, and 78 fulfilled the inclusion criteria for the study (Fig. 1).

The patients' baseline characteristics are described in Table 1. The included patients

**TABLE 1** Baseline characteristics of 78 patients with *P. aeruginosa* bacteremia<sup>a</sup>

Characteristic	Value for the following group:			P value
	Total cohort	Patients who survived in hospital	Patients who died	
Total no. (%) of patients	78	64 (82)	14 (18)	
Mean (SD) age (yr)	65 (17.95)	65 (18.27)	68 (16.82)	0.568
No. (%) of female patients	29 (37.1)	24 (37.5)	5 (35.7)	0.900
Median (IQR) wt (kg)	73.9 (80.75, 62.25)	74 (84.25, 62.75)	71 (74, 61.75)	0.108
Mean (SD) modified APACHE II score on culture day	11.5 (5.46)	10.8 (5.61)	14.5 (3.48)	0.022
No. (%) of patients with the following sources of infection:				
Respiratory	22 (28.2)	14 (21.8)	8 (57)	0.011
Intra-abdominal	7 (8.9)	7 (10.9)	0 (0)	0.991
Urinary	14 (17.9)	13 (20.3)	1 (7.1)	0.269
Skin and wound	11 (14.1)	10 (15.6)	1 (7.1)	0.442
Central line	9 (11.5)	9 (14)	0 (0)	0.994
Unknown	15 (19.2)	11 (17.2)	4 (28.6)	0.333
No. (%) of patients with the following medical history:				
Hypertension	39 (50)	32 (50)	7 (50)	1
Type 2 diabetes	29 (37.2)	23 (35.9)	6 (42.8)	0.627
IHD	12 (15.4)	10 (15.6)	2 (14.3)	0.900
Heart failure	17 (21.8)	11 (17.2)	6 (42.8)	0.035
Hyperlipidemia	28 (35.9)	23 (35.9)	5 (35.7)	0.987
Dementia	9 (11.5)	8 (12.5)	1 (7.1)	0.57
CKD	25 (32)	18 (28.1)	7 (50)	0.112
COPD	9 (11.5)	5 (7.8)	4 (28.5)	0.025
Receipt of immunosuppression (90 days)	12 (15.4)	7 (10.9)	5 (35.7)	0.02
Median (IQR) creatinine clearance (ml/min)	53.5 (97, 23.25)	59.5 (98.5, 26.95)	26.5 (78.25, 13.525)	0.214
No. (%) of patients with AKI	16 (20.5)	9 (14)	7 (50)	0.003
No. (%) of patients with:				
Solid tumors	18 (23)	13 (20.3)	5 (35.7)	0.22
Hematological malignancies	4 (5.1)	2 (3.1)	2 (14.1)	0.117
Median (IQR) duration of hospitalization (days) until collection of index culture sample	1 (7, 0)	1 (7, 0)	0 (9.5, 0)	0.952
Median (IQR) time (days) until appropriate antipseudomonal therapy	1 (2, 0)	1 (2, 0)	1 (2.75, 1)	0.603
No. (%) of patients hospitalized in ICU	7 (9)	3 (4.7)	4 (28.6)	0.005

<sup>a</sup>IQR, interquartile range; IHD, ischemic heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; ICU, intensive care unit.

had a mean  $\pm$  standard deviation (SD) age of  $65 \pm 17.95$  years, 37.1% were female, and the mean  $\pm$  SD modified acute physiology and chronic health evaluation II (APACHE II) score on the day that the specimen was collected for culture was  $11.5 \pm 5.46$ . Patients had a median creatinine clearance of 53.5 ml/min (interquartile range [IQR] = 23.25 to 97 ml/min), and 16 patients (20.5%) had an acute kidney injury (AKI). The most common source of bacteremia was respiratory (28.2%), and 7 (9%) patients were treated in the intensive care unit (ICU). The median MIC was 8  $\mu$ g/ml and was similar for isolates from patients who survived and patients who died.

The primary outcome of in-hospital survival occurred in 64 (82%) of the included patients. Patients who survived had a lower APACHE II score, had fewer cases of AKI, and were less frequently hospitalized in the ICU than patients who died (10.8 versus 14.5 [ $P = 0.022$ ], 14% versus 50% [ $P = 0.003$ ], and 4.7% versus 28.6% [ $P = 0.005$ ], respectively).

The estimated median volume of distribution of piperacillin was 23.19 liters (IQR = 18.47 to 30.19 liters), and the estimated median elimination rate constant was  $0.56 \text{ h}^{-1}$  (IQR = 0.36 to  $0.86 \text{ h}^{-1}$ ). The mean  $\%fT_{>MIC}$  calculated from the pharmacokinetic model and estimated parameters was 63% (IQR = 47 to 85%). Table 2 presents the median  $\%fT_{>MIC}$  by the different creatinine clearance groups. Patients with a

**TABLE 2** % $fT_{>MIC}$  by the different creatinine clearance groups

Creatinine clearance (ml/min)	% $fT_{>MIC}$	
	Median	IQR
0–20 ( <i>n</i> = 19)	82	69–89
21–40 ( <i>n</i> = 19)	65	45–85
41–60 ( <i>n</i> = 5)	47	43–90
61–80 ( <i>n</i> = 5)	69	55–99
81–100 ( <i>n</i> = 11)	53	40–70
101–120 ( <i>n</i> = 6)	54	50–60
>120 ( <i>n</i> = 13)	56	35–75

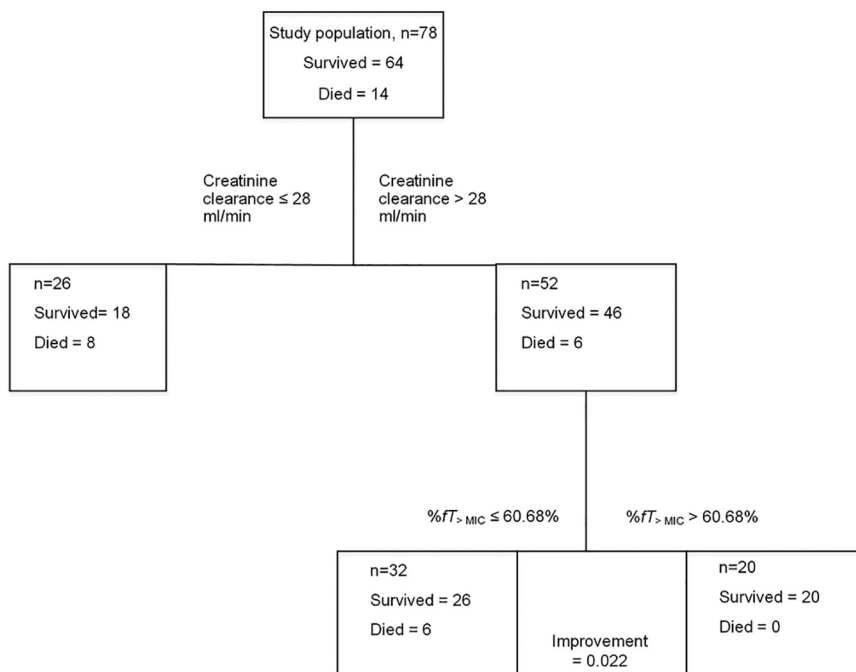
creatinine clearance of less than 20 ml/min had a higher median % $fT_{>MIC}$  than patients with a creatinine clearance above 20 ml/min (82% and 59%, respectively).

Classification and regression tree analysis (CART) identified a % $fT_{>MIC}$  threshold of 60.68% to be associated with improved in-hospital survival, after adjusting for creatinine clearance (Fig. 2).

The final logistic regression model included AKI, a modified APACHE II score of  $\geq 14$ , and an interaction term between them as independent variables, in addition to the CART-derived % $fT_{>MIC}$  threshold. A % $fT_{>MIC}$  of >60.68% was entered in the final model as a categorical variable. The adjusted odds ratio (OR) of achieving the threshold of a % $fT_{>MIC}$  of >60.68% was 7.74 (95% confidence interval [CI] = 1.32 to 45.2) (Table 3). A comparison of the final model and the competing models is summarized in Table S1 in the supplemental material.

The goodness of fit and regression diagnostics of the final model are summarized in Tables S2 to S4. The results of an internal validation with bootstrap analysis are summarized in Tables S5 and S6. Moreover, other % $fT_{>MIC}$  thresholds were tested by adjusting for the same covariates, as shown in Table 4. A % $fT_{>MIC}$  of >40% and a % $fT_{>MIC}$  of >50%, as well as a % $fT_{>MIC}$  of >70% and a % $fT_{>MIC}$  of >80%, were not significant predictors of in-hospital survival.

Eleven patients received concomitant treatment with other antimicrobial agents: ciprofloxacin (*n* = 9), levofloxacin (*n* = 1), and gentamicin (*n* = 1). In a univariable

**FIG 2** CART-derived % $fT_{>MIC}$  threshold.

**TABLE 3** Logistic regression model of in-hospital survival

Parameter	Adjusted OR for in-hospital survival	P value	95% CI
%fT <sub>&gt;MIC</sub> > 60%	7.74	0.023	1.32–45.2
AKI	0.14	0.003	0.001–0.234
Modified APACHE II score ≥ 14	0.113	0.018	0.019–0.685
AKI · modified APACHE II score ≥ 14	20.65	0.05	1.99–420.8

analysis for 30-day survival, the OR of concomitant treatment was 0.3 ( $P = 0.0984$ ). In the multivariable logistic regression, adding this variable did not increase the explanatory power of the model (Akaike information criterion = 64.41,  $-2 \log$  likelihood = 52.41) compared to that of the final model.

## DISCUSSION

The key finding of this study is the fact that the CART-derived threshold of a %fT<sub>>MIC</sub> of TZP of >60.68% was found to be a significant predictor of in-hospital survival in patients with *P. aeruginosa* bacteremia, adjusting for covariates. Lower thresholds (%fT<sub>>MIC</sub> > 40% and %fT<sub>>MIC</sub> > 50%), as well as higher thresholds (%fT<sub>>MIC</sub> > 70% and %fT<sub>>MIC</sub> > 80%), were not significant predictors of in-hospital survival. To the best of our knowledge, this is the first study to report a %fT<sub>>MIC</sub> threshold of TZP that is associated with improved survival.

The results of this study are consistent with those of other clinical studies concerning the effects of the %fT<sub>>MIC</sub> of  $\beta$ -lactams on clinical outcomes. In the DALI study, achieving a %fT<sub>>MIC</sub> of >50% and %fT<sub>>MIC</sub> of >100% was associated with improved clinical outcomes (24). This cohort had a relatively lower mean modified APACHE II score compared to that for the cohort in the DALI study (11.5 and 18, respectively). Interestingly, in the DALI study, the adjusted odds ratios of a %fT<sub>>MIC</sub> of >50% and a %fT<sub>>MIC</sub> of >100% for an improved clinical outcome were similar among patients who did not receive renal replacement therapy (1.03 [95% CI = 1.01 to 1.04] and 1.02 [95% CI = 1.01 to 1.05], respectively). The latter finding is consistent with the threshold of a %fT<sub>>MIC</sub> of >60% reported in this study.

Ariano et al. studied the influence of the %fT<sub>>MIC</sub> of meropenem in neutropenic patients with bacteremia and found an average %fT<sub>>MIC</sub> of 83% among 42 clinical responders and an average %fT<sub>>MIC</sub> of 59% among 18 nonresponders ( $P = 0.04$ ), but in their study, no adjustment for severity of illness was performed (25). Rhodes et al. reported two %fT<sub>>MIC</sub> thresholds for cefepime (68% and 74%) that were associated with improved survival (adjusted OR = 7.12 [95% CI = 1.9 to 26.7] and 6.48 [95% CI = 1.9 to 22.1], respectively) (27), similar to our results, although our patient population had a lower mean modified APACHE II score than the population in the study by Rhodes et al. (27) (11.5 and 14.6, respectively) and a lower median creatinine clearance (59.5 ml/min among patients who survived and 53.5 ml/min among patients who died in our study and 74.9 ml/min and 83 ml/min, respectively, in the study by Rhodes et al. [27]).

The EUCAST rationale document for TZP states that a piperacillin %fT<sub>>MIC</sub> of 30 to 35% is needed for stasis against *P. aeruginosa* and that a %fT<sub>>MIC</sub> of 40% is required for a 2-log drop in the viable organism count in animal models. This statement is based on limited data (30). Yet a higher dose of 4.5 g four times daily is recommended. This higher dose, according to EUCAST, renders all wild-type *P. aeruginosa* isolates susceptible to TZP and allows a clinical MIC breakpoint of 16 mg/liter. The former conclusion was based on a Monte Carlo simulation of various dosing regimens. It did not consider special populations, such as critically ill patients, who usually have a higher piperacillin volume of distribution, and patients with augmented renal clearance, whose piperacillin clearance is significantly increased. Indeed, Udy et al. demonstrated that patients with augmented renal clearance had increased clearance of piperacillin (31). They concluded that, when considering the MIC distribution of *P. aeruginosa*, the regimen of 4.5 g four times daily administered as a 30-min infusion is not expected to achieve a

**TABLE 4** Effect of different %fT<sub>>MIC</sub> thresholds on in-hospital survival

%fT <sub>&gt;MIC</sub>	Adjusted OR for in-hospital survival	P value	95% CI
>40	3.70	0.151	0.62–22
>50	3.76	0.100	0.77–18.18
>60	7.74	0.023	1.32–45.2
>70	2.55	0.199	0.61–10.65
>80	2.25	0.280	0.52–9.82

%fT<sub>>MIC</sub> of 50% in a significant portion of critically ill patients (31). The cohort in this study was too small to analyze the optimal dosing regimen.

There are some limitations to this study. First, this was a retrospective, single-center study with the limitations resulting from the study design. Still, the results contribute to evidence in an area in which there is limited literature available. Second, the small sample size may have affected the estimation of the adjusted odds ratio of the %fT<sub>>MIC</sub> of TZP of >60% on in-hospital survival, as reflected by large confidence intervals in some of the results. Third, TZP concentrations were not measured in any patient, and former studies have shown substantial variability in TZP concentrations in hospitalized patients (24). Nevertheless, the piperacillin volume of distribution and elimination rate constant were estimated for each patient using a highly qualified population model. Moreover, across various population pharmacokinetics studies, weight and creatinine clearance were identified as the main covariates affecting piperacillin's volume of distribution and clearance, respectively. Concentrations were predicted for each patient, controlling for weight and creatinine clearance. Therefore, concentration prediction and imputation represented the best available strategy to study the influence of %fT<sub>>MIC</sub> on in-hospital survival in our patient cohort.

This study has several strengths. First, the data were extracted and reviewed by two health care professionals reviewing all medical records. Second, exact dosing times were used to calculate %fT<sub>>MIC</sub>, and symmetric dosing intervals were not assumed, an assumption that is mostly inaccurate in the hospital setting (31). Third, creatinine clearance was estimated using three different methods, to account for patients with unstable serum creatinine levels and patients whose weight was 30% higher than their ideal body weight. Fourth, the logistic regression model utilized purposeful variable selection as a model-building strategy that included testing for interactions between selected variables. Fifth, the final logistic model was tested for goodness of fit, rigorous regression diagnostics were performed, and the final model was internally validated by bootstrap analysis.

Additionally, the findings of the present study support individualization of the TZP dose with the aim of achieving a threshold of a %fT<sub>>MIC</sub> of 60%. In settings where therapeutic drug monitoring of TZP is available, concentration monitoring is recommended for critically ill patients with *P. aeruginosa* bacteremia in order to achieve the pharmacodynamic target of a %fT<sub>>MIC</sub> of 60%.

In conclusion, we have found that achieving a %fT<sub>>MIC</sub> of TZP of 60% was associated with improved in-hospital survival in patients with *P. aeruginosa* bacteremia. Until more data become available, it is prudent to recommend dosing TZP with the aim of achieving the pharmacodynamic target of a %fT<sub>>MIC</sub> of at least 60% in patients with *P. aeruginosa* bacteremia.

## MATERIALS AND METHODS

This retrospective study was conducted at a secondary university-affiliated hospital with 495 beds. The study methods were approved by the ethics committees at Hillel Yaffe Medical Center, Hadera, Israel, and Robert Gordon University, Aberdeen, Scotland. Patients above 18 years old who had a blood culture positive for *P. aeruginosa* and who were hospitalized in the Hillel Yaffe Medical Center between January 2012 and October 2018 were reviewed for inclusion. Patients not treated with TZP, for whom treatment was delayed by >96 h from the time of collection of blood for the index blood culture, who had polymicrobial blood culture findings, or for whose isolates the MIC of TZP was not reported were excluded. Moreover, patients who died less than 72 h after a blood sample for culture was obtained were



excluded. If a patient had two episodes of *P. aeruginosa*-positive blood cultures in less than 3 months, only the data for the first episode were included.

Information was extracted from paper-based and electronic patient records. Data for patients with *P. aeruginosa*-positive blood cultures were extracted from the microbiology laboratory database, as were the MICs for TZP. The extracted data included age, gender, comorbidities, modified APACHE II score (32, 33), Glasgow coma scale, absolute neutrophil count, weight, serum creatinine concentration, TZP dose, and dosing interval. For patients with stable serum creatinine concentrations (defined as a difference of less than 0.3 mg/dl between two consecutive serum creatinine levels), creatinine clearance was estimated using the Cockcroft and Gault equation for patients whose actual body weight was no more than 30% greater than their ideal body weight; otherwise, the Salazar-Corcoran equation was used. In patients with unstable serum creatinine levels, the Jelliffe equation was used.

**Pharmacokinetic analysis.** To estimate the  $\%fT_{>MIC}$  of piperacillin, we utilized the population pharmacokinetics 1-compartment model published by Chen et al. (15). This model was selected because it best fitted the population in our study, reported intersubject variability, was qualified by visual predictive checks, and was validated using nonparametric bootstrap analysis. Using the NONMEM (version 7.4) program, the volume of distribution and clearance were estimated for each patient. Subsequently, for each patient, the free fraction piperacillin concentration was generated every 15 min for the first 48 h of TZP treatment, assuming a mean protein binding of 25%. The cumulative time above the MIC was calculated and divided by 48, giving the estimated  $\%fT_{>MIC}$  of piperacillin. MICs were determined using a Vitek 2 system (Vitek 2; bioMérieux). The primary outcome was in-hospital survival.

**Statistical analysis.** Statistical analysis was performed with SPSS (version 25) and R software. The  $\%fT_{>MIC}$  threshold associated with improved survival was derived by using the classification and regression tree (CART) analysis function in SPSS (version 25) software, using  $\%fT_{>MIC}$  and creatinine clearance as continuous independent variables.

To test the influence of the CART-derived  $\%fT_{>MIC}$  threshold on in-hospital survival, adjusting for significant covariates, a logistic regression model was utilized. Variable selection was performed using purposeful variable selection (34). In brief, candidate variables at a univariate level of significance of a *P* value of  $<0.25$  were assessed as possible predictors of in-hospital survival. The importance of each variable was tested using the likelihood ratio test with 1 degree of freedom. Variables were retained in the model if their deletion resulted in a change in the likelihood ratio of  $>3.84$ . Moreover, the presence of interactions among the retained variables was explored, and significant interactions were added into the final model (34). Goodness of fit was assessed using the Hosmer and Lemeshow test in SPSS (version 25) software, and regression diagnostics were performed using the car package in R software (35) (see the supplemental material). Internal validation of the final model was performed with bootstrap analysis using the boot package in R software (20,000 replications; confidence intervals were calculated using the percentile method; see the supplemental material).

## SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1**, PDF file, 0.1 MB.

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