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RESEARCH

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Validation of a predictive risk score of aggressive PK/PD target non-attainment with continuous infusion piperacillin/tazobactam or meropenem in critically ill patients having documented Gram-negative infections

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Abstract

Objective To validate a predictive risk score of early aggressive pharmacokinetic/pharmacodynamic (PK/PD) target non-attainment with continuous infusion (CI) piperacillin/tazobactam or meropenem in a retrospective cohort of critically ill patients having documented Gram-negative infections.

Methods Critically ill adult patients receiving treatment of documented Gram-negative infections with CI piperacillin-tazobactam or meropenem and undergoing first real-time beta-lactam therapeutic drug monitoring (TDM) instance within 72 h from starting standard dosing regimens were retrospectively included. A receiving operating characteristic (ROC) curve analysis was performed by using the proposed predictive score as the test variable and early aggressive PK/PD target non-attainment as the state variable. Area under the curve (AUC) and 95% confidence interval were calculated. The identified cut-off risk values were used for stratifying patients and assessing the impact on clinical/microbiological outcome in each sub-cohort of patients receiving targeted monotherapy.

Results Overall, 209 and 203 patients receiving CI piperacillin-tazobactam and meropenem were included, respectively. Early aggressive PK/PD target non-attainment was reported in 33 cases (15.8%) receiving piperacillin-tazobactam and in 8 (3.9%) of those treated with meropenem. A score threshold ≥ 2 points for piperacillin-tazobactam (*AUC* 0.81; 95% *CI* 0.75–0.86; $p < 0.0001$) and ≥ 3 points for patients treated with meropenem (*AUC* 0.96; 95% *CI* 0.93–0.99; $p < 0.0001$) were significantly associated with early aggressive PK/PD target non-attainment. Patients achieving the cut-off predictive score showed a significant higher microbiological failure rate in both piperacillin-tazobactam (56.3% vs. 28.6%, $p = 0.044$) and meropenem sub-cohorts (50.0% vs. 10.4%, $p = 0.028$).

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Conclusions Our findings suggest that the proposed predictive cut-off risk score may represent a valuable tool for identifying promptly critically ill patients at high risk of early aggressive PK/PD target non-attainment with CI piperacillin-tazobactam or meropenem for whom a more intensified CI dosing regimens should be promptly applied bedside.

Keywords Critically ill patients, Beta-lactams, Early aggressive PK/PD target attainment, Score validation, Microbiological failure

Introduction

Sepsis and/or septic shock may be life-threatening conditions often requiring intensive care unit (ICU) admission or complicating ICU stay among critically ill patients [1–3]. First-line antimicrobial treatment of these conditions is based on broad spectrum beta-lactams covering both Enterobacterales and *Pseudomonas aeruginosa*, among which the most frequently used are piperacillin/tazobactam and meropenem, eventually combined with empirical therapy covering resistant Gram-positives whenever needed [4].

Beta-lactams have time-dependent antimicrobial activity, meaning that efficacy depends strictly on the time persisting with free concentrations above the minimum inhibitory concentration of the bacterial pathogen during the dosing interval (%$fT_{> MIC}$) [5]. Traditionally, the minimum threshold of $fT_{> MIC}$ adopted for assessing clinical efficacy of beta-lactams in clinical trials for regulatory approval was set at around 40–100% [6]. Recent findings suggest that this threshold could be suboptimal in the critical setting, especially for the purposes of preventing both breakthrough infections and resistance development [7, 8]. A recent meta-analysis showed that attaining a much higher PK/PD target, defined as aggressive and corresponding to 100% $fT_{> 4xMIC}$, may greatly improve the overall efficacy of beta-lactams for treating Gram-negative infections in the critically ill patients [9]. Aggressive PK/PD target attainment was associated with both better clinical cure rates (*OR* 1.69, 95% *CI* 1.15–2.49, $p = 0.007$) and lower risk of beta-lactam resistance development (*OR* 0.06, 95% *CI* 0.01–0.29, $p < 0.001$) compared to conservative PK/PD target of 100% $fT_{>MIC}$. Conversely, aggressive PK/PD target non-attainment was associated with an increased risk of microbiological failure (*OR* 26.08, 95% *CI* 8.72–77.95, $p < 0.001$) [9].

Several clinical studies showed that early aggressive PK/PD target attainment may be quite challenging whenever using standard doses of beta-lactams among critically ill patients. The proportions of non-attainment reported in different studies were as high as 40% to 60% [10–12]. Delivering dosage by extended infusion (EI) or by continuous infusion (CI) and providing dosing adaptation based on real-time therapeutic drug monitoring (TDM) were shown to be valuable approaches for increasing the likelihood of early aggressive PK/PD target attainment with both meropenem and piperacillin-tazobactam in this scenario [13, 14]. At our center, for several years, we started applying either CI administration or real-time-TDM dosing adaptations with the intent of optimizing early aggressive PK/PD target attainment of beta-lactams [13]. Unfortunately, whereas administering beta-lactams by CI may be easily implementable in every ICU, implementing a real-time TDM-guided strategy for optimizing beta-lactam exposure, although currently recommended [15], is not yet widely applied in the ICU setting [16]. Consequently, establishing a priori the reliability of a risk score in predicting early aggressive beta-lactam PK/PD target non-attainment would be extremely helpful among critically ill patients treated with standard CI beta-lactams.

The aim of this study was to validate a predictive risk score of early aggressive PK/PD target non-attainment with CI piperacillin/tazobactam or meropenem in a retrospective cohort of critically ill patients having documented Gram-negative infections.

Methods

Study design

This study aimed to validate a risk score of early aggressive PK/PD target non-attainment with CI beta-lactams in a retrospective cohort of adult critically ill patients. The selected patients were retrieved from those admitted to either the general ICU or the posttransplant ICU of the IRCCS Azienda Ospedaliero-Universitaria of Bologna, Italy, in the period between 1st January 2021 and 31st August 2024. Eligible patients had a documented Gram-negative infection treated with CI meropenem or piperacillin-tazobactam and a first real-time beta-lactam TDM instance within 72 h from starting standard dosing regimens. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Local Ethics Committee (No. 308/2021/Oss/AOUBo on 17 May 2021, No. EM232–2022_308/2021/Oss/AOUBo on 16 March 2022, EM449-2023_308/2021/Oss/AOUBo on 17 April 2024).

The under-validation risk score was previously developed by ourselves within a systematic review and meta-analysis that assessed the impact of attaining aggressive

vs. conservative PK/PD target on the efficacy of beta-lactams for the treatment of Gram-negative infections in the critically ill patients [9]. Specifically, meta-analyzed risk factors were at first retrieved from a systematic review of those studies providing adjusted independent predictors of aggressive PK/PD target non-attainment. Subsequently, the final score was developed by assigning to each of the statistically significant meta-analyzed risk factor a point value corresponding to the natural log of the estimate rounded to the nearest integer. Overall, four increasing risk predictors (namely male gender, body mass index (BMI) > 30 kg/m^2, augmented renal clearance [ARC], and MIC above the clinical breakpoint) and a decreasing one (namely prolonged/continuous infusion) contributed to the final score, each with a specific point value as summarized in Table 1. Since beta-lactams are always administered by CI at our institution, validation concerned the four increasing risk predictors, with a final score ranging from 0 to 6.

The validation process was based at first on receiver operating characteristic (ROC) curve analysis for identifying the cut-off value predicting early aggressive PK/PD target non-attainment for each agent. Youden's index was used to balance sensitivity and specificity [sensitivity (%) + specificity (%) − 100]. Specifically, the four increasing risk predictors [9] were set as the test variable, and early aggressive PK/PD target non-attainment was set as the state variable. Once that the corresponding cut-off risk score was identified, the relationship between the true-positive rate (sensitivity) and the false-positive rate (1-specificity) was calculated in each subgroup. This was performed by plotting the proportion of ICU patients having concordance between early aggressive PK/PD target non-attainment and cut-off risk score attainment (true positives) against that of false alarms (false positives, namely those having discordance between the two). Area under curve (AUC) along with 95% confidence interval (CI) were also calculated. The corresponding cut-off risk value was used for stratifying patients and assessing the impact on clinical/microbiological outcome in each sub-cohort of patients receiving targeted monotherapy.

Table 1 Proposed risk score of aggressive PK/PD target non-attainment of beta-lactams [9]

	Score
Increasing risk predictors	
Male gender	+1 point
Body mass index (BMI) > 30 kg/m^2	+1 point
Augmented renal clearance (ARC)	+2 points
MIC above the clinical breakpoint	+2 points
Decreasing risk predictors	
Prolonged/continuous infusion	−2 points

Early aggressive beta-lactam PK/PD target attainment or non-attainment was assessed at the first TDM instance and defined as follows. For meropenem, aggressive PK/PD target attainment or non-attainment was defined as fC_{ss}/MIC ratio ≥ 4 or < 4, respectively, as previously reported [17]. For piperacillin-tazobactam, aggressive joint PK/PD target attainment was defined as a piperacillin fC_{ss}/MIC ratio ≥ 4 coupled with a tazobactam fC_{ss}/target concentration (C_T) ratio > 1 (where C_T corresponded to the fixed tazobactam target concentration of 4 mg/L defined by the EUCAST for testing the in vitro standard susceptibility of piperacillin/tazobactam). Conversely, non-attainment was defined as the achievement of only one or none of the two thresholds, as previously reported [17].

In order to avoid any potential bias on findings due to dosing adaptation, only the TDM results of meropenem and piperacillin-tazobactam performed at the first instance, namely before applying any TDM-guided dosing adaptation, were considered. At that stage, all of the patients had received similar standard treatment. This was based on an initial loading dose (namely 2 g over 2-h infusion for meropenem or 9 g over 2-h infusion for piperacillin-tazobactam), subsequently followed by a CI maintenance dose (MD) initially selected on the basis of the patient's renal function (namely, 1 g q6h over 6 h by CI for meropenem or 18 g/day by CI for piperacillin-tazobactam in patients without renal dysfunction; 0.5 g or 0.25 g q6h over 6 h by CI for meropenem and 13.5 g or 9.0 g/day by CI for piperacillin-tazobactam in those with moderate or severe chronic renal disease, respectively). In order to ensure proper stability during CI, aqueous solutions of meropenem were reconstituted every 6–8 h and infused over 6–8 h and those of piperacillin/tazobactam every 24 h and infused over 24 h [18]. Total meropenem and piperacillin-tazobactam plasma C_{ss} were measured by means of a validated chromatography-tandem mass spectrometry method [19]. The fC_{ss} of each compound was calculated by applying the specific plasma protein binding rate reported in the literature (namely 2% for meropenem [20], 20% for piperacillin [21], and 23% for tazobactam [21]).

Characteristics and definition of outcome variables in the retrospective cohort

Demographics (age, sex, BMI, and obesity occurrence, defined as a BMI > 30 kg/m^2), clinical/laboratory data (SOFA score at starting beta-lactam treatment [22], need for vasopressors, need for mechanical ventilation, baseline creatinine clearance [CLCr], requirement for

continuous renal replacement therapy [CRRT], occurrence of ARC [23], calculation of the proposed score [9]), microbiological data (site/type of infection, microbiological isolate, and MIC value for meropenem or piperacillin-tazobactam), meropenem or piperacillin-tazobactam treatment data (starting dosing regimen, steady-state free concentrations (fC_{ss}), mono- or combination therapy), and outcome data (microbiological outcome, clinical outcome) were retrieved for each included patient.

Documented Gram-negative infections were defined as the isolation of a Gram-negative pathogen from an infection site identified clinically and/or radiologically and subsequently confirmed by means of a microbiological culture (i.e., of blood, bronchoalveolar lavage, abdominal/biliary specimens, urine, and/or skin/soft tissue biopsies) [24, 25]. Types of infection were defined according to the Centers for Disease Control and Prevention (CDC) criteria [24, 25]. Specifically, bloodstream infection (BSI) was defined as the isolation of a Gram-negative pathogen from at least one blood culture [24, 25]. Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) were defined as the isolation of a Gram-negative pathogen with a bacterial load $\geq 10^4$ CFU/mL from the bronchoalveolar lavage fluid culture or $\geq 10^6$ from the endotracheal aspirate after > 48 h from hospital admission or from endotracheal intubation and start of mechanical ventilation, respectively [24, 25]. Intra-abdominal (IAI) and/or biliary infection was defined as the isolation of a Gram-negative pathogen from the peritoneal fluid or from abdominal/biliary specimens [24, 25]. Urinary tract infection (UTI) was defined as the isolation of a Gram-negative pathogen from urine culture with a bacterial load $\geq 10^5$ CFU/mL [25]. Skin and soft tissue infection (SSTI) was defined as the isolation of one or more Gram-negative pathogens from a biopsy sample of the advancing margin skin lesion [26].

Microbiological eradication and microbiological failure were defined as the absence or the persistence, respectively, of the index Gram-negative pathogen at the follow-up microbiological cultures at the infection site performed after more than 7 days from starting beta-lactam treatment [27]. Clinical cure and clinical failure were defined as the complete or the incomplete resolution, respectively, of signs and symptoms of infection (i.e., defervescence, negativization of inflammatory biomarkers, and reduction or discontinuation of vasopressor support coupled with documented microbiological eradication at the end of treatment and the absence of recurrence or relapse) [28] and were assessed independently by two authors after checking clinical records at 30 days after starting beta-lactam treatment. Delta SOFA score at 72 h was calculated as baseline SOFA score (i.e., at starting beta-lactam treatment) — SOFA score at 72 h and considered clinically relevant whenever ≥ 2 points [29, 30].

Statistical analysis

Patient's data were summarized by means of absolute frequencies and percentages for categorical variables or median and interquartile range (IQR) for continuous variables. Univariate analysis for comparing the between-group characteristics was performed by means of the Fisher's exact test or the chi-squared test (for categorical variables) or the Mann–Whitney *U*-test (for continuous variables). Statistical significance was defined as a p-value < 0.05. Statistical analyses were performed by means of MedCalc for Windows (MedCalc statistical software, version 19.6.1, MedCalc Software Ltd., Ostend, Belgium).

Results

In the overall study period, a total of 696 and of 364 critically ill patients were treated with CI piperacillin-tazobactam (Fig. 1) or meropenem (Fig. 2), respectively. After excluding patients receiving empirical treatment (487 and 161, respectively), 209 and 203 patients receiving CI piperacillin-tazobactam or meropenem-targeted therapy, respectively, were included in each validation cohort. Among these, after excluding those not having assessable outcomes and/or receiving combination therapy, the subcohorts of patients for assessing the impact of the cut-off risk score on clinical and microbiological outcome were composed by 65 and 78 patients in the piperacillin-tazobactam group, respectively, and by 83 and 90 patients in the meropenem group, respectively.

Demographics and clinical features of patients receiving targeted therapy with CI piperacillin-tazobactam vs. meropenem are summarized in Table 2. Patients treated with piperacillin-tazobactam had higher age (median 68.0 vs. 65.0 years, $p = 0.05$) and higher prevalence of bowel perforation as underlying disease (28.2% vs. 17.3%, $p = 0.008$), of HAP/VAP occurrence (37.3% vs. 28.1%, $p = 0.05$), and of *Escherichia coli* as clinical isolate (35.7% vs. 23.6%, $p = 0.004$). Patients treated with meropenem had higher median SOFA score (9 vs. 8 points, $p < 0.001$) and higher prevalences of solid organ transplantation as underlying disease (25.1% vs. 10.1%, $p < 0.001$), of vasopressor support (43.8% vs. 34.0%, $p = 0.04$), of need for mechanical ventilation > 48 h (34.5% vs. 24.4%, $p = 0.02$), of need for CRRT (21.2% vs. 8.6%, $p < 0.001$), of BSI occurrence (40.3% vs. 27.8%, $p = 0.007$), of bacteremic HAP/VAP occurrence (7.4% vs. 2.9%, $p = 0.04$), and of both *Klebsiella pneumoniae* (33.6% vs. 16.8%, $p < 0.001$) and *Acinetobacter baumannii* (3.0% vs. 0.0%, $p = 0.007$) as clinical isolates.

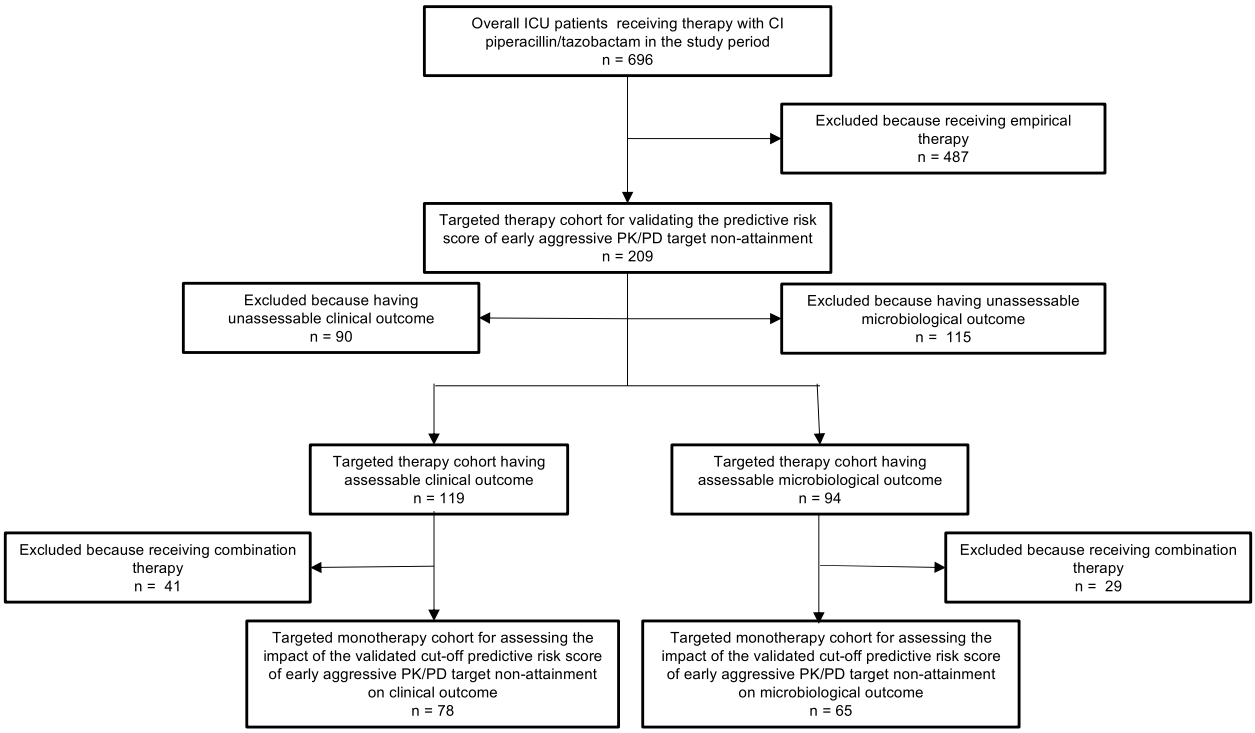

Fig. 1 Flowchart of inclusion and exclusion criteria for patients receiving CI piperacillin-tazobactam

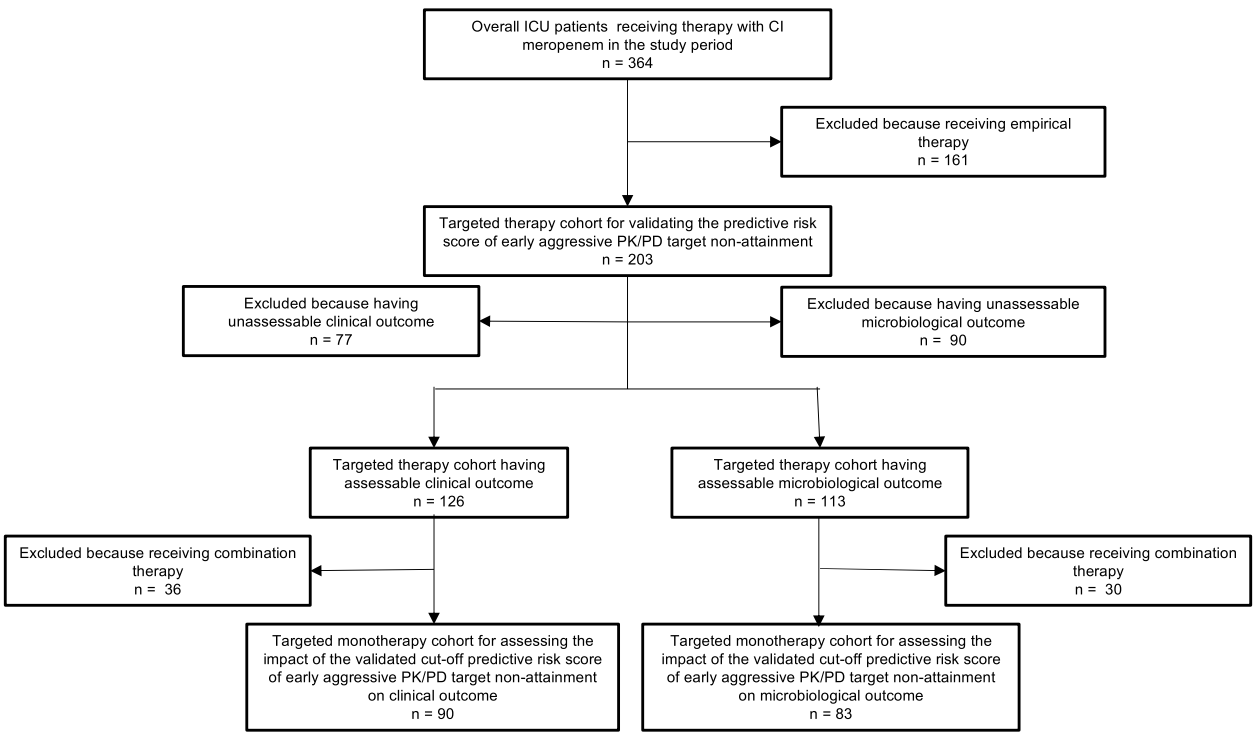

Fig. 2 Flowchart of inclusion and exclusion criteria for patients receiving CI meropenem

Table 2 Demographics and clinical features of critically ill patients

Variables	Piperacillin-tazobactam (*n* = 209)	Meropenem (*n* = 203)	*p*-value
Demographics			
Age (median, [IQR])	68.0 (59.0–75.0)	65.0 (57.5–73.0)	**0.05**
Gender (male/female, *n* [%])	136/73 (65.1/34.9)	144/59 (70.9/29.1)	0.20
Body mass index (median, [IQR])	26.0 (23.2–28.3)	25.4 (22.6–29.3)	0.59
Obesity (*n* [%])	42 (20.1)	38 (18.7)	0.72
Underlying disease			
Bowel perforation	59 (28.2)	35 (17.3)	**0.008**
Solid organ transplant recipients	21 (10.1)	51 (25.1)	**< 0.001**
Acute respiratory failure	32 (15.3)	25 (12.3)	0.38
Hepatic cirrhosis	26 (12.5)	18 (8.9)	0.24
Solid cancer	6 (2.9)	10 (4.9)	0.28
Cerebral hemorrhage	5 (2.4)	7 (3.4)	0.52
Oncohematological disease	3 (1.4)	9 (4.4)	0.08
Gastrointestinal hemorrhage	5 (2.4)	6 (3.0)	0.72
Acute pancreatitis	5 (2.4)	5 (2.5)	0.96
Cardiocirculatory arrest	3 (1.4)	2 (1.0)	0.99
Acute poisoning	3 (1.4)	0 (0.0)	0.25
Others	41 (19.6)	35 (17.2)	0.53
Pathophysiological conditions			
SOFA score at starting beta-lactam therapy (median [IQR])	8 (3–10)	9 (5–11)	**< 0.001**
Vasopressors (*n*, [%])	71 (34.0)	89 (43.8)	**0.04**
Mechanical ventilation > 48 h (*n*, [%])	51 (24.4)	70 (34.5)	**0.02**
Baseline creatinine clearance (median [IQR], mg/dL)	62.5 (30.3–92.5)	64.0 (30.5–99.0)	0.49
Continuous renal replacement therapy (*n*, [%])	18 (8.6)	43 (21.2)	**< 0.001**
Augmented renal clearance (*n*, [%])	14 (6.7)	16 (7.9)	0.64
Site of infection (*n*, [%])			
BSI	58 (27.8)	82 (40.3)	**0.007**
HAP/VAP	78 (37.3)	57 (28.1)	**0.05**
IAI	40 (19.1)	33 (16.2)	0.44
HAP/VAP + BSI	6 (2.9)	15 (7.4)	**0.04**
UTI	14 (6.7)	6 (3.0)	0.08
SSTI	5 (2.4)	3 (1.5)	0.72
IAI + BSI	3 (1.4)	3 (1.5)	0.99
UTI + BSI	4 (1.9)	1 (0.5)	0.37
IAI + HAP/VAP	1 (0.5)	3 (1.5)	0.37
Pathogens (*n*, [%])*			
Escherichia coli	83 (35.7)	54 (23.6)	**0.004**
Klebsiella pneumoniae	39 (16.8)	77 (33.6)	**< 0.001**
Pseudomonas aeruginosa	32 (13.8)	33 (14.3)	0.86
Enterobacter cloacae	15 (6.5)	19 (8.3)	0.46
Klebsiella oxytoca	13 (5.6)	6 (2.6)	0.11
Serratia marcescens	9 (3.9)	8 (3.5)	0.82
Klebsiella aerogenes	8 (3.4)	8 (3.5)	0.99
Proteus mirabilis	6 (2.6)	7 (3.0)	0.77
Citrobacter spp.	8 (3.4)	3 (1.3)	0.22
Acinetobacter baumannii	0 (0.0)	7 (3.0)	**0.007**
Hafnia alvei	2 (0.9)	4 (1.7)	0.45
Morganella morganii	3 (1.3)	1 (0.4)	0.62
Proteus vulgaris	2 (0.9)	1 (0.4)	0.99

Table 2 (continued)

Variables	Piperacillin-tazobactam (*n* = 209)	Meropenem (*n* = 203)	*p*-value
Prevotella spp.	1 (0.4)	1 (0.4)	0.99
Enterobacter kobei	2 (0.9)	0 (0.0)	0.50
Bacteroides spp.	2 (0.9)	0 (0.0)	0.50
Klebsiella ornithinolytica	1 (0.4)	1 (0.4)	0.99
Klebsiella variicola	2 (0.9)	0 (0.0)	0.50
Aeromonas spp.	2 (0.9)	0 (0.0)	0.50
Achromobacter spp.	1 (0.4)	0 (0.0)	0.99
Haemophilus influenzae	1 (0.4)	0 (0.0)	0.99
MIC above the clinical breakpoint	21 (10.0)	12 (5.9)	0.12
Beta-lactam treatment regimens and PK/PD target attainment			
Daily beta-lactam CI MD (median [IQR], g/day)	18.0 (18.0–18.0)	4.0 (2.0–4.0)	-
Beta-lactam fC_{ss} (median [IQR], mg/L)	108.0 (64.25–156.5)	23.1 (15.4–34.4)	-
Tazobactam fC_{ss} (median [IQR], mg/L)	14.1 (8.45–21.95)	-	-
Beta-lactam fC_{ss}/MIC ratio (median [IQR])	12.5 (6.4–21.8)	144.6 (74.7–244.6)	-
Tazobactam fC_{ss}/C_T ratio (median [IQR])	2.7 (1.6–4.2)	-	-
Combination therapy (*n*, [%])	65 (31.1)	57 (28.1)	0.50
Aggressive PK/PD target attainment (*n*, [%])	176 (84.2)	195 (96.1)	**< 0.001**
Aggressive PK/PD target non-attainment (*n*, [%])	33 (15.8)	8 (3.9)	
Outcome (*n*, [%])			
Microbiological failure**	23/65 (35.4)	11/83 (13.3)	**0.001**
Clinical failure***	33/78 (42.3)	22/90 (24.4)	**0.01**
Reduction ≥ 2 points in SOFA score at 48 h	45 (21.5)	47 (23.2)	0.69
30-day mortality rate	45 (21.5)	58 (28.6)	0.10

BSI bloodstream infection, *CI* continuous infusion, C_T target concentration, fC_{ss} free steady-state concentration, *HAP* hospital-acquired pneumonia, *IAI* intrabdominal infection, *IQR* interquartile range, *MD* maintenance dose, *MIC* minimum inhibitory concentration, *PK/PD* pharmacokinetic/pharmacodynamic, *SOFA* Sequential Organ Failure Assessment, *SSTI* skin and soft tissue infection, *UTI* urinary tract infection, *VAP* ventilator-associated pneumonia

*A total of 462 pathogens were isolated in 412 patients (232 and 230 in piperacillin-tazobactam and meropenem cohort, respectively)

**Microbiological failure was evaluable in 148/412 of included patients after excluding those with no assessable outcome and those receiving combination therapy

***Clinical failure was evaluable in 168/412 patients of included patients after excluding those with no assessable outcome and those receiving combination therapy

At time of first TDM assessment, median (IQR) standard CI daily doses of meropenem and piperacillin-tazobactam were 1 g q6h over 6 h (0.5–1 g q6h over 6 h) and 18 g q24h over 24 h (18–18 g q24h over 24 h), respectively. Median (IQR) fC_{ss} of meropenem, piperacillin, and tazobactam were 23.1 mg/L (15.4–34.4 mg/L), 108.0 mg/L (64.25–156.5 mg/L), and 14.1 mg/L (8.45–21.95 mg/L), respectively. Combination therapy was used in 122 cases (29.1%). Overall, the proportion of early aggressive PK/PD target non-attainment was higher in patients treated with CI piperacillin-tazobactam than in those treated with CI meropenem (15.8% vs. 3.9%, $p < 0.001$).

The findings emerging from ROC analysis are summarized in Table 3. Overall, the cut-off risk score best predicting aggressive PK/PD target non-attainment was of ≥ 2 points among patients receiving targeted CI

Table 3 ROC curve analysis identifying specific cut-off risk value of aggressive PK/PD target non-attainment

Beta-lactam by continuous infusion	No. of patients	Aggressive PK/PD target non-attainment	Cut-off risk value	Sensitivity (95% *CI*)	Specificity (95% *CI*)	AUC (95% *CI*)	*p*-value
Piperacillin-tazobactam	209	33 (15.8%)	≥ 2 points	69.7 (51.3–84.4)	85.2 (79.1–90.1)	0.81 (0.75–0.86)	< 0.0001
Meropenem	203	8 (3.9%)	≥ 3 points	100.0 (63.1–100.0)	92.8 (88.2–96.0)	0.96 (0.93–0.99)	< 0.0001

AUC area under curve, *CI* confidence interval, *ROC* receiver operating characteristic

piperacillin-tazobactam therapy (sensitivity of 69.7% and specificity of 85.2%) and of ≥ 3 points among those receiving targeted therapy with CI meropenem (sensitivity of 100.0% and specificity of 92.8%) The corresponding AUCs were of 0.81 (95% *CI* 0.75–0.86, $p < 0.0001$, Fig. 3A) and of 0.96 (95% *CI* 0.93–0.99, $p < 0.0001$, Fig. 3B), respectively.

Univariate analysis comparing clinical/microbiological outcomes between patients reaching or not the corresponding cut-off risk score during targeted monotherapy with CI piperacillin/tazobactam and meropenem was reported in Tables 4 and in Table 5, respectively. In the piperacillin/tazobactam group, patients reaching the cut-off score had higher microbiological failure rate (9/16 [56.3%] vs. 14/49 [28.6%], $p = 0.044$) and a trend toward higher clinical failure rate (12/20 [60.0%] vs. 21/58 [36.2%], $p = 0.06$) compared to those not reaching it. Likewise, in the meropenem group, patients reaching the cut-off score showed higher microbiological failure rate (3/6 [50.0%] vs. 8/77 [10.4%], $p = 0.028$) compared to those not reaching it, whereas no difference emerged in terms of clinical failure rate (3/7 [33.3%] vs. 19/83 [22.9%], $p = 0.36$).

Discussion

To the best of our knowledge, this study first validated a predictive risk score [9] of early aggressive PK/PD target non-attainment in a large cohort of ICU patients receiving treatment with CI piperacillin-tazobactam or meropenem for documented Gram-negative infections.

Overall, the findings suggested that among critically ill patients receiving standard beta-lactam dosing regimens delivered by CI, a cut-off risk score of ≥ 2 and ≥ 3 points during treatment with piperacillin-tazobactam and meropenem, respectively, may significantly increase the likelihood of early aggressive beta-lactam PK/PD target

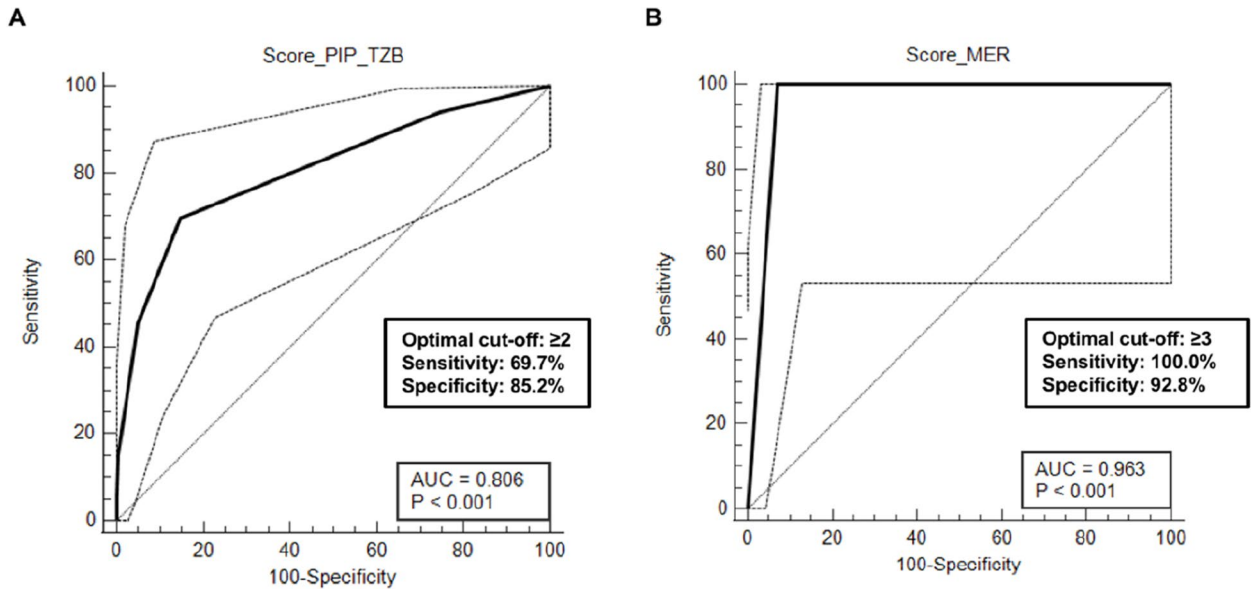

Fig. 3 ROC curve analysis for failure in attaining aggressive PK/PD target with piperacillin-tazobactam (**A**) and meropenem (**B**). The 100-specificity (false-positive rate) and sensitivity (true-positive rate) are plotted on the *X*- and *Y*-axes, respectively. Optimal thresholds of the proposed score ≥ 2 and ≥ 3 for piperacillin-tazobactam and meropenem were found, respectively. Continuous and dotted lines represent the ROC curve and 95% confidence intervals, respectively

Table 4 Univariate analysis comparing outcomes between patients reaching or not the cut-off predictive risk score of ≥ 2 points during targeted CI piperacillin/tazobactam monotherapy

Variables	Patients reaching a cut-off risk score ≥ 2 points ($n = 49$)	Patients reaching a cut-off risk score < 2 points ($n = 160$)	Univariate *p*-value
Clinical failure*	12/20 (60.0)	21/58 (36.2)	0.06
Microbiological failure**	9/16 (56.3)	14/49 (28.6)	**0.044**

*As specified in Fig. 1, the targeted monotherapy cohort for assessing the impact of the validated cut-off predictive risk score of early aggressive PK/PD target non-attainment on clinical outcome was composed overall by 78 patients receiving monotherapy, namely in 20/49 and in 58/160, respectively

**As specified in Fig. 1, the targeted monotherapy cohort for assessing the impact of the validated cut-off predictive risk score of early aggressive PK/PD target non-attainment on microbiological outcome was composed overall by 65 patients receiving monotherapy, namely in 16/49 and in 49/160, respectively

Table 5 Univariate analysis comparing outcomes between patients reaching or not the cut-off risk score of ≥ 3 points during targeted CI meropenem monotherapy

Variables	Patients reaching a cut-off risk score ≥ 3 points ($n = 22$)	Patients not reaching a cut-off risk score < 3 points ($n = 181$)	Univariate *p*-value
Clinical failure*	3/7 (33.3)	19/83 (22.9)	0.36
Microbiological failure**	3/6 (50.0)	8/77 (10.4)	**0.028**

*As specified in Fig. 2, the targeted monotherapy cohort for assessing the impact of the validated cut-off predictive risk score of early aggressive PK/PD target non-attainment on clinical outcome was composed overall by 90 patients receiving monotherapy, namely in 7/22 and in 83/181, respectively

**As specified in Fig. 2, the targeted monotherapy cohort for assessing the impact of the validated cut-off predictive risk score of early aggressive PK/PD target non-attainment on microbiological outcome was composed overall by 83 patients receiving monotherapy, namely in 6/22 and in 77/181 patients, respectively

non-attainment. In turn, this may lead to an increased probability of microbiological failure.

The corresponding cut-off risk score was lower for piperacillin-tazobactam than for meropenem. This may suggest that dealing with the aggressive joint PK/PD target of a beta-lactam/beta-lactamase inhibitor combination may be more challenging than dealing with that of a sole beta-lactam. This may be the case especially whenever the pharmacokinetics of two combined drugs differs each other in relation to kidney function strata. Specifically, a population pharmacokinetic study conducted among 257 critically ill patients treated with CI piperacillin-tazobactam showed that the clearance of tazobactam may be much faster than that of piperacillin as renal function increases. Consequently, the piperacillin-to-tazobactam ratio of plasma C_{ss} was shown to increase from 6:1 to 10:1 between an eGFR of < 20 mL/min and > 120 mL/min. This means that attaining an aggressive joint PK/PD target of piperacillin-tazobactam with standard dosages in patients without renal dysfunction may become hard [31]. In this regard, the model predicted that the CI MD needed for attaining optimal probability (namely > 90%) of aggressive joint PK/PD target against Enterobacterales having an MIC value up to the EUCAST clinical breakpoint (namely 8 mg/L) in patients having an eGFR of 100 mL/min may be as high as 22.5 g/day. Importantly, neither this dosage may suffice in patients having ARC [31]. Conversely, in regard to meropenem, this aspect should not represent an issue. A population pharmacokinetic study carried out among 114 critically ill patients showed that the dosage of 1 g q6h over 6 h by CI, namely that initially adopted by ours, may grant an optimal aggressive PK/PD target against Gram-negative pathogens having an MIC value up to the EUCAST clinical breakpoint (namely 2 mg/L) even in patients with ARC [32]. If dealing with pathogens having borderline susceptibility (i.e., 4–8 mg/L), increasing dosages up to 1.5–2 g q6h over 6 h may be needed for granting the same goal in patients without renal dysfunction [32]. It is worth noting that these considerations may explain why the rate of early aggressive PK/PD target non-attainment was approximately fourfold higher in patients treated with CI piperacillin-tazobactam compared to those treated with CI meropenem.

The prevalence of the different risk factors may vary across critically ill patients based on types of ICU admission and may be very high among some settings. Just to mention, obesity is increasingly present in ICU patients, with rates reported between 28.2% and 36% [33]. Likewise, the prevalence of ARC may be always > 30% among critically ill patients according to a recent meta-analysis, ranging from 33% in the sepsis ICU up to 74% in the neuro ICU [34]. Overall, this suggest that a relevant proportion of critically ill patients could reach or even exceed the corresponding cut-off risk value, having therefore an increased risk of aggressive PK/PD target non-attainment under standard dosing regimens. Consequently, there is the need of purposing a predefined decision-making algorithm of more intensified CI dosing regimens to be promptly applied bedside in these cases. A preliminary proposal based on currently available evidence is depicted in Fig. 4.

In each of the two groups, the corresponding cut-off risk score was associated with an increased probability of microbiological failure regardless that real-time TDM-guided dosing adjustments were provided in our scenario within 72 h maximum. This highlights the time-dependent impact that aggressive beta-lactam PK/PD target attainment may have on microbiological outcome. In this regard, a retrospective monocentric study including 204 critically ill patients receiving treatment with different beta-lactams for Gram-negative BSIs showed that attaining an aggressive PK/PD target within the first 24 h independently predicted microbiological eradication at day 7 follow-up blood cultures [35]. This may suggest that aggressive PK/PD target attainment may be fundamental in abating the bacterial burden at the infection site during the first 24 h, especially whenever high inocula are present [36, 37]. This should minimize the risk of bacterial regrowth leading to microbiological failure, as previously shown in preclinical models [38, 39]. Accordingly, in agreement with recent recommendations [40], a call for action should be urgently made in scenarios having TDM-guided dosing adjustments of beta-lactams, like

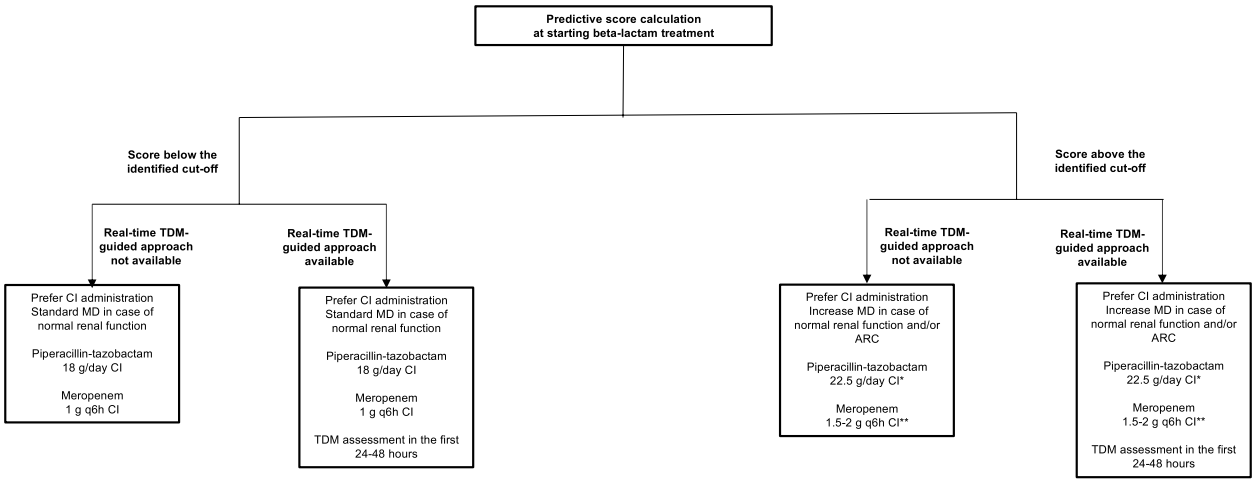

Fig. 4 Proposal of a predefined decision-making algorithm of more intensified CI dosing regimens of piperacillin-tazobactam or meropenem to be applied bedside in patients reaching the corresponding cut-off risk score. ARC, augmented renal clearance; CI, continuous infusion; MD, maintenance dosing; TDM, therapeutic drug monitoring. *According to reference [31]. **According to reference [32]

ours, for moving from a timeframe of first assessment within 72 h to a more restrictive one, ideally of 24 h, for maximizing the likelihood of microbiological eradication in critically ill patients.

Limitations of our study should be recognized. First, the retrospective monocentric study design could limit the generalizability of our findings to other settings. Second, not having a control group of patients treated with beta-lactams by intermittent infusion precluded us from assessing the protective impact of prolonged/CI on the predictive score. Third, microbiological and clinical outcomes were assessable only in approximately 50% of cases receiving monotherapy, this potentially introducing a selection bias. Fourth, only total meropenem and piperacillin-tazobactam concentrations were measured, whereas the free fractions were calculated based on the corresponding plasma protein binding retrieved from the literature. Fifth, toxicity risk was not assessed. Sixth, we performed qualitative grading of the identified risk factors. We are aware that quantitative grading would have increased score accuracy, but unfortunately this was unfeasible because actual data of each single patient included in the meta-analyzed studies were unavailable. Finally, we recognize that a sensitivity cut-off risk score at ROC analysis of < 70% could have affected the accuracy in predicting the risk of aggressive joint PK/PD target non-attainment with CI piperacillin-tazobactam, causing a potential risk of overestimating the number of cases with a true need of increasing dosing regimens, especially among male obese patients having renal dysfunction. Conversely, validating the predictive score in a homogeneous and large sample size, as well as assessing microbiological/clinical outcome only in patients receiving monotherapy, may represent points of strength of our study.

In conclusion, our findings suggest that the proposed predictive cut-off risk score may represent a valuable tool for identifying promptly critically ill patients at high risk of early aggressive PK/PD target non-attainment with CI piperacillin-tazobactam or meropenem for whom a more intensified CI dosing regimens should be promptly applied bedside. Prospective confirmatory studies are warranted.

Abbreviations

ARC	Augmented renal clearance
AUC	Area under curve
BMI	Body mass index
BSI	Bloodstream infection
CI	Continuous infusion
CLCr	Creatinine clearance
CRRT	Continuous renal replacement therapy
ECPA	Expert clinical pharmacological advice
fC_{min}	Free trough concentration
fC_{ss}	Free steady-state concentration
fC_T	Free target concentration
HAP	Hospital-acquired pneumonia
IAI	Intra-abdominal infection
ICU	Intensive care unit
LD	Loading dose
MD	Maintenance dose
MIC	Minimum inhibitory concentration
OR	Odds ratio
PK/PD	Pharmacokinetic/pharmacodynamic
SOFA	Sequential Organ Failure Assessment
SSTI	Skin and soft tissue infection
TDM	Therapeutic drug monitoring
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia

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None.

Authors' contributions
Conceptualization, M.G., P.G., and F.P.; methodology, M.G. and F.P.; formal analysis, M.G., P.G. and M.R.; data curation, M.G., P.G. and M.R.; writing—original draft preparation, M.G. and P.G.; writing—review and editing, A.S., T.T., P.V. and F.P. All authors have read and agreed to the published version of the manuscript.

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None to declare.

Data availability
All data and materials generated during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local ethical committee (No. 308/2021/Oss/AOUBo on 17 May 2021, No. EM232–2022_308/2021/Oss/AOUBo on 16 March 2022, EM449-2023_308/2021/Oss/AOUBo on 17 April 2024). Informed written consent was waived due to the retrospective and observational nature of the study.

Consent for publication
All authors approved the final version submitted for publication.

Competing interests
M.G. received personal fees from Angelini, AdvanzPharma, and Viatris; P.V. has served as a consultant for Biomerieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher and Venatorx, and received payment for serving on the speaker's bureau for Correvio, Gilead, MerckSharp & Dohme, Nordic Pharma, and Pfizer; F.P. participated in speaker bureau for Angelini, BeiGene, Gilead, InfectoPharm, Menarini, Merck Sharp & Dohme, Pfizer, and Shionogi, and in advisory boards for BeiGene, Merck Sharp & Dohme, Pfizer, and Viatris. The authors report no other conflicts of interest in this work.

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