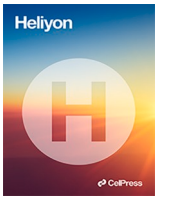
Heliyon 9 (2023) e16542

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

The effect of meropenem versus piperacillin-tazobactam in critically ill patients with sepsis and septic shock☆

Yang Sun, Yu Liu, Jixia Wang, Can Cui *

EICU, Xinyang Central Hospital, 464000, China

ARTICLE INFO

Keywords:
Meropenem
Piperacillin-tazobactam
Sepsis
Septic shock

ABSTRACT

Background: Antibiotics are a popular and efficient treatment for sepsis and septic shock. However, there is presently little proof of Meropenem with piperacillin-therapeutic tazobactam's benefits.

Methods: From January 1, 2010 to January 1, 2021, we treated a total of 1244 patients with sepsis and septic shock using either Meropenem (n = 622, 1 g every 8 h) or piperacillin-tazobactam (n = 622, 3.375 g or 4.5 g every 8 h). The intervention was administered for 7 days following randomization and continued for up to 14 days thereafter, or until the patient was discharged from the critical care unit or passed away, whichever occurred first.

Results: First, we discovered that there were no significant changes in the duration of stay in ICU, Cardiovascular in SOFA, Coagulation in SOFA, Hepatic in SOFA, or Central Nervous System in SOFA between the meropenem alone group and the piperacillin-tazobactam group. In addition, WBC beyond the standard limit was 68.00% in the meropenem alone group against 61.89% in the piperacillin-tazobactam group (P = 0.03). However, Meropenem had a lower mortality rate on ventilator-free days, vasopressor-free days, and hospital-free days.

Conclusion: This procedure may offer clinical evidence for the safety and efficacy of meropenem with piperacillin-tazobactam in critically sick patients with sepsis and septic shock.

1. Introduction

Sepsis and septic shock are significant factors leading to mortality among patients receiving hospital care. These conditions disrupt the body's response to infection, causing inflammation and damage to multiple organ systems [1]. Globally, the incidence of sepsis in adults requiring hospitalization is estimated at 270 per 100,000, with an overall fatality rate of 26%. This translates to approximately 19.4 million cases and 5.3 million deaths annually worldwide, without taking into account cases of sepsis in children or those occurring outside of hospital settings [2]. Despite significant progress in critical care medicine, following evidence-based standards is still linked with high mortality: sepsis remains the primary cause of death in one in every five to one in every two patients. Multiple organ failure was the cause of death [3]. Recent sepsis treatment recommendations advocate for prompt and sufficient antibiotic therapy, fluid ventilation, and vasopressin as needed, followed by supportive care for organ failure [4,5]. Furthermore, the first 6 h of hemodynamic stabilization treatment and goal-directed therapy may reduce mortality in sepsis patients since a delay in initiating suitable antimicrobial medication has been linked to increased mortality [6]. As a result, the first selection of suitable antimicrobials for suspected

☆ This work was undertaken in Xinyang Central Hospital.

* Corresponding author.
E-mail address: cuican20220311@163.com (C. Cui).

https://doi.org/10.1016/j.heliyon.2023.e16542
Received 6 February 2023; Received in revised form 11 May 2023; Accepted 19 May 2023
Available online 20 May 2023

infections is characterized in terms of broad-spectrum and sufficient chosen antimicrobials.

Meropenem, a carbapenem, is commonly used as an initial treatment for sepsis and septic shock due to its broad-spectrum action and low toxicity [7]. Its comprehensive range efficacy and low toxicity make it a viable therapy option for severe infections in critically ill patients [8]. Piperacillin-tazobactam is a combination of a β-lactam and a β-lactamase inhibitor with broad antibacterial activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria [9]. Clinical studies have shown that piperacillin-tazobactam is effective in treating various infections, including intra-abdominal infections, skin and soft tissue infections, lower respiratory tract infections, complex urinary tract infections, gynecological infections, and febrile neutropenia [10]. Our sepsis guidelines recommend selecting antimicrobial drugs based on the predicted source of infection, local susceptibility, and the environment of suspected infection, as extensive antibiotic and household usage can affect the choice of therapy [11]. While the empirical combination of meropenem and piperacillin-tazobactam has become the standard of therapy in our institution, it may not be suitable for all clinical situations, as determining the causative organisms of sepsis in patients with sepsis and septic shock is often impossible.

The therapeutic benefits of meropenem and piperacillin-tazobactam for critically ill patients with sepsis remain uncertain. This study aimed to test the hypothesis that meropenem has a greater impact than piperacillin-tazobactam in treating sepsis and septic shock in critically ill patients, while also comparing the safety of the two treatment regimens. Additionally, we examined the potential complications associated with both therapy strategies.

2. Materials and methods

2.1. Patients

All patients with sepsis and septic shock (1244 instances) were included in our research. Sepsis and sepsis shock were admitted using ICD-10 diagnosis and adhere to the majority of recommendations for sepsis definition [12]. The patients are separated into two groups: Meropenem and piperacillin-tazobactam, blinding of patients and/or medical staff, with 622 patients in each group, and the allocation results are concealed. During the time period when a database was maintained, the senior attending physician in critical care examined all critically ill patients suspected of having severe sepsis or septic shock and added them to a registry that was being prospectively enrolled. Patients were classified as having severe sepsis if they exhibited two or more criteria of systemic inflammatory response syndrome (SIRS), such as a heart rate of over 90 beats per minute, a respiratory rate of over 20 breaths per minute, a temperature above 38.3 °C or below 36 °C, a white blood cell count of over 12,000 cells/mm^3, 4000 cells/mm^3, or more than 10% immature bands.

2.2. Inclusion and exclusion criteria

To be included in the study, patients had to meet the following criteria: (1) have been diagnosed with sepsis upon arrival at the emergency department, (2) have started or continued antibiotics upon admission, and (3) have received either VPT or VC within the first 12 h after presentation. Patients who were under 18 years old, pregnant, in end-stage renal disease and receiving RRT before admission, transferred from another institution, moved to another facility within 72 h of presentation, or presented after cardiac arrest were excluded from the study. Additionally, patients who received both regimens during the first 24 h after presentation were also excluded.

2.3. Intervention

Patients who met the criteria for severe sepsis or septic shock in critically ill patients and were 18 years old or older were eligible for inclusion in the study. Intravenous Meropenem and piperacillin-tazobactam were administered as early antimicrobial treatment to severely ill patients. At least one dose of intravenous meropenem or piperacillin-tazobactam was required as the first two antimicrobial drugs, and patients who had taken these drugs orally were excluded. Patients who received additional antimicrobial drugs 2 h after receiving meropenem or piperacillin-tazobactam were still eligible for inclusion. The cut-off time for initiating meropenem or piperacillin-tazobactam treatment was set at 2 h to allow clinicians enough time to study the medical record and make necessary adjustments to the first antibiotic regimen. Patients who had been transferred from another hospital, transferred to another acute care facility, or were on hospice care at the time of admission were excluded. Patients whose culture results were negative for bacterial growth were also excluded [13,14].

Once the diagnosis of scurvy was met and treatment was initiated, enrolled patients were included in the study and treatment was ended when their blood culture results were negative.

2.4. Clinical outcomes

The intervention was recommended for a period of seven days after randomization and up to 14 days thereafter, or until the patient was discharged from the intensive care unit (ICU) or died, whichever occurred first. Prior to treatment, as well as at the test-of-cure visit and on day 21 or upon discharge from the ICU, whichever occurred first, clinical, microbiological, and laboratory tests were conducted. According to the guidelines of the German Sepsis Society, all patients were treated for sepsis-related cardiovascular, pulmonary, renal, and metabolic failure [15].

The primary outcome was sepsis-related organ failure, as measured by the mean of daily total Sequential Organ Failure Assessment

(SOFA) 18 scores during 14 days or release from the ICU, whichever came first. The SOFA score ranges from 0 to 24, with higher scores indicating more severe organ failure. SOFA subscores range from 0 to 4 for each of the six organ systems, resulting in a total score of 0–24. The mean SOFA score was calculated as the average daily SOFA score for each patient throughout their ICU stay [16].

Secondary endpoints included 28-day and 90-day all-cause mortality, mean SOFA subscores, duration of ICU and hospital stay, clinical and microbiological treatment response, intervention-free days with a ventilator, vasopressor, dialysis, or antibiotic, secondary infections, emergence of antibiotic-resistant bacteria, and adverse events. Adverse events were reported in accordance with ICH guidelines and classified using the Medical Dictionary for Regulatory Activities version 13.1.

2.5. Sample size

The trial was designed to detect a difference of 1.1 points in the mean SOFA score between the two therapies, with a significance level of 0.05 and a power level of 90%. This difference was projected to reduce the 28-day mortality rate from 40% to 30%. To achieve this, 600 patients were to be enrolled, assuming a standard deviation of 3.8 points and a dropout rate of approximately 15%. An interim analysis was planned and conducted after half of the expected sample size was recruited. The expenditure method was used to adjust the significance threshold to 0.00288, based on the O'Brien and Fleming multiple testing techniques. Consequently, the significance threshold for the final confirmatory analysis was set at 0.047.

2.6. Statistical analysis

In order to investigate the primary endpoint, which was the mean SOFA score, an independent *t*-test was employed. For the secondary efficacy and safety endpoints, if applicable, the $X2$ test, Fisher exact test, and Mann-Whitney test were utilized. Overall survival was calculated using the Kaplan-Meier technique. Proportional hazard models and generalized linear models were used to identify variables that impacted overall mortality and mean SOFA score. All presented P values are two-sided. The statistical analysis was conducted using SAS version 9.1.3, provided by SAS Institute Inc.

Table 1
Demographics and baseline Characteristics.

	All patient (n = 1244)	Meropenem alone (N = 622)	piperacillin-tazobactam (N = 622)	P
Age, mean (SD),y	65.3 ± 21.3	64.2 ± 23.4	66.32 ± 17.34	0.67
Male sex,	632 (50.8)	301 (48.4)	331 (53.2)	0.32
Body mass index, mean (SD)	24.2 (4.2)	25.3 (7.3)	24.1 (3.4)	0.23
APACHE II score, mean (SD)	21.3 (2.3)	21,1 (3.1)	21.8 (2.3)	0.34
SOFA score, mean (SD)	9.23 (3.02)	9.32 (3.22)	9.34 (4.23)	0.76
Laboratory value, mean(SD)				
White blood cell count, cells/ul	14.89 (1.23)	14.23 (0.78)	15.02 (1.34)	0.23
Plasma *C*-reactive protein, mg/L	242.98 (23.21)	221,43 (31.76)	254.12 (24.52)	0.42
Plasma lactate, mg/dL	24,88 (4.21)	23.44 (2.93)	25,23 (1.87)	0.12
Plasma creatinine, mg/dL	1.62 (0.23)	1.56 (0.21)	1.61 (0.22)	0.67
Creatinine clearance, mL/min	49.12 (4.23)	52.19 (4.99)	48.23 (3.52)	0.43
Plasma albumin, g/dL	2.93 (0.52)	2.82 (0.73)	2.97 (0.52)	0.87
History of diabetes,No. (%)	323 (25.96)	158 (25.40)	165 (26.53)	0.88
Recent trauma,No. (%)	381 (30.61)	200 (32.15)	181 (29.09)	0.67
Corticosteroid use,No. (%)	271 (21.78)	130 (20.90)	141 (22.67)	0.83
Heart failure,No. (%)	186 (14.95)	88 (14.14)	98 (15.75)	0.88
Cerebrovascular disease,No. (%)	97 (7.79)	45 (7.23)	52 (8.36)	0.32
Renal dysfunction,No. (%)	248 (19.93)	118 (18.9)	130 (20.9)	0.83
Chronic obstructive pulmonary disease,No. (%)	62 (4.98)	32 (5.14)	30 (4.82)	0.12
Liver cirrhosis,No. (%)	18 (1.44)	8 (1.2)	10 (1.6)	0.23
History of cancer,No. (%)	311 (25.0)	148 (23.79)	163 (26.20)	0.43
Immunosuppression,No. (%)	63 (5.06)	31 (4.98)	32 (5.14)	0.42
Required mechanical ventilation, No. (%)	995 (77.16)	479 (77.02)	516 (82.13)	0.78
Septic shock, No. (%)	486 (39.06)	236 (37.23)	250 (40.19)	0.42
suspected source of infection, No. (%)				
Urinary tract or genitourinary, No. (%)	398 (31.99)	205 (32.95)	193 (31.03)	0.87
Respiratory, No. (%)	223 (17.92)	105 (16.88)	118 (18.97)	0.67
Gastrointestinal or intra-abdominal. NO(%)	211 (16.96)	111 (17.84)	100 (16.07)	0.32
Soft tissue or skin	100 (8.04)	48 (7.71)	52 (8.36)	0.12
Cardiac	24 (1.92)	13 (2.09)	11 (1.77)	0.09
Central nervous system	12 (0.96)	7 (1.13)	5 (0.80)	0.78
Multiple	121 (9.72)	57 (9.16)	64 (10.29)	0.32
Other	87 (6.99)	46 (7.39)	41 (6.59)	0.78
Unknown	68 (5.46)	30 (4.82)	38 (6.11)	0.32

3. Results

One thousand three hundred sixty-nine people were eligible between January 1, 2010, and January 1, 2021. Among the remaining 1244 evaluable patients, demographic and baseline features, infection location and source (Table 1), and pathogens present at enrolment were examined (Table 2). The median time from enrollment to the start of the study antibiotics in the meropenem alone treatment group was 103 min, compared to 123 min in the piperacillin-tazobactam group (P = 0.08). Table 3 shows the most prevalent pathogens cultivated from the enrollment sample.

Blood cultures were positive in 646 patients (51.93%), with Gram-positive bacteria being the most prevalent. Gram-negative blood cultures were positive in 559 individuals (44.93%). Fungi blood cultures were positive in 385 individuals (30.9%).

3.1. Clinical outcome

The mean SOFA score in the meropenem alone group was 7.22 points (95% CI, 7.10–8.92 points) compared to 8.62 points (95% CI, 7.15–9.25 points) in the piperacillin-tazobactam group (P = 0.25). The ICU mortality in the meropenem alone group was 17.84% compared to 16.39% in the piperacillin-tazobactam group (P = 0.22).

In Respiratory of SOFA, the meropenem alone group scored 2.15 points (95% CI, 0.95–3.48 points), whereas the piperacillin-tazobactam group scored 2.66 points (95% CI, 1.11–3.22 points) (P = 0.01). Renal in SOFA was 0.33 (95% CI, 0.21–0.65) in the meropenem alone group vs. 0.46 (95% CI, 0.36–0.69) in the piperacillin-tazobactam group (P = 0.04). The length of hospital stay in the meropenem alone group was 33 days (median (IQR), 18–37 days) compared to 31 days (median (IQR), 21–42 days) in the piperacillin-tazobactam group (P = 0.02). There were no significant changes in the duration of stay in ICU, Cardiovascular in SOFA, Coagulation in SOFA, Hepatic in SOFA, or Central Nervous System in SOFA between the meropenem alone group and the piperacillin-tazobactam group (Table 4).

The rates of death at 28 and 90 days were not statistically different between the two therapy groups. By day 28, the meropenem alone therapy group had 155 deaths (24.929%; 95% CI, 11.58% −28.62%) compared to 159 deaths (25.56%; 95% CI, 13.95% −22.56%) in the piperacillin-tazobactam group (P = 0.36). By day 90, the meropenem alone therapy group had 205 deaths (32.95%; 95% CI, 22.69% −35.92%) compared to 223 deaths (37.45%; 95% CI, 23.95% −39.52%) in the piperacillin-tazobactam group (P = 0.15). Clinical response at EOT was 87.94% in the meropenem alone group vs. 81.99% in the piperacillin-tazobactam group (P = 0.03). WBC beyond the standard limit was 68.00% in the meropenem alone group against 61.89% in the piperacillin-tazobactam group (P = 0.03). However, there were no significant differences in microbiological response, WBC normalization, Time to WBC normalization, or secondary infection between the meropenem alone group and the piperacillin-tazobactam group. However, with WBC levels over the usual range, we discovered that meropenem alone was more effective than piperacillin-tazobactam alone (Table 5). The findings of the per-protocol analysis of the 28-day and 90-day death rates did not vary substantially between the two research groups, either (Fig. 1). By 28 days, 115 people had died (24.92%, [95% CI, 11.58% −28.62%]) from meropenem alone, compared to 159 people who died from piperacillin-tazobactam alone (25.56%, [95% CI, 13.95% −22.56%]). By 908 days, 205 people had died (32.95%, [95% CI, 22.69% −35.92%]) from meropenem alone, compared to 223 people who died from piperacillin-tazobactam alone (37.45%, [95% CI, 23.95% −39.52%]) (see Fig. 2).

3.2. Multivariable analyses

The general linear model risk factors identified three risk factors for higher mean SOFA score at 14 days: SOFA score at enrollment (regression coefficient per point, 0.66 [95% CI, 0.45–0.73]; P0.001), renal failure at registration (regression coefficient, 4.23 [95% CI, 2.73–4.87]; P.001), and age (regression coefficient per year, 0.42 [95% CI, 0.13–0.32]; P = 0.04). Meanwhile, study medication, previous antibiotic treatment, bacterial resistance, and gram-negative enrollment pathogens were found to have no relation to the mean SOFA score or time to death. In Cox regression analysis, the independent risk factors for time to death were SOFA score at baseline (hazard ratio [HR] per point, 2.11 [95% CI, 2.31–3.24]; P = 0.02), renal failure at enrollment (HR, 4.23 [95% CI, 2.92–5.98];

Table 2
Clinical characteristic of patients with septic shock.

characteristic	All patient (n = 1244)	Meropenem alone (N = 622)	piperacillin-tazobactam (N = 622)	P
Mean time to first antimicrobial ± SD – min	112.36 ± 21.62	103 ± 42	123 ± 32.12	0.78
Antibiotics given before cultures drawn – no. (%)	14 (1.25)	9 (1.44)	5 (0.088)	0.33
Mean lactate level ± SD – mmol/L		1.76 ± 1.08	1.83 ± 0.78	0.63
Fluid administration in first 6 h ± SD – mL/kg	38.56 ± 6.32	38.23 ± 12.12	39.23 ± 11.23	0.78
Vasopressor within first 6 h	2062 ± 452	2092 ± 303	2032 ± 783	0.82
Estimated GFR‡ prior to admissione—mL/min/1.73 m^2	84.52 ± 29.62	83 ± 43.23	89.21 ± 23.42	0.69
Initial estimated GFR‡—mL/min/1.73 m^2	56.62 ± 22.62	58.32 ± 23.12	55.11 ± 21.21	0.82
Acute kidney injury at presentation	704 (56.59)	322 (51.77)	382 (61.41)	0.79
Acute kidney injury stage at presentation				0.11
No acute kidney injury	590 (47.43)	304 (48.87)	286 (45.98)	0.82
Stage 1	273 (21.94)	130 (21.23)	143 (22.99)	0.83
Stage 2	235 (18.89)	111 (17.83)	124 (19.93)	0.32
Stage 3	82 (6.59)	63 (10.12)	19 (3.05)	0.37

Table 3
Gram-positive,Gram-negative and fungi pathogens at enrollment.

	All patient (n = 1244)		Meropenem alone (N = 622)		piperacillin-tazobactam (N = 622)	
	Proven by any material	Proven by any blood culture	Proven by any material	Proven by any blood culture	Proven by any material	Proven by any blood culture
Gram-positive pathogen	646 (51.93)	223 (17.92)	323 (51.92)	99 (15.91)	360 (57.87)	124 (19.93)
Staphylococcus aureus	224 (18.00)	49 (3.94)	87 (13.98)	32 (5.14)	111 (17.82)	38 (6.10)
Methicillin-resistant S aureus	38 (3.05)	14 (1.13)	19 (3.06)	6 (0.93)	30 (4.82)	8 (1.28)
Coagulase-negative staphylococci	311 (25.00)	111 (8.92)	220 (35.36)	52 (8.36)	155 (24.91)	9 (1.44)
Methicillin-resistant coagulase-negative staphylococci	37 (2.97)	43 (3.45)	47 (7.56)	9 (1.44)	44 (7.07)	15 (2.41)
Streptococcus pneumoniae	31 (2.49)	34 (2.73)	9 (1.44)	8 (1.28)	36 (5.78)	8 (1.28)
Enterococcus species	124 (9.96)	41 (3.29)	110 (17.68)	15 (2.41)	39 (6.27)	17 (2.73)
Vancomycin-resistant Enterococcus species	87 (6.99)	14 (1.13)	62 (9.96)	9 (1.44)	49 (7.87)	8 (1.22)
Other Streptococcus species	233 (17.92)	35 (2.81)	89 (14.30)	8 (1.22)	89 (14.31)	9 (1.45)
other	93 (7.47)	18 (1.45)	38 (6.25)	7 (1.12)	39 (6.27)	8 (1.22)
Gram-negative pathogen	559 (44.93)	136 (10.93)	386 (62.05)	111 (17.84)	344 (55.31)	58 (9.23)
Escherichia coli	348 (27.97)	104 (8.36)	192 (30.86)	68 (10.93)	174 (28.61)	45 (7.23)
Klebsiella species	126 (10.13)	16 (1.24)	84 (13.56)	4 (0.625)	52 (8.36)	8 (1.28)
Proteus species	83 (6.71)	11 (0.84)	52 (8.36)	4 (0.625)	47 (7.55)	9 (1.44)
Enterobacter	92 (7.39)	19 (1.53)	47 (7.55)	7 (1.12)	47 (7.55)	15 (2.41)
Pseudomonas aeruginosa	76 (6.10)	15 (1.21)	50 (8.03)	7 (1.12)	38 (6.25)	4 (0.625)
Other Pseudomonas species	14 (1.13)	2 (0.24)	8 (1.22)	4 (0.625)	7 (1.12)	7 (1.12)
Serratia	41 (3.29)	3 (0.21)	16 (2.57)	4 (0.625)	15 (2.41)	4 (0.625)
Citrobacter	44 (3.54)	5 (0.40)	26 (4.18)	7 (1.12)	15 (2.41)	4 (0.625)
Acinetobacter	18 (1.44)	2 (0.24)	7 (1.12)	4 (0.625)	15 (2.41)	5 (0.852)
Haemophilus	46 (3.69)	4 (0.32)	7 (1.12)	4 (0.625)	7 (1.12)	7 (1.12)
Bacteroides species	51 (4.10)	3 (0.21)	7 (1.12)	4 (0.625)	20 (3.20)	7 (1.12)
Other	77 (6.18)	2 (0.24)	8 (1.28)	4 (0.625)	15 (2.41)	4 (0.625)
Fungi	385 (30.9)	39 (3.15)	222 (35.69)	20 (3.20)	177 (28.45)	12 (1.92)
Candida albicans	235 (18.9)	2 (0.24)	149 (24.00)	7 (1.12)	145 (12.23)	3 (0.425)
Other Candida species	176 (14.1)	2 (0.24)	4 (0.625)	7 (1.12)	8 (1.28)	4 (0.625)
Aspergillus species	5 (0.40)	0	4 (0.625)	7 (1.12)	4 (0.625)	5 (0.852)
Other	65 (5.22)	2 (0.24)	8 (1.28)	7 (1.12)	5 (0.883)	5 (0.852)

Table 4
Primary outcome in treatment with meropenem alone or piperacillin-tazobactam.

	Meropenem alone (N = 622)	piperacillin-tazobactam (N = 622)	P
Primary Outcome			
SOFA score, mean (95% CI)	7.22 (7.10–8.92)	8.62 (7.15–9.25)	0.25
ICU mortality	111 (17.84)	102 (16.39)	0.22
Mortality at 28 day (%, 95% CI)	155 (24.92)[11.58–28.62]	159 (25.56)[13.95–22.56]	0.36
Mortality at 90 day (%, 95% CI)	205 (32.95)[22.69–35.92]	223 (37.45)[23.95–39.52]	0.15
length of stay in ICU, days	13 (3–22)	11 (5–18)	0.55
length of stay in hospital, days	33 (18–37)	31 (21–42)	0.02
Cardiovascular in SOFA, median (IQR)	2.69 (1.95–3.11)	2.02 (1.25–3.02)	0.21
Respiratory in SOFA, median (IQR)	2.15 (0.95–3.48)	2.66 (1.11–3.22)	0.01
Coagualtion in SOFA, median (IQR)	0.58 (0.22–0.69)	0.51 (0.11–0.96)	0.36
Renal in SOFA, median (IQR)	0.33 (0.21–0.65)	0.46 (0.36–0.69)	0.04
Hepatic in SOFA, median (IQR)	0.11 (0.02–0.36)	0.06 (0.01–0.25)	0.36
Central nervous system in SOFA, median (IQR)	0.99 (0.25–1.92)	0.89 (0.36–1.69)	0.37
Intervention-free days form ventilator, median (IQR)	3 (0–5)	3 (1–6)	0.68
Intervention-free days form Renal replacement therapy, median (IQR)	9 (2–13)	11 (5–18)	0.04
Intervention-free days form antibiotic, median (IQR)	1 (0–3)	1 (0–3)	0.89
Intervention-free days form vasopressor, median (IQR)	4 (1–9)	3 (2–11)	0.85

P = 0.03), and age (HR per year, 3.21 [95% CI, 1.78–3.92]; P = 0.02).

3.3. Subgroup analyses

There were no significant differences found in survival or mean SOFA score in unplanned subgroup studies that were stratified by pre-randomization SOFA score, patients' location and origin of infection, or enrollment organisms. Additionally, a planned analysis that excluded individuals who were treated with trial medication for less than 19 days did not reveal any significant changes.

Table 5
Secondary Outcomes in treatment with meropenem alone or piperacillin-tazobactam.

	Meropenem alone (N = 622)	piperacillin-tazobactam (N = 622)	P
Clinical response at EOT	547 (87.94)	510 (81.99)	0.03
Microbiological response (n = 125 patients with repeat cultures)	13/65 (20.0)	14/60 (22.25)	0.36
WBC outside normal limit	422 (68.00)	385 (61.89)	0.02
WBC normalized	323 (51.92)	342 (55.20)	0.48
Time to WBC normalization, days	3 (2–9)	4 (2–9)	0.39
Secondary infrection, no (%)[95% CI]	194 (31.19) [22.69–39.61]	211 (34.00) [25.98–39.42]	0.15

EOT, end of therapy

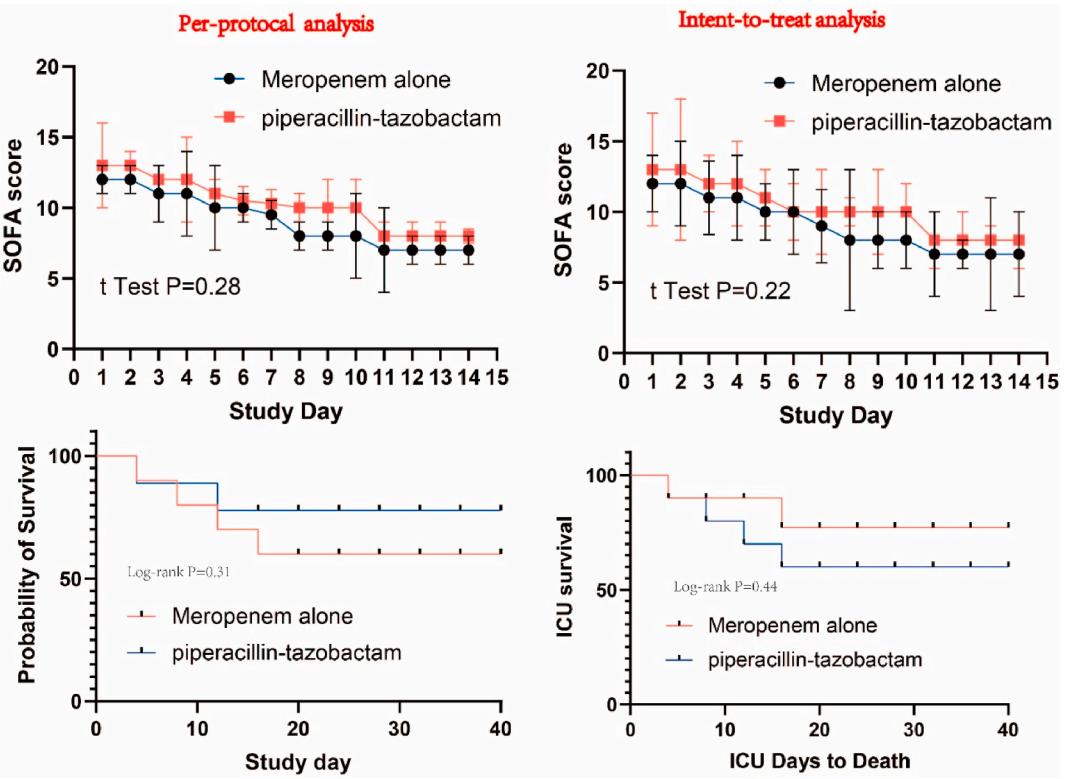


Fig. 1. SOFA Score, probability of survival and ICU survival between meropenem alone and piperacillin-tazobactam group.

4. Safety end points

Among the patients who received meropenem therapy (n = 622), at least one adverse event occurred in 38.25% (95% CI, 32.02%–42.51%). In comparison, the piperacillin-tazobactam group (n = 622) had a lower incidence of adverse events at 15.25% (95% CI, 11.20%–36.25%) (P = 0.62). The study reported a higher number of study-related adverse events (n = 52; 4.85% [95% CI, 0.58%–10.25%]; P = 0.03). However, there were no significant differences in the rates of serious adverse events, serious and study-related adverse events, adverse events resulting in death, or study-related adverse events resulting in death between the two groups. The incidence of adverse events related to cardiac disorders was reported in 35 patients in the meropenem group and 42 patients in the piperacillin-tazobactam group (P = 0.52). Similarly, the incidence of adverse events related to hepatobiliary disorders was reported in 15 patients in the meropenem group and 10 patients in the piperacillin-tazobactam group (P = 0.52), with only one event classified as serious in the piperacillin-tazobactam group.

5. Discussion

In this clinical trial involving 1244 patients with severe sepsis or septic shock, combination therapy with meropenem alone and piperacillin-tazobactam alone did not show any benefit in terms of the 14-day mean SOFA score. However, we did observe improvements in hospital stay duration, respiratory and renal SOFA scores, and intervention-free days from renal replacement therapy. The incidence of severe or major adverse events did not differ significantly between the two research groups.

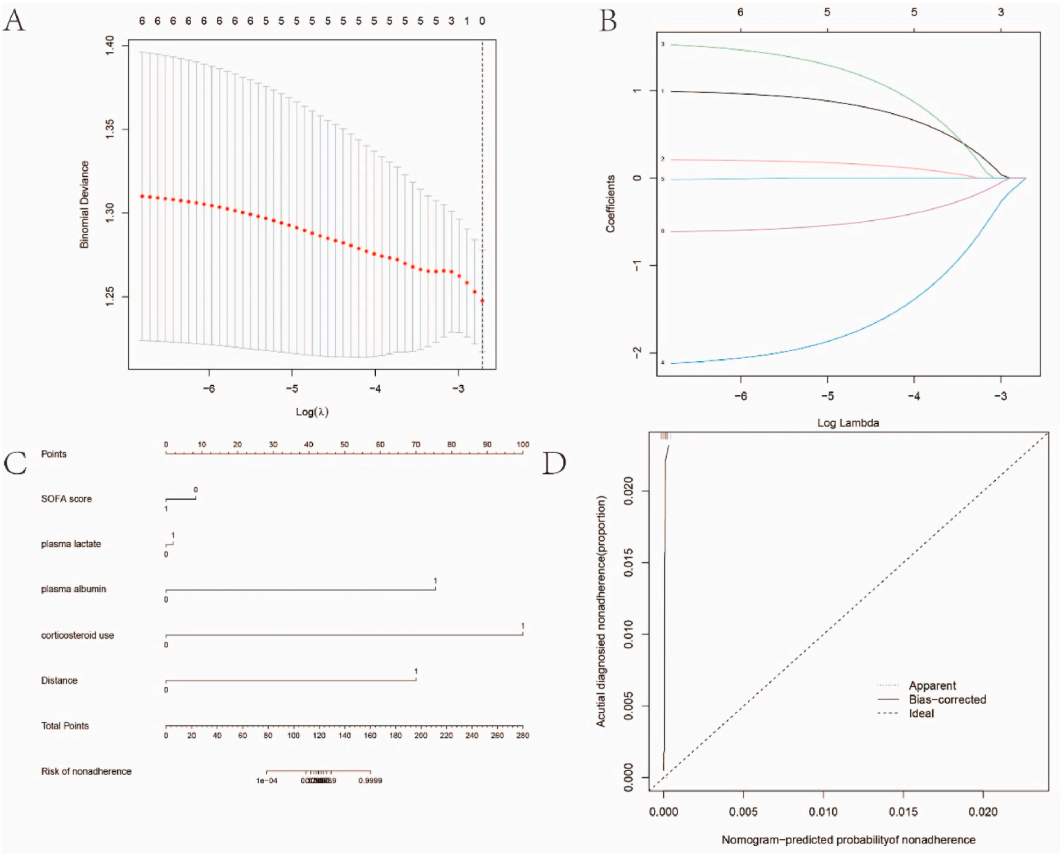


Fig. 2. LASSO regression analysis in meropenem alone and piperacillin-tazobactam group. (A) Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation via minimum criteria.(B) LASSO coefficient profiles of the 58 features. A coefficient profile plot was produced against the log (lambda) sequence.(C) Developed prediction nomogram. (D)Calibration curves.

This study is the first randomized comparison of meropenem alone and piperacillin-tazobactam alone in patients with severe sepsis or septic shock. Previous randomized trials have shown the potential for clinically relevant antimicrobial synergism with appropriate antibiotic combinations in pneumonia bloodstream infection, MIC and beta-lactam resistance genes, urinary tract infection, and peritoneal daily solution [11,17–20].

Our research aligns with a clinical trial study that focused on patients with E coli or K pneumoniae bloodstream infection and ceftriaxone resistance. The study found that definitive treatment with piperacillin-tazobactam versus meropenem did not result in non-inferior 30-day mortality [11]. Our findings are consistent with prior research that found a link between SOFA score and mortality at 28 and 90 days. Meropenem 120 mg/kg/day as a 1-h drip infusion three times a day against piperacillin-tazobactam 337.5 mg/kg/day as a 1-h drip infusion for febrile neutropenia in pediatric patients. The success rate in patients 15 years of age was improved in the piperacillin-tazobactam group [21]. F our research indicates that a brief corticotropin test at the onset of septic shock can help identify individuals who would benefit from corticosteroid replacement treatment. However, it is important to note that the time required to obtain accurate cortisol detection results (e.g., enzymatic method, radioimmunoassay) can vary, and medication should be administered promptly after the test.

The sample size was determined using a 1-sided formulation to detect a 20% difference in the 28-day death rate between two groups of non-responders. This formulation was adopted due to early reports provided during the study's preparation phase [11,17,19]. However, in accordance with the 9th International Conference on Harmonization's suggestion, all tests were conducted using a 2-sided formulation during analysis, and all reported P values were 2-sided. The sample size was also calculated based on the assumptions of a death rate of 95% in the non-responder placebo subgroup and a frequency of non-responders of 40% in the septic shock population. The observed mortality rate in the non-responder placebo category (63%) was substantially lower than predicted based on the data available during the study's design phase [21–23].

There are several limitations to this study. Firstly, the research team faced challenges in controlling empirical treatment due to the time-consuming nature of processing blood cultures and susceptibility testing. As a result, some patients assigned to meropenem were given a BLBLI, while those assigned to piperacillin-tazobactam received a carbapenem. This medication exposure "contamination" between the two groups could potentially confuse the conclusions drawn from the study, although it does favor noninferiority. The study was designed to reflect real-world clinical scenarios when prescribers are faced with a choice point in treating ceftriaxone

nonsusceptibility, rather than resembling registration medication trials. Additionally, it is unclear whether appropriate source control was achieved in patients with complicated bloodstream infections, which could have impacted mortality if imbalances existed.

6. Conclusion

To sum up, our findings indicate that Meropenem is associated with a lower mortality rate and more ventilator-free days, vasopressor-free days, and hospital-free days compared to piperacillin-tazobactam in patients with sepsis and septic shock. However, further research is required to determine which of these two drugs should be preferred. The potential advantages of piperacillin-tazobactam or meropenem treatment in septic shock patients should be explored in more detail.

Author contribution statement

Yang Sun, Yu Liu: Contributed reagents, materials, analysis tools or data; Conceived and designed the experiments.
Jixia Wang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.
Can Cui: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data included in article/supp. Material/referenced in article.

Author contribution statement

Yang Sun, Yu Liu, Jixia Wang, Can Cui: Conceived and designed the experiments.
Jixia Wang, Can Cui: Performed the experiments.
Jixia Wang, Can Cui: Analyzed and interpreted the data.
Yang Sun, Yu Liu: Contributed reagents, materials, analysis tools or data.
Can Cui: Wrote the paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

SOFA Sequential Organ Failure Assessment scores

References

[1] M.D. Font, B. Thyagarajan, A.K. Khanna, Sepsis and Septic Shock - basics of diagnosis, pathophysiology and clinical decision making, Med. Clin. 104 (4) (2020) 573–585.
[2] C. Fleischmann, et al., Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations, Am. J. Respir. Crit. Care Med. 193 (3) (2016) 259–272.
[3] T. Abe, et al., Characteristics, management, and in-hospital mortality among patients with severe sepsis in intensive care units in Japan: the FORECAST study, Crit. Care 22 (1) (2018) 322.
[4] M. Cecconi, et al., Sepsis and septic shock, Lancet 392 (10141) (2018) 75–87.
[5] D.C. Angus, T. van der Poll, Severe sepsis and septic shock, N. Engl. J. Med. 369 (9) (2013) 840–851.
[6] J.A. Roberts, A. Kumar, J. Lipman, Right dose, right now: customized drug dosing in the critically ill, Crit. Care Med. 45 (2) (2017) 331–336.
[7] C. Thomas, J. Priano, T.L. Smith, Meropenem as an antidote for intentional valproic acid overdose, Am. J. Emerg. Med. 38 (3) (2020) 690.e1–690.e2.
[8] N. Ahmed, et al., Evaluation of meropenem extended versus intermittent infusion dosing protocol in critically ill patients, J. Intensive Care Med. 35 (8) (2020) 763–771.
[9] A. Gin, et al., Piperacillin-tazobactam: a beta-lactam/beta-lactamase inhibitor combination, Expert Rev. Anti Infect. Ther. 5 (3) (2007) 365–383.
[10] A.N. Schuetz, S. Reyes, P.D. Tamma, Point-counterpoint: piperacillin-tazobactam should Be used to treat infections with extended-spectrum-beta-lactamase-positive organisms, J. Clin. Microbiol. 56 (3) (2018).
[11] P.N.A. Harris, et al., Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial, JAMA 320 (10) (2018) 984–994.
[12] M. Singer, et al., The third international consensus definitions for sepsis and septic shock (Sepsis-3), JAMA 315 (8) (2016) 801–810.
[13] A. Labelle, et al., The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment*, Crit. Care Med. 40 (7) (2012) 2016–2021.
[14] C. Vazquez-Guillamet, et al., Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock, Crit. Care Med. 42 (11) (2014) 2342–2349.
[15] K. Reinhart, et al., [Prevention, diagnosis, treatment, and follow-up care of sepsis. First revision of the S2k guidelines of the German sepsis society (DSG) and the German interdisciplinary association for intensive and emergency care medicine (DIVI)], Anaesthesist 59 (4) (2010) 347–370.

[16] R. Moreno, 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. 25 (7) (1999) 686–696.
[17] P.N. Harris, et al., Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible Escherichia coli and Klebsiella spp (the MERINO trial): study protocol for a randomised controlled trial, Trials 16 (2015) 24.
[18] A. Henderson, et al., Association between minimum inhibitory concentration, beta-lactamase genes and mortality for patients treated with piperacillin/tazobactam or meropenem from the MERINO study, Clin. Infect. Dis. 73 (11) (2021) e3842–e3850.
[19] K.S. Kaye, et al., Effect of meropenem-vaborbactam vs piperacillin-tazobactam on clinical cure or improvement and microbial eradication in complicated urinary tract infection: the TANGO I randomized clinical trial, JAMA 319 (8) (2018) 788–799.
[20] K. Mendes, et al., Stability of meropenem and piperacillin/tazobactam with heparin in various peritoneal dialysis solutions, Perit. Dial. Int. 38 (6) (2018) 430–440.
[21] R. Kobayashi, et al., Meropenem versus piperacillin/tazobactam for febrile neutropenia in pediatric patients: efficacy of piperacillin/tazobactam as a 1-h drip infusion four times a day, Int. J. Hematol. 113 (3) (2021) 430–435.
[22] L. Cheng, et al., Piperacillin-tazobactam versus other antibacterial agents for treatment of bloodstream infections due to AmpC β-lactamase-producing enterobacteriaceae, Antimicrob. Agents Chemother. 61 (6) (2017).
[23] M.L. Joly-Guillou, et al., Comparative in vitro activity of Meropenem, Imipenem and Piperacillin/tazobactam against 1071 clinical isolates using 2 different methods: a French multicentre study, BMC Infect. Dis. 10 (2010) 72.