DANISH MEDICAL JOURNAL

Original Article

Use of piperacillin/tazobactam and meropenem in a Danish intensive care unit

Hanna Jernberg[1], Marie Warrer Munch[1], Maj-Brit Nørregaard Kjær[1], Marie Helleberg[2, 3], Morten Hylander Møller[1, 4] & Anders Perner[1, 4]

1) Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, 2) Department of Infectious Disease, Copenhagen University Hospital – Rigshospitalet, 3) Centre of Excellence for Health, Immunity and Infections, 4) Department of Clinical Medicine, University of Copenhagen, Denmark

Dan Med J 2024;71(x):A02240081. doi: 10.61409/A02240081

ABSTRACT

INTRODUCTION. Intensive care unit (ICU) patients often have infections, and early empirical treatment with broad-spectrum antibiotics is recommended. As the choice between different agents is not supported by high-certainty evidence and as a part of a larger research programme, we aimed to describe the use of piperacillin/tazobactam (PTZ) and meropenem (MER) in patients in a university hospital ICU in Denmark and the patient outcomes of each of these treatments.

METHODS. We prospectively screened all patients admitted to the general 24-bed ICU at Rigshospitalet for 12 consecutive weeks as from 1 November 2022. Patients were included if they received PTZ or MER during their ICU stay. The primary outcome was 90-day mortality.

RESULTS. Among 286 patients, 184 (64%) received PTZ and/or MER; 112 (61%) were men, and 161 (88%) received life support. Among these, 80 (43%) received PTZ, 76 (41%) received MER and 28 (15%) received both agents, mainly as empirical treatment. At 90 days, 22 (28%) had died among patients receiving PTZ, 19 (26%) among those receiving MER and eight (29%) among those receiving both agents. At 90 days, 19 cases of a bacterium with new acquired resistance were identified in 17 of the 184 patients (9%) (eight cases among those receiving PTZ, five among those receiving MER, and six among those treated with both agents); vancomycin-resistant enterococci (VRE) accounted for 16 of the 19 cases.

CONCLUSIONS. Most patients in the ICU of a Danish university hospital received antibiotic treatment with PTZ and/or MER, mainly as empirical treatment. Mortality and the occurrence of bacteria with new acquired resistance, mainly VRE, appeared to the same extent in the groups.

FUNDING. None.

TRIAL REGISTRATION. Not relevant.

Severe infections, including sepsis, are life-threatening conditions that often require admission to the intensive care unit (ICU) and are associated with high mortality, morbidity and healthcare costs [1, 2]. Early empirical treatment with broad-spectrum antibiotics is recommended in these patients [3], and approximately three in every four ICU patients receive antimicrobial agents during their ICU stay [4]. However, excessive use of broad-spectrum antimicrobial agents contributes to the development of antibiotic resistance [5].

The World Health Organization (WHO) has designated antibiotic resistance as one of the greatest threats against global health [6]. In the past decade, the use of broad-spectrum antibiotics such as piperacillin/tazobactam and meropenem has increased globally [7-9], including in Denmark [10]. Piperacillin/tazobactam may be preferred as

an empirical agent over meropenem as the use of carbapenems is associated with selection of carbapenemase-producing bacteria [11-13]. However, a recently published systematic review suggested that piperacillin/tazobactam may be associated with less favourable outcomes than carbapenems in patients with severe bacterial infections, although the certainty of the evidence was low to very low [14]. Some included trials focused exclusively on bacteremia with extended-spectrum ß-lactamase (ESBL) producing bacteria [12, 13]. Therefore, randomised clinical trials are warranted to assess the effects of piperacillin/tazobactam versus carbapenems on mortality, serious adverse events and the occurrence of resistant bacteria in general [12, 14].

As part of a research programme preparing for the Empirical Meropenem vs. Piperacillin/Tazobactam for Adult Patients with Sepsis (EMPRESS) trial, we described the use of piperacillin/tazobactam and meropenem in all ICU patients admitted to a Danish university hospital ICU during 12 consecutive weeks.

Methods

Study design

We prospectively screened all patients admitted to the Department of Intensive Care at Copenhagen University Hospital - Rigshospitalet, Denmark, from 1 November 2022 to 23 January 2023. This general 24-bed ICU provides Critical Care Level 3 (advanced respiratory support, monitoring and support for two or more organs) for surgical and medical patients, including haematology and oncology patients and children aged more than one year. The hospital has specialised ICUs for cardiothoracic/cardiac, neurosurgical/neurological and neonatal cases.

Because of its observational and descriptive design, the study was approved as a quality control study. The head of the ICU approved the protocol, and no consent was required.

Participants/patients

Patients were eligible for inclusion if they received piperacillin/tazobactam and/or meropenem during their ICU stay. They were only included once in the study. We did include patients who had not been included during their primary admission if they met the eligibility criteria during their readmission (within the 12 weeks).

Data collection

Data were collected using RedCap, including demographics, baseline characteristics, daily use of piperacillin/tazobactam and meropenem, life support use, length of ICU stay and mortality. The complete list of variables is presented in the **Supplementary File**. Trained research staff performed data entry, and one author (HJ) validated the data. If any questions emerged during data entry, the responsible intensivist or co-author MHM or AP was counselled.

Outcomes

The primary outcome was 90-day mortality. Secondary outcomes were discharging to a ward or another ICU, duration of ICU stay, duration of antibiotic treatment and occurrence of antibiotic-resistant bacteria during index hospital admission, including a positive culture with methicillin-resistant *Staphylococcus aureus*, carbapenemase-producing organisms (CPO), ESBL, vancomycin-resistant enterococci (VRE) or other bacteria with acquired resistance.

Statistical methods

We analysed the data using R version 4.1.0 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). We present data descriptively, i.e. as numbers (%) with 95% confidence intervals (CI) for categorical data and medians with interquartile ranges (IQR) for continuous data. We stratified the data using

piperacillin/tazobactam versus meropenem versus both agents during the ICU stay.

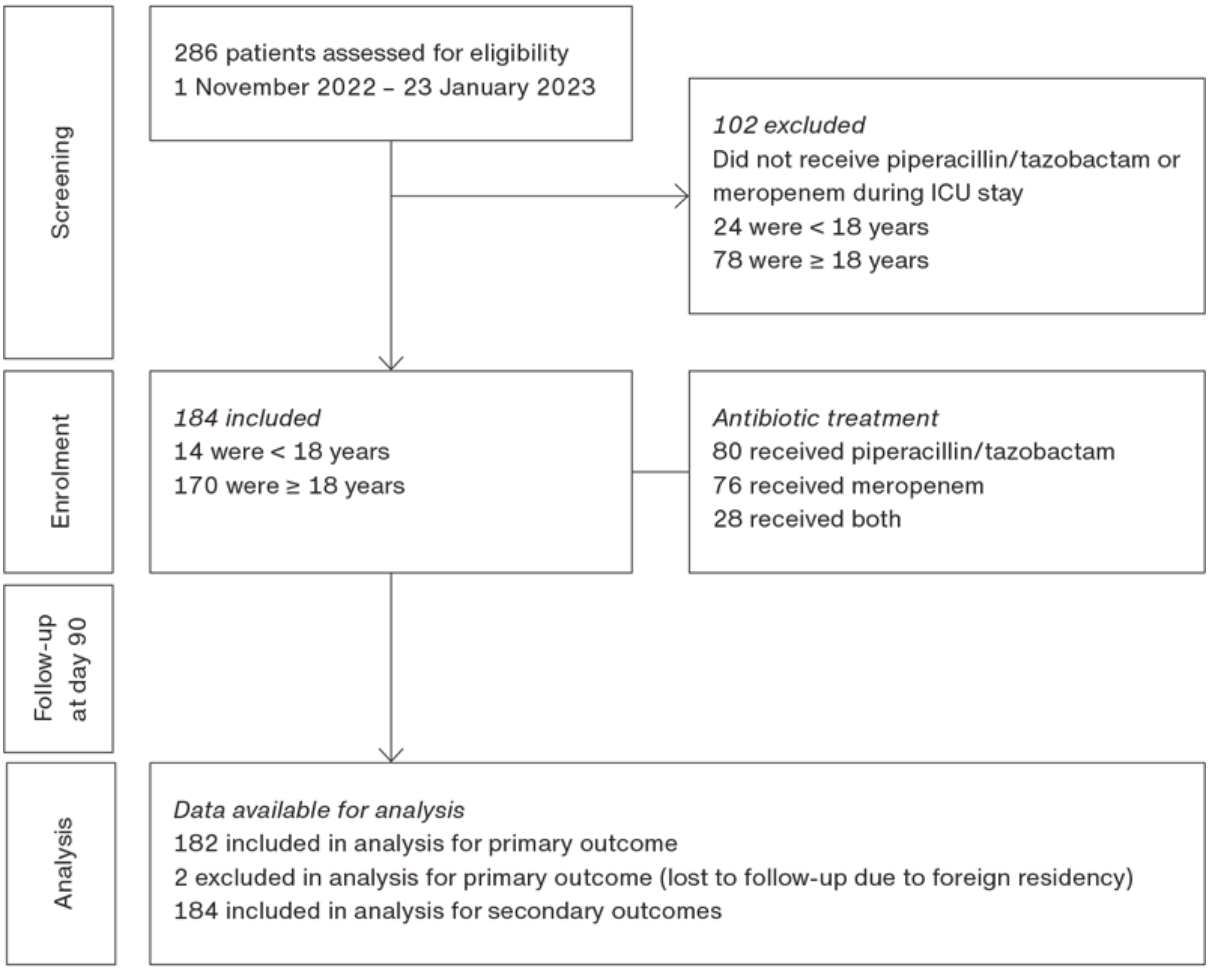
Trial registration: not relevant.

Results

Demographic and clinical characteristics of patients

A total of 286 patients were admitted to the ICU during the study period. Among these, we included 184 patients (64.3%) who received piperacillin/tazobactam and/or meropenem; 112 (61.9%) were men (**Figure 1**). The population had a median age of 63.3 (IQR: 48.0-71.3) years. Acute kidney injury (28.8%) was the most common coexisting condition at baseline. Most patients, 161 (87.5%), received at least one life-supportive intervention. During their ICU stay, a total of 80 (43.5%) patients received piperacillin/tazobactam, 76 (41.3%) received meropenem and 28 (15.2%) received both within 90 days of their ICU stay (**Table 1**). A total of 29 (38.2%) of the patients receiving meropenem had suspected skin and/or soft tissue infection at baseline. The most common focus of infection in the other treatment groups was pulmonary (32.5% of patients treated with piperacillin/tazobactam and 39.3% among patients receiving both agents during admission). More patients treated with meropenem received invasive mechanical ventilation (75.0%), vasopressors (86.6%) and renal replacement therapy (25.0%) than patients treated with piperacillin/tazobactam (52.5%, 72.5% and 16.3%, respectively) (Table 1).

FIGURE 1 Assessment, inclusion and analysis.



ICU = intensive care unit.

TABLE 1 Demographic and clinical characteristics of patients[a].

	Overall		Meropenem		Piperacillin/tazobactam		Meropenem and piperacillin/tazobactam	
	N = 184	N = 155[j]	N = 76	N = 74	N = 80	N = 55	N = 28	N = 26
Age, median (IQR), yrs	63.3 (48.0-71.3)		59.9 (46.6-67.3)		63.0 (48.3-74.2)		68.2 (58.8-74.7)	
Adult, n (%)	170 (92.4)		71 (93.4)		73 (91.3)		26 (92.9)	
Male sex, n (%)	112 (60.9)		47 (61.8)		51 (63.8)		14 (50.0)	
Coexisting conditions, n (%)								
Diabetes[b]	36 (19.6)		18 (23.7)		14 (17.5)		4 (14.3)	
Haematologic cancer	17 (9.2)		11 (14.5)		4 (5.0)		2 (7.1)	
Use of corticosteroids within 3 mos. prior to admission[c]	14 (7.6)		9 (11.8)		3 (3.8)		2 (7.1)	
Metastatic cancer[d]	14 (7.6)		5 (6.6)		8 (10.0)		1 (3.6)	
Solid organ transplant[e]	15 (8.2)		3 (3.9)		10 (12.5)		2 (7.1)	
Chronic kidney disease[f]	8 (4.3)		6 (7.9)		1 (1.3)		1 (3.6)	
Acute kidney injury[g]	53 (28.8)		19 (25.0)		24 (30.0)		10 (35.7)	
Length of hospital stay prior to ICU admission, median (IQR), days	1.5 (0.5-5.5)		1.5 (0.5-6)		2 (0.5-4.5)		3 (1.5-8)	
Source of ICU admission, n (%)								
Emergency department or trauma centre	35 (19.0)		16 (21)		13 (16.3)		6 (21.5)	
Hospital ward	47 (25.5)		21 (27.6)		21 (26.3)		5 (17.9)	
Another ICU	43 (23.4)		18 (23.7)		16 (20.0)		9 (32.1)	
Operating or recovery room:								
Planned surgery	18 (9.8)		5 (6.6)		11 (13.8)		2 (7.1)	
Acute surgery	41 (22.3)		16 (21.1)		19 (23.8)		6 (21.4)	
Subtotal	59 (32.1)		21 (27.6)		30 (37.5)		8 (28.6)	
Known colonisation[h] with a bacterium with acquired antibiotic resistance, n (%)								
Methicillin-resistant *Staphylococcus aureus*	1 (0.5)		1 (1.3)		0		0	
CPO	1 (0.5)		1 (1.3)		0		0	
ESBL	0		0		0		0	
VRE	6 (3.3)		4 (5.3)		2 (2.5)		0	
Suspected infection at inclusion?, n (%)								
Yes	155 (84.2)		74 (97.4)		55 (68.8)		26 (92.9)	
No[i]	29 (15.8)		2 (2.6)		25 (31.3)		2 (7.1)	
Source of infection, n (%)								
Community acquired infection[k]		81 (52.3)		41 (55.4)		27 (49.1)		13 (50.0)
Nosocomial infection[l]		69 (44.5)		29 (39.2)		28 (50.9)		12 (46.2)
Unknown		5 (3.2)		4 (5.4)		0		1 (3.8)
Focus of infection, n (%)								
Central nervous system	8 (4.3)		7 (9.2)		0		1 (3.6)[m]	
Pulmonary	57 (31.0)		20 (26.3)		26 (32.5)		11 (39.3)[m]	
Skin or soft tissue	34 (18.5)		29 (38.2)		0		5 (17.9)[m]	
Abdominal	24 (13.0)		6 (7.9)		13 (16.3)		5 (17.9)[m]	
Urinary tract	5 (2.7)		1 (1.3)		2 (2.5)		2 (7.1)[m]	
Catheter-related infection	1 (0.5)		1 (1.3)		0		0[m]	
Unknown focus	24 (13.0)		9 (11.8)		13 (16.3)		2 (7.1)[m]	
Other	2 (1.1)		1 (1.3)		1 (1.3)		0[m]	
SAPS-3[n] score, median (IQR)	63.0 (52.5-73.5)		64.0 (57.0-71.5)		60.5 (49.8-75.5)		66.5 (55.8-76.0)	
Life support, 1st 24 hrs in ICU, n (%)								
Invasive mechanical ventilation[o]	119 (64.7)		57 (75.0)		42 (52.5)		20 (71.4)	
Vasopressors[p]	150 (81.5)		66 (86.8)		58 (72.5)		26 (92.9)	
Renal replacement therapy[q]	36 (19.6)		19 (25.0)		13 (16.3)		4 (14.3)	
No use of life support first 24 hrs in ICU	23 (12.5)		6 (7.9)		16 (20.0)		1 (3.6)	
Indication for antibiotic treatment at inclusion[r]:	184		83 (45.1)		101 (54.9)		-	
Prophylactic	34 (18.5)		4 (4.8)		30 (29.7)			
Empirical	143 (77.7)		73 (88.0)		70 (69.3)			
Definitive	6 (3.3)		5 (6.0)		1 (1.0)			
Unknown	1 (0.5)		1 (1.2)		0			

Continues >

TABLE 1 CONTINUED Demographic and clinical characteristics of patients[a].

	Overall		Meropenem		Piperacillin/tazobactam		Meropenem and piperacillin/tazobactam	
	N = 184	N = 155[j]	N = 76	N = 74	N = 80	N = 55	N = 28	N = 26
Antibiotic treatment prior to ICU admission, n (%)								
Treated with piperacillin/tazobactam at ICU admission[s]	69 (37.5)		2 (2.6)		51 (63.8)		16 (57.1)	
Treated with meropenem at ICU admission:	60 (32.6)		53 (69.7)		1 (1.3)		6 (21.4)	
Had received piperacillin/tazobactam before meropenem was prescribed	24 (13.0)		18 (23.7)		1 (1.3)		5 (17.9)	
Treated with both agents at ICU admission	2 (1.1)		2 (2.6)		0		0	
Antibiotic treatment during ICU-admission, n (%)								
Change[t] from meropenem to piperacillin/tazobactam	4 (2.2)		-		1 (1.3)		3 (10.7)	
Reason for change:								
Enhanced microbial coverage	3 (1.6)		-		1 (1.2)		2 (7.1)	
Other	1 (0.5)		-		0		1 (3.6)	
Changet from piperacillin/tazobactam to meropenem	21 (11.4)		1 (1.3)		-		20 (71.4)	
Reason for change:								
Clinical deterioration	7 (3.8)		0		-		7 (25.0)	
Enhanced microbial coverage	14 (7.6)		1 (1.3)		-		13 (46.4)	
Resistance	1 (0.5)		0		-		1 (3.6)	
Other	3 (1.6)		0		-		3 (10.7)	
Unknown	1 (0.5)		0		-		1 (3.6)	

CPAP = continuous positive airway pressure; CPO = carbapenemase-producing organisms; ESBL = extended spectrum beta-lactamase; ICU = intensive care unit; IQR = interquartile range; SAPS-3 = Simplified Acute Physiology Score III; VRE = vancomycin-resistant enterococci.
a) For a table with all results, please see the Supplementary File.
b) Treatment at time of hospital admission with any anti-diabetic medications.
c) Adults: daily use of prednisolone ≥ 20 mg or other steroid-equivalent dose for min. 10 consecutive days; paediatric patients: daily use of prednisolone 1 mg/kg/body weight or other steroid in an equivalent dose for min. 10 consecutive days.
d) Proven non-haematological metastasis by surgery, computed tomography or any other method.
e) Any transplant of liver, kidney, heart, pancreas or lung(s).
f) Need for chronic renal support including continuous or intermittent renal replacement therapy or S-creatinine > 300 µmol/l prior to hospital admission or "chronic kidney disease"/"CKD" found written in the text of the medical record by physician.
g) Serum creatinine 3 × baseline or increase in serum creatinine to 353.6 mmol/l or initiation of renal replacement therapy or "acute kidney injury"/"AKI"/"akut nyresvigt" found written in the text of the medical record by physician.
h) Antibiotic resistance confirmed by positive cultures registered in the medical record prior to ICU admission or positive screening test for bacterium with acquired antibiotic resistance ≤ 12 hrs after ICU admission.
i) No clinical or paraclinical signs of infection.
j) Only registered among those with suspected infection at inclusion, N = 155.
k) Infection present on admission to hospital or developing within 48 hrs of admission.
l) Infection not present on admission to hospital. However, developed ≥ 48 hrs after admission or secondary to a medical/surgical intervention.
m) Patients who received both agents during their ICU stay received these sequentially, i.e. they received one of the two agents at inclusion, which was hereafter changed to the other (typically piperacillin/tazobactam first); baseline characteristics regarding status of infection represent data from the first antibiotic treatment registered.
n) Only registered on adult patients; score missing for 65 (35.3%) patients; 21 (27.6%) of the patients who received meropenem, 32 (40%) of the patients receiving piperacillin/tazobactam and 12 (42.9%) of the patients receiving both agents.
o) Invasive mechanical ventilation, defined as the use of positive pressure ventilation using a ventilator via a cuffed tube: oral, nasal or tracheostomy; CPAP is not invasive mechanical ventilation.
p) Any continuous treatment with norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosimendan.
q) Any form of renal replacement therapy, e.g., dialysis, haemofiltration or haemodiafiltration.
r) No patients were in simultaneous therapy with piperacillin/tazobactam and meropenem during their ICU stay; indication for treatment is presented for the antibiotics respectively and not by stratification model. Thus, patients treated with both antibiotics during their ICU stay were already included when the change to the other studied antibiotic agent was made; the table reflects that those patients receiving both agents during their ICU stay typically started with piperacillin/tazobactam.
s) None of the patients treated with piperacillin/tazobactam upon ICU admission had received meropenem within 24 hrs before receiving piperacillin/tazobactam.
t) ≤ 24 hrs between termination of piperacillin/tazobactam and initiating treatment with meropenem, or vice versa.

Patients who received both agents during their ICU stay received these sequentially, i.e. they received one of the two agents at inclusion, which was hereafter changed to the other (typically piperacillin/tazobactam first). The most common reason for switching from piperacillin/tazobactam to meropenem was a need for extended-spectrum coverage (46.4%) (Table 1). Patients who received both antibiotics during their ICU stay had higher age, Simplified Acute Physiology Score III (SAPS-3), were more often transferred from another ICU and had a longer ICU stay than patients only receiving piperacillin/tazobactam or meropenem during their ICU stay (Table 1).

Most patients (71.2%) received the antibiotics upon ICU admission; 69 (37.5%) received piperacillin/tazobactam, 60 (32.6%) meropenem and two (1.1%) both agents. The two patients who received both agents upon ICU admission were adjusted to monotherapy soon after their arrival at the ICU. None of the patients treated with piperacillin/tazobactam upon ICU admission had received meropenem within 24 hours before receiving piperacillin/tazobactam. Twenty-four (40.0%) of the patients administered meropenem upon ICU admission had

received piperacillin/tazobactam within 24 hours before receiving meropenem (Table 1). The most prescribed dose of piperacillin/tazobactam, pre-ICU and in the ICU, was 4/0.5 g four times daily. The most prescribed dose of meropenem pre-ICU was 2 g three times daily and 1 g four times daily in the ICU (**Table 2**).

TABLE 2 Antibiotic dosing[a].

Dose	Overall, n (%)	Pre-ICU[c], n (%)	ICU, n (%)
Meropenem			
1 g × 2 daily	23 (15.3)	4 (6.5)	19 (21.6)
1 g × 3 daily	31 (20.7)	18 (29.0)	13 (14.8)
1 g × 4 daily	35 (23.3)	4 (6.5)	31 (35.2)
2 g × 3 daily	41 (27.3)	27 (43.5)	14 (15.9)
Other dosed	20 (13.3)	9 (14.5)	11 (12.5)
Subtotal	150[b]	62	88
Piperacillin/tazobactam			
4/0.5 g × 2 daily	16 (12.7)	6 (8.8)	10 (17.2)
4/0.5 g × 3 daily	22 (17.5)	14 (20.6)	8 (13.8)
4/0.5 g × 4 daily	77 (61.1)	44 (64.7)	33 (56.9)
Other dose[d]	11 (8.7)	4 (5.9)	7 (12.1)
Subtotal	126[b]	68	58

ICU = intensive care unit.
a) Bolus doses (n = 20, all prescribed in the ICU) have been excluded from the table.
b) Note that antibiotic dosing records have a higher numerical value than the patients included; a new record was opened
every time there were changes in dosing and changes between agents included in this study, i.e. a single patient can have
several antibiotic dosing records.
c) If a patient continued with the same prescribed pre-ICU dose at ICU admission, this dose is registered as "pre-ICU".
d) For practical reasons, odd/unique doses are grouped as "other dose".

Primary outcome

A total of 182 patients were included in the primary outcome analysis; two patients in the meropenem group were lost to follow-up at day 90 due to foreign residency. The 90-day mortality appeared similar between the groups: 19 (25.7%) (95% CI: 16.2-37.2%) in patients treated with meropenem, 22 (27.5%) (95% CI: 18.1-38.6%) in patients treated with piperacillin/tazobactam and eight (28.6%) (95% CI: 13.2-48.7%) in patients who received both agents upon ICU admission died within 90-days (**Table 3**).

TABLE 3 Primary and secondary outcomes[a].

	Meropenem (N = 76)	Piperacillin/ tazobactam (N = 80)	Meropenem and piperacillin/tazobactam (N = 28)	Overall (N = 184)	Pre-ICU	ICU
90-day mortality[b], n (% [95% CI])[c]	19 (25.7 [16.2-37.2])	22 (27.5 [18.1-38.6])	8 (28.6 [13.2-48.7])	49 (26.9 [20.6-34.0])	-	-
Outcome ICU stay, n (% [95% CI])[c]						
Discharged to another ICU	10 (13.2 [6.5-22.9])	12 (15.0 [8.0-24.7])	5 (17.9 [6.1-36.9])	27 (14.7 [9.9-20.6])	-	-
Discharged to ward	52 (68.4 [56.7-78.6])	57 (71.3 [60.0-80.8])	19 (67.9 [47.6-84.1])	128 (69.6 [62.4-76.1])	-	-
Death	14 (18.4 [10.5-29.0])	11 (13.8 [7.1-23.3])	4 (14.3 [4.0-32.7])	29 (15.8 [10.8-21.8])	-	-
ICU readmission[d], n (% [95% CI])	4 (5.3 [1.8-15.7])	6 (7.5 [3.3-18.0])	3 (10.7 [2.7-32.4])	13 (7.1 [4.5-13.9])	-	-
Length of ICU stay, median (IQR), days	5.5 (2.5-9.5)	2.5 (1.5-4.5)	9.5 (3.5-18)	3.5 (2.5-8.5)	-	-
Renal replacement therapy in ICU, n (% [95% CI])[c]	19 (25.0 [15.8-36.3])	14 (17.5 [9.9-27.6])	8 (28.6 [13.2-48.7])	41 (22.3 [16.5-29.0])	-	-
Antibiotic resistance, n (% [95% CI])[c]						
New positive culture with a resistant bacteria in specimen in the ICU[e, f] :						
VRE[g]	0	0	2 (7.1)	2 (1.1)	-	-
Linezolid-resistant enterococci	0 (0 [0.0-4.7])	0 (0 [0.0-4.5])	1 (3.6 [0.1-18.3])	1 (0.5 [0.0-3.0])	-	-
New positive culture with a resistant bacteria in specimen after ICU discharge but during index hospital admission[h]:						
CPO	0 (0 [0.0-4.7])	0 (0 [0.0-4.5])	1 (3.6 [0.1-18.3])	1 (0.5 [0.0-3.0])	-	-
VRE[g]	3 3.9%)	4 (5.0)	0	7 (3.8)	-	-
Linezolid-resistant enterococci	0 (0 [0.0-4.7])	1 (1.3 [0.0-6.8])	0 (0 [0.0-12.3])	1 (0.5 [0.0-3.0])	-	-
New positive culture with a resistant bacterium in specimen, time for development unknown due to missing tests[i] :						
VRE	2 (2.6)	3 (3.8)	2 (7.1)	7 (3.8)	-	-
Treatment duration, median (IQR), days						
Meropenem				12 (8-17.5)[j]	2 (1-4)	5 (3-11)
Piperacillin/tazobactam				6 (4-10)[j]	2 (1-3)	3 (2-5)

CI = confidence interval; CPO = carbapenemase-producing organisms; IQR = interquartile range; ICU = intensive care unit; VRE = vancomycin-resistant enterococci.
a) For a table with all results, please see the Supplementary File.
b) 2 (1.1%) patients were lost to analysis on the primary outcome; both patients were treated with meropenem, corresponding to 2.6% of the patients in this group.
c) Only presented for frequencies.
d) Patient discharged from the ICU and returning after ≥ 24 hrs.
e) Antibiotic resistance not present at baseline test; antibiotic resistance confirmed by positive cultures collected during ICU admission but no earlier than ≥ 12 hrs after admission.
f) Information on this variable is missing for 1 patient (0.5%).
g) In this analysis, we have excluded 95% CI due to insecurities in time for development for 7 (43.8%) new cases of VRE during hospital stay.
h) Antibiotic resistance not present at baseline test or during ICU stay; antibiotic resistance confirmed by positive cultures collected after ICU discharge but within same hospital stay.
i) This part of the table represents new cases of antibiotic resistance where time of development is unknown. Therefore 95% CI is not presented.
j) Includes treatment duration pre-ICU, during the ICU stay and after ICU discharge; patients who received both antibiotics in the ICU within 90 days have, for practical reasons, been excluded from the analysis; the corresponding treatment duration for patients receiving both antibiotics within 90 days is a median 12 days (IQR: 7-19.2).

Secondary outcome treatment duration

The duration of antibiotic treatment in the ICU and in total for patients treated with meropenem was five (IQR: 3-11) days and 12 (IQR: 8-18) days, respectively. The corresponding results for those treated with piperacillin/tazobactam were three (IQR: 2-5) days and six (IQR: 4-10) days, respectively (Table 3).

Antibiotic resistance

At baseline, eight patients (4.3%) had a known colonisation with a bacterium with acquired antibiotic resistance; six (3.3%) of these were VRE, one (0.5%) was CPO and one (0.5%) was methicillin-resistant *S. aureus*. Nineteen cases of a new positive culture with a bacterium with acquired antibiotic resistance were identified in 17 patients (9.2% of our study population). Among these, VRE was the most common pathogen (Table 3); where identification was possible, most patients had these identified in hospital after ICU discharge (7 (3.8%)). There appeared to be no major differences in resistance patterns between the three antibiotic groups (Table 3). See Table 3 for a full report on secondary outcomes.

Discussion

In this single-centre cohort study with prospective data collection, we observed that more than half of the general ICU patients received piperacillin/tazobactam and/or meropenem during their ICU stay. The 90-day mortality and occurrence of antibiotic-resistant bacteria appeared similar between the groups.

In our report, piperacillin/tazobactam was the preferred antibiotic treatment before ICU admission. Patients administered meropenem upon ICU admission were more likely to have previously received

piperacillin/tazobactam within 24 hours. In contrast, none of the patients treated with piperacillin/tazobactam had received meropenem within the same timeframe before receiving piperacillin/tazobactam. This may indicate that clinicians were more restrictive in prescribing meropenem than piperacillin/tazobactam. Restrictive use of carbapenems as a last resort antimicrobial drug is in line with the guidelines on antibiotic use issued by the Danish health authorities [15].

Slightly less than one in every ten patients were identified with a new positive culture with a bacterium with acquired antibiotic resistance during their hospital stay, most of which were VRE. Infections with *Enterococcus* are often caused by *E. faecalis* or *E. faecium*, the latter having limited susceptibility to most antibiotics, including piperacillin/tazobactam and meropenem. This gives *E. faecium* a selective advantage in healthcare settings [10]. Thus, piperacillin/tazobactam and meropenem do not a priori induce vancomycin resistance, but they select for *E. faecium*. Furthermore, *E. faecium* has a high prevalence of acquired vancomycin resistance due to use and overuse of vancomycin, contributing to VRE selection [16, 17]. The incidence of VRE has increased in Denmark since 2002 [18]. In 2022, vancomycin resistance was found in 12.0% of invasive human *E. faecium* isolates [10]. In total, 22 (12.0%) patients were colonised or infected with VRE in our cohort. Our findings are, therefore, expected and in line with the previously documented incidence [10].

The study period coincided with an increased incidence of invasive Group A streptococcus infections [19]. In severe cases, infection with this bacterium may progress to necrotising soft tissue infection (NSTI). Copenhagen University Hospital - Rigshospitalet is national referral for NSTI. During the study period, we experienced an increase in NSTIs. Although we did not register the primary reason for ICU admission, the outbreak is reflected in the high proportion of patients with skin and soft tissue infections. In Denmark, meropenem, in combination with clindamycin, is the recommended empirical treatment for NSTI. The standard empirical dose of meropenem for NSTI is 2 g three times daily [20], which was the most prescribed dose of meropenem before ICU admission. Thus, meropenem may have been used more frequently and in higher doses during the study period than in general.

Patients treated with meropenem were younger, more likely to require life-support at baseline, and antibiotic treatment duration and length of ICU stay was longer for these patients than for patients treated with piperacillin/tazobactam. Piperacillin/tazobactam was more often used for patients who had undergone elective surgery, and patients treated with piperacillin/tazobactam represented the highest proportion of patients who did not use any type of life-support during their first 24 hours in ICU. This may explain some of the observed differences in disease severity, duration of antibiotic treatment and length of stay. Despite these differences, mortality appeared similar between the groups. While our study was descriptive, it has previously been reported that piperacillin/tazobactam may be associated with less favourable outcomes than carbapenems in patients with severe bacterial infections. However, the certainty of evidence was low to very low [14]. While our findings cannot be used to infer causality, they support the need for relevant trials assessing this question.

Strengths and limitations

We included patients from a large, general ICU with mixed medical and surgical beds for 12 consecutive weeks with 90-day follow-up. Data were entered manually and validated in a dedicated database by trained research staff. ICU specialists (co-authors) were available for counselling to minimise risk of data entry errors. There are, however, also limitations. First, this was a single-centre observational study conducted within a limited period; therefore, the sample size was limited. Although our cohort represents a wide range of ICU patients, it may not be directly representative of ICUs with a different case mix. We did not register the reason(s) for termination of antibiotic treatment, which could have contributed to further knowledge about antibiotic escalation and de-escalation in the ICU. We were unable to control for confounders.

Our findings will inform the design of the upcoming EMPRESS trial, ClinicalTrial.gov identifier NCT06184659.

Conclusions

In this single-centre cohort study with prospective data collection, we observed that more than half of the general ICU patients received piperacillin/tazobactam and/or meropenem during their ICU stay, mainly as empirical treatment. Mortality and the occurrence of resistant bacteria with new acquired resistance, mainly VRE, appeared to the same extent between the groups.

Correspondence *Hanna Jernberg*. E-mail: hanna.erika.leontina.jernberg@regionh.dk

Accepted 23 May 2024

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2024;71(x):A02240081

doi 10.61409/A02240081

https://content.ugeskriftet.dk/sites/default/files/2024-05/a02240081-supplementary.pdf

REFERENCES

1. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006;42(suppl 2):S82-S89. https://doi.org/10.1086/499406
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-55. https://doi.org/10.1016/S0140-6736(21)02724-0
3. Evans L, Rhodes A, Alhazzani W et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063-e1143. https://doi.org/10.1097/CCM.0000000000005337
4. Vincent JL, Rello J, Marshall J et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323. https://doi.org/10.1001/jama.2009.1754
5. World Health Organization. Global action plan on antimicrobial resistance. World Health Organization, 2015. https://apps.who.int/iris/handle/10665/193736 (14 Apr 2023)
6. World Health Organization. Antimicrobial resistance. www.who.int/news-room/fact-sheets/detail/antibiotic-resistance (15 May 2023)
7. Ohnuma T, Hayashi Y, Yamashita K et al. A nationwide survey of intravenous antimicrobial use in intensive care units in Japan. Int J Antimicrob Agents. 2018;51(4):636-41. https://doi.org/10.1016/j.ijantimicag.2018.01.022
8. Balkhy HH, El-Saed A, El-Metwally A et al. Antimicrobial consumption in five adult intensive care units: a 33-month surveillance study. Antimicrob Resist Infect Control. 2018;7:156. https://doi.org/10.1186/s13756-018-0451-9
9. European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2021. European Centre for Disease Prevention and Control, 2022. www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2021 (19 Apr 2023)
10. DANMAP. Report - 2022. www.danmap.org/reports/2022 (30 Jan 2024)
11. El-Gamal MI, Brahim I, Hisham N et al. Recent updates of carbapenem antibiotics. Eur J Med Chem. 2017;131:185-95. https://doi.org/10.1016/j.ejmech.2017.03.022
12. Harris PNA, Tambyah PA, Lye DC 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. 2018;320(10):984-94. https://doi.org/10.1001/jama.2018.12163

13. Tamma PD, Han JH, Rock C et al. Carbapenem therapy is associated with improved survival compared with piperacillin-tazobactam for patients with extended-spectrum β-lactamase bacteremia. Clin Infect Dis. 2015;60(9):1319-25. https://doi.org/10.1093/cid/civ003
14. Munch MW, Granholm A, Jonsson AB et al. Piperacillin/tazobactam versus carbapenems in patients with severe bacterial infections: a systematic review with meta&;analysis. Acta Anaesthesiol Scand. 2023;67(7):853-68. https://doi.org/10.1111/aas.14239
15. Indenrigs- og Sundhedsministeriet. VEJ nr 10126 af 15/11/2012. Vejledning om ordination af antibiotika. www.retsinformation.dk/eli/retsinfo/2012/10126 (15 Dec 2023)
16. Fiore E, Van Tyne D, Gilmore MS. Pathogenicity of enterococci. Microbiol Spectr. 2019;7(4):10.1128/microbiolspec.gpp3-0053-2018. https://doi.org/10.1128/microbiolspec.gpp3-0053-2018
17. UpToDate. Vancomycin-resistant enterococci: epidemiology, prevention, and control. www.uptodate.com/contents/vancomycin-resistant-enterococci-epidemiology-prevention-and-control?search=enterococcus%20faecium&topicRef=3160&source=see_link (24 Jan 2024)
18. European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS Net) 2016. European Centre for Disease Prevention and Control, 2017. https://data.europa.eu/doi/10.2900/296939 (3 May 2023)
19. World Health Organization. Increased incidence of scarlet fever and invasive Group A Streptococcus infection - multi-country. www.who.int/emergencies/disease-outbreak-news/item/2022-DON429 (19 Apr 2023)
20. Nekrotiserende bløddelsinfektioner. Lægehåndbogen. www.sundhed.dk/sundhedsfaglig/laegehaandbogen/infektioner/tilstande-og-sygdomme/bakteriesygdomme/nekrotiserende-bloeddelsinfektioner/ (17 May 2023)

