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Carbapenem-resistant Gram-negative pathogens associated with septic shock: a review of 120 cases

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ABSTRACT

This study aimed to evaluate the influencing variables for outcomes in patients with septic shock having culture-proven carbapenem-resistant Gram-negative pathogens. It included 120 patients (mean age 64.29 ± 1.35 years and 58.3% female). The mean Sequential Organ Failure Assessment score during septic shock diagnosis was found to be 11.22 ± 0.43 and 9 ± 0.79 among the patients with mortality and among the survivors, respectively (P = 0.017). The logistic regression analysis showed that empirical treatment as mono Gram-negative bacteria–oriented antibiotic therapy (P = 0.016, odds ratio (OR) = 17.730, 95% confidence interval (CI): 1.728−182.691), Charlson Comorbidity Index >2 (P = 0.032, OR = 7.312, 95% CI: 5.7−18.3), and systemic inflammatory response syndrome score 3 or 4 during septic shock diagnosis (P = 0.014, OR = 5.675, 95% CI: 1.424−22.619) were found as independent risk factors for day 30 mortality. Despite early diagnosis and effective management of patients with septic shock, the mortality rates are quite high in CRGNP-infected patients.

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Carbapenem resistance; Gram-negative pathogens; septic shock

Introduction

Carbapenem-resistant Gram-negative bacteria have become a major worldwide alarming healthcare problem causing high mortality due to limited treatment options [1]. According to the Centres for Disease Control and Prevention (CDC) 2019 report, estimates showed 13,100 carbapenem-resistant Enterobacteriaceae cases in hospitalized patients causing 1100 deaths in 2017 in the United States. The report emphasized the problem with urgent threat level [2].

According to the data of the European Antimicrobial Resistance Surveillance Network in 2019, the percentage of resistance to carbapenems (imipenem or/and meropenem) was reported to be >25% in invasive *Klebsiella pneumoniae* isolates in several European Union or European Economic Area countries [3]. The problem was most notable in the south and south-central parts of Europe such as Greece (58.3%), Romania (32.3%), Italy (28.5%), and Bulgaria (27%). Turkey was not an exception. A recently published study from Turkey included 493 *Escherichia coli* or *K. pneumoniae* strains (community-acquired infection–related strains comprised 31%), which were collected from 26 hospitals between March 01 and August 31 or April 01 and September 30, 2019. Carbapenem resistance in Gram-negative Enterobacteriaceae was reported to be 49.7%, and the most common carbapenemase was OXA-48 (52.2%) [4].

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Sepsis and septic shock also leads to varying but significant mortality and morbidity worldwide. The 1-month septic shock mortality rate was reported to be 33.7% [95% confidence interval (CI): 31.5–35.9] in North America, 32.5% (95% CI: 31.7–33.3) in Europe, and 26.4% (95% CI: 18.1–34.6) in Australia in a recent meta-analysis [5]. On the contrary, the in-hospital crude mortality rate of septic shock was as high as 72.6% in a multicenter, retrospective cohort study from Turkey [6]. This study aimed to evaluate the outcomes and influencing variables in the subgroup of patients with both highly mortal problems, that is, septic shock + culture-proven carbapenem-resistant Gram-negative pathogens (CRGNP).

Methods

Setting

This observational and noninterventional study was conducted in an 1800+ bedded tertiary-care educational hospital located in a city populated 4.394,694 in 2020 and 4,061,074 in 2013 [7].

Study group definitions

Data of patients with septic shock and consulted by Infectious Diseases consultants in our setting between December 01, 2013, and January 01, 2021, were collected prospectively and analyzed retrospectively. We analyzed the clinical outcomes and associated factors. Besides, we analyzed outcomes according to enrollment years as 2013–2017 (first group) and 2018–2021 (second group).

Septic shock definition was considered to be sepsis with hypotension requiring vasopressors to maintain a mean arterial blood pressure above 65 mm Hg despite adequate fluid resuscitation [5]. An elevated serum lactate concentration (arterial lactate level of >2 mg/dL) was added as an inclusion criterion for septic shock according to the Third International Sepsis and Septic Shock Consensus Statement after February 28, 2016 [8]. Two or more points increase in the Sequential Organ Failure Assessment (SOFA) score, two or three points increase in the Quick SOFA (qSOFA) score, and at least two or more points increase in the systemic inflammatory response syndrome (SIRS) score with suspected infection were used for the definition of sepsis [5, 8]. For qSOFA, the following data were used: 1 point for each of (i) systolic arterial blood pressure ≤100 mm Hg, (ii) respiratory rate > 21 breaths/minute, and (iii) altered mental status. For the SIRS score, the following data were used: 1 point for each of (i) fever >38.0 °C or hypothermia <36.0 °C, (ii) tachycardia >90 beats/minute, (iii) tachypnea >20 breaths/minute or pCO_2 <32 mm Hg, and (iv) leukocytosis >12,000/mm^3 or leucopoenia <4000/mm^3. The Charlson Comorbidity Index (CCI) was used to evaluate the patients' comorbidities [9].

Case record forms included demographical (sex and age) data, clinical findings, data on qSOFA and SIRS scores and infection sites, and biochemical findings [C-reactive protein (CRP) levels, blood leucocyte levels, and lactate levels] of patients with septic shock at the time of septic shock diagnosis (at the first visit referred to at the time of septic shock diagnosis after here), as well as microbiological culture results and day 30 mortality.

The study inclusion and exclusion criteria were as follows:

Inclusion criteria:

- Age ≥18 years old (only adult patients were included)
- Meeting the criteria of the septic shock defined earlier
- Bacterial culture positivity for CRGNP in clinical specimens
- Among the positive results of urinary cultures, peripheral or catheter blood cultures, and respiratory specimen cultures, meeting the criteria of community-acquired pneumonia (CAP)/hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) or urinary tract infection (UTI) or bloodstream infection or catheter-related bloodstream infection (CRBI) defined later [10–13].

Exclusion criteria:

- Presence of a noninfectious source of shock such as cardiogenic, hypovolemic, or neurogenic
- Referral from our center to other centers due to the lack of available beds in intensive care units (ICUs).

Diagnostic criteria for infection types

The diagnosis of CAP was made based on a history of cough, dyspnea, pleuritic pain, or acute functional or cognitive decline, with abnormal vital signs (e.g. fever and tachycardia), lung examination, and radiological findings [10]. HAP was defined as pneumonia not incubating at the time of hospital admission and occurring 48 h or more after admission, while VAP was defined as pneumonia occurring >48 h after endotracheal intubation [11]. UTI criteria were based

on findings as significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract, such as new onset or worsening of fever, rigors, altered mental status, malaise, lethargy with no other identified cause, flank pain, costovertebral angle tenderness, acute hematuria, and pelvic discomfort and dysuria, urgent or frequent urination, or suprapubic pain or tenderness in those whose catheters had been removed [12]. Bloodstream infection was defined as the positivity of a microbial pathogen in blood culture by virtue of infection, not specimen contamination. Finally, CRBI was defined as bloodstream infection attributed to an intravascular catheter by quantitative culture of the catheter tip or by differences in growth between the catheter and peripheral blood culture specimens [13].

Microbiological evaluation, sensitivity tests, and definition of adequate antibiotic regimen

Antibiotic sensitivity tests were performed using the VITEK2 (BioMerieux, France) system. Antibacterial susceptibility tests were evaluated according to the Clinical Laboratory Standards Institute criteria until 2014 and EUCAST between 2015 and 2021 [14]. Carbapenem minimum inhibitory concentration levels were determined by gradient tests (E test, BioMerieux, France).

Antimicrobial treatment started at the first visit/time of septic shock consultation and, to which the causative pathogen was found to be sensitive in antibiotic susceptibility tests, was defined as an adequate regimen [14]. Multidrug resistance (MDR) was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories [15]. The following antibiotics were considered to be Gram-negative bacteria–oriented antibiotics: carbapenems (meropenem, imipenem, and ertapenem), colistin, aminoglycosides (amikacin and gentamicin), cephalosporins (ceftazidime, cefepime, and cefoperazone), piperacillin–tazobactam, tigecycline, fosfomycin, quinolones (ciprofloxacin, levofloxacin, and moxifloxacin), trimethoprim-sulfamethoxazole, and rifampicin. Regardless of susceptibility data, treatment with one of these antibiotics was considered to be 'empirical antibiotic therapy comprising Gram-negative bacteria–oriented antibiotics.'

Ethics

The local Institutional Review Board approved the study (21-6.1 T/63 on June 25, 2021).

Statistical analysis

The SPSS 23.0 program (Statistical Package for the Social Sciences) was used for the statistical analysis. The categorical values between the two groups were compared using the Chi-square test. The Student *t* test was used for comparing the numerical values in the independent groups. Statistical analysis was performed via univariate and binary logistic regression analysis. A *P* value less than 0.05 indicated a significant difference.

Binary logistic regression analysis was performed using the enter method. Mortality was the dependent variable, and the variables with a *P* value <0.05 in univariate analysis were used as covariates.

Results

General characteristics

A total of 120 patients (mean age 64.29 ± 1.35 years and 58.3% female) fulfilled the study inclusion criteria (Table 1). The mean SOFA and CCI scores at the first visit were 10.72 ± 0.39 and 2.18 ± 0.24, respectively. All the patients had a SIRS score of 2 or more at the first visit. The mean CRP, leukocyte count, and procalcitonin levels at the first visit were 132.34 ± 10.96 mg/L, $14{,}008 \pm 937/mm^3$, and 28.74 ± 6.17 µg/L, respectively. The arterial lactate levels were available in 92 patients at the first visit, and the mean level was 6.70 ± 1.29 mg/dL. Fifty-three patients were documented between 2013 and 2017 and 67 patients between 2018 and 2021 (Table 1).

Underlying diseases

A total of 53 patients had at least one underlying disease. The mortality rate among these versus others did not differ significantly (79%, 42/53 versus 84%, 56/67, $P = 0.542$). The most common three underlying

Table 1. Demographical features of the patients.

Patient characteristic	Value
Age (year), mean ± standard deviation	64.29 ± 1.35
Sex, number (*n*) and percentage (%)	
Female	70 (58.3%)
Male	50 (41.7%)
Comorbidities, (*n*, %)	
Solid-organ malignancy	29 (24.2%)
Coronary artery disease	21 (17.5%)
Diabetes mellitus	15 (12.5%)
Chronic renal failure	6 (5%)
Charlson Comorbidity Index, mean ± standard deviation	2.18 ± 0.24 points
Patients' enrollment years, (*n*, %)	
2011–2017	53 (44.2%)
2018–2021	67 (55.8%)

Table 2. Univariate analysis for day 30 mortality.

Variables (*n*, %)		Day 30 mortality		*P* value	Odds ratio (OR)	95% Confidence interval (CI)
		Present	Absent			
Age	**(year)**	64.44 ± 1.55	63.64 ± 2.62	0.818	1.004	0.973–1.035
Sex	**Male**	44 (88%)	6 (12%)	0.136	0.460	0.166–1.275
	Female	54 (77%)	16 (23%)			
Charlson Comorbidity Index		2.42 ± 0.27	1.09 ± 0.4	**0.040**	1.272	1.011–1.600
Charlson Comorbidity Index <3 points	**Present**	60 (75%)	20 (25%)	**0.017**	0.158	0.035–0.714
	Absent	38 (95%)	2 (5%)			
At least one underlying disease	**Present**	42 (79%)	11 (21%)	0.543	0.750	0.297–1.894
	Absent	56 (84%)	11 (16%)			
Solid-organ malignancy	**Present**	26 (90%)	3 (10%)	0.211	2.287	0.625–8.372
	Absent	72 (79%)	19 (21%)			
Coronary artery disease	**Present**	17 (81%)	4 (19%)	0.926	0.944	0.284–3.145
	Absent	81 (82%)	18 (18%)			
Diabetes mellitus	**Present**	11 (73%)	4 (27%)	0.377	0.569	0.163–1.990
	Absent	87 (83%)	18 (17%)			
Chronic renal failure	**Present**	5 (83%)	1 (17%)	0.914	1.129	0.125–10.176
	Absent	93 (82%)	21 (18%)			
Nosocomial infection	**Present**	85 (82%)	19 (18%)	0.963	1.032	0.268–3.984
	Absent	13 (81%)	3 (19%)			
Leucocyte level	**(/mm^3)**	13,636 ± 1037	15,668 ± 2198	0.404	1.000	1.000–1.000
Leucocyte level as >12.000/mm^3 or <4000/mm^3	**Present**	60 (81%)	14 (19%)	0.833	0.902	0.346–2.354
	Absent	38 (83%)	8 (17%)			
C-reactive protein	**(mg/L)**	134.6 ± 11.08	122.07 ± 26.79	0.631	1.001	0.997–1.005
Procalcitonin	**(ug/L)**	27.2 ± 6.8	35.8 ± 15.6	0.592	0.994	0.970–1.017
Lactate levels	**mmol/L**	7.49 ± 1.61	3.67 ± 0.42	**0.171**		
Lactate >4 mg/dL	**Present**	31 (70%)	13 (30%)	**0.042**	3.937	1.054–14.700
	Absent	42 (88%)	6 (12%)			
SOFA score		11.22 ± 0.43	9 ± 0.79	**0.023**	1.249	1.032–1.512
SOFA score <11 points	**Present**	28 (72%)	11 (28%)	0.237	0.509	0.166–1.561
qSOFA = 1 point	**Present**	11 (69%)	5 (31%)	0.160	0.430	0.132–1.396
	Absent	87 (84%)	17 (16%)			
qSOFA = 2 points	**Present**	39 (80%)	10 (20%)	0.626	0.793	0.312–2.014
	Absent	59 (83%)	12 (17%)			
qSOFA = 3 points	**Present**	48 (87%)	7 (13%)	0.149	2.057	0.772–5.485
	Absent	50 (77%)	15 (23%)			
Systemic inflammatory response syndrome score 3 or 4	**Present**	61 (88%)	8 (12%)	**0.031**	2.885	1.105–7.534
	Absent	37 (73%)	14 (27%)			
Adequate empirical regimen	**Present**	41 (72%)	16 (28%)	**0.012**	0.270	0.097–0.748
	Absent	57 (90%)	6 (10%)			
Empirical treatment with combination Gram-negative bacteria–oriented antibiotic therapy	**Present**	58 (74%)	20 (26%)	**0.012**	0.145	0.032–0.655
	Absent	40 (95%)	2 (5%)			
Empirical treatment with combination of three Gram-negative bacteria–oriented antibiotic therapy	**Present**	23 (82%)	5 (18%)	0.941	1.043	0.347–3.136
	Absent	75 (82%)	17 (18%)			
Empirical treatment including colistin	**Present**	52 (87%)	8 (13%)	0.161	1.978	0.761–5.141
	Absent	46 (74%)	14 (26%)			
Empirical treatment including double carbapenem	**Present**	13 (87%)	2 (13%)	0.595	1.529	0.319–7.325
	Absent	85 (81%)	20 (19%)			
Empirical treatment including tigecycline	**Present**	35 (81%)	8 (19%)	0.954	0.972	0.372–2.544
	Absent	63 (82%)	14 (18%)			
Peripheral blood or catheter culture positivity	**Present**	37 (84%)	7 (16%)	0.602	1.300	0.485–3.483
	Absent					
Urinary culture positivity	**Present**	40 (85%)	7 (15%)	0.436	1.478	0.553–3.951
	Absent					
Respiratory tract culture positivity	**Present**	30 (73%)	11 (27%)	0.088	0.441	0.172–1.129
	Absent					
***Acinetobacter* spp. culture positivity**	**Present**	49 (83%)	10 (17%)	0.700	1.200	0.474–3.035
	Absent					
***Klebsiella* spp. culture positivity**	**Present**	47 (85%)	8 (15%)	0.327	1.613	0.621–4.190
	Absent					
***Pseudomonas aeruginosa* culture positivity**	**Present**	11 (69%)	5 (31%)	0.160	0.430	0.132–1.396
	Absent					
Receiving antibiotics within the first hour of vasopressor treatment	**Present**	8 (73%)	3 (27%)	0.492	0.602	0.142–2.562
	Absent					

(*continued*)

Table 2. Continued.

Variables (*n*, %)		Day 30 mortality: Present	Day 30 mortality: Absent	*P* value	Odds ratio (OR)	95% Confidence interval (CI)
Septic shock diagnosis in the emergency department	**Present**	11 (85%)	2 (15%)	0.718	0.571	0.028–11.849
	Absent					
Concomitant culture positivity for Gram-positive pathogens and/or yeasts	**Present**	15 (94%)	1 (6%)	0.250	3.443	0.419–28.280
	Absent	61 (81%)	14 (19%)			
Groups of the patients according to years	**2013–2017**	45 (85%)	8 (15%)	0.416	0.673	0.259–1.749
	2018–2021	53 (79%)	14 (21%)			

diseases were solid-organ malignancy 24.2% (29/120), coronary artery disease 17.5% (21/120), and diabetes mellitus 12.5% (15/120) (Table 1). Chronic renal failure, solid-organ malignancy, coronary artery disease, diabetes mellitus, or organ transplant were not associated with significantly higher mortality in the univariate analysis (Table 2).

Pathogens

The infecting pathogens were *Acinetobacter* spp. (49.2%, 59/120), *Klebsiella* spp. (45.8% 55/120), and *Pseudomonas aeruginosa* (13.3%, 16/120). All strains were MDR. The sources of the positive bacteriological culture results for CRGNP were urine cultures (39.1%, 47/120), peripheral or catheter blood cultures (36.7%, 44/120), and respiratory tract specimens' cultures (34.2%, 41/120). Among the patients with positive peripheral or catheter blood cultures, the concomitant bacterial culture positivity rate was 36.4% (16/44) for urinary cultures, 22.7% (10/44) for respiratory tract cultures, and 15.9% (7/44) for other cultures. Further, *Acinetobacter* spp. culture positivity was found to be significantly higher in the respiratory tract specimens versus others (46%, 27/59 versus 23%, 14/61, $P = 0.008$).

Concomitant culture positivity for Gram-positive pathogens and/or yeasts was recorded in 16 patients, and the mortality rate did not differ significantly among these versus others (94%, 15/16 versus 81.3%, 61/75, $P = 0.456$).

Mortality and results of the univariate analysis

The mortality rate was 29.2% after 72 h, while the overall day 14 and day 30 mortality rate was 55.8% and 81.7%, respectively. The day 30 mortality rate among the patients was found as 85% (45/53) in the 2013–2017 cohort versus 79% (53/67) in the 2018 and after cohort a, but the difference was not found to be statistically significant in the univariate analysis ($P = 0.414$, Table 2).

Mortality versus risk assumption scores

The mean SOFA and CCI scores as well as the mean lactate level at the first visit were significantly higher in the day 30 mortality group versus others (Table 2). In 81 patients, the arterial lactate level at the first visit was higher than 2 mg/dL, but the day 30 mortality rate among these versus others was similar (64/81, 79% versus 9/11, 82%, $P = 1.000$). However, the day 30 mortality rate was significantly lower among the patients with CCI <3 points versus others (60/80 vs 38/40, $P = 0.017$) and among the patients with a lactate level 2–4 mg/dL than >4 mg/dL (31/44 vs 42/48, $P = 0.049$). The qSOFA score was 3 at the first visit in 55 patients; the mortality rate was 87% among these and 77% in others ($P = 0.149$). The SIRS score was 3 or 4 in 69 patients at the first visit, and the mortality rate was significantly higher in this cohort compared with those with the SIRS score 2 (8/69 vs 14/51, $P = 0.026$). Besides, the mean SOFA score at the first visit was significantly higher among the patients with mortality versus survivors (11.22 ± 0.43 vs 9 ± 0.79, $P = 0.017$).

Mortality versus infectious source and etiology

Among the 44 patients with bloodstream or CRBI, the day 30 mortality rate was 84% (37/44). The day 30 mortality rate of *P. aeruginosa* culture–positive patients was significantly lower versus others (2/5, 40% vs 35/39, 90%, $P = 0.023$) in this subgroup, but no significant difference was found between *Acinetobacter* spp. culture–positive patients and others (18/19, 95% vs 19/25, 76%, $P = 0.119$) and *Klebsiella* spp. culture–positive patients and others (21/24, 88% vs 16/20, 80%, $P = 0.684$).

Among the 41 patients with community- or hospital-acquired and/or VAP, the day 30 mortality rate was 73% (30/41). No significant difference was found between *Acinetobacter* spp. culture–positive patients and others (20/27, 74% vs 10/14, 71%, $P = 1.000$), *Klebsiella* spp. culture–positive patients and others (8/11, 88% vs 22/30, 73%, $P = 1.000$), and *P. aeruginosa*

culture–positive patients and others (7/9, 78% vs 23/32, 72%, $P = 1.000$).

Among the 47 patients with UTI, the day 30 mortality rate was 85% (40/47). The mortality rates of *Acinetobacter* spp. culture–positive patients versus others (11/13, 85% vs 29/34, 85%, $P = 1.000$), *Klebsiella* spp. culture–positive patients versus others (31/34, 91% vs 9/13, 69%, $P = 0.080$), and *P. aeruginosa* culture–positive patients versus others (3/5, 60% vs 37/42, 69%, $P = 0.154$) did not differ significantly.

Concomitant culture positivity was detected in 10 patients. Among these, respiratory, urinary, and peripheral/catheter blood culture positivity was recorded in six, four, and five patients, respectively. The mortality rate in this subgroup versus others did not differ significantly (9/10, 90% vs 89/110, 80.9%, $P = 0.687$).

Mortality versus infectious source and etiology in antibacterial treatment

Antibiotic therapy was started within the first hour of vasopressor treatment in 11 (9.2%) patients, but mortality did not differ among these versus others (Table 2). Adequate regimen was significantly more common between 2013–2017 versus 2018 and after ($P < 0.001$). A total of 63 patients (52.5%) had inadequate regimens (not covering the pathogen) at the first visit, and the day 30 mortality rate among these was significantly higher than that among others (57/63, 90.4% vs 41/57, 71.9%, $P = 0.012$). Regardless of sensitivity results, the mortality rate among the patients who had received Gram-negative bacteria–oriented empirical monotherapy was higher than that among the patients who had received Gram-negative bacteria–oriented combination empirical antibiotic therapy (40/42, 95.2% vs 58/78, 74.4%, $P = 0.012$).

In the subgroup of *Klebsiella* spp. culture–positive patients ($n = 55$), no statistically significant difference was observed in the day 30 mortality rate among the group receiving empirical double carbapenem treatment versus others (12/14 vs 35/41, $P = 1.000$). Finally, colistin-containing empirical antibiotic regimens (vs others) as well as tigecycline-containing empirical antibiotic regimens (vs others) had no significant effect on day 30 mortality (Table 2).

Mortality versus other variables

Sex, age, underlying diseases, septic shock diagnosis in the Emergency Service (vs others), acquiring nosocomial infection–related septic shock, procalcitonin and CRP levels, and leukocyte counts at the first visit did not change the day 30 mortality rate significantly (Table 2). The univariate analysis results of all evaluated variables for day 30 mortality are shown in Table 2.

Table 3. Binary logistic regression analysis for day 30 mortality.

Variable	*P* value	Odds ratio	95% CI
Empirical treatment with one Gram-negative bacteria–oriented antibiotic therapy	**0.016**	**17.730**	1.728–182.691
Charlson Comorbidity Index >2	**0.032**	**7.312**	1.181–45.279
Systemic Inflammatory Response Syndrome score 3 or 4	**0.014**	**5.675**	1.424–22.619
Inadequate empirical antibacterial regimen	0.612	1.406	0.377–5.237
Having a lactate level >4 mg/dL	0.232	2.456	0.562–10.730

Multivariate analysis for mortality

In the logistic regression analysis, empirical treatment via mono Gram-negative bacteria–oriented antibiotic therapy [$P = 0.016$, odds ratio (OR) = 17.730, 95% CI = 1.728–182.691], CCI >2 ($P = 0.032$, OR = 7.312, 95% CI = 5.7–18.3), and SIRS score 3 or 4 ($P = 0.014$, OR = 5.675, 95% CI = 1.424–22.619) at the first visit were found to be independent risk factors for day 30 mortality (Table 2). On the contrary, variables such as adequate empirical regimen and having a lactate level >4 mg/dL at the first visit did not affect mortality significantly (Table 3).

Discussion

The Turkish Ministry of Finance is responsible for the payback of more than 90% of the health expenditures of the country population. According to their instructions to regulate the use of parenteral antibiotics inside and outside of the hospitals, the reimbursement of extended-spectrum antibiotics (vancomycin, teicoplanin, meropenem, imipenem, antifungals, etc.) is made only with the prior approval of an infectious diseases specialist (IDS) since the year 2003 in Turkey. Hence, all patients with septic shock who received extended-spectrum antibiotics, who were consulted by IDSs, were included in the study [16–18].

Empirical antibiotic treatment should cover possible bacterial pathogens in sepsis and septic shock. MDR Gram-negative bacilli should be explicitly considered during the care of patients with sepsis and septic shock, especially in hospital-acquired cases, via the use of local or hospital epidemiologic data [16]. Hence, after analyzing our data in 2017, we adopted our empirical treatment regimen to cover CRGNP in the management of septic shock developing in most parts of the hospital. This was probably the main

reason for the higher rates of adequate regimens during 2018 and after.

Gualtero et al. evaluated 131 patients with carbapenem-resistant Enterobacteriaceae (CRE) infections and reported the overall day 30 mortality rate as 38.17%. Mortality was found to be associated with septic shock (OR 26.7, $P < 0.01$), CCI $\geq$3, and post-chemotherapy febrile neutropenia in the multivariate analysis [19]. Similarly, in a retrospective cohort study including 115 patients with pan-drug-resistant *K. pneumoniae* bacteremia, the day 30 mortality rate was 39.1%. Furthermore, the day 30 mortality rate was 54.9% in the septic shock subgroup comprising 51 patients. The development of septic shock (OR: 5.2; 95% CI: 1.8–15, $P = 0.002$), bacteremia other than primary or catheter-related (OR: 6.4; 95% CI: 2–20.2, $P = 0.001$), and one-point increase in CCI (OR:1.2; 95% CI: 1–1.3, $P = 0.012$) were found to be independent risk factors, whereas the combination of minimum three antimicrobials (OR: 0.105; 95% CI: 0.032–0.344, $P < 0.001$) was found to be a protective factor in terms of mortality [20]. Sabino et al. analyzed the clinical outcomes of 1.190 sepsis episodes, 69 of which were caused by CRE. They reported a significantly higher day 30 mortality rate (63.8% vs 33.4%, $P < 0.01$) that was associated with the presence of septic shock ($P < 0.01$) and a lower rate of appropriate empirical therapy ($P < 0.01$) among the patients with CRE infections [21]. Falcone et al. evaluated 111 ICU patients with septic shock caused by carbapenemase-producing *K. pneumoniae* (KPC-Kp) and concluded that treatment with at least two antibiotics displaying *in vitro* activity against the KPC-Kp isolates was one of the most important protective factors for mortality (HR: 0.08, 95% CI: 0.02–0.21, $P < 0.001$) [22]. Oliva et al. evaluated 90 patients with septic shock caused by KPC-Kp and carbapenem-resistant *Acinetobacter baumannii*. They reported the overall mortality rate as 48.9%. The treatment using at least two *in vitro* active antibiotics (HR: 0.21, 95% Cl: 0.06–0.73, $P = 0.014$) was found to be a protective factor for mortality in the multivariate analysis [23]. The very recent 2021 Surviving Sepsis Campaign Guidelines also recommend using two antimicrobials with Gram-negative coverage for empiric treatment over one Gram-negative coverage empirical agent for patients at high risk of exposure to MDR organisms. In concordance with recent guidelines' recommendations as well as the results of Falcone et al. [22] and Oliva et al. [23], we found that the patients who received empirical therapy with one Gram-negative bacteria–oriented antibiotic and had a score of CCI or SIRS above 2 points were associated with higher mortality in the multivariate analysis. However, empirical treatment with a combination of three Gram-negative bacteria–oriented antibiotics was not associated with less mortality. Besides, the mean CCI score was found to be 2.42 ± 0.27 among the patients with mortality versus 1.09 ± 0.40 among the survivors ($P = 0.04$).

Another critical change in 2021 guidelines was the recommendation of not using qSOFA but using SIRS, National Early Warning Score (NEWS), or The Modified Early Warning Score (MEWS) as a single screening tool for sepsis or septic shock [24]. A systematic review and meta-analysis showed that SIRS was significantly superior to qSOFA for sepsis diagnosis (risk ratio = 1.32, 95% CI: 0.40–2.24, $P < 0.001$, $I^2 = 100\%$) whereas qSOFA was more specific but less sensitive than having two of four SIRS criteria for the early identification of infection-induced organ dysfunction [24, 25]. In our study, all patients had a SIRS score of 2 or more. The mortality rate among the patients having an SIRS score 3 or 4 was 88% (61/69) versus 73% (37/51) among those with an SIRS score 2 points ($P = 0.026$).

Double carbapenem therapy (DCT) is considered to be among alternative salvage therapy options for treating CRE infections. However, a systematic review and meta-analysis comprising 315 patients showed that the clinical and microbiological responses were similar between DCT and other regimens in CRE infections while lower mortality was detected in the DCT group (OR = 0.44, 95% CI: 0.24–0.82, $P = 0.009$) [26]. In our study, we did not find a significant difference in mortality in the group that received DCT empirically ($P = 0.595$). Not only the CRE and urinary tract infections but also CRGNP and other sources of infections were evaluated in our study. This might have been the reason of our relatively discordant results.

Zak-Doron et al. evaluated the association of empirical antibiotic coverage with mortality in a prospective study including a cohort of 406 patients with CRGNP (77% *Acinetobacter*). They showed that the empirical use of colistin, with or without a carbapenem, was not associated with survival in severe CRGNP infections [27]. In fact, they reported that covering antibiotics (defined as being susceptible *in vitro* to the antibiotics used) were not significantly associated with mortality (OR, 1.42; 95% CI: 0.91–2.22) in the propensity score–matched subcohort with 338 patients [27]. In our study, inadequate empirical antibacterial treatment was found as a risk

factor in the univariate analysis for day 30 mortality; however, the multivariate analysis did not reveal a statistically significant effect.

Balkhair et al. evaluated 227 patients with bacteremia (87.2%, healthcare-associated) having carbapenem-resistant *P. aeruginosa*, *A. baumannii*, or *K. pneumoniae*. They reported the day 30 mortality rate among healthcare-associated CRGNP as 119/198 (60.1%) with the subgroup rates of *P. aeruginosa* (22/26, 61.1%), *A. baumannii* (58/105, 55.2%), and *K. pneumoniae* (39/57, 68.4%) [28]. Our study comprised not all but only patients with septic shock–associated CRGNP. Among the 44 patients with peripheral or catheter blood culture positivity, the day 30 mortality rate was 95% for *Acinetobacter* spp. culture–positive patients and 88% for *Klebsiella* spp. culture–positive patients; while the mortality rate of *P. aeruginosa* culture–positive patients was recorded as 40%. Although we could not analyze the resistance data for each antibiotic in our study, one of the possible explanations for this difference might have been the multidrug resistance pattern of *Acinetobacter* isolates. Boral et al. showed that colistin was the most susceptible antibiotic (98.8%) in a multicenter study from Turkey [29]. On the contrary, Acar et al. analyzed the antimicrobial resistance trends for *P. aeruginosa* isolates in Turkey. They reported pooled resistance to piperacillin–tazobactam, ceftazidime, cefepime, ciprofloxacin, gentamicin, amikacin, tobramycin, and colistin as 33.9%, 38.6%, 35.6%, 30.7%, 28.2%, 17.8%, 15.7%, and 2.2%, respectively [30]. Thus, susceptibility to other antibiotics such as anti-pseudomonal cephalosporins or aminoglycosides or quinolones, besides colistin, might be another explanation for the relatively lower mortality rate in the *P. aeruginosa* subgroup in our study.

Colistin-containing treatment (polymyxin b was not available in the country during the study period) can be preferred particularly in *Acinetobacter* spp. infections. However, emerging data suggest that the combination of a cephalosporin and β-lactamase inhibitor such as ceftazidime–avibactam confers a better safety profile and a lower day 30 hospital mortality rate (9% vs 32%, $P = 0.001$) compared with colistin in treating CRE-infected patients [31–33]. Pogue et al. evaluated the MDR and/or extensively drug-resistant *P. aeruginosa*–infected patients and found that ceftolozane/tazobactam treatment was independently associated with clinical cure (aOR: 2.63; 95% CI = 1.31–5.30) and protective against acute kidney injury (aOR: 0.08; 95% CI = 0.03–0.22), which supported the use of ceftolozane–tazobactam over polymyxins or aminoglycosides for drug-resistant *P. aeruginosa* infections [34]. The recent Infectious Diseases Society of America guidelines recommend ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–cilastatin–relebactam for both CRE and difficult-to-treat (DTR) *P. aeruginosa* infections [35]. In our study, although the empirical Gram-negative bacteria–oriented combination treatment was found to be a protective factor, empirical treatment including colistin was not found to be a significant risk factor for the septic shock associated with CRGNP ($P = 0.161$). Unfortunately, ceftazidime–avibactam, ceftolozane–tazobactam, and meropenem–vaborbactam were not available in our country during the study period. We also believed that this was probably associated with our relatively higher day 30 mortality rate compared with results of van Duin et al. [31] and Pogue et al. [34] The lack of these new antibiotics might also have contributed to the relatively lower decrease in day 30 mortality in 2013–2017 versus 2018–2021 in our study.

Alataby et al. analyzed the clinical outcomes of 427 patients with sepsis and septic shock. They reported that the elevated level of serum lactate (>4 mmol/L) was an independent predictor for the day 30 mortality (aOR: 3.19) [36]. Moreover, a prospective, observational, nonrandomized controlled study from France with 183 patients with septic shock revealed that a pre-hospital blood lactate level ≥4 mmol/L significantly predicted the day 30 mortality rate ($P = 0.04$) [37]. In our study, the lactate level >4 mg/dL was found to be a risk factor in the univariate analysis for day 30 mortality but not in the multivariate analysis.

This study had several limitations. (1) It had a retrospective design. (2) We could not investigate the outcomes of regimens such as ceftazidime–avibactam, ceftolozane–tazobactam, or meropenem–vaborbactam because they were not available during the study period. (3) The mortality rates were recorded as all-cause mortality (autopsy could not be performed). (4) The antimicrobial resistance patterns of the infecting strains were not analyzed specifically. However, this was one of the rare studies performed solely on patients with septic shock and carbapenem-resistant Gram-negative bacteria.

Conclusions

In conclusion, despite early diagnosis and effective management of patients with septic shock, the mortality rates were quite high in CRGNP-infected patients. Empirical treatment with one Gram-negative

bacteria–oriented antibacterial therapy, SIRS score 3 or 4, and CCI ≥3 were found to be the independent risk factors for day 30 mortality in the multivariate analysis of our cohort. Effective and feasible infection control measures are needed to decrease CRGNP infections in developing countries. Finally, as Gram-positive bacteria–oriented antibacterials, globally accessible and effective carbapenem-resistant bacteria–oriented antibiotics are needed urgently.

Disclosure statement

The authors report no conflicts of interest.

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