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CLINICAL THERAPEUTICS

Comparison of Septic Shock Due to Multidrug-Resistant *Acinetobacter baumannii* or *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* in Intensive Care Unit Patients

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ABSTRACT A significant cause of mortality in the intensive care unit (ICU) is multidrug-resistant (MDR) Gram-negative bacteria, such as MDR *Acinetobacter baumannii* (MDR-AB) and *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp). The aim of the present study was to compare the clinical features, therapy, and outcome of patients who developed septic shock due to either MDR-AB or KPC-Kp. We retrospectively analyzed patients admitted to the ICU of a teaching hospital from November 2010 to December 2015 who developed septic shock due to MDR-AB or KPC-Kp infection. Data from 220 patients were analyzed: 128 patients (58.2%) were diagnosed with septic shock due to KPC-Kp, and 92 patients (41.8%) were diagnosed with septic shock due to MDR-AB. The 30-day mortality rate was significantly higher for the MDR-AB group than the KPC-Kp group (84.8% versus 44.5%, respectively; $P < 0.001$). Steroid exposure and pneumonia were associated with MDR-AB infection, whereas hospitalization in the previous 90 days, primary bacteremia, and KPC-Kp colonization were associated with KPC-Kp infection. For patients with KPC-Kp infections, the use of ≥2 *in vitro*-active antibiotics as empirical or definitive therapy was associated with higher 30-day survival, while isolation of colistin-resistant strains was linked to mortality. Patients with MDR-AB infections, age >60 years, and a simplified acute physiology score II (SAPS II) of >45 points were associated with increased mortality rates. We concluded that septic shock due to MDR-AB infection is associated with very high mortality rates compared to those with septic shock due to KPC-Kp. Analysis of the clinical features of these critically ill patients might help physicians in choosing appropriate empirical antimicrobial therapy.

KEYWORDS septic shock, *Acinetobacter*, *Klebsiella*, intensive care unit, multidrug resistant

The dysregulated host response to infection leading to sepsis and septic shock is a life-threatening event that, despite advances in organ support and antimicrobial therapy, is associated with a mortality rate of >30% (1).

In recent years, infections due to multidrug-resistant (MDR) Gram-negative pathogens, such as MDR *Acinetobacter baumannii* (MDR-AB) and *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp), have been increasingly observed among critically ill patients admitted to the intensive care unit (ICU) (2–5).

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The management of critically ill patients includes early diagnosis and immediate administration of antimicrobials (6, 7). Previous observations about septic patients with infections due to MDR Gram-negative bacteria highlighted the crucial role of timely empirical antimicrobial treatment and the importance of a definitive anti-infective therapy with *in vitro* activity against the microbial isolates, emphasizing also the importance of an adequate and early source control of infection (8–10). Moreover, the pharmacokinetic and pharmacodynamic properties of antibiotics should be considered because of changes in clearance and volume of distribution that are frequently observed in critically ill patients, with the potential to influence concentration of the drug at site of infections (11). Of interest, apart from an inadequate antimicrobial treatment, KPC-producing isolates seem to be highly virulent in a low-tumor necrosis factor alpha (low-TNF-α)-release environment, suggesting an immunoparalysis induction mechanism (12).

Recently, new drugs for the treatment of severe infections due to MDR Gram-negative pathogens have been approved: most of these new agents show activity against KPC-Kp (13). Equally important, new agents with activity against MDR-AB strains have been developed and might be available for therapy in the near future (14–16). Thus, it is important for physicians to recognize peculiar clinical characteristics of MDR-AB or KPC-Kp infections in ICU patients with sepsis or septic shock in order to promptly use antibiotics which are potentially active *in vitro*. Based on this scenario, the aim of this study was to analyze the clinical features and outcomes of ICU patients who developed septic shock due to MDR-AB or KPC-Kp infections.

RESULTS

During the study period, 193 bacteremic KPC-Kp infections were observed. Out of these, 104 (53.8%) infections were primary bacteremias and 89 (46.2%) infections were secondary bacteremias; 121 (62.7%) infections were associated with septic shock. In the MDR-AB group, 146 bacteremic infections were documented. Among them, 35 (23.9%) infections were primary bacteremias, and 114 (78.1%) infections were secondary bacteremias; 84 (57.5%) bacteremic infections were complicated by septic shock. Additionally, nonbacteremic infections associated with septic shock were reported in 15 patients, with 7 (46.7%) caused by KPC-Kp and 8 (53.3%) caused by MDR-AB.

A total of 220 patients developed septic shock and met our inclusion criteria: 128 (58.2%) patients were diagnosed with KPC-Kp infection, while in 92 (41.8%) patients, an MDR-AB infection was observed. KPC-Kp strain susceptibility tests showed the following resistance rates: colistin, 44.5%; gentamicin, 45.8%; and amikacin, 99.8%. All strains displayed susceptibility to tigecycline using the Etest technique. The meropenem MICs were $\geq$16 μg/ml for all KPC-Kp isolates. Conversely, for MDR-AB strains, the following resistance rates were documented: colistin, 1.1%; gentamicin, 87.9%; amikacin, 89.3%; rifampin, 88.2%; and meropenem, 99.8%. On this basis, 44.5% of *K. pneumoniae* strains were classified as pandrug resistant (PDR) and 55.5% as extensively drug resistant (XDR), while 98.9% of *A. baumannii* strains were considered XDR and 1.1% considered PDR.

As reported in Tables 1, no differences in age, sex, comorbidities, SAPS II score, or cause of ICU admission (except for stroke) were shown between patients with septic shock due to KPC-Kp and MDR-AB; patients with septic shock due to KPC-Kp were statistically significantly more likely to be hospitalized in the previous 90 days (43.8% versus 19.6%, respectively; $P < 0.001$), to be colonized at time of ICU admission (48.4% versus 4.3%, respectively; $P < 0.001$), and to be exposed to steroids during ICU stay (11.7% versus 63%, respectively; $P < 0.001$) than were patients with septic shock due to MDR-AB. Regarding the source of infection, septic shock patients with KPC-Kp isolation showed a higher frequency of primary bacteremia (49.2% versus 18.5%, respectively; $P < 0.001$), central venous catheter (CVC)-related bloodstream infections (19.5% versus 4.3%, respectively; $P = 0.001$), catheter-associated urinary tract infections (21.1% versus 0%, $P < 0.001$), and skin and soft tissue infections (14.1% versus 2.1%, respectively; $P < 0.001$) than did those with MDR-AB septic shock. Conversely, pneu-

TABLE 1 Comparison between KPC-Kp and MDR-AB infections in septic patients hospitalized in the same ICU[a]

Variable[b]	KPC-Kp (n = 128)	MDR-AB (n = 92)	P[c]
Age (mean ± SD) (yr)	60.1 ± 15.9	60.6 ± 17.2	0.8
Male sex	89 (69.5)	64 (69.6)	1.0
Cause of ICU admission			
Respiratory failure	34 (26.5)	17 (18.5)	0.22
Trauma	25 (19.5)	23 (25)	0.43
Septic shock not caused by KPC-Kp or MDR-AB	28 (21.8)	30 (32.6)	0.1
Stroke	9 (7)	0	**0.02**
Cardiac/hemorrhagic shock/postsurgery	32 (25)	22 (23.9)	1.0
Comorbidities			
Chronic liver disease	4 (3.1)	4 (4.3)	0.7
Neoplasm	15 (11.7)	7 (7.6)	0.3
Diabetes	23 (18)	18 (19.6)	0.8
Heart failure	16 (12.5)	13 (14.1)	0.8
Coronary artery disease	46 (35.9)	42 (45.7)	0.1
Chronic renal disease	11 (8.6)	12 (13)	0.3
COPD	22 (17.2)	23 (25)	0.1
Previous hospitalization (90 days)	56 (43.8)	18 (19.6)	**<0.001**
Previous ICU admission (90 days)	13 (10.2)	12 (13)	0.5
Previous surgery (30 days)	50 (39.1)	38 (41.3)	0.7
Previous antibiotic therapy (30 days)	51 (39.8)	45 (48.9)	0.2
Colonization at time of ICU admission	62 (48.4)	4 (4.3)	**<0.001**
Source of infection			
Primary bacteremia	63 (49.2)	17 (18.5)	**<0.001**
CVC-related bacteremia	25 (19.5)	4 (4.3)	**0.001**
Pneumonia	55 (43)	64 (69.6)	**<0.001**
Catheter-related urinary tract	27 (21.1)	0	**<0.001**
SSTI	18 (14.1)	2 (2.1)	**<0.001**
Intra-abdominal	14 (10.9)	5 (5.4)	0.2
Isolation of a colistin-resistant strain	57 (44.5)	1 (1.1)	**<0.001**
Other infections during ICU stay	69 (53.9)	21 (22.8)	**<0.001**
Steroid therapy during ICU stay	15 (11.7)	58 (63)	**<0.001**
Length of hospitalization (mean ± SD) (days)	36.4 ± 23.8	30.2 ± 17.2	**0.03**
Length of ICU stay (mean ± SD) (days)	29.8 ± 23.3	22.9 ± 15.7	**0.01**
Length of antibiotic therapy (mean ± SD) (days)	11.7 ± 8.3	9.8 ± 9.7	0.1
SAPS II at time of infection onset (mean ± SD)	37.1 ± 5.6	39.2 ± 6.3	0.5
SAPS II at time of septic shock onset (mean ± SD)	43.7 ± 10.7	46.4 ± 14.2	0.1
30-day mortality	57 (44.5)	78 (84.8)	**<0.001**

[a]Data are presented as the number (%), unless otherwise stated.
[b]KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; CVC, central venous catheter; SSTI, skin and soft tissue infection; SAPS, simplified acute physiology score.
[c]*P* values in bold are statistically significant.

monia was more frequently diagnosed (69.6% versus 43%, respectively; $P < 0.001$) in septic patients with MDR-AB. The isolation of a colistin-resistant strain was observed only in 1 (1.1%) patient with MDR-AB, compared to 57 (44.5%) out of 128 patients in the KPC-Kp group ($P < 0.001$). Finally, a higher 30-day mortality was found in MDR-AB patients than in those with KPC-Kp (84.8% versus 44.5%, respectively; $P < 0.001$).

The characteristics of the antibiotic regimens used to manage KPC-Kp and MDR-AB infections are reported in Table 2. No differences were observed in the two study groups regarding the use of carbapenems. In the study group of patients with septic shock caused by MDR-AB, a definitive antibiotic regimen containing colistin (79.3% versus 52.3%, respectively; $P < 0001$) or rifampin (39.1% versus 12.5%, respectively; $P < 0.001$) was more frequently used; on the contrary, an antibiotic regimen containing tigecycline (71.1% versus 38%, respectively; $P < 0.001$) or gentamicin (27.3% versus 5.4%, respectively; $P < 0.001$) was mainly used in septic shock patients with KPC-Kp

TABLE 2 Characteristics of antibiotic regimens used during KPC-Kp or MDR-AB infection[a]

Antibiotic therapy[b]	KPC-Kp ($n = 128$)	MDR-AB ($n = 92$)	P[c]
No. of antibiotics used			
Only 1 as definitive therapy	7 (5.5)	9 (9.8)	0.2
2 in combination as definitive therapy	41 (32)	28 (30.4)	0.8
3 in combination as definitive therapy	53 (41.4)	38 (41.3)	1.0
4 in combination as definitive therapy	27 (21.1)	10 (10.9)	0.06
5 in combination as definitive therapy	0	1 (1.1)	0.4
Colistin-containing regimen as definitive therapy	67 (52.3)	73 (79.3)	**<0.001**
Tigecycline-containing regimen as definitive therapy	91 (71.1)	35 (38)	**<0.001**
Gentamicin-containing regimen as definitive therapy	35 (27.3)	5 (5.4)	**<0.001**
Rifampin-containing regimen as definitive therapy	16 (12.5)	36 (39.1)	**<0.001**
Carbapenem-containing regimen as definitive therapy	98 (76.5)	67 (72.8)	0.6
Use of colistin aerosol inhalation therapy	0	13 (14.1)	**<0.001**
≥2 *in vitro*-active antibiotics used within 24 h	48 (37.5)	1 (1.1)	**<0.001**
Definitive therapy with ≥2 antibiotics displaying *in vitro* activity	61 (47.7)	5 (5.4)	**<0.001**
Time to initial definitive therapy (mean ± SD) (days)	2.7 ± 0.8	3.1 ± 0.7	0.08

[a]Data are presented as the number (%), unless otherwise stated. KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.
[b]During the study period, the usual antimicrobial dosages, adopted for the most used antibiotics, were the following: for colistin, a loading dose of 6 to 9 million IU, followed by 3 million IU every 8 h (in the period from 2010 to 2011) or a loading dose of 9 million IU followed by 4.5 million IU every 12 h; for tigecycline, a loading dose of 150 to 200 mg followed by 100 mg every 12 h; for gentamicin, a dosage of 5 mg/kg every 24 h; for rifampin, a dosage of 10 mg/kg/day; for meropenem, a dosage of 2 g every 8 h or 1.5 g every 6 h.
[c]*P* values in bold are statistically significant.

infections. In the first 24 h of infection, an antibiotic regimen with 2 or more antibiotics displaying *in vitro* activity was reported only in 1 patient with MDR-AB (1.1% versus 37.5%, respectively; $P < 0.001$), compared to KPC-Kp infections. Definitive therapy with 2 or more antibiotics displaying *in vitro* activity was more frequently observed in KPC-Kp patients than in those with MDR-AB infection (47.7% versus 5.4%, respectively; $P < 0.001$). In the group of KPC-Kp infections, the combination of colistin, tigecycline, and meropenem more commonly included at least 2 agents with *in vitro* activity (63.5% of patients treated with this regimen) than the combination of colistin, tigecycline, meropenem, and gentamicin (42.4% of in patients treated with this regimen); in the group of MDR-AB infections, the combination which more frequently consisted of at least 2 *in vitro*-active drugs was meropenem, colistin, rifampin, and tigecycline (22.2% of patients treated with this regimen).

The results of a logistic regression analysis about the characteristics of patients with KPC-Kp or MDR-AB infection are reported in Table 3. Hospitalization in the previous 90 days (odds ratio [OR], 5.01; 95% confidence interval [95% CI], 2.15 to 11.6; $P < 0.001$), diagnosis of primary bacteremia (OR, 2.3; 95% CI, 1.1 to 5.5; $P = 0.04$), and KPC-Kp colonization at time of ICU admission (OR, 13.8; 95% CI, 4.3 to 44.7; $P < 0.001$) were associated with diagnosis of septic shock due to KPC-Kp infection; instead, steroid therapy during ICU stay (OR, 0.1; 95% CI, 0.04 to 0.25; $P < 0.001$) and pneumonia as

TABLE 3 Logistic regression analysis of characteristics of KPC-Kp or MDR-AB infection[a]

Variable	OR[b]	95% CI	P
Previous hospitalization (90 days)	5.01	2.15–11.6	<0.001
Steroid therapy during ICU stay	0.1	0.04–0.25	<0.001
Primary bacteremia	2.3	1.1–5.5	0.04
Pneumonia	0.4	0.18–0.96	0.04
KPC-Kp colonization at time of ICU admission	13.8	4.3–44.7	<0.001

[a]KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.
[b]An OR of >1 indicates a factor leading to KPC-Kp over MDR-AB infection, and an OR of <1 indicates a factor leading to MDR-AB over KPC-Kp infection.

TABLE 4 Univariate and multivariate Cox regression analysis about factors associated with outcome at 30 days in KPC-Kp infections[a]

	Univariate			Multivariate		
Variable[b]	HR	95% CI	*P*	HR	95% CI	*P*
Age	0.89	0.45–1.41	0.8			
Male sex	1.25	0.59–2.71	0.56			
Cause of ICU admission						
Respiratory failure	1.42	0.76–2.1	0.09			
Trauma	1.65	0.87–1.98	0.51			
Septic shock not caused by KPC-Kp or MDR-AB	1.11	0.65–1.99	0.65			
Stroke	0.87	0.45–1.32	0.9			
Cardiac/hemorrhagic shock/postsurgery	0.65	0.44–1.97	0.09			
Comorbidities						
Chronic liver disease	2.5	0.22–2.8	0.58			
Neoplasm	0.58	0.18–1.8	0.41			
Diabetes	0.76	0.3–1.91	0.64			
Heart failure	0.78	0.24–2.11	0.6			
Coronary artery disease	0.93	0.45–1.93	1.0			
Chronic renal disease	1.04	0.3–3.6	1.0			
COPD	1.04	0.41–2.63	1.0			
Previous hospitalization (90 days)	1.14	0.56–2.31	0.72			
Previous ICU admission (90 days)	1.51	0.48–4.79	0.56			
Previous surgery (30 days)	1.25	0.61–2.57	0.58			
Previous antibiotic therapy (30 days)	2.01	0.98–4.13	0.07			
Colonization at time of ICU admission	2.27	1.11–4.62	0.03			
Source of infection						
Primary bacteremia	1.45	0.72–2.92	0.37			
CVC-related bacteremia	1.45	0.6–3.49	0.5			
Pneumonia	0.93	0.46–1.89	1.0			
Catheter-related urinary tract	1.45	0.62–3.4	0.39			
SSTI	2.18	0.78–6.06	0.2			
Intra-abdominal	0.46	0.13–1.55	0.26			
Isolation of a colistin-resistant strain	6.38	2.94–13.82	<0.001	25.1	4.9–127.8	<0.001
Other infections during ICU stay	1.17	0.58–2.36	0.72			
Steroid therapy during ICU stay	0.27	0.07–1.02	0.054			
Length of hospitalization	0.76	0.36–1.66	0.6			
Length of ICU stay	1.1	0.31–1.33	0.8			
Length of antibiotic therapy	1.45	0.64–2.2	0.49			
SAPS II at time of infection onset	0.87	0.76–1.45	0.4			
SAPS II at time of septic shock onset	1.11	0.87–2.1	0.5			
Use of only 1 antibiotic as definitive therapy	0.48	0.09–2.57	0.46			
Use of 2 antibiotics in combination as definitive therapy	0.83	0.39–1.76	0.7			
Use of 3 antibiotics in combination as definitive therapy	1.05	0.51–2.13	1.0			
Use of 4 antibiotics in combination as definitive therapy	1.45	0.62–3.4	0.39			
Colistin-containing regimen as definitive therapy	1.02	0.5–2.05	1.0			
Tigecycline-containing regimen as definitive therapy	0.79	0.36–1.7	0.56			
Gentamicin-containing regimen as definitive therapy	1.46	0.67–3.19	0.42			
Rifampin-containing regimen as definitive therapy	1.28	0.45–3.66	0.78			
Carbapenem-containing regimen as definitive therapy	1.66	0.78–3.52	0.19			
≥2 *in vitro*-active antibiotics used within 24 h	0.1	0.04–0.25	<0.001	0.19	0.04–0.85	0.03
Definitive therapy with ≥2 antibiotics displaying *in vitro* activity	0.02	0.009–0.76	<0.001	0.02	0.004–0.14	<0.001
Time to initial definitive therapy	0.65	0.23–1.12	0.08			

[a]KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*.

[b]MDR-AB, multidrug-resistant *Acinetobacter baumannii*; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; SSTI, skin and soft tissue infection; SAPS, simplified acute physiology score.

cause of septic shock (OR, 0.4; 95% CI, 0.18 to 0.96; $P = 0.04$) were mainly observed in septic shock patients with MDR-AB infection.

As reported in Table 4, a Cox regression analysis of factors associated with outcome in KPC-Kp infections showed that the use of ≥2 *in vitro*-active antibiotics as initial (hazard ratio [HR], 0.19; 95% CI, 0.04 to 0.85; $P = 0.03$) or definitive (HR, 0.02; 95% CI,

TABLE 5 Univariate and multivariate Cox regression analysis about factors associated with outcome at 30 days in MDR-AB infections[a]

	Univariate			Multivariate		
Variable[b]	HR	95% CI	*P*	HR	95% CI	*P*
Age	1.01	0.78–1.12	0.09	1.01	1.001–1.03	0.04[c]
Male sex	1.73	0.44–1.17	0.53			
Cause of ICU admission						
Respiratory failure	1.87	0.89–2.2	0.08			
Trauma	1.1	0.78–1.22	0.71			
Septic shock not caused by KPC-Kp or MDR-AB	1.24	0.98–1.65	0.65			
Cardiac/hemorrhagic shock/postsurgery	0.87	0.76–1.31	0.42			
Comorbidities						
Chronic liver disease	0.84	0.76–1.22	1.0			
Neoplasm	1.08	0.12–9.75	1.0			
Diabetes	3.62	0.44–29.69	0.28			
Heart failure	0.82	0.74–1.9	0.2			
Coronary artery disease	3.66	0.94–14.1	0.07			
Chronic renal disease	2.13	0.25–17.9	0.68			
COPD	1.26	0.32–4.99	1.0			
Previous hospitalization (90 days)	3.62	0.44–29.6	0.28			
Previous ICU admission (90 days)	2.13	0.25–17.98	0.68			
Previous surgery (30 days)	1.93	0.55–6.69	0.38			
Previous antibiotic therapy (30 days)	1.89	0.58–6.16	0.38			
Colonization at time of ICU admission	0.52	0.05–5.39	0.48			
Source of infection						
Primary bacteremia	3.35	0.4–27.5	0.45			
CVC-related bacteremia	0.84	0.67–1.31	1.0			
Pneumonia	0.57	0.14–2.25	0.53			
SSTI	0.44	0.08–1.02	0.15			
Intra-abdominal	0.7	0.07–6.79	0.57			
Isolation of a colistin-resistant strain	0.87	0.81–1.02	1.0			
Other infections during ICU stay	1.93	0.39–9.41	0.51			
Steroid therapy during ICU stay	0.64	0.18–2.2	0.56			
Length of hospitalization	1.13	0.68–1.36	0.71			
Length of ICU stay	0.8	0.7–1.33	0.54			
Length of antibiotic therapy	0.77	0.56–1.81	0.8			
SAPS II at time of infection onset	1.09	0.87–1.49	0.6			
SAPS II at time of septic shock onset	1.17	0.28–1.56	0.82	1.02	1.003–1.04	0.02[d]
No. of antibiotics used						
Only 1 as definitive therapy	0.45	0.22–1.12	0.34			
2 in combination as definitive therapy	1.73	0.44–6.75	0.53			
3 in combination as definitive therapy	0.66	0.21–2.06	0.56			
4 in combination as definitive therapy	0.36	0.08–1.61	0.17			
5 in combination as definitive therapy	0.66	0.45–1.32	1.0			
Colistin-containing regimen as definitive therapy	0.25	0.03–2.09	0.28			
Tigecycline-containing regimen as definitive therapy	1.64	0.47–5.7	0.55			
Gentamicin-containing regimen as definitive therapy	0.87	0.76–2.1	0.7			
Rifampin-containing regimen as definitive therapy	0.29	0.09–1.01	0.07			
Carbapenem-containing regimen as definitive therapy	0.84	0.24–2.96	1.0			
Use of colistin aerosol inhalation therapy	0.53	0.12–2.27	0.41			
≥2 *in vitro* active antibiotics used within 24 h	0.56	0.41–2.12	0.22			
Definitive therapy with ≥2 antibiotics displaying *in vitro* activity	0.7	0.07–6.79	0.57			
Time to initial definitive therapy	0.64	0.31–1.96	0.9			

[a]MDR-AB, multidrug-resistant *Acinetobacter baumannii*.
[b]ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; CVC, central venous catheter; SSTI, skin and soft tissue infection; SAPS, simplified acute physiology score.
[c]Age >60 years.
[d]SAPS II >45 points.

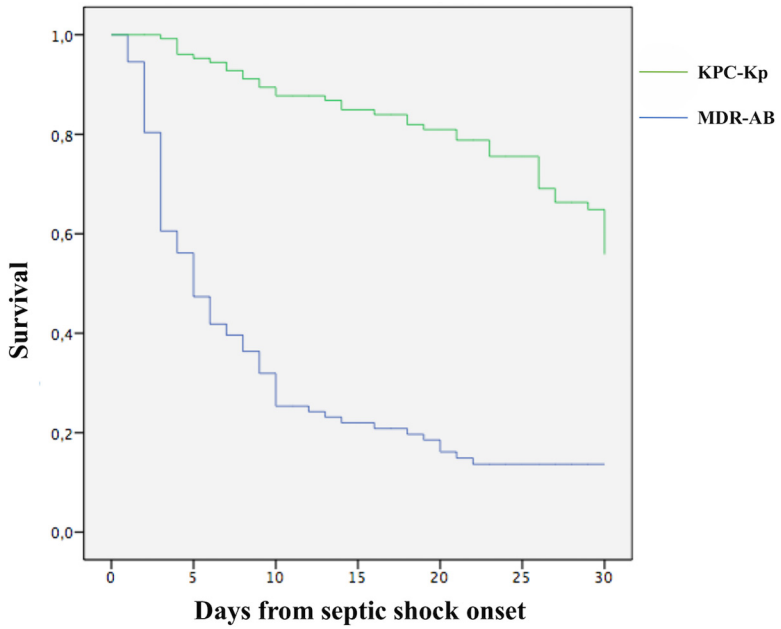

FIG 1 Kaplan-Meier curves for 30-day survival of KPC-Kp or MDR-AB infections. *, $P < 0.001$. KPC-Kp, *Klebsiella pneumoniae* carbapenem-resistant *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.

0.004 to 0.14; $P < 0.001$) therapy was associated with increased 30-day survival, while the isolation of a colistin-resistant strain was linked to higher 30-day mortality (HR, 25.1; 95% CI, 4.9 to 127.8; $P < 0.001$).

Cox regression analysis of factors associated with outcome in MDR-AB infections showed that age of >60 years (HR, 1.01; 95% CI, 1.001 to 1.03; $P = 0.04$) and SAPS II of >45 points (HR, 1.02; 95% CI, 1.003 to 1.04; $P = 0.02$) were associated with greater 30-day mortality (see Table 5).

Finally, the results of Kaplan-Meier analysis of 30-day survival of patients with KPC-Kp and MDR-AB septic shock are reported in Fig. 1.

DISCUSSION

This study analyzed and compared the clinical features and outcome of septic shock due to MDR-AB and KPC-Kp in a population of patients admitted to the same ICU. Of importance, very high rates of 30-day mortality (84.8%) were observed in patients with MDR-AB infection compared to patients with KPC-Kp infection (44.5% of mortality at 30 days). Moreover, in patients with MDR-AB, the 7-day mortality was 64.6% (as reported in Fig. 1).

Few studies have analyzed the impact on survival of septic shock due to MDR-AB infection. Recently, Busani and coworkers (17) reported data about patients with septic shock caused by MDR bacteria in the ICU; a diagnosis of infection caused by MDR-AB was independently associated with an increased risk of death and high mortality rates (62.5% of patients). This high mortality related to *Acinetobacter baumannii* infections was comparable to that reported in patients with hematologic malignancies (18). Furthermore, our data appear to confirm those reported by Freire et al., who evaluated risk factors associated with mortality after bloodstream infections caused by MDR-AB in patients with hematologic and solid tumors; the reported 7-day and 30-day mortality rates of 71.7% and 83.7%, respectively, are consistent with our data (19).

We have evaluated factors affecting the 30-day outcome. As previously reported (8, 20), in KPC-Kp infections, the isolation of a colistin-resistant strain was associated with unfavorable outcome, while the administration of at least two *in vitro*-active antibiotics, as initial or definitive therapy, was independently associated with survival. Extensive

literature data about KPC-Kp infections support these observations (21–23). Indeed, different antibiotic combinations active against KPC-Kp and including gentamicin, tigecycline, trimethoprim-sulfamethoxazole, or double-carbapenem therapy are reported in the literature (24–26). In our population of patients with KPC-Kp septic shock, a carbapenem was the most used antibiotic, mainly in combination with colistin, tigecycline, and/or gentamicin. On the other hand, a carbapenem was used in combination with colistin and/or rifampin for the treatment of MDR-AB infections (27–29). Despite the observation of only 1 patient with MDR-AB infection due to a colistin-resistant strain, a very low proportion of patients were treated with 2 or more antibiotics showing *in vitro* activity against the isolates of MDR-AB; this probably explains the very high mortality rates observed in this population.

However, the recent EUCAST recommendations (30), along with the study of Matuschek and coworkers (31), demonstrated that false susceptibilities to colistin are obtained in approximately 50% of *Acinetobacter baumannii* strains using automated systems or Etest, while broth microdilution is the only recommended method for MIC determination. Therefore, the considerable difference in mortality rates (44.5% versus 84.8%) might be also attributed to colistin administration for the treatment of infections caused by *A. baumannii* strains with false susceptibility to this drug.

Different antibiotic combinations were studied for the treatment of severe infections due to MDR-AB. Durante-Mangoni and coworkers (32) showed that in patients with MDR-AB infections, mortality at 30 days was not reduced by the addition of rifampin to colistin; other *in vitro* studies explored the synergism of some drug combinations, especially polymyxins plus carbapenem for the treatment of MDR-AB infections (33, 34), suggesting that the use of this combination is supported by high synergy rates. On this basis, the combination of a carbapenem plus colistin seems to be the first option for the treatment of MDR-AB infections (35). Another possible synergistic combination is based on the addition of vancomycin to colistin (in our study population, this combination was used in 9 patients, and 3 of them survived at 30 days) (36–38). However, no definitive data about *in vivo* efficacy are available, so systematic use of the vancomycin and colistin combination for MDR-AB cannot yet be encouraged.

We analyzed factors independently associated with a diagnosis of MDR-AB and KPC-Kp infection. We found an association between exposure to steroid therapy and development of MDR-AB infection. This distinguishing feature of MDR-AB infections was recently reported by Ballouz and coworkers (39), but the meaning of this association is not yet understood. Since most of patients with MDR-AB infection had pneumonia (69.6%), it is possible that the link between steroid use and MDR-AB infection might be due to steroid administration in the management of severe pneumonia to reduce inflammation (40).

Hospitalization in the previous 90 days, colonization at the time of ICU admission, and primary bacteremia turned out to be distinguishing features of KPC-Kp infection. The importance of previous hospitalization and gut colonization by KPC-Kp at the time of ICU admission was yet assessed (41). Considering the high prevalence of KPC-Kp enteric carriage in ICU patients and the significant mortality associated with KPC-Kp infection, early identification and isolation of carriers are of uttermost importance. Patients admitted to our ICU were actively screened for KPC-Kp gastrointestinal carriage at ICU admission and subsequently on a weekly basis. Conversely, as reported in Materials and Methods, an active screening of rectal carriage was not performed for MDR-AB; therefore, we cannot definitively exclude the possibility of similar results in terms of outcome if similar screening measures were applied for MDR-AB.

Our study shows some limitations that should be acknowledged. First, the study was performed in a single center, and the results might not be generalizable to other institutions. Second, the observational nature of the study brings about an intrinsic limitation in the analysis. Third, the number of patients is relatively low, and further multicenter prospective studies are needed to confirm our findings. Finally, the underlying mechanisms of resistance in MDR-AB strains were not routinely assessed in our population, and *in vitro* synergistic combinations were performed only in few cases.

However, this is a real-life clinical experience providing useful suggestions to clinicians about the management of difficult-to-treat and poorly studied infections, such as septic shock caused by MDR-AB or KPC-Kp strains.

In conclusion, our data showed the peculiar clinical features and the high rates of mortality in ICU patients with septic shock due to MDR-AB infections compared to septic shock due to KPC-Kp. The lack of scientific data helping clinicians in choosing optimal antimicrobial regimens that are effective against MDR-AB might explain the very high mortality rate observed in this population of patients (42, 43). All these findings suggest that it is crucial to obtain new antibiotic options for the treatment of ICU patients with MDR-AB infection, improve treatment strategies, and reduce mortality.

MATERIALS AND METHODS

Study design and patient selection. This was a retrospective observational study conducted at the University-Hospital Policlinico Umberto I in Rome, Italy. All clinical data of patients hospitalized in the same ICU from November 2010 to December 2015 were systematically analyzed, and patients who fulfilled the following criteria were enrolled in the study: (i) age ≥18 years, and (ii) septic shock due to documented MDR-AB or KPC-Kp infection. The present study was conducted according to the principles stated in the Declaration of Helsinki. The local ethical committees approved the study (no. 4547-2017).

Baseline assessment. Patient data were extracted from medical records and from hospital computerized databases or clinical charts according to a preestablished questionnaire. The following information was reviewed: demographics, clinical and laboratory findings, comorbid conditions, microbiological data, duration of ICU and hospital stay, incidence of infections during hospitalization, treatments and procedures administered during hospitalization and/or in the 90 days prior to infection, classes of antibiotics received on admission and/or after admission before a positive culture of a biological sample was obtained, the simplified acute physiology score II (SAPS II) at the time of infection, source of infection, antibiotic regimens used for MDR-AB or KPC-Kp infections, and 30-day mortality. According to hospital's guidelines, colonization with KPC-Kp and MDR-AB strains was routinely evaluated by respiratory specimens and urine culture at the time of ICU admission and every week afterwards. Conversely, during the study period, colonization by rectal/stool swab culture was routinely evaluated only for KPC-Kp strains.

Definitions. Infections were defined according to the standard definitions of the European Centers for Disease Control and Prevention (ECDC) (44).

An MDR-AB or KPC-Kp infection was defined as clinical signs of the systemic inflammatory response syndrome and culture of blood, urine, or a biological sample from skin and skin structures, lung, or abdomen yielding an MDR-AB or a KPC-Kp strain (45). Infection onset was defined as the date of collection of the index culture (i.e., the first blood culture that yielded the study isolate). Infections were defined as hospital acquired if the index culture had been collected >48 h after hospital admission and no signs or symptoms of infection had been noted at admission. Primary bloodstream infection (BSI) was defined as BSI occurring in patients without a recognized source of infection. The central venous catheter (CVC) was considered a source of infection if one of the following was present: (i) a positive result of semiquantitative (>15 CFU per catheter segment) catheter culture, whereby the same organism (species) was isolated from the catheter segment and a peripheral blood culture; or (ii) growth in a culture of blood obtained through a catheter hub was detected by an automated system at least 2 h earlier than a culture of simultaneously drawn equal volume of peripheral blood, provided that the same organism (species) was isolated (46).

Septic shock was defined according to international definitions (47). The severity of clinical conditions was determined by using SAPS II score calculated at the time of infection and septic shock onset (48). Length of hospital and ICU stay were calculated as the number of days from the date of admission to the date of discharge or death.

K. pneumoniae and *A. baumannii* isolates were classified as multidrug resistant (MDR), extensively drug resistant (XDR), or pandrug resistant (PDR), according to Magiorakos et al. (49).

Antimicrobial treatment evaluation. Depending on the number of drugs used (1 or >1), treatment regimens were classified as monotherapy or combination therapy. Initial antibiotic therapy, defined as antimicrobial chemotherapy implemented within 24 h after the onset of infection, was assessed along with definitive antibiotic therapy, defined as antimicrobial treatment based on *in vitro* MDR-AB or KPC-Kp isolate susceptibilities. Antibiotic regimens were also classified according to the following: <2 antibiotics displaying *in vitro* activity, and ≥2 antibiotics displaying *in vitro* activity. Time to initial definitive therapy was the time between infection onset and initial definitive therapy.

MDR-AB and KPC-Kp identification. The Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) was used for isolate identification and antimicrobial susceptibility testing. MICs were established according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (50). Susceptibility to tigecycline was evaluated by the Etest technique, to avoid MIC overestimation by Vitek2 system, and the U.S. Food and Drug Administration (FDA) recommendations were used for breakpoints (susceptible, MIC ≥2 mg/liter; resistant, MIC ≥8 mg/liter) (51). The presence of a bla_{KPC} gene was determined by PCR and sequencing (52).

Statistical analysis. To detect significant differences between the MDR-AB group and KPC-Kp group, we used the chi-square test or Fisher's exact test for categorical variables and the 2-tailed *t* test or

Mann-Whitney test for continuous variables, when appropriate. Logistic regression analysis was performed to identify differences between groups with MDR-AB and KPC-Kp infection. In a multivariate analysis of survival, the Cox regression model was used to determine the effects of different variables on 30-day survival in patients with KPC-Kp or MDR-AB isolation, respectively. Wald confidence intervals and tests for hazard ratios and odds ratios were computed based on the estimated standard errors. Possible confounding factors and interactions were weighted during analyses. Statistical significance was established at ≤ 0.05. All reported *P* values are 2-tailed. The results obtained were analyzed using a commercially available statistical software package (SPSS, version 20.0; SPSS, Inc., Chicago, IL).

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