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What is the optimal antibiotic treatment strategy for carbapenem-resistant *Acinetobacter baumannii* (CRAB)? A multicentre study in Korea

Hyeri Seok[a,1], Won Suk Choi[a,1], Shinwon Lee[b], Chisook Moon[c], Dae Won Park[a], Joon Young Song[a], Hee Jin Cheong[a], Jieun Kim[d], Jin Yong Kim[e], Mi Na Park[f], Yang Ree Kim[g], Hyo-Jin Lee[g], Bongyoung Kim[d], Hyunjoo Pai[d], Yu Mi Jo[a], Jong Hun Kim[a], Jang Wook Sohn[a,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea*
[b] *Department of Internal Medicine, Pusan National University School of Medicine and Medical Research Institute, Pusan National University Hospital, Busan, Republic of Korea*
[c] *Division of Infectious Diseases, Busan Paik Hospital, Inje University, Busan, Republic of Korea*
[d] *Division of Infectious Diseases, Hanyang University College of Medicine, Seoul, Republic of Korea*
[e] *Department of Internal Medicine, Incheon Medical Center, Incheon, Republic of Korea*
[f] *Infection Control Office, Incheon Medical Center, Incheon, Republic of Korea*
[g] *Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*

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ABSTRACT

Objectives: The optimal treatment option for carbapenem-resistant *Acinetobacter baumannii* (CRAB) is still limited. This study investigated the efficacy of three or more antibiotic types and regimens for treatment of CRAB infection in high CRAB endemic areas.
Methods: A multicentre retrospective study was conducted to evaluate the efficacy of treatment types and regimens of CRAB infections in 10 tertiary hospitals in the Republic of Korea. The outcomes comprised 7-day and 28-day mortality, and clinical and microbiological responses at 7 days, 28 days, and the end of treatment. Nephrotoxicity and hepatotoxicity were evaluated as drug adverse reactions.
Results: A total of 282 patients were included in the study. Among the CRAB strains, the two most susceptible antibiotics were colistin (99.6%) and minocycline (80.4%). A combination of colistin and carbapenem significantly reduced 7-day mortality, and a sulbactam-containing regimen significantly reduced 28-day mortality. Colistin monotherapy was significantly associated with increased 7-day and 28-day mortality. A minocycline-containing regimen showed the best microbiological responses at 7 days, 28 days, and the end of treatment. Colistin and tigecycline were associated with increased nephrotoxicity and hepatotoxicity, respectively. Subgroup analysis of patients with pneumonia showed similar results to the overall CRAB infection.
Conclusions: A combination of colistin and carbapenem and sulbactam-containing regimen may contribute improved mortality in CRAB infections. Colistin monotherapy should be considered cautiously in severe CRAB infections or CRAB pneumonia. A minocycline-containing regimen showed the best microbiological responses, and further studies may be needed to evaluate improved mortality.

1. Background

The threat of *Acinetobacter baumannii* is increasing among global antimicrobial resistance problems [1]. *Acinetobacter baumannii*—one of the difficult-to-treat ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species)—is identified particularly in intensive care units

* Corresponding author at: Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Republic of Korea.
E-mail address: jwsohn@korea.ac.kr (J.W. Sohn).
[1] These authors contributed equally to this article.

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(ICUs) and contributes to high morbidity and mortality in critically ill patients [2–7]. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) has increased worldwide as antibiotic use increases, with up to 15% in northern European countries and 50% in southern European countries including Spain, Italy, and Greece [8,9]. In the United States, more than half the *A. baumannii* in hospital-related infections were non-susceptible to carbapenem, accounting for 52% of mortality [10]. In South Korea, a country with high CRAB rates, the ICU's CRAB rates increased from 52.9% in 2006 to 89.8% in 2013 according to the Korean Nosocomial Infections Surveillance System (KONIS) [11]. As CRAB causes not only the problem of high resistance rate itself but also high mortality, CRAB ranked at the top for critical-priority bacteria, which require development of new antibiotics analysed by the World Health Organization (WHO) [12].

The treatment options for CRAB infection are limited with regards to the severity of disease, and the results of clinical or

Table 1
Overall characteristics of patients with infections caused by CRAB.

Variables	Overall CRAB infection (n = 282)	Pneumonia (n = 257)
Age, y	67.0 ± 14.9 (59–77)	67.5 ± 14.8 (60–78)
Gender, male	192/282 (68.1)	178/257 (69.3)
Underlying diseases, one or more	247/282 (87.6)	225/257 (87.5)
Hypertension	128/282 (45.4)	115/257 (44.7)
Diabetes mellitus	85/282 (30.1)	77/257 (30.0)
Cerebrovascular vascular diseases	69/282 (24.5)	66/257 (25.7)
Neuromuscular diseases	8/282 (2.8)	8/257 (3.1)
Dementia	15/282 (5.3)	15/257 (5.8)
Congestive heart failure	25/282 (8.9)	23/257 (8.9)
Ischaemic heart diseases	23/282 (8.2)	21/257 (8.2)
Valvular heart diseases	2/282 (0.7)	1/257 (0.4)
Chronic obstructive lung diseases/asthma	38/282 (13.5)	35/257 (13.6)
Chronic liver diseases	30/282 (10.6)	20/257 (7.8)
Chronic renal diseases	35/282 (12.4)	31/257 (12.1)
Haemodialysis/peritoneal dialysis	12/282 (4.3)	12/257 (4.7)
Malignant solid tumour	33/282 (11.7)	31/257 (12.1)
Hematologic malignancy	7/282 (2.5)	6/257 (2.3)
Stem cell transplantation	1/282 (0.4)	1/257 (0.4)
Solid organ transplantation	1/282 (0.4)	0/257 (0)
Taking immunosuppressive agents	3/282 (1.1)	3/257 (1.2)
Taken emergency operation within 1 month	38/282 (13.5)	34/257 (13.2)
Taken elective operation within 1 month	14/282 (5.0)	13/257 (5.1)
Age adjusted Charlson Comorbidity Index score	3.7 ± 2.3 (2–5)	4.0 ± 2.2 (2–5)
APACHE II score	19.3 ± 6.9 (14–24)	19.3 ± 6.8 (14–24)
SAPS II	48.6 ± 15.3 (38–59)	48.6 ± 14.9 (38–60)
Use of medical devices		
Mechanical ventilator	215/282 (76.2)	200/257 (77.8)
Central catheter	218/282 (77.3)	197/257 (76.7)
Foley catheter	270/282 (95.7)	246/257 (95.7)
Nasogastric tube	244/282 (86.5)	223/257 (86.8)
Classification of infection		
Pneumonia	257/282 (91.1)	
With bacteraemia	68/257 (26.5)	68/257 (26.5)
Ventilator-associated pneumonia	180/257 (70.0)	180/257 (70.0)
Urinary tract infection	4/282 (1.4)	
Primary bacteraemia	20/282 (7.1)	
Susceptibility of CRAB		
Susceptible to colistin	281/282 (99.6)	256/257 (99.6)
Susceptible to sulbactam	22/262 (8.4)	21/243 (8.6)
Susceptible to tigecycline	150/168 (53.2)	140/156 (89.7)
Susceptible to minocycline	205/255 (80.4)	191/237 (80.6)
Susceptible to TMP/SMX	26/282 (9.2)	25/257 (9.7)
Susceptible to amikacin	60/128 (46.9)	52/147 (47.3)
Mortality		
7-day mortality	57/282 (20.2)	49/257 (19.1)
28-day mortality	108/267 (40.4)	97/246 (39.4)
Clinical response, success or improve		
14 days	133/243 (54.7)	121/220 (55.0)
28 days	108/220 (49.1)	97/198 (49.0)
End of treatment	138/275 (50.2)	126/250 (50.4)
Microbiological response, success		
14 days	84/162 (51.9)	74/150 (49.3)
28 days	79/112 (70.5)	70/102 (68.6)
End of treatment	87/162 (53.1)	77/151 (51.0)
Duration of the hospital stay, d	33.0 ± 36.3 (11–42)	34.0 ± 37.2 (11–44)
Alive, d	43.3 ± 42.0 (16–58)	44.7 ± 42.9 (17–60)
Expired, d	19.6 ± 21.4 (6–24)	19.6 ± 22.0 (6–24)
Antibiotic adverse reactions		
Nephrotoxicity	156/282 (55.3)	144/257 (56.0)
Hepatotoxicity	36/282 (12.8)	33/257 (12.8)

Data are expressed as number of patients/total patients (%) or mean ± standard deviation (interquartile range) unless otherwise indicated. CRAB = carbapenem-resistant *Acinetobacter baumannii*; HIV = human immunodeficiency virus; AIDS = acquired immune deficiency syndrome; APACHE = acute physiology and chronic health evaluation; SAPS = simplified acute physiology score; TMP/SMX = trimethoprim/sulfamethoxazole.

microbiological responses of antibiotics for CRAB vary depending on the studies. In previous studies, antibiotics used for CRAB infection included sulbactam, colistin, aminoglycoside, tigecycline, minocycline, rifampin, etc. The studies involved monotherapy, combination therapy with carbapenem or other antibiotics, and additional colistin nebuliser therapy [13–25]. Colistin is the most commonly used antibiotic for CRAB treatment, as monotherapy or combination therapy with other antibiotics. One study reported that colistin monotherapy showed higher mortality rate compared with sulbactam monotherapy, and other studies showed that combination therapy of colistin and rifampin reduced ventilator-associated pneumonia (VAP)-related mortality or higher microbiological responses than colistin monotherapy [13–15]. Colistin-containing combination therapy has shown no significant improvement in mortality compared with colistin monotherapy in other studies [16–19]. Tigecycline has been reported to improve the microbiological response in the treatment of CRAB, but had no significant effect on clinical improvement [20,21]. Previous studies compared two or three regimens, but in practice, various regimens have been used for CRAB treatments, and no study has compared regimens together. This study investigated the clinical and microbiological responses of various antibiotic regimens for CRAB treatment in several tertiary hospitals in Korea, where the CRAB rates are relatively high.

2. Methods

2.1. Study design, study population, and data collection

A multicentre, retrospective cohort study was conducted to evaluate treatment regimens for infections caused by CRAB complex. The crude study population was composed of the adult patients in intensive care units (ICU) diagnosed with CRAB infections between November 2015 and November 2016 at 10 large Korean clinical centres. Superimposed infections during the treatment of CRAB infections and infections caused by pathogens other than CRAB in clinical specimens were excluded from this study. The demographic data, comorbidity status based on the Charlson comorbidity index, and severity index such as acute physiology and chronic health evaluation (APACHE) II score, and simplified acute physiology score (SAPS) were collected. CRAB infections were classified according to the site of infection and the type and regimen of antibiotics used. Antibiotic treatment responses were assessed by clinical and microbiological responses and were evaluated at 14 days and 28 days after treatment, and at the end of treatment. Clinical response to antibiotic therapy consisted of mortality, duration of hospital stay, and treatment success. Antibiotic adverse reactions were checked as serum creatinine and liver function tests.

2.2. Definition

CRAB was defined as *A. baumannii* with minimum inhibitory concentration (MIC) >8 mg/L for imipenem or meropenem, or as *A. baumannii* reported as resistance to imipenem or meropenem in automated systems such as VITEK or Microscan. CRAB pneumonia was defined as when CRAB has been identified in respiratory samples (such as sputum, bronchoalveolar lavage [BAL], or protected specimen brush [PSB] culture) with newly developed or progressing infiltration, consolidation, or cavity on chest x-ray while satisfying two or more of the following clinical symptoms; cough, purulent sputum, crackles, dyspnoea, hypoxia, or need for ventilator, and systemic inflammatory response syndrome (SIRS) score 2 or higher. CRAB urinary tract infection (UTI) included only symptomatic UTI, defined as when CRAB was identified in more than 10^5 colonies/mL in urine culture, along with fever above 38 ℃, urinary urgency, frequency, dysuria, suprapubic tenderness, and costovertebral angle tenderness. Significant samples in culture were considered to be 10^3 to 10^5 colonies/mL by dipstick, microscopy, and Gram stain. Central-line associated bloodstream infection (CLABSI) was defined as the case where the central line was inserted 48 h before the initial positive blood culture without any other cause of infection. All sulbactams were administered in the form of ampicillin/sulbactam. All minocycline used in this study were oral formulations. The clinical response was classified as success, improvement, and failure. Success was defined as the discontinuation of antibiotics because of clinical response to antibiotics including defervescence, no need for vasopressor, reversal of symptoms and signs, and normalization of laboratory findings. Improvement was defined as the maintenance of antibiotics with clinical response. Failure was defined as death or change to other antibiotics because of clinical deterioration. Microbiological success was defined as the maintenance of no growth in the specimen which was initially positive. Antibiotic-induced nephrotoxicity was evaluated as creatinine according to the RIFLE criteria [26]. Antibiotic-induced liver toxicity was evaluated according to Hy's Law [27].

2.3. Statistical analysis

For comparison, Pearson χ^2 tests and Fisher's exact tests were used for categorical variables, and Student's t test and Mann–Whitney U tests were used for continuous variables, as appropriate. Cox proportional hazards regression analysis was used to evaluate the association between the antibiotic regimens and the outcomes including mortality, clinical responses, and microbiological responses. The types and regimens of antibiotics were analysed separately to avoid duplicate variables in multivariate analysis. The Kaplan–Meier curve was used to evaluate the mortality according to the antibiotic regimens. All statistical analyses were performed using SPSS Statistics version 20.0 for Windows (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Overall characteristics of patients in this study

During the study period, 429 patients were collected from 10 clinical centres. After 147 patients were excluded who did not maintain antibiotics targeting CRAB for more than 48 h because of referral to other hospitals, death, or being without infection, a total of 282 patients were finally enrolled in this study. The overall characteristics of the study population are shown in Table 1. The mean age was 67 y, and 192 patients (68.1%) were male. Two-hundred and forty-seven (87.6%) patients had at least one underlying disease. The most common comorbidities were hypertension (45.4%) and diabetes mellitus (30.1%), and the mean age-adjusted Charlson Comorbidity Index was 4 (interquartile range [IQR] 0–13). More than 70% of patients had mechanical ventilators, central catheters, foley catheters, or nasogastric tubes. Sites of infection caused by CRAB are pneumonia (91.1%), primary bacteraemia (7.1%), and UTI (1.4%) in the order of prevalence. Of the CRAB pneumonia, 75% were VAP. Overall, 282 CRAB strains were susceptible to colistin except one strain, and 205 patients (80.4%) were susceptible to minocycline. The susceptibility rates of tigecycline and amikacin against CRAB were 53.2% and 46.9%, respectively. The baseline characteristics were not different according to the pneumonia subgroup and antibiotic regimens compared with the overall study population.

The all-cause 7-day and 28-day mortality were 20.2% (57/281) and 40.4% (108/267), respectively. The overall study population showed treatment clinical success or improvement in

approximately 50% at 14 days, 28 days, and at the end of treatment. In the concurrent microbiological evaluation, the treatment success rate was 51.9%, 70.5%, and 53.1% at 14 days, 28 days, and at the end of treatment, respectively. The mean lengths of hospital stay for all patients and survivors of CRAB infection were 33 days (2–354) and 43 days (3–354), respectively. In the subgroup analysis of patients with pneumonia, overall characteristics including demographic and outcome data showed no significant differences among overall patients.

3.2. Mortality rates of CRAB infections by the types and regimens of antibiotics

The antibiotics used in the treatment of CRAB were colistin, carbapenem, sulbactam, minocycline, amikacin, and tigecycline in order of frequency (Table 2). Among the types of antibiotics, a colistin-containing regimen showed the highest 7-day mortality rate (22.8%) whereas a sulbactam-containing regimen showed the lowest 7-day mortality rate (13.0%). The 28-day mortality was the highest in a tigecycline-containing regimen (50.0%) and the lowest in a minocycline-containing regimen (28.3%). Among the regimens of antibiotics, combination of colistin and rifampin showed the highest 7-day mortality. All patients treated with sulbactam monotherapy survived on day 7, and combination therapy of sulbactam and minocycline showed 7-day mortality of 7.1%. The 28-day mortality was highest in colistin monotherapy (50.0%) and lowest in the combination of colistin and rifampin (10.0%). In the univariate analysis, combination therapy of colistin and carbapenem decreased 7-day mortality, a sulbactam-containing regimen decreased both 7-day and 28-day

Table 2
Types and regimens of antibiotics for CRAB infections and the resulting mortality rate.

Types and regimens of antibiotics	Overall CRAB infection	7-day mortality	Univariate analysis		Multivariate analysis		28-day mortality	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age			0.99 (0.98–1.02)	0.952				1.00 (0.99–1.01)	0.970		
Sex			0.95 (0.55–1.63)	0.839				0.94 (0.63–1.39)	0.756		
Any underlying diseases			0.68 (0.32–1.44)	0.310				0.91 (0.50–1.67)	0.764		
Charlson Comorbidity Index			1.00 (0.88–1.14)	0.966				0.98 (0.88–1.08)	0.638		
APACHE II score			1.04 (0.99–1.08)	0.070	0.99 (0.95–1.05)	0.828		1.04 (1.00–1.06)	0.015	1.02 (0.98–1.06)	0.306
SAPS II			1.02 (1.00–1.04)	0.012	1.02 (1.01–1.04)	0.002		1.02 (1.01–1.03)	0.003	1.02 (1.01–1.03)	0.001
Colistin-containing regimen	171/282 (60.6)	39/171 (22.8)	1.24 (0.70–2.19)	0.463			73/166 (44.0)	1.30 (0.86–1.96)	0.210		
Colistin monotherapy	58/282 (20.6)	20/58 (34.5)	2.05 (1.18–3.54)	0.011	1.66 (0.95–2.90)	0.075	28/56 (50.0)	1.53 (0.99–2.37)	0.053	1.79 (1.15–2.79)	0.011
Colistin + carbapenem	41/282 (14.5)	2/41 (4.9)	0.19 (0.05–0.76)	0.020	0.18 (0.04–0.73)	0.017	16/39 (41.0)	0.83 (0.48–1.41)	0.486		
Colistin + minocycline	22/282 (7.8)	4/22 (18.2)	1.03 (0.37–2.84)	0.957			7/22 (31.8)	0.95 (0.44–2.06)	0.903		
Colistin + rifampin	17/282 (6.0)	7/17 (41.2)	1.69 (0.76–3.72)	0.196			4/18 (22.2)	1.71 (0.88–3.29)	0.112		
Colistin + sulbactam	15/282 (5.3)	3/15 (20.0)	0.92 (0.29–2.96)	0.897			6/15 (40.0)	0.76 (0.33–1.73)	0.512		
With colistin nebuliser	13/282 (4.6)	2/13 (15.4)	1.01 (0.25–4.13)	0.992			4/12 (33.3)	1.88 (0.68–5.17)	0.222		
Carbapenem-containing regimen	97/282 (34.4)	16/97 (16.5)	0.68 (0.38–1.23)	0.206			36/92 (39.1)	0.90 (0.60–1.34)	0.593		
Carbapenem + sulbactam	18/282 (6.4)	2/18 (11.1)	0.49 (0.12–2.00)	0.319			4/18 (22.2)	0.51 (0.19–1.38)	0.184		
Carbapenem + rifampin	10/282 (3.5)	1/10 (10.0)	1.51 (0.21–10.90)	0.684			1/10 (10.0)	0.44 (0.06–3.18)	0.418		
Carbapenem + amikacin	9/282 (3.2)	3/9 (33.3)	3.39 (1.05–10.93)	0.041	2.22 (0.60–8.28)	0.234	3/8 (37.5)	3.43 (1.06–11.04)	0.039	3.04 (0.88–10.50)	0.078
Sulbactam-containing regimen	69/282 (24.5)	9/69 (13.0)	0.53 (0.26–1.08)	0.081	0.52 (0.26–1.07)	0.074	21/66 (31.8)	0.53 (0.33–0.86)	0.011	0.53 (0.32–0.85)	0.009
Sulbactam monotherapy	9/282 (3.2)	0/9	0.05 (0.01–35.37)	0.366			2/8 (25.0)	0.44 (0.11–1.79)	0.253		
Sulbactam + minocycline	14/282 (5.0)	1/14 (7.1)	0.62 (0.09–4.44)	0.629			2/14 (14.3)	0.42 (0.10–1.73)	0.231		
Minocycline-containing regimen	46/282 (16.3)	8/46 (17.4)	1.14 (0.54–2.40)	0.737			13/46 (28.3)	0.83 (0.46–1.49)	0.534		
Amikacin-containing regimen	22/282 (7.8)	3/22 (13.6)	1.11 (0.35–3.54)	0.865			6/18 (33.3)	1.36 (0.59–3.11)	0.469		
Tigecycline-containing regimen	12/282 (4.3)	2/12 (16.7)	0.78 (0.19–3.20)	0.730			5/10 (50.0)	0.86 (0.35–2.11)	0.737		
Tigecycline monotherapy	7/282 (2.5)	1/7 (14.3)	0.05 (0.01–154.80)	0.462			2/5 (40.0)	0.56 (0.14–2.28)	0.419		

Data are expressed as number of patients/total patients (%) unless otherwise indicated. All sulbactams were administered in the form of ampicillin/sulbactam. CRAB = carbapenem-resistant *Acinetobacter baumannii*; HR = hazard ratio; CI = confidence interval; APACHE = acute physiology and chronic health evaluation; SAPS = simplified acute physiology score.

mortality, whereas colistin monotherapy and combination therapy of carbapenem and amikacin increased both 7-day and 28-day mortality. In multivariate analysis, combination therapy of colistin and carbapenem decreased 7-day mortality (Adjusted hazard ratio [aHR] 0.18, 95% confidence interval [CI] 0.04–0.73, *P* value = 0.017), and sulbactam-containing regimen decreased 28-day mortality (aHR 0.53, 95% CI 0.32–0.85, *P* = 0.009), whereas colistin monotherapy increased 28-day mortality (HR 1.79, 95% CI 1.15–2.79, *P* = 0.011). Higher SAPS increased both 7-day and 28-day mortality. Combination therapy with colistin and carbapenem was not associated with decreased 28-day mortality, and most patients died from CRAB infections with high average APACHE scores and SAPS.

In Kaplan–Meier curves, patients treated with a sulbactam-containing regimen tended to have higher 7-day survival rates without significance, and significantly higher 28-day survival rates (Fig. 1). The combination therapy of colistin and carbapenem had significantly higher 7-day and survival rate, whereas 7-day and 28-day mortality rates were significantly higher in patients treated with colistin monotherapy.

In CRAB pneumonia subgroup analysis, combination therapy of colistin and carbapenem (aHR 0.16, 95% CI 0.04–0.65, *P* = 0.011) and carbapenem-containing regimen (aHR 0.48, 95% CI 0.24–0.94, *P* = 0.033) significantly decreased 7-day mortality in multivariate analysis (Supplementary Table 1). A sulbactam-containing regimen decreased 28-day mortality in CRAB pneumonia (aHR 0.53,

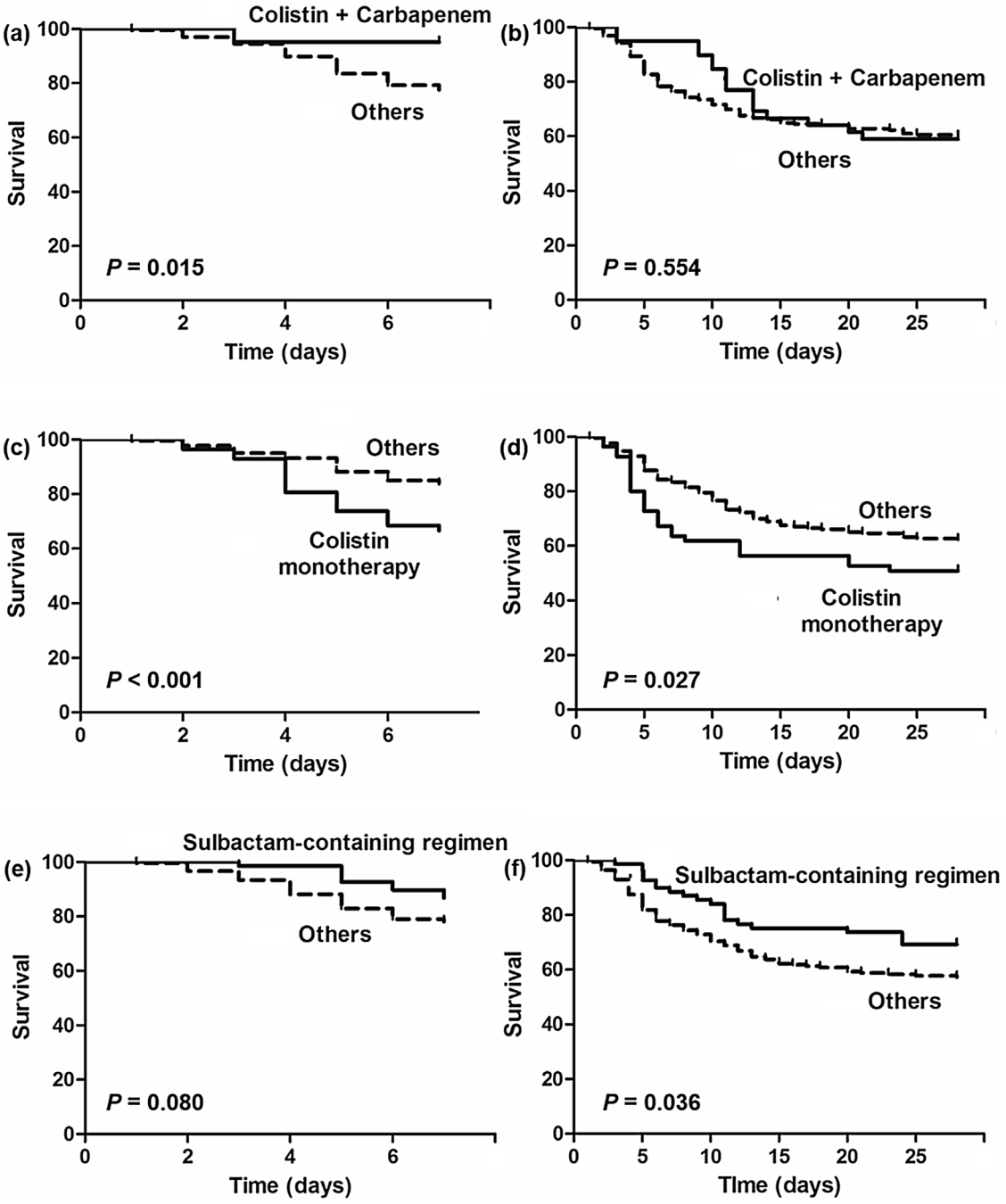

Fig. 1. Kaplan–Meier curves for 7-day and 28-day survival according to types and regimens of antibiotics for CRAB infection.

Table 3
Types and regimens of antibiotics for CRAB infections and the resulting clinical responses.

Types and regimens of antibiotics	14 days	Univariate analysis		Multivariate analysis		28 days	Univariate analysis		Multivariate analysis		End of treatment	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age		0.98 (0.96–0.99)	0.012	0.98 (0.97–1.00)	0.085		0.97 (0.95–0.99)	0.001	0.98 (0.96–0.99)	0.015		0.97 (0.95–0.99)	<0.001	0.98 (0.96–0.99)	0.010
Sex		1.24 (0.73–2.11)	0.420				1.20 (0.69–2.07)	0.524				1.23 (0.74–2.04)	0.416		
Any underlying diseases		0.86 (0.39–1.84)	0.690				0.74 (0.33–1.67)	0.474				0.71 (0.34–1.49)	0.367		
Charlson Comorbidity Index		0.90 (0.80–1.01)	0.070	0.92 (0.80–1.06)	0.260		0.85 (0.74–0.96)	0.010	0.90 (0.77–1.04)	0.151		0.86 (0.77–0.96)	0.009	0.94 (0.83–1.07)	0.330
APACHE II score		0.92 (0.89–0.96)	<0.001	0.99 (0.94–1.05)	0.786		0.92 (0.88–0.96)	<0.001	0.98 (0.93–1.04)	0.579		0.93 (0.90–0.97)	<0.001	1.00 (0.94–1.05)	0.871
SAPS II score		0.95 (0.93–0.97)	<0.001	0.95 (0.94–0.97)	<0.001		0.95 (0.93–0.97)	<0.001	0.95 (0.93–0.71)	<0.001		0.96 (0.94–0.97)	<0.001	0.95 (0.94–0.97)	<0.001
Colistin-containing regimen	77/146 (52.7)	0.81 (0.50–1.30)	0.373			67/135 (49.6)	1.10 (0.67–1.80)	0.705			81/167 (48.5)	0.84 (0.52–1.37)	0.489		
Colistin monotherapy	25/49 (51.0)	0.81 (0.46–1.46)	0.488			23/46 (50.0)	1.08 (0.60–1.94)	0.811			28/56 (50.0)	0.99 (0.55–1.78)	0.976		
Colistin + carbapenem	16/36 (44.4)	0.68 (0.35–1.33)	0.261			14/33 (42.4)	0.81 (0.41–1.63)	0.555			17/41 (41.5)	0.66 (0.34–1.30)	0.228		
Colistin + minocycline	12/19 (63.2)	1.38 (0.58–3.30)	0.472			11/19 (57.9)	1,68 (0.70–4.02)	0.244			12/21 (57.1)	1.35 (0.55–3.33)	0.508		
Colistin + rifampin	6/12 (50.0)	0.59 (0.213–1.649)	0.317			5/11 (45.5)	0.66 (0.22–1.92)	0.440			5/16 (31.3)	0.43 (0.15–1.27)	0.128		
Colistin + sulbactam	8/12 (66.7)	1.30 (0.46–3.68)	0.624			6/10 (60.0)	1.08 (0.37–3.12)	0.889			9/15 (60.0)	0.76 (0.33–1.73)	0.437		
With colistin nebuliser	7/11 (63.6)	1.32 (0.43–4.04)	0.622			4/9 (44.4)	0.71 (0.21–2.35)	0.569			8/12 (66.7)	2.05 (0.60–6.96)	0.252		
Carbapenem-containing regimen	39/83 (45.0)	0.65 (0.40–1.07)	0.091	1.00 (0.54–1.87)	0.994	29/75 (38.7)	0.57 (0.34–0.97)	0.037	0.69 (0.37–1.30)	0.251	39/96 (40.6)	0.55 (0.33–0.91)	0.021	0.66 (0.38–1.15)	0.145
Carbapenem + sulbactam	11/18 (61.1)	1.83 (0.69–4.86)	0.226			7/17 (41.2)	1.03 (0.39–2.74)	0.957			10/18 (55.6)	1.26 (0.48–3.29)	0.638		
Carbapenem + rifampin	4/5 (80.0)	0.74 (0.20–2.68)	0.739			3/4 (75.0)	0.68 (0.17–2.69)	0.585			3/10 (30.0)	0.41 (0.10–1.63)	0.207		
Carbapenem + amikacin	4/7 (57.1)	0.89 (0.24–3.40)	0.686			1/4 (25.0)	0.19 (0.02–1.57)	0.125			6/9 (66.7)	2.03 (0.50–8.29)	0.324		
Sulbactam-containing regimen	40/64 (62.5)	1.78 (1.03–3.08)	0.040	1.69 (0.89–3.19)	0.107	28/54 (51.9)	1.14 (0.65–1.98)	0.654			38/68 (55.9)	1.36 (0.78–2.35)	0.279		
Sulbactam monotherapy	5/9 (55.6)	1.42 (0.37–5.39)	0.610			5/8 (62.5)	2.06 (0.54–7.86)	0.289			6/9 (66.7)	2.03 (0.50–8.29)	0.324		
Sulbactam + minocycline	10/13 (76.9)	2.95 (0.90–9.63)	0.074	3.12 (0.80–12.19)	0.101	6/9 (66.7)	1.22 (0.41–3.62)	0.719			8/12 (66.7)	2.05 (0.60–6.96)	0.252		
Minocycline-containing regimen	28/41 (68.3)	1.94 (1.02–3.70)	0.044	1.97 (0.92–4.19)	0.080	21/36 (58.3)	1.44 (0.76–2.72)	0.264			25/43 (58.1)	1.46 (0.76–2.83)	0.258		
Amikacin-containing regimen	11/18 (61.1)	1.13 (0.47–2.70)	0.781			8/15 (53.3)	0.91 (0.37–2.26)	0.846			16/22 (72.7)	2.86 (1.09–7.55)	0.034	4.65 (1.58–13.67)	0.005
Tigecycline-containing regimen	5/11 (45.5)	0.79 (0.25–2.56)	0.697			4/10 (40.0)	0.80 (0.23–2.72)	0.718			6/12 (50.0)	0.99 (0.31–3.16)	0.990		

Table 3 (*Continued*)

Types and regimens of antibiotics	14 days	Univariate analysis		Multivariate analysis		28 days	Univariate analysis		Multivariate analysis		End of treatment	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Tigecycline monotherapy	4/6 (66.7)	1.51 (0.33–6.87)	0.595			3/5 (60.0)	1.21 (0.27–5.53)	0.802			5/7 (71.4)	2.54 (0.48–13.31)	0.271		

Data are expressed as number of patients/total patients (%) unless otherwise indicated. All sulbactams were administered in the form of ampicillin/sulbactam. CRAB = carbapenem-resistant *Acinetobacter baumannii*; OR = odds ratio; CI = confidence interval; APACHE = acute physiology and chronic health evaluation; SAPS = simplified acute physiology score.

95% CI 0.32–0.87, $P = 0.013$). Colistin monotherapy (aHR 2.07, 95% CI 1.27–3.35, $P = 0.003$) and combination therapy of colistin and rifampin (aHR 2.01, 95% CI 1.02–3.97, $P = 0.043$) were related to increased 28-day mortality.

3.3. Clinical and microbiological responses of CRAB infections by the types and regimens of antibiotics

The clinical responses of antibiotics for CRAB infection varied depending on the types and regimens of antibiotics: 50–80% at 14 days, 40–75% at 28 days after treatment, and 30–72% at the end of treatment (Table 3). A minocycline-containing regimen showed the most clinical responses at 14 days (68.3%) and 28 days (58.3%) of treatment, and an amikacin-containing regimen had the highest clinical response rates (72.7%) at the end of treatment. Among the regimens of antibiotics, the combination of carbapenem and rifampin showed the most clinical responses at 14 days (80.0%) and 28 days (75.0%) after treatment. Sulbactam monotherapy (66.7%) and a combination of sulbactam and minocycline (66.7%) had the highest clinical responses at the end of treatment. All types and regimens of antibiotics for CRAB infection did not show significant clinical responses except for amikacin-containing regimens. These were associated with more clinical improvement at the end of treatment (adjusted odds ratio [aOR] 4.65, 95% CI 1.58–13.67, $P = 0.005$). Younger patients showed more clinical improvements at 14 days and 28 days after treatment, and SAPS were associated with clinical improvement at 14 days and 28 days after treatment, and at the end of treatment. In the pneumonia subgroup, the significant variables related to clinical improvements were the same as for the overall study population (Supplementary Table 2).

A minocycline-containing regimen showed the highest microbiological responses at 14 days (80.6%) and 28 days (91.7%) after treatment, and at the end of treatment (92.0%) (Table 4). All patients treated with sulbactam monotherapy had microbiological responses at 14 days and 28 days after treatment, and at the end of treatment. In multivariate analysis, colistin-containing therapy (aOR 2.88, 95% CI 1.40–5.90. $P = 0.004$) and minocycline-containing regimen (aOR 6.88, 95% CI 2.49–18.97, $P < 0.001$) were associated with increased microbiological responses at 14 days after treatment. The combination of carbapenem and sulbactam were associated with decreased microbiological responses (aOR 0.25, 95% CI 0.07–0.86, $P = 0.028$), whereas the minocycline-containing regimen was associated with increased microbiological responses (aOR 6.46, 95% CI 1.40–29.83, $P = 0.017$) at 28 days after treatment. A minocycline-containing regimen was also associated with increased microbiological response (aOR 11.08, 95% CI 2.37–51.72, $P = 0.002$) at the end of treatment. In the pneumonia subgroup, a minocycline-containing regimen was also associated with increased microbiological responses at 14 days (aOR 7.98, 95% CI 2.77–22.84, $P < 0.001$) and 28 days after treatment (aOR 6.09, 95% CI 1.30–28.58, $P = 0.022$) and at the end of treatment (aOR 11.35, 95% CI 2.41–53.33, $P = 0.002$) (Supplementary Table 3). A colistin-containing regimen (aOR 4.21, 95% CI 1.88–9.40, $P < 0.001$) and the combination of colistin and minocycline (aOR 13.88, 95% CI 1.76–109.43, $P = 0.013$) were associated with increased microbiological responses at 14 days after treatment. The combination of carbapenem and sulbactam decreased microbiological responses at 14 days (aOR 0.18, 95% CI 0.04–0.83, $P = 0.028$) and 28 days after treatment (aOR 0.28, 95% CI 0.08–0.95, $P = 0.041$).

Another outcome indicator—duration of hospital stay—did not differ depending on the types and regimens of antibiotics in the treatment of CRAB infection.

3.4. Nephrotoxicity and hepatotoxicity by the types and regimens of antibiotics

Nephrotoxicity occurred in 35–100% and hepatotoxicity in 8–42% of patients depending on the types and regimens of antimicrobial therapy (Table 5). In multivariate analysis, a colistin-containing regimen increased nephrotoxicity (aOR 2.42, 95% CI 1.44–4.06, $P = 0.001$) whereas a carbapenem-containing regimen (aOR 0.55, 95% CI 0.32–0.94, $P = 0.028$), the combination of carbapenem and sulbactam (aOR 0.04, 95% CI 0.01–0.30, $P = 0.002$), and the combination of carbapenem and rifampin (aOR 0.14, 95% CI 0.03–0.68, $P = 0.015$) were associated with decreased nephrotoxicity. The underlying disease was at risk of nephrotoxicity. In the pneumonia subgroup, the colistin-containing regimen was associated with increased nephrotoxicity, whereas the carbapenem regimen was associated with decreased nephrotoxicity (Supplementary Table 4). In hepatotoxicity, tigecycline was the only antibiotic associated with the risk of liver toxicity in the overall study population as well as the pneumonia subgroup.

4. Discussion

To our knowledge, this is the first study to compare the efficacy of three or more types and regimens of antibiotics simultaneously for CRAB infections through a multicentre study in a high endemic area. The combination therapy of colistin and carbapenem decreased 7-day mortality and a sulbactam-containing regimen decreased 28-day mortality, whereas colistin monotherapy increased 7-day and 28-day mortality. An amikacin-containing regimen was associated with increased clinical responses at the end of treatment. A minocycline-containing regimen was associated with increased microbiological responses at 14 days, 28 days, and at the end of treatment.

Patients in this study were of relatively higher age (mean 67 y), and had higher rates of bacteraemia (31%) than in previous studies, and had one or more underlying diseases. This study may also provide useful indications for CRAB pneumonia given that most CRAB infections involve pneumonia and that 70% of pneumonia cases are VAP. All CRAB strains except one were susceptible to colistin and the susceptibility of minocycline remained relatively high at 80%. The susceptibility rates of ampicillin/sulbactam and

Table 4
Types and regimens of antibiotics for CRAB infections and the resulting microbiological responses.

Types and regimens of antibiotics	14-day	Univariate analysis		Multivariate analysis		28-day	Univariate analysis		Multivariate analysis		End of treatment	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age		0.98 (0.96–0.99)	0.042	0.97 (0.95–0.99)	0.017		0.98 (0.95–1.00)	0.103				0.98 (0.96–1.00)	0.053	0.99 (0.96–1.02)	0.431
Sex		1.49 (0.76–2.89)	0.245				1.58 (0.68–3.70)	0.290				1.34 (0.69–2.61)	0.380		
Any underlying diseases		0.57 (0.23–1.45)	0.238				0.33 (0.07–1.54)	0.158				0.53 (0.19–1.49)	0.226		
Charlson Comorbidity Index		0.88 (0.76–1.03)	0.102				0.83 (0.69–1.01)	0.054	0.82 (0.68–0.99)	0.042		0.79 (0.67–0.92)	0.003	0.78 (0.66–0.93)	0.005
APACHE II score		0.96 (0.91–1.01)	0.088	0.99 (0.94–1.05)	0.735		0.96 (0.90–1.03)	0.289				0.96 (0.91–1.02)	0.162		
SAPS II score		0.99 (0.97–1.02)	0.590				1.01 (0.98–1.04)	0.608				1.00 (0.98–1.03)	0.888		
Colistin-containing regimen	61/102 (59.8)	2.39 (1.25–4.60)	0.009	2.88 (1.40–5.90)	0.004	51/67 (76.1)	1.94 (0.85–4.41)	0.116	0.73 (0.29–1.84)	0.500	56/103 (54.4)	1.15 (0.61–2.19)	0.666		
Colistin monotherapy	13/30 (43.3)	0.66 (0.30–1.46)	0.303			10/17 (58.8)	0.54 (0.19–1.56)	0.255			13/31 (41.9)	0.57 (0.26–1.27)	0.169		
Colistin + carbapenem	15/27 (55.6)	1.20 (0.52–2.74)	0.673			12/15 (80.0)	1.79 (0.47–6.82)	0.393			15/28 (53.6)	1.02 (0.45–2.32)	0.955		
Colistin + minocycline	14/15 (93.3)	15.40 (1.97–120.16)	0.009			13/13 (100)		0.999			13/13 (100)		0.998		
Colistin + rifampin	5/8 (62.5)	1.58 (0.36–6.85)	0.540			5/7 (71.4)	1.05 (0.19–5.69)	0.957			4/9 (44.4)	0.69 (0.18–2.68)	0.595		
Colistin + sulbactam	5/10 (50.0)	0.92 (0.26–3.23)	0.904			4/7 (57.1)	0.53 (0.11–2.53)	0.428			5/10 (50.0)	0.88 (0.24–3.15)	0.840		
With colistin nebuliser	5/7 (71.4)	2.41 (0.45–12.77)	0.303			4/4 (100)		0.999			4/6 (66.7)	1.81 (0.32–10.14)	0.503		
Carbapenem-containing regimen	19/54 (35.2)	0.36 (0.18–0.71)	0.003	0.70 (0.32–1.53)	0.370	19/33 (57.6)	0.43 (0.18–1.02)	0.055	0.73 (0.29–1.84)	0.500	20/58 (34.5)	0.30 (0.16–0.59)	0.001	0.49 (0.24–1.01)	0.051
Carbapenem + sulbactam	2/14 (14.3)	0.13 (0.03–0.62)	0.010			5/12 (41.7)	0.25 (0.07–0.86)	0.028	0.25 (0.07–0.86)	0.028	4/14 (28.6)	0.32 (0.10–1.07)	0.065	0.42 (0.12–1.46)	0.172
Carbapenem + rifampin	0/4		0.999			1/2 (50.0)	0.41 (0.03–6.76)	0.533			0/6		0.999		
Carbapenem + amikacin	1/3 (33.3)	0.46 (0.04–5.15)	0.527			1/2 (50.0)	0.41 (0.025–6.761)	0.533			1/4 (25.0)	0.29 (0.03–2.81)	0.283		
Sulbactam-containing regimen	22/48 (45.8)	0.71 (0.36–1.40)	0.321			22/36 (61.1)	0.52 (0.22–1.22)	0.135			23/43 (53.5)	1.02 (0.51–2.06)	0.951		
Sulbactam monotherapy	6/6 (100)		0.999			6/6 (100)		0.999			5/5 (100)		0.999		
Sulbactam + minocycline	5/10 (50.0)	0.92 (0.26–3.32)	0.904			4/6 (66.7)	0.83 (0.14–4.75)	0.831			5/7 (71.4)	2.28 (0.43–12.13)	0.332		
Minocycline-containing regimen	25/31 (80.6)	5.09 (1.96–13.22)	0.001	6.88 (2.49–18.97)	<0.001	22/24 (91.7)	5.98 (1.32–27.14)	0.020	6.46 (1.40–29.83)	0.017	23/25 (92.0)	13.51 (3.06–59.55)	0.001	11.08 (2.37–51.72)	0.002
Amikacin-containing regimen	4/12 (33.3)	0.44 (0.13–1.52)	0.192			5/9 (55.6)	0.49 (0.12–1.95)	0.312			7/13 (53.8)	1.03 (0.33–3.22)	0.954		
Tigecycline-containing regimen	2/6 (33.3)	0.45 (0.08–2.54)	0.366			3/5 (60.0)	0.61 (0.10–3.84)	0.600			5/7 (71.4)	2.28 (0.43–12.13)	0.332		

Table 4 (*Continued*)

Types and regimens of antibiotics	14-day	Univariate analysis		Multivariate analysis		28-day	Univariate analysis		Multivariate analysis		End of treatment	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Tigecycline monotherapy	1/3 (33.3)	0.46 (0.04–5.15)	0.527			2/3 (66.7)	0.83 (0.07–9.49)	0.882			4/4 (100.0)		0.999		

Data are expressed as number of patients/total patients (%) unless otherwise indicated. All sulbactams were administered in the form of ampicillin/sulbactam. CRAB = carbapenem-resistant *Acinetobacter baumannii*; OR = odds ratio; CI = confidence interval; APACHE = acute physiology and chronic health evaluation; SAPS = simplified acute physiology score.

Table 5
Nephrotoxicity and hepatotoxicity by the types and regimens of antibiotics for CRAB infections.

Types and regimens of antibiotics	Nephrotoxicity	Univariate analysis		Multivariate analysis		Hepatotoxicity	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age		0.99 (0.98–1.01)	0.825				1.01 (0.98–1.03)	0.552		
Sex		1.67 (1.01–2.77)	0.046	1.64 (0.95–2.81)	0.074		0.81 (0.39–1.68)	0.564		
Any underlying diseases		0.32 (0.14–0.74)	0.008	0.38 (0.16–0.90)	0.029		0.86 (0.31–2.39)	0.774		
Charlson Comorbidity Index		0.98 (0.88–1.09)	0.708				0.97 (0.83–1.14)	0.723		
APACHE II score		0.95 (0.92–0.99)	0.006	0.96 (0.93–1.01)	0.055		0.98 (0.93–1.028)	0.350		
SAPS II score		0.99 (0.97–1.01)	0.106				0.98 (0.95–1.01)	0.078	0.98 (0.95–1.01)	0.064
Colistin-containing regimen	60/171 (35.1)	2.71 (1.66–4.44)	<0.001	2.42 (1.44–4.06)	0.001	23/171 (13.5)	1.17 (0.57–2.42)	0.669		
Colistin monotherapy	26/58 (44.8)	0.99 (0.56–1.77)	0.980			7/58 (12.1)	0.92 (0.38–2.23)	0.858		
Colistin + carbapenem	17/41 (41.5)	1.17 (0.60–2.28)	0.654			5/41 (12.2)	0.94 (0.34–2.58)	0.906		
Colistin + minocycline	0/22		0.998			3/22 (13.6)	1.09 (0.31–3.87)	0.899		
Colistin + rifampin	4/17 (23.5)	2.77 (0.88–8.73)	0.081	1.99 (0.61–6.56)	0.255	3/17 (17.6)	0.75 (0.09–6.12)	0.790		
Colistin + sulbactam	5/15 (33.3)	1.66 (0.55–4.98)	0.368			1/15 (6.7)	0.47 (0.06–3.71)	0.477		
With colistin nebuliser	3/13 (23.1)	2.81 (0.76–10.43)	0.123			2/13 (15.4)	1.26 (0.27–5.92)	0.773		
Carbapenem-containing regimen	57/97 (58.8)	0.42 (0.25–0.69)	0.001	0.55 (0.32–0.94)	0.028	13/97 (13.4)	1.09 (0.53–2.26)	0.817		
Carbapenem + sulbactam	17/18 (94.4)	0.04 (0.01–0.32)	0.002	0.04 (0.01–0.30)	0.002	1/18 (5.6)	0.39 (0.05–2.98)	0.361		
Carbapenem + rifampin	8/10 (80.0)	0.19 (0.04–0.92)	0.039	0.14 (0.03–0.68)	0.015	1/10 (10.0)	0.75 (0.09–6.12)	0.790		
Carbapenem + amikacin	7/9 (77.8)	0.22 (0.05–1.08)	0.063	0.24 (0.05–1.20)	0.082	0/9		0.999		
Sulbactam-containing regimen	35/69 (50.7)	0.73 (0.42–1.25)	0.246			6/69 (8.7)	0.58 (0.23–1.46)	0.248		
Sulbactam monotherapy	5/9 (55.6)	0.64 (0.17–2.42)	0.508			1/9 (11.1)	0.85 (0.10–7.00)	0.880		
Sulbactam + minocycline	0/14		0.998			1/14 (7.1)	0.51 (0.07–4.04)	0.525		
Minocycline-containing regimen	0/46		0.997			7/46 (15.2)	1.28 (0.52–3.13)	0.587		
Amikacin-containing regimen	16/22 (72.7)	0.28 (0.10–0.73)	0.009	0.53 (0.18–1.56)	0.247	0/22		0.998		
Tigecycline-containing regimen	8/12 (66.7)	0.39 (0.11–1.32)	0.130			4/12 (33.3)	3.72 (1.06–13.05)	0.040	4.59 (1.25–16.82)	0.021
Tigecycline monotherapy	7/7 (100)		0.999			3/7 (42.9)	5.50 (1.18–25.67)	0.030	7.00 (1.35–36.34)	0.021

Data are expressed as number of patients/total patients (%) unless otherwise indicated. All sulbactams were administered in the form of ampicillin/sulbactam. CRAB = carbapenem-resistant *Acinetobacter baumannii*; OR = odds ratio; CI = confidence interval; APACHE = acute physiology and chronic health evaluation; SAPS = simplified acute physiology score.

trimethoprim/sulfamethoxazole were <10%. The most frequently used regimen in the treatment of CRAB infection was a colistin-containing regimen. Among colistin-containing regimens, colistin monotherapy was the most commonly used, and carbapenems were the most frequently used antibiotics in combination therapy with colistin.

The combination of colistin and carbapenem, which showed 7-day survival improvement, was consistent with results which may contribute to the reduction in mortality in previous studies [28]. This combination has been proven to have a high synergistic effect against CRAB in an in vitro study [29]. Although 28-day survival improvement was not shown with the combination of colistin and carbapenem, the potential result from higher APACHE score and SAPS in the death group should be considered in the interpretation. Considering the increased mortality, colistin monotherapy should be used cautiously in treatment for severe CRAB infection or pneumonia.

A sulbactam-containing regimen contributed significantly to the increased survival rate, which is notable for high survival despite the low susceptibility of sulbactam. In sulbactam monotherapy, all patients survived at day 7, despite a 22.2% resistance rate. Most sulbactam-resistant strains were treated with a combination of sulbactam and minocycline, which showed relatively low mortality and good clinical and microbiological responses without statistical significance. Research on the combination of sulbactam and minocycline is limited, and additional basic and clinical studies may be needed based on this result. In addition, all sulbactams used in this study were ampicillin/sulbactam combinations, suggesting that the development of a single sulbactam formulation may be required for use as high-dose sulbactam.

Minocycline had the best microbiological responses at any time and tended to have low mortality rate without statistical significance. Minocycline had bactericidal activity against CRAB and synergistic effects with other antibiotics [25]. Previous studies showed good clinical and microbiological responses in treatment of CRAB infections when used intravenously alone or in combination, but results on improving survival are limited [25,30,31]. A decrease in mortality without statistical significance may be related to the inferiority of the oral formulation despite high oral bioavailability of minocycline. Regarding the 80% susceptibility rate of minocycline, additional study may be needed to evaluate the efficacy of intravenous minocycline. Tigecycline, an analogue of tetracycline such as minocycline, showed no significant results in this study. It is presumed that most of the infections in this study were pneumonia, and tigecycline levels in epithelial lining fluid and alveolar cells are relatively low [32].

An amikacin-containing regimen showed good clinical response at the end of treatment, but this result alone is insufficient to judge the efficacy of amikacin for CRAB infections because of limited prior studies and low lung tissue penetration [33]. Further studies on amikacin may be needed in that the possible confounding variables such as demographic data, Charlson comorbidity index, APACHE score, SAPS, mortality, and antibiotic duration were not significantly different between amikacin and non-amikacin groups.

Colistin was significantly associated with the development of any stage of nephrotoxicity and tigecycline was significantly related to development of hepatotoxicity, as shown in previous studies [34,35]. When colistin or tigecycline is used for treatment of CRAB infections, careful monitoring is needed for side effects.

This study has several limitations. First, this study is retrospective and non-randomized, so some biases may occur. The types, number, and duration of antibiotics vary from group to group, and the choices of antibiotics were determined by each clinician. Additional prospective studies may be needed for the antibiotics which were statistically significant in this study, such as the combination of colistin and carbapenem, sulbactam-containing regimen, and minocycline-containing regimen. Second, the optimal dose of sulbactam was not administered and an oral formulation of minocycline was used in this study. Nevertheless, sulbactam and minocycline contributed to survival improvement and microbiological responses, respectively, which suggests the need for further microbiological or clinical studies.

Based on these results, a combination of colistin and carbapenem, and a sulbactam-containing regimen may improve survival rate in treatment of CRAB infections. A minocycline-containing regimen showed consistent significant improvement in microbiological responses, and further studies may be needed to evaluate improved mortality. Colistin monotherapy should be considered cautiously for severe CRAB infections given its significant association with increased 7-day and 28-day mortality.

Author contributions

WSC, HJC, HYK, YRK, HP, and JWS conceived the idea. WSC, SL, CM, DWP, JYS, JK, MNP, HJL, BK, YMJ, and JHK collected the data. JS, WSC, SL, CM, HJC, JYK, YRK, JP, and JWS analysed the data. HS, CWC, and JWS prepared the manuscript and final edition of the document. All authors read and approved the final manuscript.

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Conflict of interest

All authors certify that there are no potential conflicts of interest to declare.

Ethics approval

The study protocol was approved by the institutional review board of Korea University Anam Hospital (no. 2015AN0325). This retrospective study was waived the need for informed consent.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2021.01.018.

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