ORIGINAL ARTICLE

Clinical Outcomes and Associated Factors for Mortality among Pediatric Patients with Carbapenem-Resistant *Acinetobacter baumannii*

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Background: *Acinetobacter baumannii* bacteremia is a hospital-acquired infection with a high mortality rate. Up to 80% of hospital-acquired *A. baumannii* infections are caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) strains.

Objective: To determine the overall 30-day mortality rate, factors associated with mortality, and antibiotic drug susceptibility patterns of CRAB isolates among children with hospital-acquired CRAB bloodstream infections.

Materials and Methods: A retrospective review was conducted among hospitalized pediatric patients between January 2017 and September 2022 at King Chulalongkorn Memorial Hospital, Bangkok. The inclusion criteria were CRAB bacteremia in children under 18 years of age. Thirty-day mortality after CRAB bacteremia was analyzed using Kaplan-Meier estimates. Associated factors were analyzed by Poisson regression. Antibiotic susceptibility patterns of nine antimicrobial agents were summarized.

Results: Fifty-eight patients with 66 episodes of CRAB bacteremia were identified. The median age was 7.5 months (IQR 0.8 to 60.0), and 86.4% of the patients were admitted to the intensive care unit. Central line-associated bloodstream infections (CLABSI) were identified in 90.9% of cases. Most patients (74.2%) received colistin combination with sulbactam regimen. The 30-day mortality rate was 19.7% (95% CI 10.9 to 31.3). Associated factors for mortality rate were septic shock (aRR 7.6, 95% CI 2.3 to 25.0) and underlying congenital heart disease (aRR 3.4, 95% CI 1.0 to 11.7). Drug susceptibility of colistin and tigecycline were 93% and 48%, respectively. Sulbactam was not susceptible.

Conclusion: One-fifth of children with CRAB bacteremia died within 30 days. Associated factors with mortality were septic shock and congenital heart disease. Colistin had the highest in vitro drug susceptibility rate. The common regimen used in the present study was colistin combination with sulbactam therapy.

Keywords: *Acinetobacter baumannii*; Bacteremia; Carbapenem resistance; Susceptibility; Mortality; Pediatrics

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Acinetobacter baumannii is a gram-negative coccobacillus. It is a common causative organism of hospital-acquired infections. According to the World Health Organization (WHO), *A. baumannii* is one of the most problematic human pathogens globally with a high mortality rate. There are more than one million cases of *A. baumannii* infections per year around the world[1,2]. This pathogen affects many infection sites such as pneumonia, bloodstream, urinary tract, surgical site, and central venous system[3]. Most patients with *A. baumannii* infection are admitted to the intensive care units[4,5].

Globally, *A. baumannii* can resist multiple classes of antibiotics[4,6-8]. Carbapenem-resistant *Acinetobacter baumannii* (CRAB) was considered to be an urgent threat worldwide due to its high mortality rate[4,9,10]. However, a higher prevalence was found in developing countries such as Asia and Africa with 70% to 80% compared with developed countries such as United States of America with 40% to 50% and Europe with 5% to 20%[11-13]. In Thailand, the National Antimicrobial Resistant Surveillance

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Centre, Thailand (NARST) reported that the prevalence of CRAB was as high as 70% in 2021[14]. Nevertheless, studies on the pediatric population in East and Southeast Asia reported a lower prevalence of CRAB at 35% to 40%, with an incidence of 12 cases per 10,000 hospitalized children[6,15-17]. As a result of the high rate of resistance, only a few effective antibiotics are available including colistin, tigecycline, and sulbactam, with susceptibility rates of 90% to 100%, 90%, and 7% to 27%, respectively[17,18]. In the earlier decades, colistin or ampicillin-sulbactam monotherapy was widely used[17,19]. Because of the intensifying rate of CRAB infections[20,21], the updated Infectious Diseases Society of America (IDSA) guidelines in 2022 suggested ampicillin-sulbactam monotherapy only for mild CRAB infections and combination therapy for moderate to severe CRAB infections. High-dose ampicillin-sulbactam or polymyxin B or tigecycline can be included in the combination regimens[22-26].

CRAB bloodstream infection was considered to have one of the highest mortality rates[25]. Recent studies in adults show that the 30-day mortality rate in bacteremia was as high as 55% to 70%[18,27,28]. The factors associated with mortality include septic shock, malignancy-associated febrile neutropenia, immunosuppressant use, and pneumonia[15,17,18,27]. However, limited studies in the pediatric population are reported[15,17]. Thus, the objective of the present study was to determine the overall 30-day mortality rate among children with hospital-acquired CRAB bloodstream infections and the factors associated with mortality and the antibiotic drug susceptibility patterns.

Materials and Methods

Study population and data collection

The present study was a retrospective study conducted at King Chulalongkorn Memorial Hospital, a 1,435-bed tertiary care university hospital in Bangkok, Thailand. The eligible criteria were hospitalized children under 18 years of age who had CRAB bacteremia. CRAB isolates were defined as those resistant to at least one carbapenem class antibiotic as imipenem, meropenem, or doripenem. Patients were considered to have CRAB bacteremia if they had clinical symptoms of systemic inflammatory response syndrome (SIRS) documented in their medical records. SIRS criteria included at least two of the following criteria, body temperature greater than 38.5 or less than 36 degrees Celsius, heart rate greater than two standard deviations above the mean age range, respiratory rate greater than two standard deviations above the mean age range, elevated or depressed leukocyte count number according to age, and immature neutrophils greater than 10% of total leukocytes[29].

Cases were identified by searching the hospital's microbiological laboratory database of *A. baumannii* clinical isolates between January 2017 and September 2022. Medical chart records were retrieved from the hospital's electronic medical records to review eligibility criteria. For eligible participants, medical records were reviewed by two investigators (MS, PS) including demographic data, co-morbidities, clinical syndromes, antibiotic treatment regimens, and treatment outcomes. *A. baumannii* drug susceptibility patterns were collected from the patients' medical records and microbiological database. The present study was approved by the Institutional Review Board of the Faculty of Medicine Chulalongkorn University, Bangkok, Thailand (IRB no. 354/64). Patient data were managed confidentially and reported without patient identifiers.

Definitions of clinical syndrome

Sources of infection prior to CRAB bacteremia were categorized as 1) Central line-associated bloodstream infection (CLABSI) was identified if a patient had a central venous catheter or an arterial catheter in place for 48 hours before a positive blood culture[30]. 2) Ventilator-associated pneumonia (VAP) if pneumonia occurred 14 days prior of bacteremia[30], which is the criteria for VAP diagnosis that followed the U.S. Centers for Disease Control and Prevention (CDC) guidelines for infants and children[31]. 3) Surgical site infection or other organ-specific infections were defined as simultaneous *A. baumannii* infections at the time of bacteremia[30]. Septic shock defined as sepsis with cardiovascular dysfunction, either hypotension, the need for inotropes, or impaired perfusion[32].

Empirical antibiotic regimens were defined as treatment started within 24 hours of initial blood culture collection. Definitive antibiotic regimens were defined as treatment prescribed after *A. baumannii* was first reported to the clinicians. Persistent positive hemoculture was defined when CRAB remained in the blood beyond 96 hours of antibiotic treatment or grew again after sterility was documented once during antibiotic therapy or no evidence of sterility before death.

Antimicrobial susceptibility pattern of *A. baumannii*

A. baumannii isolate was speciated by the automated VITEK 2XL system (bioMerieux, Durham, North Carolina) and VITEK MS (bioMerieux SA, France). If there were multiple clinical isolates for an infection episode, only data from the first isolate was included in the analysis. Susceptibility testing of antibiotics including ceftazidime, imipenem, meropenem, doripenem, gentamicin, amikacin, trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, and levofloxacin were performed by the disk diffusion method. The Clinical and Laboratory Standards Institute (CLSI) susceptibility interpretive criteria were used for most antibiotic agents[33]. Minimal inhibitory concentrations (MIC) of colistin, tigecycline and sulbactam were determined only upon the request of the primary physician.

MIC of colistin was performed by broth microdilution method where MICs of 2 or less and of 4 or more mg/L were considered susceptible and resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guideline[34]. MIC of tigecycline was performed by the E-test method (bioMerieux, Durham, North Carolina). Given the lack of standard interpretative criteria, tigecycline MIC breakpoints of Enterobacterales were used according to the Tygacil package insert, such as 2 or less mg/L for susceptibility and 8 or more mg/L for resistance. MIC of sulbactam was determined between 2020 and 2022 using MIC Test Strip (Liofilchem, Roseto Degli Abruzzi, Italy). MIC sulbactam of 4 or less and 16 or more mg/L were considered susceptible and resistant, respectively, according to the breakpoints of CLSI's ampicillin/sulbactam.

Statistical analysis

Continuous data were presented using means with standard deviations or medians with interquartile range, and categorical data was presented using percentages. The 30-day mortality rates were presented as percentages with 95% confidence intervals (CIs). The Kaplan-Meier method was used for survival analysis. Poisson regressions were utilized to assess the associations between independent risk factors and 30-day mortality rates, presented in rate ratios (RRs) with 95% CIs and p-value for Z-test. Factors with the association of p-value less than 0.1 in univariable analysis were selected for further multivariable analysis. A p-value of less than 0.05 was considered statistically significant. Percentage of susceptibility of CRAB to each antibiotic agent was reported with MIC range, MIC50, and MIC90 where available. MIC50 and MIC90 were defined as the MIC of the antibiotic at which 50% and 90% of CRAB isolates were inhibited, respectively. Statistical analyses were performed using Stata, version 13 (StataCorp LP, College Station, TX, USA).

Results

Demographic data

Between January 2017 and September 2022, there were 1,214 *A. baumannii* clinical isolates recovered from all pediatric clinical samples, of which 863 isolates (71%) were carbapenem-resistant organisms. One hundred four isolates were identified from blood cultures (69 first isolates and 35 secondary isolates within the same clinical episode). Sixty-six hospital-acquired CRAB bacteremia episodes from 58 participants were included in the analysis. Three episodes were excluded because these were polymicrobial bacteremia and no treatment prescribed for *A. baumannii* as upfront physician classified them as colonization. Besides, the treatment was given for the other pathogen instead. Demographic data and clinical characteristics are shown in Table 1. The median age of patients was 7.5 months (IQR 0.8 to 60.0). The percentages of neonates and infants were 25.8% and 31.8% respectively. Common co-morbidities were congenital heart diseases (40.9%), hepatobiliary/gastrointestinal diseases (24.2%), and neurological diseases (15.2%). During the study period, there were 55,311 hospitalized children younger than 18 years old. The incidence rate of CRAB bacteremia was 11.9 (95% CI 9.2 to 15.2) episodes per 10,000 hospitalized children.

The median time to CRAB bacteremia was 26.5 days (IQR 12.0 to 81.8) after admission. The majority of patients (86.4%) were admitted to the intensive care unit at the time of CRAB bacteremia. Sources of CRAB bacteremia were CLABSI (90.9%) and VAP (28.8%) within 14 days of bacteremia. The median catheter indwelling time before CRAB bacteremia was 10.0 days (IQR 5.3 to 18.8).

Clinical characteristics

There were 31 episodes of CRAB bacteremia, of which had CRAB in other sites, including 29 cases of pneumonia (43.9%), five cases of urinary tract infections (7.6%), two cases of surgical site infections (3%), one case of tracheitis (1.5%), one case of mediastinitis (1.5%), and one case of intraabdominal infection (1.5%). There were 39 episodes as polymicrobial bacteremia, including 29 episodes

Table 1. Demographic and clinical characteristics for 66 episodes of hospital acquired carbapenem-resistant *Acinetobacter baumannii* bacteremia

Characteristics	n (%)
Male; n (%)	35 (53.0)
Age (months); median (IQR)	7.5 (0.8, 60.0)
Duration of hospitalization prior to bacteremia (days); median (IQR)	26.5 (12.0, 83.0)
ICU admission; n (%)	57 (86.4)
Comorbidities; n (%)	
Congenital heart diseases	27 (40.9)
Hepatobiliary and gastrointestinal diseases	16 (24.2)
Neurological diseases	10 (15.2)
Immunocompromised statesκ	8 (12.1)
Respiratory diseases	7 (10.6)
Congenital anomalies	7 (10.6)
Burn injury	6 (9.1)
Catheters and devices†; n (%)	
Central venous catheters	63 (95.5)
Arterial catheters	26 (39.4)
Endotracheal tubes/tracheostomy tube	44 (66.7)
Colonization with CRAB before bacteremia episodes; n (%)	
Respiratory tract	12 (18.2)
Pus/wound/drain	7 (10.6)
Urine	2 (3.0)
Sources of infection prior to CRAB bacteremia; n (%)	
CLABSI	60 (90.9)
VAP	19 (28.8)
Tracheitis, mediastinitis	2 (3.0)
Septic shock; n (%)	20 (30.3)
Polymicrobial bacteremia*; n (%)	39 (59.1)
Gram negative pathogen	29 (43.9)
Gram positive pathogen	12 (18.2)
Candida species	5 (7.6)
Empirical antibiotic regimens; n (%)	
Colistin-based regimen	37 (56.0)
• Colistin and sulbactam	26 (39.4)
• Colistin and meropenem	10 (15.1)
• Colistin and cephalosporin	1 (1.5)
Other regimens	29 (44.0)
• Meropenem	24 (36.4)
• Others	5 (7.6)
Definitive antibiotic regimens; n (%)	
Colistin combination with sulbactam	49 (74.2)
• Colistin and sulbactam	23 (34.8)
• Colistin and sulbactam with tigecycline	12 (18.2)
• Colistin and sulbactam with others	14 (21.2)
Colistin combination	8 (12.1)
Cefoperazone-sulbactam and amikacin	2 (3.0)
Other regimens	7 (10.6)
Length of stay** (days); median (IQR)	96.5 (43, 180)

ICU=intensive care unit; CRAB=carbapenem-resistant *Acinetobacter baumannii*; CLABSI=central line-associated bloodstream infection; VAP=ventilator-associated pneumonia; IQR=interquartile range

κ Received chemotherapy or immunosuppressive drugs within 30 days or primary immune deficiency (3 malignancies, 2 hematopoietic stem cell transplants, 2 solid organ transplants, 1 autoimmune disease); † Catheters and devices remained in situ on the day of hemoculture first positive in each episode; * Concomitant bacteremia which occurred during CRAB bacteremia episodes (33 single pathogen, 5 double pathogens, 1 triple pathogens); ** Length of stay defined as duration from admission to discharge or death

of gram-negative pathogens with eleven *Klebsiella pneumoniae*, nine *Stenotrophomonas maltophilia*, six *Pseudomonas aeruginosa*, and three other pathogens, twelve episodes of gram-positive pathogens with eight *Enterococcus* species and four *Staphylococcus* species, and five episodes of *Candida* species.

Antibiotic susceptibility patterns and antibiotic treatment regimens

The antibiotic susceptibility patterns of CRAB isolates are shown in Table 2. Colistin was susceptible in 93% of isolates. Tigecycline was susceptible in 48% of isolates. Although none of CRAB isolates were susceptible to sulbactam, eight (25.0%) and 19 (59.4%) isolates had sulbactam MIC of 16 or less and 32 or less mg/L, respectively. Twenty percent of isolates showed susceptibility to TMP/SMX, while less than 15% remained sensitive to aminoglycosides, ceftazidime, and quinolones.

The definitive antibiotic regimens are described in Table 1. The most common regimen was a colistin combination with sulbactam at 74.2%, followed by colistin combination at 12.1%, cefoperazone-sulbactam and amikacin at 3.0%, and other regimens at 10.6%.

The colistin dosage was 5 mg/kg/day or less in 91.2% of colistin containing regimens, median of tigecycline dosage was 2.5 mg/kg/day (range 2.0 to 6.0), and the sulbactam dosage was 200 mg/kg/day or more in 76.5% of sulbactam containing regimens.

Treatment outcome and mortality rate

Among 66 CRAB bacteremia events, thirteen patients died within 30 days of the event. The 30-day mortality was 19.7% (95% CI 10.5 to 33.7). The 30-day mortality rate in colistin combination

Table 2. Antibiotic susceptibility profiles of hospital acquired carbapenem-resistant *Acinetobacter baumannii* isolates

Antibiotic agents	Susceptible isolates (%)	MIC range (mg/L)	MIC50 (mg/L)	MIC90 (mg/L)
Colistin* (n=27)	25 (93)	0.125 to 8	0.5	2
Tigecycline* (n=46)	22 (48)	0.25 to 32	3	12
Sulbactam* (n=32)	0 (0)	6 to >256	24	64
Trimethoprim/sulfamethoxazole (n=66)	13 (20)			
Amikacin (n=66)	9 (14)			
Gentamicin (n=66)	6 (9)			
Ceftazidime (n=66)	3 (5)			
Ciprofloxacin (n=66)	2 (3)			
Levofloxacin (n=66)	2 (3)			

MIC=minimal inhibitory concentration

* Definition of susceptible: colistin MICs of ≤2 mg/L, tigecycline MICs of ≤2 mg/L, sulbactam MICs of ≤4 mg/L

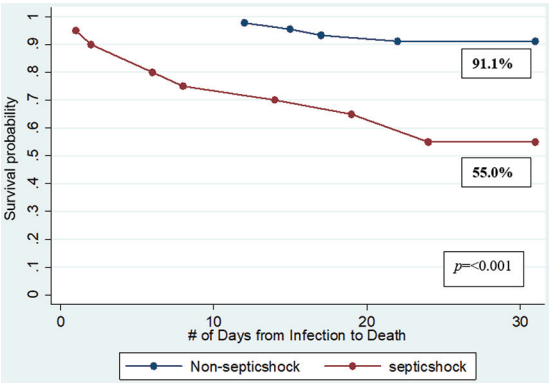

Figure 1. Survival probability among pediatric patients with hospital acquired carbapenem resistance *A. baumannii* blood stream infection: non septic shock vs. septic shock.

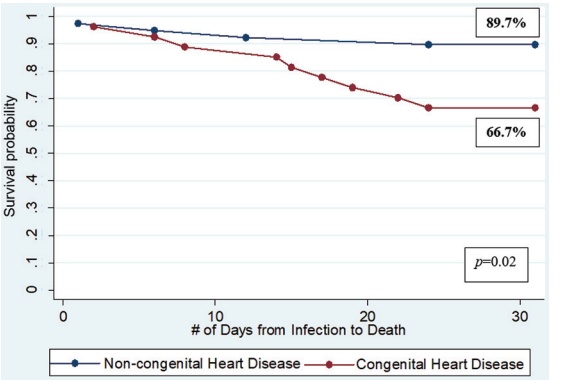

Figure 2. Survival probability among pediatric patients with hospital acquired carbapenem resistance *A. baumannii* blood stream infection: non-congenital heart disease versus congenital heart disease

with sulbactam, cefoperazone-sulbactam, amikacin, and other regimens were 20.4%, 25.0%, 0%, and 14.3%, respectively (p>0.05). The median time from diagnosis to death was 13.5 days (IQR 5.0 to 21.0).

In sixty-three episodes, follow-up blood cultures were drawn at least once after documented growth in a blood culture bottle, with a median of two times per week and a range of 2 to 4. Three episodes did not have a repeat blood culture due to early death. The median time for bacterial eradication was 2.5 days (range 1 to 11, IQR 2 to 3). Eighteen episodes had *A. baumannii* persistent positives hemoculture with 12 that had CRAB remained in the blood beyond 96 hours, four that had CRAB grew again after sterility was documented once during antibiotic therapy, and two that had no evidence of sterility before death.

The associated factors with mortality are shown in Table 3. In multivariable analysis, septic shock was associated with 30-day mortality at an adjusted RR of 7.6 (95% CI 2.3 to 24.9), while congenital heart disease co-morbidity was associated with 30-day mortality at an adjusted RR of 3.4 (95% CI 1.0 to 11.7). The proportion of survivors among pediatric patients with hospital acquired carbapenem resistance *A. baumannii* blood stream infection with and without septic shock were 55.0%, and 91.1%, respectively, as shown in Figure 1. Whereas, the proportion of survivors among pediatric patients with hospital acquired carbapenem resistance *A. baumannii* blood stream infection with and without congenital heart disease were 66.7%, and 89.7%, respectively, as shown in Figure 2.

Discussion

In the present study, the 30-day mortality rate was one-fifth, which was lower than the previous study that ranged from 25% to 70%[15,17,35]. Independent factors that associated with death included septic shock and congenital heart disease. Colistin confers the best drug susceptibility against this pathogen, followed by tigecycline and trimethoprim/sulfamethoxazole,

Table 3. Association of factors and 30-day mortality rate of hospital acquired carbapenem-resistant *Acinetobacter baumannii* bacteremia

Characteristic	n	30-day mortality; n (%)	Crude RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Sex						
Male	35	9 (25.7)	1			
Female	31	4 (12.9)	0.41 (0.13 to 1.33)	0.14[a]		
Comorbidities						
Congenital heart diseases						
• No	39	4 (10.3)	1			
• Yes	27	9 (33.3)	4.14 (1.28 to 13.45)	0.02[a]	3.42 (1.00 to 11.67)	0.05[a]
Hepatobiliary and gastrointestinal diseases						
• No	50	11 (22.0)	1			
• Yes	16	2 (12.5)	0.40 (0.09 to 1.81)	0.24[a]		
Neurological diseases						
• No	56	13 (23.2)		0.19[b]		
• Yes	10	0 (0.0)				
Immunocompromised states						
• No	58	11 (19.0)	1			
• Yes	8	2 (25.0)	0.86 (0.19 to 3.89)	0.85[a]		
Respiratory diseases						
• No	59	11 (18.6)	1			
• Yes	7	2 (28.6)	1.73 (0.38 to 7.79)	0.48[a]		
Congenital anomalies						
• No	59	11 (18.6)	1			
• Yes	7	2 (28.6)	1.75 (0.39 to 7.89)	0.47[a]		
Severity						
Insertion of the endotracheal tube						
• No	22	1 (4.6)	1			
• Yes	44	12 (27.3)	8.50 (1.10 to 65.35)	0.04[a]	3.88 (0.44 to 33.80)	0.22[a]
Septic shock						
• No	45	4 (8.9)	1			
• Yes	20	9 (45.0)	7.48 (2.30 to 24.28)	0.001[a]	7.64 (2.34 to 24.96)	0.001[a]
VAP as a source of bacteremia						
• No	47	6 (12.8)	1			
• Yes	19	7 (36.8)	3.47 (1.17 to 10.34)	0.03[a]	1.47 (0.46 to 4.73)	0.52[a]
Polymicrobial bacteremia						
• No	27	7 (25.9)	1			
• Yes	39	6 (15.4)	0.57 (0.19 to 1.69)	0.31[a]		
Empirical antibiotic regimens						
Colistin-based regimen						
• No	29	4 (13.8)	1			
• Yes	37	9 (24.3)	1.85 (0.57 to 6.01)	0.30[a]		
Other regimens						
• No	37	9 (24.3)	1			
• Yes	29	4 (13.8)	0.54 (0.17 to 1.75)	0.30[a]		
Definitive antibiotic regimens						
Colistin combination with sulbactam						
• No	17	3 (17.6)	1			
• Yes	49	10 (20.4)	1.42 (0.39 to 5.17)	0.59[a]		
Colistin combination						
• No	58	11 (19.0)	1			
• Yes	8	2 (25.0)	0.92 (0.20 to 4.16)	0.92[a]		

VAP=ventilator-associated pneumonia; RR=rate ratio; CI=confidence interval

[a] p-value for Z-test of RR, [b] p-value for Fisher's Exact test between the 30-day mortality proportions

respectively. The common regimen used in the present study was colistin combination with sulbactam therapy.

There is limited data regarding the outcomes of CRAB infection in children. Compared to a previous study on *A. baumannii* infection among Thai children in 2005 to 2010, the 30-day mortality rate after an *A. baumannii* bacteremia episode was 26.1%. It was higher than in the present study. This may be due to the differing sites of infection in which higher mortality was found in patients with bacteremia. Furthermore, the mortality rate may not accurately represent the mortality from CRAB due to the existence of other contributing factors, particularly underlying comorbidities[35]. A previous study from 2014 in Thai children with a median age of 62 days demonstrated that the 30-day mortality rate was 42%. The differences from the authors' analysis of mortality include age, comorbidities, and drug regimens. More than half of the patients in that study received non-susceptible antibiotic regimens because of pending hemoculture results at the time of treatment. All 30-day mortality cases in 2014 study died before the return of hemoculture results. Febrile neutropenia was statistically associated with mortality (p=0.001). This is contrary to the present research, in which febrile neutropenia was found not to be statistically related to mortality due to the low incidence of CRAB bacteremia. Septic shock, however, was found to be statistically associated with mortality in both studies[17]. Another study in a pediatric population from South Korea conducted in 2019 demonstrated that the 30-day mortality in carbapenem non-susceptibility was 69.2%. The difference in mortality rates can be explained by the higher incidence of malignancy/hematologic disease, post-chemotherapy, post-stem cell transplants, and neutropenia in the study conducted in South Korea. Furthermore, most neutropenic patients did not receive susceptible antibiotics[15]. Another study conducted at a single center in Korea reported a mortality rate of 13.8% among patients with multidrug resistance (MDR) *A. baumannii* outbreak in the PICU, but the cause of death was not related to MDR per se[36].

Colistin was still found to be highly effective against CRAB infection, even after a decade of continuous use. A previous pediatric study from 2014 described in vitro colistin susceptibility of *A. baumannii* isolates to be 100%[17]. The exact results of the in vitro susceptibility testing in the study by Nakwan et al. at a neonatal intensive care unit in Thailand in 2012 also reported that the colistin susceptibility rate was 100%[37].

In an adult multicenter study between June 2017 and June 2018 in Italy, 281 episodes also demonstrated similar results to the present study. For colistin, the non-resistance rate was 98.6%, which was as high as that found in the present study[28]. A recent study by Son et al. reported a high colistin susceptibility rate of 93% and non-resistant isolates of tigecycline, ampicillin/sulbactam, trimethoprim-sulfamethoxazole, amikacin, and gentamicin were 89%, 7%, 13%, 15%, and 8%, respectively[18].

Most episodes of the study used high-dose sulbactam combined with an additional antibacterial agent. A large systemic review in China also showed that high-dose sulbactam combined with colistin or one additional antimicrobial agent improved clinical outcomes[38]. The resistant rate of sulbactam against CRAB in the study was high. Similar to the present study results, a large study from Thailand in 2017 to 2019 demonstrated that the MIC range, MIC50 and MIC90 of sulbactam against 317 *A. baumannii* isolates were 1 to more than 256, 32, and 64 mg/L, respectively[39]. However, there was no significant difference in 30-day mortality between patients who were or were not treated with colistin plus sulbactam-based regimen since sulbactam not only acts as a beta-lactamase inhibitor but also has intrinsic antibacterial activity against *A. baumannii*. Studies have shown excellent in vitro activity of sulbactam against CRAB when used in combination with other antibiotics[40,41]. Adding more sulbactam to sulbactam-based beta-lactam combinations resulted in reducing MIC90 of those combinations when compared to MIC90 of each antibiotic alone[42]. In a time-kill study, the colistin-sulbactam combination significantly improved bacterial killing of CRAB with sulbactam MICs range of 8 to 32 mg/L[43]. In the present study, more than 50% of CRAB isolates had sulbactam MIC of 32 or less mg/L. This implies that most of the present study patients might benefit from sulbactam-containing therapy regimens.

High-dose tigecycline is an alternative option for consideration as a component of combination therapy for CRAB bacteremia. Generally, the use of tigecycline for the treatment of CRAB bacteremia should be guided by the results of susceptibility testing and as salvage therapy only after other treatment options have been considered[22]. The U.S. Food and Drug Administration (FDA) suggested that tigecycline is not recommended for use in children unless an alternative option is ineffective. In real-

world settings, however, tigecycline is off-label and used concomitantly with other agents in critically ill patients with severe infections caused by MDR/XDR gram-negative bacteria[44].

The present study had limitations. First, most patients had at least one comorbidity, which could affect the factor of mortality. The present study used a small sample size due to the limited incidence of CRAB bacteremia. In the future, further data collection to increase the sample size might help to detect more independent factors derived by using multivariable analysis. Second, it was a single-center study with retrospective data collection. Clinical aspects and treatment decisions were made by the attending clinician. In the authors' center, however, infectious disease specialists and antibiotic stewardship were provided in most cases. Third, missing data on MIC of colistin and sulbactam in the earlier years of data collection made it challenging to assess in vitro activity of drug susceptibility. However, most of drug regimens in the present study used colistin-sulbactam combination, which had proved their synergistic effect from other studies. Fourth, due to the lack of standard susceptibility criteria of *A. baumannii* to tigecycline, MIC breakpoints of Enterobacterales were used instead.

Conclusion

In conclusion, one-fifth of children with CRAB bacteremia died within 30 days. Associated factors with mortality were septic shock and congenital heart disease. Colistin had the highest in vitro drug susceptibility rate. The common regimen used in the present study was colistin combination with sulbactam therapy.

What is already known on this topic?

CRAB infections are involved in many sites, and most of them appear in the intensive care unit. This pathogen had a high 30-day mortality rate with various antimicrobial resistance.

What this study adds?

Nowadays, hospital-acquired CRAB bacteremia is associated with mortality. There are few antibiotics to which the organism is susceptible, such as colistin and tigecycline. Consideration of the development of new drugs is required.

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Ethical approval

This study was approved by the Institutional Review Board of the Faculty of Medicine of Chulalongkorn University, Bangkok, Thailand (IRB No. 354/64).

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Conflicts of interest

The authors declare no conflict of interests.

References

1. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538-82.
2. Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. Nat Rev Drug Discov 2013;12:963.
3. Bartal C, Rolston KVI, Nesher L. Carbapenem-resistant Acinetobacter baumannii: Colonization, infection and current treatment options. Infect Dis Ther 2022;11:683-94.
4. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States [Internet]. 2019 [cited 2022 Dec 2]. Available from: https://www.cdc.gov/drugresistance/Biggest-Threats.html.
5. Howard A, O'Donoghue M, Feeney A, Sleator RD. Acinetobacter baumannii: an emerging opportunistic pathogen. Virulence 2012;3:243-50.
6. Fu P, Xu H, Jing C, Deng J, Wang H, Hua C, et al. Bacterial epidemiology and antimicrobial resistance profiles in children reported by the ISPED Program in China, 2016 to 2020. Microbiol Spectr 2021;9:e0028321.
7. National Antimicrobial Resistant Surveillance Center, Thailand. Percentage of susceptible organism isolates from blood [Internet]. 2021 [cited 2022 Dec 2]. Available from: http://narst.dmsc.moph.go.th/antibiograms/2021/12/Antibiogram_Blood2021-87H.pdf.
8. Jain AL, Harding CM, Assani K, Shrestha CL, Haga M, Leber A, et al. Characteristics of invasive Acinetobacter species isolates recovered in a pediatric academic center. BMC Infect Dis 2016;16:346.
9. American Academy of Pediatrics. Antimicrobial resistance. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, editors. Red book: 2021-2024 report of the committee on infectious diseases. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021. p. 868-9.
10. World Health Organization. WHO publishes list of

bacteria for which new antibiotics are urgently needed [Internet]. 2017 [cited 2022 Dec 2]. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.
11. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399:629-55.
12. World Health Organization. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities [Internet]. 2017 [cited 2022 Dec 2]. Available from: https://apps.who.int/iris/handle/10665/259462.
13. Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA. Carbapenem-resistant Acinetobacter baumannii and Enterobacteriaceae in South and Southeast Asia. Clin Microbiol Rev 2017;30:1-22.
14. National Antimicrobial Resistant Surveillance Centre, Thailand. Antimicrobial resistance 2000-2021(12M) [Internet]. 2021 [cited 2022 Dec 2]. Available from: http://narst.dmsc.moph.go.th/data/AMR%202000-2021-12M.pdf.
15. Choe YJ, Lee HJ, Choi EH. Risk factors for mortality in children with Acinetobacter baumannii bacteremia in South Korea: The role of carbapenem resistance. Microb Drug Resist 2019;25:1210-8.
16. Kruse AY, Thieu Chuong do H, Phuong CN, Duc T, Graff Stensballe L, Prag J, et al. Neonatal bloodstream infections in a pediatric hospital in Vietnam: a cohort study. J Trop Pediatr 2013;59:483-8.
17. Vandepitte WP, Berge J, Andersson R. Clinical outcomes of children with carbapenem-resistant Acinetobacter baumannii bacteremia. J Med Assoc Thai 2014;97 Suppl 11:S129-39.
18. Son HJ, Cho EB, Bae M, Lee SC, Sung H, Kim MN, et al. Clinical and microbiological analysis of risk factors for mortality in patients with carbapenem-resistant Acinetobacter baumannii bacteremia. Open Forum Infect Dis 2020;7:ofaa378.
19. Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant Acinetobacter spp. J Antimicrob Chemother 2008;61:1369-75.
20. Kim YA, Park YS, Youk T, Lee H, Lee K. Abrupt increase in rate of imipenem resistance in Acinetobacter baumannii complex strains isolated from general hospitals in Korea and correlation with carbapenem administration during 2002-2013. Ann Lab Med 2018;38:179-81.
21. Morfin-Otero R, Dowzicky MJ. Changes in MIC within a global collection of Acinetobacter baumannii collected as part of the Tigecycline Evaluation and Surveillance Trial, 2004 to 2009. Clin Ther 2012;34:101-12.
22. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant Acinetobacter baumannii, and Stenotrophomonas maltophilia infections. Clin Infect Dis 2022;74:2089-114.
23. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant Acinetobacter baumannii: in pursuit of an effective treatment. Clin Microbiol Infect 2019;25:951-7.
24. Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR Acinetobacter baumannii infections: a systematic review and network meta-analysis. J Antimicrob Chemother 2018;73:22-32.
25. Isler B, Doi Y, Bonomo RA, Paterson DL. New treatment options against carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother 2019;63.
26. Batirel A, Balkan, II, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. Eur J Clin Microbiol Infect Dis 2014;33:1311-22.
27. Lee CM, Kim CJ, Kim SE, Park KH, Bae JY, Choi HJ, et al. Risk factors for early mortality in patients with carbapenem-resistant Acinetobacter baumannii bacteraemia. J Glob Antimicrob Resist 2022;31:45-51.
28. Russo A, Bassetti M, Ceccarelli G, Carannante N, Losito AR, Bartoletti M, et al. Bloodstream infections caused by carbapenem-resistant Acinetobacter baumannii: Clinical features, therapy and outcome from a multicenter study. J Infect 2019;79:130-8.
29. Brilli RJ, Goldstein B. Pediatric sepsis definitions: past, present, and future. Pediatr Crit Care Med 2005;6:S6-8.
30. National Healthcare Safety Network. Bloodstream infection event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection) [Internet]. 2022 [cited 2022 Dec 2]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.
31. National Healthcare Safety Network. Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event [Internet]. 2022 [cited 2022 Dec 2]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf.
32. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46:10-67.
33. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, 32nd edition [Internet]. 2022 [cited 2022 Dec 02]. Available from: https://clsi.org/standards/

products/microbiology/documents/m100/.
34. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters [Internet]. 2022 [cited 2022 Dec 2]. Available from: https://www.eucast.org/.
35. Punpanich W, Nithitamsakun N, Treeratweeraphong V, Suntarattiwong P. Risk factors for carbapenem non-susceptibility and mortality in Acinetobacter baumannii bacteremia in children. Int J Infect Dis 2012;16:e811-5.
36. Byun JH, Park SE, Seo M, Jang J, Hwang MS, Song JY, et al. Controlling an outbreak of multidrug-resistant Acinetobacter baumannii in a Pediatric Intensive Care Unit: a retrospective analysis. J Korean Med Sci 2021;36:e307.
37. Nakwan N, Wannaro J, Nakwan N, Patungkalo W, Chokephaibulkit K. Clinical features, risk factors, and outcome of carbapenem-resistant Acinetobacter baumannii bacteremia in a Thai neonatal intensive care unit. Asian Biomed (Res Rev News) 2012;6:473-9.
38. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant Acinetobacter baumannii infections: A systematic review and network meta-analysis. J Glob Antimicrob Resist 2021;24:136-47.
39. Srisakul S, Wannigama DL, Higgins PG, Hurst C, Abe S, Hongsing P, et al. Overcoming addition of phosphoethanolamine to lipid A mediated colistin resistance in Acinetobacter baumannii clinical isolates with colistin-sulbactam combination therapy. Sci Rep 2022;12:11390.
40. Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. In vitro activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically characterized multidrug-resistant Acinetobacter baumannii strains. Antimicrob Agents Chemother 2004;48:1586-92.
41. Ji J, Du X, Chen Y, Fu Y, Wang H, Yu Y. In vitro activity of sulbactam in combination with imipenem, meropenem, panipenem or cefoperazone against clinical isolates of Acinetobacter baumannii. Int J Antimicrob Agents 2013;41:400-1.
42. Wang L, Chen Y, Han R, Huang Z, Zhang X, Hu F, et al. Sulbactam enhances in vitro activity of β-lactam antibiotics against Acinetobacter baumannii. Infect Drug Resist 2021;14:3971-7.
43. Bian X, Liu X, Feng M, Bergen PJ, Li J, Chen Y, et al. Enhanced bacterial killing with colistin/sulbactam combination against carbapenem-resistant Acinetobacter baumannii. Int J Antimicrob Agents 2021;57:106271.
44. Iosifidis E, Violaki A, Michalopoulou E, Volakli E, Diamanti E, Koliouskas D, et al. Use of tigecycline in pediatric patients with infections predominantly due to extensively drug-resistant Gram-negative bacteria. J Pediatric Infect Dis Soc 2017;6:123-8.