Clinical Outcomes of Children with Carbapenem-Resistant *Acinetobacter baumannii* Bacteremia

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Background: *A relentless increase in the rate of carbapenem-resistant among Acinetobacter baumannii has substantially reduced the access to effective antimicrobial regimens. Currently limited information is available regarding the prognosis or outcomes of children with blood stream infection caused by carbapenem resistant A. baumanii.*
Objective: *To determine the clinical outcomes and predictors for fatality among children with carbapenem-resistant A. baumannii (CRAB) blood stream infection (BSI).*
Material and Method: *A retrospective descriptive study was conducted among children hospitalized at the Queen Sirikit National Institute of Child Health (Children's Hospital), Bangkok, Thailand. Those who had CRAB isolated from blood cultures during the period between October 2005 and September 2010 were included in the study.*
Results: *A total of 89 cases of BSI caused by CRAB were identified. The incidence was 1.2 cases per 1,000 hospitalized patients. The median age at onset of bacteremia was 62 days and 88% had at least one underlying comorbidity. The 2-week and 30-day case fatality rates were 39% and 42%, respectively. A large proportion of deaths (63%) occurred before blood culture results became available. Extended spectrum resistance, defined as resistance to all other first line antibiotics at the hospital, i.e., all cephalosporins, aminoglycoside, quinolone and carbapenems, was significantly associated with a higher 2-week case fatality rate (CFR) (48% compared with 23% among their counterpart, p = 0.028) and death at an earlier stage of the bacteremia (Kaplan-Meier p = 0.016). In univariate analysis, factors associated with 2-week case fatality include malignancy-associated febrile neutropenia, fever ≥2 days before the initiation of appropriate antibiotic, presence of septic shock, organ dysfunction, and being infected by extended spectrum resistant strains. Correspondingly, CFR of cases who received ≥1 appropriate empiric antibiotics within 24 hours of clinical suspicion appears to be lower, albeit not reaching statistical significance, than their counter part, i.e., the CFRs between the two groups were 10% vs. 23%, respectively (p = 0.675). Colistin susceptibility based on disc diffusion test remained high (100%) in this sample. Nevertheless, those who received colistin treatment had a 2-week CFR of 20%. On the other hand, none of the cases infected with sulbactam susceptible strain, who received sulbactam containing regimen (n = 15), died. No significant renal toxicity was observed among children receiving colistin treatment in our sample.*
Conclusion: *Carbapenem resistant A. baumannii bacteremia exhibited a high fatality rate, which mainly occurred before the pathogen was known to the clinicians. Extended spectrum resistance was associated with high fatality rate. Early administration of effective empirical antibiotics such as colistin and sulbactam in this sample was associated with lower fatality rate among children affected by this condition.*

Keywords: *Acinetobacter baumannii, Clinical outcomes, Children, Carbapenem resistance, Bacteremia, Blood stream infection, Mortality*

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A. baumannii has recently been identified as one of the most troublesome pathogens causing nosocomial infections[1-3]. It has been shown to have a remarkable ability of adapting to the hospital environment and causing opportunistic infections among patients with debilitating conditions or prolonged hospitalization[1]. *A. baumannii* exhibits a wide range of resistance mechanism against antimicrobial agents and strains with resistance to all clinically available antibiotics[4,5]. The pathogen can form biofilms and is commonly associated with

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infections through artificial devices such as endotracheal tubes, catheters and sutures[1].

A large study of nosocomial bloodstream infections in hospitals in the United States found that *A. baumannii* was the 10th most common pathogen causing nosocomial bloodstream infections and that a majority of the *A. baumannii* infections occurred among patients in intensive care unit (ICU) wards[6]. Since critically ill patients in ICU wards are the group most burdened by *A. baumannii* infections in the bloodstream, it is not surprising that studies have reported high mortality rates, ranging from 17% to 52%[7]. However, most researchers are very careful not to attribute the high mortality rates solely to the *A. baumannii* infections due to the presence of patients' severe comorbidities[1,7]. The emergence of multidrug resistant strains of *A. baumannii* has forced clinicians to revive the old antibiotic drug colistin, which is active against gram-negative bacterial cell walls[7,8]. Colistin was discovered in 1947 but was largely abandoned in the 1970s due to its nephro- and neurotoxicity as newer and safer drugs were introduced[7].

In 2011, the high incidence and spread of multi-drug resistant pathogens was recognized as a serious challenge by Southeast Asian health ministers in the World Health Organization's publication Jaipur Declaration on Antimicrobial Resistance[9,10]. Numerous outbreaks of carbapenem-resistant *A. baumannii* have been reported from hospitals in the Eastern Asian region[8,11-14] and studies have reported a high burden in hospitals in Thailand[15-18]. An extensive overprescription of antibiotics has been reported in Thailand and recent efforts have been made to lessen their inadequate use[10].

Recently, existing literature has provided substantial information on the epidemiology, clinical characteristics and management of invasive *A. baumannii* infections in adult populations[1,7,8]. In contrast, little information is available on the pathogens role in the pediatric setting. Recent reports have found the burden of nosocomial *A. baumannii* infections in children to be comparable to those in adults and that carbapenem non-susceptibility among *A. baumannii* in children is associated with both higher mortality and increased length of hospital stay[15,16,18]. Therefore, we aim to describe clinical characteristics and treatment outcomes of children presenting carbapenem-resistant *A. baumannii* bacteremia. Our research questions are described below. 1) What was the case fatality rate (CFR) among children with this condition? 2) Was any association observed between extended antibiotic resistance, i.e., resistance to other agents than carbapenems and higher CFRs? 3) Could any of the following factors influence clinical outcomes, i.e., having adequate empirical antibiotic treatment, time for adequate antibiotic treatment and choice of antibiotic therapy? 4) What was the incidence of renal toxicity associated with colistin treatment in this population? The information obtained from this study can be used to provide a better understanding on the prognosis of *A. baumannii* blood stream infection among pediatric population receiving care at a tertiary center in Bangkok, Thailand.

Material and Method

A retrospective study was performed by reviewing medical records of patients receiving care at the Queen Sirikit National Institute of Child Health (QSNICH), a university-affiliated teaching hospital in Bangkok, Thailand. Case ascertainment was conducted by reviewing the QSNICH Microbiology Laboratory database. All children 0-18 years of age with proven carbapenem-resistant *A. baumannii* (CRAB) bloodstream infection (BSI)/bacteremia during the period between October 2005 and September 2010 were included in the present study.

Microbiology

Standard microbiological methods were used to isolate and identify *A. baumannii*. In vitro susceptibility was assessed using the standard disk diffusion method and the following antimicrobial agents were included in the susceptibility testing for *A. baumannii* at QSNICH: amikacin, cefotaxime, ceftriaxone, ceftazidime, cefoperazone/sulbactam, ciprofloxacin, co-trimoxazole, gentamicin, imipenem, netilmicin and colistin. Ampicillin/sulbactam was not included in the susceptibility testing at the hospital due to lack of sensi-discs, instead, cases with in vitro susceptibility to cefoperazone/sulbactam were considered susceptible to ampicillin/sulbactam as well. The breakpoints defined by the Clinical and Laboratory Standard Institute (CLSI) were used in the susceptibility testing. Lacking CLSI guidelines for disc-diffusion testing of colistin against *A. baumannii*[17], the authors used modified zone criteria for colistin in which isolates were considered resistant if the inhibition zone was <11 mm[17,18].

Data collection

Demographics, underlying diseases, clinical outcomes, laboratory findings, antimicrobial

susceptibility patterns and antimicrobial treatments were collected from the patients' medical charts.

The primary outcome measurement was case fatality within two weeks after the evidence of CRAB BSI was obtained, i.e., the time when the first positive blood culture for CRAB was taken.

The authors also collected data on time to defervescence (defined as having returned to baseline body temperature for a consecutive period of at least 48 hours) from the onset of fever attributable to bacteremia as a secondary outcome measurement.

Antimicrobial treatments given within 24 hours from the onset of bacteremia were defined as empiric treatments except for the ones that had been changed or cancelled within 24 hours after initiation. Antimicrobial treatments to which the infecting *A. baumannii* strains were susceptible (based on the result of in vitro susceptibility) given after the onset of bacteremia were defined as appropriate treatments.

Renal impairment was defined as a two fold increase in serum creatinine during the treatment compared with the level at the start of therapy or an increase by 1 mg/dL if initial creatinine was abnormal (1.4 mg/dL)[19].

The protocol of this research was reviewed and approved by the ethics committee of the Queen Sirikit National Institute of Child Health (IRB approval number 53-078).

Statistical analysis

The χ^2-tests were used for categorical variables except in cases where at least one of the outcome groups had an expected count of less than five. In such cases, Fisher's exact test was used. For continuous variables One-way ANOVA was used to compare means between groups. Kaplan-Meier (Breslow's test) was used to compare survival functions between groups. Two-sided tests were applied in all cases. Statistical analyses were performed with SPSS statistics version 16 and significance level was set at $p<0.05$.

Results

Demographic data

Among a total of 74,955 hospitalizations during the period between October 2005 and September 2010, 89 cases with CRAB BSI were identified giving an incidence of approximately 1.2 cases per 1,000 hospitalized patients. The median age at onset of bacteremia was 62 days (mean = 584 days) and 53% were male.

Underlying diseases

A large proportion (88%) of the patients had underlying diseases before infection. Table 1 describes the distribution of underlying diseases and other clinical characteristics of the study subjects.

Case fatality rate: In all, 35 patients (39%) died within two weeks of onset of bacteremia and an additional three patients died within 30 days. Fig. 1 displays two weeks CFRs for age and sex groups. A significantly higher two-week CFR was observed among toddlers, preschoolers and children (61%) compared with neonates and infants (34%) ($p = 0.034$). Among the infants and neonates, a significantly higher two-week CFR was found among males (45%) compared with females (21%) ($p = 0.037$).

Among the 38 patients who died from *A. baumannii* bacteremia, 47% died the same day when blood cultures were taken and a total of 63% died before culture results became available. The median time from onset to death among the patients who died from their *A. baumannii* bacteremia was 0 days (less than 24 hour) (mean = 3 days). Fig. 2, 3 display survival functions by sex and age groups, respectively.

Prognostic factors for two-week fatality

Prognostic factors associated with 2-week case fatality in univariate analyses included malignancy-associated febrile neutropenia, fever $\geq$2 days before initiating antibiotics, presence of septic shock, organ dysfunction, and being infected by extended spectrum resistant strain, i.e., resistant to amikacin, cefotaxime, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole, gentamicin, imipenem and meropenem (Table 2). Nevertheless, none of them remained significant predictors of the 2-week fatality risk when logistic regression analysis using backward stepwise approach was performed. The most likely reason for the lack of statistical significance was small sample size, i.e., 2 cells in the 2x2 contingency tables contained 0 number of cases (Table 2).

Susceptibility

Table 3 displays susceptibility patterns of the *A. baumannii* isolates. The results of the disc diffusion test for colistin susceptibility were available in 55 cases (62%), all of which exhibited a $\geq$11 mm zone size.

Extended spectrum resistance was associated with increased risk of death in the early stages after onset of bacteremia. Kaplan-Meier (Breslow's test) showed a statistically significant difference ($p = 0.015$) between survival of the patients with extended

Table 1. Demographics and clinical characteristics of cases with carbapenem-resistant *A. baumannii*

Characteristic	Age groups n (%)				
	Neonates (n = 35)	Infants (n = 36)	Toddlers & preschoolers (n = 8)	School-aged children (n = 10)	Total (n = 89)
Any underlying disease	33 (94.0)	32 (89.0)	6 (75.0)	7 (70.0)	78 (88.0)
Premature birth	24 (67.0)	8 (22.0)	0	1 (10.0)	33 (37.0)
Extremely low birth weight	15 (43.0	2 (6.0)	0	0	17 (19.0)
RDS	9 (26.0)	0	0	0	9 (10.0)
Congenital heart disease	9 (26.0)	11 (31.0)	1 (13.0)	0	21 (24.0)
Malignancy	1 (3.0)	2 (6.0)	4 (50.0)	2 (20.0)	9 (10.0)
Congenital anomaly	2 (6.0)	12 (34.0)	1 (13.0)	1 (10.0)	16 (18.0)
Chronic lung disease	0	6 (17.0)	0	0	6 (7.0)
Chronic liver disease	0	2 (6.0)	0	0	2 (2.0)
ICU admission	23 (66.0)	16 (45.0)	6 (75.0)	6 (60.0)	51 (57.0)
Mechanical ventilator use	30 (86.0)	26 (72.0)	6 (75.0)	7 (70.0)	69 (78.0)
Central venous catheter use	9 (26.0)	21 (58.0)	1 (13.0)	2 (20.0)	33 (37.0)
Median LOS prior to bacteremia (mean), days	7 (8.0)	23 (38.0)	10 (12.0)	23 (31.0)	11(23.0)

Values are represented as n (%). Age group definition: neonates (0-28 days); infants (29-364 days); toddlers & preschoolers (1-4 years); school-aged children (5-18 years). ICU = intensive care unit; LOS = length of hospital stay; RDS = respiratory distress syndrome. * Percentages shown are calculated within each age group and the total percentages are shown to the right.

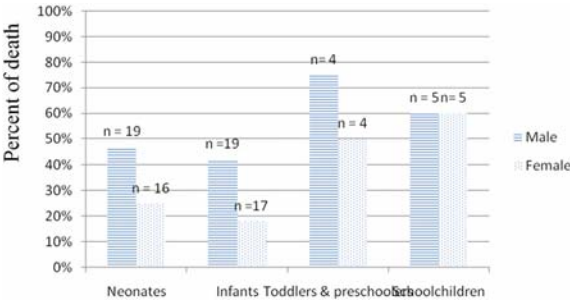

Fig. 1 Two-week CFRs for each age and sex group; n = number of total subjects in each group.

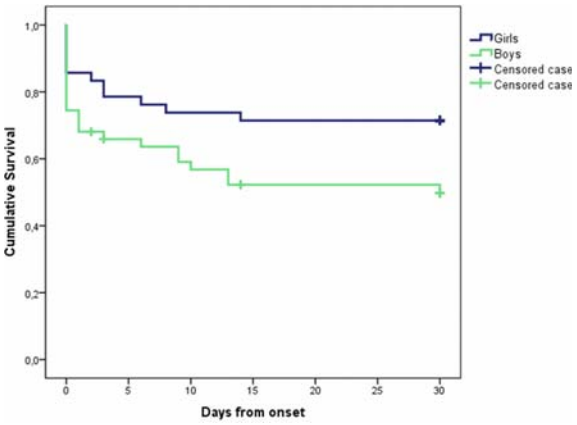

Fig. 2 Survival functions for males and females. Graph displays proportion within each group who survived at end of each day. The Kaplan-Meier (Breslow's test) was p = 0.053. Crosses symbolize censored cases, defined as cases discharged less than 30 days after the onset of bacteremia (the cross indicates which day from onset they were discharged).

spectrum resistant isolates compared with the survival of the patients with isolates susceptible to any first line antibiotics. Fig. 4 displays survival curves for the two groups. A statistically significant correlation was found between septic shock and extended spectrum resistance ($p = 0.003$) but without statistically significant associations between extended spectrum resistance and any underlying diseases nor length of hospital stay before bacteremia as displayed in Table 4.

Effect of antimicrobial treatments and outcomes

CRAB was initially identified from heart blood culture immediately after the death of 17 patients (19%). An additional six patients died before the pathogen was known to the clinicians. One patient was discharged from the hospital before the pathogen was known and died at home and three patients (3%) received palliative treatment for end of life care without antimicrobial intervention. They were all excluded from

appropriate treatment outcome analyses. Of the remaining 62 patients, 43 received at least one appropriate antimicrobial agent, i.e., with documented in vitro susceptibility test obtained later, 15 did not receive appropriate treatment and four received treatment for which the susceptibility was unknown.

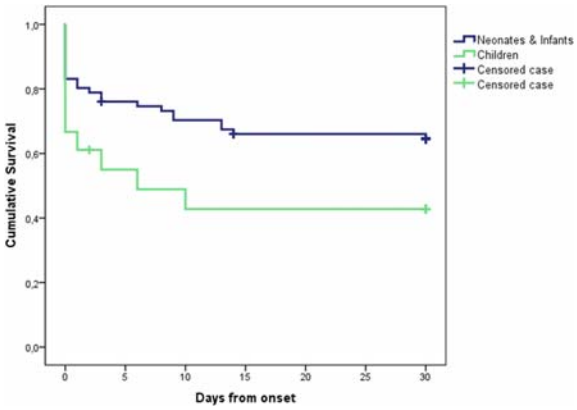

Fig. 3 Survival functions for neonates and infants (0-364 days old) and children (1-18 years old). Graph displays proportion within each group who survived at end of each day. The Kaplan-Meier (Breslow's test) was $p = 0.057$. Crosses symbolize censored cases, defined as cases discharged less than 30 days after the onset of bacteremia (the cross indicates which day from onset they were discharged).

Two-week CFRs were 12% among the 43 patients receiving appropriate treatment as compared 27% among the 15 patients who did not receive appropriate treatment ($p = 0.218$). Table 5 displays appropriate treatment used and two-week case fatality for each.

The median time from onset of bacteremia until appropriate treatment was initiated was four days (mean = 3.4). The authors did not detect any significant association between earlier start of appropriate treatment and survival due to a small number of cases included in this analysis.

Among the 15 patients who survived long enough for diagnosis but still did not receive appropriate empiric treatments, a 100% survival rate was observed in the group receiving sulbactam (n = 6) compared with the group receiving other treatments (n = 9) where only 56% survived. Although the groups are too small for any statistical significance ($p = 0.103$) a trend toward higher survival was found in the sulbactam group. The most common alternative treatments were carbapenems and aminoglycosides. In all, 51% of the patients receiving sulbactam also received carbapenem.

The authors did not have enough power to detect statistical significance regarding the impact of antimicrobial susceptibility of the empiric regimen (administered within 24 hours of clinical suspicion of

Table 2. Clinical manifestations and two-week case fatality

Characteristic	2-weeks case fatality n (%)		*p*-value	cRR*	95% CI
	Yes (%) n = 35	No (%) n = 54			
Systemic inflammatory response syndrome (n = 84)	34 (97.0)	50 (93.0)	0.640	2.02	0.34, 11.90
Underlying disease (n = 78)	30 (88.0)	48 (89.0)	0.700	0.84	0.42, 1.71
Malignancy with febrile neutropenia (n = 7)	7 (20.0)	0 (0.0)	0.001	NA	NA
Septic shock (n = 40)	34 (97.0)	6 (11.0)	<0.001*	41.67	5.95, 333.33
Any organ dysfunction (n = 71)	35 (100.0)	36 (67.0)	<0.001*	NA	NA
Fever ≥2 days before initiation of antibiotic (n = 24)	13 (37.0)	11 (20.0)	0.029	1.89	1.09, 3.30
Polymicrobial bacteremia (n = 17)	6 (17.0)	11 (20.0)	0.710	0.88	0.43, 1.77
Extended spectrum resistant *A. baumannii* (n = 59)	28/35 (80.0)	31/54 (57.0)	0.028	2.03	1.01, 4.09

* cRR = crude risk ratio comparing two-week fatality risk between those with and without certain characteristics as shown in the first column, *p*-values are calculated with χ^2-tests, or Fisher's exact test when appropriate, analyzing association between two-week CFR and each variable; extended spectrum resistant strain, i.e., resistant to all available first line antimicrobial treatment at the study center including amikacin, cefotaxime, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole, gentamicin, imipenem and meropenem

bacteremia) and the two-week CFRs but a trend could be observed. The patients receiving at least one appropriate treatment within 24 hours (n = 10) had a two-week CFR of 10% and the patients resistant to all treatments administered within 24 hours (n = 56) had a two-week CFR of 23% ($p = 0.675$). The authors could not identify any significant associations between either types of empirical antimicrobial agents or whether it was a single or combination therapy and two-week CFR. No patients receiving an appropriate treatment fulfilled the criteria for renal impairment, so comparisons of adverse effects between different treatments could not be made. Ten patients presented bacteremia with renal failure, but the majority of those died within 24 hours of onset of bacteremia (n = 7); therefore, it seemed to be more related to the septicemia or septic shock rather than to the treatment.

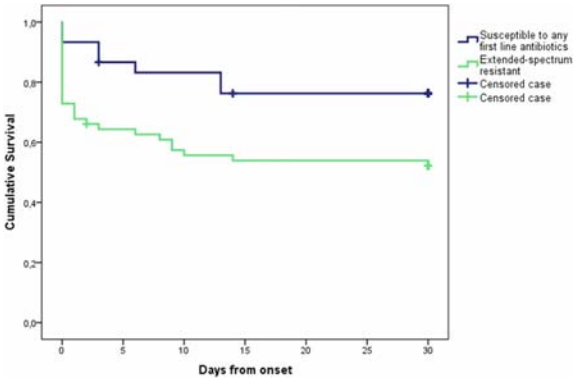

Fig. 4 Survival functions for patients with and without extended spectrum resistant *A. baumannii*. The survival curve displays proportion within each group who survived at end of each day. The Kaplan-Meier (Breslow's test) was $p = 0.016$. Crosses symbolize censored cases, defined as cases discharged less than 30 days after the onset of bacteremia (the cross indicates which day from onset they were discharged).

Table 3. In vitro susceptibility testing of carbapenem resistant *A. baumannii* based on disc diffusion test

Susceptibility to antibiotics (n = 89 unless otherwise specified)	n (%)
Colistin* (n = 55)	55 (100.0)
Cefoperazone/sulbactam	24 (27.0)
Aminoglycosides	9 (10.0)
Co-trimoxazole (n = 88)	6 (7.0)
Ciprofloxacin	3 (3.0)

*Colistin susceptibility was defined as zone size ≥11 mm on disc susceptibility test

Table 4. Factors associated with extended spectrum resistance of *A. baumannii* infection

Characteristic	Extended spectrum resistance n (%)*		*p*-value	cRR	95% CI
	Yes n = 59	No n = 30			
Underlying diseases (n = 78)	54 (92.0)	24 (80.0)	0.118	1.52	0.78, 2.96
Preterm birth (n = 33)	25 (42.0)	8 (27.0)	0.147	1.24	0.93, 1.66
Median length of hospital stay before onset of bacteremia, days (mean)	10 (21.6)	16 (26.4)	0.490	NA	NA

* unless otherwise specified, CRR = crude risk ratio

Table 5. Appropriate treatment received and two-week case fatality

Appropriate treatment* (n = 43)	Two-week case fatality n (%)
Colistin (n = 25)	5 (20.0)
Sulbactam** (n = 9)	0
Combined sulbactam** and aminoglycoside or colistin (n = 6)	0
Others (n = 3)	0

* Only treatments to which the infecting *A. baumannii* strains were susceptible are presented in this table. Most patients received several antibiotics during the course of their bacteremia

** Sulbactam was always administered together with cefoperazone or ampicillin

Among the 35 patients who survived and who received appropriate treatment, only 16 cases had a clearly defined time of defervescence. The median time from start of appropriate treatment until defervescence among those 16 cases was 8 days (mean = 8.4). No statistically significant difference was found when comparing mean time until defervescence for appropriate treatment groups.

Discussion

The 2-week and 30-day CFRs in our patient group comprised 39% and 43%, respectively. This finding is in accordance with other studies of CRAB bacteremia. Kuo et al reported a 30-day mortality rate of 49% in a study from 2007 of multidrug-resistant *A. baumannii* bacteremia among 55 patients of mixed ages at their hospital[20] and Lim et al reported a 30-day mortality rate of 37% in their study of bloodstream infections with *Acinetobacter spp.* among 70 patients of mixed ages at a tertiary hospital[21]. Exact comparisons are difficult since the inclusion criteria varied between studies and some researchers excluded patients who died before receiving antibiotic treatments from their analysis. Recent studies in Thai neonates showed that the fatality rates among multi/extensively drug resistant *A. baumannii* bacteremia ranged from 42.9-50%[15,16], which is rather comparable to the 30-day CFR of 39% in the neonatal subgroup admitted to the ICU in the present study.

One of our main findings is that such a high proportion (63%) of all deaths from CRAB BSI in our patient group occurred before the pathogen was known to the clinicians. Other studies have also identified the problem with deaths occurring before diagnosis and treatment initiation. Oliveira et al reported that 74 patients died within 72 hours from specimen collection in their study of 283 adult patients with carbapenem-resistant *Acinetobacter spp.* infections[19] and Kuo et al reported in their study from 2007 that 11 of 55 patients died within three days of onset of multidrug-resistant *A. baumannii* bacteremia. One interpretation of our finding is that outcomes could be improved if an adequate empiric antimicrobial regimen with coverage against multi-resistant *A. baumannii* was provided as soon as blood stream infection was suspected. The finding showed significant proportions of children with preceding fever for two days or more before bacteremia was suspected (blood cultures were taken), i.e., 37% among the patients who died within two weeks and 46% among the patients who died before the pathogen was known. If the techniques for detecting *A. baumannii* in blood samples could be improved it might have an impact on clinical outcomes. How polymerase chain reaction techniques could improve accuracy and speed of microbiologic diagnosis in community acquired pneumonia[22] and in enteropathogenic bacteremia has been reported[23].

In the present study the authors also found extended spectrum resistance to be significantly associated with death in early stage bacteremia. A possible explanation for this finding could be that few patients received empiric antimicrobial treatments to which extended spectrum resistant *A. baumannii* strains were susceptible. Although patients who received inappropriate empirical antimicrobial agents had a 2.2 times higher two-week fatality rate, the difference did not reach significant levels due probably to the small sample size. Comparisons with other studies is difficult since susceptibility testing protocols as well as the definitions of multidrug-resistance and extended spectrum resistance varied across studies[8]. However, Tseng et al reported a 61% 30-day CFR among adult cases with extensively resistant *A. baumannii* bacteremia[14]. Their definition of extensively resistant *A. baumannii* was comparable to ours except for the inclusion of resistance to tazobactam containing regimens rather than sulbactam containing regimens used in the present study.

In a previous report on 180 patients with *A. baumannii* bacteremia at QSNICH[18] (from which the subset of 89 cases with CRAB BSI are included in this study), significantly higher 30-day CFRs were observed among patients with more resistant *A. baumannii* strains ($p<0.001$). Specifically, the 30-day CFR comprised 12% for the carbapenem susceptible cases (n = 89), 30% for carbapenem-resistant cases, which were sensitive to any other first line antibiotics (n = 30) and 49% for extended spectrum resistant cases (n = 59)[1]. Punpanich et al also reported a significantly longer hospital stay before bacteremia and higher incidence of low birth weight and use of mechanical ventilation among the carbapenem resistant group[18]. Nevertheless, these factors were not significantly more prevalent among patients infected with extended spectrum resistant strains compared with those with CRAB strain, which was susceptible to any other first line antibiotics.

The authors could not identify any significant association between particular antimicrobial agents, neither as empiric nor as appropriate treatment and survival. However, a trend was observed toward higher case fatality when colistin was used as appropriate

treatment compared with other appropriate treatments. This finding corresponds to previous reports by Oliveira et al who demonstrated a higher mortality during treatment for patients treated with colistin compared with patients treated with ampicillin/sulbactam in their study of adult patients with carbapenem resistant *A. baumannii* infections[19]. Further, Lim et al did not find any survival benefit among patients treated with colistin compared with patients without adequate antibiotic treatments in their study of multidrug resistant *Acinetobacter spp.* bacteremia in a mixed patient group[21]. In parallel, a trend toward higher survival among patients receiving appropriate treatments was observed especially among those who received appropriate empirical antibiotics, although this association did not reach statistical significance. The lack of significance might be explained by the small number of cases as most deaths occurred before initiating antimicrobial agents.

*The sum of the groups is 178 and not 180 as expected because two patients included in the first study were later excluded: one due to unconfirmed bacteremia of the *baumannii* subtype of *Acinetobacter spp.* and another due to unknown in vitro susceptibility of the bacteremia.

In many cases, sulbactam containing regimens were administered to patients with isolates displaying its in vitro resistance. A study by Lee et al demonstrated the synergistic effect of sulbactam and carbapenem. They identified the in vitro susceptibility to the combinations of sulbactam and carbapenem when tested simultaneously among *A. baumannii* strains displaying in vitro resistance to each agents when tested separately[12]. In the present study, among patients who did not receive any appropriate treatments (n = 42), the overall CFR was 27% whereas all of those who received sulbactam treatments survived (n = 6). Nevertheless, the sample size was too small and thus failed to reach statistical significant difference.

Limitations

The key limitation of the present study was its retrospective nature and lack of random allocation. Therefore, it was difficult to draw any strong conclusion regarding the effectiveness of different antibiotic regimens. For example, colistin might have been administered only to critically ill patients, while sulbactam might have been administered to cases with less severe or nonlife-threatening infection. Furthermore, any claims of causality between *A. baumannii* bacteremia and mortality must be made with caution since about 90% of our cases had at least one underlying comorbidity. In addition, the present study did not have enough power to detect independent risk factors for fatality using multivariate analysis due to the relatively small number of cases.

Nevertheless, to the best of our knowledge, only a limited number of studies have been conducted on CRAB BSI in children and most published reports present a relatively small number of cases[15,16,24]. In the present study the authors have described the characteristics of 89 children. Given that blood cultures were generally taken anytime children presented symptoms of septicemia, we are confident that all clinically significant carbapenem resistant *A. baumannii* bacteremia at our hospital during the study period were included.

Conclusion

Carbapenem resistant *A. baumannii* bacteremia exhibited a high fatality rate, mainly occurring before the causative pathogen had been identified. The finding that 63% of all deaths occurred before the pathogen was known to the clinicians suggests the outcomes could have been improved had adequate empiric antimicrobial regimens such as colistin, sulbactam in this setting been provided at as early as possible.

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What is already known on this topic?

Blood stream infection caused by CRAB has become an increasing important cause of severe life threatening nosocomial infection associated with high mortality and morbidity. Colistin or sulbactam has been reported to be effective treatment options in adult populations. However, prognostic factors and treatment outcomes of children affected by this condition have not been well characterized in the current literature.

What this study adds?

1) The two-week case fatality rate among children with this condition was approximately 40%, the majority of which occurred before the culture

results became available for physicians. 2) Extended antibiotic resistance, malignancy-associated febrile neutropenia, and fever ≥2 days before initiating appropriate antibiotics, presence of septic shock, and organ dysfunction are significant prognostic factors for fatality. 3) Having adequate empirical antibiotic treatment administered within 24 hours of clinical suspicion is likely to increase patient's survival. 4) Renal toxicity associated with colistin treatment was not identified, and thus should not be an important issue when dealing with this type of infection among pediatric populations.

Potential conflicts of interest

None.

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ผลการรักษาผู้ป่วยเด็กที่ติดเชื้อ Acinetobacter baumannii ที่ดื้อยาคาร์บาพีเนมในกระแสเลือด

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ภูมิหลัง: อัตราการดื้อยาคาร์บาพีเนมที่เพิ่มสูงขึ้นอย่างต่อเนื่องของเชื้อ Acinetobacter baumannii ทำให้ปัจจุบันแทบจะไม่มียาปฏิชีวนะมาใช้ในการรักษา ปัจจุบันข้อมูลในด้านของการพยากรณ์และผลการรักษา โรคติดเชื้อชนิดนี้ในกระแสเลือดในเด็กยังมีจำกัด

วัตถุประสงค์: เพื่อประเมินผลการรักษาทางคลินิก และศึกษาปัจจัยที่มีผลต่อการพยากรณ์โรคของเด็กที่ติดเชื้อ A. baumannii ที่ดื้อต่อคาร์บาพีเนมในกระเสเลือด

วัสดุและวิธีการ: ทำการศึกษาย้อนหลังเชิงพรรณนาในเด็กที่มีผลการเพาะเชื้อในกระแสเลือดขึ้น A. baumannii ที่ดื้อยาคาร์บาพีเนม (carbapenem resistant) และเข้ารับการรักษาแบบผู้ป่วยในที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี (โรงพยาบาลเด็ก, กรุงเทพมหานคร) ในช่วงเวลาตั้งแต่เดือนตุลาคม พ.ศ. 2548 ถึง เดือนกันยายน พ.ศ. 2553

ผลการศึกษา: มีผู้ป่วยทั้งสิ้นจำนวน 89 รายที่คิดเป็นอุบัติการณ์ 1.2 รายต่อ 1,000 ผู้ป่วยในส่วนใหญ่เป็นเด็กทารก โดยมีค่ามัธยฐานของอายุที่ 2 เดือน และร้อยละ 88 มีโรคประจำตัวอื่นร่วมด้วย อัตราตายที่ 2 สัปดาห์ และ 30 วันเท่ากับร้อยละ 39 และ 42 ตามลำดับ ผู้ป่วยส่วนใหญ่ (ร้อยละ 63) เสียชีวิตก่อนได้ผลเพาะเชื้อ การดื้อยาหลายขนานหรือการดื้อยาทุกตัวที่ใช้เป็นขนาดแรกของสถาบัน (ยาทุกตัวในกลุ่มเซฟาโลสปอริน อะมิโนไกลโคไซด์ ควิโนโลนและคาร์บาพีเนม) สัมพันธ์กับอัตราการเสียชีวิตที่ 2 สัปดาห์อย่างมีนัยสำคัญ (ร้อยละ 48 และ 23, p = 0.028) และการเสียชีวิตในเวลาอันสั้นหลังการติดเชื้อ (Kaplan-Meier p = 0.016) จากการวิเคราะห์โดยวิธี univariate analysis พบว่าปัจจัยที่สัมพันธ์กับอัตราตายภายใน 2 สัปดาห์ ได้แก่ ภาวะเม็ดเลือดขาวต่ำในผู้ป่วยโรคมะเร็ง, การเริ่มยาหลังจากเริ่มมีไข้นานกว่าหรือเท่ากับ 2 วัน, การมีภาวะช็อค, อวัยวะทำงานผิดปกติ และการติดเชื้อดื้อยาหลายขนาน อัตราตายในเด็กที่ได้ยาปฏิชีวนะที่เหมาะสมอย่างน้อย 1 ชนิด ภายใน 24 ชั่วโมงแรก มีแนวโน้มต่ำกว่ากลุ่มที่ไม่ได้รับโดยมีอัตราตายในกลุ่มแรก และกลุ่มที่ 2 ร้อยละ 10 และ 23 ตามลำดับ (p = 0.675) ความไวของโคลิสตินยังสูงถึงร้อยละ 100 อย่างไรก็ตามอัตราตายของผู้ป่วยที่ได้รับโคลิสตินเท่ากับร้อยละ 20 ส่วนผู้ที่ติดเชื้อสายพันธุ์ที่ไวต่อซัลแบคแตมและได้รับการรักษาด้วยซัลแบคแตมไม่มีผู้ใดเสียชีวิต (n = 15) ไม่พบมีภาวะพิษต่อไตในผู้ที่ได้รับการรักษาด้วยโคลิสตินในการศึกษาครั้งนี้

สรุป: การติดเชื้อ A. baumannii ที่ดื้อคาร์บาพีเนมในกระแสเลือด มีอัตราตายสูงและเกิดขึ้นค่อนข้างเร็ว ก่อนที่จะทราบผลเพาะเชื้อ การดื้อยาหลายขนาดสัมพันธ์กับอัตราตายที่สูงขึ้น การรักษาโดยการให้ยาปฏิชีวนะ ที่เหมาะสมอย่างทันท่วงที โดยเฉพาะการให้ภายใน 24 ชั่วโมงแรก (ได้แก่ โคลิสตินและซัลแบคแตม) สัมพันธ์กับอัตราการรอดชีวิตในเด็กกลุ่มนี้