Prognosis of adult patients with bacteremia caused by extensively resistant *Acinetobacter baumannii*

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Abstract

Nosocomial bacteremia caused by extensively resistant *Acinetobacter baumannii* (ERAB) is an emerging problem in Taiwanese hospitals. Accordingly, we retrospectively investigated the epidemiology and outcomes of adult patients with ERAB bacteremia (ERABB) after different treatments from January 2001 to September 2004 at the National Taiwan University Hospital, Taipei, Taiwan. A total of 56 adult patients with ERABB and without other simultaneous infections were enrolled. Demographic, clinical, and laboratory data were obtained from medical records. Clinical data included underlying diseases and conditions with onset within 7 days after ERABB, severity of ERABB, antibiotic regimens for ERABB, and clinical outcomes. Laboratory data included hemograms, liver function tests, renal function tests, and albumin levels. Coagulation profiles were obtained at ERABB onset and 7 days before and after onset. All 56 episodes of ERABB were hospital-acquired. Most patients had Acute Physiology Scores and Chronic Health Evaluation II scores ≥ 17 (66.1%) and Pitt bacteremia score ≥ 4 (66.1%). Many had comorbid diseases at ERABB onset. Crude mortality rates on days 2, 7, 15, 30, and at discharge were 23.2%, 30.4%, 37.5%, 48.2%, and 60.7%, respectively. High severity of ERABB (Pitt bacteremia score ≥ 4) and presence of immunosuppression were the only 2 predictors for day 30 mortality (odds ratios of 18.53 and 8.06, respectively). Antibiotic regimens for ERABB did not have a significant influence on ERABB outcomes.

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Keywords: *Acinetobacter baumannii*; Antibiotic resistance; Bacteremia; Prognosis; Antibiotics

1. Introduction

Acinetobacter spp. are aerobic, encapsulated, nonmotile, nonfermentative, Gram-negative coccobacilli with low virulence (Lai et al., 1999; Chang et al., 1995; Kuo et al., 2003; Wang et al., 2003; Allen et al., 2000). Free-living *Acinetobacter* can be found on both animate and inanimate objects (Allen et al., 2000), colonize humans, survive on dry inanimate objects for several days, and emerge as important

opportunistic pathogens, especially among critically ill patients (Manikal et al., 2000).

Nosocomial infections caused by *Acinetobacter baumannii* have increased in recent years, especially in patients staying in intensive care units (ICU) (Cisneros et al., 1996) and in immunosuppressed hosts (Levin et al., 2003; Seifert et al., 1995) or burn patients (Cisneros et al., 1996). Although there are significant differences in antimicrobial resistance patterns for *A. baumannii* demonstrated in various studies, the overall trend is toward increasing resistance (Allen et al., 2000). Therefore, the antibiotics of choice for treating *A. baumannii* infection have become more and more limited (Lai et al., 1999; Chang et al., 1995; Kuo et al., 2003).

A strain of extensively resistant *A. baumannii* (ERAB), which is resistant to all currently available antipseudomonal antibiotics available in Taiwan, has emerged rapidly at the

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National Taiwan University Hospital (NTUH), Taipei, Taiwan, since 1998 (Hsueh et al., 2002a, 2002b). Since then, ERAB was found in many hospitals in Taiwan (Center of Diseases Control, Taiwan; unpublished data) and caused some nosocomial outbreaks (Wang et al., 2003). Among various infections caused by ERAB, bacteremia is of special concern because of its high mortality (Kuo et al., 2003). However, prognostic factors and outcomes of patients with ERAB bacteremia (ERABB) have not been well studied (Kuo et al., 2003; Lee et al., 2005). Furthermore, the most effective antibiotic regimen for treatment of ERABB has not been determined.

Therefore, our study was designed to identify prognostic factors and compare treatment effects of different antibiotic regimens used for treating ERABB.

2. Patients and methods

2.1. Hospital settings and patients

NTUH, which is in northern Taiwan, is a major teaching hospital with a total capacity of 2200 beds. It offers both primary and tertiary care for patients with acute diseases. Since early 1980s at NTUH, there has been a well-trained and organized infection control team in charge of hospital-wide surveillance for nosocomial infections and resistant pathogens isolated from all clinical specimens.

From January 2001 to September 2004, all hospitalized adult patients (aged ≥ 18 years) at NTUH who had ERABB were enrolled in our study. Patients who had other microorganisms isolated concomitantly from blood or other infections caused by any microorganisms other than ERAB within 2 days of onset of ERABB were excluded.

2.2. Definition of ERAB and ERABB

ERAB was defined as an isolate of *A. baumannii* resistant to trimethoprim/sulfamethoxazole, piperacillin/tazobactam, aztreonam, ceftazidime, ceftriaxone, cefepime, ciprofloxacin, levofloxacin, gentamicin, amikacin, and meropenem determined by disc diffusion method (National Committee For Clinical Laboratory Standards, 2000).

At NTUH, the blood culture system used is Bactec 2-bottle culture system (Becton Dickinson, Maryland). Patients with ERABB was defined as who had clinical symptoms and signs of infection (such as fever, leukocytosis, elevated C-reactive protein [CRP], or sepsis) and one or more positive blood culture of ERAB at the same time. Primary ERABB was defined as ERABB without an identifiable infection focus or those due to catheter-related infection (Wang et al., 2004a, 2004b).

Nosocomial bacteremia was defined as bacteremia that occurred more than 48 h after hospital admission or bacteremia that occurred less than 48 h after admission to the hospital in patients who had been hospitalized in any hospital within 2 weeks before admission (Lautenbach et al., 2001).

2.3. Definition of organ failure and dysfunction

Heart failure was defined according to criteria proposed by Ho et al. (1993). Respiratory failure was defined as partial pressure of oxygen of arterial blood <60 mm Hg with a fraction of inspired oxygen >0.5 , or alveolar–arterial oxygen tension difference >300 mm Hg with a fraction of inspired oxygen of >0.5 , or requirement for mechanical ventilation (Garcia-Garmendia et al., 2001). Abnormal liver function was defined as >5 consecutive positive tests for elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and the peak level being greater than 5 times of the normal limit (for AST, 36 U/L for male patient and 30 U/L for female patient; for ALT, 40 U/L for male patient and 30 U/L for female patient). Hepatic failure was defined as serum bilirubin >3.0 mg/dL and prothrombin time >15 s, or biopsy evidence of cirrhosis or necrosis (Linden et al., 1997). Cirrhosis was considered as a definite diagnosis if histologic evidence was present or a probable diagnosis if clinical and analytical data suggested chronic liver disease, hepatocellular dysfunction, and portal hypertension (Caballero-Granado et al., 2001). Acute renal failure was defined as an increase of 0.5 mg/dL in normal serum creatinine levels or of 1 mg/dL in abnormal serum creatinine levels. Chronic renal insufficiency was defined as a creatinine level in plasma >2 mg/dL and a medical record that suggested that it was a chronic disturbance (i.e., confirmation of its previous existence, normocytic normochromic anemia, renal atrophy, and renal osteodystrophy) (Caballero-Granado et al., 2001). Chronic renal failure was defined as chronic renal disease progression to the point where creatinine clearance was <10 mL/min.

2.4. Study design and data collection

This is a retrospective cohort study. A standardized case record form was used to collect patients' demographic, clinical, and laboratory data. The clinical data consisted of 1) underlying diseases, 2) invasive procedures before the onset of ERABB, 3) severity of the underlying condition at ERABB onset using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Knaus et al., 1985), 4) severity of ERABB by Pitt bacteremia score (≥ 4) and the presence of septic shock according to the classification recommended by the American College of Chest Physicians/Society of Critical Care Medicine (The American College of Chest Physicians/Society of Critical Medicine, 1992; Chow and Yu, 1999), 5) treatment regimen for ERABB, 6) complications related to ERABB, and 7) outcome.

Immunosuppression was defined as the presence of prior organ transplantation, human immunodeficiency virus infection, and immunosuppressive therapy, which included antineoplastic therapy within 6 weeks of onset of ERABB (Tilley and Roberts, 1994), corticosteroids at a dose equivalent to or higher than 20 mg of prednisolone daily for at least 2 weeks or 30 mg of prednisolone daily for at least 1 week before a positive blood culture for ERAB (Esel et al.,

Table 1

Demographic data and clinical conditions for patients ($n = 56$) with ERABB

Variable	No.	(%)	Mean	SD	Median	Range
Age (years)			65.5	16.0	68	20–92
Sex: male/female	30/26	(53.6/46.4)				
Ward at ERABB onset						
General ward	16	(28.6)				
Emergency room	1	(1.8)				
ICU	39	(69.6)				
ICU experience before ERABB	48	(85.7)				
Underlying disease						
Cerebrovascular accident	13	(23.2)				
Diabetes mellitus	20	(35.7)				
Cardiovascular diseases	32	(57.1)				
Hypertension	26	(46.4)				
Congestive heart failure	10	(17.9)				
Coronary artery disease	15	(26.8)				
VHD	4	(7.1)				
Others	1	(1.8)				
Shock	21	(37.5)				
Respiratory diseases	46	(82.1)				
COPD	7	(12.5)				
Respiratory failure	45	(80.4)				
Hepatobiliary diseases	19	(33.3)				
Hepatic failure/cirrhosis	5	(8.9)				
Renal diseases	23	(41.1)				
End-stage renal disease	7	(12.5)				
Dialysis dependence	16	(28.6)				
Autoimmune diseases	5	(8.9)				
Malignancy	19	(33.9)				
Solid tumor	11	(19.6)				
Hematologic malignancy	8	(14.3)				
Immunologically suppressed?	24	(42.9)				
SIRS criteria at ERABB onset						
Without septic shock	34	(60.7)				
With septic shock	22	(39.3)				
Pitt bacteremia score at ERABB onset			4.34	2.56	4	0–14
Critical (Pitt score ≥ 4)	37	(66.1)				
APACHE II score at ERABB onset			20.8	9.3	19	6–39
≥ 17	37	(66.1)				
DIC at ERABB onset	11	(19.6)				
WBC count	55	(98.2)	11 864	8475	9400	20–39 310
Neutropenia	3	(5.4)				
Leukocytosis	26	(47.3)				
Hemoglobin (g/dL) (data for 55 patients)			9.86	1.71	9.7	6.5–17.2
Anemia	9	(16.4)				
Albumin (g/dL) (35 patients)	35	(62.5)	2.57	0.45	2.80	1.62–3.98
CRP (mg/dL) (28 patients)			8.84	4.90	8.85	1.03–21.2
CRP ≥ 5	21	(75.0)				
Scr (mg/dL) (51 patients)			1.88	1.53	1.20	0.23–6.67
Elevated (>1.5 mg/dL)	23	(45.1)				
LDH (8 patients data)			761.5	813.81	515.5	238–2753
Elevated (>460 U/L)	6	(75)				
Total bilirubin (37 patients)			8.05	18.72	1.22	0.25–109.00
Elevated (>1.5 mg/dL)	17	(45.9)				
ALT (only 22 patients had data)			89.81	259.73	29.5	10–1248
Elevated (>40 U/L)	8	(36.4)				
Infection source of ERABB						
Primary ERABB	39	(69.6)				
No identifiable source	32	(57.1)				
CVC	7	(12.5)				
Secondary—respiratory tract	15	(26.8)				
Secondary—others	2	(3.6)				
Total length of hospital stay (days)			92.8	97.6	68	3–590

(continued on next page)

Table 1 (continued)

Variable	No.	(%)	Mean	SD	Median	Range
Before ERABB onset			50.1	55.3	34	0–292
After ERABB onset			42.6	64.7	22.5	1–331
Overall mortality						
At 15 days after ERABB onset	21	(37.5)				
At 30 days after ERABB onset	27	(48.2)				
At discharge	34	(60.7)				

COPD = chronic obstructive pulmonary disease; WBC = white blood cell; Scr = serum creatinine concentration; LDH = lactate dehydrogenase; ALT = alanine transaminase; VHD = valvular heart disease.

2003; Galofre et al., 1994), and other immunosuppressants such as azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, and sirolimus.

Invasive procedures included i) usage of central venous catheters (CVCs), arterial catheters, port A catheters, endotracheal tubes, nasogastric/nasoduodenal tubes, and peripheral venous catheters, thoracentesis, and paracentesis within 7 days before onset of ERABB; ii) simple operation under local anesthesia within 7 days before onset of ERABB; and iii) operations under general anesthesia within 30 days previous to onset of ERABB (Levin et al., 2003).

The severity of ERABB was defined as critical if the Pitt bacteremia score was equal to or greater than 4. The severity of patients' clinical condition was defined as severe if the APACHE II score was equal to or greater than 17 (Chow and Yu, 1999; Smolyakov et al., 2003). New organ failure was defined as that which developed within 7 days of ERABB onset, and new bacterial infection was defined as that which occurred within 30 days after onset of ERABB.

Antibiotics regimens used for ERABB were evaluated at 2 different stages, that is, as initial or definite treatments. Initial treatment was the regimen used within 48 h after onset of ERABB, when the blood culture result was usually not available. Definite treatment was the regimen used after the availability of blood culture results. To evaluate the potential benefit of antibiotic treatment, both initial and definite treatments were further classified into 2 groups by 3 different classification methods. First, regimens containing ampicillin/sulbactam were classified into one group and all others into another group. Second, regimens containing carbapenem (imipenem or meropenem) and ampicillin/sulbactam were classified into one group and all others into another group. Third, regimens containing both carbapenems (imipenem or meropenem) and aminoglycosides were classified into one group and all others into another group.

Laboratory data including hemogram, CRP, liver function test, renal function test, albumin level, and profile of disseminated intravascular coagulopathy (DIC) were evaluated before and after the onset of ERABB.

2.5. Mortality of ERABB

We evaluated all-cause mortality by days 2, 7, 15, and 30 after the onset of ERABB, and at discharge. For patients who were discharged before day 30, clinical status

was determined by the records of follow-up visits in outpatient clinics.

2.6. Statistical analyses

Statistical analyses were executed using SAS 9.1.3 (SAS Institute, Cary, NC). Continuous variables were described as mean $\pm$ SD and median. They were compared using Student's *t* test. Categorical variables were compared with a χ^2 test or, if the expected values were below 10, a Fisher's exact test. Predictors for day 30 mortality were identified using logistic regression. All clinical and laboratory parameters were tested for univariate analysis first. The parameters with a *P* value less than 0.2 and those with potentially biologic meanings would be put into the model of multivariate analysis. However, the parameters with collinearity [variance inflation factors (VIF) >10 determined by linear regression model using the option of VIF in SAS program] would not be put in the final model simultaneously. A stepwise model comparison and selection were used to determine the final model of multiple variables analysis. All tests were 2 tailed. A *P* value less than 0.05 was considered statistically significant.

3. Results

During the study period, there were 59 cases that met the definition of ERABB. Three patients with missing medical records were excluded from the analysis.

The demographic, clinical, and laboratory data for the 56 patients with ERABB are listed in Table 1. All 56 episodes of ERABB were nosocomial. The male-to-female ratio was 1.2:1. The mean age was 65.5 years (range, 20–92 years). Among them, 54 (96.4%) had various underlying diseases. Thirty-nine (69.6%) developed ERABB while in ICUs, 16 (28.6%) while in the general wards, and 1 while in the emergency room. Of the 16 who developed ERABB in general wards, 8 (50.0%) had stayed in an ICU before the onset of ERABB during the same hospitalization. The mean APACHE II scores for all 56 patients were 20.8 ± 9.3 (median, 19; range, 6–39). At the onset of ERABB, all 56 patients met the criteria for sepsis, and 22 (39.3%) had septic shock. The Pitt bacteremia scores were 4.34 ± 2.56 (median, 4; range, 0–14). Twenty-four patients (42.9%) were

Fig. 1. Antibiotic regimens for ERABB patients as initial treatment and definite treatment.

classified as immunosuppressed hosts during ERABB onset. Among these 24 patients, 4 were recipients of organ transplantation, 2 received chemotherapy, and 19 received corticosteroids. The average length of total hospital stays was 92.8 ± 97.6 days (median, 68 days; range, 3–590 days). The average length of hospital stays before the onset of ERABB was 50.1 ± 55.3 days (median, 34 days; range, 0–292 days). The average length of hospital stays after the onset of ERABB was 42.6 ± 67.4 days (median, 22.5 days; range, 1–331 days). Thirty-four patients (60.7%) had died by the time of discharge.

Most ERABB episodes were classified as primary bacteremia (69.6%). Eleven (19.6%) of the 56 patients had DIC. Among the 55 patients whose hemograms were checked during the onset of ERABB, 3 (5.4%) had neutropenia ($<1500/\mu\text{L}$), 26 (47.3%) had leukocytosis ($>11\,000/\mu\text{L}$), and 9 had anemia (hemoglobin $<11\text{ g/dL}$). Fifty-one patients had available renal function test results, and 23 (45.1%) of them had abnormal serum creatinine levels ($>1.5\text{ mg/dL}$). The serum level of alanine transami-

nase was available for 22 patients, and 8 (36.4%) of them were abnormal ($>40\text{ U/L}$). Thirty-seven patients had available serum bilirubin levels, and 17 (45.9%) of them were abnormal. Other laboratory data are shown in Table 1.

Fig. 2. Cumulative mortality rate of 56 patients with ERABB.

Table 2

Comparative parameters and univariate analysis of mortality on day 30 for ERABB patients

Variables	Alive, <i>n</i> = 29		Dead, <i>n</i> = 27		<i>P</i> ^a	Logistic regression		
	No.	(%)	No.	(%)		OR	95% confidence interval	<i>P</i>
Cerebrovascular accident	9	(31.0)	2	(7.4)	0.0420	0.18	0.03–0.92	0.0391
Diabetes mellitus	11	(37.9)	9	(33.3)	0.7849	0.82	0.27–2.45	0.7199
Cardiovascular diseases	16	(55.2)	16	(59.3)	0.7928	1.18	0.41–3.41	0.7578
Respiratory diseases	20	(69.0)	24	(88.9)	0.1043	3.60	0.86–15.12	0.0802
Respiratory failure	17	(58.6)	24	(88.9)	0.0154	5.65	1.38–23.12	0.0161
Abnormal liver function	7	(24.1)	13	(48.15)	0.0940	2.918	0.936–9.099	0.0649
Hepatic failure/cirrhosis	1	(3.5)	4	(14.8)	0.1855	4.869	0.51–46.65	0.1697
Abnormal renal function	10	(34.5)	17	(63.0)	0.0601	3.23	1.08–9.64	0.0357
Acute renal failure	5	(17.2)	14	(51.9)	0.0104	5.17	1.52–17.58	0.0085
Chronic renal insufficiency	4	(13.8)	3	(11.1)	1.0000	0.76	0.16–3.86	0.7621
Autoimmune diseases	1	(3.5)	4	(14.8)	0.1855	4.87	0.51–46.65	0.1697
Malignancy	8	(27.6)	11	(40.7)	0.3991	1.81	0.59–5.53	0.3011
Immunosuppression	6	(20.7)	18	(66.7)	9.915E04	7.67	2.30–25.53	0.0009
Transplantation recipient	1	(3.5)	3	(11.1)	0.4558	2.91	0.40–21.38	0.2942
No	28	(36.6)	24	(88.9)		baseline		
Bone marrow	1	(3.5)	2	(7.4)		2.24	0.19–26.22	0.5206
Heart	0	(0.0)	1	(3.7)		–	–	–
Immunosuppressive therapy	5	(17.2)	16	(59.3)	0.0021	6.98	2.04–23.93	0.0020
Chemotherapy	1	(3.5)	1	(3.7)	1.0000	1.08	0.06–18.12	0.9589
Steroid	4	(13.8)	15	(55.6)	0.0016	7.81	2.13–28.67	0.0019
DIC	2	(6.9)	9	(33.3)	0.0184	6.75	1.30–34.94	0.0228
Neutropenia	0	(0.0)	3	(11.1)	0.1055	–	–	–
Subsequent new infections	14	(48.3)	11	(40.7)	0.6016	0.74	0.26–2.12	0.5713
Not caused by ERAB	9	(31.0)	4	(14.8)	0.2095	0.39	0.10–1.45	0.1586
Caused by ERAB	9	(31.0)	8	(29.6)	1.0000	0.94	0.30–2.93	0.9091
Hemoglobin					1.000	1.250	0.297–5.256	0.7607
Hemoglobin ≤11	23	(82.1)	23	(85.2)				
Hemoglobin >11	5	(17.9)	4	(14.8)				
Albumin					0.0082	10.286	1.737–60.901	0.0102
Albumin ≤2.5	2	(10.0)	8	(53.3)				
Albumin >2.5	18	(90.0)	7	(46.7)				
Invasive procedure								
Arterial catheters	16	(55.2)	23	(85.2)	0.0205	4.672	1.287–16.964	0.0191
CVCs	24	(82.8)	26	(96.3)	0.1946	5.416	0.590–49.788	0.1354
Swan-Ganz catheters	2	(6.9)	1	(3.7)	1.0000	0.519	0.044–6.079	0.6016
Urinary catheters/Foley	19	(65.5)	21	(77.8)	0.3820	1.842	0.562–6.038	0.3132
Endotracheal tubes/tracheal tubes	18	(62.1)	23	(85.2)	0.0718	3.514	0.958–12.894	0.0581
Nasogastric tube/duodenal tubes	23	(79.3)	23	(85.2)	0.7308	1.500	0.373–6.028	0.5678
Shunting surgery	5	(17.2)	10	(37.0)	0.1334	2.823	0.817–9.759	0.1010
Peripheral venous catheter	6	(20.7)	5	(18.5)	1.0000	0.871	0.232–3.272	0.8385
Thoracentesis	1	(3.45)	5	(18.5)	0.0959	6.363	0.692–58.486	0.1021
Paracentesis	5	(17.2)	2	(7.4)	0.4239	0.384	0.068–2.172	0.2790
Port A	2	(6.9)	4	(14.8)	0.4141	2.348	0.393–14.006	0.3490
Prior operations within 30 days	12	(41.4)	10	(37.0)	0.7895	0.833	0.284–2.442	0.7396
Pitt bacteremia score								
Critical (Pitt score ≥4)	12	(41.4)	25	(92.6)	0.0001	17.71	3.51–89.37	0.0005
APACHE score								
≥17	15	(51.7)	22	(81.5)	0.0252	4.11	1.22–13.83	0.0226
Severity by SIRS criteria								
With septic shock	5	(17.2)	17	(63.0)	8.359E04	8.160	2.361–28.207	0.0009
Without septic shock	24	(82.8)	10	(37.0)				
Antibiotics treatment								
Initial treatment alone								
Ampicillin/sulbactam	7	(24.1)	4	(14.8)	0.5064	0.55	0.14–2.13	0.3842
Carbapenems + ampicillin/sulbactam (±aminoglycosides)	4	(13.8)	4	(14.8)	1.0000	1.09	0.24–4.86	0.9130
Carbapenems + aminoglycosides (±ampicillin/sulbactam)	3	(10.3)	5	(18.5)	0.4620	1.97	0.42–9.19	0.3882
Definite treatment								
Ampicillin/sulbactam	13	(44.8)	9	(33.3)	0.4226	0.62	0.21–1.82	0.3802
Carbapenems + ampicillin/sulbactam (±aminoglycosides)	5	(17.2)	4	(14.8)	1.0000	0.84	0.20–3.50	0.8050
Carbapenems + aminoglycosides (±ampicillin/sulbactam)	9	(31.0)	10	(37.0)	0.7789	1.31	0.43–3.96	0.6358
Initial and definite treatment together								

Table 2 (continued)

Variables	Alive, <i>n</i> = 29		Dead, <i>n</i> = 27		<i>P</i> ^a	Logistic regression		
	No.	(%)	No.	(%)		OR	95% confidence interval	<i>P</i>
Ampicillin/sulbactam	7	(24.1)	4	(14.8)	0.5064	0.55	0.14–2.13	0.3842
Carbapenems + ampicillin/sulbactam (±aminoglycosides)	3	(10.3)	4	(14.8)	0.7004	1.51	0.31–7.46	0.6150
Carbapenems + aminoglycosides (ampicillin/sulbactam)	2	(6.9)	5	(18.5)	0.2442	3.07	0.54–17.37	0.2050

^a Chi-square test and Fisher's exact test.

No regimen has been demonstrated to be best for ERABB patients. Not surprisingly, then, the 56 patients had received various kinds of antibiotic treatments. All patients received antibiotics immediately after onset of ERABB. Carbapenems, penicillins, and aminoglycosides were the 3 classes of antibiotics used most frequently in both initial and definite treatments. However, most of the patients received treatment with a combination of antibiotics. The proportion of patients treated with a regimen of antibiotics containing ampicillin/sulbactam, or carbapenem + ampicillin/sulbactam, or carbapenem plus an aminoglycoside are shown in Fig. 1. For initial treatment, carbapenem plus an aminoglycoside and carbapenem plus ampicillin/sulbactam were the most frequently used regimens. For definite treatment, carbapenem plus an aminoglycoside was the most frequently used combination regimen. There was no significant difference in age, sex, underlying diseases, immune status, and severity of ERABB (determined by the Pitt bacteremia score and the APACHE II score) among patients receiving different treatment regimens (data not shown).

After ERABB onset, 10 patients (17.9%) developed new respiratory failure. Nine (16.1%) developed renal failure. Twenty-five (44.6%) developed superimposed bacterial infections after ERABB. The respiratory tract was the most common infection focus being noted in 19 of the 25 patients with superimposed infections. All-cause mortality rates were, respectively, 23.2%, 30.4%, 37.5%, 48.2%, and 60.7% on days 2, 7, 15, 30, and at discharge. The cumulative curve of mortality is shown in Fig. 2.

Comparisons for various parameters between patients who were alive and who were dead by day 30 after ERABB are listed in Table 2. For each parameter, we considered the patient to be positive for the parameter if they were positive before ERABB or if they became positive within 7 days after onset of ERABB. The parameters that differed significantly (by χ^2 test or Fisher's exact test) between these 2 groups included the severity of patients' condition at the onset of ERABB (by APACHE II score), severity of ERABB by Pitt

bacteremia score, as well as systemic inflammatory response syndrome (SIRS) criteria, cerebrovascular accident, shock status, respiratory failure, acute renal failure, immunosuppression, usage of immunosuppressive therapy, DIC, neutropenia, hypoalbuminemia, and presence of arterial catheter during the onset of ERABB.

Significant predictors for mortality by day 30 by univariate logistic regression analysis were i) the severity of ERABB either by Pitt bacteremia score dichotomized into critical status or not, or SIRS criteria dichotomized into septic shock status or not; ii) the severity of illness at the onset of ERABB (APACHE II score, treated as the dichotomous variable); iii) cerebrovascular accident; iv) shock status; v) respiratory failure; vi) abnormal renal function; vii) acute renal failure; viii) immunosuppression; ix) usage of immunosuppressive therapy; x) DIC; xi) hypoalbuminemia; and xii) presence of arterial catheters during the onset of ERABB.

By stepwise logistic regression multivariate analysis, only severity of ERABB by Pitt bacteremia score and immunosuppression status were independent predictors for day 30 mortality of ERABB patients. Treatment regimen, no matter considering initial treatment alone, definite treatment alone, or initial and definite treatments together, was not a predictor for day 30 mortality (Table 3).

4. Discussion

Infections caused by multidrug-resistant *A. baumannii* (MDRAB) are of great concern worldwide. Many studies concerning MDRAB infections have been reported, including MDRAB bacteremia (Lai et al., 1999; Manikal et al., 2000; Smolyakov et al., 2003; Go et al., 1994). However, few of them have such extensive resistance to all antipseudomonal agents as the ones we described above, and most previous studies had a mixed study population with various kinds of multidrug resistance, and probably had both monomicrobial and polymicrobial infections. To prevent these confounding influences, we selected for our study only those patients with homogenous resistance patterns and only those with monomicrobial bacteremia. Our study results demonstrate that ERABB was associated with a high mortality rate. Severity of ERABB by Pitt bacteremia score and immunosuppression status were the only 2 independent factors that predicted day 30 mortality from ERABB. Currently available treatment regimens do not seem to have any influence on the prognosis of ERABB patients.

Table 3

Multivariate analyses of prognostic factors for day 30 mortality in ERABB patients by multivariate logistic regression

Variables	Odds ratio	95% confidence interval	<i>P</i>
Critical (Pitt bacteremia score ≥ 4)	18.53	3.10–110.72	0.0014
Presence of immunosuppression	8.06	1.87–34.84	0.0052

The age distribution, male-to-female ratio in our patients, and distribution of underlying diseases are similar to previous studies of MDRAB bacteremia (Kuo et al., 2003; Tsai and Chen, 2003; Garcia-Garmendia et al., 2001; Cisneros and Rodriguez-Bano, 2002). In addition, all ERABB infections in the present study were nosocomially acquired, and most developed bacteremia while in ICUs, which means that these patients were critically ill while contracting ERABB. These results are also similar to prior reports (71–73.3%) (Lai et al., 1999; Kuo et al., 2003; Cisneros et al., 1996).

In our study, most episodes of ERABB were classified as a primary bacteremia. For those cases classified as a secondary bacteremia, the respiratory tract was the most common primary focus. These findings are also similar to previous reports concerning bacteremia caused by *A. baumannii* (Lai et al., 1999; Allen et al., 2000; Cisneros et al., 1996; Seifert et al., 1995; Cisneros and Rodriguez-Bano, 2002). The reason why patients without identifiable foci account for most of the patients with *A. baumannii* bacteremia is still unclear. Some authors proposed that intestinal origin leading to bacterial translocation, which is a phenomenon commonly seen in critically ill patients, might be important in the pathogenesis leading to *A. baumannii* bacteremia of unknown origin (Cisneros et al., 1996; Timsit et al., 1993).

In the present study, we used all-cause mortality on day 30 (after ERABB onset) as the end point for evaluating ERABB prognosis. Theoretically, mortality directly due to *A. baumannii* bacteremia is more representative of prognosis (Kuo et al., 2003; Cisneros et al., 1996). However, it is difficult to determine the direct cause of mortality precisely in these complicated cases, especially in the setting of retrospective analysis. In addition, all-cause day 30 mortality, not mortality at discharge, has been used in many studies investigating outcomes of bacteremia caused by various pathogens (Mylotte and Tayara, 2000; Kang et al., 2003; Kang et al., 2004), and most previous studies concerning the outcome of bacteremia caused by *A. baumannii* used the crude mortality rate (mortality rate evaluated at discharge) as the outcome for analysis (Kuo et al., 2003; Cisneros et al., 1996; Smolyakov et al., 2003; Blot et al., 2003). The crude mortality rate for ERABB at discharge in the present study was 60.7%, which is higher than those reported in previous studies (17–46%) (Lai et al., 1999). Disparities in microbiologic characteristics, especially in term of drug resistance and virulence, might contribute to this difference. However, the difference in crude mortality rate might also be due to the severity of underlying diseases in our patients.

Some authors reported that carbapenem plus an aminoglycoside, carbapenem plus ampicillin/sulbactam, or ampicillin/sulbactam alone seemed to be effective in the treatment of MDRAB infections, including those caused by carbapenem-resistant strains (Wang et al., 2004a, 2004b; Choi et al., 2004). Therefore, these regimens were commonly used in our patients with ERABB. However, it seems that these

antibiotic regimens did not have any significant influence on the prognosis in our present retrospective study. By multivariate logistic regression analysis in determining predictors for day 30 mortality and using 3 models based on 3 different methods of grouping patients according to the treatment regimens, we identified only 2 independent predictors (severity of ERABB by Pitt bacteremia score and presence of immunosuppression). Considering initial treatment alone, or definite treatment alone, or initial and definite treatments together, whether they included ampicillin/sulbactam or not, or carbapenem plus ampicillin/sulbactam or not, or carbapenem plus aminoglycosides or not, no any one treatment regimen had statistically significant influence on day 30 mortality (Table 3). One previous study of ERABB patients, but with a smaller study population, indicated that underlying heart disease, shock, need of resuscitation, acute respiratory distress syndrome, mechanical ventilation, and multiple organ dysfunction score were significant predictors (by univariate analysis) for ERABB-associated mortality (Kuo et al., 2003). They also found that treatment regimen did not have any influence on the outcome.

We can think of 3 interpretations why treatment regimens are not an independent factor affecting prognosis of ERABB. First, the prognosis of ERABB was mainly dependent on the host condition, such as severity of disease and immune status, and thus, the antibiotic treatment did not play a role. Second, all individual antibiotics were not active against ERAB isolates. Therefore, no differences could be found even between different combinations. Third, it was possible that the day 30 mortality might not reflect the effect of treatment. However, we had evaluated the predictive variables for day 15 all-cause mortality using multivariate logistic regression model. Severity of ERABB by Pitt bacteremia score and immunosuppression status were still the only 2 independent variables predictive for day 15 mortality (P value <0.001 and 0.006, respectively). To clarify these 3 possibilities, we need further studies.

The Pitt bacteremia score evaluated patients along 5 dimensions, including body temperature, blood pressure/shock status, ventilator dependence, cardiac arrest, and consciousness at the onset of ERABB. Scoring is easy, is validated, and correlates well with clinical outcomes in studies of bloodstream infections such as *Pseudomonas aeruginosa*, *Enterobacter*, *Klebsiella*, pneumococcus, and others (Yu et al., 2003; Hill et al., 2001). Our study demonstrated that the Pitt bacteremia score is an independent predictive factor for day 30 mortality of patients with ERABB.

There are limitations in our study. First, the number of cases included in this study was small. This was inevitable because this kind of ERAB is a new emerging strain of MDRAB, and we want to have homogeneity of the study group for analysis. Second, this study was a retrospective study. It was therefore difficult to identify the source of ERABB in some patients, it was inevitable that there would be some incomplete data, and there were no fixed treatment

regimens. Third, only adult patients were enrolled in this study. So the results of this study probably cannot be applied to children and adolescents with ERABB.

Because no definitely effective regimen has been found for ERABB patients and there is a high mortality rate, prevention of ERABB becomes the most important thing we can do currently. In addition to strict adherence to contact isolation measures to prevent transmission of ERAB by health care workers, previous work showed that decreased usage of broad-spectrum antibiotics, especially ceftazidime, meropenem, and imipenem, might also play a role in reducing ERAB transmission (Tsai et al., 2003).

We conclude that severity of illness at the onset of ERABB and presence of immunosuppression are the only 2 significant predictive factors for day 30 mortality. Currently available antibiotic regimens do not affect clinical outcomes of patients with ERABB.

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