An Outbreak of Imipenem-Resistant Acinetobacter Baumannii at Songklanagarind Hospital: The Risk Factors and Patient Prognosis

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Objective: *To investigate for the factors associated with acquisition of imipenem-resistant Acinetobacter baumannii (IRAB) at Songklanagarind Hospital and the subsequent patient mortality outcome.*
Design: *A case-control study was conducted to evaluate the risk factors for IRAB acquisition using imipenem-sensitive A. baumannii (ISAB) as controls. A retrospective cohort study was employed to assess the factors associated with mortality in the hospital.*
Setting: *An 850-bed university hospital served as a medical school, training hospital, tertiary care, and referral center for the southern part of Thailand.*
Patients: *The patients who acquired A. baumannii during their stay in the hospital.*
Results: *Between July 2003 and September 2005, there were 2,130 isolates of A. baumannii from clinical specimens of 1,237 hospitalized patients. The medical records of 899 admissions to the hospital were available for review. The significant risk factors associated with IRAB acquisition, identified from a case-control study and multiple logistic regression analysis included previous admission to medical-surgical intensive care unit (ICU), respiratory care unit (RCU), previous use of multiple classes of antibiotics, and previous use of imipenem. The cohort study revealed that the mortality rate in the patients with IRAB compared to ISAB were 33.8% and 24.1% respectively, yielding an unadjusted odds ratio of 1.6 (95% CI = 1.2-2.2). However, after controlling for confounding factors by multivariate analysis IRAB did not show the increased mortality.*
Conclusion: *The outbreak of IRAB at Songklanagarind Hospital is associated with increasing antibiotic pressure particularly imipenem and the admission to the ICU and RCU. The excess patient mortality rate attributable to IRAB is not significantly different from that attributable to ISAB.*

Keywords: *Epidemic, Outbreak, Acinetobacter baumannii, Antimicrobial-resistant, Imipenem*

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Acinetobacter baumannii is an aerobic, non-fermentative, Gram-negative coccobacillus that may be isolated from soil, water, human skin, and the environment. It is an important opportunistic nosocomial pathogen causing a variety of nosocomial infections including pneumonia, bloodstream infection, urinary tract infection, and meningitis. However, its predominant role is as an agent of ventilator-associated pneumonia[1]. Infection caused by this organism poses crucial problems in both its treatment and control due to its ability to survive in a long period in the environment and to rapidly develop resistance to multiple antimicrobial agents[2-4].

Imipenem is a carbapenem antimicrobial agent used to treat a variety of serious infections caused by bacteria resistant to the primary agent of choice. Imipenem has retained in vitro activities that are superior to those other antimicrobials, and consequently in many centers, it is the drug of choice for patients with infection caused by *A. baumannii*[5].

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Infections caused by imipenem-resistant *A. baumannii* (IRAB) pose the difficult therapeutic problems to the clinicians because of the widespread resistance of all major classes of antibiotics in these bacteria. These therapeutic difficulties are coupled with the facts that these bacteria have a significant capacity for prolonged survival in the hospital environment and the potential for enhanced opportunity of transmission between patients either via human reservoir or via inanimate materials.

Over the last decade, nosocomial outbreaks of IRAB have been reported with increasing frequency, especially in intensive care units (ICU) and burn units[6-17].

In 2005, it was recognized by the physicians in Songklanagarind Hospital that the frequency of IRAB had been increasing. The present study was conducted with the primary intention to determine the risk factors associated with the resistant strains acquisition and the prognosis of the patients who acquired them.

Material and Method

Setting

The present study was conducted at Songklanagarind Hospital, an 850-bed medical school, training, and referral center for the southern part of Thailand. The hospital has three intensive care units, an adult medical-surgical intensive care unit, a pediatric intensive care unit, and a neonatal intensive care unit with 19, 7 and 15 beds, respectively. The hospital also has a 16-bed respiratory care unit (RCU).

Bacteriology

All *A. baumannii* samples were inoculated on sheep blood agars and incubated at 35°C. Typical colonies were examined. The genus was identified by Gram staining, cell and colony morphology, oxidation/fermentation test activity, absence of motility and negative oxidase and positive catalase reactions. The species identification of *A. baumannii* was determined by lactose and glucose fermentation.

The antibiotic susceptibility of the *A. baumannii* isolates were determined by the disk diffusion method on Mueller-Hinton agar plates[18]. Antibiotic susceptibility was determined routinely for 12 different antibiotics agents including gentamicin, amikacin, ampicillin, cephalothin, cefoxitin, ceftazidime, ceftriaxone, imipenem, meropenem, and sulperazone (cefoperazone/sulbactam), ciprofloxacin, and cotrimoxazole.

Sources of Data

Inclusion Criteria

Data of *A. baumannii* cultures including ward and date of isolation, specimen, patient identification, and antibiotic susceptibility were retrieved from microbiology laboratory computer records. Patient risk factors and mortality outcomes were reviewed from patient medical records. The amount of imipenem prescribed in the hospital was obtained from the pharmacy department.

Study Designs

Exclusion criteria

The medical records with "incomplete" or "unavailable information needed" were discarded from the review. Patients in whom *A. baumannii* was isolated within 48 hours of admission were excluded from the present study as well as patients who acquired *A. baumannii* from other hospitals.

Definitions

Outbreak was defined as the occurrence of IRAB in excess of upper limit of 95%C.I of the IRAB usually isolated. NNIS CDC criteria were used for diagnosing nosocomial infection[19,20]. In cases where the criterion for diagnosing infection was not fulfilled, colonization by *A. baumannii* was assigned. If there was more than one episode of infection or colonization by *A. baumannii* presented during a single hospital admission, only the first episode was used for analysis. The American Society Association (ASA) score was used to classify the patients into five groups with different degrees of severity of illness at admission[21].

A medical patient was defined as a patient who was cared for primarily by an internist or a pediatrician. A patient other than a medical patient was assigned as a surgical patient. Neutropenia was defined as the number of neutrophils less than 500/ml at the time of admission. Device-day was the sum of duration of each invasive device (intravenous catheter, urinary catheter, and mechanical ventilator support) prior to *A. baumannii* acquisition. In the same way, antibiotic-day was the sum of the duration of each systemic antibiotic given to a patient before *A. baumannii* was isolated.

Descriptive study

The authors used the data from the hospital microbiology unit to describe the time trend of the IRAB outbreak by analyzing for the proportion of the resistant strains isolated in each month. The frequencies

of the identified resistant strains were stratified by patient wards and sites of isolation.

Case-control study

To assess the potential risk factors associated with IRAB acquisition, the authors did a case-control study using a patient with IRAB as a case. For comparison with cases, a control group was defined as the patients with infection or colonization with imipenem-sensitive *A. baumannii* (ISAB).

Retrospective cohort study

To assess the impact of IRAB acquisition on the mortality outcome of the patients, a retrospective cohort study was conducted comparing the hospital mortality rates between the patients who acquired IRAB and the patients in whom ISAB were isolated. The other mortality prognostic factors were used to control confounding effects. These included ASA score, hospital service, age, neutropenia, and site of infection or colonization with *A. baumannii*.

Statistical analysis

The proportions of IRAB were reported in terms of percentages and the 95% confidence interval (C.I) was estimated by the mean of the exact binomial statistics. The relationship between the amount of imipenem received and the proportion of IRAB isolations was measured with Pearson Product Moment Correlation Coefficient (r). The associations between each of the potential risk factors and IRAB acquisition or mortality outcome were first evaluated by univariate analysis using the contingency tables with chi-square or Fisher's exact statistics. Odds ratio (OR) and the corresponding 95% confidence intervals (95% C.I) were computed. The variables, which were found statistically significant from the univariate analysis, were subsequently included in the multivariate analysis. The stepwise multiple logistic regression model with backward deletion was used in the multivariate analysis to identify independent variables that were significantly associated with the occurrence of IRAB and the mortality outcome. Statistical analyses were done by using statistical software STATA v.7 (Stata Corp. College Station, Tex). To improve statistical power, continuous or ordinal variables were partitioned in two or three levels.

To assess the effect of imipenem resistance on the patient mortality outcome in various groups, the authors compared the mortality rates between the patients with IRAB and ISAB by mean of stratification. The prognostic factors identified from univariate analysis as statistically significant associated with hospital mortality were used for stratification.

Results

***A. baumannii* isolation**

Two thousand one hundred and thirty isolates of *A. baumannii* were identified from clinical specimens of 1,237 hospitalized patients between July 2003 and September 2005. The frequencies of IRAB isolations according to anatomical sites of isolation and patient wards are displayed in Table 1 and Table 2. The most common site of IRAB isolations was the respiratory tract, which accounted for more than half (61.9%) of all IRAB isolated. The hospital unit where IRAB was most frequently isolated was the ICU, followed by the RCU. The antibiotics resistance patterns of the IRAB and ISAB are given in Table 3. The IRAB were also resistant to other antibiotics particularly cephalosporins and quinolone compounds. Thus, 14.8% of all IRAB isolates were resistant to all the routinely tested antibiotics.

Description of the outbreak

The authors reviewed the data of bacterial isolations from the hospital microbiology database and found that there had been an outbreak of IRAB since July 2003. While the numbers of isolations of *A. baumannii* were relatively constant from the year 2000, the proportions of IRAB isolations had been increasing since July 2003 (Fig. 1).

To determine whether antibiotic selection pressure could explain this outbreak, the authors studied the relationship between an imipenem use and the incidence of IRAB isolations. The information from the hospital pharmacy department showed a parallel between these two events with a correlation coefficient $(r) = 0.82$ and $p < 0.0001$ (Fig. 1). The amount of imipenem consumption in the hospital increased from 2,850-3,150 grams, in the years 2000-2002, to more than twice (6900 grams) during the first nine months of 2005.

Patient characteristics

Among 1,237 patients who were identified as harboring *A. baumannii* during their hospital stay, 899 patient's charts were available for review. Three hundred and thirty eight (27.3%) charts were excluded because of unavailable or incomplete information, acquisition of *A. baumannii* from other hospitals, or *A. baumannii* was isolated within 48 hours after hospital admission.

Table 1. Proportions of imipenem-resistant *A. baumannii* isolated from various specimens

Specimens	Total isolates	Resistant strains isolated	Percentage	95%CI
Sputum	1256	458	36.5	33.8-39.2
Wound pus	381	149	39.1	34.2-44.2
Urine	257	68	26.5	21.2-32.3
Blood	109	24	22.0	14.6-31.0
Pleural fluid	45	15	33.3	20.0-49.0
Peritoneal fluid	23	6	26.1	10.2-48.4
Cerebrospinal fluid	19	8	42.1	20.3-66.5
Others	40	12	30.0	16.6-46.5
Total	2130	740	34.7	32.7-36.8

CI: Confidence interval

Table 2. Proportions of IRAB isolated in various patient wards

Patient ward	Total isolates	Resist strains isolated	Percentage	95%CI
ICU	397	198	49.9	44.8-54.9
RCU	247	126	51.0	44.6-57.4
Medicine (male)	283	109	38.5	32.8-44.5
Surgery	313	91	29.1	24.1-34.4
Trauma-Neurosurgery	245	83	33.9	28.0-40.2
Medicine (female)	174	41	23.6	17.5-30.6
PICU and NICU	135	32	23.7	16.8-31.8
Pediatric	100	17	17.0	10.2-25.8
Orthopaedic	63	23	36.5	24.7-49.6
Others	152	15	9.9	5.6-15.8
Unavailable information	21	5	23.8	8.2-47.2
Total	2130	740	34.7	32.7-36.8

ICU: Intensive care unit, RCU: Respiratory care unit, PICU: Pediatric intensive care unit, NICU: Neonatal intensive care unit, CI: Confidence interval

Table 3. Antibiotic susceptibility of IRAB and ISAB

Antibiotics	Percentage of sensitive isolated	
	IRAB	ISAB
Gentamicin	21.4	63.8
Amikacin	44.8	75.2
Ampicillin	-	3.4
Cephalothin	0.3	0.8
Cefoxitin	-	4.0
Ceftazidime	5.6	60.6
Ceftriaxone	0.3	6.9
Meropenem	-	100.0
Ciprofloxacin	6.1	67.9
Cotrimoxazole	20.9	58.0
Sulperazone	41.2	95.4

Risk factors

The results of the case-control study indicated that prolonged hospitalization was associated with IRAB infection or colonization. When hospital stay extended from less than one week to 1-2 weeks and more than two weeks, the odds of IRAB acquisition increased from 1.60 to 2.36 times compared to ISAB. These associations were statistically significant at the level of less than 0.05 (Table 4).

Medical patients (internal medicine and pediatric) were at a higher risk of IRAB acquisition than surgical patients. Previous admission to ICU or RCU was associated with subsequent IRAB acquisition and the associations increased with the duration of stay in these units.

Table 4. Factors associated with IRAB acquisition, derived from univariate analysis

Factors	IRAB	n	%	Odds ratio	95%CI	p-value*
Hospital stay						
< 1 week	60	314	19.1	1	-	
1-2 weeks	79	271	29.2	1.74	1.12-2.56	0.005
> 2 weeks	121	314	38.5	2.65	1.85-3.81	<0.001
Male	168	545	30.8	1.27	0.94-1.71	>0.05
Age more than 65 years	101	308	32.8	1.33	0.98-1.79	>0.05
ASA score more than 3	66	217	30.4	1.10	0.79-1.53	>0.05
Medical patient	147	461	31.9	1.35	1.01-1.80	0.04
Neutropenia	15	30	50.0	2.55	1.23-5.29	0.01
Previously admission to						
ICU	107	270	39.6	2.04	1.51-2.77	<0.001
RCU	59	117	50.4	2.94	1.98-4.37	<0.001
PICU	15	65	23.1	0.72	0.40-1.31	>0.05
NICU	3	7	42.9	1.85	0.41-8.34	>0.05
Duration of prior admission to ICU						
None	153	629	24.3	1	-	
1-7 days	73	201	36.3	1.77	1.26-2.49	0.001
> 7 days	34	69	49.3	3.02	1.82-5.01	<0.001
Duration of prior admission to RCU						
None	201	782	25.7	1	-	
1-7 days	29	59	49.2	2.79	1.64-4.77	<0.001
> 7 days	30	58	51.7	3.10	1.81-5.31	<0.001
Device-day						
No device	40	181	22.1	1	-	
1-7 days	83	345	24.1	1.12	0.73-1.72	>0.05
More than 2 weeks	137	373	36.7	2.05	1.36-3.08	0.001
Ventilation supported	177	549	32.2	1.53	1.13-2.08	0.006
Central-line indwelling	84	241	34.9	1.47	1.07-2.01	0.02
Urinary catheter retaining	181	569	31.8	1.48	1.09-2.02	0.01
Antibiotic-day						
No antibiotic	23	161	14.3	1	-	
1-2 weeks	150	541	27.7	2.30	1.42-3.72	0.001
More than 2 weeks	87	197	44.2	4.75	2.81-8.01	<0.001
Number of antibiotics						
No antibiotic	20	150	13.3	1	-	
1-3 antibiotics	127	503	25.2	2.20	1.32-3.66	0.003
More than 3 antibiotics	113	246	45.9	5.52	3.23-9.41	<0.001
Imipenem administered	55	92	59.8	4.37	2.80-6.82	<0.001
Cephalosporins administered	205	626	32.7	1.93	1.37-2.71	<0.001

* Chi-square or Fisher's exact test, ICU: Intensive care unit, RCU: Respiratory care unit, PICU: Pediatric intensive care unit, NICU: Neonatal intensive care unit, CI: Confidence interval

The patients with a prolonged device-day were related to subsequent IRAB acquisition, particularly with ventilation support, central venous catheter indwelling, and urinary catheterization. Previous antibiotic administration was associated with IRAB acquisition, both in term of number and the duration of use. The prior use of antibiotics that were significantly associated with subsequent IRAB acquisition was imipenem and cephalosporins. Imipenem was the antibiotic that had the strongest association with IRAB acquisition (OR = 4.37; 95% CI = 2.80-6.82).

Stepwise multiple logistic regression analysis revealed that previous admission to ICU and RCU were independently associated with IRAB acquisition as well as the number of prior antibiotic administration and previous use of imipenem (Table 5).

Table 5. Association between risk factors and acquisition of IRAB, derived from multivariate analysis

	OR	95%CI	p-value
Hospital stay			
< 1 week	1	-	
1-2 weeks	1.39	0.93-2.07	>0.05
> 2 weeks	1.46	0.97-2.22	>0.05
Neutropenia	1.82	0.83-4.01	>0.05
Previously admission to			
ICU	1.63	1.18-2.25	0.003
RCU	2.21	1.44-3.37	<0.001
Number of antibiotics			
No antibiotic	1	-	
1-3 antibiotics	1.83	1.08-3.08	0.02
More than 3 antibiotics	2.92	1.61-5.31	<0.001
Imipenem administered	2.12	1.27-3.54	0.004

Prognostic factors

In order to assess the effect of imipenem resistance on the mortality outcome of the patients in various groups, the authors compared the mortality rates between the patients with IRAB and the patients with ISAB by means of stratification.

Among 899 hospital admissions, 242 patients who died in the hospital yielding an overall mortality rate of 26.9%. The mortality rate of the patients with IRAB (33.8%) was significantly (p = 0.003) higher than the patients with ISAB (24.1%) given the odds ratio of 1.61 (95% CI = 1.18-2.21). The difference of fatality rates was highest among the patients who acquired bloodstream infections (73.3% vs. 13.0%) (Table 6). Infection or colonization by IRAB was also associated with a significantly higher mortality rate when compared to ISAB in patients younger than or equal to 65 years of age. In the patients with less severity of illness (ASA 1-3), in the patients with prior hospital stay of more than two weeks, in the medical patients, in nonneutropenic patients, in patients with previously admission to the ICU, and in the patients who received more than three antibiotics prior to *A. baumannii* acquisition.

The univariate analysis identified 16 factors that were statistically significantly associated with patient mortality, including prolonged hospital stay, male sex, ASA score more than three, medical patient, neutropenia, previous admission to the ICU or the RCU, previous ventilation support, prior central-line catheter indwelling, greater number of or duration of antibiotics, prior receiving imipenem, prior receiving cephalosporins, and the presence of *A. baumannii* pneumonia.

After control for the effect of other covariates by means of stepwise multiple logic regression analysis, six prognosis factors remained statistically significant. These included:- medical patient, ASA score more than 3, prior hospital stay more than two weeks, presence of prior central venous line, prior receiving more than three antibiotics, and *A. baumanii* pneumonia (Table 7).

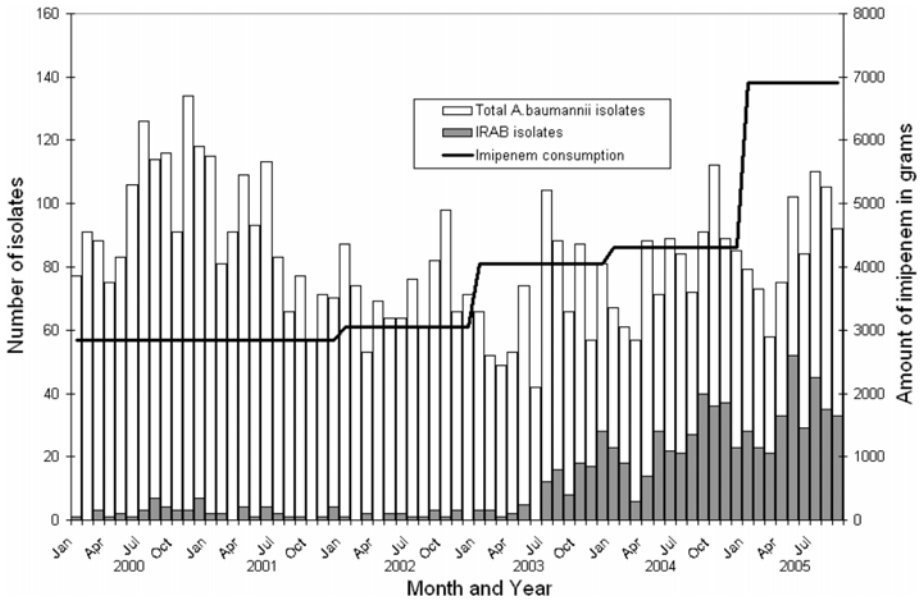

Fig. 1 Temporal trend of imipenem-resistant *A. baumannii* isolated and amount of imipenem consumption in the hospital

Table 6. Mortality rates associated with imipenem resistance stratified by various prognostic factors

Prognosis factors	IRAB			ISAB			OR	95%CI	p-value
	N	Die	%	N	Die	%			
Male	168	50	29.8	377	83	22.0	1.50	0.99-2.26	>0.05
Age ≤ 65 years	159	56	35.2	432	100	23.1	1.81	1.22-2.68	0.003
Age > 65 years	101	32	31.7	207	54	26.1	1.31	0.78-2.21	>0.05
ASA score									
1-3	194	55	28.4	488	92	18.9	1.70	1.16-2.51	0.007
4-5	66	33	50.0	151	62	41.1	1.44	0.80-2.57	>0.05
Hospital stay									
< 1 week	60	17	28.3	254	51	20.1	1.57	0.83-2.98	>0.05
1-2 weeks	79	21	26.6	192	45	23.4	1.18	0.65-2.16	>0.05
> 2 weeks	50	121	41.3	58	193	30.1	1.63	1.02-2.64	0.041
Hospital services									
Medical patient	147	67	45.6	314	102	32.5	1.74	1.17-2.60	0.007
Surgical patient	113	21	18.6	325	52	16.0	1.20	0.69-2.97	>0.05
Total neutrophils count									
< 500 cells/mL	15	8	53.3	15	7	46.7	1.31	0.31-5.48	>0.05
> 499 cells/mL	245	80	32.7	624	147	23.6	1.57	1.14-2.18	0.006
Previously admission to									
ICU	107	45	42.1	163	43	26.4	2.03	1.21-3.40	0.008
RCU	59	23	39.0	58	19	32.8	1.31	0.61-2.80	>0.05
Ventilation supported	177	64	36.2	372	105	28.2	1.44	0.98-2.11	>0.05
Central-line indwelling	84	34	40.5	157	51	32.5	1.41	0.82-2.45	>0.05
Antibiotic-day									
No antibiotic	23	8	34.8	138	28	20.3	2.10	0.81-5.43	>0.05
1-2 weeks	150	45	30.0	391	88	22.5	1.48	0.96-2.25	>0.05
More than 2 weeks	87	35	40.2	110	38	34.5	1.28	0.71-2.28	>0.05
Number of antibiotics									
No antibiotic	20	7	35.0	130	23	17.7	2.51	0.90-6.97	>0.05
1-3 antibiotics	127	26	20.5	376	88	23.4	0.84	0.51-1.38	>0.05
More than 3 antibiotics	113	55	48.7	133	43	32.3	1.98	1.18-3.33	0.009
Imipenem administered	55	27	49.1	37	15	40.5	1.41	0.61-3.28	>0.05
Cephalosporins administered	205	71	34.6	421	118	28.0	1.36	0.95-1.95	>0.05
Sites of infections or colonization									
Bloodstream infection	15	11	73.3	46	6	13.0	18.33	4.39-76.63	<0.001
Pneumonia	64	29	45.3	96	35	36.5	1.44	0.76-2.75	>0.05
Tracheobronchitis	67	23	34.3	214	58	27.1	1.41	0.78-2.53	>0.05
Open wound or drain	39	5	12.8	36	7	19.4	0.86	0.24-3.07	>0.05
Skin	10	1	10.0	20	1	5.0	2.11	0.12-37.72	>0.05
Urinary tract infection	17	2	11.8	55	12	21.8	0.48	0.10-2.39	>0.05
Colonization	49	14	28.6	151	31	20.5	1.55	0.12-37.72	>0.05
Other sites	9	3	33.3	21	4	19.0	2.13	0.36-12.38	>0.05
Overall	260	88	33.8	639	154	24.1	1.61	1.18-2.21	0.003

Discussion

There was an outbreak of IRAB in Songklanagarind Hospital starting in July 2003. It was not until September 2005, more than two years later, that the present study was conducted to document the outbreak. This reflects the defect in the nosocomial surveillance system that it could not detect earlier the abnormal increase of multidrug resistant organisms in the hospital.

The outbreak was likely related to increasing antibiotic pressure particularly imipenem. The amount of imipenem used in the hospital had increased con-

Table 7. Factors associated with hospital mortality in the patients who acquired *A. baumannii*. Data derived from multivariate analysis

Prognosis factors	Odds ratio	95%CI	p-value
ASA score 4-5	2.51	1.78-3.55	<0.001
Hospital stay > 2 weeks	1.53	1.07-2.20	0.02
Medical patient	2.82	2.01-3.95	<0.001
Central-line indwelling	1.52	1.06-2.17	0.02
Received more than 3 antibiotics	1.64	1.13-2.39	0.009
A. baumanii Pneumonia	2.00	1.36-2.95	<0.001

CI: Confidence interval

tinuously for about one year before the outbreak (Fig. 1). This phenomenon of an increasing frequency of IRAB following an increasing amount of imipenem consumption can also be found in other reports[6,22-25]. The present study also demonstrated that receiving imipenem was an independent risk factor of IRAB acquisition in the hospital (Table 4). The association between imipenem and IRAB acquisition remained statistically significant after controlling for other independent factors while the use of cephalosporins was not (Table 5). The combined effect of other antibiotics may also exert selective pressure on the bacteria harboring in the patients. As can be seen from Table 3 the antibiotic susceptibility of IRAB was lower than the ISAB in every antibiotic tested. Administration of any antibiotics to the patient will increase the chance to get rid of ISAB more than IRAB. This could be an explanation for the association between receiving more than three antibiotics and the risk of IRAB acquisition (Table 7).

The present study was performed as an initial investigation into the outbreak of IRAB. The investigation was conducted by means of a retrospective study, so an environmental culture survey was not done to identify the reservoir of IRAB. However, there was evidence from at least three of the results of the present study that indicated that the mechanical ventilators were the most probable sources of IRAB. *First*, the sputum was the most common clinical specimen from which the IRAB were isolated (Table 1). *Second*, IRAB was most prevalent in the RCU where mechanical ventilators were applied to most of the patients (Table 2). *Third*, IRAB was found significantly more often in the group of patients with mechanical ventilation support than ISAB (Table 4).

The respiratory tract was the most frequent site where both IRAB and ISAB were isolated. This may be due to the ability of *A. baumannii* to adhere well to bronchial epithelium[26]. And this ability does not appear to be different between epidemic and non-epidemic strains. Then even though, in univariate analysis, there was a significant difference between frequency isolation of IRAB and ISAB in patients with ventilation support, (Table 4) the significance disappeared after multivariate analysis (Table 5).

Imipenem resistance could create a serious problem in the clinical treatment of *A. baumannii* infection. The resistance was not only confined to imipenem but also to other antibiotics as well (Table 3). Nor could any other empirical antibiotic be administered with confidence even with sulfoperazone or amikacin. Furthermore, 14.8% of all the IRAB isolates were panantibiotic-resistant.

The findings of the case-control and cohort study in the present study should be interpolated in the context of the study design.

First, because the present study compared IRAB with ISAB, the difference between cases and controls should be interpreted as the results from the difference between imipenem resistance and imipenem susceptibility. The independent factors should be viewed as the factors that promoted the acquisition of a resistant strain rather than the susceptible one. The way that the authors selected controls from the patients with ISAB is different from some of the previous studies[8,15,17,27-30], and the same as some previous studies[6,13,33].

Second, the authors combined the patients with infection or colonization into the same group. Theoretically, some of the risk factors for infection may be different from colonization. Doing this may bias the association toward unity and some risk factors may go undetected. The authors merged infection and colonization into the same group because it is usually difficult to differentiate between infection and colonization in a retrospective study.

Third, the authors limited the analysis to the first positive culture of *A. baumannii* only. Doing this might exclude the information of the subsequent IRAB acquisition that followed the ISAB and lessen the difference between the IRAB and ISAB group. The association between risk factors and IRAB acquisition was then biased toward unity in the case-control study. In the same way, the outcome difference between IRAB and ISAB may be decreased, and the association between resistant strain acquisition and mortality

outcome may be biased toward unity. Then the authors could not demonstrate that IRAB was a risk factor for mortality in multivariate analysis (Table 7). In the situation that the second episode of acquiring the same pathogen can rarely occur such as in the bloodstream infection, the authors documented that patients with IRAB bloodstream infections had a significantly higher fatality rate than patients with ISAB bloodstream infections (Table 6).

Fourth, because the authors defined the independent variables as the factors that the patients were exposed to before *A. baumannii* acquisition, then the information after that was not available for analysis. This could produce a significant effect in the cohort study. For example, the authors could not evaluate and control the effect of the appropriateness of *A. baumannii* treatment. So the influence of the other factors, which could lead to mortality, may not be completely controlled.

In conclusion, the present study shows that the outbreak may be due to increasing antibiotic selective pressure especially imipenem and the outbreak confined mainly to the patients in the ICU and the RCU. The excess patient mortality rate attributable to IRAB could not be demonstrated.

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References

1. Bergogne-Berezin E, Towner KJ. Acinetobacter spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin Microbiol Rev 1996; 9: 148-65.
2. Wagenvoort JH, Joosten EJ. An outbreak Acinetobacter baumannii that mimics MRSA in its environmental longevity. J Hosp Infect 2002; 52: 226-7.
3. Wendt C, Dietze B, Dietz E, Ruden H. Survival of Acinetobacter baumannii on dry surfaces. J Clin Microbiol 1997; 35: 1394-7.
4. Jawad A, Seifert H, Snelling AM, Heritage J, Hawkey PM. Survival of Acinetobacter baumannii on dry surfaces: comparison of outbreak and sporadic isolates. J Clin Microbiol 1998; 36: 1938-41.
5. Cisneros JM, Rodriguez-Bano J. Nosocomial bacteremia due to Acinetobacter baumannii: epidemiology, clinical features and treatment. Clin Microbiol Infect 2002; 8: 687-93.
6. del Mar TM, Cartelle M, Pertega S, Beceiro A, Llinares P, Canle D, et al. Hospital outbreak caused by a carbapenem-resistant strain of Acinetobacter baumannii: patient prognosis and risk-factors for colonisation and infection. Clin Microbiol Infect 2005; 11: 540-6.
7. Wilson SJ, Knipe CJ, Zieger MJ, Gabehart KM, Goodman JE, Volk HM, et al. Direct costs of multidrug-resistant Acinetobacter baumannii in the burn unit of a public teaching hospital. Am J Infect Control 2004; 32: 342-4.
8. Simor AE, Lee M, Vearncombe M, Jones-Paul L, Barry C, Gomez M, et al. An outbreak due to multiresistant Acinetobacter baumannii in a burn unit: risk factors for acquisition and management. Infect Control Hosp Epidemiol 2002; 23: 261-7.
9. Bayat A, Shaaban H, Dodgson A, Dunn KW. Implications for Burns Unit design following outbreak of multi-resistant Acinetobacter infection in ICU and Burns Unit. Burns 2003; 29: 303-6.
10. Heritier C, Dubouix A, Poirel L, Marty N, Nordmann P. A nosocomial outbreak of Acinetobacter baumannii isolates expressing the carbapenem-hydrolysing oxacillinase OXA-58. J Antimicrob Chemother 2005; 55: 115-8.
11. von Dolinger dB, Oliveira EJ, Abdallah VO, Costa Darini AL, Filho PP. An outbreak of Acinetobacter baumannii septicemia in a neonatal intensive care unit of a university hospital in Brazil. Braz J Infect Dis 2005; 9: 301-9.
12. Dalla-Costa LM, Coelho JM, Souza HA, Castro ME, Stier CJ, Bragagnolo KL, et al. Outbreak of carbapenem-resistant Acinetobacter baumannii producing the OXA-23 enzyme in Curitiba, Brazil. J Clin Microbiol 2003; 41: 3403-6.
13. Corbella X, Montero A, Pujol M, Dominguez MA, Ayats J, Argerich MJ, et al. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant Acinetobacter baumannii. J Clin Microbiol 2000; 38: 4086-95.
14. Maslow JN, Glaze T, Adams P, Lataillade M. Concurrent outbreak of multidrug-resistant and susceptible subclones of Acinetobacter baumannii affecting different wards of a single hospital. Infect Control Hosp Epidemiol 2005; 26: 69-75.
15. Husni RN, Goldstein LS, Arroliga AC, Hall GS, Fatica C, Stoller JK, et al. Risk factors for an outbreak of multi-drug-resistant Acinetobacter nosocomial pneumonia among intubated patients. Chest 1999; 115: 1378-82.

16. Wong TH, Tan BH, Ling ML, Song C. Multi-resistant Acinetobacter baumannii on a burns unit clinical risk factors and prognosis. Burns 2002; 28: 349-57.
17. Roberts SA, Findlay R, Lang SD. Investigation of an outbreak of multi-drug resistant Acinetobacter baumannii in an intensive care burns unit. J Hosp Infect 2001; 48: 228-32.
18. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial disk susceptibility. Approved standard M2-A5, Villanova, PA: NCCLS; 2000.
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988; 16: 128-40.
20. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol 1992; 13: 606-8.
21. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. Anesthesiology 1978; 49: 239-43.
22. Hsueh PR, Chen WH, Luh KT. Relationships between antimicrobial use and antimicrobial resistance in Gram-negative bacteria causing nosocomial infections from 1991- 2003 at a university hospital in Taiwan. Int J Antimicrob Agents 2005; 26: 463-72.
23. Das I, Lambert P, Hill D, Noy M, Bion J, Elliott T. Carbapenem-resistant Acinetobacter and role of curtains in an outbreak in intensive care units. J Hosp Infect 2002; 50: 110-4.
24. Bencic I, Bencic I, Vukuicevic-Baudoin D. Imipenem consumption and gram-negative pathogen resistance to imipenem at sestre milosrdnice University Hospital. Acta Clin Croat 2001; 40: 185-9.
25. Urban C, Go E, Mariano N, Berger BJ, Avraham I, Rubin D, et al. Effect of sulbactam on infections caused by imipenem-resistant Acinetobacter calcoaceticus biotype anitratus. J Infect Dis 1993; 167: 448-51.
26. Lee JC, Koerten H, van den BP, Beekhuizen H, Wolterbeek R, van den BM, et al. Adherence of Acinetobacter baumannii strains to human bronchial epithelial cells. Res Microbiol 2006; 157: 360 -6.
27. Lee SO, Kim NJ, Choi SH, Hyong KT, Chung JW, Woo JH, et al. Risk factors for acquisition of imipenem-resistant Acinetobacter baumannii: a case-control study. Antimicrob Agents Chemother 2004; 48: 224-8.
28. Fierobe L, Lucet JC, Decre D, Muller-Serieys C, Deleuze A, Joly-Guillou ML, et al. An outbreak of imipenem-resistant Acinetobacter baumannii in critically ill surgical patients. Infect Control Hosp Epidemiol 2001; 22: 35-40.
29. Koeleman JG, Parlevliet GA, Dijkshoorn L, Savelkoul PH, Vandenbroucke-Grauls CM. Nosocomial outbreak of multi-resistant Acinetobacter baumannii on a surgical ward: epidemiology and risk factors for acquisition. J Hosp Infect 1997; 37: 113-23.
30. Maragakis LL, Cosgrove SE, Song X, Kim D, Rosenbaum P, Ciesla N, et al. An outbreak of multidrug-resistant Acinetobacter baumannii associated with pulsatile lavage wound treatment. JAMA 2004; 292: 3006-11.
31. Cisneros JM, Rodriguez-Bano J, Fernandez-Cuenca F, Ribera A, Vila J, Pascual A, et al. Risk-factors for the acquisition of imipenem-resistant Acinetobacter baumannii in Spain: a nationwide study. Clin Microbiol Infect 2005; 11: 874-9.
32. Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant Acinetobacter baumannii bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J Hosp Infect 2003; 54: 32-8.

การระบาดของเชื้อ *Acinetobacter baumannii* ที่ดื้อต่อยา imipenem ในโรงพยาบาลสงขลานครินทร์: ปัจจัยเสี่ยงและพยากรณ์โรค

สีลม แจ่มอุลิตรัตน์, สมจิตร์ ทองปิยะภูมิ, นงลักษณ์ สุวลักษณ์

การศึกษาถึงปัจจัยที่มีผลต่อการพบเชื้อ Acinetobacter baumannii ที่ดื้อต่อยา imipenem (IRAB) และปัจจัยที่อิทธิพลต่อการพยากรณ์โรคของผู้ป่วย ได้ทำการศึกษาในผู้ป่วยที่รับเข้ารักษาในโรงพยาบาลสงขลานครินทร์ ซึ่งเป็นโรงพยาบาลมหาวิทยาลัย ขนาด 850 เตียง ซึ่งทำหน้าที่เป็นสถานฝึกอบรมและส่งต่อผู้ป่วยของภาคใต้ของประเทศไทย การศึกษาทำในช่วงกรกฎาคม พ.ศ. 2546 ถึง กันยายน พ.ศ. 2548 โดยใช้วิธีการศึกษาแบบ case-control และแบบ cohort ผลการศึกษาพบว่า มีการแยกได้เชื้อ A. baumannii 2,130 ครั้ง จากผู้ป่วย 1,237 ราย ในจำนวนนี้สามารถค้นเวชระเบียนผู้ป่วยเพื่อศึกษาได้ 899 ราย และจากวิธีการศึกษาแบบ case-control และวิเคราะห์ข้อมูลแบบ multiple logistic regression พบว่า ปัจจัยที่มีความสัมพันธ์กับการพบเชื้อ IRAB อย่างนัยสำคัญทางสถิติ คือ การเข้าพักรักษาตัวในหออภิบาลผู้ป่วยอายุรกรรมและศัลยกรรม การเข้าพักรักษาตัวในหออภิบาลผู้ป่วยทางเดินหายใจ การได้รับยาปฏิชีวนะหลายชนิด และการได้รับยา imipenem ผลการศึกษาแบบ cohort พบว่าอัตราตายของผู้ป่วยที่พบเชื้อดื้อยา imipenem เท่ากับร้อยละ 33.8 ซึ่งสูงกว่าอัตราตายในผู้ป่วยที่พบเชื้อไม่ดื้อยาคือร้อยละ 24.1 อย่างมีนัยสำคัญทางสถิติ ซึ่งเมื่อเปรียบเทียบกันด้วยวิธีวิเคราะห์แบบ univariate จะได้ค่า odds ratio เท่ากับ 1.6 (95%CI = 1.2-2.2) แต่เมื่อปรับปัจจัยที่เกี่ยวข้องอื่น ๆ ด้วยวิธีวิเคราะห์แบบ multivariate แล้วกลับไม่พบว่าการพบเชื้อ IRAB ทำให้อัตราตายสูงขึ้นจนถึงระดับที่มีนัยสำคัญทางสถิติ