Original Article

Comparison of Virulence Attributable to Different Levels of Antimicrobial Resistant *Acinetobacter baumannii* Bacteremia

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Objective: To determine the mortality rate and severity of sepsis in patients who have acquired drug resistant *Acinetobacter baumannii* (AB) bacteremia (ABB).

Materials and Methods: Microbiology data and information of adult patients hospitalized at Songklanagarind Hospital with positive blood culture for AB between January 2008 and April 2017 were retrieved and reviewed. Antimicrobial resistance was classified into four categories comprising of non-multidrug-resistant (nMDR), multidrug-resistant (MDR), extensively-drug-resistant (XDR), and possible-pandrug-resistant (pPDR). The primary outcome of bacteremia was the in-hospital mortality rate, with the additional outcome, being severity of sepsis represented by the Sepsis Severity Score (SSS). The differences in mortality rates were assessed by Cox proportional hazard model. Results of analysis were reported in terms of hazard ratio (HR) and corresponding 95% confidence interval (CI). Comparison of SSS was evaluated by generalized linear model (GLM) and reported in term of odds ratio (OR).

Results: The present study identified 480 patients with hospital-acquired ABB. The proportions among resistance categories were 11%, 39%, 47%, and 3% with crude mortality rates of 20%, 34%, 69%, and 75% for nMDR, MDR, XDR, and pPDR, respectively. GLM analysis showed ORs for higher SSS score in the appropriate treated MDR, and XDR were 1.09 (1.01 to 1.19), and 1.12 (1.03 to 1.22), respectively. The inappropriate treatment ORs for nMDR, MDR, XDR, and pPDR were 1.17 (0.99 to 1.39), 1.30 (1.17 to 1.45), 1.17 (1.08 to 1.28), and 1.01 (0.87 to 1.17), respectively.

Conclusion: The virulence of AB was not reduced when its level of antibiotic resistance was upgraded.

Keywords: *Acinetobacter baumannii*; Drug resistance; Bacteremia; Mortality; Virulence

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Acinetobacter baumannii (AB) is an obligate aerobic non-fermentative Gram-negative coccobacillus bacterium usually found in soil, water, and sewage, and it was once thought to be an opportunistic human pathogen with minimal virulence. Over the last few decades, AB has emerged as one of the six most important nosocomial pathogens (ESKAPE: *Enterococcus faecium*/*faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, AB, *Pseudomonas aeruginosa*, and *Enterobacter* species)[1,2]. The success of AB is partly due to its ability to survive on dry surface and being able to develop resistance rapidly after contact with antimicrobial agents[3-6].

Antimicrobial agent resistance usually occurs by genetic mutation or by horizontal gene transfer. These genetic changes often have disadvantageous effects on the micro-organism by impairing competitive functions or conferred metabolic burden[7]. This result leads to a reduction of fitness, which may be expressed as decreased survival, reduced replication rate, or less virulence. Afterwards some bacteria may compensate these fitness losses by chromosomal mutation[8]. When fitness cost compensation has developed, bacterial virulence resumes and interacts with inappropriate antibiotic treatment, thus jeopardizing infection outcomes.

For these reasons, the authors conducted a study to re-evaluate the virulence of AB in patients with acquired AB bacteremia (ABB) during their stay in the hospital. In the present study, the virulence was assessed in terms of in-hospital mortality rates, and in terms of the Sepsis Severity Score (SSS)[9]. The

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authors also determined the virulence, according to the levels of antibiotic resistance (LDR) in AB.

Materials and Methods

Setting

The present study was conducted in Songklanagarind Hospital, a tertiary care, medical school, and training hospital in the southern part of Thailand. Clinical blood culture samples were usually collected at the bedside, by two separated specimens from different venipuncture sites. Antimicrobial susceptibility was performed by disk diffusion method, and the results were interpreted according to the Clinical Laboratory Standards Institute criteria[10]. Intermediate resistance was regarded as resistance in the present study.

Studied samples

Samples were collected from the patients aged above 15 years admitted to the hospital, whose clinical blood cultures were positive for AB obtained between January 2008 and April 2017.

Studied variables

The microbiology and patient data were reviewed for antimicrobial sensitivity test, patient demographic data, clinical data, medical treatment, and outcomes. Antimicrobial susceptibility was routinely determined by disc diffusion method in microbiology laboratory. LDR was classified into non-multidrug-resistant (nMDR), multidrug-resistant (MDR), extensively-drug-resistant (XDR), and possible-pandrug-resistant (pPDR), according to international expert definitions, with minor modifications[11]. The present study hospital's microbiology laboratory had never tested for tetracycline susceptibility in AB but used the susceptibility test to minocycline and tigecycline instead. Severity of patient organ function impairment was assessed via the Sequential Organ Failure Assessment (SOFA) score, 24 hours before onset of bloodstream infection (BSI)[12]. The six variables needed for SOFA assessment including respiration, coagulation, liver, cardiovascular, central nervous, and renal were retrieved from medical records and laboratory results. The American Society of Anesthesia (ASA) score was another variable used for assessment of severity of underlying diseases before onset of bloodstream infection[13]. Location as to where the patient resided at the onset of BSI was denoted as the place of infection acquisition. Appropriateness of antimicrobial treatment was defined as appropriate if at least one of the antimicrobials administered during clinical manifestation of BSI was matched to the sensitivity test and continued for at least 72 hours. Primary outcomes of bacteremia were defined as in-hospital mortality rates, and SSS within 24 hours after onset of BSI.

Statistical analysis

Statistical data analyses were conducted with R-Program, version 2.14.0. Data were described in terms of arithmetic mean, geometric mean, or percentage with corresponding 95% confidence intervals (CI), according to the types of variables. Continuous data were transformed into categorical data during data analyses for determining associated factors.

Mortality rates were calculated and reported as cumulative incidence, by dividing the number of fatal cases with the number of patients at risk, multiplied by 100, and reported in terms of percentage. Because there is controversy regarding the proper time between onset of BSI and mortality outcome, the authors then evaluated the mortality rates within four different intervals, which were 7-days, 14-days, 30 days, and in-hospital mortality rates.

Test of correlation between categorical data were done by Pearson chi-square test. Because the high correlation between LDR and appropriateness of antimicrobial treatment (chi-square 71.5, $p<0.0001$) may cause collinearity in the regression analysis model, the authors combined the two variables into one 8-combination, and then assigned: 1 for appropriate treated nMDR, 2 for inappropriate treated nMDR, and so forth; until ending with 8 for inappropriate treated pPDR. In the same way the authors found high correlation between the ASA score and SOFA score as they both measured the same identity, which was the patient severity of underlying disease before onset of BSI, the authors were able to discard ASA from the multivariate analysis model.

The associated mortality rates were assessed by Cox proportional hazard model. Results of analyses were reported in terms of hazard ratio (HR), and a corresponding 95% CI. Cox proportional hazard model was deployed, both in univariate and multivariate analyses. To adjust for any confounding effects from extraneous variables, only the variables with statistically significant HR were included in the multivariate model.

Results

Patient characteristics

The present study identified 480 patients with

Table 1. Mortality rates attributable to hospital-acquired *A. baumannii* bacteremia stratified by appropriateness of antibiotic treatment, levels of drug resistant, and number of days after onset of bacteremia

Antibiotic treatment by levels of resistance	Mortality rates (%) in parenthesis (95% CI)			
	7-day (n=137)	14-day (n=169)	30-day (n=206)	In-hospital (n=242)
Appropriate antibiotic treated				
nMDR	4.4 (1.1 to 16.4)	6.7 (2.1 to 19.0)	11.1 (4.6 to 24.3)	20.0 (10.6 to 34.4)
MDR	10.3 (6.3 to 16.4)	17.1 (11.8 to 24.2)	26.0 (19.5 to 33.8)	32.2 (25.1 to 40.2)
XDR	18.3 (12.1 to 26.8)	23.9 (16.7 to 32.8)	35.8 (27.3 to 45.3)	52.3 (42.9 to 61.6)
pPDR	-	-	-	-
Total	12.3 (9.1 to 16.6)	18.0 (14.0 to 22.8)	27.3 (22.6 to 32.7)	37.7 (32.3 to 43.3)
Inappropriate antibiotic treated				
nMDR	11.1 (1.3 to 53.5)	22.2 (5.1 to 60.5)	22.2 (5.1 to 60.5)	22.2 (2.8 to 60.0)
MDR	35.0 (21.7 to 51.1)	40.0 (25.9 to 56.0)	42.5 (28.1 to 58.3)	42.5 (27.0 to 59.1)
XDR	67.0 (57.8 to 75.0)	76.5 (67.8 to 83.4)	81.7 (73.5 to 87.3)	85.2 (77.4 to 91.1)
pPDR	50.0 (26.5 to 73.5)	56.3 (31.5 to 78.2)	68.8 (42.3 to 86.8)	75.0 (47.6 to 92.7)
Total	55.6 (48.2 to 62.7)	63.9 (56.5 to 70.6)	68.9 (61.7 to 75.3)	71.7 (64.6 to 77.8)
Grand total	28.5 (24.7 to 32.8)	35.2 (31.0 to 39.6)	42.9 (38.5 to 47.4)	50.4 (46.0 to 55.0)

nMDR=non-multidrug-resistant; MDR=multidrug-resistance; XDR=extensively-drug-resistant; pPDR=possible-pan-drug resistant; CI=confidence interval

hospital-acquired ABB. The patient's average age was 56.5 years (95% CI 54.8 to 58.2), with about five percent more men than women (54.8%; 95% CI 50.2 to 59.3). Geometric means of prior hospital stay and SOFA score before onset of BSI were 13.3 days (95% CI 10.2 to 19.3) and 4.9, (95% CI 4.6 to 5.3), respectively. ABB was most prevalent in surgical specialties (37.5%; 95% CI 33.3 to 41.9), intensive care units (36.3%; 95% CI 32.1 to 40.7), and patients with an ASA score IV (38.3%; 95% CI 34.1 to 42.8). The frequencies of LDR, at 95% CI 58.1 to 66.7 of cases with BSI.

Drug resistance and antimicrobial treatment

Distribution of drug resistance in AB causing bacteremia was 11.2% (95% CI 8.7 to 14.4), 38.8% (95% CI 34.5 to 43.2), 46.7% (95% CI 42.2 to 51.2), 3.3% (95% CI 2.0 to 5.4), for nMDR, MDR, XDR, and pPDR, respectively. Antimicrobial treatment was considered appropriate in 62.5% (95% CI 58.1 to 66.7) of cases.

Outcomes

The geometric mean of post bacteremia length of hospital stay was 10.9 days (95% CI 9.6 to 12.3). The overall in-hospital mortality rate was 50.4% (95% CI 46.0 to 55.0), and those attributable to LDR to be 20.4%, 34.4%, 69.2%, and 75.0% for nMDR, MDR, XDR, and pPDR, respectively. Mortality rates trended to increase with LDR, in both appropriate and inappropriate antibiotic treatment groups as well as in all time intervals, from onset of BSI to fatality (Table 1).

Results of both univariate and multivariate Cox analysis for the association between various variables and mortality rates in the patients acquired ABB, are shown in Table 2 and 3. The significant mortality determinants derived from univariate Cox proportional hazard model were age of more than 60 years, location where the patient acquired bacteremia, SOFA score, an ASA of more than two scores, and levels of drug resistance. Except for the ASA score, these significant variables were recruited in the multivariate model and the remaining significant determinants were an age more than 60 years, location where the patient acquired bacteremia, SOFA score, and levels of drug resistance.

The severity of BSI caused by AB was assessed in term of SSS and compared between LDR. The results of univariate and multivariate analyses by GLM are illustrated in Table 4. The severity of infection appeared to increase with LDR in the appropriate antibiotic treated group but not in the inappropriate subgroup.

Discussion

Antimicrobial resistance in AB has globally emerged as an increasing threat within healthcare settings and incidence rates of extensive drug-resistance have risen rapidly in recent years, including

Table 2. Univariate Cox proportional hazard analysis for the association between various variables and mortality rates in the patients acquired *A. baumannii* bacteremia stratified by duration after onset of bacteremia

Variables	n	7-day mortality			14-day mortality			30-day mortality			In-hospital mortality		
		HR	95% CI	p-value	HR	95%CI	p-value	HR	95% CI	p-value	HR	95%C.I	p-value
Age >60 years	219	1.5	1.1 to 2.1	0.02	1.6	1.1 to 2.1	0.004	1.4	1.1 to 1.9	0.008	1.6	1.3 to 2.1	<0.001
Sex: male	263	0.9	0.6 to 1.2	0.4	0.9	0.7 to 1.2	0.5	0.9	0.7 to 1.2	0.5	0.9	0.7 to 1.2	0.6
Service specialty or unit													
Surgical	180	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
ICU	174	4.0	2.5 to 6.5	<0.001	3.7	2.4 to 5.5	<0.001	3.1	2.2 to 4.5	<0.001	2.7	2.0 to 3.8	<0.001
Medicine	126	4.1	2.4 to 6.8	<0.001	3.5	2.2 to 5.5	<0.001	3.3	2.3 to 4.9	<0.001	2.8	2.0 to 4.1	<0.001
Prior hospital stay													
≤1 week	136	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
1 to 3 weeks	202	0.9	0.6 to 1.4	0.8	1.1	0.7 to 1.6	0.9	1.1	0.8 to 1.5	0.6	1.1	0.8 to 1.5	0.7
>3 weeks	142	1.1	0.7 to 1.7	0.8	1.2	0.8 to 1.9	0.3	0.4	0.2 to 0.6	<0.001	1.4	1.0 to 1.9	0.06
SOFA score													
<9	381	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
9 to 13	85	2.3	1.6 to 3.3	<0.001	2.1	1.5 to 3.0	<0.001	1.7	1.3 to 2.4	<0.001	1.7	1.3 to 2.3	<0.001
>13	14	7.0	3.8 to 13.0	<0.001	6.0	3.9 to 11.0	<0.001	3.7	2.1 to 6.4	<0.001	6.2	3.5 to 10.8	<0.001
ASA >2	383	1.9	1.1 to 3.1	0.02	2.0	1.2 to 3.1	0.005	1.5	1.1 to 2.2	0.04	1.8	1.2 to 2.6	0.002
Appropriate antibiotic treated													
nMDR	45	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
MDR	146	2.3	0.5 to 9.8	0.3	2.5	0.8 to 8.3	0.1	2.3	0.9 to 5.7	0.09	1.7	0.8 to 3.4	0.2
XDR	109	4.1	1.0 to 17.6	0.06	3.5	1.1 to 11.5	0.04	2.9	1.1 to 7.4	0.03	2.2	1.1 to 4.5	0.03
pPDR	-	-	-	-	-	-	-	-	-	-	-	-	-
Inappropriate antibiotic treated													
nMDR	9	3.3	0.3 to 36.5	0.3	4.8	0.8 to 29.0	0.08	3.3	0.6 to 16.8	0.2	2.3	0.5 to 10.4	0.3
MDR	40	9.2	2.1 to 40.4	0.003	7.5	2.2 to 25.9	0.001	5.3	1.9 to 14.2	0.001	3.3	1.5 to 7.4	0.004
XDR	115	21.9	5.4 to 89.3	<0.001	18.9	6.0 to 59.9	<0.001	13.5	5.5 to 33.1	<0.001	8.9	4.5 to 17.7	<0.001
pPDR	16	14.9	3.2 to 70.0	0.001	11.5	3.1 to 42.6	<0.001	9.0	3.1 to 26.0	<0.001	6.7	2.8 to 15.9	<0.001

HR=hazard ratio; CI=confidence interval; ICU=intensive care unit; SOFA=Sequential Organ Failure Assessment; ASA=American Society of Anesthesia; nMDR=non-multi-drug resistant; MDR=multi-drug resistant; XDR=extensively-drug-resistant; pPDR=possible-pan-drug resistant; Ref.=reference level that confidence interval and p-value are meaningless

resistance to last-line antimicrobial agents, such as carbapenems and Colistin. As infections with extensive drug-resistant AB are often extremely difficult to treat, the hope is then relying on the low virulence potential of the organism, resulting from the cost of the adaptation of resistant genes.

AB was once considered a low pathogenic micro-organism. Previously, it was rarely found in community-acquired infections. In the mouse pulmonary model, most of strains do not infect immunocompetent mice, and in the infected mice, AB induced only a self-limiting pneumonia, with no or limited local bacterial replication[14].

In 2009, the authors could not demonstrate an increased mortality associated with ABB[15]. This, however, may have been due to many reasons including the compensation for fitness cost of the bacteria having not yet occurred. The reports of a fatal outbreak in a relatively immunocompetent patients coupled with a community-acquired infection has since stimulated the authors' interest in re-examining the virulence of MDR AB[16-18].

There are several limitations in the present study. The present data were retrieved from medical records as secondary information. Completeness of the data depended on individual healthcare providers in charge. Experimental study for bacterial virulence in humans is unethical, and animal experiments may be limited in clinical application. Under these limitations, the authors had to choose observational study for determining the virulence of AB.

To determine the virulence of drug-resistant in AB, a study was conducted in patients who acquired bacteremia during hospitalization. In the present

Table 3. Multivariate Cox proportional hazard analysis for the association between various variables and mortality rates in the patients acquired *A. baumannii* bacteremia stratified by duration after onset of bacteremia

Variables	7-day mortality			14-day mortality			30-day mortality			In-hospital mortality		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age >60 years	1.1	0.8 to 1.6	0.6	1.2	0.9 to 1.6	0.3	1.1	0.9 to 1.5	0.4	1.3	1.0 to 1.7	0.04
Service specialty or unit												
Surgical	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
ICU	1.9	1.2 to 3.2	0.01	2.0	1.3 to 3.1	0.003	2.2	1.5 to 3.3	<0.001	1.8	1.3 to 2.6	0.001
Medicine	3.1	1.8 to 5.2	<0.001	2.9	1.9 to 4.7	<0.001	3.4	2.3 to 5.2	<0.001	2.8	1.9 to 4.0	<0.001
SOFA score												
<9	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
9 to 13	1.6	1.1 to 2.3	0.03	1.6	1.1 to 2.2	0.02	1.5	1.1 to 2.1	0.009	1.4	1.1 to 1.9	0.02
>13	3.1	1.7 to 5.9	<0.001	3.2	1.8 to 5.8	<0.001	3.5	2.0 to 6.3	<0.001	3.4	1.9 to 6.1	<0.001
Appropriate antibiotic treated												
nMDR	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.	1.0	Ref.	Ref.
MDR	1.9	0.4 to 8.2	0.4	2.2	0.6 to 7.2	0.2	2.0	0.8 to 5.0	0.2	1.6	0.8 to 3.4	0.2
XDR	3.3	0.8 to 14.0	0.1	2.8	0.8 to 9.4	0.09	2.4	0.9 to 6.0	0.07	2.1	1.0 to 4.3	0.04
pPDR	-	-	-	-	-	-	-	-	-	-	-	-
Inappropriate antibiotic treated												
nMDR	2.9	0.3 to 31.7	0.4	4.3	0.7 to 25.9	0.1	3.1	0.6 to 16.0	0.2	2.3	0.5 to 10.6	0.3
MDR	7.3	1.6 to 32.3	0.009	6.1	1.8 to 21.1	0.004	4.3	1.6 to 11.9	0.004	3.2	1.4 to 7.3	0.005
XDR	15.5	3.8 to 63.7	<0.001	14.0	4.4 to 44.8	<0.001	10.6	4.2 to 26.3	<0.001	8.1	4.0 to 16.2	<0.001
pPDR	7.9	1.6 to 40.0	0.01	6.3	1.6 to 24.6	0.009	5.0	1.6 to 15.2	0.004	4.4	1.8 to 11.2	0.002

HR=hazard ratio; CI=confidence interval; ICU=intensive care unit; SOFA=Sequential Organ Failure Assessment; nMDR=non-multi-drug resistant; MDR=multi-drug resistant; XDR=extensively-drug-resistant; pPDR=possible-pan-drug resistant; Ref.=reference level that confidence interval and p-value are meaningless

study, the authors classified drug-resistance into multi-levels, and defined virulence of AB infection in terms of mortality rate. The present study limited to only the patients who acquired bacteremia because of the high mortality rate and relative clear definition in this kind of infection. The present study did not include pediatric patient because the definition of sepsis and severity of illness is different from adult patients.

Because the severity of a patients underlying condition is strongly associated with mortality rate and severity of sepsis, the authors had to control this confounding effect to minimize the bias that may have incurred during analyses. Both ASA scores and SOFA scores can be utilized as the proxy variables for measuring patient severity of illness. After carefully examining the analysis results, the authors decided in favor of the SOFA score over the ASA score, because the SOFA made good dose-response relationships with the outcomes.

The present study found that in-hospital mortality rates attributable to ABB varied widely between 20.0% and 75.0%. This is in accordance with the previous reports (Table 1)[19,20]. The wide variation of the mortality rates reported depended largely on the definition used, apart from the appropriateness of antibiotic treatment. To make the present study results comparable to the others, the authors additionally analyzed the mortality rates according to the 7-day, 14-day and 30-day mortality.

The authors also employed multivariate Cox proportional hazard statistical model to control potential confounding factors associated with mortality outcomes, including severity of underlying diseases, severity of sepsis, and service specialties. The results of the analyses revealed that the risk of fatality increased consistently with levels of antimicrobial resistance until reaching pPDR for all time intervals between onset of bacteremia to the time of fatality. In the patients with pPDR bacteremia, the risk of mortality declined relative to the XDR level (Table 3). These patterns of mortality trends can also be found prior to adjustment for confounding factors (Table 1, 2). The explanation for this phenomenon

Table 4. Unadjusted and adjusted odds ratios (ORs) for one Sepsis Severity Score (SSS) increasing, derived from univariate and multivariate generalized linear regression analysis for the association between various variables and SSS in the patients acquired *A. baumannii* bacteremia

Variables	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Age >60 years	1.05	1.00 to 1.10	0.06			
Sex: male	1.06	1.01 to 1.11	0.01	1.06	1.01 to 1.10	0.02
Department or unit						
Surgical	1.00	Ref.	Ref.	1.0	Ref.	Ref.
ICU	1.17	1.11 to 1.23	<0.001	1.11	1.05 to 1.17	<0.001
Medicine	1.09	1.03 to 1.15	0.004	1.07	1.01 to 1.13	0.02
Prior hospital stay						
≤1 week	1.00	Ref.	Ref.			
1 to 3 weeks	0.98	0.93 to 1.04	0.6			
>3 weeks	0.99	0.93 to 1.06	0.8			
SOFA score						
<9	1.00	Ref.	Ref.	1.0	Ref.	Ref.
9 to 13	1.14	1.07 to 1.21	<0.001	1.09	1.03 to 1.15	0.005
>13	1.35	1.18 to 1.55	<0.001	1.25	1.10 to 1.43	0.001
ASA >2	1.15	1.08 to 1.21	<0.001			
Appropriate antibiotic treated						
nMDR	1.00	Ref.	Ref.	1.0	Ref.	Ref.
MDR	1.13	1.03 to 1.22	0.06	1.09	1.01 to 1.19	0.03
XDR	1.19	1.09 to 1.30	<0.001	1.12	1.03 to 1.22	0.01
pPDR	-	-	-	-	-	-
Inappropriate antibiotic treated						
nMDR	1.21	1.01 to 1.45	0.04	1.17	0.99 to 1.39	0.07
MDR	1.38	1.24 to 1.53	<0.001	1.30	1.17 to 1.45	<0.001
XDR	1.27	1.17 to 1.39	<0.001	1.17	1.08 to 1.28	<0.001
pPDR	1.13	0.98 to 1.30	0.09	1.01	0.87 to 1.17	0.9

OR=odds ratio for one SSS increased; CI=confidence interval; ICU=intensive care unit; SOFA=Sequential Organ Failure Assessment; ASA=American Society of Anesthesia; nMDR=non multi-drug resistant; MDR=multi-drug resistant; XDR=extensively-drug resistant; pPDR=possible-pan-drug resistant; Ref.=referent level that confidence interval and p-value are meaningless

may be partly explained by the compromising of mutation compensation of the bacteria. When more genes are required for the creation of higher antibiotic resistance, the cost of fitness and virulence may be unable to cope with it.

The analysis results for severity of sepsis outcome conducted by GLM are demonstrated in Table 4. The trend of the odds of an increasing severity score were the same as the trend of mortality rates and the trend of hazard ratio of fatality risk. The GLM analysis results support the increasing virulence of ABB along with LDR.

This consistent evidence suggest that AB has regained its virulence and it is not a low pathogenic anymore. In future, the war with AB must be emphasized on preventive measures and reduction of antimicrobial pressure.

Conclusion

The present study highlights the clue that AB has resumed the virulence that was previously loss during the development of drug resistance. Further study is warranted to find the appropriate preventive control measures.

What is already known on this topic?

Infections caused by AB have become a serious threat in healthcare settings due to its propensity to acquire multidrug resistance rapidly. Antimicrobial resistance initially costs the bacterium to lose it fitness

and virulence; however, the virulence loss in AB may be compensated and regained after some time.

What this study adds?

The virulence of ABB was high and did not decrease with higher levels of drug resistance, until it reached the highest drug resistance level. This evidence indicates that AB has regained it virulence.

Ethical approval and funding disclosure

The study protocol was approved by the Ethics Committees of the Faculty of Medicine, Prince of Songkla University (EC: 59-231-09-1) and funded by the departmental research development fund.

Conflicts of interest

All of authors named in the present article certify that there is no financial nor non-financial conflicts of interest. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analyses. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published. All authors contributed to study design, data collection and analysis, and interpretation of results, as well as to the writing and final approval of this manuscript.

References

1. Jamulitrat S, Thongpiyapoom S, Suwalak N. An outbreak of imipenem-resistant *Acinetobacter baumannii* at Songklanagarind Hospital: the risk factors and patient prognosis. J Med Assoc Thai 2007;90:2181-91.
2. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1-12.
3. Gonzalez-Villoria AM, Valverde-Garduno V. Antibiotic-resistant *Acinetobacter baumannii* increasing success remains a challenge as a nosocomial pathogen. J Pathog 2016;2016:7318075.
4. Espinal P, Martí S, Vila J. Effect of biofilm formation on the survival of *Acinetobacter baumannii* on dry surfaces. J Hosp Infect 2012;80:56-60.
5. 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.
6. Wendt C, Dietze B, Dietz E, Rüden H. Survival of *Acinetobacter baumannii* on dry surfaces. J Clin Microbiol 1997;35:1394-7.
7. Melnyk AH, Wong A, Kassen R. The fitness costs of antibiotic resistance mutations. Evol Appl 2015;8:273-83.
8. Schulz zur Wiesch P, Engelstädter J, Bonhoeffer S. Compensation of fitness costs and reversibility of antibiotic resistance mutations. Antimicrob Agents Chemother 2010;54:2085-95.
9. Osborn TM, Phillips G, Lemeshow S, Townsend S, Schorr CA, Levy MM, et al. Sepsis severity score: an internationally derived scoring system from the surviving sepsis campaign database*. Crit Care Med 2014;42:1969-76.
10. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard. 9th ed. CLSI document M07-A9. Wayne, PA: CLSI; 2012.
11. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268-81.
12. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.
13. Moreno RP, Pearse R, Rhodes A. American Society of Anesthesiologists Score: still useful after 60 years? Results of the EuSOS Study. Rev Bras Ter Intensiva 2015;27:105-12.
14. de Breij A, Eveillard M, Dijkshoorn L, van den Broek PJ, Nibbering PH, Joly-Guillou ML. Differences in *Acinetobacter baumannii* strains and host innate immune response determine morbidity and mortality in experimental pneumonia. PLoS One 2012;7:e30673.
15. Jamulitrat S, Arunpan P, Phainuphong P. Attributable mortality of imipenem-resistant nosocomial *Acinetobacter baumannii* bloodstream infection. J Med Assoc Thai 2009;92:413-9.
16. Jones CL, Clancy M, Honnold C, Singh S, Snesrud E, Onmus-Leone F, et al. Fatal outbreak of an emerging clone of extensively drug-resistant *Acinetobacter baumannii* with enhanced virulence. Clin Infect Dis 2015;61:145-54.
17. Patamatamkul S, Klungboonkrong V, Praisarnti P, Jirakiat K. A case-control study of community-acquired *Acinetobacter baumannii* pneumonia and melioidosis pneumonia in northeast Thailand: an emerging fatal disease with unique clinical features. Diagn Microbiol Infect Dis 2017;87:79-86.
18. Dexter C, Murray GL, Paulsen IT, Peleg AY. Community-acquired *Acinetobacter baumannii*: clinical characteristics, epidemiology and pathogenesis. Expert Rev Anti Infect Ther 2015;13:567-73.
19. Cheng A, Chuang YC, Sun HY, Sheng WH, Yang

CJ, Liao CH, et al. Excess mortality associated with colistin-tigecycline compared with colistin-carbapenem combination therapy for extensively drug-resistant *Acinetobacter baumannii* bacteremia: A multicenter prospective observational study. Crit Care Med 2015;43:1194-204.
20. Ballouz T, Aridi J, Afif C, Irani J, Lakis C, Nasreddine R, et al. Risk factors, clinical presentation, and outcome of *Acinetobacter baumannii* bacteremia. Front Cell Infect Microbiol 2017;7:156.