Original Article

Factors Associated with Colistin-Resistant *Acinetobacter baumannii* Acquisition among Hospitalized Patients

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Background: The emergence of multidrug-resistant *Acinetobacter baumannii* has led to the re-use of colistin. Colistin-resistant *A. baumannii* [CRA] was rare but is being reported more often now.

Objective: To explore the factors associated with CRA.

Materials and Methods: A retrospective case-control study has conducted. The medical records of 20 patients with CRA and 80 patients with colistin-susceptible *A. baumannii* [CSA] were reviewed.

Results: Univariate analysis showed that presence of five co-morbidities, intensive care unit stay, prior use of colistin, duration of colistin use, and some prior antibiotics were associated with CRA ($p<0.05$). However, using multivariate analysis, prior colistin and meropenem use had adjusted odds ratios [AOR] of 21.04; 95% CI of 3.11 to 142.32 ($p = 0.002$) and 13.54; 95% CI of 1.15 to 159.64 ($p = 0.038$), respectively, for CRA. Colistin duration (days) was significantly associated with resistance (AOR 1.22, 95% CI of 1.04 to 1.44, $p = 0.013$).

Conclusion: These results should increase awareness of appropriate colistin administration i.e., the duration of colistin used.

Keywords: *Acinetobacter baumannii*, Colistin-resistant, Antibiotic used, Resistant factors, Polymyxin

J Med Assoc Thai 2018; 101 (8): 1051-4
Website: http://www.jmatonline.com

Colistin is a rescue antibiotic used to overcome extensive drug-resistant gram-negative infection, particularly from *Acinetobacter baumannii*[1]. Only 16% to 19% of all *A. baumannii* isolates at our institute (Siriraj Hospital, Bangkok, Thailand) were susceptible to carbapenems and fewer than 10% were susceptible to other available antibiotics against *A. baumannii*. Colistin has been used worldwide for empiric and specific treatment for *A. baumannii*. The increasing use of colistin worldwide, including at Siriraj Hospital, should be done with caution and the possibility of resistance considered. Several studies have reported colistin-resistant *A. baumannii* [CRA], including increasing heteroresistance and resistance of *A. baumannii* especially in Asia and Europe[2] since the first report in 1999 from the Czech Republic[3]. The study from Korea also reported CRA, but the authors did not highlight any risk factors[4]. At Siriraj Hospital, Bangkok, Thailand, most *A. baumannii* from clinical isolates (99%) were susceptible to colistin. However, there have been reports of CRA from clinical specimens from patients in our hospital. The factors associated with CRA should be explored and hopefully provide data that are helpful in preventing the increase in CRA, the last antibiotic using to combat multidrug-resistant *A. baumannii* infection. Therefore, the present study aimed to determine the factors associated with CRA to guide physicians regarding strategies to avoid colistin resistance.

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Materials and Methods

Study design

The present retrospective, 1:4 case-control, study was conducted at Siriraj Hospital, a 2300-bed university hospital, in Bangkok, Thailand. The study was approved by Siriraj Hospital Institutional Review Board.

Inclusion criteria of case group

All patients of Siriraj Hospital who had a culture of CRA from clinical specimens between January 2010 and January 2011 were included.

How to cite this article: Pantuwadeethorn P, Leelaporn A, Koomanachai P. Factors associated with colistin-resistant Acinetobacter baumannii acquisition among hospitalized patients. J Med Assoc Thai 2018;101:1051-4.

Inclusion criteria of control group

Patients of Siriraj Hospital who had a culture of colistin-susceptible *A. baumannii* [CSA] from clinical specimens between January 2010 and January 2011 were included. The sample size of the control group was four times that of the case group because CRA was considered a rare condition.

Microbiological data

The minimum inhibitory concentration and susceptibility of colistin against *A. baumannii* were determined by E-test. The microbiology and antibiotic susceptibility were performed at the microbiology department of the institute. The susceptibility determination was interpreted based on the data that Clinical and Laboratory Standards Institute breakpoints where applicable[5].

Clinical data

The authors reviewed the medical records of all cases and controls. The patients' characteristics, co-morbid diseases, prior antibiotics used, including colistin, unit of admission, length of hospital and/or intensive care unit [ICU] stay, and mechanical ventilator use were recorded.

Statistical analysis

The patients' demographic data were analyzed using descriptive analysis. The associated factors of CRA were analyzed using Chi-square or Fisher's exact test. The difference between the factors was analyzed using independent t-test or Mann-Whitney test. All significant data were reported with 95% confidence interval [CI] and *p*-value smaller than 0.05. All association factors with *p*-value smaller than 0.05 were analyzed with multiple logistic regression and reported as adjusted odds ratios [AOR].

Ethical approval

This study was approved by Siriraj Institutional Board Review.

Results

Between January 2010 and January 2011, 20 patients with CRA isolates from clinical specimens were included in the case group and 80 patients with CSA isolates from clinical specimens were included as controls. The patients' demographic data are shown in Table 1. Sputum was the most common specimen that grew *A. baumannii* (cases and controls). Hypertension was the most common co-morbid underlying disease (63.8%) followed by diabetes mellitus (43.8%), and malignancy (38.8%). The others were dyslipidemia, chronic kidney disease, chronic lung disease, coronary artery disease, cerebrovascular disease, and AIDS. However, presence of five co-morbidities was one factor associated with CRA. The potential factors associated with CRA are summarized in Table 2 with ORs (95% CI) and ORs adjusted for ventilator use. The authors used multiple logistic regression for all potential variables i.e., ventilator use, duration of hospital stay, ICU stay and duration of ICU stay, central vascular catheter, and prior antibiotics used (levofloxacin, vancomycin, meropenem, linezolid, and colistin). The authors performed subgroup analysis for only those patients with *A. baumannii* isolates who had

Table 1. The patients' demographic data

	CRA (n = 20) n (%)	CSA (n = 80) n (%)	*p*-value
Age (years)			1.000
Mean (SD)	61.1 (20.5)	61.57 (17.8)	
Median (min, max)	64 (26, 97)	65 (27, 101)	
Gender			
Male	9 (45.0)	41 (50.6)	0.841
Comorbidities	17 (85.0)	71 (87.7)	0.718
1 disease	3 (15.0)	29 (35.8)	0.059
2 diseases	5 (25.0)	21 (25.9)	0.932
3 diseases	0 (0.0)	6 (7.4)	0.596
4 diseases	3 (15.0)	8 (9.9)	0.452
5 diseases	6 (30.0)	7 (8.6)	0.016
Mechanical ventilator	20 (100)	52 (64.2)	0.004
Duration ventilator			<0.001
Mean (SD)	77.45 (229.8)	11.14 (20.4)	
Median (min, max)	24 (16, 1,053)	3 (0, 104)	
Hospital stay (days)			
Mean (SD)	96.1 (227.6)	26 (31.3)	0.028
ICU stay (days)			
Mean (SD)	31 (24.7)	7.9 (17.8)	0.001
Prior antibiotics used	20 (100)	78 (96.3)	1.000
Levofloxacin	9 (45.0)	10 (12.3)	0.002
Vancomycin	16 (80.0)	39 (48.1)	0.015
Meropenem	19 (95.0)	47 (58.0)	0.013
Linezolid	3 (15.0)	1 (1.2)	0.025
Colistin	17 (85.0)	18 (22.2)	<0.001
Colistin days			
Mean (SD)	20 (20.6)	2.16 (4.6)	<0.001
Intervention			
Tracheostomy	10 (50.0)	20 (24.7)	0.052
Foley cath	16 (80.0)	56 (69.1)	0.493
Nasogastic tube	20 (100)	58 (71.6)	0.006
Central venous catheter	16 (80.0)	37 (45.7)	0.012

CRA = colistin-resistant *A. baumannii*; CSA = colistin-susceptible *A. baumannii*; ICU = intensive care unit

Table 2. The association between potential factors and colistin resistance in all patients

Factors	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value
5 comorbid diseases	4.53 (1.32 to 15.52)	0.016	3.48 (0.60 to 20.07)	0.163
Hospital stay (days)	1.02 (1.00 to 1.03)	0.028	1.00 (0.99 to 1.01)	0.416
ICU	12.55 (2.72 to 57.81)	0.001	6.27 (0.63 to 62.77)	0.118
ICU stay (days)	1.05 (1.02 to 1.07)	0.001	0.98 (0.95 to 1.02)	0.398
Central venous catheter	4.76 (1.46 to 15.48)	0.010	1.15 (0.19 to 6.91)	0.879
Levofloxacin	5.81 (1.93 to 17.49)	0.002	0.83 (0.16 to 4.27)	0.824
Vancomycin	4.31 (1.33 to 14.01)	0.015	0.35 (0.05 to 2.22)	0.263
Meropenem	13.75 (1.75 to 107.70)	0.013	13.54 (1.15 to 159.64)	0.038
Linezolid	14.12 (1.38 to 144.08)	0.025	7.46 (0.37 to 151.20)	0.191
Colistin	19.83 (5.22 to 75.33)	<0.001	21.04 (3.11 to 142.32)	0.002

CI = confidence interval; ICU = intensive care unit

Table 3. The association between potential factors and CRA in patients with colistin used

Factors	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	*p*-value
Meropenem	10.18 (1.09 to 94.83)	0.042	12.21 (0.71 to 211.30)	0.085
Colistin use days	1.22 (1.05 to 1.44)	0.011	1.22 (1.05 to 1.44)	0.013

CI = confidence interval

prior colistin use (17 cases and 18 controls). The results shown in Table 3 demonstrate that colistin duration (days) was the strongest factor associated with CRA.

Discussion

The present study demonstrated 10 factors associated with CRA, which are presence of five co-morbidities, duration of hospital stay, admission into the ICU, duration of ICU stay, mechanical ventilator use, central venous catheter, nasogastric tube, and prior use of antibiotics (levofloxacin, vancomycin, meropenem, linezolid, and colistin). These findings may reflect the factors most often found in severely ill patients at high risk of developing hospital-acquired infection, particularly pneumonia caused by *A. baumannii*[1] in whom colistin is a treatment of choice. The authors adjusted ORs for mechanical ventilator use and found that two factors, meropenem and colistin use, remained strongly associated with CRA with AOR of 13.5 (p<0.038) and 21.04 (p<0.002), respectively. Most of the patients with hospital-acquired infection caused by *A. baumannii* were treated with meropenem. This may provide a reasonable explanation for this result. Our results reflect those in a previous study[6], a case-control study that reported several potential risk factors for isolation of colistin-resistant Gram-negative pathogens, which are duration of ICU stay, prior antibiotic used (particularly colistin), prior monobactam used, duration of antifungal use, and prior surgery. The multivariate analysis demonstrated that only colistin use was an independent statistically significant risk factor for resistance to colistin (AOR 7.78; p = 0.002)[5]. The present study included a subgroup analysis of patients exposed to colistin and found that the duration of colistin use was the strongest factor associated with CRA (AOR 1.22; p = 0.013), which is also consistent with a previous study[6]. Another study indicated that most colistin-resistant *Acinetobacter* spp. isolates from Korean hospitals arose independently of the increasing use of colistin[4]. The mechanism of colistin resistance may be explained by two hypotheses, (i) loss of lipopolysaccharide[7-9] and (ii) mutations in the pmrA and pmrB genes[4,10]. The link between these two mechanisms of resistance and the associated factors is not yet clear. The recent study by Qureshi et al reported CRA among patients who had received colistin methanesulfonate for treatment of carbapenem-resistant, CSA infection[11]. This result is reasonable given that colistin use and duration of colistin use (days) were associated with CRA. The authors expect the result of our study to be useful and raise the awareness of appropriate use of colistin, particularly the indication, dosage regimen, and duration of administration.

The limitations of the present study were that, first, the authors did not demonstrate the clinical outcome related to CRA, and secondly, some data may be missing because of the retrospective study design. However, the authors had sufficient data for analysis to achieve the study objective.

Conclusion

Prior colistin and meropenem use were the most significant factors associated with CRA. The duration and prior use of colistin resulted in increased colistin exposure and were strongly related to CRA. The mechanism of resistance and associated factors of CRA including clinical outcomes and mortality should be further studied.

What is already known on this topic?

Several studies explored the risk factors associated to colistin-resistant. The organism resistant gene has been studied but may not reflect the clinical factors associated to causes of resistance. Some clinical data associated factors were similar in many studies such as prior use of colistin, including the present study.

What this study adds?

The present study showed similar results as previous studies. The authors also showed the duration of colistin use and each accumulative day of colistin-used was strongly associated with CRA strain. This result should assist the physician to be careful about colistin prescription, i.e., the appropriate duration.

Acknowledgement

The authors would like to thank Dr. Sasima Thongsai for helping with the statistical analysis.

Funding

This study was supported by Siriraj Research Development Fund.

Potential conflicts of interest

The authors declare no conflict of interest.

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