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Risk Factors Associated with Colistin-Resistant *Acinetobacter baumannii* Infection

Hae-Sun Chung[1,2], Chorong Hahm[1,3], Miae Lee[1,2]*

[1]Department of Diagnostic Laboratory Medicine, Ewha Womans University College of Medicine, Seoul, Korea

[2]Ewha Education and Research Center for Infection, Ewha Womans University Medical Center, Seoul, Korea,

[3]Department of Laboratory Medicine, Ewha Laboratories, Incheon, Korea

***Corresponding author:** Miae Lee, miae@ewha.ac.kr

Abstract

Acinetobacter baumannii is an important cause of healthcare-associated infections and is resistant to almost all antimicrobial agents, with strains recently reported to be resistant to colistin. In this study, we aimed to identify the risk factors associated with colistin-resistant *A. baumannii* infections by comparing colistin-resistant and -susceptible *A. baumannii* isolates. We retrospectively reviewed the medical records of 51 and 100 cases in which colistin-resistant and -susceptible *A. baumannii* were isolated, respectively. Univariate analysis showed that compared with patients with colistin-sensitive infections, patients with colistin-resistant *A. baumannii* infections had a combined pulmonary disease ($P = 0.017$), were admitted to intensive care unit ($P = 0.020$), and had prior mechanical ventilation ($P = 0.003$), tracheostomy ($P = 0.043$), percutaneous drainage ($P = 0.070$), hemodialysis ($P = 0.002$); use of colistin ($P = 0.000$), carbapenem ($P = 0.000$), and teicoplanin ($P = 0.004$); and co-infection ($P = 0.035$). Multivariate analysis indicated that eight variables were related to the likelihood of colistin-resistant *A. baumannii* infections: use of teicoplanin (odds ratio [OR]: 3.140, 95% confidence interval [CI]: 0.529–18.650), prior hemodialysis (OR: 2.722, 95% CI: 0.851–8.709), combined pulmonary disease (OR: 2.286, 95% CI: 0.998–5.283), prior use of carbapenem (OR: 0.199, 95% CI: 0.863–5.603), co-infection (OR: 1.706, 95% CI: 0.746–3.898), prior mechanical ventilation (OR: 1.614, 95% CI, 0.684–3.809), intensive care unit admission (OR: 1.387, 95% CI: 0.560–3.435), and prior tracheostomy (OR: 1.102, 95% CI: 0.344–3.527); however, no statistical differences were observed. Although colistin use could not be proven in multivariate analysis, the possibility of being a risk factor cannot be ruled out.

Keywords

Acinetobacter baumannii
Colistin
Risk factor

1. Introduction

Acinetobacter baumannii is an important cause of healthcare-associated infections, causing nosocomial outbreaks in hospitals, and infections in patients with severe underlying medical conditions are associated with higher mortality rates than in other patients [1]. The frequency of multidrug-resistant *A. baumannii*, which is resistant to three or more antimicrobial drug classes, has increased significantly, and the rate of extensively drug-resistant *A. baumannii*, which is susceptible to only one or two antimicrobial drug classes and all others are non-susceptible, has reached 70%–80%, especially in general hospitals [2]. For serious healthcare-associated infections caused by multidrug-resistant *A. baumannii*, there are few therapeutic options and the only option is to combine several antimicrobials or use antimicrobials such as colistin [3].

Colistin was withdrawn from use in the 1970s due to severe nephrotoxicity and neurotoxicity. Since the 2000s, its use has increased due to its relatively high cure rates for severe multidrug-resistant Gram-negative bacterial infections (especially *Pseudomonas aeruginosa*, *A. baumannii*, and *Klebsiella pneumoniae*) [4]. However, recently, multidrug-resistant strains of *A. baumannii* have been reported to be resistant to colistin [5,6]. The colistin resistance rate of *A. baumannii* is reported to be low, less than 5% in most countries, but it is increasing, and most cases of colistin-resistant *A. baumannii* are pandrug-resistant *A. baumannii*, which is resistant to all antimicrobials, so there are no antimicrobials available for treatment, which is a serious problem.

Existing studies on risk factors for colistin-resistant Gram-negative rod bacterial infections have mainly focused on *K. pneumoniae*, and have suggested a history of treatment with antimicrobials such as colistin or carbapenem, a history of carbapenem-resistant isolates, recent hospitalization, and comorbidities as risk factors [7-9]. Studies on risk factors for colistin-resistant *A. baumannii* infections have similar findings, but most have included small numbers of colistin-resistant *A. baumannii*, and data are still scarce [10-14].

In this study, we aimed to identify the risk factors for colistin-resistant *A. baumannii* infection by comparing colistin-resistant and -susceptible *A. baumannii* infection groups.

2. Methods

We retrospectively reviewed the medical records of 51 cases of colistin-resistant *A. baumannii* isolated and 100 cases of colistin-susceptible *A. baumannii* strains among patients who visited Ewha Womans University Medical Center from 1 January 2014 to 31 December 2018. Specimens from which colistin-resistant *A. baumannii* were isolated included perineal aspirates (n = 20), sputum (n = 17), and urine (n = 9). The 100 control cases in which colistin-susceptible strains were isolated around the same time, and the proportion of specimen types from which colistin-susceptible *A. baumannii* was isolated was similar. This study was approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (IRB No. EUMC 2019-09-013-003).

Age, gender, length of hospitalization, underlying disease (history of diabetes, cancer, chronic kidney disease, chronic liver disease, cardiovascular disease, digestive system disease, respiratory system disease), length of hospitalization before isolation of *A. baumannii* strain, hospitalization within 1 year, *A. baumannii* strain isolation, the history and type of antimicrobial treatment within 28 days before the isolation, admission to the intensive care unit within 28 days, invasive procedures such as mechanical ventilation, central line insertion, tracheostomy, percutaneous drainage, and hemodialysis within the last 3 months, coinfection with other strains isolated from the same or different specimens within 3 days of *A. baumannii* isolation, and antimicrobial resistance, including carbapenem, were analyzed for risk factors.

For the analysis of clinical risk factors for colistin-resistant *A. baumannii* infection, Students *t*-test or

Mann-Whitney U-test was performed for age, length of hospitalization before *A. baumannii* detection, gender, hospitalization, underlying diseases, history of hospitalization within one year, and *A. baumannii* strain isolation, whereas antimicrobial treatment history and type, intensive care unit admission, invasive procedures within the last 3 months, presence of overlapping infections, and antimicrobial resistance were analyzed for clinical characteristics of colistin-resistant and -susceptible groups using Chi-square test or Fisher's exact test. Variables with significant differences ($P < 0.05$) in univariate analysis were subjected to multivariate logistic regression analysis, and significant differences were evaluated if the *P*-value was less than 0.05. Statistical analyses were performed using SPSS 23.0 software (IBM Corp, Armonk, NY, USA).

3. Results

When comparing 51 cases of colistin-resistant *A. baumannii* with 100 cases of colistin-susceptible *A. baumannii*, there was a significant trend toward resistance to all antimicrobials tested in the colistin-resistant group (**Table 1**).

Risk factors such as age, gender, hospitalization, co-morbidities, duration of hospital stay before isolation, history of hospitalization, invasive procedures, antimicrobial use, and co-infections were analyzed and presented in **Table 2**. In univariate analysis, history of respiratory disease ($P = 0.017$), duration of hospitalization before isolation ($P = 0.004$), ICU admission ($P = 0.020$), previous mechanical ventilation ($P = 0.003$), tracheostomy ($P = 0.043$), hemodialysis ($P = 0.002$), colistin use ($P = 0.000$), carbapenem class antimicrobials ($P = 0.000$), teicoplanin use ($P = 0.004$), and co-infections ($P = 0.035$) were significantly different in the colistin-resistant and susceptible groups (**Table 2**).

In multiple regression analysis, history of teicoplanin use (odds ratio [OR], 3.140; 95% confidence interval [CI], 0.529–18.650; $P = 0.208$), previous hemodialysis (OR, 2.722; 95% CI, 0.851–8.709; $P = 0.091$), history of respiratory disease (OR, 2.286; 95% CI, 0.998–5.283; $P = 0.053$), use of carbapenem class antimicrobials (OR, 2.199; 95% CI, 0.863–5.603; $P = 0.099$), co-infections (OR, 1.706; 95% CI, 0.746–3.898; $P = 0.205$), previous mechanical ventilation (OR, 1.614; 95% CI, 0.684–3.809; $P = 0.275$), previous intensive care unit admission (OR, 1.387; 95% CI, 0.560–3.435; $P = 0.480$), and previous tracheostomy (OR, 1.102; 95% CI, 0.344–3.527; $P =$

Table 1. Antimicrobial resistance of colistin-resistant *A. baumannii* and colistin-susceptible *A. baumannii* groups [*n* (%)]

Antimicrobial	Colistin-resistant group($n = 51$)	Colistin-susceptible group($n = 100$)	*P*-value
Amikacin	45 (88.2)	55 (55.0)	0.000
Ampicillin / Sulbactam	33(64.7)	51 (51.0)	0.000
Cefepime	47 (92.2)	60 (60.0)	0.000
Cefotaxime	50 (98.0)	60 (60.0)	0.000
Ceftazidime	47 (92.2)	60 (60.0)	0.000
Ciprofloxacin	46 (90.2)	58 (58.0)	0.000
Gentamicin	46 (90.2)	56 (56.0)	0.000
Imipenem	51 (100.0)	58 (58.0)	0.000
Meropenem	48 (94.1)	59 (59.0)	0.000
Minocycline	23 (45.1)	25 (25.0)	0.004
Piperacillin	49 (96.1)	62 (62.0)	0.000
Ticarcillin / Clavulanic	48 (94.1)	59 (59.0)	0.000
Trimethoprim / Sulfamethoxazole	44 (86.3)	55 (55.0)	0.000

Table 2. Univariate analysis of risk factors for the development of colistin-resistant *A. baumannii* infection

Factor	Colistin-resistant group(*n* = 51)	Colistin-susceptible group(*n* = 100)	*P*-value
Age (yr)	68.9 (1–94)	69.7 (1–97)	0.850
Sex			0.806
Male	23 (45.1)	43 (43.0)	
Female	28 (54.9)	57 (57.0)	
Admission department			0.496
Internal medicine	31 (60.8)	48 (48.0)	
General surgery	6 (11.8)	9 (9.0)	
Pediatrics	1 (2.0)	1 (1.0)	
Orthopedics	3 (5.9)	3 (3.0)	
Neurosurgery	5 (9.8)	17 (17.0)	
Neurology	2 (3.9)	7 (7.0)	
Rehabilitation medicine	1 (2.0)	4 (4.0)	
Other	2 (3.9)	11 (11.0)	
Co-morbidity			
Diabetes mellitus	11 (21.6)	22 (22.0)	0.952
Cancer	19 (37.3)	23 (23.0)	0.064
Chronic kidney disease	7 (13.7)	13 (13.0)	0.901
Chronic liver disease	2 (3.9)	4 (4.0)	0.981
Cardiovascular disease	17 (33.3)	49 (49.0)	0.066
Gastro-intestinal disease	5 (9.8)	9 (9.0)	0.872
Pulmonary disease	20 (39.2)	21 (21.0)	0.017
Length of hospital stay before *A. baumannii* infection (day)	38	21	0.004
Hospitalization (last 1 year)	17 (33.3)	26 (26.0)	0.448
Previous antibiotic use (last 28 days)	20 (39.2)	32 (32.0)	0.109
ICU stay	21 (41.2)	23 (23.0)	0.020
Invasive procedure			
Mechanical ventilation	31 (60.8)	35 (35.0)	0.003
Central venous catheter	18 (35.3)	36 (36.0)	0.932
Tracheostomy	12 (23.5)	11 (11.0)	0.043
Percutaneous drainage	6 (11.8)	4 (4.0)	0.070
Hemodialysis	13 (25.5)	7 (7.0)	0.002
Previous antibiotic use			
Cephalosporin	13 (25.5)	32 (32.0)	0.408
Fluoroquinolone	7 (13.7)	12 (12.0)	0.762
Carbapenem	20 (39.2)	14 (14.0)	0.000
Aminoglycoside	3 (5.9)	2 (2.0)	0.207
Penicillin	18 (35.3)	27 (27.0)	0.292
Colistin	10 (19.6)	0 (0.0)	0.000
Vancomycin	17 (33.3)	22 (22.0)	0.132
Teicoplanin	7 (13.7)	2 (2.0)	0.004
Macrolide	1 (2.0)	0 (0.0)	0.160
Linezolid	1 (2.0)	0 (0.0)	0.160
Tigecycline	1 (2.0)	0 (0.0)	0.160
Co-infection*	38 (74.5)	57 (57.0)	0.035

Values are presented as the median (range) or *n* (%) or *n*. *Other bacteria are isolated from the same or other samples within 3 days of *A. baumannii* isolation. Abbreviations: ICU, intensive care unit.

0.870) were associated with higher risk in the colistin-resistant group, but all were not statistically significant (**Table 3**).

4. Discussion

Comparing 51 cases of colistin-resistant *A. baumannii* with 100 cases of colistin-susceptible *A. baumannii*, univariate analysis showed significant differences ($P < 0.05$) in history of respiratory illness, duration of hospital stay before isolation, previous intensive care unit admission, previous mechanical ventilation, tracheostomy, percutaneous abscess drainage, hemodialysis, previous use of colistin antimicrobials, use of carbapenem class antimicrobials, use of teicoplanin, and overlapping infections. Multiple regression analysis showed that teicoplanin use, history of respiratory illness, use of carbapenem antimicrobials, overlapping infections, previous mechanical ventilation, intensive care unit admission, and previous tracheostomy were associated with an increased risk of colistin-resistant infections (OR > 1), but none were statistically significant. For a history of respiratory disease, the lower limit of the 95% confidence interval of the risk was close to 1 (0.998) and the *P*-value was 0.053, suggesting a high probability of the risk factor.

Mantzarlis *et al.* studied the risk factors for colistin-resistant *A. baumannii* infection and found that the use of antibacterial agents with antimicrobial activity against Gram-negative bacteria such as carbapenem, duration of mechanical ventilation, invasive procedures, and tracheostomy were associated, and carbapenem use was an independent risk factor [10]. On the other hand, a study by Yilmaz *et al.* found that quinolone and colistin use within 3 months were significant risk factors for colistin-resistant infections in Gram-negative bacteria (29 *A. baumannii*, 18 *P. aeruginosa*, 9 *Klebsiella* spp.) [11]. In another study, which included 12 patients with pandrug-resistant *A. baumannii* infection out of a total of 337 patients, colistin (OR, 155.95; 95% CI, 8.00–3,041.98) and carbapenem (OR, 12.84; 95% CI, 1.60–103.20) use were reported as strong risk factors [12]. In a study of colistin-resistant Gram-negative bacteria, including six Acinetobacter strains, previous colistin use, monobactam class antibacterial use, and antifungal use were different in the colistin-resistant and susceptible groups in univariate analysis, and only colistin use was significant in multivariate analysis [13]. In this study, carbapenem, colistin, and teicoplanin use were significantly different between the two groups in univariate analysis but did not appear as independent risk factors in multiple regression analysis. However, in the case of colistin use, there was a significant difference in univariate analysis, but because there were no patients in the colistin-susceptible group (0.0%),

Table 3. Multivariate analysis of risk factors for the development of colistin-resistant *A. baumannii* infection

Variable	Colistin-resistant *A. baumannii* infection		
	OR	95% CI	*P*-value
Use of teicoplanin	3.140	0.529–18.650	0.208
Hemodialysis	2.722	0.851–8.709	0.091
Pulmonary disease	2.286	0.998–5.283	0.053
Use of carbapenem	2.199	0.863–5.603	0.099
Co-infection*	1.706	0.746–3.898	0.205
Mechanical ventilation	1.614	0.684–3.809	0.275
ICU stay	1.387	0.560–3.435	0.480
Tracheostomy	1.102	0.344–3.527	0.870
Length of hospital stay before *A. baumannii* infection (day)	0.991	0.978–1.003	0.143

*Other bacteria are isolated from the same or other samples within 3 days of *A. baumannii* isolation. Abbreviations: OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

multiple regression analysis could not be performed due to error.

In this study, the proportion of colistin use in the colistin-resistant group was significantly lower (19.6%). This is different from previous studies analyzing risk factors for colistin-resistant *A. baumannii*, where colistin use was approximately 30%–80% in the colistin-resistant group. One possible explanation for this is that not all isolates of *A. baumannii* are infectious, and there is a significant proportion of colonizations that are not treated with antimicrobials.

There are several limitations to this study. This was a retrospective study, which means that the information analyzed was limited, there were limitations in controlling for various variables, and there is a possibility of bias. Since we compared colistin-resistant and -susceptible groups regardless of sample type, the heterogeneous patient composition may have prevented the risk factor analysis from being significant. In the case of antimicrobial agents, proper use of dosing, loading dose, etc. is important to achieve effective antimicrobial activity and inhibit the development of resistance. However, this study did not specifically identify the use of antimicrobials. Another major limitation was the lack of colistin use in the colistin-susceptible group, which prevented us from performing a multiple regression analysis.

Although this study did not identify any significant risk factors for colistin-resistant *A. baumannii* infection, we found that a history of respiratory illness, intensive care unit admission, previous tracheostomy, mechanical ventilation, hemodialysis, use of carbapenem antimicrobials within 28 days of bacterial detection, use of teicoplanin, and overlapping infections may increase the risk of colistin-resistant *A. baumannii* infection. In addition, although colistin use could not be demonstrated in the multiple regression analysis, we cannot exclude the possibility that it is a risk factor.

Disclosure statement

The authors declare no conflict of interest.

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References

[1] Moubareck CA, Halat DH, 2020, Insights into *Acinetobacter baumannii*: A Review of Microbiological, Virulence, and Resistance Traits in a Threatening Nosocomial Pathogen. Antibiotics (Basel), 9: 119.

[2] National Antimicrobial Resistance Surveillance in Korea 2020 Annual Report, Division of Antimicrobial Resistance Control, Korea Disease Control and Prevention Agency, 2021, Cheongju, 125–126.

[3] Karakonstantis S, Kritsotakis EI, Gikas A, 2020, Pandrug-Resistant Gram-Negative Bacteria: A Systematic Review of Current Epidemiology, Prognosis and Treatment Options. J Antimicrob Chemother, 75: 271–282.

[4] Biswas S, Brunel JM, Dubus JC, et al., 2012, Colistin: An Update on the Antibiotic of the 21st Century. Expert Rev Anti Infect Ther, 10: 917–934.

[5] Pormohammad A, Mehdinejadiani K, Gholizadeh P, et al., 2020, Global Prevalence of Colistin Resistance in Clinical Isolates of *Acinetobacter baumannii*: A Systematic Review and Meta-Analysis. Microb Pathog, 139: 103887.

[6] Novovic K, Jovcic B, 2023, Colistin Resistance in *Acinetobacter baumannii*: Molecular Mechanisms and Epidemiology. Antibiotics (Basel), 12: 516.

[7] Richter SE, Miller L, Uslan DZ, et al., 2018, Risk Factors for Colistin Resistance among Gram-Negative Rods and *Klebsiella pneumoniae* Isolates. J Clin Microbiol, 56: e00149-18.

[8] Giamarellou H, 2016, Epidemiology of Infections Caused by Polymyxin-Resistant Pathogens. Int J Antimicrob Agents, 48: 614–621.

[9] van Duin D, Doi Y, 2015, Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae*: Are We at the End of the Road? J Clin Microbiol, 53: 3116–3117.

[10] Mantzarlis K, Makris D, Zakynthinos E, 2020, Risk Factors for the First Episode of *Acinetobacter baumannii* Resistant to Colistin Infection and Outcome in Critically Ill Patients. J Med Microbiol, 69: 35–40.

[11] Yilmaz GR, Dizbay M, Guven T, et al., 2016, Risk Factors for Infection with Colistin-Resistant Gram-Negative Microorganisms: A Multicenter Study. Ann Saudi Med, 36: 216–222.

[12] Inchai J, Liwsrisakun C, Theerakittikul T, et al., 2015, Risk Factors of Multidrug-Resistant, Extensively Drug-Resistant and Pandrug-Resistant *Acinetobacter baumannii* Ventilator-Associated Pneumonia in a Medical Intensive Care Unit of University Hospital in Thailand. J Infect Chemother, 21: 570–574.

[13] Matthaiou DK, Michalopoulos A, Rafailidis PI, et al., 2008, Risk Factors Associated with the Isolation of Colistin-Resistant Gram-Negative Bacteria: A Matched Case-Control Study. Crit Care Med, 36: 807–811.

[14] Elham B, Fawzia A, 2019, Colistin Resistance in *Acinetobacter baumannii* Isolated from Critically Ill Patients: Clinical Characteristics, Antimicrobial Susceptibility and Outcome. Afr Health Sci, 19: 2400–2406.