

Original Article

Antimicrobial Resistance Patterns of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* Isolated From Vulnerable Patients in Korea, 2021

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2021년 국내의 감염에 취약한 환자에서 분리된 *Acinetobacter baumannii*와 *Pseudomonas aeruginosa*의 항균 내성 패턴

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ABSTRACT

Background: We compared the antimicrobial resistance rates (AMRs) of major glucose non-fermenting gram-negative bacilli, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, under different clinical conditions. The purpose of the study was to provide useful background data to set up infection control strategies for infection-vulnerable patients.

Methods: The AMRs of blood isolates were compared in various clinical conditions, using data from the Antimicrobial Resistance Surveillance System in Korea.

Results: *A. baumannii* blood isolates from patients with healthcare-associated infections, inpatients, or intensive care unit (ICU)-admitted patients consistently exhibited higher AMRs to most antimicrobials, except minocycline, tigecycline, and colistin, compared with those from patients with community-acquired infections, outpatients, or non-ICU-admitted patients, respectively. *P. aeruginosa* blood isolates from patients with healthcare-associated infections showed higher AMRs to most antimicrobials, except ceftazidime and aztreonam, compared with those from patients with community-acquired infections, but not compared to those from inpatients or ICU-admitted patients.

Conclusion: Higher AMRs were associated with *A. baumannii* bloodstream infections under various clinical conditions, such as healthcare-associated infections and infections in inpatients and ICU-admitted patients. Considering the high AMRs and the limited number of treatment options of *A. baumannii*, vigorous efforts should be used to prevent the spreading of *A. baumannii* infections in patients with vulnerable conditions.

Keywords: Antimicrobial resistance rate, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*

INTRODUCTION

Acinetobacter baumannii is a major cause of healthcare-associated infections, resulting in pneumonia, sepsis, endocarditis, urinary tract infection, wound infection, and meningitis, especially in immunocompromised patients [1]. Compared to *A. baumannii* infections, half of *Pseudomonas aeruginosa* isolates come from community-acquired infections but also play an important role in healthcare-associated infections [2].

Several factors contribute to outcomes in patients with bacterial infections, including host factors (for example, underlying diseases, demographic conditions), bacteriological factors (for example, virulence factors, antimicrobial susceptibility), and therapeutic modalities (for example, empirical antimicrobial treatment, definitive antimicrobial treatment) [3]. Increasing antimicrobial resistance rates (AMRs) of clinically important glucose non-fermenters such as *A. baumannii* and *P. aeruginosa* have become serious problems especially in treating immunocompromised patients.

Our study aims to evaluate the differences of AMRs of *A. baumannii* or *P. aeruginosa* blood isolates according to clinical conditions. The purpose of the study is to provide useful background data in setting up infection control strategies for infection vulnerable patients.

MATERIALS AND METHODS

Non-duplicated *A. baumannii* and *P. aeruginosa* blood isolates were serially collected from nine nationwide general hospitals in 2021, using the Antimicrobial Resistance Surveillance System in Korea protocols [4]. *A. baumannii* (n = 229) and *P. aeruginosa* (n = 233) were included in this study. We verified the bacterial species by using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Biotyper, Bruker Daltonics GmbH, Bremen, Germany) and confirmed *A. baumannii* isolates using oxacillinase (OXA)-51 polymerase chain reaction [4].

Antimicrobial susceptibility was mainly determined with the disk diffusion test according to the Clinical and Laboratory Standards Institute guidelines [5]. Colistin susceptibility was tested by the broth microdilution method, a reference method used for colistin testing [6]. The *A. baumannii* test panel included piperacillin, ampicillin-sulbactam, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, minocycline, tigecycline, and colistin. The *P. aeruginosa* test panel included piperacillin, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamicin, tobramycin, ciprofloxacin, and aztreonam.

We compared clinical conditions, reflecting host clinical conditions such as community-acquired infection/healthcare-associated infection, intensive care unit (ICU)/non-ICU, and inpatient/outpatient. Community-acquired infection was defined when the specimen was taken either from an outpatient or from a patient hospitalized for less than two calendar days. Healthcare-associated infection was defined when the specimen was taken from a patient hospitalized for two or more calendar days overall, including the hospitalization days in another healthcare facility before transfer. Outpatients also included emergency room patients.

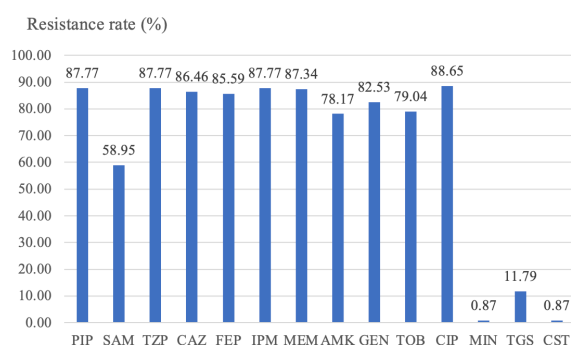
For statistical analysis, we used the Chi-square test and Fisher's exact test with SAS version 9.4 (SAS Institute, Cary, NC, USA), and categorical variables were expressed in number (%). This study was approved by Institutional Review Board of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2022-06-010-002).

RESULTS

AMRs of *A. baumannii* and *P. aeruginosa* blood isolates

The resistance rate of *A. baumannii* was very high in most antimicrobials except for minocycline, tigecycline, and colistin, whose sensitivity is well preserved (Fig. 1A). The carbapenem resistance rate was as high as approximately 87%. The *P. aeruginosa* showed less resistant AMRs than that of *A. baumannii*, with the 37% of imipenem resistance rate (Fig. 1B).

(A)



(B)

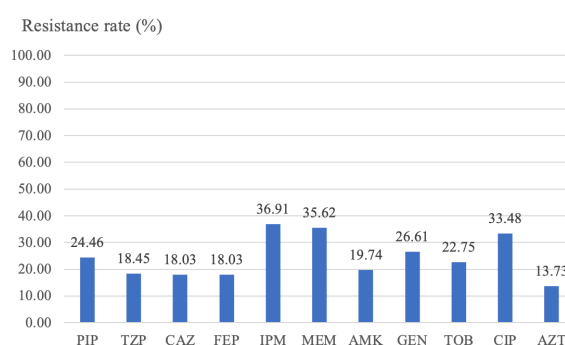


Fig. 1. AMRs of *Acinetobacter baumannii* (A) and *Pseudomonas aeruginosa* blood isolates (B). Abbreviations: AMR, antimicrobial resistance rates; PIP, piperacillin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; MIN, minocycline; TGS, tigecycline; CST, colistin; AZT, aztreonam.

Comparison of *A. baumannii* AMRs in groups

Patients with healthcare-associated infections, inpatients, or ICU-admitted patients consistently exhibited higher AMRs to most antimicrobials except for minocycline, tigecycline, and colistin, compared with that of community-acquired infections, outpatients or non-ICU-admitted patients, respectively (Table 1, Fig. 2).

Table 1. Comparison of antimicrobial resistance rates of *Acinetobacter baumannii* blood isolates in groups

ANTI	CA (n = 31)		HA (n = 198)		P-value	Non-ICU (n = 97)		ICU (n = 132)		P-value	Inpatient (n = 206)		Outpatient (n = 23)		P-value		
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)
PIP					<0.0001					<0.0001					<0.0001		
S or I	13	(41.94)	15	(7.58)		24	(24.74)	4	(3.03)		18	(8.74)	10	(43.48)			
R	18	(58.06)	183	(92.42)		73	(75.26)	128	(96.97)		188	(91.26)	13	(56.52)			
SAM					0.0932					0.0009					0.0007		
S or I	17	(54.84)	77	(38.89)		52	(53.61)	42	(31.82)		77	(37.38)	17	(73.91)			
R	14	(45.16)	121	(61.11)		45	(46.39)	90	(68.18)		129	(62.62)	6	(26.09)			
TZP					<0.0001					<0.0001					<0.0001		
S or I	13	(41.94)	15	(7.58)		24	(24.74)	4	(3.03)		18	(8.74)	10	(43.48)			
R	18	(58.06)	183	(92.42)		73	(75.26)	128	(96.97)		188	(91.26)	13	(56.52)			
CAZ					<0.0001					<0.0001					0.0002		
S or I	13	(41.94)	18	(9.09)		27	(27.84)	4	(3.03)		21	(10.19)	10	(43.48)			
R	18	(58.06)	180	(90.91)		70	(72.16)	128	(96.97)		185	(89.81)	13	(56.52)			
FEP					<0.0001					<0.0001					<0.0001		
S or I	13	(41.94)	20	(10.10)		26	(26.80)	7	(5.3)		22	(10.68)	11	(47.83)			
R	18	(58.06)	178	(89.90)		71	(73.20)	125	(94.7)		184	(89.32)	12	(52.17)			
IPM					<0.0001					<0.0001					0.0004		
S or I	12	(38.71)	16	(8.08)		24	(24.74)	4	(3.03)		19	(9.22)	9	(39.13)			
R	19	(61.29)	182	(91.92)		73	(75.26)	128	(96.97)		187	(90.78)	14	(60.87)			
MEM					<0.0001					<0.0001					<0.0001		
S or I	13	(41.94)	16	(8.08)		25	(25.77)	4	(3.03)		19	(9.22)	10	(43.48)			
R	18	(58.06)	182	(91.92)		72	(74.23)	128	(96.97)		187	(90.78)	13	(56.52)			
AMK					<0.0001					<0.0001					<0.0001		
S or I	17	(54.84)	33	(16.67)		39	(40.21)	11	(8.33)		36	(17.48)	14	(60.87)			
R	14	(45.16)	165	(83.33)		58	(59.79)	121	(91.67)		170	(82.52)	9	(39.13)			
GEN					<0.0001					<0.0001					0.0004		
S or I	15	(48.39)	25	(12.63)		33	(34.02)	7	(5.3)		29	(14.08)	11	(47.83)			
R	16	(51.61)	173	(87.37)		64	(65.98)	125	(94.7)		177	(85.92)	12	(52.17)			
TOB					<0.0001					<0.0001					<0.0001		
S or I	16	(51.61)	32	(16.16)		39	(40.21)	9	(6.82)		35	(16.99)	13	(56.52)			
R	15	(48.39)	166	(83.84)		58	(59.79)	123	(93.18)		171	(83.01)	10	(43.48)			
CIP					<0.0001					<0.0001					0.0002		
S or I	12	(38.71)	14	(7.07)		22	(22.68)	4	(3.03)		17	(8.25)	9	(39.13)			
R	19	(61.29)	184	(92.93)		75	(77.32)	128	(96.97)		189	(91.75)	14	(60.87)			
MIN					>0.9999					>0.9999					>0.9999		
S or I	31	(100.00)	196	(98.99)		96	(98.97)	131	(99.24)		204	(99.03)	23	(100.00)			
R	-	0	2	(1.01)		1	(1.03)	1	(0.76)		2	(0.97)	-	0			
TGC					0.5474					0.3123					0.3264		
S or I	29	(93.55)	173	(87.37)		88	(90.72)	114	(86.36)		183	(88.83)	19	(82.61)			
R	2	(6.45)	25	(12.63)		9	(9.28)	18	(13.64)		23	(11.17)	4	(17.39)			
CST					>0.9999					>0.9999					>0.9999		
S or I	31	(100.00)	196	(98.99)		96	(98.97)	131	(99.24)		204	(99.03)	23	(100.00)			
R	-	0	2	(1.01)		1	(1.03)	1	(0.76)		2	(0.97)	-	0			

Bold form: statistically significant.

Abbreviations: ANTI, antimicrobials; CA, community-acquired infection; HA, healthcare-associated infection; ICU, intensive care unit; PIP, piperacillin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; MIN, minocycline; TGC, tigecycline; CST, colistin; S, susceptible; I, intermediate; R, resistant.

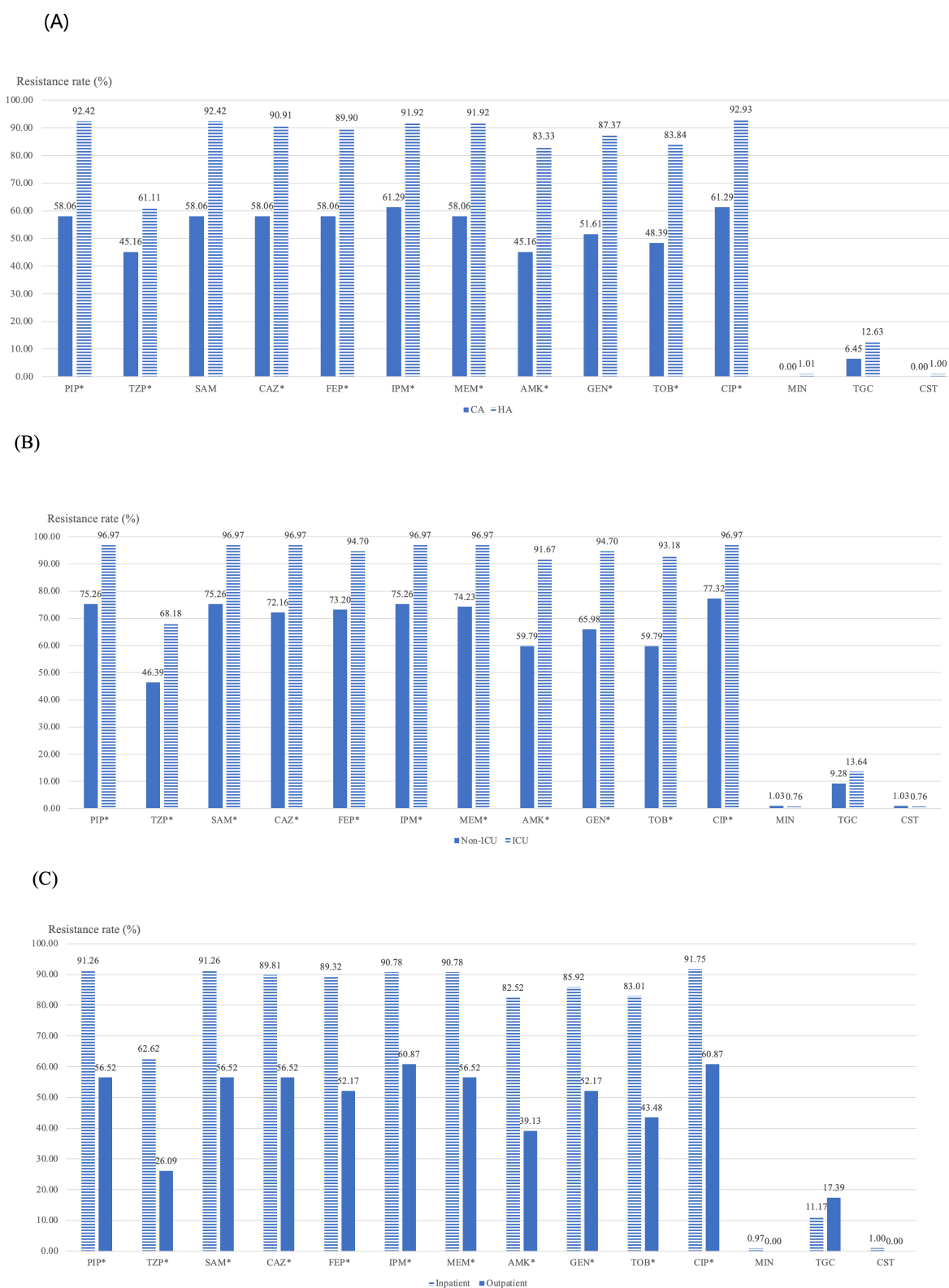


Fig. 2. AMRs of *Acinetobacter baumannii* in various clinical conditions. (A) CA versus HA, (B) ICU versus non-ICU-admitted patients, (C) inpatients versus outpatients. *Statistically significant (P -value < 0.05). Abbreviations: AMR, antimicrobial resistance rates; CA, community-acquired infection; HA, healthcare-associated infection; ICU, intensive care unit; PIP, piperacillin; TZP, piperacillin-tazobactam; SAM, ampicillin-sulbactam; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; MIN, minocycline; TGC, tigecycline; CST, colistin

Comparison of *P. aeruginosa* AMRs in groups

Patients with healthcare-associated infection showed higher AMRs to most antimicrobials except for ceftazidime and aztreonam, compared with that of community-acquired infections (Table 2). These differences were not prominent in ICU-admitted patients or inpatients, compared to that of non-ICU-admitted patients or outpatients, respectively.

Table 2. Comparison of antimicrobial resistance rates of *Pseudomonas aeruginosa* blood isolates in groups

ANTI	CA (n = 100)		HA (n = 133)		P-value	Non-ICU (n = 168)		ICU (n = 65)		P-value	Inpatient (n = 179)		Outpatient (n = 54)		P-value
	No.	(%)	No.	(%)		No.	(%)	No.	(%)		No.	(%)	No.	(%)	
PIP					0.0092					0.4758					0.0249
S or I	84	(84.00)	92	(69.17)		129	(76.79)	47	(72.31)		129	(72.07)	47	(87.04)	
R	16	(16.00)	41	(30.83)		39	(23.21)	18	(27.69)		50	(27.93)	7	(12.96)	
TZP					0.0039					0.258					0.0469
S or I	90	(90.00)	100	(75.19)		140	(83.33)	50	(76.92)		141	(78.77)	49	(90.74)	
R	10	(10.00)	33	(24.81)		28	(16.67)	15	(23.08)		38	(21.23)	5	(9.26)	
CAZ					0.1657					0.7853					0.2695
S or I	86	(86.00)	105	(78.95)		137	(81.55)	54	(83.08)		144	(80.45)	47	(87.04)	
R	14	(14.00)	28	(21.05)		31	(18.45)	11	(16.92)		35	(19.55)	7	(12.96)	
FEP					0.0156					0.5142					0.0559
S or I	89	(89.00)	102	(76.69)		136	(80.95)	55	(84.62)		142	(79.33)	49	(90.74)	
R	11	(11.00)	31	(23.31)		32	(19.05)	10	(15.38)		37	(20.67)	5	(9.26)	
IPM					<0.0001					0.0064					0.0004
S or I	79	(79.00)	68	(51.13)		115	(68.45)	32	(49.23)		102	(56.98)	45	(83.33)	
R	21	(21.00)	65	(48.87)		53	(31.55)	33	(50.77)		77	(43.02)	9	(16.67)	
MEM					0.0005					0.007					0.0432
S or I	77	(77.00)	73	(54.89)		117	(69.64)	33	(50.77)		109	(60.89)	41	(75.93)	
R	23	(23.00)	60	(45.11)		51	(30.36)	32	(49.23)		70	(39.11)	13	(24.07)	
AMK					0.01					0.1262					0.1533
S or I	88	(88.00)	99	(74.44)		139	(82.74)	48	(73.85)		140	(78.21)	47	(87.04)	
R	12	(12.00)	34	(25.56)		29	(17.26)	17	(26.15)		39	(21.79)	7	(12.96)	
GEN					0.004					0.12					0.0252
S or I	83	(83.00)	88	(66.17)		128	(76.19)	43	(66.15)		125	(69.83)	46	(85.19)	
R	17	(17.00)	45	(33.83)		40	(23.81)	22	(33.85)		54	(30.17)	8	(14.81)	
TOB					0.0057					0.1419					0.0504
S or I	86	(86.00)	94	(70.68)		134	(79.76)	46	(70.77)		133	(74.3)	47	(87.04)	
R	14	(14.00)	39	(29.32)		34	(20.24)	19	(29.23)		46	(25.7)	7	(12.96)	
CIP					0.0033					0.1893					0.1798
S or I	77	(77.00)	78	(58.65)		116	(69.05)	39	(60.00)		115	(64.25)	40	(74.07)	
R	23	(23.00)	55	(41.35)		52	(30.95)	26	(40.00)		64	(35.75)	14	(25.93)	
ATM					0.2931					0.6940					0.1233
S or I	89	(89.00)	112	(84.21)		144	(85.71)	57	(87.69)		151	(84.36)	50	(92.59)	
R	11	(11.00)	21	(15.79)		24	(14.29)	8	(12.31)		28	(15.64)	4	(7.41)	

Bold form: statistically significant.

Abbreviations: ANTI, antimicrobials; CA, community-acquired infection; HA, healthcare-associated infection; ICU, intensive care unit; PIP, piperacillin; TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; IPM, imipenem; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; ATM, aztreonam; S, susceptible; I, intermediate; R, resistant

DISCUSSION

Carbapenem has been widely used as the treatment of choice for extended-spectrum- β -lactamase *Escherichia coli* or *Klebsiella pneumoniae* infections [7]. We have already reported that frequent use of carbapenem is associated with the rapid growth of carbapenem-resistant *A. baumannii* (CRAB) infections in Korea since 2007 [8]. Carbapenem resistance of clinically important glucose non-fermenters such as *A. baumannii* and *P. aeruginosa* has been regarded as an urgent or serious antimicrobial resistance threat [9].

The main resistance mechanism to CRAB is oxacillinase (OXA)-type β -lactamase, and since the mid-2000s, it has been reported that most CRAB isolates produce OXA-23 [10]. Unfortunately, most CRAB isolates exhibit multidrug-resistance or even broad drug-resistance because they carry antimicrobial resistance determinants together with aminoglycosides, fluoroquinolones, and tetracyclines [11]. CRAB treatment options are seriously restricted to last-resort agents such as colistin or tigecycline [11]. But declining colistin or tigecycline efficacy have been reported, and this growing resistance is becoming a major concern [12,13]. This study found a resistance rate of 0.87% to colistin and 11.79% to tigecycline. It is necessary to evaluate the resistance mechanism of tigecycline-resistant *A. baumannii* strains emerging in Korea with the recent introduction of a plasmid-mediated resistance mechanism.

Since VIM-2-producing *P. aeruginosa* in Korea was reported in 2002 [14], the resistance mechanism of carbapenem-resistant *P. aeruginosa* (CRPA) is mainly because of metallo- β -lactamase [15]. CRPA also commonly manifests multidrug-resistance [16]. Treatment options are restricted, and combination therapies have been tried [17].

New effective drugs such as ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, and cefiderocol have been introduced and for the past 10 years have been safely used in the US and Europe [18]. According to the American Society of Infectious Disease guidelines, these new agents are recommended as primary treatment options for treating multidrug-resistant Gram-negative bacteria [19,20]. However, in Korea, the introduction of these drugs has been delayed or the national health insurance does not cover them [21], so adequate treatment modalities are lacking.

In this study, the isolates of *A. baumannii* from bloodstream infections showed higher AMRs to most antimicrobials in conditions of healthcare-associated infections, inpatients, or ICU-admissions. Although it is not definitely suggestive of immunocompromised conditions without reviewing underlying diseases, chemotherapy or immune depressing agents, it is important to define vulnerable conditions, considering high AMRs and limitation of treatment options.

요약

배경: 본 연구에서는 혈액배양에서 분리된 주요 포도당 비발효 그람 음성 간균인 *Acinetobacter baumannii*와 *Pseudomonas aeruginosa*의 주요 항균제에 대한 항균 내성률을 임상 군별로 비교하였다. 본 연구의 목적은 취약한 환자에 대한 감염관리 전략의 근거 자료를 제공하고자 한다.

방법: 국내 항균제 내성균 조사사업(Antimicrobial Resistance Surveillance System in Korea)를 통해 얻은 자료를 가지고 혈액배양에서 분리된 *A. baumannii*와 *P. aeruginosa*의 항균제 내성률을 다양한 임상군으로 나누어 비교하였다.

결과: 혈액배양에서 분리된 *A. baumannii*의 항균제 내성률은 의료관련 감염, 입원 환자 또는 중환자실 재원인 경우 각각 지역사회 감염, 외래환자 또는 중환자실 비입실인 경우에 비해 minocycline, tigecycline, 및 colistin을 제외한 대부분의 항균제에서 일관되게 더 높았다. 의료관련 감염 환자의 혈액배양에서 분리된 *P. aeruginosa*의 경우 지역사회 감염군에 비해 ceftazidime과 aztreonam을 제외한 대부분의 항균제에서 더 높은 내성률을 보였다. 그러나 입원 환자나 중환자실 입원 환자에서는 이런 차이가 분명하지 않았다.

결론: 혈액배양에서 분리된 *A. baumannii*의 주요 항균제 내성률은 의료관련 감염, 입원 환자 또는 중환자실 재원인 경우 그렇지 않은 군에 비해 더 높았다. *A. baumannii*의 높은 항균제 내성률과 치료제의 심각한 제한을 고려하면, 취약한 환자군에서의 적극적인 *A. baumannii*의 감염관리가 매우 중요하겠다.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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