Prevalence and mechanisms of carbapenem resistance in *Acinetobacter* spp. isolated from South Korea

Woonhyoung Lee

Department of Medicine

The Graduate School, Yonsei University

Prevalence and mechanisms of carbapenem resistance in *Acinetobacter* spp. isolated from South Korea

Directed by Professor Seok Hoon Jeong

The Doctoral Dissertation
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Doctor of Philosophy

Woonhyoung Lee

June 2015

This certifies that the Doctoral Dissertation of Woonhyoung Lee is approved.

Thesis Supervisor : Seok Hoon Jeong

Thesis Committee Member#1 : Kyungwon Lee

Thesis Committee Member#2 : Yong Hwan Lee

Thesis Committee Member#3: Hee Cheol Kang

Thesis Committee Member#4: Sang Sun Yoon

The Graduate School
Yonsei University

June 2015

<TABLE OF CONTENTS>

LIST OF TABLES

ABSTRACT

Prevalence and mechanisms of carbapenem resistance in *Acinetobacter* spp. isolated from South Korea

Woonhyoung Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Seok Hoon Jeong)

The persistent increase of carbapenem-resistant *Acinetobacter* spp. is a global issue. This study was performed to investigate the prevalence of carbapenem-resistant *Acinetobacter* spp. and to determine resistance mechanisms in Korea.

A total of 418 non-duplicate *Acinetobacter* clinical isolates were collected from 28 general hospitals in Korea from October to December 2013. Species identification was performed using *rpoB* gene sequencing. Antimicrobial susceptibilities were determined by disk diffusion assays following CLSI guidelines. Genes encoding carbapenemases were amplified by PCR, and amplified products were directly sequenced. Multilocus sequence typing (MLST) was used for characterizing isolates.

Of 407 collected isolates, 356 (87.5%) were identified as *A. baumannii*, and non-*baumannii Acinetobacter* (NBA) isolates were identified as *A. nosocomialis* (n = 26, 6.4%), *A. pitti* (n = 22, 5.4%), *A. berezinae* (n = 1), *A. gyllenbergii* (n = 1), and *A. haemolyticus* (n = 1).

While only 12.4% (44/356) and 11.8% (42/356) of *A. baumannii* clinical isolates were susceptible to imipenem and meropenem, respectively, susceptible rates of NBA clinical isolates to imipenem (43/58, 84.3%) and meropenem (43/58, 84.3%) were higher.

The $bla_{\text{OXA-23}}$ gene was detected in 310 *A. baumannii* isolates, while the

insertion sequence IS*Aba1* element associated with the $bla_{\text{OXA-51-like}}$ gene was detected in only 13 *A. baumannii* isolates. The $bla_{\text{OXA-58}}$ gene was detected in 2 NBA isolates. The $bla_{\text{OXA-24}}$ and $bla_{\text{OXA-182}}$ genes were not detected in this study. The $bla_{\text{IMP-1}}$ gene was detected in 1 NBA isolate. While *A. baumannii* acquired carbapenem resistance by producing OXA-23 carbapenemase or overproducing OXA-51 or both of them, *A. nosocomialis* and *A. pitti* acquired that by producing IMP-1 or OXA-58.

Of the 356 *A. baumannii* clinical isolates, 292 isolates were identified as clonal complex 92 (CC92) by MLST, and remaining isolates were identified as CC110 (n = 7), CC397 (n = 3), CC20 (n = 20), and other sequence types (STs, n = 34).

The isolates belonging to CC92 exhibited different antibiogram compared to the isolates not belonged to CC92. Of 292 CC92 isolates, only 1.4% (4 isolates) were susceptible to carbapenems. Of 66 isolates not belonged to CC92, 62.1% (41 isolates) were susceptible to carbapenems.

Regardless of belonging to CC92 or not, the $bla_{\text{OXA-23}}$ gene was detected in 301 *A. baumannii* isolates (301/356, 84.6%).

OXA-23-producing *A. baumannii* clinical isolates not belonging to CC92 and *A. nosocomialis* have emerged in Korea.

Key words : *Acinetobacter*, Carbapenem, OXA carbapenemase, Metallo-β-lactamase

Prevalence and mechanisms of carbapenem resistance in *Acinetobacter* spp. isolated from South Korea

Woonhyoung Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Seok Hoon Jeong)

I. INTRODUCTION

Antimicrobial agents (antibiotics) are extremely important drugs to fight against bacterial infection.[1] However, bacteria have increasingly been resisting to antimicrobial therapy.[2] Resistance problem has relatively worsened in Gram-negative bacilli.[3,4] *Acinetobacter baumannii* causes various nosocomial infections with high mortality, and the infection caused by multidrug-resistant *A. baumannii* is currently among the most difficult ones to treat.[5] A few extensive reviews have been published on *Acinetobacter* bacteriology and infection.[6-8] In most Asian countries, including Korea, *Acinetobacter* infections are relatively more prevalent and the organisms are more often resistant.[9]

Seven mechanisms of antibiotic resistance are known in Gram-negative bacteria: loss of porins, production of β-lactamases, increased expression of efflux pumps, presence of antibiotic-modifying enzymes, target site mutations, ribosomal mutations or modifications, metabolic bypass mechanisms, and a mutation in the lipopolysaccharide.[10]

Acinetobacter spp. are intrinsically less susceptible to antimicrobial agents than the species of *Enterobacteriaceae.*[2] Outer membrane permeability of *A. baumannii* is less than 5% compared with other Gram-negative bacilli, because of small number and size of porins.[11] Porins are pore forming proteins on the outer membrane (OMP) of bacteria.[2] Three OMPs (33-36 kDa, 29 kDa, and 43 kDa) have been reported to be missing in the imipenem-resistant strains of *A.*

baumannii.[2] Decreased expression of OmpW was reported in a colistin-resistant *A. baumannii* mutant.[2]

All bacteria have efflux systems.[2] The multidrug efflux pumps actively export multiple, structurally-distinct classes of antimicrobials out of the bacterial cell.[2] The most common antimicrobials expelled by the efflux pumps are macrolides, tetracyclines and quinolones.[11] Overexpression of efflux pump further increases resistance level.[2] Among the six families of multidrug efflux systems, major facilitator superfamily (MFS) and resistance-nodulation-division (RND) family are often associated with antimicrobial resistance in *A. baumannii.*[2] Tet(A) and Tet(B) pumps belong to the MFS, and confers resistance to tetracycline, and both tetracycline and minocycline, respectively.[2] AdeM pump is a member of the multidrug and toxic compound extrusion (MATE) family, and confers resistance to norfloxacin, ofloxacin, ciprofloxacin, and gentamicin.[11] AdeABC is a three-component efflux pump, where AdeA is the membrane fusion protein, AdeB is the multidrug transporter, and AdeC is the OMP.[2] AdeABC pump belongs to the RND family and confers resistance to aminoglycosides, β-lactams, chloramphenicol, erythromycin and tetracyclines, and reduced susceptibility to fluoroquinolones.[2]

A. baumannii carries intrinsic bla_{AmpC} genes encoding *Acinetobacter*-derived cephalosporinases which confer natural resistance to cefoxitin,[2] as are many other species of Gram-negative bacilli.[2,12] Inducible AmpC expression does not occur in *A. baumannii*, unlike that of AmpC enzymes found in other Gram-negative bacilli.[2] Presence of upstream IS*Aba1* is involved in the overexpression of this gene, resulting in resistance to 3rd generation cephalosporins.[13,14] *A. baumannii* also naturally carries intrinsic $bla_{\text{OXA-51}}$-like genes, and presence of upstream IS*Aba1* renders the organism resistant to carbapenems.[2] IS*Aba1*, IS*Aba2*, IS*Aba3*, and IS*Aba4* could increase expression of $bla_{\text{OXA-51}}$-like genes.[2] Increased expression of $bla_{\text{OXA-23}}$ by the upstream IS*Aba10* was reported in a group of *A. baumannii* isolates.[15]

Carbapenem-resistant *Acinetobacter* spp. have been increasingly reported worldwide.[16] It was reported that imipenem susceptibility decreased from 72.2%

in 2005 to 37.6% in 2009 among the worldwide collection of *Acinetobacter* spp.[17] In a Korean nationwide study, the imipenem resistance rate of *Acinetobacter* spp. was 51% in 2009.[18] OXA-type carbapenemases have emerged as the main resistance mechanism to carbapenems in *Acinetobacter* spp..[7,8] OXA-type carbapenemases are categorized into 4 groups, including OXA-23-like, OXA-24-like, OXA-58-like, and OXA-51-like clusters.[8]

The prevalent *bla*$_{OXA}$ genes are known to vary significantly depending on the date and place of isolation.[16] In the United Kingdom, it was reported that the proportion of isolates with IS*Aba1*-associated *bla*$_{OXA-51}$-like genes decreased significantly from 2003 to 2005, while those with bla$_{OXA-23}$-like genes remained prevalent.[19] In Italy, isolates harboring the *bla*$_{OXA-23}$-like gene emerged in 2007, replacing the previously prevalent *bla*$_{OXA-58}$-like genes.[20] A high prevalence of *bla*$_{OXA-143}$ was reported in Brazil,[21] which is where this novel gene was discovered.[22] In 2005 nationwide Korean surveillance, the majority of *Acinetobacter* isolates harbored either *bla*$_{OXA-23}$-like or *bla*$_{OXA-51}$-like genes.[18] In another study, a novel bla$_{OXA-182}$ gene (GenBank no. JQ964242) whose encoded protein has 93% amino acid identity to the OXA-143 protein was detected.[23]

The aim of this study was to determine the prevalence and the spreading pattern of *Acinetobacter* spp. isolated from many hospitals in South Korea.

II. MATERIALS AND METHODS

A total of 418 non-duplicate *Acinetobacter* clinical isolates were collected from 28 general hospitals in Korea between October and December 2013.

- Phylogenetic grouping based on partial *rpoB* gene sequencing: The 450 bp sequence (zone 2) of the *rpoB* gene was amplified using the primers Ac1005F (5′-GTGATAARATGGCBGGTCGT-3′) and Ac1598R (5′-CGBGCRTGCATYTTGTCRT-3′) as previously described.[24] The phylogenetic relationship based on the *rpoB* zone 2 sequence was estimated using the neighbour-joining method in molecular evolutionary genetic analysis software.

- Antimicrobial Susceptibility Testing (Disk diffusion method): Antimicrobial disks were dispensed onto the surface of the inoculated Mueller-Hinton agar plate. After 16 to 18 hours of incubation, the diameters of the zones of complete inhibition (as judged by the unaided eye) were measured, including the diameter of the disk.

- PCR and sequencing for genes encoding MBLs and OXA carbapenemases: Whole-cell lysates of the test organisms were used as templates for PCR amplification. PCR experiments were carried out to detect the genes encoding MBLs and OXA carbapenemases. The PCR procedure initiated denaturation (94◦C for 5 min) consisted of 30 cycles of denaturation at 94◦C for 25 sec, annealing at 52◦C for 40 sec and extension at 72◦C for 50 sec, followed by a final extension at 72◦C for 6 min.

- Multilocus sequence typing (MLST): MLST was performed using the method of Bartual et al.[25] Fragments of seven housekeeping genes (*gltA, gyrB, gdhB, recA, cpn60, gpi* and *rpoD*) were amplified by PCR and sequenced. Allele numbers were assigned an ST after the distinct allele sequences were submitted to a dedicated database (www.pubmist.org).

III. RESULTS

1. Of 407 collected isolates, 356 (87.5%) were identified as *A. baumannii*, and non-*baumannii Acinetobacter* (NBA) isolates were identified as *A. nosocomialis* (n = 26, 6.4%), *A. pitti* (n = 22, 5.4%), *A. berezinae* (n = 1), *A. gyllenbergii* (n = 1), and *A. haemolyticus* (n = 1) (Table 1).

Of the 356 *A. baumannii* clinical isolates, 292 isolates were identified as clonal complex 92 (CC92) by MLST, and remaining isolates were identified as CC110 (n = 7), CC397 (n = 3), CC20 (n = 20), and other sequence types (STs, n = 34) (Table 1).

Table 1. Species & Strains

Species	Specimen										Total	
	Respiratory		Blood		Urine		Pus		Body fluid			
	n	%	n	%	n	%	n	%	n	%	n	%
A. baumannii	252	89.0	21	65.6	25	92.3	54	90.0	5	83.3	356	87.5
CC92	210	71.9	16	5.5	18	6.2	44	15.1	4	1.4	292	82.0
CC110	7	100.0	-	-	-	-	-	-	-	-	7	2.0
CC397	3	100.0	-	-	-	-	-	-	-	-	3	0.8
CC447	12	60.0	1	5.0	2	10.0	4	20.0	1	5.0	20	5.6
Others	20	58.8	4	11.8	4	11.8	6	17.6	-	-	34	9.6
A. nosocomialis	15	5.3	7	21.9	1	3.8	3	5.0	-	-	26	6.4
A. pitti	14	4.9	4	12.5	1	3.8	2	3.3	1	16.7	22	5.4
A. berezinae	1	0.4	-	-	-	-	-	-	-	-	1	0.2
A. gyllenbergii	1	0.4	-	-	-	-	-	-	-	-	1	0.2
A. haemolyticus	-	-	-	-	-	-	1	1.7	-	-	1	0.2
Total	283	100	34	100	28	100	60	100	6	100	415	100

Abbreviations: n, number.

2. While only 12.4% (44/356) and 11.8% (42/356) of *A. baumannii* clinical isolates were susceptible to imipenem and meropenem, respectively, susceptible rates of NBA clinical isolates to imipenem and meropenem were 84.3% (43/58) and 84.3% (43/58), respectively (Table 2).

Table 2. Antimicrobial susceptibilities (%) of *A. baumannii* and non-*baumannii Acinetobacter* clinical isolates

Antimicrobial agents	*A. baumannii*						NBA				Total
	CC92	CC110	CC397	CC20	Others	Subtotal	*A. nosocomialis*	*A. pittii*	Other NBAs	Subtotal	
	(n=292)	(n=7)	(n=3)	(n=20)	(n=34)	(n=356)	(n=26)	(n=22)	(n=3)	(n=51)	(n=407)
Piperacillin	0.3	0.0	0.0	15.0	75.0	8.7	57.7	40.9	100.0	52.9	14.0
Ticarcillin	0.7	0.0	0.0	45.0	88.9	12.0	80.8	86.4	100.0	84.3	20.9
Ampicillin-sulbactam	2.1	14.3	0.0	45.0	88.9	13.4	92.3	86.4	100.0	90.2	22.9
Piperacillin-tazobactam	0.7	0.0	0.0	40.0	88.9	11.7	76.9	90.9	66.7	82.4	20.4
Cefotaxime	0.0	0.0	0.0	0.0	8.3	0.8	3.8	18.2	0.0	9.8	1.7
Ceftazidime	0.3	14.3	0.0	85.0	91.7	14.5	92.3	86.4	100.0	90.2	23.8
Cefepime	2.4	14.3	0.0	45.0	88.9	13.7	69.2	86.4	100.0	78.4	21.6
Imipenem	1.4	0.0	0.0	45.0	88.9	12.6	80.8	86.4	100.0	84.3	21.4
Meropenem	0.7	0.0	0.0	45.0	88.9	12.0	80.8	86.4	100.0	84.3	20.9
Amikacin	18.2	0.0	0.0	95.0	94.4	29.6	80.8	86.4	100.0	84.3	36.4
Gentamicin	7.5	0.0	33.3	95.0	94.4	21.2	61.5	90.9	100.0	76.5	28.0
Tobramycin	14.0	0.0	100.0	95.0	94.4	27.1	73.1	86.4	66.7	78.4	33.4
Ciprofloxacin	0.3	0.0	0.0	45.0	91.7	12.0	65.4	90.9	100.0	78.4	20.1
Tetracycline	5.8	0.0	0.0	50.0	91.7	16.8	65.4	100	100.0	82.4	24.8
Trimethoprim-sulfamethoxazole	2.1	0.0	0.0	40.0	94.4	13.4	92.3	77.3	100.0	86.3	22.4

Antimicrobial agents	*A. baumannii*						NBA				Total
	CC92	CC110	CC397	CC20	Others	Subtotal	*A. nosocomialis*	*A. pittii*	Other NBAs	Subtotal	
	(n=292)	(n=7)	(n=3)	(n=20)	(n=34)	(n=356)	(n=26)	(n=22)	(n=3)	(n=51)	(n=407)
Colistin	99.7	100.0	100.0	100.0	100.0	99.7	100.0	100	100.0	100.0	99.8
Tigecycline	27.1	100.0	0.0	95.0	94.4	38.8	84.6	100	100.0	92.2	45.2

Abbreviations: NBA, non-*baumannii Acinetobacter*; CC, clonal complex.

3. The *bla*$_{\text{OXA-23}}$ gene was detected in 310 *A. baumannii* isolates, while the IS*Aba1* element associated with the *bla*$_{\text{OXA-51}}$-like gene was detected in only 13 *A. baumannii* isolates. The *bla*$_{\text{OXA-58}}$ gene was detected in 2 NBA isolates. The *bla*$_{\text{OXA-24}}$ and *bla*$_{\text{OXA-182}}$ genes were not detected in this study. The *bla*$_{\text{IMP-1}}$ gene was detected in 1 NBA isolate (Table 3). While *A. baumannii* acquired carbapenem resistance by producing OXA-23 carbapenemase or overproducing OXA-51 or both of them. *A. nosocomialis* and *A. pitti* acquired carbapenem resistance by producing IMP-1 or OXA-58.

Table 3. No. of *Acinetobacter* clinical isolates producing carbapenemases

Species		Carbapenem resistance determinant						Total
		bla$_{OXA-23}$	*bla*$_{OXA-23}$ + IS*Aba1*-*bla*$_{OXA-51}$	IS*Aba1*-*bla*$_{OXA-51}$	*bla*$_{OXA-58}$	*bla*$_{IMP-1}$	non	
A. baumannii	CC92	278	9	3	0	0	2	292
	CC110	6	0	1	0	0	0	7
	CC397	3	0	0	0	0	0	3
	CC20	11	0	0	0	0	9	20
	others	3	0	0	0	0	31	34
	Subtotal	301	9	4	0	0	42	356
NBA	*A. nosocomialis*	4	0	0	2	1	21	26
	A. pittii	0	0	0	1	1	20	22
	Other NBAs	0	0	0	0	0	3	3
	Subtotal	3	0	0	3	2	44	51
Total		301	9	4	3	2	86	407

Abbreviations: NBA, non-*baumannii Acinetobacter*; non, no carbapenem resistance determinant.

4. CC92 comprised of ST191 (n = 148), ST208 (n = 38), ST219 (n = 1), ST357 (n = 50), ST358 (n = 1), ST368 (n = 4), ST369 (n = 13), ST451 (n = 16), ST737 (n = 3), ST858 (n = 4), ST784 (n = 12), and others comprised of ST* (n = 1); CC110 comprised of ST229 (n = 5) and others comprised of ST* (n = 2); CC397 comprised of ST* (n = 3); CC20 comprised of ST620 (n = 1) and other comprised of ST* (n = 19); Others comprised of ST359 (n = 1), ST454 (n = 1), ST707 (n = 1), ST739 (n = 1) , ST688 (n = 1), ST552 (n = 2) and ST* (n = 27). Novel STs found in this study are indicated (Table 4).

Table 4. MLST of 358 *A. baumannii* isolates

CC	ST	Alleic type							No. of isolates	Total
		gltA	gyrB	gdhB	recA	cpn60	gpi	rpoD		
CC92	191	1	3	3	2	2	94	3	148	292
	208	1	3	3	2	2	97	3	38	
	219	1	3	3	2	2	101	3	1	
	357	1	12	3	2	2	145	3	50	
	358	1	3	3	2	2	145	3	1	
	368	1	3	3	2	2	140	3	4	
	369	1	3	3	2	2	106	3	13	
	373	1	12	12	11	4	103	3	1	
	451	1	3	3	2	2	142	3	16	
	737	1	31	3	2	2	158	3	3	
	858[#]	1	12	3	2	2	140	3	4	
	784[#]	1	3	3	2	2	107	3	12	
	*	1	3	3	2	2	94	21	1	
CC110	229	1	15	2	28	1	107	32	5	7
	*	1	15	120	28	1	107	32	1	
	*	1	15	2	28	48	107	32	1	
CC397	*	10	53	4	6	4	98	5	1	3
	*	10	53	4	64	4	98	5	1	
	*	10	53	132	6	4	98	5	1	
CC20	620	1	1	13	12	4	16	2	1	20
	*	1	1	13	60	4	16	2	1	
	*	1	15	13	43	4	106	2	1	
	*	1	15	13	60	4	106	2	12	
	*	1	15	13	60	4	163	2	5	
Other	359	21	38	127	1	4	146	43	1	34
	454	1	17	80	28	35	97	30	1	
	701	1	34	62	31	4	61	45	1	
	739	1	15	59	28	4	144	45	1	
	*	1	12	56	36	4	149	45	1	
	*	1	35	12	6	4	94	3	1	
	*	1	47	67	28	1	103	6	1	
	*	1	12	3	28	1	107	4	1	
	688	1	15	135	6	35	187	45	1	
	*	1	56	13	48	4	107	6	1	
	*	1	90	67	60	1	94	4	1	

CC	ST	Alleic type							No. of isolates	Total
		gltA	gyrB	gdhB	recA	cpn60	gpi	rpoD		
Other	*	1	90	38	6	26	187	5	1	
	*	1	12	13	33	4	173	2	1	
	*	1	17	82	39	1	107	7	1	
	*	1	93	139	6	1	153	6	1	
	*	1	34	59	28	4	157	6	1	
	*	2	38	42	36	4	178	41	1	
	*	18	93	135	6	4	187	50	1	
	*	21	35	2	28	22	145	4	1	
	552	21	35	2	28	1	145	4	2	
	*	21	12	2	28	1	84	5	1	
	*	21	48	58	42	36	140	4	1	
	*	21	35	2	28	1	145	3	1	
	*	23	61	134	26	4	160	4	1	
	*	24	17	71	60	1	153	52	1	
	*	33	31	2	28	1	144	5	2	
	*	33	58	11	36	11	153	40	1	
	*	35	15	13	12	4	163	2	1	
	*	36	12	59	28	4	94	4	1	
	*	37	15	58	42	4	98	41	1	
	*	49	68	3	53	41	145	58	1	
	*	29	46	67	6	30	195	4	1	

5. The isolates belonging to CC92 exhibited different antibiogram compared to the isolates not belonged to CC92. Of 292 isolates of CC92, only 1.4% (4 isolates) was susceptible to carbapenems. Of 66 isolates not belonged to CC92, 62.1% (41 isolates) was susceptible to carbapenems. Regardless of belonging to CC92 or not, the $bla_{\text{OXA-23}}$ gene was detected in 301 *A. baumannii* isolates (301/356, 84.6%). Carbapenem susceptibility patterns were summarized according to ST in *A. baumannii* isolated (Table 5).

Table 5. Carbapenem susceptibility patterns according to ST in *A. baumannii* isolated.

Clonal Complex	ST	No. of isolates	No. (%) of carbapenem-susceptible isolates	Carbapenem-resistance determinant		
				bla_{OXA-23}	bla_{OXA-23} + IS*Aba1*-bla_{OXA-51}	IS*Aba1*-bla_{OXA-51}
CC92	ST191	147	2 (1.4)	144	3	
	ST208	38	0 (0)	37	1	
	ST219	1	0 (0)	1		
	ST357	50	0 (0)	50		
	ST358	1	0 (0)	1		
	ST368	4	0 (0)	4		
	ST369	13	0 (0)	5	5	3
	ST373	1	0 (0)	1		
	ST451	16	0 (0)	16		
	ST737	3	0 (0)	3		
	*	4	0 (0)	4		
	*	12	0 (0)	12		
	Subtotal	290	2 (0.7)	278	9	3
Non-CC92		21	0 (0)	20	0	1

Abbreviations: Non-CC92, *A. baumannii* clinical isolates not belonging to CC92

IV. DISCUSSION

OXA-type β-lactamases are molecular class D enzymes.[26] OXA-type β-lactamases include narrow spectrum, extended-spectrum, and carbapenem-hydrolyzing ones.[2] Of the OXA type β-lactamases, those with carbapenemase activity are the most concerned.[2] The first OXA-type carbapenemase, OXA-23, was detected in 1985 from an *A. baumannii* strain from Scotland.[2] The *bla*$_{\text{OXA-23}}$ gene was located on transferable plasmid.[2] Four main groups of OXA carbapenemases include OXA-23-like, OXA-40-like, OXA-51-like, and OXA-58 enzymes.[27]

An outbreak of *A. baumannii* with OXA-23 was first reported at a Korean hospital in 2003 involving 36 patients.[28] At another hospital in 2006-2007, all 49 isolates of *A. baumannii* with OXA-23 were found to have identical or closely related PFGE patterns, indicating that rapid increase of this determinant was due to clonal spread.[29] In a Korean surveillance study in 2000-2001, only 27 of 267 (10.1%) imipenem-nonsusceptible *Acinetobacter* spp. isolates had MBLs.[30] In another study in 2005,[18] vast majority of imipenem resistance in *Acinetobacter* spp. isolates were due to OXA carbapenemase production: among the 144 imipenem-resistant isolates only 19.4% had MBLs, whereas 74.3% had OXA carbapenemases.

Prevalent types of OXA carbapenemase varied significantly depending on reports in Korea.[2] In a surveillance study in 2005,[18] among the 105 imipenem-resistant isolates of *A. baumannii*, 47 had *bla*$_{\text{OXA-23}}$-like and 56 had upstream IS*Aba1*-associated *bla*$_{\text{OXA-51}}$-like genes. In another study in 2007,[23] among 178 isolates of *A. baumannii*, isolates with *bla*$_{\text{OXA-23}}$-like genes were more prevalent (80%) than those with IS*Aba1*-asssociated *bla*$_{\text{OXA-51}}$-like genes (12%). It is of an interest to note in this study that 12 isolates had a novel *bla*$_{\text{OXA-182}}$ which is related to *bla*$_{\text{OXA-143}}$, first reported in Brazil in 2004.[22] At a Taiwanese regional hospital, among imipenem-resistant *A. baumannii* isolates, *bla*$_{\text{OXA-23}}$-like gene was detected in only 2 of 97 isolates in 2005 and 2006, but the gene was detected in 24 of 38 isolates in 2007.[31] Presence of an identical PFGE type in 18 of the 38 isolates indicated that the rapid increase was due to outbreaks. In a study, among 544 *Acinetobacter* isolates collected from 10 Asia Pacific countries in 2006-2007,[32]

230 (42.3%) were nonsusceptible to carbapenems and OXA-23 was detected in 134 of 156 *A. baumannii* isolates from China, Hong Kong, India, Korea, Singapore, and Thailand. *A. baumannii* isolates from China, Indonesia, Taiwan and Thailand carried other OXA carbapenemase: OXA-24/40 (n=5), OXA-58 (n=2), OXA-23 plus OXA-58 (n=11), OXA-24 plus OXA-58 (n=1), and OXA-23 plus OXA-24/40 plus OXA-58 (n=3). PFGE showed clonal dissemination of OXA carbapenemase-producing *A. baumannii* isolates within medical centers among different countries.

Carbapenems, colistin, and tigecycline were active against over 80% of *A. baumannii* complex isolated in 2000.[33] A high colistin resistance rate of 30.6% among *A. baumannii* isolates from 2 Korean hospitals[34] indicated necessity of colistin susceptibility testing in other settings.

In recent years, *Acinetobacter* spp. have been described as important pathogens in outbreaks of nosocomial infection worldwide, especially in intensive care units.[6] In particular, the species *A.baumannii* has presented an increased rate of antimicrobial resistance.[8,35] Carbapenems, once regarded as the treatment of choice for infections caused by *Acinetobacter* spp., are no longer effective in some cases.[8] The main mechanism of carbapenem resistance among *Acinetobacter* spp. is the production of β-lactamases, in particular class D β-lactamases (oxacillinases), associated with promoter gene sequence IS*Aba1*.[35] Among oxacillinases, the most prevalent one is *bla*$_{\text{OXA-23}}$, identified in mobile genetic elements.[36] Chromosomally located *bla*$_{\text{OXA-51}}$ genes, in turn, do not always confer carbapenem resistance but are used to identify *A. baumannii*, as it is believed to be intrinsic to this species.[37-39]

Traditionally, the *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-51}}$ genes are associated with *A. baumannii* only, but recently some authors have described the presence of such genes in non-*A. baumannii* species.[36] The *bla*$_{\text{OXA-23}}$ gene was found in *A. pittii* (Acinetobacter genomic species 3) in the Irish Republic in 2006 and in *A. nosocomialis* (Acinetobacter genomic species 13TU) in South Korea and Thailand in 2012.[40,41] Moreover, *bla*$_{\text{OXA-51}}$ preceded by IS*Aba1* has been found in carbapenem-resistant *A. nosocomialis* in Taiwan.[42]

The presence of oxacillinase genes in non-*A. baumannii* isolates had already been described in studies from China, South Korea, and Singapore, which underscores the potential clinical significance of these species.[36,40-43]

More generally, it is apparent that the population structure of *A. baumannii* comprises three major international lineages, named European clones I, II, and III.[44,45] A subgroup of European clone II involving clonal complex (CC) 92 has spread globally[46] and is widespread in China[47] and Korea[48]; it is also recorded in Australia.[49]

Although ST92 has been the global epidemic clone among carbapenem-non-susceptible *A. baumannii,*[50] 13 of 14 carbapenem-non-susceptible *A. baumannii* isolates belonged to ST208 or its single variant ST219, the member of CC92 in a study.[51] The fact that the isolates carrying *bla*$_{\text{OXA-66}}$ belonged to CC92 is compatible[51] with the finding that the isolates carrying *bla*$_{\text{OXA-66}}$ often belonged to STs such as ST98 (formerly ST34) included in CC92, as demonstrated in a recent report.[52] CC92 has increasingly been documented as a globally disseminated linage included in European clone II, often with multidrug resistance.[46,49] The *bla*$_{\text{OXA-51}}$-like gene can confer carbapenem non-susceptibility to the bacteria if IS*Aba1* providing promoter sequences for overexpression is located adjacent to *bla*$_{\text{OXA-51}}$-like.[53]

There was a previously performed survey in 2008 to define the epidemiological traits of XDR-ABA in Korea.[54] A total of 547 non-duplicated clinical isolates of *Acinetobacter* spp. were collected from 19 different hospitals in six provinces of Korea. The isolates were identified as ABA (n = 388, 70.9%), *A. nosocomialis* (n = 82, 15.0%), *A. pittii* (n = 62, 11.3%), *A. berezinae* (n = 13, 2.4%), and *Acinetobacter* genomospecies 14TU (n = 2, 0.4%) by *rpoB* gene sequencing. While 70% (272/388) of ABA isolates exhibited non-susceptibility to imipenem and/or meropenem, only 6.9% (11/159) of non-*baumannii Acinetobacter* (NBA) isolates exhibited that. ABA and NBA acquired carbapenem resistance by different mechanisms. While XDR-ABA clinical isolates acquired carbapenem resistance by production of OXA-23 carbapenemase (62.1%, 169/272) or

overproduction of chromosomal OXA-51-like carbapenemase (32.7%, 89/272) or both of them (5.1%, 14/272), all XDR-NBA clinical isolates acquired that by production of IMP-1 (n = 6) or VIM-2 (n = 4) MBL, with the exception of an *A. pitti* isolate producing OXA-23. MLST experiments following the Bartual scheme on 388 ABA isolates identified 57 different STs. Interestingly, all 272 XDR-ABA isolates were identified as CC92 (ST92, n = 159; ST75, n = 64; ST137, n = 3; ST138, n = 38; and ST69, n = 8). The study showed that XDR-ABA CC92 producing OXA-23 and/or overproducing OXA-51-like have clonally disseminated in Korea.

Compared to the previous study[54], proportion of XDR-ABA isolates producing OXA-23 has increased from 47.2% (183/388) to 87.1% (310/356), while that of XDR-ABA isolates overproducing OXA-51-like has decreased from 26.5% (103/388) to 3.7% (13/356). XDR-NBA clinical isolates acquired carbapenem resistance by production of OXA-23 (*A. nosocomialis*, n = 4), OXA-58 (*A. nosocomialis*, n = 1; *A. pittii*, n = 1), or IMP-1 (*A. pittii*, n = 1). Compared to the previous survey, the proportion of MBL-producing NBA has decreased from 6.3% (10/159) to 2.0% (1/51). ABA clinical isolates were identified as Bartual CC20 (5.6%, 20/356), CC92 (82.0%, 292/356), CC110 (2.0%, 7/356), CC397 (0.9%, 3/356), and other 32 different STs (9.6%, 34/356) by MLST experiments. OXA-23-producing ABA isolates were identified as Bartual CC20 (3.5%, 11/310), CC92 (93.0%, 287/310), CC110 (1.9%, 6/310), CC397 (1.0%, 3/310), and other 3 different STs (1.0%, 3/310), and OXA-51-like-overproducing ABA isolates were identified as Bartual CC92 (n = 12) and CC110 (n = 1).

V. CONCLUSION

The results show that XDR-ABA producing OXA-23 carbapenemase has further disseminated in Korea during past 5 years. While all XDR-ABA isolates collected in 2008 were identified as CC92[54], those collected in this study were identified as diverse clones. There is no evidence whether XDR-ABA of non-CC92 got into Korea from foreign countries or the strains acquired OXA-23 gene by horizontal transfer in this country. However, diversification of OXA-23-producing XDR-ABA strains in Korea might be a signal for further dissemination of the microorganisms in Korea.

REFERENCES

1. Salyers AA, Whitt DD. Revenge of the microbes : how bacterial resistance is undermining the antibiotic miracle. Washington, D.C.: ASM Press; 2005.
2. Lee K, Yong D, Jeong SH, Chong Y. Multidrug-resistant Acinetobacter spp.: increasingly problematic nosocomial pathogens. Yonsei Med J 2011;52:879-91.
3. Ho J, Tambyah PA, Paterson DL. Multiresistant Gram-negative infections: a global perspective. Curr Opin Infect Dis 2010;23:546-53.
4. Marchaim D, Zaidenstein R, Lazarovitch T, Karpuch Y, Ziv T, Weinberger M. Epidemiology of bacteremia episodes in a single center: increase in Gram-negative isolates, antibiotics resistance, and patient age. Eur J Clin Microbiol Infect Dis 2008;27:1045-51.
5. Maragakis LL, Perl TM. Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 2008;46:1254-63.
6. Bergogne-Berezin E, Towner KJ. Acinetobacter spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin Microbiol Rev 1996;9:148-65.
7. Munoz-Price LS, Weinstein RA. Acinetobacter infection. N Engl J Med 2008;358:1271-81.
8. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev 2008;21:538-82.
9. Jean SS, Hsueh PR. High burden of antimicrobial resistance in Asia. Int J Antimicrob Agents 2011;37:291-5.
10. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. N Engl J Med 2010;362:1804-13.
11. Vila J, Marti S, Sanchez-Cespedes J. Porins, efflux pumps and multidrug resistance in Acinetobacter baumannii. J Antimicrob Chemother 2007;59:1210-5.
12. Hujer KM, Hamza NS, Hujer AM, Perez F, Helfand MS, Bethel CR, et al. Identification of a new allelic variant of the Acinetobacter baumannii cephalosporinase, ADC-7 beta-lactamase: defining a unique family of class C enzymes. Antimicrob Agents Chemother 2005;49:2941-8.
13. Corvec S, Caroff N, Espaze E, Giraudeau C, Drugeon H, Reynaud A. AmpC cephalosporinase hyperproduction in Acinetobacter baumannii clinical strains. J Antimicrob Chemother 2003;52:629-35.
14. Lin YC, Hsia KC, Chen YC, Sheng WH, Chang SC, Liao MH, et al. Genetic basis of multidrug resistance in Acinetobacter clinical isolates in Taiwan. Antimicrob Agents Chemother 2010;54:2078-84.
15. Lee Y, Kim CK, Lee H, Jeong SH, Yong D, Lee K. A novel insertion sequence, ISAba10, inserted into ISAba1 adjacent to the bla(OXA-23) gene and disrupting the outer membrane protein gene carO in Acinetobacter baumannii. Antimicrob Agents Chemother 2011;55:361-3.
16. Lee Y, Kim YR, Kim J, Park YJ, Song W, Shin JH, et al. Increasing prevalence of blaOXA-23-carrying Acinetobacter baumannii and the emergence of blaOXA-182-carrying Acinetobacter nosocomialis in Korea. Diagn Microbiol Infect Dis 2013;77:160-3.

17. Mendes RE, Farrell DJ, Sader HS, Jones RN. Comprehensive assessment of tigecycline activity tested against a worldwide collection of Acinetobacter spp. (2005-2009). Diagn Microbiol Infect Dis 2010;68:307-11.
18. Lee K, Kim MN, Choi TY, Cho SE, Lee S, Whang DH, et al. Wide dissemination of OXA-type carbapenemases in clinical Acinetobacter spp. isolates from South Korea. Int J Antimicrob Agents 2009;33:520-4.
19. Coelho JM, Turton JF, Kaufmann ME, Glover J, Woodford N, Warner M, et al. Occurrence of carbapenem-resistant Acinetobacter baumannii clones at multiple hospitals in London and Southeast England. J Clin Microbiol 2006;44:3623-7.
20. D'Arezzo S, Principe L, Capone A, Petrosillo N, Petrucca A, Visca P. Changing carbapenemase gene pattern in an epidemic multidrug-resistant Acinetobacter baumannii lineage causing multiple outbreaks in central Italy. J Antimicrob Chemother 2011;66:54-61.
21. Antonio CS, Neves PR, Medeiros M, Mamizuka EM, Elmor de Araujo MR, Lincopan N. High prevalence of carbapenem-resistant Acinetobacter baumannii carrying the blaOXA-143 gene in Brazilian hospitals. Antimicrob Agents Chemother 2011;55:1322-3.
22. Higgins PG, Poirel L, Lehmann M, Nordmann P, Seifert H. OXA-143, a novel carbapenem-hydrolyzing class D beta-lactamase in Acinetobacter baumannii. Antimicrob Agents Chemother 2009;53:5035-8.
23. Kim CK, Lee Y, Lee H, Woo GJ, Song W, Kim MN, et al. Prevalence and diversity of carbapenemases among imipenem-nonsusceptible Acinetobacter isolates in Korea: emergence of a novel OXA-182. Diagn Microbiol Infect Dis 2010;68:432-8.
24. La Scola B, Gundi VA, Khamis A, Raoult D. Sequencing of the rpoB gene and flanking spacers for molecular identification of Acinetobacter species. J Clin Microbiol 2006;44:827-32.
25. Bartual SG, Seifert H, Hippler C, Luzon MA, Wisplinghoff H, Rodriguez-Valera F. Development of a multilocus sequence typing scheme for characterization of clinical isolates of Acinetobacter baumannii. J Clin Microbiol 2005;43:4382-90.
26. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother 2010;54:969-76.
27. Brown S, Amyes S. OXA (beta)-lactamases in Acinetobacter: the story so far. J Antimicrob Chemother 2006;57:1-3.
28. Jeon BC, Jeong SH, Bae IK, Kwon SB, Lee K, Young D, et al. Investigation of a nosocomial outbreak of imipenem-resistant Acinetobacter baumannii producing the OXA-23 beta-lactamase in korea. J Clin Microbiol 2005;43:2241-5.
29. Yang HY, Lee HJ, Suh JT, Lee KM. Outbreaks of imipenem resistant Acinetobacter baumannii producing OXA-23 beta-lactamase in a tertiary care hospital in Korea. Yonsei Med J 2009;50:764-70.
30. Lee K, Lee WG, Uh Y, Ha GY, Cho J, Chong Y, et al. VIM- and IMP-type metallo-beta-lactamase-producing Pseudomonas spp. and Acinetobacter spp. in Korean hospitals. Emerg Infect Dis 2003;9:868-71.
31. Lin MF, Kuo HY, Yeh HW, Yang CM, Sung CH, Tu CC, et al. Emergence and dissemination of blaOXA-23-carrying imipenem-resistant Acineto

bacter sp in a regional hospital in Taiwan. J Microbiol Immunol Infect 2011;44:39-44.
32. Mendes RE, Bell JM, Turnidge JD, Castanheira M, Jones RN. Emergence and widespread dissemination of OXA-23, -24/40 and -58 carbapenemases among Acinetobacter spp. in Asia-Pacific nations: report from the SENTRY Surveillance Program. J Antimicrob Chemother 2009;63:55-9.
33. Henwood CJ, Gatward T, Warner M, James D, Stockdale MW, Spence RP, et al. Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936). J Antimicrob Chemother 2002;49:479-87.
34. Ko KS, Suh JY, Kwon KT, Jung SI, Park KH, Kang CI, et al. High rates of resistance to colistin and polymyxin B in subgroups of Acinetobacter baumannii isolates from Korea. J Antimicrob Chemother 2007;60:1163-7.
35. Poirel L, Nordmann P. Carbapenem resistance in Acinetobacter baumannii: mechanisms and epidemiology. Clin Microbiol Infect 2006;12:826-36.
36. Teixeira AB, Martins AF, Barin J, Hermes DM, Pitt CP, Barth AL. First report of carbapenem-resistant Acinetobacter nosocomialis isolates harboring ISAba1-blaOXA-23 genes in Latin America. J Clin Microbiol 2013;51:2739-41.
37. Donald HM, Scaife W, Amyes SG, Young HK. Sequence analysis of ARI-1, a novel OXA beta-lactamase, responsible for imipenem resistance in Acinetobacter baumannii 6B92. Antimicrob Agents Chemother 2000;44:196-9.
38. Turton JF, Woodford N, Glover J, Yarde S, Kaufmann ME, Pitt TL. Identification of Acinetobacter baumannii by detection of the blaOXA-51-like carbapenemase gene intrinsic to this species. J Clin Microbiol 2006;44:2974-6.
39. Walther-Rasmussen J, Hoiby N. OXA-type carbapenemases. J Antimicrob Chemother 2006;57:373-83.
40. Boo TW, Walsh F, Crowley B. First report of OXA-23 carbapenemase in clinical isolates of Acinetobacter species in the Irish Republic. J Antimicrob Chemother 2006;58:1101-2.
41. Kim DH, Choi JY, Jung SI, Thamlikitkul V, Song JH, Ko KS. AbaR4-type resistance island including the blaOXA-23 gene in Acinetobacter nosocomialis isolates. Antimicrob Agents Chemother 2012;56:4548-9.
42. Lee YT, Kuo SC, Chiang MC, Yang SP, Chen CP, Chen TL, et al. Emergence of carbapenem-resistant non-baumannii species of Acinetobacter harboring a blaOXA-51-like gene that is intrinsic to A. baumannii. Antimicrob Agents Chemother 2012;56:1124-7.
43. Pagano M, Martins AF, Machado AB, Barin J, Barth AL. Carbapenem-susceptible Acinetobacter baumannii carrying the ISAba1 upstream blaOXA-51-like gene in Porto Alegre, southern Brazil. Epidemiol Infect 2013;141:330-3.
44. Dijkshoorn L, Aucken H, Gerner-Smidt P, Janssen P, Kaufmann ME, Garaizar J, et al. Comparison of outbreak and nonoutbreak Acinetobacter baumannii strains by genotypic and phenotypic methods. J Clin Microbiol 1996;34:1519-25.

45. van Dessel H, Dijkshoorn L, van der Reijden T, Bakker N, Paauw A, v an den Broek P, et al. Identification of a new geographically widespread multiresistant Acinetobacter baumannii clone from European hospitals. R es Microbiol 2004;155:105-12.
46. Mugnier PD, Poirel L, Naas T, Nordmann P. Worldwide dissemination of the blaOXA-23 carbapenemase gene of Acinetobacter baumannii. Emerg Infect Dis 2010;16:35-40.
47. Fu Y, Zhou J, Zhou H, Yang Q, Wei Z, Yu Y, et al. Wide disseminatio n of OXA-23-producing carbapenem-resistant Acinetobacter baumannii clo nal complex 22 in multiple cities of China. J Antimicrob Chemother 201 0;65:644-50.
48. Park YK, Choi JY, Jung SI, Park KH, Lee H, Jung DS, et al. Two disti nct clones of carbapenem-resistant Acinetobacter baumannii isolates from Korean hospitals. Diagn Microbiol Infect Dis 2009;64:389-95.
49. Runnegar N, Sidjabat H, Goh HM, Nimmo GR, Schembri MA, Paterson DL. Molecular epidemiology of multidrug-resistant Acinetobacter bauma nnii in a single institution over a 10-year period. J Clin Microbiol 2010; 48:4051-6.
50. Adams-Haduch JM, Onuoha EO, Bogdanovich T, Tian GB, Marschall J, Urban CM, et al. Molecular epidemiology of carbapenem-nonsusceptible Acinetobacter baumannii in the United States. J Clin Microbiol 2011;49:3 849-54.
51. Kouyama Y, Harada S, Ishii Y, Saga T, Yoshizumi A, Tateda K, et al. Molecular characterization of carbapenem-non-susceptible Acinetobacter sp p. in Japan: predominance of multidrug-resistant Acinetobacter baumannii clonal complex 92 and IMP-type metallo-beta-lactamase-producing non-b aumannii Acinetobacter species. J Infect Chemother 2012;18:522-8.
52. Hamouda A, Evans BA, Towner KJ, Amyes SG. Characterization of epid emiologically unrelated Acinetobacter baumannii isolates from four contin ents by use of multilocus sequence typing, pulsed-field gel electrophoresi s, and sequence-based typing of bla(OXA-51-like) genes. J Clin Microbio l 2010;48:2476-83.
53. Turton JF, Ward ME, Woodford N, Kaufmann ME, Pike R, Livermore D M, et al. The role of ISAba1 in expression of OXA carbapenemase gene s in Acinetobacter baumannii. FEMS Microbiol Lett 2006;258:72-7.
54. Lee Y, Lee J, Jeong SH, Lee J, Bae IK, Lee K. Carbapenem-non-suscep tible Acinetobacter baumannii of sequence type 92 or its single-locus var iants with a G428T substitution in zone 2 of the rpoB gene. J Antimicr ob Chemother 2011;66:66-72.

ABSTRACT(IN KOREAN)

국내에서 분리된 Acinetobacter 균속의 carbapenem계 항균제 내성 현황 및 기전

<지도교수 정석훈>

연세대학교 대학원 의학과

이 운 형

최근 Acinetobacter 균속에서 carbapenem계 항균제에 대한 내성률이 현저히 증가하고 있다. 본 연구는 국내에서 분리된 Acinetobacter 균속의 carbapenem계 항균제 내성 기전 및 역학을 조사하고자 한다.

본 연구에는 2013년 10월부터 12월까지 전체 28 대학 및 종합병원에서 본 연구에 참여하였다. 연구기간 중 수집된 Acinetobacter 균주는 전체 418주이었다. Acinetobacter 균속의 동정은 rpoB gene의 염기서열 분석을 통하여 확인하였다. 항균제의 최소억제농도(minimum inhibitory concentration, MIC)는 CLSI 한천희석법으로 측정하였다. Carbapenemase의 유전형을 고안된 primer를 사용하여 PCR로 확인한다. MLST 등을 이용하여 분자역학적 성상을 규명하였다.

본 연구를 통해 수집된 Acinetobacter 407주 중 A. baumannii로 동정된 것은 356주 (87.5%)이었다. Non-baumannii Acinetobacter(NBA) 가운데 *A. nosocomialis 26*주 (6.4%), *A. pitti* 22주 (5.4%), *A. berezinae* 1주, *A. gyllenbergii* 1주, 그리고 *A.*

haemolyticus 1주이었다.
전체 수집된 A. baumannii 356주 가운데 44주(12.4%)가 imipenem 감수성이었고, 42주 (11.8%)가 meropenem 감수성이었다. NBA 58주 중 imipenem 및 meropenem 감수성인 균주는 각각 43주(84.3%), 43주(84.3%)로 높았다.

A. baumannii로 확인된 310주는 blaOXA-23 유전자를 보유하고 있었고, A. baumannii 13주에서만 염색체성 OXA-51 유전자의 상류에 ISAba1이 확인되었다. NBA 2주는 $bla_{\text{OXA-58}}$ 유전자를 보유하고 있었다. 본 연구에서는 $bla_{\text{OXA-24}}$ 와 $bla_{\text{OXA-182}}$ 유전자는 확인되지 않았다. NBA 1주는 $bla_{\text{IMP-1}}$ 유전자를 보유하고 있었다. A. baumannii의 carbapenem 내성 기전은 OXA-23과 OXA-51 carbapenemase의 생성 및 과발현에 의한 반면, *A. nosocomialis* 와 *A. pitti* 는 IMP-1 또는 OXA-58에 의했다.
A. baumannii로 확인된 356주 중 clonal complex(CC) 92 292주, CC110 7주, CC397 3주, CC20 20주, 그리고 그외 34주로 MLST에 의해 분자역학적 성상이 규명되었다.

CC92에 속한 균주의 antibiogram은 CC92에 속하지 않은 균주와 다른 성상을 보였다. CC92 292주 중 4주(1.4%)만 carbapenem감수성이었다. 비CC92 66주 중 41주(62.1%)가 carbapenem감수성이었다.

CC92 여부와 상관없이, A. baumannii 356주 중 301주가 $bla_{\text{OXA-23}}$ 유전자를 보유하였다. CC92에 속하지 않은 OXA-23 carbapenemase를 생산하는 A. baumannii균주와 A. nosocomialis가

국내에 증가하고 있었다.

핵심되는 말 : *Acinetobacter*, Carbapenem, OXA carbapenemase, Metallo-β-lactamase