Molecular epidemiology and antibiotic susceptibility pattern of *Acinetobacter baumannii* isolated from children in a Turkish university hospital

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The aim of the present study is to investigate the types of healthcare-associated infections (HC-AIs) caused by *Acinetobacter baumannii* and the related antibiotic susceptibility patterns as well as the genotypic characteristics of the *Acinetobacter baumannii* isolates from our center. Sixty-nine *Acinetobacter baumannii* isolates originating from various samples collected from 69 pediatric patients during their hospital stays were included in the study. The types of healthcare-associated infections caused by these isolates were evaluated, and the antibiotic susceptibility pattern and the genotypic characteristics of the isolates were determined using the pulsed-field gel electrophoresis (PFGE) method. Fifty of the 69 children were observed to have HC-AIs, and 19 children had *Acinetobacter baumannii* colonization. Healthcare-associated pneumonia (58%) was the most common type of these infections. The rate of carbapenem resistance was found as 91.3%, while tigecycline resistance was found as 18.84%. No colistin resistance was observed in any of the isolates. A total of 10 groups, comprising eight major and two minor groups, were determined using the pulsed-field gel electrophoresis method. *Acinetobacter baumannii* isolates are the leading cause of healthcare-associated infections, and they show high rates of multidrug antibiotic resistance. Molecular epidemiological evaluation using PFGE plays an important role in preventing healthcare-associated infections.

Key words: Acinetobacter baumanni, pulsed-field gel electrophoresis, healthcare-associated infections, antibiotic resistance, children.

Members of the genus Acinetobacter have been increasingly responsible for healthcare-associated infections, especially in intensive care units, in recent years[1]. The most frequently isolated type of Acinetobacter from clinical samples, *Acinetobacter baumannii (A. baumannii)*, has a low virulence and usually leads to opportunistic infections, including primarily ventilator-associated pneumonia and bacteremia, urinary system infections, meningitis and skin and soft tissue infections in patients admitted to intensive care units[2-4]. *A. baumannii* has developed resistance to various types of antibiotics, including carbapenems, and multi-resistant epidemics of *A. baumannii* have recently been reported[5-8].

In order to control HC-AIs and epidemics, it is of vital importance to know the origins and transmission routes of the isolates. In the past, phenotypic methods were used in order to compare the similarities and differences among isolates originating from different sources in healthcare-associated infections or epidemics. In recent years, this approach has changed in parallel to the progress in the molecular typing methods based on deoxyribonucleic acid

(DNA). Today, pulsed-field gel electrophoresis (PFGE) is accepted as the gold standard among the frequently used DNA-based molecular typing methods[9].

Material and Methods

The present study was conducted at the Cukurova University Medical Faculty Hospital between February 2010 and October 2011. For the purposes of the study, approval was granted by the Cukurova University Medical Faculty Ethics Committee. The study had a prospective design based on the *A. baumannii* strains isolated from various clinical samples routinely sent to the microbiology laboratory from pediatric patients admitted to the Cukurova University Medical Faculty Hospital. In cases where more than one *A. baumannii* isolate was derived from a single patient, only one of the isolates was included in the study. The epidemiologic, clinical and demographic characteristics of the patients were recorded. The clinical data gathered included the patient's age, gender, duration of hospital stay, sites of infection, time from admission until collection of the sample, and any comorbidities or major risk factors (e.g., intensive care unit stay, intravenous catheterization, mechanical ventilation). The definitions of healthcare-associated infections and colonization were based on the U.S. Centers for Disease Control and Prevention (CDC) criteria[10].

Assessment of Antibiotic Susceptibility

Antibiotic susceptibility was tested using the Vitek-2 Compact automated system. The MIC values of the antibiotics are presented in Table I[11]. Intermediate-level susceptible strains were also accepted as resistant.

The Pulsed-Field Gel Electrophoresis Method

Plug preparation, lysis, cell washing, restriction digestion and electrophoresis were performed as has been previously described[12]. For the electrophoresis, a CHEF-DR II (Bio-Rad Laboratories, Nazareth, Belgium) device was used. The band profiles were analyzed using GelCompar II software (version 5.0; Applied Maths, Sint-Martens-Latem, Belgium). The band and profile tolerance was taken as 1.5% in the calculation of the similarity coefficient. The isolates where the band profiles showed an 80% similarity were evaluated within the same group and designated with capital letters. Subtypes within the same group were indicated with numbers.

Results

Sixty-nine *Acinetobacter baumannii* isolates originating from various clinical samples collected from 69 pediatric patients during their hospital stays were included in the study.

When the patients were assessed in terms of the infections that developed due to *A. baumannii* and the risk factors for colonization, all of them were observed to be under treatment with extended-spectrum antibiotics. The risk factors are presented in Table II.

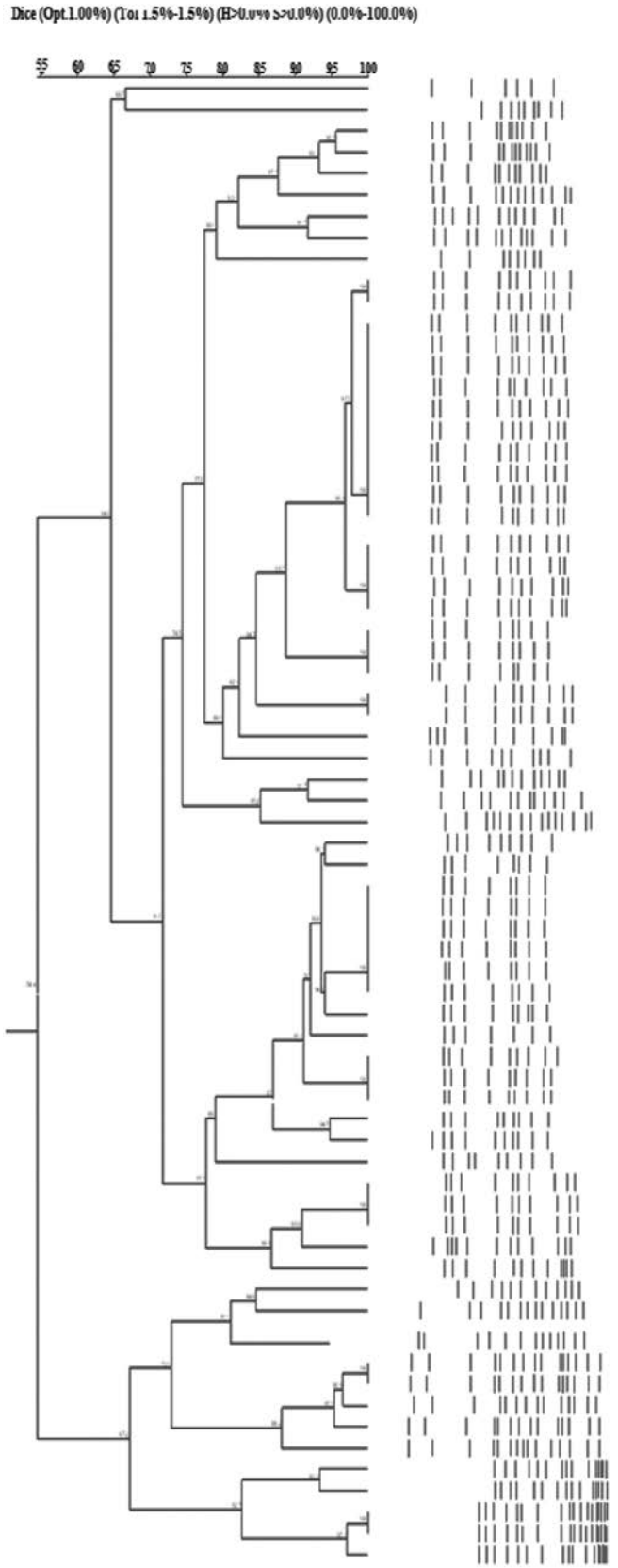
In this study, 50 among the 69 isolates (72.74%) were the agents of healthcare-associated infections; the most frequently observed infection (50%) was ventilator-associated pneumonia. In 19 patients (27.53%), the isolated *A. baumannii* was accepted as colonization. The diagnoses of the patients are presented in Table III.

Antibiotic susceptibility results

Among the isolates included in the study, 67 (100%) were observed to be susceptible to colistin. No antibiogram was performed against colistin for the two isolates included in the study. The antibiotic susceptibility of the isolates included in the study is presented in Table IV.

Pulsed-Field Gel Electrophoresis Results

The pulsed-field gel electrophoresis results indicated 10 different clones (A-J), including eight major groups and two separate isolates, with more than 80% band profile similarity among the 69 isolates. The largest group among these clones was group D, with 23 isolates. Seven subtypes were detected within group D (D1-D7). Group F was the second largest group, with 16 isolates and nine subtypes (F1-F9). Group C included seven isolates and seven subtypes (C1-C7); group E had three isolates and three subtypes (E1-E3); group G comprised five isolates and three subtypes (G1-G3); group H had three isolates and three subtypes (H1-H3); group I included five isolates and four subtypes (I1-I4), and group J comprised five isolates and four subtypes (J1-J4). The dendrogram obtained through the pulsed-field gel electrophoresis analysis is presented in Figure 1.



İsolate	Clinics	Date	PFGE type
323	Pediatric İntensive Care Unit	9.3.2011	A
333	Pediatric İntensive Care Unit	30.4.2011	B
176	Pediatric İntensive Care Unit	2.9.2010	C1
316	Neonatal İntensive Care Unit	15.2.2011	C2
328	Pediatri	7.3.2011	C3
128	Neonatal İntensive Care Unit	30.7.2010	C4
301	Pediatric İntensive Care Unit	16.7.2010	C5
326	Burn Unit	14.03.2011	C6
338	Pediatric İntensive Care Unit	16.3.2011	C7
166	Pediatric Haemotology	27.9.2010	D1
310	Pediatric Intensive Care Unit	20.12.2010	D1
102	Pediatri	20.07.2010	D2
109	Pediatric Intensive Care Unit	2.8.2010	D2
111	Pediatric Surgery ICU	24.7.2010	D2
148	Pediatric Intensive Care Unit	8.8.2010	D2
185	Pediatric Intensive Care Unit	14.9.2010	D2
197	Pediatric Surgery ICU	2.8.2010	D2
199	Burn Unit	25.10.2010	D2
311	Pediatric Intensive Care Unit	5.12.2010	D2
340	Pediarti	27.4.2011	D2
346	Burn Unit	9.5.2011	D2
151	Pediatric Haemotology	19.9.2010	D3
325	Pediatric Intensive Care Unit	3.3.2011	D3
305	Pediatric Intensive Care Unit	16.5.2010	D3
321	Pediatric Surgery ICU	21.02.2011	D3
332	Pediatric Intensive Care Unit	9.3.2011	D4
334	Pediatric Intensive Care Unit	15.3.2011	D4
335	Burn Unit	14.3.2011	D4
317	Pediatric Intensive Care Unit	28.3.2010	D5
318	Pediatric Intensive Care Unit	14.2.2011	D5
342	Burn Unit	27.9.2010	D6
302	Neurosurgery ICU	9.5.2010	D7
345	Pediatri	4.5.2011	E1
348	Pediatric Oncology	3.10.2011	E2
351	Plastic and Reconstructive Surgery	7.9.2011	E3
195	Pediatric Intensive Care Unit	13.7.2010	F1
337	Pediatric Intensive Care Unit	2.8.2010	F2
179	Pediatric Intensive Care Unit	3.5.2010	F3
180	Pediatric Haemotology	18.9.2010	F3
181	Pediatric Oncology	23.9.2010	F3
324	Pediatri	26.02.2011	F3
327	Pediatri	23.8.2010	F3
330	Pediatric Intensive Care Unit	3.9.2010	F3
339	Pediatric Intensive Care Unit	27.3.2011	F4
192	Pediatric Intensive Care Unit	12.9.2010	F5
194	Cardiovascular surgery ICU	1.11.2010	F6
303	Neonatal Intensive Care Unit	3.6.2010	F6
313	Pediatric Intensive Care Unit	20.02.2010	F6
101	Neurosurgery ICU	18.7.2010	F7
331	Neonatal Intensive Care Unit	16.7.2010	F8
307	Reanimation	24.5.2010	F9
125	Pediatric Intensive Care Unit	2.8.2010	G1
149	Neurosurgery ICU	15.8.2010	G1
150	Pediatric Intensive Care Unit	10.8.2010	G1
344	Pediatric Surgery ICU	29.4.2011	G2
341	Pediatri	26.2.2011	G3
329	Pediatric Intensive Care Unit	22.7.2010	H1
349	Burn unit	24.8.2011	H2
350	Pediatric Intensive Care Unit	22.8.2011	H3
354	Cardiovasculer Surgery ICU	5.9.2011	I1
355	Neurosurgery ICU	19.8.2011	I1
352	Pediatric Intensive Care Unit	14.8.2011	I2
356	Pediatric Intensive Care Unit	12.9.2011	I3
357	Pediatric Intensive Care Unit	4.9.2011	I4
306	Pediatri	17.5.2010	J1
312	Burn Unit	20.2.2010	J2
315	Pediatric Intensive Care Unit	12.12.2010	J3
320	Cardiovascular Surgery ICU	20.2.2011	J3
304	Pediatric Intensive Care Unit	2.9.2010	J4

Fig. 1. Pulsed-field gel electrophoresis dendrogram of the isolates included in the study

Our study has demonstrated that different clones may be present within the same hospital units, while the same clones may be present in different units. The clone with the longest lifespan was in group D, and these isolates were first detected in the pediatric intensive care unit and last in the burn unit. This clone has been demonstrated to have persisted in different services in our hospital between 28 March 2010 and 09 May 2011. Also, we have observed that the PFGE type C clone persisted in the pediatric intensive care unit in the period between 16 July 2010 and 16 March 2011.

Discussion

Healthcare-associated infections caused by resistant microorganisms and especially by carbapenem-resistant *A. baumannii* strains have become an important cause of morbidity and mortality in hospitals in recent years[13]. According to the data from the infection control committee of our hospital, *A. baumannii* was the most frequently observed microorganism, with a ratio of 16.34% in terms of the distribution according to the species of the agents isolated from the infections originating in the Intensive Care Units of our hospital during our study.

A prolonged hospital stay, surgical intervention, wounds, previous infections and extended-spectrum antibiotic use, central venous or urinary system catheterization, an intensive care stay, a burn unit stay, parenteral nutrition, mechanical ventilation and shortcomings in the infection control program are the risk factors for healthcare-associated infections caused by *Acinetobacter baumanni*[14-16]. In our study, the most common risk factor was extended-spectrum antibiotic use, which was observed in all of the patients. The other risk factors found in our patients were (in descending order) use of a central venous catheter, mechanical ventilation, an intensive care stay, surgical intervention, total parenteral nutrition, urinary system catheterization, presence of wounds disrupting the integrity of the skin, and a burn unit stay.

Healthcare-associated infections due to *A. baumannii* may involve any site. In most institutions, *A. baumannii* is an increasingly important cause of healthcare-associated pneumonia in the intensive care unit, particularly in patients with ventilator-associated pneumonia, representing between 5% and 10% of the cases[9,17]. *A. baumannii* may lead to healthcare-associated bacteremia and infections of the skin and soft tissue, genitourinary system or intracranial system[2,9,18]. Among the 69 *A. baumannii* isolates in our study, 19 (27.53%) were defined as colonizations. More than half (58%) of the 50 isolates thought to have

Table **I.** The Antibiotics and MIC Values[11]

Antibiotic	MIC	Interpretation
Ampicillin/Sulbactam	≥ 32	Resistant
Piperacillin	≥128	Resistant
Piperacillin/tazobactam	≥128	Resistant
Ceftazidime	≥64	Resistant
Cefoperazone/sulbactam	32	Intermediate-level susceptible
Cefepime	≥64	Resistant
Imipenem	≥16	Resistant
Meropenem	≥16	Resistant
Amikacin	32	Intermediate-level susceptible
Gentamicin	≤ 1	Susceptible
Netilmicin	8	Susceptible
Ciprofloxacin	≥4	Resistant
Levofloxacin	4	Intermediate-level susceptible
Tetracycline	≥16	Resistant
Tigecycline	2	Susceptible
Colistin	≤ 0.5	Susceptible
Trimethoprim/Sulfamethoxazole	≥320	Resistant

Table II. Frequency of the Risk Factors That May Lead to *Acinetobacter baumannii* Infections in the Patients Included in the Study

Risk Factors	Number of patients	%
Underlying disease	49	71.01
Surgical intervention	38	55.07
Wounds on the body	11	15.94
Treatment with extended-spectrum antibiotics	69	100
Central venous catheter	56	81.15
Urinary system catheter	32	46.37
Intensive care stay	48	69.59
Burn unit stay	7	10.14
Total parenteral nutrition	43	62.31
Mechanical ventilation	47	68.11

caused healthcare-associated infections were assessed to be agents associated with ventilator-associated pneumonia. Although this ratio is in correlation with the studies reporting that *A. baumannii* most often leads to healthcare-associated pneumonia, it seems to be higher than the ratios reported in the literature. This higher ratio observed in our patients may be explained by the fact that the majority of our patients were mechanically ventilated or in the ICU. The other infections observed in our patients related to *A. baumannii* were (in descending order) central line-associated bloodstream infections, laboratory-evidenced bacteremia, meningitis, surgical site infections, burn wounds, permanent catheter-related bloodstream infections, infected decubitus ulcers, urinary system infections and rectal abscesses.

As in rest of the world, the *A.baumannii* strains were multi-antibiotic resistant. In a multicenter study conducted in Europe in 1999, susceptibility among the Acinetobacter strains isolated from intensive care units was observed to be greatest to imipenem[19]. Similarly, according to the industry-supported MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) report, which evaluated antibiotic resistance in 490 *Acinetobacter baumannii* isolates collected between 1997 and 2000 from 37 centers in 11 European countries, imipenem and meropenem were the two most effective antibiotics against *A. baumanni,* although resistance was also observed in ratios of 16% and 14%, respectively[20]. However, according to the MYSTIC report dated 2006, the resistance against these two antibiotics had shown a significant increase and reached 40%[21]. Studies supporting these data and observing carbapenem resistance rates

Table III. Types of Infection Caused by the Strains Included in the Study, and Colonization Rates

	Number of patients (n=69)	%
Type of healthcare-associated infection	(n=50; 72.47%)	
Ventilator-associated pneumonia	29	58
Catheter-associated bloodstream infection	6	12
Laboratory-confirmed bloodstream infection	4	8
Meningitis or ventriculitis	3	6
Incisional surgical site infection	3	6
Burn wound infection	2	4
Decubitus ulcer infection	1	2
Catheter-related urinary tract infection	1	2
Gastrointestinal tract infection (rectal abscess)	1	2
Colonization	19	(27.53%)

Table IV. Antibiotic Susceptibility of the Isolates Included in the Study

Antibiotic	Susceptible isolate		Resistant isolate	
	n	%	n	%
Amikacin	24	34.78	45	65.21
Ampicillin/Sulbactam	5	7.57	61	92.42
Ciprofloxacin	6	9.09	60	90.90
Colistin	67	100	0	0
Ceftriaxone	1	1.47	67	98.52
Cefepime	5	7.24	64	92.75
Gentamicin	22	31.88	47	68.11
Imipenem	6	8.69	63	91.30
Meropenem	6	8.69	63	91.30
Levofloxacin	5	7.35	63	92.64
Piperacillin	1	1.49	66	98.50
Piperacillin/tazobactam	5	7.35	63	92.64
Ceftazidime	4	5.79	65	94.20
Cefoperazone/sulbactam	9	13.04	60	86.95
Ticarcillin	3	4.54	63	95.45
Trimethoprim/Sulfamethoxazole	3	4.41	65	95.58
Tetracycline	9	13.43	58	86.56
Tigecycline	56	81.15	13	18.84
Tobramycin	35	53.84	30	46.15

up to 100% have been reported from various geographical regions around the world[22,23,24]. Studies from Turkey have reported carbapenem resistance rates of 78% for imipenem and 71% for meropenem[25,26]. Parallel to these data, our study has also pointed out high rates of imipenem and meropenem resistance, both reaching 91.3%. The carbapenem resistance we observed in the strains isolated from our patients seems to be higher than the ratios reported by other centers in our country. This high resistance against carbapenems may be explained by a number of factors. Firstly, the majority of our subjects were ICU patients. Secondly, all the patients had a history of treatment with extended-spectrum antibiotics. And finally, they were frequently hospitalized patients due to other underlying diseases.

The high carbapenem resistance observed in *Acinetobacter baumannii* has led to a search for new treatment options. Certain studies have reported a 97-98.5% susceptibility to colistin[27-30]. On the other hand, some studies have reported no resistance to colistin[25,31,32], while a study from our country has reported a 12.1% resistance[33]. In different studies, the resistance rates to tigecycline varied from 5 to 78%[34-37]. In a study that evaluated 492 carbapenem-resistant *Acinetobacter baumannii* isolates from various regions in the world, including Turkey, susceptibility to tigecycline and minocycline was reported to be over 80%, although the susceptibility to other antibiotics was low (38%). As observed in these studies, the antibiotics with the lowest resistance rates for the treatment of multiresistant *Acinetobacter baumannii* infections are colistin and tigecycline[34-37]. In line with the literature, our study has also shown high resistance rates to other antibiotics, while the resistance to tigecycline was only 18.84%, and no colistin resistance was observed in any of the strains.

Numerous publications have reported the phenotypic and genotypic features of the strains isolated during epidemics. The most common method currently used for the genotyping of *A. baumannii* is pulsed-field gel electrophoresis (PFGE). Although certain clones are present with widespread dissemination, isolates of *A. baumannii* from hospitals in the same country—or even from a single hospital—may show significant genetic diversity[12, 24,31,39-45].

Our study also revealed that many different PFGE genotypes were present during the 1.5 year period. We have determined that clonally related strains can survive for a long time in our hospital and cause healthcare-associated infections at different times. The PFGE molecular typing of the *Acinetobacter baumannii* strains isolated during the 1.5 year period of our study has revealed that the same isolates were found in different units and some isolates persisted in the units for long periods. These findings point to the transmission of infections between the units and a lack of efficient measures for infection control.

In conclusion, it can be claimed that *A. baumannii* plays an important role in healthcare-associated infections, and high antibiotic resistance is observed in this agent. The increasing costs of the morbidity, mortality and treatment related to healthcare-associated infections call for the implementation of infection control strategies. For every center, studying the patient profile, the microorganisms composing the hospital flora together with their resistance patterns, and the distribution and frequency of healthcare-associated infections in each unit will help in developing the right strategies. Pulsed field gel electrophoresis, which is the gold standard among molecular typing methods, should be employed in long-term surveillance in order to prevent healthcare-associated infections, determine the transmission sources and routes of microorganisms, and monitor the spread of these strains throughout the hospital.

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