ORIGINAL REPORT

Antimicrobial Resistance of Nosocomial Strain of *Acinetobacter baumannii* in Children's Medical Center of Tehran: A 6-Year Prospective Study

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Abstract- There are increasing reports of emergence of multiple drug resistant (MDR) *Acinetobacter spp* in the world; however there are a few reports in our country. 145 *A. baumannii* isolates from distinct wards and Children's Medical Center (CMC) in Tehran were studied in order to find the profile of antibiotic resistance among them. 40.6% (59/145) of *A. baumannii* isolates were identified as MDR. Overall susceptibility rates to cotrimoxazole, chloramphenicole and ciprofloxacin were 23.4%, 16.9% and 20.1%, respectively. Frequency susceptibility rates to amikacin, kanamycin, gentamycin and tobramycin decreased gradually from 81.2%, 50%, 50% and 62.5% in 2002 to 25%, 15.6%, 28.1% and 25% in 2007 respectively. Overall susceptibility rates to cephalosporines cephalotin, ceftazidime, cefteriaxon, ceftizoxime and cefixime were 9.3%, 14.7%, 16.2%, 15.9% and 18%, respectively. Susceptibility to carbapenems was assessed only in 2007. The susceptibility rates of Imipenem and meropenem were shown to be 50% and 46.8%, respectively. Our data indicates that MDR *A. baumannii* strains are spreading and carbapenem resistance is becoming more common in Iran. Our findings also highlight the importance of clinicians' access to updated susceptibility data regarding *A. baumannii* in developing countries such as Iran.

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Keywords: Drug resistance, multiple; Acinetobacter baumannii; cross infection

Introduction

Acinetobacter baumannii has emerged as an important nosocomial pathogen and may cause pneumonia, endocarditis, meningitis, and wound and urinary tract infections (1-3). Hospital outbreaks have been described from various geographic areas (4-7), and this organism has become endemic in some of these countries. *A. baumannii* infections are often difficult to eradicate due to high-level resistance to a wide range of antibiotics as a result of both intrinsic and acquired mechanisms (8, 9). Almost 25 years ago, researchers observed acquired resistance of *A. baumannii* to antimicrobial drugs commonly used at that time, among them aminopenicillins, ureidopenicillins, first and second-generation cephalosporins, cephamycins, most aminoglycosides, chloramphenicol and tetracycline (10). In Iran, there is different epidemiological pattern for antimicrobial susceptibility, suggesting differences in the quality of Iranian antimicrobial susceptibility programs in each era. Although, there are increasing reports of emergence of MDR *Acinetobacter* spp in the world (11), there are a few reports from Iran (12-15). The objective of the present investigation was to assess the samples received from 2002 to 2007 in order to find the profile of antibiotic resistance among *A. baumannii* strains isolated from children with nosocomial infections in our country. Knowledge on incidence of MDR Acinetobacter in our country may help physicians to properly treat infections due to MDR *A. baumannii*.

Patients and Methods

Study population and bacterial isolates

Children's Medical Center (CMC) was selected for this investigation. It is the greatest medical center for child-

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ren in Iran, which admits patients from all over the country.

The study included 145 *A. baumannii* isolates from patients with nosocomial infections between 2002 and 2007. All presumptive Acinetobacter isolates, which were oxidase-negative, non-lactose fermentative, and gram-negative diplococci, were identified as *Acinetobacter baumannii* by using the conventional biochemical tests and growth potential at 37˚C and 44˚C. Biochemical tests used for detection of A. baumannii included growth on MacConkey medium, oxidation of glucose, hydrolysis of esculin, decarboxylation of lysine, hydrolysis of arginine, and reduction of nitrate (16).

Antimicrobial susceptibility tests

Antimicrobial susceptibility was determined by the Kirby-Bauer Disk diffusion Agar method according to Clinical Laboratory Standard Institute (previously known as NCCLS) guidelines (17, 18). Bacterial isolation disk diffusion test was performed on Muller-Hinton agar (Oxoid, UK), using an inoculum of 10^5 CFU and disks (Oxoid) of ampicillin (Amp10), cotrimoxazole (SXT_{25}), amikacin (AMK_{30}), kanamycin (KAN_{30}), gentamycin (GEN_{10}), tobramycin (TOB_{10}), cephalothin (CEF_{30}), ceftazidime (CAZ_{30}), ceftriaxon (CRO_{30}), cefixime (CFM_{M5}), ceftizoxime (CAZ_{30}), ciprofloxacin (CIP_5), chloramphenicol (CHL_{30}). Imipenem (IMP_{10}) and meropenem (MER_{10}) were also used only at 2007. Quality control organisms were utilized routinely in the CMS hospital and Department of Microbiology laboratories to ensure accurate performance of the susceptibility tests. Owing to the high risk of nosocomial infections due to *A. baumannii* strains, isolates that showed intermediate susceptibility to an antimicrobial agent were categorized as resistant isolates for data analysis and presentation. We defined *A. baumannii* as MDR, when the organisms were resistant to all studied antimicrobial agents.

Results

Totally, 145 strains were identified as *A. baumannii*, out of which 140 were isolated from patients with more than 72 h of hospitalization (defined as nosocomial infections). Only 5 of them were isolated from outpatients (no nosocomial origin was documented). Sites from which *A. baumannii* was initially isolated included respiratory tract 47/145(32.4%), sterile fluids and catheter tube 36/145 (25%), CSF 28/145(19.3%), blood 24/145(16.5%) and wound 10/145(6.8%). *A. baumannii* was initially isolated from 9 different wards. A high concentration was isolated in 3 wards: Pediatrics ICU (PICU), Infectious disease (I Division) and Neonatal ICU (NICU) with 74/145(51.1%), 25/145(17.2%) and 15/145(10.3%), respectively. Distribution of *A. baumannii* isolates according to dates and hospital wards is shown in Table 1. 40.6% (59/145) of *A. baumannii* isolates were identified as MDR, because showing resistance to all antimicrobial agents used in any given year of this study. Distribution of MDR *A. baumannii* according to samples, wards and dates of isolation are shown in Tables 2 and 3. Susceptibility rates of *A. baumannii* isolates were various in different years. Frequency of susceptibility to ampicillin decreased from 18.7% in 2002 to 3.1% in 2007 (Table 4).

Table 1. Distribution of *A. baumannii* isolates according to date of isolation and hospital wards

Wards*	Date of Isolation						
	2002	2003	2004	2005	2006	2007	Total
I	1	0	5	7	11	1	25
II	0	0	4	0	0	1	5
III	1	2	0	0	2	0	5
IV	5	1	3	1	0	0	10
V	0	0	0	0	1	0	1
VI	2	1	2	0	0	0	5
PICU	6	16	8	1	13	30	74
NICU	0	3	6	4	2	0	15
OPD	1	0	1	1	2	0	5

Abbreviations: **I**: Infectious diseases; **II**: Surgery; **III**: Hematology & Endocrinology; **IV**: Gastrointestinal & Roumatology; **V**: Neurology; **VI**: General Pediatrics; **PICU**: Pediatrics ICU; **NICU**: Neonatal ICU and **OPD**: Outpatients Division.

Table 2. Distribution of multidrug resistant (MDR) A. baumannii according to sample origins, hospital wards and date of isolation between 2002 and 2005

Date of isolation	Sample origin	Hospital ward
2002	Wound	IV
	Respiratory tract	PICU
2003	Wound	PICU
	Catheter	PICU
	Respiratory tract	PICU
	Catheter	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	IV
2004	Respiratory tract	NICU
	Wound	II
	CSF	II
	Sterile fluids	IV
	Wound	NICU
	Respiratory tract	II
	Respiratory tract	NICU
	Wound	I
	Blood	NICU
	Blood	PICU
	Blood	IV
2005	CSF	I
	Respiratory tract	NICU
	Wound	I
	Respiratory tract	NICU
	Respiratory tract	NICU

Abbreviations: **I**: Infectious diseases; **II**: Surgery; **III**: Hematology & Endocrinology; **IV**: Gastrointestinal & Rheumatology; **V**: Neurology; **VI**: General Pediatrics; **PICU**: Pediatrics ICU; **NICU**: Neonatal ICU and **OPD**: Outpatients Division.**MDR:** Organisms were shown resistant phenotype to all studied antimicrobial agents.

Overall susceptibility rates to cotrimoxazole, chloramphenicol and ciprofloxacin were 23.4%, 16.9% and 20.1% respectively. Frequency susceptibility rates to amikacin, kanamycin, gentamycin and tobramycin decreased gradually from 81.2%, 50%, 50% and 62.5% in 2002 to 25%, 15.6%, 28.1% and 25% in 2007 respectively. Among aminoglycosides, overall susceptibility rates ranged from 41.5% to amikacin and 38.4% to tobramycin, respectively. Susceptibility rates to cephalotin, ceftazidime, cefteriaxon, ceftizoxime and cefixime were 31.2%, 50%, 43.7%, 31.2% and 50% in 2001 to 0%, 0%, 9.3%, 18.7% and 0% in 2007, respectively. Overall susceptibility rates to cephalosporines were 9.3%, 14.7%, 16.2%, 15.9% and 18% to cephalotin, ceftazidime, cefteriaxone, ceftizoxime and cefixime, respectively. Susceptibility test for carbapenem antibiotics was performed only in 2007. Imipenem and meropenem were shown susceptibility rates of 50% and 46.8%, respectively (Table 4).

Table 3. Distribution of multidrug resistant (MDR) A. baumannii according to sample origins, hospital wards and date of isolation between 2006 and 2007

Date of isolation	Sample origin	Hospital ward
2006	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	CSF	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	Wound	PICU
	Derange	PICU
	Respiratory tract	PICU
	Respiratory tract	PICU
	CSF	PICU
2007		
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	CSF	PICU
	Respiratory tract	PICU
	Respiratory tract	I
	Respiratory tract	PICU

Abbreviations: **I**: Infectious diseases; **II**: Surgery; **III**: Hematology & Endocrinology; **IV**: Gastrointestinal & Roumatology; **V**: Neurology; **VI**: General Pediatrics; **PICU**: Pediatrics ICU; **NICU**: Neonatal ICU and **OPD**: Outpatients Division. **MDR:** Organisms were shown resistant phenotype to all studied antimicrobial agents.

Table 4. Antimicrobial susceptibility patterns of *A. baumannii* strains isolated from patients with *Acinetobacter baumannii* infections at Children's Medical Center (CMC), Tehran, Iran, between 2002 and 2007

Years	Numbers	Antimicrobial Susceptibility (%)*														
		AMP	SXT	CHL	CIP	AMK	KAN	GEN	TOB	CEF	CAZ	CRO	ZOX	CFM	IMP	MER
2001	16	18.7	31.2	43.7	37.5	81.2	50	50	62.5	31.2	50	43.7	31.2	50	NT**	NT
2002	23	0	37.5	4.3	37.5	37.4	8.6	21.7	30.4	4.3	21.7	4.3	13	30.4	NT	NT
2003	29	10.3	13.7	6.8	13.7	27.5	34.4	24.1	34.4	6.8	3.4	3.4	3.4	10.3	NT	NT
2004	14	14.2	7.1	21.4	7.1	42.8	35.5	50	42.8	7.1	7.1	14.2	7.1	14.2	NT	NT
2005	31	16.1	32.2	19.3	3.2	35.4	25.8	32.2	35.4	6.4	6.4	22.5	22.5	3.2	NT	NT
2006	32	3.1	18.7	6.2	21.8	25	15.6	28.1	25	0	0	9.3	18.7	0	50	46.8
2007	145	10.4	23.4	16.9	20.1	41.5	28.3	34.3	38.4	9.3	14.7	16.2	15.9	18	50	46.8

Abbreviations: *AMP: Ampicillin; SXT: Sulfumetoxazole; CHL: Chloramphenicole; AMK: Amikacin; KAN: Kanamycin; GEN: Gentamicin; TOB: Tobramycin; CEF: Cephalotin; CAZ: Ceftazidime; CRO: Ceftriaxon; ZOX: Ceftizoxime; CFM: Cefixime; IMP: Imipenem; MER: Meropenem. ** No tested. Imipenem and meropenem were used only in 2007.

Discussion

At present, *Acinetobacter spp*., especially *A. baumannii* accounts for a substantial proportion of endemic nosocomial infections. Recent trends indicate increasing antimicrobial resistance of *Acinetobacter* isolates, poising a serious treat to hospitalized patients (19-23).

The spread of antimicrobial resistance among *Acinetobacter spp*., in Iran has emerged as an important challenge for the Iranian medical community. According to global surveillance reports, at present, *Acinetobacter* isolates are the best candidates for the study of antimicrobial susceptibility among microorganisms responsible for nosocomial infections. Unfortunately, data regarding to antimicrobial agents are scarce in Iran and most of Middle East countries. The need for reliable and comprehensive data regarding antimicrobial susceptibility patterns of *A. baumannii* isolates specific to Iran promoted this 6-year investigation. Our data shed light on the the serious problem of antimicrobial resistance among *A. baumannii* isolates in Tehran, Iran.

In present study, more than 50% of *A. baumannii* strains were isolated from pediatric ICU. As shown in other reports, ICUs are high-risk areas for nosocomial infections because of the severity of underlying diseases, the duration of stay and the use of invasive procedures. Surveillance studies have shown that 20-25% of nosocomial infections develop in ICUs in Europe (20).

Our data show that antimicrobial susceptibility rates have been highly decreased between 2002 and 2007among *A. baumannii* isolates. *Acinetobacter* isolates investigated were generally more resistant to antibiotics than those from other regions of the world (21). As shown in Table 3, with the exception of carbapenems, amikacin was relatively the most active antimicrobial agent against most isolates of *A. baumannii* (with susceptibility rate of 41.5%). Aminoglycosides are widely used for the treatment of *Acinetobacter* infection in Iran, but at present, increasing emergence of highly resistant strains causes a major concern in our hospital. Our results on susceptibility rates to aminoglycosides were nearly similar to reports from Latin America. In this SENTRY antimicrobial surveillance program, overall susceptibility rates to amikacin, gentamycin and tobramycin were 34%, 32.9% and 41.5% respectively (22). Resistance to aminiglycosides is relatively common in isolates of *Acinetobacter* among European countries (23). Our results show that the resistance rate to gentamycin in Iran was higher than Belgium and Spain (18% and 0% respectively) and nearly similar to Portugal and France (64% and 66% respectively), (23, 24). Susceptibility rate to amikacin in Iran is in sharp contrast with those from European countries. Susceptibility rates to amikacin in European countries ranged 90% in Portugal to 49% in Spain (23, 24). In the latest European SENTRY study, overall susceptibility rates to tobramycin, amikacin and gentamycin were 60.2%, 58.1% and 43.4%, respectively (25).

Until 1988, quinolones had good activity against *Acinetobacter* strains; however, at now, resistance to these antibiotics has emerged rapidly in clinical isolates (26, 27).

Our results show that only 20.1% of *A. baumannii* isolates were susceptible to ciprofloxacin. We found that susceptibility rates to ciprofloxacin decreased gradually among *Acinetobacter* isolates in Iran as shown in Table 3. These finding was similar to some European countries such as France, Spain and Turkey (with susceptibility

rates of 18%, 10% and 26.4%, respectively) (28-30), but was lower than repots from USA and Canada (39.7% and 72.1% respectively) (31).

Results of our investigation raise more concerns about increasing resistance to β-lactam antibiotics among Iranian *Acinetobacter* isolates. Our findings indicate that overall susceptibility rates to ampicillin and third-generation broad spectrum cephalosporines among *Acinetobacter* isolates were highly decreased in our country. Although cephalosprines used in this investigation, i.e. cefixime and ceftriaxone, were relatively more effective on *Acinetobacter* isolates (susceptibility rates of 18% and 16.2%, respectively), these susceptibility rates were very low. Percentages of susceptibility to cephalosporines in this study were similar to reports from some European countries (31). In this study, susceptibility rate to ceftriaxone was similar to reports from USA, higher than Italy and France, and lower than Germany and Canada (31, 32). In USA, Canada and Germany, ceftazidime has a relatively good effect on *Acinetobacter spp*; however, susceptibility rate to ceftazidime in our study was under 15%. Although we cannot detect resistance genes by molecular methods, high resistance to broad spectrum cephalosporines is suggestive of the presence of extended – spectrum β-lactamase (ESBL).

Carbapenems have become the preferred treatment for serious *Acinetobacter* infections in many centers, and have retained better activity than other antimicrobial agents have. However, the number of reports of carbapenem resistance is growing steadily, which raises concern. Carbapenem resistant *Acinetobacter* isolates are reported worldwide (32, 33).

Although we only tested susceptibility to imipenem and meropenm at 200, we observed highly resistant species to carbapenems in this investigation. Carbapenems have been used in Iran for the last 5 years, but there is some evidence that increased and uncontrolled use of these antibiotics favors the emergence of resistance to these antibiotics. Although we cannot detect resistance to carbapenems genetically, a combination of several mechanisms such as loss of outer membrane proteins, altered PBPs and acquired carbapenemases including class B, A and D β-lactamase (34), may play a role in resistance to carbapenems.

Increased resistance to carbapenems causes a real concern over an imminent threat of untreatable *Acinetobacter* infections. One of the major concerns in treatment of *Acinetobacter* infections is emergence of multidrug and pundrug resistant *Acinetobacter* isolates. Some outbreaks related to MDR *Acinetobacter spp* have been recently described in several countries (22). In this study, 40.6% (59/145) of *A. baumannii* isolates were multidrug resistant. These isolates were resistant to all of antimicrobial agents including cephalosporines and carbapenems. As infection with *A. baumannii* is associated with significantly higher mortalities in critically ill patients, spread of MDR *A. baumannii* strains in our hospitals is more serious in such patients. The real reason for the spread of MDR A. baumannii in our hospital is unknown. Although we were unable to determine the source of these MDR *A. baumannii* strains, we believe that patient -to- patient transmission, transfer of patients between wards and the presence of substational number of undetected carriers may be play a role in spreading and persistence of MDR *A. baumannii* strains in our hospital.

Similar to other reports from USA (31), we found antimicrobial resistance rates in Iran are increasing albeit slowly for most agents. In conclusion, our data indicate that MDA *A. baumannii* strains are spreading and carbapenem resistance is becoming more common in Iran. Our findings also highlight the importance of clinicians' access to updated susceptibility data regarding *A. baumannii* in developing countries such as Iran. Continuous monitoring of changes in *Acinetobacter* resistance will help set national priorities for local intervention efforts in Iran. Our data draws attention to the importance of vigilance of physicians to identify MDR *A. baumannii* during treating patients with nosocomial infections due to *A. baumannii* and underscores the need for devising a national strategy to control the spread of MDR *A. baumannii* in Iran. Regarding the paucity of reports on updated susceptibility data about *Acinetobacter spp*. in Iran, we believe that our findings are in concert with other data from all regions of Iran and the Middle East. This will further strengthen the reliability of ongoing global surveillance program in developing countries. In addition, we believe that our data regarding MDR *A. baumannii* in Iran will encourage attempts to fight against the spread of these strains worldwide.

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