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Increasing resistance of nosocomial *Acinetobacter baumannii*: are we going to be defeated?

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Aim: To investigate the change of the antibiotic resistance profiles of the nosocomial *Acinetobacter baumannii* isolates in intensive care units (ICUs) between the years 2008 and 2011.

Materials and methods: *A. baumannii* isolates that were responsible for ICU-acquired nosocomial infections between 2008 and 2011 were included in the study. The susceptibility rates of the antibiotics that are mainly used in the treatment of *Acinetobacter* infections were compared by years. Clinical and Laboratory Standards Institute criteria were used to determine antimicrobial susceptibility.

Results: There were 252 infection episodes detected in 229 hospitalized patients in the ICU that were caused by *A. baumannii*. Imipenem resistance was found as 98.9% in 2011 whereas it was 54% in 2008. A significant increase was observed for meropenem resistance from 2008 (73.5%) to 2011 (98.9%). Colistin resistance, confirmed by E-test, was found in 4 strains. The resistance rates of other antimicrobial agents were as follows: ampicillin/sulbactam 95.7% and 93.5%, cefoperazone/sulbactam 45.7% and 90.3%, netilmicin 41.7% and 53%, gentamicin 96% and 87.2%, and trimethoprim-sulfamethoxazole 91.7% and 72%, in 2008 and 2011, respectively. The resistance rate to tigecycline increased to 81.3% in 2011 from 12.5% in 2008.

Conclusion: The increasing resistance rates to carbapenems and developing resistance to colistin are making the situation more serious and complicated.

Key words: *Acinetobacter*, resistance, carbapenem, nosocomial

1. Introduction

There are problems regarding treatment approaches to *Acinetobacter* spp. in clinical practice because of their increasing resistance rates (1). The resistance rate to the antibacterial agents differs between hospitals. This is why it is important to know the resistance trends of specific microorganisms causing problems for each hospital, so as to apply an appropriate treatment protocol. The aim of this study was to investigate nosocomial infections caused by *A. baumannii* in the intensive care units (ICUs) of Atatürk Training and Research Hospital and determine resistance rates by years.

2. Materials and methods

Infections due to *A. baumannii* that were diagnosed and treated in ICUs of Atatürk Training and Research Hospital were evaluated.

2.1. Settings and patients

Atatürk Training and Research Hospital has 550 beds and 4 ICUs: reanimation, coronary, cardiovascular, and neurosurgery-neurology. The number of the ICUs' beds was 36 in 2008 and this increased to 52 in 2011. Patients treated for more than 48 h in these ICUs and diagnosed with nosocomial infection caused by *A. baumannii* between 2008 and 2011 were included in the study.

2.2. Surveillance and infection diagnosis

Active prospective patient-based surveillance was conducted by infection control nurses in the study period as a part of the National Nosocomial Infection Surveillance Program. Centers for Disease Control and Prevention (CDC) criteria were used for nosocomial infection diagnosis (2–5). In patients assisted by mechanical ventilation, pneumonia was diagnosed when a new or progressive infiltrate or consolidation was found on chest

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X-ray in the presence of purulent tracheal secretions, supported by a growth of ≥10^5 CFU/mL bacteria in a quantitative culture of deep endotracheal aspirate. For nonventilated patients, the diagnosis of nosocomial pneumonia was considered when they had a compatible chest X-ray and purulent sputum, with Gram staining and sputum culture documenting the presence of a pathogenic microorganism. Bacteremia was diagnosed by these criteria: a recognized pathogen cultured from 1 or more blood cultures or fever (>38 °C), chills or hypotension, and the presence of at least 1 of the following: 1) common skin contaminants (diphtheroids, *Bacillus* spp., *Propionibacterium* spp., coagulase-negative *Staphylococci*, or *Micrococcus* spp.) cultured from 2 or more blood cultures drawn on separate occasions, and 2) common skin contaminants cultured in at least 1 blood culture from patients with central line catheters already undergoing antibiotic therapy. A urinary tract infection in a patient with an indwelling bladder catheter was diagnosed with the detection of pyuria (≥10 leukocytes/mm^3), growth of ≥10^5 CFU/mL bacteria (no more than 2 species) in urine culture, and clinical signs of infection (fever of ≥38 °C, leucocytosis, abnormal macroscopic appearance of urine, presence of urinary nitrites). Other site-specific infections were diagnosed based on the CDC criteria (2–5).

2.3. Microbiological identification and resistance determination

The strains of *A. baumannii* were identified and defined through use of Gram staining, oxidase test, and half-automatized BBL crystal kits according to the manufacturer's recommendations. Consecutive isolates in the same nosocomial infection episode were excluded from the study. Susceptibility testing was done using the Kirby–Bauer disk diffusion method according to Clinical Laboratory Standards Institute (CLSI) criteria (6).

Ampicillin/sulbactam (241/252), amikacin (246/252), gentamicin (248/252), netilmicin (183/252), tobramycin (243/252), trimethoprim/sulfamethoxazole (242/252), cefotaxime (242/252), ceftazidime (234/252), ciprofloxacin (243/252), ticarcillin/clavulanate (199/252), piperacillin/tazobactam (247/252), cefepime (229/252), cefoperazone/sulbactam (221/252), imipenem (251/252), and meropenem (247/252) susceptibility testing was performed on most *A. baumannii* isolates. Doripenem (9/252), tigecycline (145/252), and colistin (139/252) susceptibility testing was performed only on multidrug-resistant *Acinetobacter* isolates.

Colistin susceptibility was performed with 10-µg colistin disks and isolates were considered susceptible to colistin if inhibition zones were ≥11 mm, as recommended by the CLSI for *Pseudomonas aeruginosa*. E-test or microdilution was performed as a confirmatory test for strains found resistant to colistin in the disk diffusion method. For tigecycline susceptibility, the FDA clinical minimum inhibitory concentration (MIC) breakpoints for Enterobacteriaceae (<2 mg/L, sensitive) were used. Cefoperazone/sulbactam susceptibility was analyzed via the disk diffusion test; CLSI criteria for susceptibility breakpoints for cefoperazone were used (6). The susceptibility rates of antibiotics were compared by year from 2008 to 2011.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 11.5 (SPSS Inc., Chicago, IL, USA). The statistical significance was set as $P < 0.05$. Pearson's chi-square test was used to compare categorical variables.

3. Results

A total of 252 infection episodes due to *A. baumannii* were detected in 229 patients during the study period. Nineteen patients had 2 or more infection episodes. Most infection episodes were diagnosed in the reanimation ICU. This unit was followed by the neurosurgery-neurology ICU (Table 1). When data were evaluated according to infection site, the ranking and distribution of *Acinetobacter* infections were as follows: ventilator-associated pneumonia (76.7%), catheter-related blood-stream infection (12.3%), and primary bacteremia (7.9%) (Table 2). The resistance rate to imipenem increased to 98.4% in 2011 from 54.0% in 2008. The resistance rate of meropenem increased, as

Table 1. *Acinetobacter baumannii* infections according to ICU types and years.

ICU	2008 (%) n = 50	2009 (%) n = 52	2010 (%) n = 55	2011 (%) n = 95
Reanimation	56	53.8	50.9	87.4
Neurosurgery-neurology	36	40.4	38.2	NA
Cardiovascular surgery	6	1.9	3.6	8.4
Coronary	2	3.8	7.3	4.2

ICU: intensive care unit. NA: not available (neurosurgery-neurology ICU was transferred to the reanimation ICU).

Table 2. Nosocomial *Acinetobacter baumannii* infections according to infection site.

Infection site	2008	2009	2010	2011
VAP	39	39	42	67
Primary bacteremia	0	5	7	8
Catheter related bloodstream infection	6	5	3	17
Soft tissue infection	3	1	0	2
Pneumonia	1	0	1	0
Urinary tract infection	0	2	1	1
Meningitis	1	0	1	0
Total (n = 252)	50	52	55	95

VAP: Ventilator-associated pneumonia.

well (73.5% in 2008, 98.9% in 2011). The resistance rates of other antimicrobial agents were as follows: ampicillin/sulbactam 95.7% and 93.5%, netilmicin 41.7% and 53%, cefoperazone/sulbactam 45.7% and 90.3%, and tobramycin 54.2% and 68.1%, in 2008 and 2011, respectively. The resistance rate to tigecycline increased to 81.3% in 2011 from 12.5% in 2008 (Table 3). Colistin resistance was found in 4 *A. baumannii* strains by E-test.

Table 3. Resistance rates of *Acinetobacter baumannii* by years.

Antibiotic	2008	2009	2010	2011	P*
Ampicillin/sulbactam (n = 241)	95.7	97.9	90.6	93.5	0.72
Amikacin (n = 246)	88	84.6	81.8	84.2	0.27
Gentamicin (n = 248)	96	76.5	66	87.2	0.14
Netilmicin (n = 183)	41.7	52.1	57.6	53	0.37
Tobramycin (n = 243)	54.2	54	46.3	68.1	0.15
Trimethoprim/sulfamethoxazole (n = 242)	91.7	85.4	73.6	72	0.013**
Cefotaxime (n = 242)	98	100	98	97.8	1.0
Ceftazidime (n = 234)	100	97.8	97.9	98.9	1.0
Ciprofloxacin (n = 243)	98	100	96.2	97.8	1.0
Ticarcillin/clavulanate (n = 199)	97.9	100	97.1	98.5	1.0
Piperacillin/tazobactam (n = 247)	91.7	100	98.1	98.9	0.045
Cefepime (n = 229)	97.6	100	100	96.8	1.0
Cefoperazone/sulbactam (n = 221)	45.7	88.4	78	90.3	0.000
Imipenem (n = 251)	54	92.3	94.4	98.9	0.000
Meropenem (n = 247)	73.5	98	94.4	98.9	0.000
Doripenem (n = 9)	NA	NA	NA	100.0	NA
Tigecycline (n = 145)	NA	12.5	34.8	81.3	0.000
Colistin (n = 139)	NA	NA	NA	2.9	NA

*: The resistance rates in 2008 were compared to the resistance rates in 2011 for antibiotics except tigecycline. For tigecycline, 2009 resistance rates were compared to those of 2011.
**: This decrease in the resistance rates was found to be significant statistically.
NA: not available.

4. Discussion

Acinetobacter species have not been accepted as etiologic agents because of their low pathogenicity, even though they were isolated from clinical specimens half a century ago. However, currently this microorganism is responsible for nosocomial infections causing high morbidity and mortality rates, especially in ICUs. Recently, a high resistance rate to carbapenems has led to the increased use of polymyxins for treatment purposes. Unfortunately, resistance to polymyxin, which is often the only treatment option, is now being reported (7).

Acinetobacter multiresistance is identified in 2 ways: either as carbapenem resistance or as resistance to 3 different classes of antibiotics. Carbapenem resistance mechanisms in *Acinetobacter* species can be listed as follows: metallo-beta-lactamases, similar to IMP, VIM, SIM, NDM-1, and NDM-2; oxacillinases, such as OXA-23, OXA-24, OXA-58, and OXA-51; decrease in PBP-2 expression due to changes in PBP; and changes in outer membrane proteins. The most worrying resistance mechanism is that of carbapenemase activity among beta-lactamases, because resistance determinants can be found through plasma or transposons and transferred laterally among bacteria (7).

Imipenem resistance was found to be 54% in 2008 and 98.9% in 2011 in our study. Meropenem resistance was detected as 78.5% and 98.5% in the same years. The difference in the resistance rates was found to be statistically significant for each carbapenem (Table 3). Greatly increased carbapenem resistance rates have been reported recently in south European countries such as Turkey. A multicenter study, including 43 centers from North America, 30 centers from 14 European countries including Israel and Turkey, 10 centers from 4 countries in Latin America, and 74 countries from the Asia-Pacific region, has been recently published. Imipenem resistance and colistin resistance were reported as 40.3% and 0.9% in this study, which included 4686 *Acinetobacter* spp. that were isolated in the years between 2006 and 2009. When the regions were evaluated separately, imipenem resistance increased to 54.9% in 2011 from 35.3% in 2006 for the 14 European countries including Israel and Turkey (8). Resistance rates of imipenem and meropenem were found as 12.6% and 12% in the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Europe 2007 Study, including 166 *Acinetobacter* spp. from 28 centers in 8 European countries. The low resistance rates were explained by there being no data from south European countries (9). According to the Turkish data included in the MYSTIC study, imipenem and meropenem resistance rates were 51% and 45%, respectively, for 779 *Acinetobacter* spp. from 9 centers for the years between 2002 and 2003 (10). In 2 studies from Turkey, the imipenem resistance rate among *A. baumannii* strains was found as 57.1% by Akıncı et al. between June 2005 and October 2006 and 73% by Alp et al. between December 2004 and January 2006 (11,12). There are 4 studies from Turkey that included *Acinetobacter* spp. isolated in 2008, and the resistance rates of imipenem were reported as being between 62% and 94.6% (13–16). Meropenem resistance was evaluated in 3 of these 4 studies and it was reported as 91.1% by Dizbay et al., 63.7% by Mansur et al., and 85.2% by Candevir et al. (13,14,16). In another study performed at the Konya Education and Research Hospital, imipenem resistance was reported as 50% in 2008 and 83% in 2010 (17). The imipenem resistance rate was found as 91.7% in the *Acinetobacter* isolates that were responsible for ventilator-associated pneumonia between January 2009 and January and March 2011 by Tasbakan et al. (18). When compared to other studies, the lower resistance rates in our hospital in 2008 may be related to the fact that patients have only been admitted to ICUs since the beginning of 2007. However, it is difficult to compare these rates without "defined daily dosage" data for each hospital.

In the cephalosporin group, the resistance rate of cefoperazone/sulbactam was found to be higher than the previous rates (45.7% in 2008 versus 90.3% in 2011). The difference was statistically significant. In a study performed in Turkey by Dizbay et al., the cefoperazone/sulbactam resistance rate was detected as 77% in the 2008 isolates (13). The resistance rate of cefoperazone/sulbactam was reported as 63.9% for *Acinetobacter* spp. isolated between 2009 and 2011 by Tasbakan et al. and 73.6% isolated in 2009 by Çevik et al. (18,19). Sulbactam seems to be a potential alternative agent in the treatment of multidrug-resistant *Acinetobacter* infections due to the intrinsic activity against these isolates (20–22). However, there is no well-controlled clinical study proving this effect in the published English literature. It is not possible to comment with any certainty about cefoperazone/sulbactam resistance because no defined criteria have been determined by the CLSI for these agents. The resistance rate for sulbactam could not be evaluated because sulbactam was not available as a single agent in Turkey during the study period.

The resistance rates of cefepime and ampicillin/sulbactam decreased to 96.8% and 93.5% in 2011 from 97.6% and 95.7% in 2008. We thought that this may be related to infrequent usage of these antibiotics in the treatment of ICU-acquired infections due to high resistance rates.

When we evaluated aminoglycosides, there was no significant difference in the resistance rates for amikacin and gentamicin by year, but the resistance rates of tobramycin and netilmicin rose. However, this increase was not found to be statistically significant. The resistance

rate of netilmicin was reported as 24.9% in a study performed by Özdemir et al. (15). Tasbakan et al. reported a 54.2% netilmicin resistance rate in the isolates that were the responsible agents of ventilator-associated pneumonia between 2009 and 2011 (18). The resistance rate was reported as 71% in another study performed by Mansur et al. (14).

The resistance rates to amikacin and gentamicin decreased in 2011 in comparison with 2008. Netilmicin was preferred over other aminoglycosides due to the increasing resistance rates of *Acinetobacter* infections. This may explain the decreasing resistance rates to amikacin and gentamicin and the increasing resistance to netilmicin. The resistance rate to trimethoprim/sulfamethoxazole decreased to 72% in 2011 from 91.7% in 2008. The difference in the resistance rates was statistically significant ($P < 0.05$). The reason for this difference may be related to the low usage rate of trimethoprim/sulfamethoxazole to treat ICU-acquired infections. Trimethoprim/sulfamethoxazole could be an alternative, or additional, agent in the treatment of pan-drug–resistant *A. baumannii* infections.

The other alternative antimicrobial agent in the treatment of infections due to multidrug-resistant *Acinetobacter* spp. is tigecycline. Tigecycline has been used since 2007 and resistance to this antibiotic developed rapidly in our hospital (Table 3). We think that this situation may be due to the intensive usage of tigecycline in the treatment of nonapproved indications, such as nosocomial pneumonia, because of the limited availability of colistin until 2010 (23). The tigecycline resistance rates were reported as 0.9% and 0% in the studies performed by Özdemir et al. and Mansur et al. in 2008 (14,15). Kurtoğlu et al. reported 12% and 21% resistance rates in 2009 and 2010, respectively (17). Similar rates were found in our study for the same years.

There is not a high resistance to colistin in Turkey, and there is only one published case of colistin-resistant *A. baumannii* from Turkey (24). Because of this, colistin susceptibility was performed via disk diffusion method and E-test as a confirmatory method, although it was not recommended by the CLSI. A total of 4 isolates were found to be colistin-resistant, and these were confirmed by E-test. The pathogenesis of emerging resistance in *Acinetobacter* is not well identified. In a recent study it was shown that loss of lipopolysaccharide (LPS) production can cause this resistance without previous colistin usage (25). In another report, mechanisms were defined as mutations in 2 genes that constitute a 2-component system (PmrAB) involved in the modification of lipid A, the major constituent of LPS membranes, and mutations, deletions, or insertions in genes essential for the synthesis of lipid A (26). Colistin resistance among *Acinetobacter* strains, especially in *A. baumannii*, is increasing. In different parts of the world such as France (26), Argentina (27), Spain (28), Kuwait (29), and India (30), colistin-resistant *Acinetobacter* strains have been identified. There has been only one case of colistin-resistant *Acinetobacter* infection reported from Turkey (24).

In conclusion, there is a continuing problem regarding infections due to *A. baumannii* in our hospital and in Turkey. The increasing resistance rates to carbapenems and developing resistance to colistin are making the situation more serious and complicated.

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