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Antibiotic sensitivity pattern and multidrug resistance Index in *Acinetobacter baumannii* among clinical isolates in, Denizli

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Abstract
To determine the level of resistance to the widely used antibiotics in clinical isolates of *Acinetobacter baumannii* 48 isolates were collected from special hospital in Denizli and recorded at specimens. Antibiotic resistance was determined by agar disc diffusion method using Mueller-Hinton agar according to Clinical and Laboratory Standards Institute recommendations. All isolates were determined as amikacin and colistin sensitive. The sensitivity rates for Trimetroprim /sulfametaksazol, gentamicin,, and meropenem were 75%, 50%, 31% and 30%, respectively. All of 48 isolates, 3 (100%) isolates showed Multiple Antibiotic Resistance four to twelve antibiotics.

Keywords: *Acinetobacter baumannii*, antibiotic resistance, clinical isolates

Introduction
Members of the genus Acinetobacter have emerged from organisms of questionable pathogenicity to pan resistant nosocomial pathogens worldwide in the past two or three decades (Munoz-Price and Weinstein, 2008) [1]. There are more than 30 genomic types of Acinetobacter identified so far, of which more than two third of Acinetobacter infections are due to *Acinetobacter baumannii*. *A. baumannii* colonizes healthy humans transiently at a low density on the warm and moist skin of axilla, groin, between toes, throat, nares and intestinal tract but it generally does not cause infection (Young *et al*., 2007) [2].
A. baumannii causes different nosocomial infections, including bacteremia, urinary tract infection and secondary meningitis, but it has a significant role in the development of pneumonia, especially the pneumonia caused by upper respiratory tract of patients in intensive care units. Several studies such as Bassetti *et al*. (2008) [3] showed that more than 80% of *A. baumannii* isolated from patients, become resistant against the most of the prescribed antibiotics. The studies of) some researchers revealed that the different strains of *A. baumannii* were resistant to the majority of consumed antibiotics (Leung *et al*. (2006) [4] Michalopoulos and Falagas, 2010) [5]. Multidrug-resistant *A. baumannii* (MDR *A. baumannii*) is resistant to more than two antimicrobial classes such as anti pseudomonal cephalosporins, anti pseudomonal carb apenems, β-lactam/β-lactamase inhibitors, aminoglycosides, and fluoroquinolones.
The aim of this study was to determine the characteristics and patterns of antibiotic resistance among isolates of *A. baumannii* recovered from clinical specimens in Denizli.

Materials and Methods
Microbiological analyses and antibiotic susceptibility testing Bacterial Isolates
48 *A. baumannii* were isolate from clinical samples in Denizli. Bacterial isolates were identified to level of species and subspecies by using the morphological and traditional biochemical tests according to standard methods described by (Holt *et al*, 1994; Macfaddin, 2000) [6, 7]. The isolates are defined as the agent of hospital acquired infections, if they emerged after 72 hours of hospitalization. All isolates were obtained from patients at intensive care units. In total, 48 *A. baumannii* were isolated from various clinical samples and detected by the VITEK 2 Compact system (Bio Merieux, France) at the microbiology laboratory of our hospital between from September to October 2015.

Antibiogram Pattern of *Acinetobacter baumannii*
Antibiotic resistance was determined by an agar disc diffusion test (Bauer *et al*., 1966) [8] using Mueller-Hinton agar (Difco) according to Clinical and Laboratory Standards Institute (CLSI) recommendations (CLSI., 2005) [9]. Fourteen different antibiotics were used. For antibiotic resistance determination, the isolates were grown in Luria-Bertani (LB) broth until the turbidity equal to the 0.5 Mc Farland standart (approximately 108cfu/ml). Cultures were swabbed on to the Mueller–Hinton agar and all isolates were tested against. Amikacin (AN, 30µg/ml), Colistin (CS, 10µg/ml), Sulfamethaxol/ trimetroprim (SXT, 25µg/ml), Gentamicin (GEN, 10µg/ml), Meropenem (MEM, 10µg/ml), Imipenem (IPM,10µg/ml), Ceftazidime (CAZ, 10µg/ml), Tazobactam/ piperacillin (TZP,30µg/ml), Ciprofloxacin (CIP, 5µg/ml), Cefepime (FEP, 30µg/ml), Ampicillin (AMP,10µg/ml), Cefuroxime (CFX30µg/ml), Cefazolin (CEF 30µg/ml). The isolates those grown in inoculation were evaluated as resistant and the others were evaluated as susceptible. The antibiotic discs were dispensed sufficiently separated from each other so as to avoid overlapping of inhibition zones. The plates were incubated at 37°C, and the diameters of the inhibition zones were measured after 18 hr. All susceptibility tests were carried out in duplicate and were repeated twice if discordant results had been obtained.

Multiple Antibiotic Resistance Index

For all isolates, we calculated the MAR index values (a/b, where a represents the number of antibiotics the isolate was resistant to, b represents the total number of antibiotics the isolate tested against). A MAR index value ≥ 0.2 is observed when isolates are exposed to high risk sources of human or animal contamination, where antibiotics use is common; in contrast a MAR index value <or = 0.2 observed when antibiotics are seldom or never used (Krum perman, 1985; Matyar *et al*., 2008) [11, 10].

Results and Discussion

The results of the antibiotic susceptibility of the isolates are shown in Table 1. The antibiotic susceptibility was determined by the disc agar diffusion method in accordance with the instructions of the antibiotic disc manufacture (Oxoid). The number of isolates are shown in Figure 1.

All isolates were determined as amikacin and colistin sensitive. The sensitivity rates for, Trimetroprim/ sulfametaksazol, gentamicin, and meropenem were 75%, 50%, 31% and 30%, respectively.

Table 1: Antibiotic suspectibility pattern of *A.baumannii i*solated from clinical samples

Antibiotics	Sensitive	Resistance	Intermediate
AN	48(100%)	0(0%)	0 (0%)
CS	48(100%)	0(0%)	0 (0%)
SXT	36 (75%)	8(17%)	4(8%)
GEN	24 (50%)	24(50%)	0(%0)
MEM	15(31%)	29(60%)	4 (8%)
IPM	9 (19%)	18 (%38)	21 (%44)
CAZ	8(17%)	38 (79%)	9(8%)
TZP	5(10%)	35 (73%)	8 (17%)
CIP	5(10%)	43 (90%)	0 (0%)
FEP	1(2%)	35 (73%)	8 (17%)
CFT	1(2%)	47(98%)	0 (0%)
AMP	0 (0%)	48(100%)	0 (0%)
CFX	0 (0%)	48(100%)	0 (0%)
CEF	0 (0%)	48(100%)	0 (0%)

Abrevations; AN; Amikacin, CS; Colistin, SXT; Sulfamethaxol/ trimetroprim, GEN; Gentamicin, MEM; Meropenem, IPM; Imipenem, CAZ; Ceftazidime, TZP; Tazobactam/ piperacillin, CIP;Ciprofloxacin, FEP; Cefepime, CFT; Ceftriaxon, AMP; Ampicillin, CFX; Cefuroxime, CEF; Cefazolin.

In our study, among the aminoglycosides, sensitivity to Amikacin was seen in 100% of the isolates. Some researchers have reported Amikacin sensitivity rate to *A.baumannii* in clinical samples (Lõivukene *et al*.,2006; Ozdemir *et al*.,2009; Hassan *et al*.,2010; Kurtoglu *et al*.,2011;Iraz *et al*.,2012; Mirnejad and Vafaei., 2013; Uludag-Altun *et al*.,2014; Ece *et al*.,2014; Celik *et al*.,2014; Atasoy *et al*.,2014; Guven *et al*.,2014; Direkel *et al*., 2015; Ahmed *et al*.,2015; Guckan *et al*.,2015) [12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26]. In a study that performed by Hoe Koo *et al* in years 2007 to 2008, they determined amikacin as the most effective drug among nine antimicrobial agents, like, in this study (Hoe Koo *et al*., 2010) [27]

Colistin sensitivity was seen in 100% isolates in our study. Colistins are the most common polymyxin derivatives used in clinical practice. These antibiotics are effective against many gram negative bacterium including *Acinetobacter* types *P.aeruginosa*, *Klebsiella* and *Enterobacter* (Nordmann *et al*.,. 2009) [28]. While Ozdemir *et al*.(2009) [13], Somily *et al*.,(2012) [29], Ece *et al*.,(2014) [20] and Gozutok *et al*. (2013) [30] determined 100% sensitive to colistin like our results, Iraz *et al*. (2012) [16] determined a resistance rate of 1% and Dogan *et al.* (2014) [17] a resistance of 1.4%.

Our rate of trimetroprim /sulfametaxazol sensitivity was 50%. Some researchers have reported trimetroprim /sulfametaxazol sensitivity rate to *A.baumannii* in clinical samples (Lõivukene *et al*.,2006; Celik *et al*.,2014; Guven *et al*.,2014;Direkel *et al.,* 2015; Guckan *et al*.,2015;; Mughis *et al*.,2015) [12, 21, 23, 26]. Our results were similiar to Mayasari and Siregar (2014) [32] who also reported sensitivity to trimetroprim /sulfametaxazol was 51.5%.

We found that 31% isolates were sensitive to Meropenem in our study. Some researchers have reported Meropenem sensitivity rate to *A.baumannii* in clinical samples (Gazi *et al*.,2005; Somily *et al*.,2012; Mirnejad and Vafaei., 2013; Gozutok *et al*. 2013; Atasoy *et al*.,2014; He *et al*.,2014; Celik *et al*., 2014; Uludag-Altun *et al*.,2014; Ece *et al*.,2014; Guven *et al*.,2014; Guckan *et al*.,2015; Ahmed *et al*.,2015) [33, 29, 18, 30, 22, 34, 21, 19, 20, 23, 26, 31]. In a study that in year 1998 to 2001 was conducted by Karlowsky *et al*., 90% of *A. baumannii* strains were sensitive to meropenem, but in this investigation, only 31% of strains showed resistance to meropenem(Karlowsky *et al*., 2003) [35].

Our rate of Imipenem sensitivity was 19%. Some researchers have reported Imipenem sensitivity rate to *A.baumannii* in clinical samples (Lõivukene *et al*.,2006; Somily *et al*.,2012; Mirnejad and Vafaei., 2013; Gozutok *et al*. 2013; He *et al*.,2014; Atasoy *et al*.,2014; Tunyapanit *et al*., 2014; Celik *et al*., 2014; Guven *et al*.,2014; Ahmed *et al*.,2015; Mughis *et al*., 2015; Yadegarynia *et al*.,2015; Direkel *et al.,* 2015) [12, 29, 18, 30, 34, 22, 36, 21, 23, 31, 37, 24]

Our rate of ceftazidime sensitivity was 17%. Some researchers have reported ceftazidime sensitivity rate to *A.baumannii* in clinical samples (Karsligil *et al*.,2004; Javed *et al*.,2012; Sieniawski *et al*.,2013; Guven *et al*.,2014; Celik *et al.,* 2014; He *et al*.,2014; Guckan *et al*.,2015; Mughis *et al*.,2015; Yadegarynia *et al*.,2015) [38, 42, 39, 23, 21, 34, 26, 37]. Our results were similiar to Karsligil *et al* (2004) [38] who also reported sensitivity to ceftazidime was 19%.

Our rate of Piperacillin/Tazobactam sensitivity was 10%. Some researchers have reported Piperacillin/Tazobactam sensitivity rate to *A.baumannii* in clinical samples (Huang *et al*., 2007; Hassan *et al*.,2010; Al-Mously and Hakawi.,2013; Mirnejad and Vafaei., 2013; Gozutok *et al*. 2013; Javed *et al*.,2012; Sieniawski *et al*.,2013; Guven *et al*.,2014; Celik *et al.,* 2014; He *et al*.,2014; Direkel *et al.,* 2015; Ahmed *et al*.,2015) [40, 14, 44, 18, 30, 42, 39, 23, 21, 34, 24, 31]. Our results were similiar to Ahmed *et al* (2015) who also reported sensitivity to Piperacillin/Tazobactam was 9%.

Our rate of ciprofloxacin sensitivity was 10%. Some researchers have reported ciprofloxacin sensitivity rate to *A.baumannii* in clinical samples (Karsligil *et al*.,2004; Huang *et al*., 2007; Sheth *et al*.,2012; Javed *et al*.,2012; Mushtaq *et al*.,2013; Gozutok *et al*. 2013; Hakawi.,2013; Atasoy *et al*.,2014; Al-Mously and; Celik *et al.,* 2014; Ece *et al*.,2014; He *et al*.,2014; Sieniawski *et al*.,2013;; Guven *et al*.,2014; Guckan *et al*.,2015; Mughis *et al*.,2015; Direkel *et al.,* 2015) [38, 40, 41, 42, 21, 43, 30, 44, 22, 20, 34, 39, 23, 26, 24].

Our rate of Cefepime sensitivity was 2%. Some researchers have reported Cefepime sensitivity rate to *A.baumannii* in clinical samples (Huang *et al*., 2007; Mostofi *et al*.,2011; Javed *et al*.,2012; Gozutok *et al*. 2013; Sieniawski *et al*.,2013; Mirnejad and Vafaei., 2013; Al-Mously and

Hakawi.,2013; Mushtaq *et al*.,2013; Ece *et al.*,2014; Celik *et al.,* 2014; He *et al*.,2014; Atasoy *et al*.,2014; Mughis *et al*.,2015; Guckan *et al*.,2015; Direkel *et al.,* 2015; Yadegarynia *et al*., 2015) [40, 45, 42, 30, 34, 18, 22, 43, 34, 20, 39, 23, 24, 37]. Our results were similiar to Yadegarynia *et al* (2015) and Mirnejad and Vafaei., (2013) who also reported sensitivity to Cefepime was 2%.

Our rate of ampicillin, cefuroxime and cefazolin sensitivity was 0%. Ampicillin, Cefuroxime and Cefazolin were the most ineffective antibiotics, according to our results. Some researchers have reported ampicillin, cefuroxime and cefazolin sensitivity rate to *A.baumannii* in clinical samples (Shi *et al*.,1996; Brink *et al*.,2007; Javed *et al*.,2012; Atalan *et al*.,2012; Mayasari and Siregar.,2014; Egwu *et al*.,2015) [46, 47, 42, 48, 32, 49].

Table 2: Number of clinical samples and Multiple Antibiotic Resistance Index 48 *A.baumannii* strains

Source of isolates	Number of isolates	Multiple Antibiotic Resistance Index (MAR)
Abcess	5	0.30 (1isl), 0.54(2 isl), 0.70(2 isl)
Blood	8	0.30(1isl), 0.38(1isl), 0.70(1isl), 0.77(4isl), 0.85(1isl)
Urine	10	0.46(1isl), 0.54(1isl), 0.61(2isl), 0.70(4isl), 0.85(2isl)
Tracheal aspirate	24	0.30(1isl), 0.54(2isl), 0.61(1isl), 0.70(7isl), 0.77(9isl), 0.85(3isl), 0.9 2(1isl)
Mucus	1	0.77(1isl)

All of the *A. baumannii* strains, 48 (100%) isolates showed Multiple Antibiotic Resistance four to twelve antibiotics. It is commonly known that MDR (Multidrug Resistance) and PDR (Pan Drug Resistance) strain rates are high in nosocomial *A. baumannii* infections (Deveci *et al*.,2012; Zhang *et al*.,2013) [50, 51]. Joung *et al*.(2010) found the MDR and PDR resistance rates to be 60.3% and 15.5%, respectively. Aimsaad *et al*.(2009) [53] reported these rates to be 67.5% and 21.1%, respectively. In a study conducted in our country, Eser *et al*.(2009) [54] reported the MDR *Acinetobacter* antibiotic resistance rate to be 41%. A review of resistance distributions of antibiotics used in our study over a period of five years showed increasing rates of MDR and PDR strains. Particularly, the 4.7% PDR strain rate in 2007 was found to be 20.9% in 2011. These resistance rates are considered indicators of a gradual increase in difficulties treating *Acinetobacter* infections.

Conclusion

The primary goals for the control of multidrug resistant *Acinetobacter* infection are recognizing its presence in a hospital or long-term care facility at an early stage, controlling spread aggressively, and preventing the establishment of endemic strains. Control measures are based almost entirely on experiences from outbreaks of *Acinetobacter* infection and generally address the organism's major epidemic modes of transmission and the excessive use of broad-spectrum antibiotics. Additionally, we also recommend that the intensive care unit personnel must be informed about bacteria infection control practices because of the tendency of these pathogens to persist and spread in the hospital environment easily.

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