Pak J Med Res
Vol. 51, No. 4, 2012

Original Article

Drug Resistance Patterns of *Acinetobacter baumannii* in Makkah, Saudi Arabia

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Abstract

Background: *Acinetobacter baumannii* causes infections of respiratory, urinary tract, blood stream and surgical sites. Its clinical significance has increased due to its rapidly developing resistance to major groups of antibiotics used for its treatment. There is limited data available on antimicrobial susceptibility of *A.baumannii* from Saudi Arabia.
Objectives: To determine the patterns of drug resistance of *Acinetobacter baumannii* and predisposing factors for its acquisition.
Subjects and Methods: In this descriptive study, 72 hospitalized patients infected with *A.baumannii* were studied. The clinical and demographic data of the patients were collected using a predesigned questionnaire. Isolation and identification of *A.baumannii* from all clinical specimens were done using standard microbiological methods. Antibiotic susceptibility testing was performed by disk diffusion method recommended by Clinical Laboratory Standards Institute.
Results: Majority of the isolates (61.1%) were from respiratory tract infections. *A.baumannii* isolates showed high drug resistance to piperacillin (93.1%), aztreonam (80.5%), ticarcillin, ampicillin, and tetracycline (76.4%, each) and cefotaxime (75%). Only amikacin showed low rate of resistance compared to other antibiotics (40.3%). About 36% patients had some underlying diseases with diabetes mellitus (11%) being the predominant underlying disease.
Conclusions: High antimicrobial resistance to commonly used antibiotics was seen against *A.baumannii* isolates. Only amikacin was most effective against it.
Key words: *Acinetobacter baumannii*, drug resistance, nosocomial infection.

Introduction

Acinetobacter baumannii are gram-negative coccobacilli and grow aerobically at an optimum temperature of 33–37°C on usual laboratory media. It is non-motile, non-spore forming, catalase positive and oxidase negative organism[1]. It is capable of causing both community and hospital acquired infections targeting critically ill patients with breaches in skin integrity and airways. Hospital acquired infections is the major characteristic of multi-drug resistant *A.baumannii* mainly causing respiratory tract infection, urinary tract infection, septicaemia, and surgical site infections[2].

Acinetobacter baumannii has been a significant clinical concern in many parts of the world. In Europe, during last thirty years, hospital outbreaks of *A.baumannii* have been reported in many countries which include England, France, Spain, Italy and Netherlands[3]. In the United States of America multidrug resistant *A.baumannii* infections including carbapenem resistance has been reported from various parts of the country[4,5]. In Asia and the Middle East, outbreaks due to drug-resistant *A.baumannii* have been reported from health care institutions[6-8].

The importance of *A.baumannii* has greatly increased because of its ability to rapidly develop resistance to the major groups of antibiotics used for its treatment. The data available on antibiotic susceptibility of *A.baumannii* from Saudi Arabia is limited and few studies conducted so far, have reported a high rate of resistance among *A.baumannii* to common group of antibiotics, including imipenem[9-11]. It is important to know the changing pattern of antimicrobial susceptibility for adequate therapy of *A.baumannii* infection. Therefore, this study was undertaken to determine the patterns of drug resistance of *A.baumannii* and predisposing factors for acquisition of infection caused by this organism.

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Subjects and Methods

This descriptive study was carried over three months from February-April 2011. Seven different

hospitals of Makkah and Jeddah Cities were included. A total of 72 patients infected with *A.baumannii* were studied and their distribution among participating hospitals were: Al-Noor Specialist hospital Makkah (13); Hera'a General hospital, Makkah (3); Maternity and Children hospital, Makkah (6); King Abdul Aziz hospital, Makkah (16); King Faisal hospital, Makkah (5); Saudi National Guards hospital, Jeddah (7); King Abdul Aziz University hospital, Jeddah (22).

The patients admitted for ≥48 hours in any of the participating hospitals and suffering either from respiratory tract, urinary tract, blood stream or surgical site infections, were included in the study. The clinical and demographic data of patients were collected using a predesigned questionnaire. Demographic information collected included age, gender and place of residence. Clinical data included information about any underlying disease e.g., diabetes mellitus, chronic renal failure, cancer, hepatitis, heart conditions etc, presence or absence of intravascular or urinary catheters, name of admission ward, history of intensive care unit and length of stay, being on mechanical ventilation, history of previous antibiotic therapy, recent hospitalization and recent surgery, if any.

Depending on the nature of the disease, relevant clinical specimens were collected. In case of respiratory tract infections, sputum and respiratory or endotracheal aspirate specimens were collected. Urine specimens were collected from patients suffering from urinary tract infection or having urinary catheter in place. From surgical site infections pus or pus swab was collected. Blood for culture was also obtained from the patients having systemic infection.

All clinical specimens except blood were directly cultured on MacConkey and blood agar plates. Blood specimens were initially inoculated into blood culture broth bottles and incubated using BACTEC identification system (Beckton Dickinson). Blood culture bottles on the indication of positive growth were sub-cultured on blood agar plates. All plates were incubated at 37°C for 18-24 hours. After incubation period, all agar plates were examined for suspected colonies. Identification was made using standard microbiological techniques[12].

Antimicrobial susceptibility testing of all isolates was performed using Kirby Bauer disk diffusion method as recommended by Clinical Laboratory and Standards Institute[13]. All antibiotic disks were obtained from Oxoid (Basingstoke, UK). Briefly, a suspension of each isolate was prepared and turbidity was adjusted to 0.05 McFarland standards and then plated onto Muller Hinton agar plates. Antibiotic sensitivity disks were then placed and plates incubated at 37°C for 18-24 hours. After incubation, zone of inhibition for each antibiotic was measured, using standard interpretive tables of CLSI, the test organism was classified as susceptible, intermediate or resistant to the panel of antimicrobials used.

Results

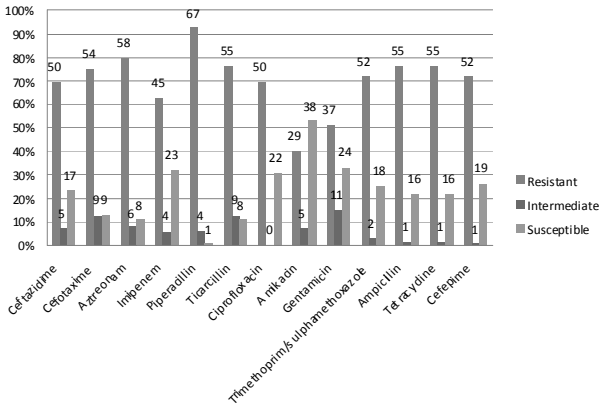
A total of 72 hospitalized patients infected with *A.baumannii* from various hospitals of Makkah and Jeddah were studied. Their ages ranged from <1 year to 80 years; with majority belonging to age group >30-40 years (31%), followed by >60-70 years (19%).

The highest isolation rate of *A.baumannii* was found in patients suffering from respiratory tract infections (61.1%), of which 49.9% suffered from lower respiratory tract infections and remainder 11.2% had upper respiratory tract infection. Wound infections accounted for 22.3% of infections, while urinary tract and blood stream infections were 8.3% each (Table-1).

Table 1: Distribution of *A.baumannii* according to site of infection.

Site of infection	*Samples examined*	*A.baumannii infected patients n(%)*
Respiratory tract	Sputum	22(30.5%)
	Endotracheal tube secretions	14(19.4%)
	Tracheal aspiration	8(11.2%)
Surgical wound	Wound swab	16(22.3 %)
Urinary tract	Urine	6(8.3 %)
Blood stream	Blood	6(8.3 %)
Total		72(100%)

Majority of the patients (60%) were admitted in different wards of the hospitals with 40% admitted in intensive care units. Of the total study population, 36% *A.baumannii* patients were suffering from one or the other underlying diseases e.g., diabetes mellitus (11%), chronic renal failure and heart problem (6% each); hepatitis (4%); asthma and hypertension (3% each).



Legends:
X-axis - Antibiotics tested, Y-axis - Percentage of susceptibility pattern

Figure: Overall frequency of drug resistance in *A.baumannii* (n=72).

Table 2: Drug resistance patterns of *A.baumannii* in participating hospitals.

Name of hospitals/ Antibiotic	*Antibiotic Resistance Patterns (%)*												
	CAZ	*CTX*	*ATM*	*IMI*	*PRL*	*TIC*	*CIP*	*AK*	*GN*	*SXT*	*AM*	*TE*	*CEF*
ASH (n=13)	61	69	62	85	100	69	69	62	23	62	69	69	62
HGH (n=3)	100	100	100	67	100	100	100	67	67	100	100	100	100
MCH (n=6)	0	0	33	0	100	67	0	0	0	0	0	0	0
KAH (n=16)	75	87	87	69	87	87	75	69	75	87	87	87	75
KFH (n=5)	40	40	80	40	100	40	40	40	40	40	40	40	40
KAUH (n=22)	82	86	90	86	86	90	77	27	50	82	90	90	90
SNGH (n=7)	100	100	100	0	100	100	100	0	100	100	100	100	100

Makkah Hospitals: ASH= Al-Noor Specialist Hospital; HGH= Hera'a General Hospital; MCH= Maternity and Children Hospital; KAH= King Abdul Aziz Hospital; KFH= King Faisal Hospital;
Jeddah Hospitals: KAUH=King Abdul Aziz University Hospital; SNGH= Saudi National Guard Hospital

CAZ=ceftazidime, CTX=cefotaxime, ATM=aztreonam, IMI=imipenem, PRL=piperacillin, TIC=ticarcillin, CIP=ciprofloxacin, AK=amikacin, GN=gentamicin, SXT=trimethoprim/sulphamethoxazole, AM=ampicillin, TE=tetracycline, CEF=cefepime

The antibiotic susceptibility results are shown in the Figure. Majority of the isolates were multi-drug resistant, showing resistance to two or more antimicrobial agents. The overall drug resistance rate was high to all drugs tested (40.3% to 93.1%); the highest resistance was shown by piperacillin (93.1%) and aztreonam (80.5%). Next in order were ampicillin, ticarcillin, and tetracycline (76.4% each). Other antibiotics also showed moderately high resistance; cefotaxime (75%), trimethoprim/sulphamethoxazole (72.2%), ceftazidime and ciprofloxacin (69.4% each) and gentamicin (51.4%). Only amikacin showed a low resiatnce rate (40.3%).

Drug resistance data of individual hospitals compared to overall resistance gave variable percentages of drug resistance for each hospital (Table-2). High imipenem resistance was seen from King Abdul Aziz University hospital, Jeddah (86%) and Al-Noor Specialist hospital, Makkah (85%) compared to other hospitals which showed resistance rates between 40-69%. However, all strains of *A.baumannii* from King Abdul Aziz University hospital, Jeddah showed high drug resistance to all the drugs tested (82% to 90%). Similar results were also seen at King Abdul Aziz hospital, Makkah where all the drugs tested showed high resistance rates of 68.7% to 87.5%. On the other hand, *A.baumannii* isolates from Maternity and Children hospital, Makkah, showed 100% sensitivity to all the drugs tested except to pipercillin and aztreonam.

Mixed patterns of drug resistance were seen at King Faisal Hospital, Makkah where most of the drugs tested showed 40% resistance, whereas at other hospitals resistance to these drugs was nearly double (~ 80%). Distinctively, the drug resistance pattern at Saudi National Guard hospital, Jeddah, was different from all other hospitals because it was found that all the *A.baumannii* isolates were 100% resistant to all the drugs tested except to imipenem and amikacin to which these isolates were 100% sensitive.

Discussion

Acinetobacter has emerged as an important pathogen and can affect any age group, but most commonly affected patients belong to 60 years and above[14,15]. An earlier study from Makkah has shown that *A.baumannii* was responsible for infections in the age groups <1 year up to 80 years, with most of the cases found in the age group 21-40 years (12.7%), followed by age group >80 years[10]. These results are similar to the present study from Makkah as the age range of the patients infected with *A.baumannii* was from <1 year to 80 years, with most of the cases been in the age group 30-40 years followed by age group >60-70 years.

Acinetobacter baumannii mainly causes respiratory tract infections in hospitalized patients, with an isolation rate ranging from 13-45% in patients suffering from lower respiratory tract infection[16-18]. These findings are in agreement with our results where *A.baumannii* was recovered from 50% patients suffering from lower respiratory tract infections. *A.baumannii* is also responsible for surgical wound infections in varying degrees. Studies reported from Turkey and Saudi Arabia have shown that, *A.baumannii* was responsible for surgical wound infections in 8.3% and 8.6% cases, respectively[10,16]. However, in the present study a slightly higher percentage of wound infections (22.3%) were seen which is similar to a study conducted in India[19], where it was found in 27.5% cases of wound infections.

The isolation rate of *A.baumannii* from urine specimens was 8.3% which is comparable to a study reported from Turkey where *A.baumannii* caused urinary tract infections in 9.3% of the total urinary tract infection cases[16]. However, a higher infection rate (30.6%) of urinary tract infections was reported from India[19]. *A.baumannii* isolated from blood in this study was 8.3% (6/72) and comparable to a recent study from India[19], that reported *A.baumannii* from 7% of the patients suffering from blood stream infections. Bacteremia associated with

intravenous catheterization was found in 2.7% of cases in this study.

Many factors including underlying diseases are associated with the acquisition and development of *Acinetobacter* infections[20]. In our study 36% *A.baumannii* isolates were from patients who had underlying diseases such as diabetes mellitus, chronic renal failure and heart disease. Similar findings were reported from India where 20% of *A.baumannii* infected patients were suffering from chronic obstructive pulmonary disease, end-stage renal disease, diabetes mellitus, malignancies, hepatic or chronic cardiac failure[19]. From Iran, a slightly higher rate (55.7%) of *A.baumannii* infection was reported from the patients with these underlying diseases[1].

The majority of the isolates were multi-drug resistant, showing resistance to two or more antimicrobial agents. The percentage of resistance against third-generation cephalosporins, extended spectrum penicillins and other β-lactam antibiotics was very high. Only amikacin showed the least resistance (40%) among all the drugs that were tested. A study conducted in Saudi Arabia during 2004-2009[11] showed noticeable increase in drug resistance trends among *A.baumannii* against imipenem (from 45% to 90%), meropenem (from 67% to 90%), ciprofloxacin (from 78% to 90%) and amikacin (from 88% to 94%) over this five year period. Our study showed very similar multi drug resistance, but with a slight difference in resistance patterns compared to the above study.

Another study carried out in Saudi Arabia from 1998-2004 showed a high rate of resistance in *Acinetobacter calcoaceticus-baumannii* complex to cefoxitin (89%), nitrofurantoin (89%) and ampicillin (86%). However, the rate of resistance to imipenem was 3%, gentamicin (26%), and ceftazidime (38%)[9]. Similar results were found in a study conducted at Makkah during 2005-2006, in which *A.baumannii* showed a high rate of resistance ranging from 50-100% to most antimicrobial agents used. All cephelosporins and other β-lactam antibiotics were highly resistant (83-100%), except piperacillin/tazobactam with 42.6% resistance. Among aminoglycosides high resistance to amikacin (84.2%) and gentamicin (76.2%) was reported. Moderate resistance rate was found among carbapenems ranging from 28-46% with meropenem 28% and imipenem 46%[10].

Imipenem is frequently used to treat infections caused by multidrug-resistant *A.baumannii*. However, due to the emergence of carbapenem-resistant *A.baumannii* in many parts of the world, leaving us no choice but to use more toxic drug e.g., colistin, polymyxin, or tigecycline for the treatment of these multi-drug resistant *A.baumannii* infections. Regional variation in resistance of *A.baumannii* to imipenem is related to patterns of antimicrobial use and risk factors. Our study is in no way different from other studies conducted worldwide as we found high drug resistance to imipenem (62.5%) and this is also similar to another study reported from Saudi Arabia[11], where an increase in imipenem resistance (from 45% to 90%) was reported over a five year period. In this study only amikacin showed minimum resistance (40%) against *A.baumannii* isolates among all antimicrobials tested. A low resistance (5-35%) to this antibiotic was also reported in other studies conducted in different parts of the world[21,22].

Drug resistance data of individual hospitals compared to overall resistance data gave variable percentages of drug resistance for each hospital. Hospitals showing high drug resistance to all antibiotics tested indicated that the majority of the isolates were from critical care areas where antibiotic usage was high, and as a result a higher percentage of resistance was found in these isolates. In contrast, the Maternity and Children hospital showed less resistance to the commonly used antibiotics indicates that majority of isolates at this hospital appear to be from community acquired infections, and this may be the reason why sensitivity patterns are different from critical care areas where most of the antibiotics tested were susceptible.

This variation in drug susceptibilities to *A.baumannii* against antimicrobial drugs is not unexpected as it has been found that resistance patterns are different among different countries, centers and even among the wards of same hospitals[1,19,22]. The reasons for this variable drug resistance in our study could possibly be due to variable sample size from various hospitals, patients' location in the hospitals (from wards or critical care areas), and site of *A.baumannii* infection in these patients and antibiotic policy followed by different hospitals.

In conclusion, the present study reported a high rate of drug resistance in *A.baumannii* to commonly used antibiotics in various hospitals of Makkah and Jeddah Cities. Only amikacin was found to be the most effective antibiotic against *A.baumannii* isolates. Underlying diseases were found to be a major risk factor for high drug resistance in *A.baumannii*.

Since drug resistance pattern of *A.baumannii* keeps on changing, local surveillance studies conducted at regular intervals will help in deciding the most adequate therapy for *Acinetobacter* infections. Furthermore prudent use of antibiotics either empirically or therapeutic for the treatment of *A.baumannii* infections should be included in the antibiotic policy of the hospital so that multi-drug resistant *Acinetobacter* strains may not develop in the near future.

Acknowledgement

The authors would like to thank Mr. Ahmad Faqeeh, Mr. Asem Ghazi Al-Lehaiby, Mr. Bader Ahmad Al-Hazmi, Mr. Khalaf Matar Al-Reeshi, Mr. Muhammad Al-Wethinani and Mr. Saud Abdullah Arif Bukhari for their excellent technical assistance. They all assisted in collection of samples and transportation from various hospitals and its processing in the laboratory.

References

1. Rahbar M, Mehrgan H, Aliakbari NH. Prevalence of antibiotic-resistant *Acinetobacter baumannii* in a 1000-bed tertiary care hospital in Tehran, Iran. Indian J Pathol Microbiol 2010; 53: 290-3.
2. Nagano N, Nagano Y, Cordevant C, Shibata N, Arakawa Y. Nosocomial transmission of CTX-M-2 beta-lactamase-producing *Acinetobacter baumannii* in a neurosurgery ward. J Clin Microbiol 2004; 42:3978–84.
3. Fournier PE, Richet H. The epidemiology and control of *Acinetobacter baumannii* in health care facilities. Clin Infect Dis 2006; 42:692-9.
4. Landman D, Bratu S, Kochar S, Panwar M, Trehan M, Doymaz M, et al. Evolution of antimicrobial resistance among Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae in Brooklyn, N.Y. J Antimicrob Chemother 2007; 60: 78–82.
5. Stephens C, Francis SJ, Abell V, DiPersio JR, Wells P. Emergence of resistant Acinetobacter baumannii in critically ill patients within an acute care teaching hospital and a long-term acute care hospital. Am J Infect Control 2007; 35:212–5.
6. Jeong SH, Bae IK, Park KO, An YJ, Sohn SG, Jang SJ, et al. Outbreaks of imipenem-resistant Acinetobacter baumannii producing carbapenemases in Korea. J Microbiol 2006; 44:423–31.
7. Abbo A, S. Navon-Venezia O, Hammer-Muntz T, Krichali Y, Siegman-Igra Y, Carmeli Y. Multidrug-resistant *Acinetobacter baumannii*. Emerg Infect Dis 2005; 11: 22–9.
8. Paul M, Weinberger M, Siegman-Igra Y, Lazarovitch T, Ostfeld I, Boldur I, et al. Acinetobacter baumannii: emergence and spread in Israeli hospitals 1997–2002. J Hosp Infect 2005; 60:256–60.
9. Al-Tawfiq JA, Mohandhas TX. Prevalence of antimicrobial resistance in Acinetobacter calcoaceticus-baumannii complex in a Saudi Arabian hospital. Infect Control Hosp Epidemiol 2007; 28:870-2.
10. Asghar AH, Faidah HS. Frequency and antimicrobial susceptibility of gram-negative bacteria isolated from 2 hospitals in Makkah, Saudi Arabia. Saudi Med J 2009; 30: 1017-23.
11. Al-Johani SM, Akhtar J, Balkhy H, El-Saed A, Younan M, Memish Z. Prevalence of antimicrobial resistance among gram-negative isolates in an adult intensive care unit at a tertiary care centre in Saudi Arabia. Ann Saud Med 2010; 30: 364-9.
12. Forbes BA, Sahm DF, Weissfeld AS, Editors. Bailey and Scott's Diagnostic Microbiology. 10 th ed. St. Louis: Mosby; 1998.
13. Wayne PA Clinical and laboratory standards institute. Performance standards for antimicrobial susceptibility testing. Twentieth informational supplement document M100-S20. Wayne PA, USA: NCCLS; 2010. P.30.
14. Bergogne-Berezin E, Towner KJ. *Acinetobacter* spp. as nosocomial pathogens: microbiological, clinical, and epidemiological features. Clin. Microbiol. Rev. 1996; 9:148–65.
15. Villers D, Espaze E, Coste-Burel M, Giauffret F, Ninin E, Nicolas F, et al. Nosocomial Acinetobacter baumannii infections: microbiological and clinical epidemiology. Ann Intern Med 1998; 129:182–9.
16. Bayram A, Balci I. Patterns of antimicrobial resistance in a surgical intensive care unit of a university hospital in Turkey. BMC Infect Dis 2006; 6:155.
17. Gonlugur U, Bakici MZ, Akkurt I, Efeoglu T. Antibiotic susceptibility patterns among respiratory isolates of Gram-negative bacilli in a Turkish university hospital. BMC Microbiol 2004; 4:32.
18. Jean SS, Teng LJ, Hseuh PR, Ho SW, Lu KT. Antimicrobial susceptibilities among clinical isolates of extended-spectrum cephalosporin-resistant gram negative in a Taiwanese University hospital. J Antimicrob Chemother 2002; 49: 69-76.
19. Joshi SG, Litake GM, Satpute MG, Telang NV, Ghole VS, Niphadkar KB. Clinical and demographic features of infection caused by Acinetobacter species. Indian J Med Sci 2006; 60:351-60.
20. Bergogne-Berezin E. Importance of Acinetobacter species. In Bergogne-Berezin E, editor. Acinetobacter biology and pathogenesis. USA: Springer Science; 2008. P.1-18.
21. Rhomberg PR, Jones RN. Contemporary activity of meropenem and comparator broad-spectrum agents: MYSTIC program report from the United States component (2005). Diagn Microbiol Infect Dis 2007; 57:207–15.
22. Peleg AY, Seifert H, Paterson DL. Acinetobacter baumannii: Emergence of a successful pathogen. Clin Microbiol Rev 2008; 21: 538–82.