RESEARCH ARTICLE

Prevalence of Extended Spectrum Betalactamase and Metallobetalactamase Producing *Acinetobacter baumannii* Isolated from Different Infections in Baghdad City of Iraq

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ABSTRACT

Introduction: *Acinetobacter baumannii* is an important pathogen related to hospital-acquired infections worldwide. This study was designed to isolate *A. baumannii* from different clinical specimens, investigate the presence of antibiotic resistants' and detect the prevalence of extended spectrum betalactamase (ESBL) and metallobetalactamase (MBL) production among *A. baumannii* isolates.

Methods: Over a 6-months period, 500 different clinical samples were collected from four hospitals in Baghdad. Identification of bacterial isolates and antibiotic sensitivity test were performed using Vitek 2 system. *A. baumannii* isolates were screened for MBL and ESBL production.

Results: Among the collected clinical samples, (424) were bacterial isolates. Of these, 69 samples (16.27%) were identified as *A. baumannii*. A largest number of *A. baumannii* isolates were isolated from sputum (at a percentage of (50.72%) followed by blood (30.43%), urine (13.04%), cerebrospinal fluid (CSF) (2.89%) and wound (2.89%). Antimicrobial susceptibility test showed that *A. baumannii* isolates displayed different resistance rates to the applied antibiotics. It was resistant to β-lactam antibiotics: ceftazidime, piperacillin/tazobactam, cefepime and imipenem at a percentage of (90, 87, 85.5 and 74%), respectively. It was resistant to aminoglycosides (gentamycin and amikacin) at 80 and 81%, respectively. The resistance rate to trimethoprim/sulfamethoxazole was 87, and 80% to Ciprofloxacin.

In the present study, all imipenemresistant *A. baumannii* isolates 51 (74%) were positive for MBL production. 57 (82.6%) β-lactam resistant isolates were ESBL producers.

Keywords: *Acinetobacter baumannii*, Antibiotics resistance, Metallo-β-carbapenemase, Extended-spectrum β-lactamases.

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INTRODUCTION

Acinetobacter baumannii is an important pathogen related to hospital-acquired infections worldwide.[1] This bacterium is an aerobic gram-negative coccobacillus and is responsible for opportunistic infections.[2] *A. baumannii* can persist under different environmental conditions and survive on surfaces for a long time on surfaces. Thus, it considers as a frequent cause of outbreaks and healthcare-related pathogenic bacteria.[3] *A. baumannii* infections mostly occur in patients in intensive care units (ICUs).[3,4] Moreover, the incidence of community-acquired *A. baumannii* infections has been raised.[5] *A. baumannii* causes different infections such as pneumonia, meningitis, bacteremia, urinary tract infection, and skin and soft tissue infections.

It has recently been shown that increasing the infections caused by multidrugresistant (MDR) *A. baumannii* strains in the intensive care units (ICUs) have led to increased mortalities rates.[6,7] Antibiotic resistance in *A. baumannii* can be achieved *via* reducing membrane permeability or increasing efflux of the antibiotic and thus preventing access to the target. This mechanism is due to efflux pumps protein machines that use energy to pump antibiotics into outside of the cell,[8] while in the second mechanism, the bacteria can protect the antibiotic target through genetic mutation.[9] However, the most common

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resistance mechanism in *A. baumannii* is the production of extended-spectrum beta lactamases (ESBLs) belonging to ambler classes A, D and B.[6,10]

Carbapenems are used to treat infections caused by ESBL producing pathogens. However, carbapenem resistance *via* metallo-beta-lactamases (MBLs) production has been reported.[11] *A. baumannii* is a producer of MBLs. MBLs belong to ambler class B betalactamases depending on their amino acid sequence homology and to group 3, according to the Bush classification, depend on their substrate profiles (imipenem hydrolysis).[12] MBLs hydrolyse all β-lactam antibiotics except monobactams.[13]

Pathogenic bacteria express different virulence factors related to antibiotics resistance, bacterial pathogenicity and survival in hospitals.[14,15] Since *A. baumannii* can survive in a wide range of environmental conditions and emerge as a multidrug-resistant pathogenic bacterium, infections by this pathogen are a main concern for clinicians and researchers. Therefore, this study was designed to isolate *A. baumannii* from different clinical specimens, investigate the presence of antibiotic resistants' and detect the prevalence of ESBL and MBL production among *A. baumannii* isolates.

METHODS AND METHODOLOGY

Specimens

A total of (500) different clinical samples were collected from patients who were admitted to hospitals in Baghdad during the entire period of study from November 2020 to April 2021. This study included all patients who presented with symptoms of infections and those who did not take treatment in the last two weeks.

Culture of Samples

Specimens were inoculated on the culture media (MacConkey agar and Blood agar), incubated aerobically at 37°C for 18–24 hours, and then examined for bacterial growth.

Identification of Bacteria

Bacterial identification and sensitivity testing were done using the Vitex-2 compact system. This instrument uses identification/antimicrobial susceptibility cards (ID/AST cards).

Testing for the ESBL Production (Double Disk Synergy Test)

One colony of *A. baumannii* was grown in Nutrient broth at 37°C for 24 hours and the bacterial suspension turbidity was adjusted to 0.5 McFarland. Then, Muller-Hinton agar was inoculated with bacteria, and Ticarcillin + clavulanic acid (75/10 µg) disk was placed on the plate at a distance of 25 mm from that of ceftazidime (30 µg) and left to diffuse for an hour followed by replacing ticarcillin + clavulanic acid disk with another disk of ceftazidime. The plate was incubated at 37°C for 24 hours. If the diameter of the inhibition zone of the ceftazidime disk applied after ticarcillin + clavulanic acid was ≥5 mm, in comparison with the ceftazidime disk alone, it was considered as positive for ESBL production.[15]

Detection of Metallo-β-carbapenemase (MBL)

One colony of *A. baumannii* was grown in nutrient broth at 37°C for 24 hours. The bacterial suspension turbidity was adjusted to 0.5 McFarland. Muller-Hinton agar was inoculated with bacteria, 10 µg imipenem disk with ethylenediaminetetraacetic acid (EDTA) and 10 µg imipenem disk without EDTA were placed on.

The inhibition zones of the imipenem disks were compared after 24 hours of incubation at 37°C. An increase in the diameter of the inhibition zone of the imipenem with EDTA disk compared to the imipenem disk without EDTA indicated positive result.[16]

Data Analysis

Statistical analysis of data was performed using SAS (Statistical Analysis System - version 9.1). Independent t-test was applied to assess the differences between two means. In case of three groups or more, one-way ANOVA and least significant differences (LSD) post-hoc test were performed to assess significant differences among means. $p < 0.05$ is considered statistically significant.

Table 1: The prevalence of *A. baumannii* among bacterial isolates

No.	*Type of Bacteria*	*No. of Bacteria*	*%*
1	*Escherichia coli*	164	38.68
2	*Klebsiella pneumonia*	84	19.81
3	*A. baumannii*	69	16.27
4	*Pseudomonas aeruginosa*	27	6.37
5	*Enterobacter cloacae*	20	4.72
6	*proteus mirabilis*	16	3.77
7	*Burkholderia cepacia*	9	2.12
8	*Staphylococcus aureus*	7	1.65
9	*Serratia marcescens*	6	1.42
10	*Morganella morganii*	4	0.94
11	*Enterobacter aerogenes*	3	0.71
12	*Salmonella spp.*	2	0.47
13	*Klebsiella oxytoca*	2	0.47
14	*Enterococcus faecalis*	2	0.47
15	*Staphylococcus haemolyticus*	2	0.47
16	*Shigella group*	1	0.24
17	*Providencia rettgeri*	1	0.24
18	*Shigella sonnei*	1	0.24
19	*Salmonella typhi*	1	0.24
20	*Citrobacter freundii*	1	0.24
21	*Citrobacter koseri*	1	0.24
22	*Moraxella lacunata*	1	0.24
Total		424	100.00

Table 2: Distribution of *A. baumannii* in clinical samples

No.	*Sample*	*No.*	*%*	*Chi-squared*	*p-value*
1	Sputum	35	50.72	87.15	<0.0001
2	Blood	21	30.43		
3	Urine	9	13.04		
4	C.S.F	2	2.89		
5	Wound swab	2	2.89		

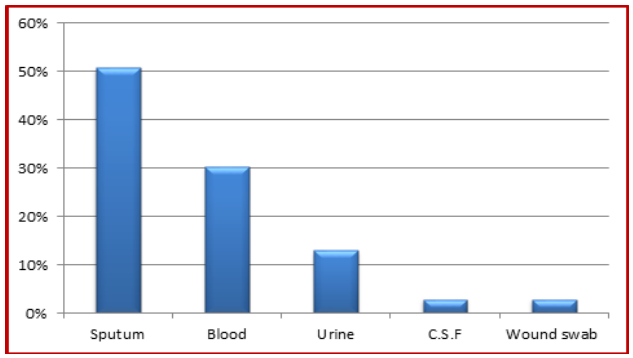

Figure 1: The percentage of distribution of *A. baumannii* in clinical samples

RESULTS

Prevalence of *A. baumannii* among Bacterial Isolates

In the current study, a total of 500 clinical sample cultures were performed over a 6 months period. Of these, (424) were bacterial isolates.

Among bacterial isolates, 69 (16.27%) isolates were identified as *Acinetobacter baumannii* (Table 1).

Distribution of *A. baumannii* isolates in Clinical Samples

A total of 69 *A. baumannii* isolates were isolated from different clinical samples. The outcomes showed that the largest number of *A. baumannii* isolates were isolated from sputum at a percentage of (50.72%) followed by blood (30.43%), urine (13.04%), CSF (2.89%) and wounds (2.89%) (Table 2, Figure 1). A significant difference was noticed at $p < 0.001$ ($\chi^2 = 87.15$). Figure 1 represents the percentage of *A. baumannii* distribution according to clinical specimens.

Antibiotic Susceptibility Profile of *A. baumannii* isolates

The antibiotic resistance profile of *A. baumannii* isolates was detected by vitek 2 system. Antimicrobial susceptibility test showed that *A. baumannii* isolates displayed different resistance rates to the antibiotics. It was resistant to β-lactam antibiotics: ceftazidime, piperacillin/tazobactam, cefepime and imipenem at a percentage of (90, 87, 85.5 and 74%), respectively. It was resistant to aminoglycosides (gentamycin and amikacin) at a percentage of 80 and 81%, respectively. The resistance rate to trimethoprim/sulfamethoxazole was 87%, and to ciprofloxacin was 80% (Table 3, Figure 2).

Antibiotic Resistance Mechanisms Characterized in *A. baumannii* isolatesI4.1 Metallo-β-carbapenemases Production

Out of 69 clinical isolates of *A. baumannii*, 51(74%) isolates were resistant to imipenem. They were subjected phenotypically to detect MBL producers (by carbapenem disks with or without EDTA). An increase in the diameter of the inhibition zone of the imipenem with EDTA disc compared to the imipenem disc without EDTA indicated as a positive result. In the present study, all imipenemresistant *A. baumannii* isolates were positive for MBL production (Figure 3).

Extended β-lactamase Production

β-lactam resistant *A. baumannii* isolates were subjected phenotypically for detection of β-lactamase. The results revealed that 57 (82.6%) isolates were ESBL producers, (rise of ≥5 mm in inhibition zone diameter of ceftazidime disk applied after diffusion of ticarcillin + clavulanic acid disks compared to ceftazidime disk indicated as positive result), (Figure 4, Table 4).

Table 3: Antibiotic susceptibility findings of *A. baumannii* isolates to different antibiotics

	Piperacillin	*Ceftazidime*	*Cefepime*	*Imipenem*	*Amikacin*	*Gentamycin*	*Ciprofloxacin*	*Trimethoprim*
R%	6087	6290	5985.5	5174	5580	5681	5580	6087
I%	11.5	11.5	00	23	11.5	57	11.5	00
S%	811.5	68.5	1014.5	1623	1318.5	812	1318.5	913

Table 4: The increase of the zone of inhibition diameter (mm) of ceftazidime (30 µg) disk applied after diffusion of Ticarcillin + clavulanic acid (75/10 µg) disk against *A. baumannii* isolates.

Specimens	*No*	*Number of ESBL Producer isolates*	*The increase of the zone of inhibition diameter (mm) Mean ± SD*
Sputum	35	31	11.87 ± 0.80a
Blood	21	16	10.27 ± 0.99a
Urine	9	6	6.71 ± 1.01b
C.S.F	2	2	7.54 ± 1.54b
Wound swab	2	2	11.11 ± 1.85a
LSD			2.67

Means with a different letter in the same column are significantly different ($p < 0.05$).

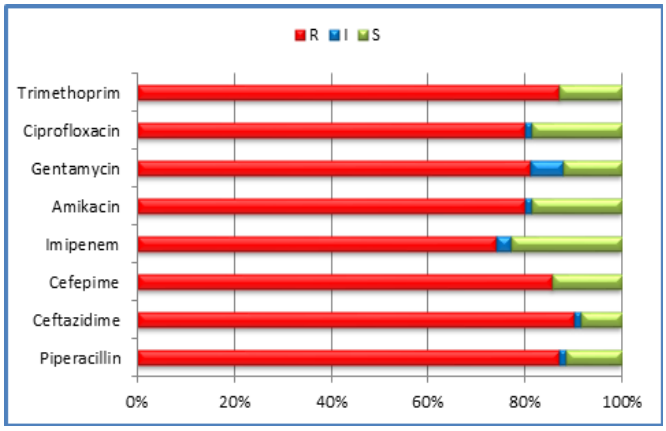

Figure 2: Percentages of susceptibility of *A. baumannii* isolates to different antibiotics

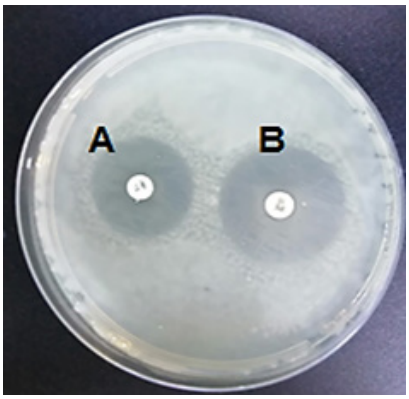

Figure 3: Metallo-β-carbapenemases production: Agar plates showing the zone of inhibition of A: carbapenem disks without EDTA, B: carbapenem disks with EDTA.

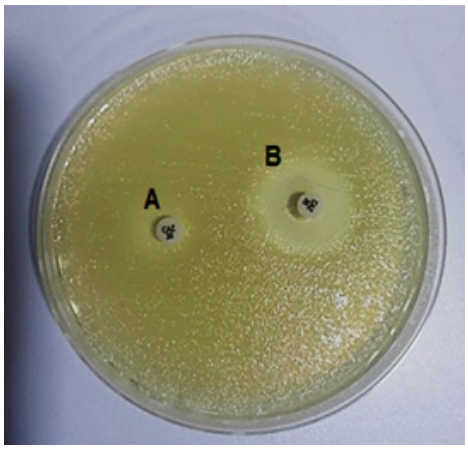

Figure 4: Extended β-lactamase production. Agar plates showing the zone of inhibition of A: ceftazidime (30 µg), B: ceftazidime (30 µg) disk applied after diffusion of a Ticarcillin + clavulanic acid (75/10 µg) disk.

DISCUSSION

Recently, it has been reported that *A. baumannii* is a nosocomial pathogenic bacterium that spreads within hospitalized patients. The clinical importance of *A. baumannii* is based on bacterial survival in hospitals and antibiotic resistance,[17,18] in addition to the expression of virulence factors that aid the bacteria in pathogenesis.[19]

In the current study, the results revealed that a predominant number of *A. baumannii* isolates were isolated from sputum (with a rate of 50.72%). This result agreed with the findings reported by Ben Haj Khalifa and Khedher,[20] who indicated the airway as the major isolation site for *A. baumannii*. Furthermore, it has been shown that *A. baumannii* is the most causative agent of hospital-acquired pneumonia.[21] *A. baumannii* caused bacteremic pneumonia with a higher mortality compared to other pathogens.[22] *A. baumannii* was isolated from blood with a rate of 30.43%. Also, it has been shown that *A. baumannii* was isolated from blood samples at a percentage of 14.51%.[23] However, other researchers reported that *A. baumannii* was isolated only at a rate of 1.3% of septicemia.[24]

Antibiotics resistance in *A. baumannii* has become a worldwide problem. This has resulted in difficulties in treating infections caused by this bacterium.[25,26] Misuse of antibiotics is the reason for higher rate of antibiotic resistance among pathogens.[27]

Recently, it has been reported that *A. baumannii* is a MDR pathogen.[28] In the current study, antibiotic susceptibility tests revealed that *A. baumannii* isolates are multidrug resistant (MDR) isolates. Resistance to ceftazidime, piperacillin/tazobactam, cefepime, imipenem, gentamycin, amikacin, trimethoprim/sulfamethpoxazole and ciprofloxacin were 90, 87, 85.5, 74, 80, 81, 87, and 80%, respectively. It has been shown that the resistance of *A. baumannii* isolates were 95.4% to ceftazidime, 95.4% to piperacillin/tazobactam, 100% to cefotaxime, 92.6% to ciprofloxacin and 91.7% to meropenem.[29] Another study revealed that the resistance rates of *A. baumannii* isolates against the tested antibiotics: piperacillin/tazobactam, imipenem, meropenem, amikacin, ciprofloxacin, and cefotaxime, were 95, 85, 94, 84, 97, and 98%, respectively.[30]

The outcomes of antimicrobial resistance in the current study and those of other researches, indicating a high rate of *A. baumannii* resistance isolates and an increase in MDR strains in recent years.

The most essential resistance mechanisms of *A. baumannii* is the production of ESBLs. Different studies around the world have been demonstrated a high rate of ESBL-producing *A. baumannii*.[31,32] In the current study, 57 isolates (82.6%), out of 69 isolates were ESBL producers. It has been shown that 84.2% of *A. baumannii* isolates were ESBL producers.[33]

Another work done by Chaudhary *et al.* revealed that 83.6% of *A. baumannii* isolates were ESBL producers.[34] In contrast, Sinha *et al.* reported that 28% of *A. baumannii* isolates were ESBL producers.[35]

Carbapenems are the good choice for treating infections caused by ESBL producing pathogens. However, recently, it has been shown that there is a resistance to imipenem *via* the production of MBL.[30,36,37] Mostly, the MBL producers can hydrolyze different antibiotics except aztreonam.[38]

In the present study, all Imipenem resistant *A. baumannii* isolates 51 (74%) were positive for metallo-β-carbapenemases MBL production. The production of metallo-β-carbapenemases has been reported by many authors. It has been shown that the production of MBL was (80.3%).[39] However, other studies revealed that the rate of MBL production by *A. baumannii* was 22–49%.[40,41]

CONCLUSION

The outcomes of the current study revealed that a high rate of *A. baumannii* isolates had MDR and the ability for ESBL and MBL production. Thus, the earlier detection of ESBL and MBL enzymes might be essential for the decrease of MDR isolates.

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