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# Molecular Characterization of Carbapenem Resistant *Acinetobacter baumannii* in Cancer Patients

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**A B S T R A C T**

This study aimed to investigate the prevalence of Multidrug resistant *Acinetobacter baumannii* (MDR-AB) as a cause of health-care associated infection (HAI) in cancer patients and study the mechanisms of carbapenem resistance in relation to different risk factors. In this study, Multidrug resistant *Acinetobacter* were isolated and subjected to Imipenem-EDTA combined disk synergy (CDST-IPM), multiplex PCR to detect four families of OXA-type carbapenamases and sequencing of $bla_{OXA-51}$ like gene. During one and a half year, MDR-AB accounted for 15% of gram negative pathogens. The majority of MDR-AB infections were in patients who spent 7 or more days in the hospital (76.8%). More than one mechanism of resistance were detected, as metallo-β-lactamase (MBL) producers, $bla_{OXA-51}$ like and $bla_{OXA-23}$ like were detected in 80%, 94% and 63% of MDR-AB; respectively. The $bla_{OXA-23}$ and MBLs coexisted simultaneously in 71% of cases ($p$=0.003); and 7% of imipenem resistant isolates were negative for MBL and $bla_{OXA-23}$ suggesting other resistance mechanisms. The presence of *Acinetobacter* resistant genes ($bla_{OXA-51}$ and $bla_{OXA-23}$) was significantly associated with carbapenem use, $p$=0.015 and 0.064; respectively. The phylogenetic analysis showed different genetic variants. In conclusion, acquisition of carbapenem resistance among MDR-AB could be related to carbapenem therapy and prolonged duration of hospitalization.

## Introduction

Hospitals worldwide are facing a crisis in the upsurge and dissemination of antimicrobial resistant bacteria. Nowadays, MDR-AB infections are increasing leading to limited therapeutic options, and high rates of morbidity and mortality (Fattouh and Nasr El-din, 2014). The evolution of MDR is relatively fast, as the main driving force is lateral gene transfer, via a wide range of mobile genetic elements. Integrons have often been found in plasmids and/or transposons that promote the spread of resistance genes (Prata-Rocha *et al*., 2013).

Carbapenem resistance is mediated by a combination of different mechanisms. The most commonly encountered mechanisms in *A. baumannii* are the production of MBLs and carbapenem hydrolyzing class D beta-lactamases (CHDLs) (Lee *et al*., 2013). The production of MBLs is one of the most worrisome resistance mechanisms because they not only limit treatment options but

also their genes are carried on highly mobile elements, allowing their easy dissemination (Mohamed and Rafaat, 2011). Thus, detection of MBLs may help to modify therapy and necessitate the initiation of effective infection control to prevent further dissemination (Fattouh and Nasr El-din, 2014). Five main subgroups of CHDLs have been recognized in *A. baumannii*, $bla_{OXA-23}$ like, $bla_{OXA-40}$ like (originally called $bla_{OXA-24}$ like), $bla_{OXA-51}$ like, $bla_{OXA-58}$ like and $bla_{OXA-143}$ like. The $bla_{OXA-51}$ like is intrinsic to *A. baumannii*, while the others are acquired (Opazo *et al*., 2012). The distribution of *A. baumannii* carrying these different acquired CHDL genes varies among different regions and even in different hospitals (Lee *et al*., 2013). Although CHDLs have a lower catalytic efficiency to hydrolyze carbapenems compared to MBLs, it is important to consider them as potentially dangerous because their expression can be regulated by the upstream insertion of insertion sequence (IS) elements such as ISAba1. This can be intensified in the presence of other resistance mechanisms, such as increased expression of efflux pumps and loss of porins (Opazo *et al*., 2012).

It has been reported that CHDL-producing carbapenem resistant *A. baumannii* (CRAB) provide a sheltering effect for carbapenem susceptible pathogens and can exacerbate the pathogenesis of polymicrobial infections in case of carbapenem treatment. This indicate a greater importance for the presence of CRAB in clinical settings and emphasize the urgent need for more effective controls of CRAB in polymicrobial infection (Liao *et al*., 2014).

Thus we aimed to investigate the prevalence of MDR-AB as a cause of HAI in cancer patients and study mechanisms of carbapenem resistance in these pathogens in relation to different risk factors including duration of hospitalization, surgical procedures, empirical carbapenem therapy and ICU admission.

## Patients and Methods

This was a retrospective study conducted at the Microbiology unit of Clinical Pathology Department at National Cancer Institute, Cairo University, Egypt, during the period from January 2012 to May 2013. Patients included in the study were adult (≥18 years) cancer patients receiving their treatment in different departments of NCI. The study was approved by the ethical committee review board of NCI, Cairo University and patients' consents were obtained.

**Data collection:** Medical records of the patients infected with MDR *Acinetobacter* species were reviewed for the following data including age, gender, the underlying disease, department (medical or surgical), ICU admission, prior hospitalization, duration of hospital stay before onset of infection, clinical site of infection, surgical procedures, chemotherapy, antibiotic received especially carbapenems, duration and clinical outcome of the episode. The isolate was considered as MDR, if resistant to more than two classes of antimicrobials (≥ 3 classes) (Vaze *et al*., 2013). Carbapenem resistant *Acinetobacter* isolates were defined as non-susceptible or with diminished susceptibility to meropenem and/or imipenem in vitro (Kim *et al*., 2012). Fourteen-day in hospital mortality after the onset of *Acinetobacter* infection was used as the main assessment of patients' outcome.

**Microbiology:** Non-duplicate MDR *Acinetobacter* organisms isolated from various clinical samples of cancer patients during the study period were collected and purity colonies were done. The isolates were

identified using Microscan Walk Away 96, Gram-negative panels. The antibiotic panel included were amikacin, amoxicillin-clavulanic acid, aztreonam, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, levofloxacin, meropenem, piperacillin-tazobactam, tobramycin and trimethoprim-sulfamethoxazole. Results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2010).

**Imipenem - EDTA combined disk synergy test (CDST-IPM):** Test organisms were inoculated on to Mueller Hinton agar plates. Two 10µg imipenem discs (Oxoid, UK) were placed on the plate, and appropriate amounts of 10µl of EDTA solution (0.5 M) was added to one disc. The inhibition zones of the imipenem and imipenem-EDTA discs were compared after 24 hours of incubation at $37^0$C. The difference of ≥7mm between the inhibition zone diameter of the imipenem -EDTA disk and that of imipenem disk alone was considered to be positive for the presence of MBLs (Hodiwala *et al*., 2013).

**Multiplex PCR:** Detection of the four families of OXA-type carbapenamases found in *A. baumannii* (*bla*$_{OXA-23}$ like, *bla*$_{OXA-40}$ like, *bla*$_{OXA-51}$ like and *bla*$_{OXA-58}$ like) was done by a multiplex PCR. Extraction of DNA was done by using The GeneJET Genomic DNA Purification Kit (Thermo Scientific, Lithuania). PCR amplification of the four *bla*$_{OXA}$ genes was performed with primers which were selected from published sequences (Karmostaji *et al*., 2013) and the four primer pairs were as follows: *bla*$_{OXA-23}$ like-F 5/-GAT CGG ATT GGA GAA CCA GA-3// *bla*$_{OXA-23}$ like-R 5/-ATT TCT GAC CGC ATT TCC AT-3/; *bla*$_{OXA-24}$ like-F 5/-GGT TAG TTG GCC CCC TTA AA-3// *bla*$_{OXA-24}$ like-R 5/-AGT TGA GCG AAA AGG GGA TT-3/; *bla*$_{OXA-51}$ like-F 5/-TAA TGC TTT GAT CGG CCT TG-3// *bla*$_{OXA-51}$ like-R 5/-TGG ATT GCA CTT CAT CTT GG-3/; *bla*$_{OXA-58}$ like-F 5/-AAG TAT TGG GGC TTG TGC TG-3// *bla*$_{OXA-58}$ like-R 5/-CCC CTC TGC GCT CTA CAT AC-3/ (Bioneer, Korea). PCR products [501 base pair (bp) (*bla*$_{OXA-23}$ like), 246 bp (*bla*$_{OXA-40}$ like), 353 bp (*bla*$_{OXA-51}$ like) and 599 bp (*bla*$_{OXA-58}$ like)] were visualized by agarose gel electrophoresis.

**Sequencing of *bla*$_{OXA-51}$ like gene:** Further sequencing of *bla*$_{OXA-51}$ like gene was done to 20 *A. baumannii* isolates chosen from ICU infected cases. Sequencing was performed using an Applied Biosystems 3730XL sequencer at Macrogen Inc. (Korea). All sequences were identified using Basic Local Alignment Search Tool (BLAST) program. Homologous sequences to the sequence of interest were identified by a BLAST search using the sequence of interest as a query (Hall, 2013). According to GeneBank nucleotide database, 15 isolates were previously detected in gene bank while 5 isolates showed no similar results to those previously recorded. Multiple sequences alignment was accomplished using the Clustalw and the MUSCLE programs (Hall, 2013). Phylogenetic tree was constructed to determine molecular relatedness between isolates.

**Statistical analysis:** Data was analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables. Infection related mortality was analyzed using Kaplan-Meier method for survival

analysis and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A *p*-value < 0.05 was considered significant.

## Results and Discussion

During one and a half year, MDR-AB were isolated from 82 non-duplicate specimens out of 544 gram negative organisms (15.1%) growing from cultures of different clinical specimens. The demographic data and clinical characteristics of infected patients are summarized in table 1. The mean age of patients was 46.3 ± 17 years. All isolates were identified as *A. baumannii* by the Microscan. The most common sites of infections by *Acinetobacter* pathogens were respiratory tract specimens accounting for 47.6% (n=39) followed by surgical site infections (n=36, 43.9%), blood (n=5, 6.1%) and urine (n=2, 2.4%).

Antimicrobial susceptibility profile of *Acinetobacter* isolates revealed sensitivity of 31 (37.8%) to tobramycin, 25 (30.5%) to gentamicin, 18 (22.0%) to amikacin, 8 (9.8%) to ciprofloxacin and 7 (8.5%) to levofloxacin. Seventy eight isolates (95.1%) were carbapenem resistant. The MBL phenotype was detected by CDST-IPM test in 66 isolates (80.5%), in both imipenem sensitive and resistant isolates (Table 2). By multiplex PCR (Figure 1), $bla_{OXA-51}$ like was detected in 77 isolates (93.9%), while $bla_{OXA-23}$ like was detected in 52 (63.4%) of isolates and they coexisted in 62.2% of isolates. None of the isolates were $bla_{OXA-40}$ and $bla_{OXA-58}$ like genes positive. Four isolates (4.9%) were negative for the four genes tested. The $bla_{OXA}$ and MBL genes were simultaneously detected. The CDST positive results were associated with a positive $bla_{OXA-51}$ and $bla_{OXA-23}$ like genes in 97% and 71% of isolates ($p$=0.049, 0.003; respectively). However, 6.9% of imipenem resistant *Acinetobacter* isolates (5/72) were non MBL and non $bla_{OXA-23}$ carbapenemase producers. The phylogenetic analysis showed presence of several different genetic variants of *A. baumannii* isolates in our hospital (Figure 2).

Of the 82 patients infected by *Acinetobacter* pathogens, 44 (53.7%) received empirical carbapenems (imipenem or meropenem), i.e. before documented proof of infection. Carbapenem therapy was significantly associated with OXA genes positivity as summarized in Table 3. The overall *Acinetobacter* infection related 14-day mortality was 32.5%. The unadjusted (crude) 14-day mortality rates were significantly higher in patients who were admitted to ICU than in patients who were not admitted to ICU (52.4% versus 12.4%, $p$<0.001). While 14-day mortality rates were not different between MBL, $bla_{OXA}$ genes ($bla_{OXA\ 51}$ and $bla_{OXA\ 23}$) positive and negative cases ($p$=0.686, $p$=0.453 and $p$=0.779; respectively).

In the present study, *Acinetobacter* constituted 15.1% of gram negative pathogens isolated from different clinical specimens of adult cancer patients. Similar figures were previously reported in cancer patients (18.7%) (Eldomany and Abdelaziz, 2011).

The increased rate of antimicrobial resistant Acinetobacter, specifically to carbapenems, constitute a problem in the management of the infections caused by these pathogens. In the current study, a high rate of carbapenem resistance has been recorded among MDR *Acinetobacter* isolates (95.1%); more pronounced against meropenem than imipenem (93.9% and 87.8%; respectively). The presence of efflux pump over expression as a resistance mechanism that pumps out meropenem but not imipenem is

a possible explanation for more meropenem resistance (Meletis *et al*., 2012).

In the current study, *A. baumannii* infections were mostly health-care acquired (98.8%), and were significantly associated with prolonged hospitalization as 76.8% of patients spent ≥7 days in hospital prior to developing infection. Similarly, Dash *et al*. reported that the majority of *A. baumannii* infections were detected from inpatients (90.5%) with 75.9% of cases spending 7 or more days in the hospital (Dash *et al*., 2013). Vaze and his colleagues recorded that 71% of patients infected by *A. baumannii* were hospitalized for more than one week (Vaze *et al*., 2013). Sixty two percent of cases were subjected to surgical procedures one month prior to infection; pointing to the importance of invasive procedures to acquisition of infection. In addition, 48.8% of *A. baumannii* infections were isolated from patients admitted to ICU. The importance of *Acinetobacter* species as a cause of ICU infections was previously confirmed (Kim *et al*., 2012).

The MBL phenotype was detected in 80.5% of *Acinetobacter* isolates in the present study; in both imipenem susceptible and imipenem resistant isolates. Similar results were reported in another Egyptian study, as MBLs were positive in 86.7% of imipenem resistant *A. baumannii* (IRAB) by CDST (Fattouh and Nasr El-din, 2014). Other studies demonstrated MBLs positivity in 50% of IRAB isolates by CDST (Hodiwala *et al*., 2013; Mohamed and Rafaat, 2011). The detection of MBLs among imipenem sensitive isolates was reported in some studies with rates up to 20% (Daef *et al*., 2012). Thus, it is evident that MBLs are detected among imipenem resistant isolates, as well as imipenem susceptible ones. The carbapenem susceptible pathogens with hidden MBL genes might disseminate resistance in health-care facilities if not screened for the presence of MBLs.

The $bla_{OXA-51}$ and $bla_{OXA-23}$ genes were positive in 93.9% and 63.4%, of *A. baumannii* pathogens in the current study, respectively. However, $bla_{OXA-40}$ and $bla_{OXA-58}$ genes were not detected in any isolate. In a similar study, $bla_{OXA-51}$ like, $bla_{OXA-23}$ like, $bla_{OXA-40}$, $bla_{OXA-58}$ like were positive in 100%, 50%, 7.5%, and 5% of IRAB isolates, from three different hospitals in Egypt (Al-Agamy *et al*., 2014). Also $bla_{OXA-51}$ like, $bla_{OXA-23}$ like, $bla_{OXA-58}$ like and $bla_{OXA-40}$ like were detected in 100.0%, 55.9%, 14.7% and 2.9%, respectively of *A. baumannii* isolates from pediatric patients in Egypt (Al-Hassan *et al*., 2013). However, $bla_{OXA-51}$ like and the $bla_{OXA-23}$ like genes were reported in all of the CRAB isolates from ICUs in 3 hospitals including NCI, in Egypt (Fouad *et al*., 2013).

Similarly, $bla_{OXA-23}$ like genes were detected in 60.0% and 100.0% of IRAB from different parts of the world, and $bla_{OXA-51}$ like was positive in all strains; whereas $bla_{OXA-40}$ like and $bla_{OXA-58}$ like genes were not detected in many studies (Prata-Rocha *et al*., 2013).

Many studies confirmed the presence of multiple genes encoding carbapenem hydrolyzing enzymes in *A. baumannii* (Fattouh and Nasr El-din, 2014). In the present study, positive CDST *Acinetobacter* isolates were significantly associated with positivity of the $bla_{OXA-51}$ (97.0%) and the $bla_{OXA-23}$ like genes (71.2%); $p$=0.049, 0.003; respectively. This was previously confirmed as 80.6% of *A. baumannii* strains with positive results in CDST were positive for the $bla_{OXA-23}$ like genes (Azimi *et al*., 2013). Still, other mechanisms of carbapenem resistance such as modification of penicillin binding proteins, loss of porins

and/or altered efflux pump activity should be investigated as 6.9% of IRAB were non MBL and non *bla*$_{OXA-23}$ carbapenemase producers.

The growing rate of carbapenem resistance in the current study, could be partially explained by the widespread clinical use of these antibiotics in our hospital, as nearly half (53.7%) of our patients received carbapenem therapy prior to documenting infection. In addition, carbapenem therapy was significantly associated with OXA genes positivity (100% and 75% for *bla*$_{OXA-51}$ and *bla*$_{OXA-23}$ with a *p*-value 0.015 and 0.064; respectively. It is evident that exposure to antibiotics effectively selects the MDR strains and allow the acquisition of more antibiotic resistance genes.

**Table.1** Demographic data and clinical characteristics

| Parameter | | Total number | Percentage (%) |
|---|---|---|---|
| **Age** | | | |
| | 18 - 40 years | 31 | 37.8 |
| | 41 - 64 years | 35 | 42.7 |
| | ≥ 65 years | 16 | 19.5 |
| **Gender** | | | |
| | Male | 35 | 42.7 |
| | Female | 47 | 57.3 |
| **Department** | | | |
| | Surgical | 57 | 69.5 |
| | Medical | 25 | 30.5 |
| **ICU admission** | | | |
| | No | 42 | 51.2 |
| | Yes | 40 | 48.8 |
| **Prior hospitalization** | | | |
| | No | 60 | 73.2 |
| | Yes | 22 | 26.8 |
| **Hospitalization** | | | |
| | Inpatient | 81 | 98.8 |
| | Outpatient | 1 | 1.2 |
| **Duration of hospital stay before infection** | | | |
| | < 7 days | 19 | 23.2 |
| | 7 days - <30 days | 47 | 57.3 |
| | ≥ 30 days | 16 | 19.5 |
| **Underlying disease** | | | |
| | Hematological tumor | 24 | 29.3 |
| | Solid tumor | 58 | 70.7 |
| **Surgery within 1 month** | | | |
| | No | 31 | 37.8 |
| | Yes | 51 | 62.2 |
| **Chemotherapy within 1 month** | | | |
| | No | 59 | 72.0 |
| | Yes | 23 | 28.0 |

**Table.2** Relation of carbapenem susceptibility to MBL production and blaoxa genes positivity

| | Imipenem (No. (%)) | | | Meropenem (No. (%)) | | |
|---|---|---|---|---|---|---|
| | Sensitive (n=10) | Resistance (n=72) | *P*-value | Sensitive (n=5) | Resistance (n=77) | *P*-value |
| **CDST-IPM test** | | | | | | |
| Negative (n=16) | 6 (60.0) | 10 (13.9) | | 3 (60.0) | 13 (16.9) | |
| Positive (n=66) | 4 (40.0) | 62 (86.1) | **0.001** | 2 (40.0) | 64 (83.1) | **0.049** |
| ***bla*$_{OXA\ 51}$** | | | | | | |
| Negative (n=5) | 3 (30.0) | 2 (2.8) | | 2 (40.0) | 3 (3.9) | |
| Positive (n=77) | 7 (70.0) | 70 (97.2) | **0.012** | 3 (60.0) | 74 (96.1) | * |
| ***bla*$_{OXA\ 23}$** | | | | | | |
| Negative (n=30) | 10 (100.0) | 20 (27.8) | | 4 (80.0) | 26 (33.8) | |
| Positive (n=52) | 0 (0.0) | 52 (72.2) | **<0.001** | 1 (20.0) | 51 (66.2) | 0.057 |

* No *p*-value because of small numbers of subgroups.
Statistically significant *p*-values are in boldface.
Isolates with intermediate susceptibility had been included in the resistant category.

**Table.3** Empirical Carbapenem use in relation to multiplex PCR results for the blaoxa genes

| | Antibiotic used (No. (%)) | | | |
|---|---|---|---|---|
| | Carbapenems* (n=44) | Double Ab** (n=10) | Other single Ab*** (n=28) | *P*-value |
| ***bla*$_{OXA\ 51}$** | | | | |
| Negative (n=5) | 0 (0.0) | 2 (20.0) | 3 (10.7) | |
| Positive (n=77) | 44 (100.0) | 8 (80.0) | 25 (89.3) | **0.015** |
| ***bla*$_{OXA\ 23}$** | | | | |
| Negative (n=30) | 11 (25.0) | 5 (50.0) | 14 (50.0) | |
| Positive (n=52) | 33 (75.0) | 5 (50.0) | 14 (50.0) | 0.064 |

Statistically significant *p*-values are in boldface.
* Imipenem or meropenem, either alone or in combination with other antibiotic(s)
** maxipime and amikacin
*** eg. ceftriaxone or levofloxacin

**Fig.1** Detection of genes encoding OXA carbapenamases by multiplex PCR. Lanes 1, 4, 6, 8, 9,18 blaOXA-51 like gene; Lanes 2, 3, 5, 7, 10-17 blaOXA-23 like and blaOXA-51 like genes; DNA ladder marker (50 bp DNA ladder)

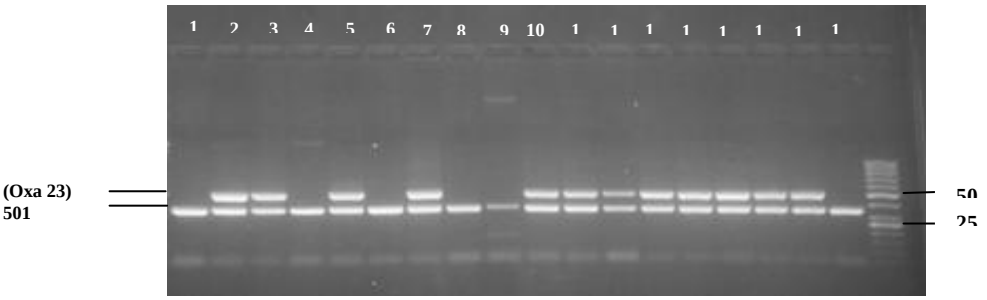
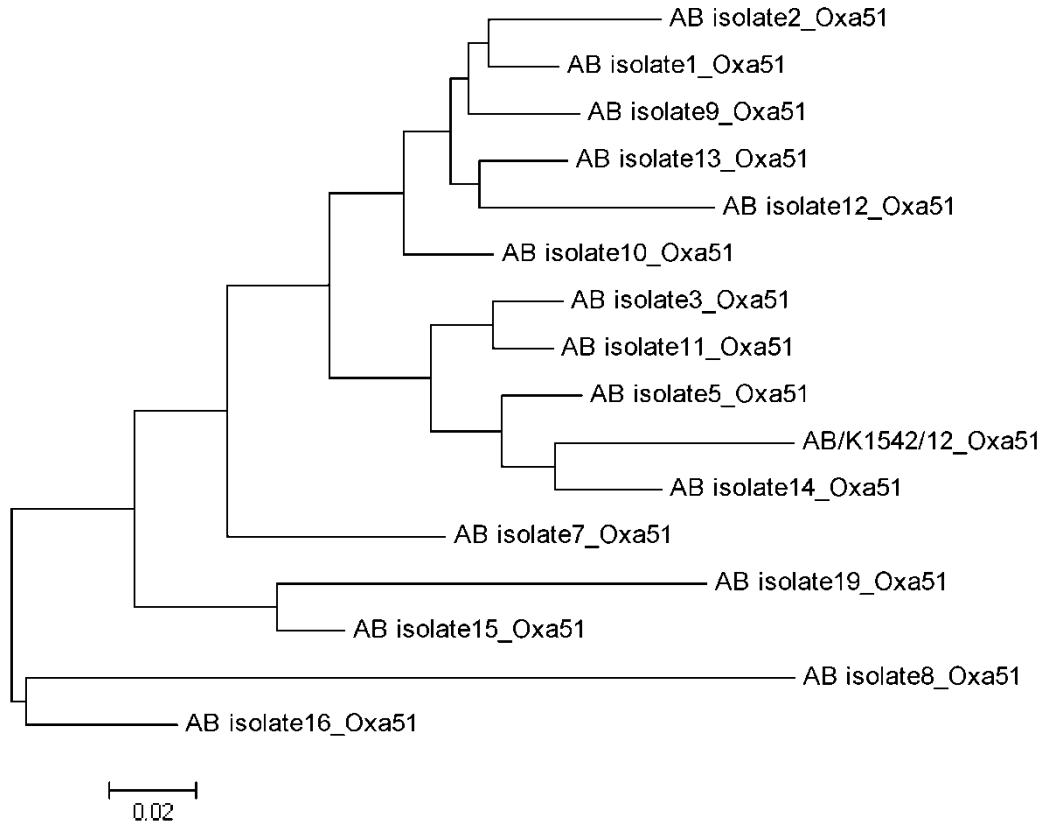


**Fig.2** Molecular Phylogenetic analysis by Maximum Likelihood method based on sequencing blaOXA-51 gene from different 15 isolates of A. baumannii. The dendrogram shows the amounts of genetic change based on multiple alignments and were generated using MEGA5 software. The bar at the bottom of the figure shows the amount of genetic change corresponding to the length of each branch




A phylogenetic tree was originally used in the assessment of the relation between DNA sequences and their hypothetical common ancestors; mainly among the species represented by those sequences. Nowadays it is used to understand the relationships among the sequences regardless of their host species, estimating the functions of genes that have not been studied experimentally, and helping in investigating microbial outbreaks (Hall, 2013). In the current study, a large diversity was found in the sequences of $bla_{OXA-51}$ like gene. This diversity suggested sporadic cases of *A. baumannii* rather than the presence of a single clone. This was against expectations, given the short duration of sample collection (1.5 years) and the fact that isolates studied were those recovered from ICU. This could be due to transfer of cases from different wards in the hospital to the ICU. The plasticity of *Acinetobacter* genetic composition allow easy inclusion of new genes, thus making it difficult to define its origin (Al-Hassan *et al*., 2013). Similarly, in a previous study done on Egyptian pediatric cancer patients, diversity of *A. baumannii* isolates was confirmed (Al-Hassan *et al*., 2013).

The most common site of infection associated with *Acinetobacter* pathogens in the present study, was hospital acquired pneumonia; as respiratory tract specimens accounted for almost half of isolates

(47.6%). This was previously documented as *A. baumannii* were isolated primarily from respiratory tract specimens (49%) (Vaze *et al*., 2013), and endotracheal secretions (33.3%) (Fattouh and Nasr El-din, 2014). In general, these opportunistic pathogens are more commonly isolated from high risk hospitalized patients subjected to invasive procedures. Thus, increased rates of MDR-AB infections and its diversity might be due to the presence of several risk factors in our patients like ICU admission, surgical procedures and prolonged hospitalization.

A high crude 14-day mortality rate was associated with infections caused by MDR *A. baumannii* infections in the present study (32.5%). Similar high 14-day mortality rates were previously recorded with *Acinetobacter* infections (Kim *et al*., 2012). Still the exact cause of mortality is not clear as these infections usually occur in high risk ICU patients with high rates of co-morbidity. Therefore, further studies are needed to focus on the possible multifactorial parameters contributing for the unfavorable outcome.

Thus, we concluded that MDR *Acinetobacter* infections constituted important causes of HAI in cancer patients. These infections were significantly associated with prolonged hospital stay and prior intake of carbapenems. It is evident that multiple mechanisms of resistance contributed to the increasing rates of carbapenem resistance in *A. baumannii*. Diversity was encountered in *A. baumannii* isolates. The diversity of isolates and multiple mechanisms of carbapenem resistance suggested that acquisition of MDR-AB infections might be a multistep complex process that took place as a result of multiple risk factors, including invasive procedures, carbapenem therapy and prolonged duration of hospitalization; rather than simple health-care associated transmission.

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## Conflict of Interest

No conflict of interest is considered for any of the authors of this study.

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