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Phenotypic and Genotypic Patterns of Antimicrobial Resistant Strains of *Acinetobacter baumannii* at Hospital Settings, Khartoum State, Sudan

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Abstract

Background: *Acinetobacter baumannii* is undoubtedly one of the most clinically important pathogens causing nosocomial infections worldwide. It is difficult to control, and the infections caused by it are difficult to treat, due to its variable mechanisms for resistance.

Objective: This study was aimed to assess the phenotypic and genotypic patterns of antimicrobial resistant strains of *Acinetobacter baumannii* at hospital settings, Khartoum, Sudan.

Methodology: A descriptive cross-sectional study was conducted to assess resistance rate of *Acinetobacter baumannii* clinical isolates. Thirty six *A. baumannii* clinical isolates were collected in nutrient agar slope and re-identified using standard bacteriological techniques. Then, antimicrobial susceptibility testing was done using modified- Kirby Bauer method. Molecular techniques were applied using both multiplex and conventional polymerase chain reaction to detect the presence of genes associated with phenotypic resistant traits; extended-spectrum B-lactamase and carbapenems.

Results: A total resistance (100%) to Ciprofloxacin, Gentamicin, Amoxicillin, Ampicillin, Ceftazidime and Ceftriaxone was reported. High resistance rate was observed in both sulfamethoxazole and imipenem with 88% and 47%, respectively. All isolated strains were extended-spectrum B-lactamase. *bla*_{TEM} gene was detected in all *ESBL* strains whereas *bla*_{CTXM9} gene detected only in 2 strains with the complete absence of *bla*_{SHV} gene in this study. In carbapenemase genes, *bla*_{OXA48} was the most common carbapenemase detected in 14 (82%) followed by *bla*_{NDM} 12 (70%) then *bla*_{GES} and *bla*_{VIM} with 5 (29%), 3 (17%) respectively. Several isolates co-harbored more than one carbapenemase genes: (*bla*_{NDM} and *bla*_{OXA48}), (*bla*_{NDM} and *bla*_{GES}), (*bla*_{OXA48} and *bla*_{GES}), (*bla*_{NDM} and *bla*_{VIM}), (*bla*_{OXA48} and *bla*_{VIM}) and (*bla*_{GES} and *bla*_{VIM}), 9 (52%), 4 (23%), 4 (23%), 2 (11%), 2 (11%) and 1 (5%), respectively. Colistin was the major therapeutic option for all resistant strains with sensitivity (100%).

Conclusion: All *A. baumannii* collected from hospitals of Khartoum state were phenotypically *ESBL* and 47% were imipenem resistant. The *bla*_{TEM} gene was found to be the most prevalent type (100%) of β -lactamase-encoding gene, a high level of imipenem resistance is mediated by *oxa*⁴⁸, *NDM* and as following: 82% and 70% respectively. All isolates were sensitive to Colistin.

Keyword: *Acinetobacter baumannii*; Nosocomial Infections; Extended-Spectrum B-Lactamase; Therapeutic Option

Abbreviations

ESBL: Extended-Spectrum β -Lactamase; MDR: Multidrug Resistance; DNA: Deoxyribonucleic Acid; PCR: Polymerase Chain Reaction; MH: Muller Hinton; rpm: Round Per Minute; snps: Single Nucleotide Polymorphisms; bp: Base Pair

Introduction

Acinetobacter baumannii is a Gram-negative bacillus that is aerobic, pleomorphic, non-motile, opportunistic pathogen and has a high incidence among immunocompromised individuals; particularly those who have experienced a prolonged (> 90d) hospital stay [1,2]. Commonly associated with aquatic environments [3] the Detection of *A. baumannii* in air, water and inanimate surface samples revealed that hospital environments could act as a potential route for transmission of *A. baumannii* infections especially in ICUs. It has been shown to colonize the skin as well as being isolated in high numbers from the respiratory and oropharynx secretions of infected individuals [4]. In recent years, it has been designated as a “red alert” human pathogen, generating alarm among the medical profession, arising largely from its extensive antibiotic resistance spectrum [5].

Several virulence factors have been identified by genomic and phenotypic analyses, including outer membrane porins, phospholipases, proteases, lipopolysaccharides (LPS), capsular polysaccharides, protein secretion systems, and iron-chelating systems that help the bacterium to establish itself in the harsh conditions of the hospital [2].

MDR *A. baumannii* infections tend to occur in immunosuppressed patients, in patients with serious underlying diseases, and in those subjected to invasive procedures and treated with broad-spectrum antibiotics. Thus, infections due to *A. baumannii* are frequently found in intensive care units (ICUs), where they are implicated as the cause of ventilator-associated pneumonia (VAP), urinary tract infections, and bacteremia. *A. baumannii* also causes with less frequency complicated skin and soft tissue, abdominal, and central nervous system infections [6]. Recent findings showed that *A. baumannii* has become a major pathogen found in combat-associated wounds [7]. The factors contributing to colonization, virulence, and invasion are being defined [8].

Currently, many resistance mechanisms are known to exist in *A. baumannii*, including β -lactamases, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and the alteration of target sites. Most of these resistance mechanisms can target different classes of antibiotics. However, several different mechanisms can work together to contribute to the resistance to a single class of antibiotics. In addition to β -lactamases with carbapenem-hydrolyzing activity as a major carbapenem resistance mechanism, which include carbapenem-hydrolyzing class D β -lactamases (CHDLs) including the genes (bla OXA-51, bla OXA-23, bla OXA-24 and bla OXA-58) and metallo- β -lactamases (MBLs), porins such as CarO and penicillin-binding protein modifications might also be involved in carbapenem resistance. The spread of multidrug-resistance determinants in *A. baumannii* is mostly through plasmid conjugation, transposon acquisition or integron mobilization to gain clusters of genes encoding resistance to several antibiotic families. Furthermore, the functional insertion sequences are important in amplifying antimicrobial resistance and gene plasticity [2,6].

The basis of polymyxin resistance in *A. baumannii* has only recently been investigated and several mechanisms have been proposed. Several genetic loci have been implicated in the resistance towards polymyxins in *Acinetobacter*, namely, the *pmrCAB* operon [9,10] and the *lpxA*, *lpxC*, *lpxD* and *lpsB* genes, that are involved in LPS biosynthesis [4,11,12]. Resistance can arise through mutations in the two-component system PmrAB, in which the downstream target PmrC catalyzes the addition of phosphoethanolamine to the lipid A component of LPS [9,10,13]. This modification reduces the net negative charge of the outer membrane thus reducing the affinity of polymyxins for the target.

Colistin is a polycationic antimicrobial peptide that targets the polyanionic bacterial lipopolysaccharide (LPS) of Gram-negative bacteria. Two different colistin resistance mechanisms have previously been reported. The first mechanism inactivates the lipid A biosynthesis pathway, leading to the complete loss of surface LPS. Mutations in *lpxC*, *lpxA*, or *lpxD* are involved in the first mechanism. The *pmrAB* two-component system mediates the second resistance mechanism. Mutations in *pmrA* and *pmrB* induce the activity of *pmrC*, which adds phosphoethanolamine (PEtn) to the hepta-acylated form of lipid A. Further mutations in *vacJ*, *pldA*, *tgg2C*, *pheS* and a conserved hypothetical protein were reported to involve in reduced colistin susceptibility through novel resistance mechanisms [15]. The *A. baumannii*

is often misidentified with other species because of phenotypic similarity and other non lactose fermenting bacteria, the misidentification leads to the selection of the wrong antibiotics [2,7]. Comprehensive infection control measures, especially those that are focused on environmental cleaning and disinfection, are critical for controlling endemic MDR *A. baumannii*. Therefore, environmental cleaning and disinfection should be emphasized for controlling endemic MDR *A. baumannii* infections [14].

Materials and Methods

Study design

A descriptive (cross-sectional) study was used in this study.

Study area and duration

This study was conducted at different hospitals in Khartoum State during the period from March to August 2018.

Sample size

Thirty six clinical isolates of *A. baumannii* were collected in this study.

Inclusion criteria

All clinical isolates identified as *A. baumannii* were included in this study.

Ethical considerations

This study was approved by Ethical Committee Board of Faculty of Medical Laboratory Sciences at Elrazi University and permission from laboratory head department in all hospitals was taken to collect study sample.

Laboratory procedures

Collection and transportation of samples

All clinical isolates identified as *A. baumannii* were collected and sub-cultured on nutrient agar slope.

Storage of samples

All inoculated nutrient agar slopes were preserved at 4°C till further processing.

Re-identification

Sub-culture on MacConkey's agar

Each inoculated slope was sub-cultured on MacConkey's agar to study colonial morphology of suspected *A. baumannii* [15].

Gram's reaction

All suspected overnight isolates on MacConkey's agar were stained by Gram stain bacterial suspension [15].

Biochemical tests

All Gram-negative coccobacilli were further identified using standard conventional biochemical tests [15].

Antimicrobial susceptibility testing

Preparation of bacterial suspension

All identified *A. baumannii* colonies were emulsified in 3 ml sterile normal saline and then bacterial suspension turbidity was adjusted against MacFarland's standard [15].

Seeding on Muller Hinton agar

Each adjusted bacterial suspension was seeded on Muller Hinton agar [15].

Placing of antibiotics

Each seeded plates of Muller and Hinton agar were tested against the following antibiotics: imipenem, colistin, ciprofloxacin, gentamicin, amoclan, ampicillin, ceftriaxone, ceftazidime and co-trimoxazole.

Reading of sensitivity testing

The diameter of inhibition zones was measured using ruler and the results were reported according to interpretative antimicrobial chart.

Molecular technique methodology

Genomic DNA extraction

Deoxyribonucleic acid (DNA) was extracted from resistant colonies using boiling cooling of 3 colonies suspended in 200 ul of normal saline and centrifuged at 13000 rpm.

Primers design

Table: K, R and Y are variable snps [16].

Primer	Sequence	Amplicon size (bp)
KPC for KPC rev	CATTCAAGGGCTTTCTTGCTGC ACGACGGCATAGTCATTTGC	538
IMP for IMP rev	TTGACACTCCATTACG GATGAGAATTAAGCCACCT	139
VIM for VIM rev	GATGGTGTTTGGTCGCATA CGAATGCGCAGCACCAG	390
Oxa ⁴⁸ for Oxa ⁴⁸ rev	GCTTGATCGCCCTCGATT GATTTGCTCCGTGGCCGAAA	281
Ges for Ges rev	AGTCGGCTAGACCGGAAAG TTTGTCCGTGCTCAGGAT	399
NDM for NDM rev	TGCCCAATATTATGCACCCGG AAGCACAGCGGCAGCAAGAAAG	621
TEM for TEMrev	TCGCCGCATACACTATTCTCAGAATGA ACGCTCACCGGCTCCAGATTTAT	445
SHV for SHVrev	ATGCGTTATATTCGCCTTGTG TGCTTTGTATTTCGGGCCAA	747
CTX for CTX rev	ATGTGCAGYACAGTAARGTKATGGC GGGTRAARTARGTSACCAGAAYCAGCG	593

Polymerase chain reaction (PCR)

PCR tube

Four micro liter of DNA was subjected to each multiplex PCR in 25 ul reaction mixture containing 8ul master mix, fixed concentration of specific-group primers (1 ul for each forward and reverse).

PCR steps (Techne®)

Polymerase chain reaction (PCR) steps were held in sequential events as to follow:

- 1) **Initial denaturation:** All PCR tubes were subjected to initial denaturation at 94°C for 10 min [16].
- 2) **PCR cycle:** A thirty cycles of (denaturation, annealing and extinction) were applied on each PCR tube as following: 94°C for 40s, 60°C for 40s and 72°C for 1 min. But, the annealing temperature of carbapenemase was optimized at to follow: 55° C for *bla*-VIM, *bla*-IMP and *bla*-KPC genes. Whereas, annealing temperature of *bla*-GES and *bla*-OXA-48 were optimized at 57°C and 58°C, respectively [16].
- 3) **Final extinction:** A final extinction step was done at 72°C for 7 min [16].

Gel electrophoresis (Techne®)

Amplicons were visualized after running at 100V for 30 min on 2% agarose gel containing ethidium bromide. A 100 bp DNA ladder was used as a size marker [16].

Results

A total of 36 clinical isolates of *A. baumannii* were collected from different hospitals in Khartoum State. The resistance rate of *A. baumannii* to Ciprofloxacin, Gentamicin, Amoclan, Ampicillin, Ceftazidime, Ceftriaxone, cotrimoxazole, Imipenem and Colistin was 100%,100%, 100%, 100%, 100%, 100%, 88%, 47% and 0.00%, respectively (Table 1). All collected clinical isolates of *A. baumannii* were Extended-spectrum β -lactamase (*ESBL*) producers. Thirty eight percent of *A. baumannii* *ESBL* producers were showed co-resistance to co-trimoxazole and Imipenem. *ESBL* strains were sensitive to colistin, imipenem and co-trimoxazole with100%, 53% and 12%, respectively (Table 1).

Table 1: *A. baumannii* antibiotics susceptibility testing results.

Antibiotics	Resistant	Sensitive
Ampicillin	36 (100%)	0 (0.00%)
Amoclan	36 (100%)	0 (0.00%)
Ceftazidime	36 (100%)	0 (0.00%)
Ceftriaxone	36 (100%)	0 (0.00%)
Ciprofloxacin	36 (100%)	0 (0.00%)
Colistin	0 (0.00%)	36 (100%)
Gentamicin	36 (100%)	0 (0.00%)
Imipenem	17 (47%)	19 (53%)
Sulfamethoxazole	32 (88%)	4 (12%)

All phenotypic detected ESBL and carbapenem resistant strains were confirmed by molecular technique using Polymerase Chain Reaction (PCR). All ESBL producers were positive to *bla*_{TEM} gene and negative to *bla*_{SHV} whereas were positive to *bla*_{CTXM9} in (2%) of isolates (Table 2).

Table 2: Percentage of extended-spectrum β-lactamase genes in *A. baumannii* clinical isolates.

Genes	Percent (%)
<i>bla</i> _{TEM}	36 (100%)
<i>bla</i> _{CTXM9}	36 (2%)
<i>bla</i> _{SHV}	36 (0%)

As for carbapenem resistant strains three classes of genes [Class D (*bla*_{KPC}, *bla*_{IMP}, *bla*_{VIM}), Class C (*bla*_{OXA48}, *bla*_{GES}) and *bla*_{NDM}] were used to confirm carbapenemase production.

Seventeen percent of carbapenem resistant strains were positive to *bla*_{VIM} gene, whereas no results with *bla*_{KPC} and *bla*_{IMP} genes in class D carbapenemase. *bla*_{OXA48} gene was showed higher percentage than *bla*_{GES} gene with 82% and 29%, respectively.

*bla*_{NDM} gene constituted 70% of all carbapenem resistant clinical isolates of *A. baumannii* (Table 3).

Table 3: Percent of carbapenem genes in *A. baumannii* clinical isolates.

Carbapenem genes	Percent (%)
Class D	
<i>bla</i> _{VIM}	3 (17%)
<i>bla</i> _{KPC}	0 (0.00%)
<i>bla</i> _{IMP}	0 (0.00%)
Class C	
<i>bla</i> _{OXA48}	14 (82%)
<i>bla</i> _{GES}	5 (29%)
<i>bla</i> _{NDM}	12 (70%)

Genes overlapping were observed in ESBL producers with genes of different classes of carbapenemase. *bla*_{TEM} gene positive strains were overlapped with class C, *bla*_{NDM} and class D with 41%, 33% and 8%, respectively, whereas *bla*_{CTXM9} gene positive strains were negative for all classes of carbapenemase (Table 4). Carbapenem resistance co-occurrence was observed in collected *A. baumannii* clinical isolates, which was to follow: class C and *bla*_{NDM}, class D and C, class D and *bla*_{NDM} and 52%, 17% and 5%, respectively (Table 5).

Table 4: ESBL and carbapenem co-occurrence of resistant genes in *A. baumannii* clinical isolates.

Shared genes	Percent
<i>bla</i> _{TEM} and class C	(41%)
<i>bla</i> _{TEM} and <i>bla</i> _{NDM}	(33%)
<i>bla</i> _{TEM} and class D	(8%)

Table 5: Carbapenem co-occurrence of resistant genes in *A. baumannii* clinical isolates.

Shared genes	Percent
Class D and <i>bla</i> _{NDM}	52%
Class D and class C	17%
Class C and <i>bla</i> _{NDM}	5%

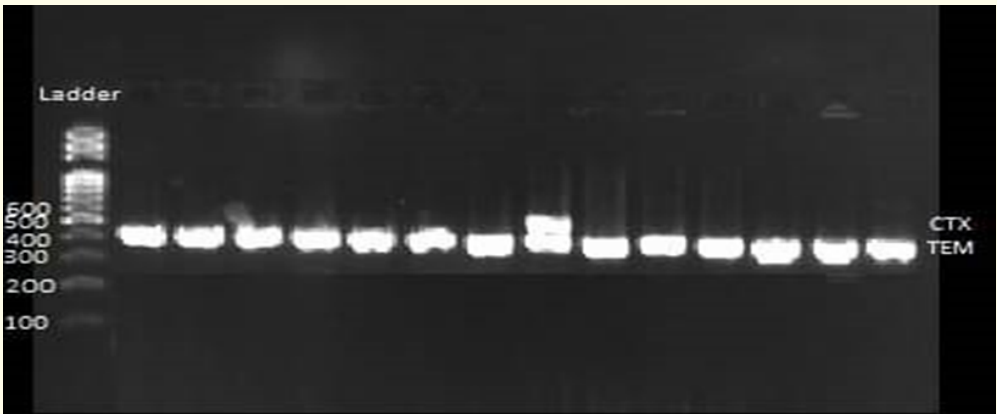


Figure 1: blaTEM and blaCTXM9 genes.



Figure 2: blaTEM positive CTX and SHV negative.

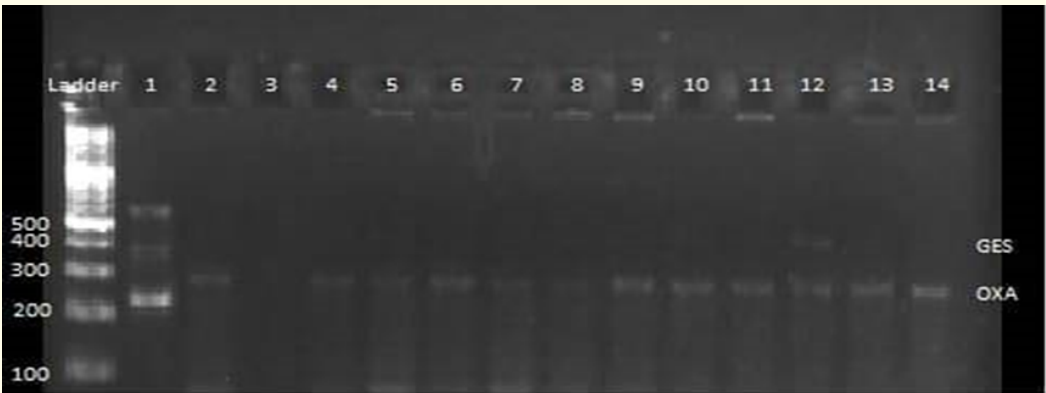


Figure 3: blaOXA48 and blaGES genes.

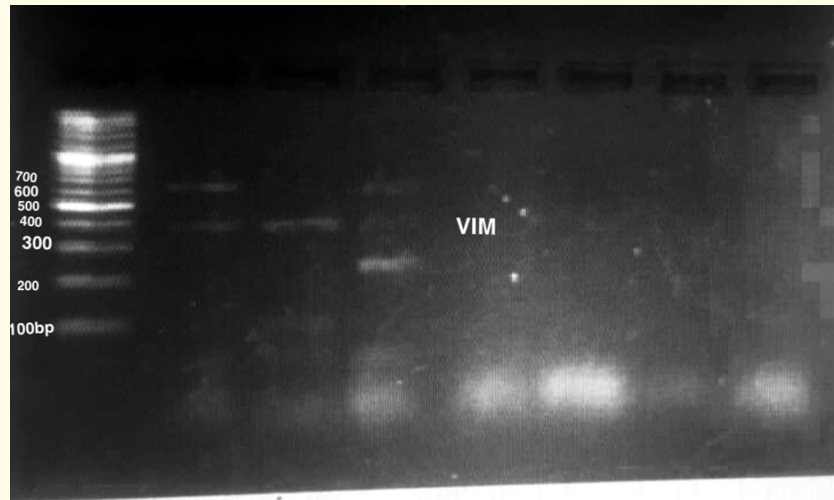


Figure 4: *blaVIM* positive *blaKPC* and *blaIMP* negative.

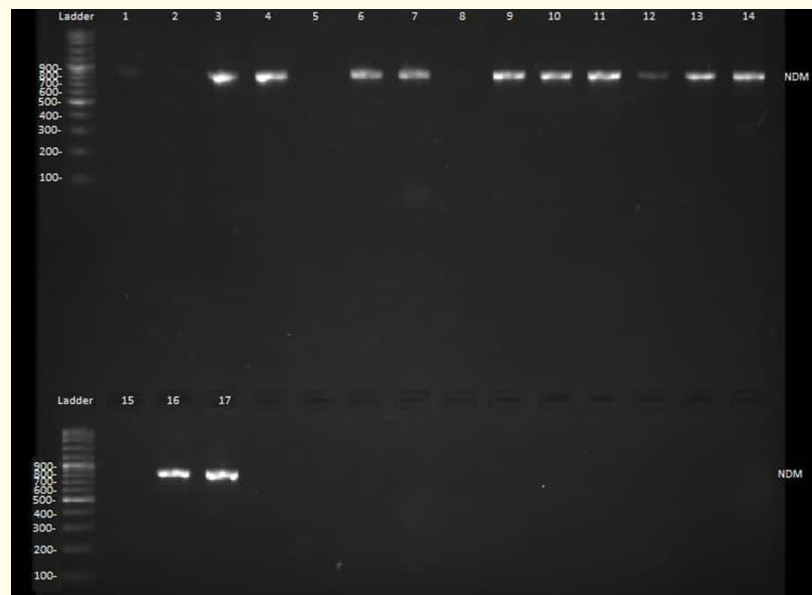


Figure 5: *blaNDM* gene.

Discussion

Acinetobacter baumannii is an important cause of nosocomial infections worldwide and the infections caused by it are difficult to treat, because of its multidrug resistant capabilities [1].

The current study reported total resistance to ciprofloxacin, gentamicin, amoxicillin, ampicillin, ceftazidime and ceftriaxone in all clinical isolates of *A. baumannii*. Similar study was carried out by Muntasir, *et al.* 2015 in Sudan showed a consistency with our results 91% ciprofloxacin, 92% gentamicin, 81% amoxicillin, 98% ampicillin, 96% ceftazidime and 95% ceftriaxone [1]. An empirical antibiotics that prescribed to treat infections like sepsis, pneumonia and urinary tract infections caused by this organism and its co-existence at hospital settings due to high ability to survive and persist in versatile environments were the major underlying reasons for dramatic increasing in antimicrobial resistance of *A. baumannii* during these three years.

Of particular interest, all *A. baumannii* strains were Extended-Spectrum β -Lactamase (ESBL) producers. This finding is highly consistent with the results demonstrated by Al-Agamy, 2014 in Egypt and Sid Ahmed, 2016 in Qatar. Who's reports showed that 100%, 99% of isolates were ESBL, respectively [16,17]. Higher prevalence of *A. baumannii* ESBL producers at hospital settings might be attributed to its ability to grow in harsh conditions and its different ways to express the resistance like plasmids, transposons and integrons and innate antimicrobial resistance mechanisms such as cell surface structures that prevent the influx of antibiotics which lead to failure of treatment [1].

An increased emerged-resistant strain of *A. baumannii* to imipenem (47%) was observed in this study, which was less than that reported by Muntasir, *et al.* 2015 (89%) [1]. This finding can be explained by inadequate adherence to infection control guidelines, in addition to inappropriate administration of carbapenem at hospital settings [18]. The quite difference between two findings might be attributed to larger sample size that has been taken over period of time in Muntasir, *et al.* study.

Treatment of patients infected with ESBLs producers is challenging due to limited therapeutic options. Currently, colistin is the drug of choice for treating multi-drug resistant *A. baumannii*. Fortunately, our finding in the present study yielded absence of resistance to colistin (0.00%). This is more optimistic than the report of Rezaee, 2013 in India that showed 47% resistance [19]. So, drastic measures should be adopted in prescription and introduction of colistin to clinical practice to prevent appearance of emerged-resistant strains of *A. baumannii*.

Among ESBLs, bla_{TEM} gene was positive in 100% of *A. baumannii* isolates higher than the result that has been reported by Rezaee, 2013 in Iran (13.15%) [20], 2% was the prevalence of bla_{CTXM9} resistance gene higher than the report of Al-Agamy, 2014 in Saudi Arabia (0.00%) [21].

The drug of choice to treat nosocomial infection caused by *A. baumannii* is the carbapenems. However, there is an increasing rate of carbapenem-resistant *A. baumannii* around the world caused by three common genes of class D (bla_{KPC} , bla_{IMP} and bla_{VIM}), class C (bla_{OXA48} and bla_{GES}) and bla_{NDM} .

Ges gene shows a relatively high prevalence (29%) with lower percentage of bla_{VIM} gene (17%), which disagreed with the study that has been conducted by Peymani, 2016 in Egypt 61% for bla_{GES} gene and 29% for bla_{VIM} gene [22], about 70% of our *A. baumannii* isolates tested positive for bla_{NDM} . This is higher than the report of Mesli, 2013 in Iran, who showed 6% prevalence [23].

Where in the study that has been done by Salma, 2016 in Sudan showed a fairly similarity with our study regarding the prevalence of ESBL bla_{TEM} gene 83% with higher prevalence of imipenem resistant gene bla_{VIM} 67% [24]. Interestingly, our study for bla_{OXA48} gene was the most predominant gene (82%) that responsible for carbapenem resistance almost in the line with the study of Al-Agamy, 2014 in Egypt that showed 85% of isolates were positive to bla_{OXA48} [25].

Conclusion

All *A. baumannii* collected from hospitals of Khartoum state were phenotypically ESBL and 47% were imipenem resistant.

The bla_{TEM} gene was found to be the most prevalent type (100%) of β -lactamase-encoding gene, a high level of imipenem resistance is mediated by bla_{OXA48} , bla_{NDM} and as following: 82% and 70% respectively. Genes overlapping of ESBL and carbapenemase producers was

obvious; the shareness of *bla*_{TEM} gene and class C was the most prevalent 41%, where the shareness between the carbapenemase producers showed 52% of class D- *bla*_{NDM} complex.

Conflict of Interest

All authors declared there is no conflict of interest.

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