Prevalence of SUL(1,2), GYR(A, B) and OXA genes among multidrug resistance Klebsiella pneumoniae isolates recovered from women suffering urinary tract infection

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**ABSTRACT**

*Klebsiella pneumoniae* is a significant concern multidrug-resistant microorganism and a one common gram negative bacteria associated with infections of women urinary tract. Therefore, this work aimed to the molecular screening of Sul(1 and 2), Gyr(A and B) and OXA genes among *K. pneumoniae* isolates in Najaf City, Iraq. Out of 250 urine specimens were collected from women showing symptoms of urinary tract infection during five months January to May 2019, bacterial growth was 157 isolates, included 133 gram negative compared with 24 gram positive bacteria while 98 specimens were no growth. According to the Vitek-2 system, 30 *K. pneumoniae* isolates were obtained. Data on current work revealed that the 26-35 age group was the highest 14 *K. pneumoniae* isolates. Results of antimicrobial susceptible recorded all isolates were multi-drug resistant (MDR) and they have a different range of resistance. However, all 30 isolates (100%) resistant to ampicillin drugs, while the lowest rate was 1 (3.33%) for Imipenem drug. PCR assay revealed exist of oxa, sul-1, sul-2, gyr-A and gyr-B genes among *K. pneumoniae* isolates with rates 20 (66.66%), 11 (36.66%), 22 (73.33%), 3 (10%) and 17 (56.66%) respectively.

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**INTRODUCTION**

Urinary tract infection (UTIs) has become of the more prevalent bacterial infections, which impact nearly one hundred and fifty million person every year globally. *Klebsiella pneumoniae* isolate has been a major opportunistic microorganism that involved in infections of the human urinary tract. It has many virulence factors such as capsule, adherence factors, lipopolysaccharide, iron acquisition, as well as biofilm formation (Flores-Mireles et al., 2015).

Previously, there was an enormous index of antibacterial agents such as beta-lactam drugs, sulfonamides, fluoroquinolones as well as aminoglycosides were more successful in creating the desired result or limiting and controlling the infections occur by human gram negative pathogen, but last years, this pathogen involved *K. pneumoniae* showed emerging concern in multiple drug resistance in worldwide. At same respect, drug resistance mostly results from overuse and misuse of antimicrobial agents badly decrease the effectiveness of these drugs, leading to growing complication in *K. pneumoniae* therapy (Franci et al., 2015; Fernandes and Martens, 2017; Caneiras et al., 2019).

However, bacterial resistance to drugs usually due to different mechanisms, one important which exploited by the pathogen is catalyzed by enzymes encoded in genes harbored in chromosome or plas-
mid-mediated. Therefore, this work aimed to investigate the spreading of some genes which have related to a resistance of bacteria to some drugs.

MATERIALS AND METHODS

Bacterial specimens

The current study was focused on the role and rate of K. pneumoniae among bacterial urinary tract infection for women that attended to clinical laboratories in Najaf city, Iraq, during five months from the beginning of January to ending of May 2019, were collected 250 urine specimens from non-duplicate women patients.

Bacterial cultivation and identification

A total of 250 urine specimens were obtained randomly from women suspected to have urinary tract infection with old ranged from 16 to 50 years, where all urine specimens were collected by sterile container, the immediately transported to bacteriology laboratory in Faculty of Science, University of Kufa, then cultured on sterile blood agar and MacConkey agar plates and overnight incubated at 37°C under aerobic condition.

All bacterial growth were identified according to microscopic morphology, lactose ferment, motility, oxidase test as well asIMViC tests and all suspected isolates were finally identified using Vitek-2 system (Macfaddin, 2000; Shlash and Tuwaij, 2018).

Antibacterial agents assay

Current work involved testing susceptibility of different commercial classes of antimicrobial agents (bioanalysis, Tuekey) against 30 isolates of K. pneumoniae on the surface of muellerhinton agar according to methods of Kirby-bauer (Bauer et al., 1966). The resistance, intermediate and sensitive of isolates were limited depending on the instructions of the Clinical and Laboratory Standards Institute (CLSI, 2017). All antimicrobial disks with their concentration enrolled in Table 5.

Total DNA extraction

Total genomic DNA of were extracted from overnight liquid growth for 30 isolates of K. pneumoniae using a genomic extraction kit (Favorgen, Biotech Corp., Korea), where the extraction was performed depending on the protocol of the company. All DNA was stored under -20°C condition using deep freezing until done PCR to the detection of oxa, Sul-1, Sul-2, gyr-A and gyr-B genes using specific primers and conditions listed in Table 2. The apparatus of gel document system (Cleaver, United Kindom), was used to see and migrate of PCR product after stained the gel with ethidium bromide.

Statistical analysis

The Significance statistical and Comparing among data of the current study was analyzed according to Fisher’s exact test (Graph pad prism version 10).

RESULTS AND DISCUSSION

Patients specimens

Results of bacterial growth on culture media among 250 non-duplicate patients have UTIs, were revealed that the rate of bacterial growth in gram negative was 133 (53.2%) while gram positive bacteria reached to 24 (9.6%), at the same time, 93 (37.2%) was no bacterial growth (Table 3).

K. pneumoniae identification and age groups

According to results of morphology, biochemical test as well as vitek-2 system, among 133 (53.2%) gram negative bacteria obtained only 30 (22.55%) isolates identified as K. pneumoniae (Table 4).

Data of Table 4 was appeared that K. pneumoniae able to cause infection to various woman age groups but at different rates. The highest rate of infection was 14 (27.45%) between 26-35 ages, while the lowest rate observed between 46-50 ages reached to 1 (7.69%).

Susceptibility of K. pneumoniae isolates using the disk diffusion method

This work also involved study the susceptibility of 30 K. pneumoniae isolates against different classes of antibacterial agents. At the same respect, the data revealed that all 30 K. pneumoniae isolates were resistance to three different antibiotic classes and considered as multi-drug resistance (MDR). However, the resistance of this pathogen was high resistances included 30(100%) Ampicillin, 27(90%) Cefotaxime, 26(86%), Ceftazidame, while Tetracycline and Trimethoprim reached to 24(80%). Lowest rate of resistance found in Imopenem, Meropenem and Netilmicin reached to 1(3.33%), 5(16.66%) and 10(33.33%) respectively. Others antibacterial agents give resistance ranged from 13(43.33%) to 20(66.66%) as shown in Table 5.

Molecular investigation

According to data analysis of PCR products, this study revealed that oxa gene has high frequency among K. pneumoniae isolates, out of 30 isolates found 20(66.66%) harbor positive band for the bla-oxa gene (Figure 1). At same respect, the results proved that K. pneumoniae isolates have both sul-I and sul-2 genes but at different rates reached to 11(36.66%) and 22(73.33%) respectively(Figures 2
### Table 1: Specific primer sequence used in this work

| Gene | Name | Sequence (5’ to 3’) | Product size (bp) | Reference |
|------|------|---------------------|------------------|-----------|
| oxa  | oxa-F | ATATCTCAGTGTGACATCTCC | 618 | Karami et al. (2008) |
|      | oxa-R | AAAACCCCTAAACCACATCC | | |
| sul-1| sul1-F | GGATGGGATTTTTCTTGAGCCCCGC | 308 | Wain et al. (2003) |
|      | sul1-R | ATCTAACCCCTGTCCTCTGTCGGTGC | | |
| sul-2| sul2-F | TCAACATAACCTGGGACAGT | 707 | Chu et al. (2001) |
|      | sul2-R | GATGAAGTCACTCCACCT | | |
| gyr-A| gyrA-F | ATGGCTGAATTAACCTCAATC | 398 | Sierra et al. (2002) |
|      | gyrA-R | GTGTAAGTTTGCTCATAAGC | | |
| gyr-B| gyrB-F | CAAAACGGCGGACTGTCAGG | 345 | Ling et al. (2003) |
|      | gyrB-R | TTCCGGCATCTGACGATGA | | |

### Table 2: PCR conditions used in this work

| PCR gene | Temperature (°C) / Time | Cycling condition | Final extension | Cycle Number |
|----------|-------------------------|------------------|----------------|--------------|
| oxa      | 94°C/5min               | Denaturation     | 72°C/1min      | 30           |
|          | 94°C/1min               | Annealing        | 72°C/10min     |              |
| sul-1    | 94°C/5min               | Denaturation     | 72°C/1min      | 30           |
|          | 94°C/1min               | Annealing        | 72°C/2min      |              |
| sul-2    | 94°C/5min               | Denaturation     | 72°C/7min      | 30           |
|          | 94°C/1min               | Annealing        | 72°C/5min      |              |
| gyr-A    | 94°C/5min               | Denaturation     | 72°C/1min      | 30           |
|          | 94°C/45sec              | Annealing        | 72°C/1min      |              |
| gyr-B    | 94°C/5min               | Denaturation     | 72°C/1min      | 30           |
|          | 94°C/1min               | Annealing        | 72°C/1min      |              |

### Table 3: Characteristics of Bacterial culture from urine specimens

| Bacterial culture | Number (percentage) | P value |
|-------------------|---------------------|---------|
| Gram positive     | 24 (9.6%)           | < 0.0001|
| Gram negative     | 133 (53.2%)***      |         |
| No growth         | 93 (37.2%)          |         |
| Total             | 250 (100%)          |         |

### Table 4: Distribution of *K. pneumoniae* isolates according to woman age groups

| Age groups (year) | Gram negative bacteria (percentage) | *K. pneumoniae* isolate (percentage) | P value |
|-------------------|-------------------------------------|-------------------------------------|---------|
| 16-25             | 28 (21.05%)                         | 6 (21.42%)                          | 0.0002  |
| 26-35             | 51 (38.34%)                         | 14 (27.45%)***                      |         |
| 36-45             | 41 (30.82)                          | 9 (21.95%)                          |         |
| 46-50             | 13 (9.77%)                          | 1 (7.69%)                           |         |
| Total             | 133 (100%)                          | 30 (22.55%)                         |         |
### Table 5: Antimicrobial susceptibility of *K. pneumoniae* isolates

| Antibiotic disk     | Sensitive | Intermediate | Resistance |
|---------------------|-----------|--------------|------------|
| Ampicillin (AMP, 10 µg) | 0(0%)    | 0(0%)        | 30(100%)  |
| Piperacillin (PRL, 100 µg) | 7(23.33%) | 3(10%)       | 20(66.66%)|
| Cefoxitin (FOX, 30 µg)    | 11(36.66%)| 4(13.33%)    | 15(50%)   |
| Cefotaxime (CTX, 30 µg)   | 3(10%)    | 0(0%)        | 27(90%)   |
| Ceftazidime (CAZ, 30 µg)  | 3(10%)    | 1(3.33%)     | 26(86%)   |
| Cefepime (FEP, 30 µg)     | 9(30%)    | 1(3.33%)     | 20(66.66%)|
| Aztreonam (ATM, 30 µg)    | 8(26.66%) | 2(6.66%)     | 20(66.66%)|
| Netilmicin (NET, 10 µg)   | 18(60%)   | 2(6.66%)     | 10(33.33%)|
| Amikacin (AK, 10 µg)      | 12(40%)   | 1(3.33%)     | 17(56.66%)|
| Tobramycin (TM, 10 µg)    | 9(30%)    | 3(10%)       | 18(60%)   |
| Ciproflaxacin (CIP, 10 µg)| 11(36.66%)| 5(16.66%)    | 14(46.66%)|
| Imipenem (IMP, 10 µg)     | 28(93%)   | 1(3.33%)     | 1(3.33%)  |
| Meropenem (MEM, 10 µg)    | 24(80%)   | 1(3.33%)     | 5(16.66%) |
| Tetracycline (TE, 30 µg)  | 6(20%)    | 0(0%)        | 24(80%)   |
| Doxycycline (DO, 30 µg)   | 15(50%)   | 2(6.66%)     | 13(43.33%)|
| Trimethoprim (TMP, 5 µg)  | 4(13.33%) | 2(6.66%)     | 24(80%)   |

**Figure 1:** Amplification product of *bla-oxa* gene among 30 isolates of *K. pneumoniae*
Figure 2: Amplification product of Sul-1 gene among 30 isolates of *K. pneumoniae*.

Figure 3: Amplification product of Sul-2 gene among 30 isolates of *K. pneumoniae*. 
Figure 4: Amplification product of Gyr-A gene among 30 isolates of *K. pneumoniae*

Figure 5: Amplification product of Gyr-B gene among 30 isolates of *K. pneumoniae*
Table 6: Phenotypic and genotypic characteristics of *K. pneumoniae* isolates

| No | Phenotypic characteristics (Antimicrobial agent resistance) | Genotypic characteristics |
|----|-----------------------------------------------------------|----------------------------|
| 1  | AMP, FOX, TMP, AK, TE                                    | -                          |
| 2  | AMP, CAZ, CTX, TMP, AK, NET, CIP, TE                     | -                          |
| 3  | AMP, PRL, FOX, CAZ, CTX, FEP, TE, DO                    | OXA, Sul-2, GyrA, GyrB     |
| 4  | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TM, AK, CIP, TE, DO | Sul-1, Sul-2, GyrB        |
| 5  | AMP, CAZ, CTX, FEP, TMP, AK, CIP, TE, DO                | OXA, Sul-2, GyrB           |
| 6  | AMP, CAZ, CTX, FEP, TMP, TM, AK, TE, DO                 | OXA, Sul-1, Sul-2, GyrB    |
| 7  | AMP, CAZ, CTX, FEP, AZM, TMP, TM, CIP, TE, DO          | OXA, Sul-2, GyrA, GyrB     |
| 8  | AMP, CTX, FEP, AZM, TMP, TM                             | OXA, Sul-1, Sul-2, GyrB    |
| 9  | AMP, CAZ, CTX, TMP, TM, TE                              | Sul-2                      |
| 10 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TM, AK, NET, CIP, TE, DO | OXA, Sul-2     |
| 11 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TM, AK, CIP, TE | OXA, Sul-1, GyrB          |
| 12 | AMP, CAZ, CTX, FEP, TMP, TM, AK, NET, MEM, IMP, CIP, TE  | OXA, Sul-1, Sul-2, GyrB    |
| 13 | AMP, PRL, FOX, CAZ, CTX, TMP, TE, DO                    | OXA, Sul-1, Sul-2, GyrB    |
| 14 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, MEM, CIP, TE    | OXA, Sul-1, Sul-2, GyrB    |
| 15 | AMP, PRL, CAZ, CTX, FEP, AZM, TM, AK, NET, TE          | -                          |
| 16 | AMP, PRL, FOX, CTX, FEP, AZM, TMP                      | OXA, Sul-1                |
| 17 | AMP, FOX, CAZ, CTX, FEP, AZM, TMP, TE, DO              | OXA, Sul-1                |
| 18 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TM, AK, NET, MEM, TE | Sul-1, Sul-2, GyrB    |
| 19 | AMP, PRL, CAZ, CTX, FEP, AZM, TMP, TE                   | OXA, Sul-1, Sul-2, GyrB    |
| 20 | AMP, PRL, CAZ, CTX, FEP, AZM, TMP, TM, AK, NET, CIP, TE, DO | OXA, Sul-2, GyrB          |
| 21 | AMP, FOX, TMP, TE, DO                                   | Sul-2                      |
| 22 | AMP, PRL, CAZ, CTX, AZM, TMP, AK, CIP, TE, DO          | OXA, Sul-2, GyrB          |
| 23 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TE             | OXA, Sul-2                |
| 24 | AMP, PRL, FOX, CAZ, CTX, FEP, AZM, TMP, TM, AK, NET, CIP, TE | OXA, Sul-2, GyrB          |
| 25 | AMP, CAZ, CTX, TM, MEM                                  | OXA, Sul-2, GyrB          |
| 26 | AMP, PRL, FOX, CAZ, CTX, AZM                           | OXA, Sul-2, GyrB          |
| 27 | AMP, CAZ, CTX, TMP, TM, AK, NET, CIP                    | Sul-2, GyrB               |
| 28 | AMP, CAZ, CTX, FEP, AZM, TMP, TM, AK, NET, CIP, TE, DO  | Sul-2, GyrB               |
| 29 | AMP, PRL, FOX, AZM, MEM                                 | Sul-2                      |
| 30 | AMP, PRL, FOX, CAZ, CTX, TMP, TM, AK, NET, CIP, TE, DO  | OXA, Sul-2, GyrB          |

and 3). On other hands, this work was investigated the frequency of gyr-A and gyr-B genes using specific primers among 30 multi-drug resistance *K. pneumoniae* isolates which reached to 3(10%) and 17(56.66%) for gyr-A and gyr-B genes respectively (Figures 4 and 5).

At same respect, 6 revealed that 2 isolates of *K. pneumoniae* (no. 6 and 12) have five genes and three isolates were negative for all tested genes in this study.

Bacterial isolates were involved in this work only predominant growth while mixed non-predominant growth was excluded. The data showed among 250 urine specimens, 30 isolates belong to *K. pneumoniae* and this result corresponds with several local and global previous studies (Aljanaby et al., 2018). In Najaf city, a study done by Shlash and Tuwaij(2018) they indicated that out of 200 urine specimens obtained 40 isolates of *K. pneumoniae*. The current study revealed that gram negative bacteria isolated more than gram positive bacteria this may be due to they are endogenous as well as exogenous. However, this data agree with (Foxman, 2014) who mention The causative of UTIs infections originate from Gram-negative bacteria, particularly Enterobacteriaceae, and some Gram-positive pathogen.

One of the main aim of current work was estimation of antibiogram profile for 30 isolates of
achieved by (Antunes and Fisher, 2014). This rate was more than a previous local study (Hayder and Aljanaby, 2016; Abrar et al., 2019; Ranjar et al., 2019). High frequency of this gene made bacterial resistance to ranges of penicillins, some cephalosporin generations and sometime extend to involve carbapenem drugs (Antunes and Fisher, 2014).

Sulfa drugs are a group of synthesized medicine agents which still wide used in treatment of urinary tract infections through effect on bacterial growth (bacteriostatic drugs) by prevent synthesis of folic acid in bacteria (Tacic et al., 2017). Here, this work focused on distribution of sulfonamide-resistant genes included sul-1 and sul-2 genes among 30 MDR K. pneumoniae isolated from women suffering from UTI. However, both genes sul-1 and sul-2 were 11(36.66%) and 22(73.33%) respectively. This rate was more than a previous local study achieved by (Hayder and Aljanaby, 2019) they found among 30 MDR Citrobacter freundii isolated from UTI patients, rate of sul-1 and sul-2 genes were 7(23.33%) and 11(36.6%) respectively. Also this rate was higher than a study done by (Shin et al., 2015) who found, rate of sul-1 and sul-2 genes were 2(18.8%) and 5(31.2%) among 15 K. pneumoniae isolates.

At the same respects, the results of molecular assays about DNA gyrase genes were estimated. gyr-B gene was high frequency compared with gyr-A gene. One reason may be due to continuous pressure to overuse of antimicrobial agents involved macrolide groups in Iraq led pathogen to acquired or mutation to resistance this medicine. However, A study achieved by (Hou et al., 2015). In china, they mention among 38 multidrug-resistance K. pneumoniae isolated from different sources found 27 isolates harbored gyrA gene while DNA gyrase gene (gyr-B), not detection. However, the data of PCR as shown in Table 6 appeared that 3 isolates of K. pneumoniae no. 1, 2 and 15 were MDR but negative for all tested genes this maybe return to other mechanisms for drugs resistance.

CONCLUSIONS

Klebsiella pneumoniae is a significant contagious among women that suffering from urinary tract infection, which has a high resistance to most antibacterial agents except imipenem drug remains the most efficient antibacterial agent against this pathogen. Molecular assay appeared that K. pneumoniae harbored oxa, sul-1, sul-2, gyr-A and gyr-B genes with different rates.

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