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Original article

Molecular Characterization of Multidrug-Resistant *Klebsiella pneumoniae* Isolated from Some Hospitals in Benghazi, Libya

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ABSTRACT

Klebsiella pneumoniae is one of the leading causes of hospital outbreaks worldwide, mainly in hospitalized or immune-compromised individuals. Also, this could be due to the emergence of Multidrug resistance (MDR) Extended Spectrum Beta Lactamase (ESBL) and carbapenemase-producing strains. This study's main goals were to evaluate the prevalence of resistance demonstrated by K. pneumoniae strains found in clinical samples from Benghazi Medical Center and AL-jalaa Hospital and to find evidence of ESBL strains and their resistance to certain antibiotic. During the study period, K. pneumoniae was isolated from 320 clinical samples (urine, sputum, blood and wound). The procedure for processing of samples, identification, susceptibility toward antimicrobials and evidence of ESBL, MBL strains were carried out according to the recommended standards. PCR was used to detect β-Lactamase and carbapenemase resistance genes. From a total K. pneumoniae isolates, 120 (37.5%) were isolated from hospital patients. The isolates exhibited high resistance to all used antibiotics. Forty-eight (40%) of the isolates were ESBL producers. MDR and XDR were identified in 89% and 56% of isolates respectively. ESBL-CTX-M-15 gene and OXA-48 were detected in all isolates. Moreover, SHV and NDM were identified in four isolates. In this study shows the high rate of MDR in clinical K. pneumoniae isolates in hospitals. There is an urgent need to implement an antibiotic resistance surveillance system to regulate and continuously monitor the emergence of antimicrobial resistance.

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INTRODUCTION

Up to 10% of nosocomial infections are caused by the Gram-negative encapsulated bacteria *Klebsiella pneumoniae*, or KP. It is increasingly linked to invasive infections that have significant morbidity and mortality rates [1]. The opportunistic pathogen; *k. pneumoniae* is a member of the Enterobacteriaceae family, that has emerged as major clinical problem causing both hospital-associated and community -acquired infections due to the rising prevalence of multidrug-resistant strains(MDR) [2,3]. MDR strains of *K. pneumoniae* can be difficult to treat, particularly in the elderly and in young children with immature immunity. *K. pneumoniae* causes a number of infections, including wound infections, bacteremia, pneumonia, and urinary tract infections. These infections are typically caused in hospitalized or immune-compromised people [4]. Since the introduction and widespread use of new generation extended range antibiotics, there has been a significant increase in the prevalence of bacterial species resistant to drugs. By producing enzymes such as carbapenemase and extended spectrum lactamases (ESBLs) [5]. Currently, *K. pneumoniae* strains producing (*ESBL*) and carbapenemases have spread globally. One pathway involves the expression of (ESBLs) that contributes to produce resistance in *K. pneumoniae* against cephalosporin and monobactam. Another extremely worse resistance mechanism is that the expression of carbapenemases by *K. pneumoniae*, which contribute to resistance of *K. pneumoniae* against most offered β-lactams as well as the carbapenems [1]. In addition, *K. pneumoniae* has been reported to be the most common pathogenic bacteria to develop resistance to broad-spectrum beta-lactam antibiotics via (ESBL). The number of people who are more prone to infection has increased due to the emergence and spread of hyper-virulent strains. Before the gene became widespread in other pathogens, *K. pneumoniae* was the source of several novel antimicrobial-resistance genes. Example of these genes are $bla_{\text{OXA-48}}$-like, $bla_{\text{SHV-X}}$, $bla_{\text{NDM-1}}$, $bla_{\text{CTX-M-15}}$ and $bla_{\text{TEM-X}}$ [6].

The relevance of MDR bacteria has increased recently in Libya especially among Gram-negative bacteria including *K. pneumoniae*, which showed the highest resistance to most of antibiotics in a previous study on patients in intensive care unit at BMC in Benghazi, Libya [7]. This might be due to the abuse of antimicrobials including Carbapenems, ESBL in hospitals and poorly applied infection control practices [8]. Genotyping methods are important in finding the genetic affinity between bacterial isolates and also in the classification of bacteria, identification the sources of infection and characterization of the most pathogenic strain. Molecular epidemiology analysis gives us the information we need to create strategies to stop the spread of clinically dangerous strains by enabling us to ascertain the global spread of high-risk clones [6]. A little information of antibiotic resistance in Libya is known and the genetic basis of Beta-lactam resistance was not available at a large scale in Libya, therefore the main goal of this study was to determine the antibiotic resistance profiles, incidence of MDR, XDR as well as Beta-lactams resistance genes among *K. Pneumonia* clinical isolates in Benghazi medical Centre (BMC) and Al-Jalaa Hospital at Benghazi, Libya.

METHODS

Bacterial isolates

Three hundred and twenty specimens (blood, urine, sputum, wound), were obtained from November 2021 to February 2022, that were collected in sterilized containers from both genders, their ages ranged between 20-75, from BMC and AL-jalaa Hospital, Benghazi, Libya. All specimens were incubated onto blood agar as a rich media, and both differential media; MacConkey agar and CLED agar. The plates were incubated for 18-24 hr at 37°C. Isolation and identification of microorganisms were done recommended standard methods. Bacteria were identified by examination of colonial morphology, Gram staining and biochemical tests include (Catalase, Oxidase, Urease, Citrate, Indole, Dnase and Triple Sugar Iron), in addition the isolated bacteria were confirmed by Phoenix system. Molecular identification was carried out by storage of isolates in Nutrient broth media with glycerol and stored in -20°C in Alakeed laboratory then transported in ice bag to isolation of genomic DNA from bacterial cells by boiling method. Then the molecular identification was done by the amplification of 16S ribosomal region using the PCR. The amplified DNA were sent to sequencing in Laboratory of Molecular Biology in Science College, Tunis El-Manar University [9]. Sequences were analyzed by BLAST and compared with those available at the National Centre for Biotechnology Information (NCBI) database) and Ribosomal Database Project (RDP) [9].

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by the method of disk diffusion according to guidelines of the National Committee for Clinical Laboratory Standards (NCCLS). The culture of each isolate was diluted to have turbidity around 0.5 McFarland standard, then plated onto Muller-Hinton agar plate (HIMEDIA). Antibiotic disks (Bioanalyze) were applied to each plate. After incubation at 37°C for 18-24hrs, the zone of inhibition diameter was measured. The isolates which were resistant common antimicrobial drug examined by synergism experiment [9].

Detection of ESBL and MBL phenotyping

Antimicrobial susceptibility testing for ESBLs. Performed in Al-Akeed Laboratory, Benghazi by Routine anti-biograms was determined by the disk diffusion method on Mueller-Hinton (MH) agar by placing disks of ceftazidime, cefotaxime, and cefepime at a distance of 30 or 20 mm (center to center) from a disk containing AMC (amoxicillin- clavulanic acid). ESBL production was inferred when the cephalosporin zone was expanded by the clavulanate (Fig. 1A), using Imipenem and EDTA-Imipenem (IEH) disc as a simple method to detect MBL producing clinical isolates (Fig. 1. B).

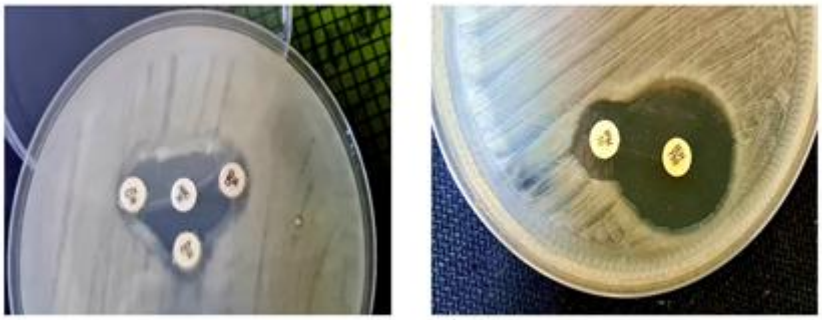

Figure 1. Phenotyping test for ESBL and MBL producing isolates.

Detection of antibiotic resistance genes

The presence of antimicrobial resistance genes was searched by PCR and sequencing in some isolates (10). Table 1 showed the primers sequences and PCR conditions of beta-lactams *bla*$_{CTX\text{-}M\text{-}15}$, *bla*$_{SHV}$, *bla*$_{OXA\text{-}48}$ and *bla*$_{NDM\text{-}1}$.

Table 1. Primers, expected fragment size and conditions of PCR experiments used for antibiotic resistance encoding genes

Primers sequences of genes	Size(pb)	Amplification conditions
***Bla*$_{NDM}$** F: GGTTTGGCGATCTGGTTTTC R: CGGAATGGCTCATCACGATC	620bp	**94ºC 5 min 1 cycle** **94ºC 30 sec** **52ºC 40 sec 36 cycles** **72ºC 40 sec** **72ºC 7 min 1 cycle**
***bla*$_{OXA\text{-}48}$** F: TTGGTGGCATCGATTATCGG R: GAGCACTTCTTTTGTGATGGC	743bp	**96ºC 5 min 1 cycle** **96ºC 1 min** **61ºC 1 min 35 cycles** **72ºC 2 min** **72ºC 10 min 1 cycle**
bla$_{CTX\text{-}M}$ F: TTT GCG ATG TGC AGT ACC AGT AA R: CGA TAT CGT TGG TGG TGC CAT A	544bp	**96ºC 5 min 1 cycle** **96ºC 15 sec** **52ºC 15 sec 24 cycles** **72ºC 2 min** **72ºC 5 min 1 cycle**
***Bla*$_{SHV}$** F: CACTCAAGGATGTATTGTG R: TTAGCGTTGCCAGTGCTCG	885bp	**96ºC 5 min 1 cycle** **96ºC 15 sec** **52ºC 15 sec 24 cycles** **72ºC 2 min** **72ºC 5 min 1 cycle**

RESULTS

In this study, from 320 different clinical specimens obtained 120 (37.5%) of the *K. pneumoniae* isolates were obtained. The highest number of the *K. pneumoniae* isolates was acquired from the urine samples (n=43; 35.5%) and the lowest number was in blood samples (n=20; 17.4%). Analogous to gender, *K. pneumoniae* afflicted male patients more frequently than female patients (n = 62; 51.7.2%), with the former having a higher incidence rate. Furthermore, studies on the frequency of *K. pneumoniae* in urine samples showed that it was more common in females than in males, on the other hand, males were more likely to have the infection in samples of blood, sputum and wounds, as shown in table 2. Phenotypically, susceptibility testing revealed that each isolated strain was highly resistant to the majority of the antibiotics used in this research. Blood samples derived *K. pneumoniae* strains were resistant to the majority of

antibiotics. (Figure 2). In contrast, Table 2 indicates that all *K. pneumonia* isolates from all samples showed low resistance to Doxycycline (urine=24%, blood=15%, wound=10% and sputum=7.5%). All *K. pneumonia* separates from all specimens showed high resistance (100%) toward amoxicillin / clavulanic acid, Azactam, Levofloxacin, and Tigecycline.

Table 2. Incidence of K. pneumoniae isolates from different clinical samples according to gender

Source	Gender		Prevalence (%)
	Males n (%)	Females n (%)	
Urine	16(13)	27(22.5)	43(35.5)
Wound	17(14)	13(10.8)	30(24.8)
Sputum	17(14)	10(8.3)	27(22.3)
Blood	12(10.7)	8(6.7)	20(17.4)
Total	62(51.7)	58(48.3)	120(100)

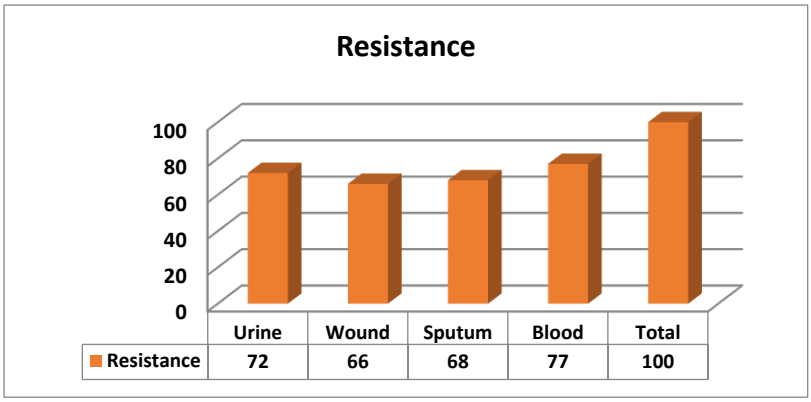

Figure 2. Distribution of antibiotic resistance of K. pneumoniae strains according to samples source.

Table 3 displayed the antibiotic resistance pattern of *K. pneumoniae* strains isolated from clinical samples. By conventional criteria, it is calculated to be designated statistically significant ($p< 0.05$). The *P*-value was 0.00001**,** comparatively, results were significant**.** Out of all the isolates, 71.2% produced MBL, while 48 (40%) of the strains generated ESBL. In addition, 89% and 56% of the organisms were found to be multidrug-resistant (MDR) and XDR, respectively. OXA-48 and NDM were found in six isolates and five isolates respectively. β-lactamase genes, ESBL-CTX-M-15 type and SHV were identified in four and three strains respectively.

Table 3. Antibiotic resistance pattern of K. pneumoniae strains.

Antibiotics	Urine n=43(%)	Wound n=30(%)	Sputum n=27(%)	Blood n=20(%)	Total n=120(%)
Amkacin	34(79)	25(83)	25(92.5)	19(95)	103(85)
Amoxicillin/clavulanic	43(100)	30(100)	27(100)	20(100)	120(100)
Azactam	43(100)	30(100)	27(100)	20(100)	120(100)
Cefixime	40(93)	30(100)	26(96)	-	96(96%)
Cefotaxime	35(81)	29(96.6)	26(96)	20(100)	110(91%)
Ceftazidime	43(100)	29(96.6)	26(96)	20(100)	118(98%)
Ceftriaxone	41(95)	29(96.6)	26(96)	20(100)	116(96%)
Ciprofloxacin	43(100)	28(93)	27(100)	20(100)	118(98%)
Doxycycline	10(24)	3(10)	2(7.5)	3(15)	18(15)
Gentamicin	43(100)	30(100)	26(96)	19(95)	118(98)
Imipenem	27(62)	22(73)	23(85)	17(85)	89(74)
Levofloxacin	43(100)	30(100)	27(100)	20(100)	120(100)
Meropenem	39(90)	24(80)	24(88)	19(95)	106(88)
Tazobactam+piperacillin	42(97.6)	29(96.6)	27(100)	20(100)	118(100)
Tetracycline	42(97.6)	30(100)	26(96)	-	80(80)
Tigecycline	43(100)	30(100)	27(100)	20(100)	120(100)
Sulfamethoxazole-trimethoprim	32(74)	28(93)	25(92.5)	20(100)	105(87)

Table 4. Molecular characteristics of the four K. pneumoniae isolates recovered from infected patients in two Benghazi Hospitals

Isolation Source	Strains	Antibiotic resistance phenotype	Antibiotic resistance genes			
			bla$_{CTX-M-15}$	*bla*$_{OXA-48}$	*bla*$_{NDM}$	*bla*$_{SHV}$
Urine	*K. pneumoniae*	IPM, MEM, ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, TPZ, DO	+	+	+	+
Wound	*K. pneumoniae*	IPM, MEM, ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, AMC, TPZ, DO, AZM	+	+	-	+
Blood	*K. pneumoniae*	IPM, MEM, ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, AMC, TPZ, DO, AZM	+	+	+	+
Sputum	*K. pneumoniae*	ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, AMC, TPZ, AZM	+	+	+	-
Blood	*K. pneumoniae*	IPM, MEM, ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, AMC, TPZ, DO, AZM, CT	-	+	+	-
Sputum	*K. pneumoniae*	IPM, MEM, ETP, CIP, LEV, CN, AK, CTX, CAZ, CRO, AMC, TPZ, DO, AZM, CT	-	+	+	-

DISCUSSION

Since *K. pneumoniae* is the cause of 14–20% of infections linked to the respiratory tract, lower biliary duct, surgical wounds, bacteremia, and urinary tract, it has gained significance in the healthcare industry [11]. Antimicrobial resistance has been recognized as an important global health dilemma over the past few decades [12]. The main causes of resistance are inadequate sanitation and hygiene, overuse of antibiotics in humans and animals, and ineffective infection prevention and control in healthcare settings. The effects of antibiotic resistance on health and the economy are profound. All clinical *K. pneumoniae* isolates detected showed high resistance to all antibiotics especially amoxicillin / clavulanic acid, Azactam, Levofloxacin and Tigecycline. In addition, the high percentage of resistance (>75%) to the tested antibiotics in this study could be caused by overuse or inappropriate use of these drugs in our country, particularly because they are easily accessible and Libya does not have an antibiotic policy in place. In a related study, high resistance to *K. pneumoniae* was reported [13,14]**.** MDR- *K. pneumoniae* infections are highly lethal and frequently linked to a higher chance of receiving insufficient antibiotic treatment [15]. High rates of MDR (89%) strains were recorded in this study besides 56% of isolates were XDR. These findings are in agreements with the results in Brazil, they found that 85% of *K. pneumoniae* isolated from intensive care unit were MDR [16]. In China, most of *K. pneumoniae* strains isolated from neurosurgery patients were MDR and XDR [17]. In this study, we found that 40% (n=48) of the *K. pneumoniae* isolates were ESBL producers. Information of ESBL production collected from different countries showed the diverse rates ESBL in the *K. pneumoniae* strains. In Syria, the frequency of ESBLs producers of *K. pneumoniae* were (67.5%) [14]. In Palestine, 59.3% of clinical *K. pneumoniae* strains were ESBLs [13]. In Arab Galf, the ESBL phenotypes among *K. pneumoniae* strains were 23.5% and 36% in Kuwait and United Arab Emirates respectively [18,19]. The CTX-M family, which codes for extended-spectrum β-lactamases, is highly prevalent particularly CTX-M-15 variant and has emerged as a significant concern in global health settings [20]. CTX-M-15 was detected in four strains in our study which has been identified in many countries [21,22]. The CTX-M-15 enzyme is known to spread quickly over numerous nations. The easy dissemination of this gene is linked with the epidemic plasmid which can be horizontally mobilized [23]. The present study identified the carbapenem resistance genes *bla*$_{OXA-48}$, and *bla*$_{NDM}$. These determinants were detected with other β-lactamases *bla*$_{CTX-M}$ and *bla*$_{SHV}$ in the same strain. There limited data about the carbapenem resistance genes in Libya. Mathlouthi et al., [24] reported *bla*$_{NDM-1}$ and *bla*$_{OXA-23}$ genes among *Acinetobacter baumannii* isolates from two Libyan hospitals. El Salabi et al., [25] detected *bla*$_{NDM-1}$ and *bla*$_{OXA-23}$ genes in clinical *A. baumannii* and *P. aeruginosa* in Libyan hospital. The most important mechanism of carbapenem resistance are capable of enabling bacteria to resist to different antimicrobial agents including third generation cephalosporins, and others [26,27]. The detection of these elements reflects the situation in Libyan hospitals and will complicate the infection treatments.

CONCLUSION

The findings from this study might add to the body of knowledge about MDR and XDR organisms in Libya. Hospitals are facing a serious threat from MDR *K. pneumoniae* strains that are growing resistant to the majority of antibacterials. The growing number of these isolates highlights the significance of selecting a suitable empirical antibiotic therapy in accordance with patterns of antibiotic susceptibility, while the optimal selection of an antimicrobial regimen requires continuous local monitoring of resistance tendencies. The results of this research showed that in the Benghazi hospitals, had a high incidence of recurrence of MDR *K. pneumoniae* isolates, XDR, and resistance genes, particularly $bla_{\text{CTX-M-15}}$, $bla_{\text{OXA-48}}$, and $bla_{\text{NDM-1}}$. This suggests that MDR and XDR strains need to receive greater attention. Further studies aimed to clarify the molecular basis of resistance mechanism will contribute to a better understanding of the *Enterobacteriaceae* species that produce ESBL.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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التوصيف الجزيئي لبكتيريا كليبسيلا الرئوية المقاومة للأدوية المتعددة المعزولة من بعض المستشفيات في بنغازي، ليبيا

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[8]قسم النبات، كلية العلوم، جامعة بنغازي، بنغازي، ليبيا
[9]قسم الأحياء الدقيقة، مستشفى الجلاء، بنغازي، ليبيا
[10]قسم الأحياء الدقيقة والمناعة، المدرسة الوطنية للطب البيطري، جامعة منوبة، سيدي ثابت، تونس

المستخلص

تعتبر الكليبسيلا الرئوية واحدة من اهم البكتيريا المسببة للعدوى داخل المستشفيات في جميع أنحاء العالم، خاصة في المرضى داخل غرف العناية الفائقة أو المرضى الذين يعانون من ضعف المناعة. وتكمن خطورة هذه البكتيريا في مقاومتها للمضادات الحيوية وظهور سلالات مقاومة للأدوية المتعددة (MDR) وانتاجها للانزيمات المقاومة لمجموعة السيفالوسبورينس ومجموعة الكاربابينمي MBL،ESBL كان هدف الدراسة هي تقييم مدى انتشار المقاومة التي أظهرتها سلالات الكلبسيلا الرئوية الموجودة في العينات السريرية من مركز بنغازي الطبي ومستشفى الجلاء وإيجاد أدلة على سلالات ESBL وMBL. خلال فترة الدراسة، تم عزل الكلبسيلا الرئوية من 320 عينة سريرية تتضمن البول والبلغم والدم والجروح. تم تعريف هذه العزلات و اختبار هذه السلالات لانتاجها ESBL و MBL وفقًا للمعايير الموصى بها. تم استخدام PCR للكشف عن جينات المقاومة β-Lactamase وcarbapenemase. من مجموع عزلات الكلبسيلا . الرئوية, أظهرت العزلات مقاومة عالية لجميع المضادات الحيوية المستخدمة. ثمانية وأربعون (48٪) من العزلات كانت منتجة لانزيم ESBL. تم التعرف على MDR وXDR في 89% و56% من العزلات على التوالي. تم تحديد وجود جين ESBL-CTX-M-15 وOXA-48 في جميع العزلات. علاوة على ذلك، تم تحديد جين SHV وNDM لبعض العزلات التي تمت دراستها . في هذه الدراسة تبين ارتفاع معدل MDR في عزلات الكليبسيلا الرئوية السريرية في المستشفيات. خطورة انتشار هذه البكتيريا يحتاج الي تنفيذ نظام مراقبة مقاومة المضادات الحيوية لتنظيم ورصد ظهور مقاومة مضادات الميكروبات بشكل مستمر.

الكلمات الدالة. K. pneumoniae، β-lactamase، MDR/XDR، تحليل تفاعل البوليميراز المتسلسل، جينات المقاومة