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# Virulence Factors of *Klebsiella pneumoniae* Isolates from Iraqi Patients

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ABSTRACT
The aim objective of this research is a review study of the virulence factors of *Klebsiella pneumoniae* isolated from Iraqi patients, where the world is currently facing a major problem orwe say a war between bacteria and antibiotics. The most important of these bacteria is *K. pneumoniae* and it is one of the opportunistic bacteria and is considered one of the causes of nosocomial infection, contamination of wounds , Urinary tract infection and contamnation of operating theaters. Where these bacteria are distinguished by their resistance to β-lactam antibiotics to produce β-lactamase as well as having a lipopolysaccharide and an important virulence factor is the capsule that resists phagocytosis. An important factor for these bacteria is their formation of biofilm, which is primarily responsible for chronic infections because of their resistance to phagocytosis and killing due to humoral and cellular immunity. The excessive use of antibiotics, which led to the resistance of bacteria to these antibiotics and is the main cause of the current problems of the world, as microorganisms have the ability to develop mechanisms that enable them to overcome these antibiotics more quickly and difficult to find alternatives to these antibiotics. Most of the changes that make bacteria resistant to many antibiotics are acquired changes that are caused by genetic changes or acquisition of resistant genes that make them resistant to many antibiotics.

**Keywords** *K.pneumoniae*, vieulence factors, β-lactamase, Lipopolysaccharid, Capsule.

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## INTRODUCTION

We will focus on the virulence factors of isolated samples from Iraqi patients to see how the *K. Pneumoniae* have developed resistance to antibiotics. The excessive use of antibiotics and the resistance of bacteria in general, especially the *K. pneumoniae*, to many of these antibiotics, despite the development taking place in the antibiotics, led to great risks in obtaining alternatives to these antibiotics due to the development of resistance in the bacteria to inhibit the action of these antibiotics and increase their virulence [1]. *K. pneumoniae* is considered one of the important cause pathogen from nosocomial infection especially for a patient who suffers from Immunocompromised or who are taking drugs immunosuppressed and who suffer from increase iron concentration in blood [2].

### Virulence factors

*K. pneumoniae* possess a number of virulence factors which share with pathogen and include capsule antigens, adhesion factors, enterotoxin produce like lipopolysaccharide as well as resistance killer effect for serum and system the gain on iron (Siderophore) and multi resistance for antibiotics which considered the main reason in spread acquired infections in hospitals, as the percentage infections 80% which led to find alternative treatments and we will mention some Iraqi research on these factors:

### The capsule

The capsule is considered fundamental to the virulence of *Klebsiella*, as it protects the bacterium from phagocytosis and prevents the bacteria by bactericidal serum factors [3]. Some serotypes or capsular types of *K. pneumoniae*, e.g. (K1, K2, K5, K54 and K57), have been correlating with invasive human infection illness. K1 was found among isolates causing Friedländers pneumonia, and has more recently been associated with pyogenic liver abscesses [4].

[5] studied the association between K-type, sequence type (ST) and virulence gene content. The authors concluded that K-types are not associated with specific *K. pneumoniae* clones and that K-types are published among unrelated clones by horizontal transmit of the *cps* operon, which encodes the synthesis of capsular polysaccharides. During recent years, several genes encoding virulence factors *K. pneumoniae* have been described: the plasmid-borne *rmpA* regulates the mucoid phenotype [6], *wcaG* is associated with reinforced bacterial get-away from phagocytosis [7], *kfu* is involved in iron acquirement, *fimH* encodes type 1 fimbriae, *mrkD* encodes type 3fimbriae and *cf29A* encodes the non-fimbrial adhesion factor CF29K [5].

In a study conducted by [8], the genotype K1 and K2 were used. Of the 46 isolate from these bacteria, eight were positive for K1, fourteen positive for K2 and 3 positives for both, while eighteen isolate did not contain either K1 or K2. In another study conducted by [9], forty isolates showed twenty three isolate carrying the K1 genotype, while eleven positive isolate of the K2 genotype and six isolates did not carry either type.

Other study by [10], one hundred sample of urine and sputum were collected from patients at Al-Yarmouk Teaching Hospital in Baghdad. 38 sample were obtained from *Klebsiella pneumoniae* and were only from UTI. These isolates showed resistance to most of the antibiotics such as Ceftazidime Augmentine, Ceftriaxone , and Cefotaxime , while lower resistance was shown to both Imipenem and Meropenem. The results also showed only four samples that were positive for the *wzy* gene, represented by K19 and K20, K21, K22.

Thirty nine isolate of *K. pneumoniae* were diagnosed in Al-Diwaniya Teaching Hospital for various cases (sputum,

urine, burns and wounds). The presence of capsule antigen (K) was detected by Multiplex PCR technique. The results showed that there were three serotypes K1, K57 and K2 that were more present than other types [11].

In another study by [12] of seven isolates of *K.pneumoniae* out of 34 sample. Thirty four samples were collected from Ramadi Teaching Hospital and Burns Specialized Hospital in baghdad, where the results showed that the isolates were resistant to most antibiotics as these seven isolates were diagnosed through a PCR to detect the mag A gene for serotype K1 and also for *rcsA* gene for genotype K2, the results showed that 5 isolates were related to type K2 and the remaining two isolates did not have any of the two types.

Lipopolysaccharide

Lipopolysaccharide represents an important and essential factor in bacterial pathogenicity, especially *K. pneumoniae*, as it is one of the superficial compositions of bacteria that help it to resist phagocytosis, and it is characterized by its ability to activate the complement factor [3]. It participates in protecting bacteria against the host's Complement System. LPS consists of three parts: Lipid A, Core polysaccharide, and O antigen, which consists of a side chain of the polysaccharide, and the antigen O is responsible for the bacteria's resistance to killing [13]. *K. pneumoniae* have eight serotypes, and serotype O1 and O2 are the most common.

*K. pneumoniae* O-antigen-deficient strains, community acquired pneumonia (CPS) protects the micro-organism against complement killing [14]. *K. pneumoniae* serotype O1:K1 plays a study role in virulence by transfer resistance to serum killing and by promoting bacterial dissemination to and colonization of internal organs after the start of bacteraemia [15].

In a study conducted by [16] where the CPS genotype was used, among 46 isolate of these bacteria, 43 were positive for this gene while only 3 isolates were missing for this gene. Two types of core polysaccharide (Type I and Type II) have been diagnosed produced by these bacteria, which are synthesized by two different groups of wa gene cluster. [17].

Outer membrane proteins

Is one of the important proteins of the gram negative bacteria are present in the outer membrane OmpA, which is characterized by most of the Enterobacteracea. OmpA is independent of the core polysaccharide in *K. pneumoniae* , which has an important role in preventing the activation of epithelial cells in the airway as it acts on NF-kB-p38- and p44 / 42- dependent pathways and thus particibate to the attenuation these cells through the inflammatory response [18].

An important factor that is produced by the *Klebsiella pneumoniae* is the expression of efflux pump AcrAB, whose action is not limited to exporting antibiotics only such as (quinolones and β- lactams), but also works to export anti-microbial agents derived from the host. The loss of AcrAB leads to a loss of the ability to cause pneumonia [19].

In a study by [20], on the resistance of multiple drugs by *K. pneumoniae*, which has the wide resistance to many antibiotics in Iraqi hospitals, Efflux pumps AcrAB was studied where 100 samples were taken from various sources from the medicine city and diagnosed by the 16S-23S rDNA gene It is present that 60 isolate were for *K. pneumoniae*, after which efflux pump AcrA gene was detected using a specific primer and it appeared that there are 26 isolates producing this gene. The results showed by studying the gene expression AcrAB-Tolc efflux pump using q(RT-PCR) that there is a relationship between the gene expression and chloramphenicol concentration, as well as the gene expression of the same gene increases from exposure to the Imipenem with some differences, while there was a decrease in the expression of Amikacin and Ciprofloxacin.

In a study in which the researcher collected 195 different clinical samples from three hospitals in the city of Al-Najaf and 50 samples from the hospital environment, where the *K. pneumoniae* was diagnosed by biochemical and cultural tests and the results showed that 89 isolates were for the *K. pneumoniae* where the resistance to quinolone antibiotics was examined by their growing on the MacConkey agar medium supported with the ciprofloxacin, it showed that 34 isolates were resistant to the ciprofloxacin antibiotic. As for the sensitivity test for 18 antibiotics, the results showed that 34 isolates had the characteristic of Multidrug resistant (MDR). Also in this study, the presence of resistance genes (*aac (6 ') -Ib-cr, qepA, qnrS and qnrB*) was detected, where the plasmid resistance gene showed *aac (6') -Ib-cr* gene is common among of other genes where it was found in 14 isolation alone or appeared with the qnrS gene, also at 8.82% for three genes *aac (6 ') -Ib-cr, qepA, qnrS* and showed 2.94% of isolates two genes are *aac (6') -Ib-cr and qnrS* while the *qnrB* gene appeared in only one isolate was sourced from wounds [21].

Hypermucoviscous phenotype

A distinguishing factor of hvKP strains is its hypermucoviscous phenotype. The great majority, but not all of the strains cause community-acquired pyogenic liver abscesses (CA-PLA) possess this phenotype [6].

In a study conducted by [16] where the *mag* viscosity gene was investigated for 46 isolates of these bacteria, it gave 21 positive isolates. and the genes responsible for regulating viscosity and mucous matter were studied using three types of genetic indicators (*rmpA1, rmpA rmpA2*). Results showed that 21 isolates contained the *rmpA* gene, while only 19 isolates gave a positive result for these indicators *rmpA1* and *rmpA2*.

In another study, forty isolates of *K. pneumoniae* were used, where the results showed that eleven strains were carriers of the rmpA gene, where five strains were carrying type K1 and also five strains of type K2 and only one strain of the two serotype together. The results also showed that the positive strains of the serotype K1 serotype gave amplification of both magA, rmpA and 16S rRNA genes while the *K. pneumoniae* strains of type K2 and non-carrier of the rmpA gene gave only amplification of serotype K2 and 16S rRNA and also the strains carrying type K1 and non-carrier of the gene were magA and 16S rRNA and finally the non-carrier

strains of the two types K1 as well as the K2 and non-carrier of the rmpA gene gave a positive result for the 16S rRNA gene. Through the results above, the results show that the genotype magA and k2A as well as any possible that is useful in detecting serotype K1 and K2 for *K. pneumoniae* [9].

Siderophores and Fimbrial adhesins

Sixty-one isolates of *K. pneumoniae* were isolated and diagnosed from 433 samples of children suffering from diarrhea in Kirkuk Hospitals, where virulence factors were determined for these bacteria and the results showed that all *K. pneumoniae* isolates were produced for the capsule, urease and siderophore. The results also showed that all isolates have the ability to adhere to human buccal cavity epithelial cells [22].

In a study in which *K. pneumoniae* were found to be able to remain in the urinary tract and their relationship to the genes responsible for forming the biological membranes *fimA, fimH, mrkA* and *mrkD*, the study included 50 isolated *K. pneumoniae* isolates from patients with UTI and these isolates were diagnosed by the VITEK 2 system apparatus or their ability to produce biofilms by using tissue culture plate method. Female infections were more than males 50/44 and 6/44 respectively, and results also showed that about 72% of isolates were biofilm production. Using the PCR technique, 12 isolates were detected, all carrying the fimA, fimH, mrkA and mrkD genes [23].

Virulence factors were detected for 32 isolates of *K. pneumoniae* isolated from various cases (sputum, urine, burns and blood) in Al-Najaf Governorate. As the capsule, hypermucoviscosity, and ability to form biofilms , produce siderophores and as well as the production of β-lactamase were revealed. PCR was used to detect genes that encode these factors (*fimH, ycfM*), (*kfu*: iron uptake system, *entB*: enterobactin, *irp-2*: yersiniabactin), capsule synthesis or invasions (*rmpA, uge, wabG*) and β-lactamase (*SHV, TEM*). The results showed that 100% of the isolates produced the capsule, biofilms and the siderophores, while for the hypermucoviscosity only 62.5% of the isolates had the ability to produce this factor. Also, most virulence genes appeared as *fimH-1, ycfM* and *entB* (100%), *uge* and *TEM* (93.75%), *wabG* and *SHV* (87.5%). While the *Kfu* and *rpmA* genes appeared 65.62 and 62.5%, respectively. The lowest percentage was for the *Irp-2* gene (37.5%). As for its ability to produce β-lactamase, 62% of the *K.pneumoniae* isolates showed their ability to produce this enzyme [24].

β–Lactam antibiotics

Due to their diversity, broad spectrum of activity and low toxicity, β- lactams are the most prescribed antibiotics worldwide. All β-lactam ring in common. Due to differences in their side chains, β-lactams may be classified into the following main groups: penicillins, cephalosporins, monobactams and carbapenems [25]. β-lactams target the bacterial cell wall synthesis and act by binding covalently to penicillin binding proteins (PBPs).

Carbapenem-**hydrolysing** β-lactamases (Carbapenemases)

Carbapenemases are clinically important because they destroy and so may confer resistance to carbapenems (and usually most other β-lactams). *K. pneumoniae* that produce class A Carbapenemases (KPC) are frequently identified worldwide [26]. *K. pneumoniae* Carbapenemases (KPCs) It is considered one of the important enzymes that work to destroy β-lactam antibiotics, as it works to break down the β-lactam ring and inhibit the action of these antibiotics, especially class A.

The researcher [27] collected 42 isolates of *K.pneumoniae* from burn infections in Baghdad hospitals, where sensitivity test was tested for all isolates for a number of antibiotics and the results showed that the ratios appeared as doxycycline (100%), tetracycline (95.23%), cefotaxime and piperacillin ( 85.71%), ceftriaxone (88.09%), trimethoprim-sulfamethoxazol (83.71), ticarcillin (78.57), aztreonam (71.2%) ceftazidime (69.4%) ciprofloxacin ( 59.52%) , gentamycin (26.16% ) , imipenem (21.42% ) and finally amikacin and meropenem (19.04 %).

In a study conducted by the researcher [28] to detect the presence of blaOXA-23 gene between 117 isolate of K. pneumoiae obtained from the hospitals in Al-Hilla, where the results showed that the highest percentage was found in stool followed by sputum samples. The initial sensitivity test of β-lactam antibiotics showed that 91 isolates were resistant to ampicillin and amoxicillin. About 17 isolates showed their resistance to carbapenems antibiotics, and the presence of blaOXA-23 gene was detected in these isolates using PCR technique, the results showed that 15 isolates of K. pneumoniae were carrier of this gene.

In another study, 135 urine samples were collected from patients with cystitis and confirmed by clinical diagnosis at Al-Hilla Teaching Hospital. The samples were diagnosed by biochemical and VITEK2 system tests. The results showed that 23 isolates were *K. pneumoniae* (31.9%) of the total samples. All of these isolates were tested for sensitivity to antibiotics, and the isolates showed high sensitivity to the amikacin 2(8.7%) norfloxacin 7(30.4%) and tobramycin 9(39.1%), while it showed resistance to the antibiotics ampicillin 23(100%), ceftazidim 20(91.3%), cefotaxime 19(82.6%) and cefepime 17(73.9%) and ertapenem 10(43.5%). The researcher used DDST as well as chromatic ESBL medium, MIC test strip and chromatic CRE medium for KPC for investigation of ESBL and KPC [29].

The ($bla_{KPC1}$ and $bla_{KPC2}$) genes were detected for a number of Iraqi samples isolated from different hospitals for patients with wounds, burns, sputum and urine in 2015 using specific primers of the first gene $bla_{KPC1}$ and the second gene $bla_{KPC2}$ where most of the samples showed their resistance to the carbapenem antibiotics and production of Carbapenemases, there are a number of variations showed compared to NCBI [30,31].

In another study conducted by [32], there was a variation in the resistance of carbapenem antibiotic, Among the 53 isolates of *Klebsiella pneumoniae* most isolates were sensitive to Meropenem and Imipenem antibiotic 90.5% and 77% respectively. The isolates showed higher resistance to third generation cephalosporins. Carbapenemases production was detected by the modified Hodge test, five carbapenem resistant *K. pneumoniae* isolates (K2, K3, K4,

K34 and K35) gave positive results for this test out of a total of 53 isolates. In the other part in this study, detection of *bla*$_{KPC}$ gene by PCR technique was carried out on all fifty-three *K. pneumonia* isolates. Even though five isolates gave positive modified Hodge test, only one isolate (K2) gave specific identification for *bla*$_{KPC}$ gene.

Another study, the results showed that 27 isolates of *K. pneumoniae* bacteria in Al-Hilla Teaching Hospital for isolated samples of urine and wound infection, that there is resistance to tetracycline and ceftriaxoneh antibiotics, and showed sensitivity to amikacin as well as imipenem [33].

In a study that collected 61 urine and stool samples in Al-Diwaniyah governorate to detect encoded genes for β-lactamase from patients with bladder and colon cancer. Where the results showed that *E. coli* and *K. pneumoniae* in urine samples 17 out of 23 samples, while the stool samples were 19 out of 26 samples and the samples were resistant to three classes of antibiotics. The PCR technique was used to detect the *bla*$_{TEM}$ and *bla*$_{SHV}$ genes, where it was found that most isolates carried at least one of the genes, and the highest was the *bla*$_{SHV}$ gene, then *bla*$_{TEM}$ at a rate of (66.7%) and (55.6%), respectively [34].

In a study conducted by [35] eighty isolates of *K. pneumoniae* among elderly patients (smokers and non-smokers) with chronic pneumonia in Al-Najaf Hospital. The results showed the sensitivity of a number of antibiotics that there was a variation in the levels of resistance between the antibiotics (amoxicillin, nitrofurantoin, Amoxiclav, Cefotaxime, Ceftriaxone, Ceftazidime, Gentamicin, Amikacin , Tobramycin and Tetracycline), and it was also found through the results that all the isolates of *K. pneumoniae* from smoking patients were resistant to all antibiotics compared to non-smokers. The results revealed that through detection of genotypic, 45 were carriers of the *bla*$_{TEM}$ gene, 31 were carriers of the *bla*$_{SHV}$ gene, while 18 isolates were carriers of both genes.

Due of the necessity of detection resistance genes, the researchers [36] collected eighty seven isolated urine samples from Al-Hilla Teaching Hospital for patients suffering from UTI, 34 isolate were gram negative bacilli , including 14 isolates that were for *K. pneumoniae* was produced for carbapenemase. The genotype was detected by the PCR of the *bla*-$_{IMP}$ and *bla* $_{OXA-48}$ genes, where results showed that 5 (35.7%) and 3 (21.4%) of *K. pneumoniae* were positive for *bla*$_{IMP}$ genes and *bla*$_{OXA-48}$ genes respectively .

Histamine- producing bacteria (HPB)

In a study by [37], fifty one specimen were collected from patients with respiratory infections in the Basra city . *K. pneumonia* was diagnosed by morphology and biochemical characteristics, as well as colonies culture on the Niven's agar media as the colonies of purple color are an indicator of bacteria producing histamine. All samples of *K. pneumonia* are diagnosed by the *HDC* gene and its expression is detected. The results showed that only 11 strains of *Klebsiella pneumonia* were positive for the production of histamine and most of them were sensitive to Trimethoprim but are resistant to Ampicilin, Sulbactam / Ambicillin.

In a diagnostic study by the researcher [38] for a number of isolated samples from different clinical sources (Sputum, wounds smear and Urine) through the *16Sr RNA* gene, the results showed that among the 25 isolates 10 samples from the *K. pneumoniae* showed this evidence of the pathogenicity of these bacteria and their resistance to antibiotics.

## CONCLUSION

Through a review of many research studies of the Iraqi isolates of *K. pneumoniae* within 5 years a go, it became apparent that over time, the ability of these bacteria to resist antibiotics increases through the development of the virulence factors they possess or possess by acquiring new characteristic. This indicator shows the difficulty of discovering new antibiotics that work to kill these bacteria therefore, plant extracts have been used recently to inhibit them.

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## REFERENCES

1. Kwakman P. H. S.; De Boer, L. ; Ruyter-Spira, C. P. ;Creemers-Molenaar ,T. ; Helsper, J. P. F. G. ; Vandenbroucke-Grauls , C. M. J. E. ; Zaat, S. A. J. ; and Te Velde A. A. (2011). Medical-Grade Honey Enriched with Antimicrobial Peptides has enhanced activity against antibiotic-resistant Pathogens. Eur J Clin Microbiol Infect Dis., 30(2): 251–257.
2. Arlet, G.;Nadjar, D.; Herrmann, J.L.; Donay , J.L.; Lagrange ,P.H. and Philippon, A(2001). Plasmid-mediated rifampicin resistance encoded by an arr-z like gene cassette in *Klebsiella pneumoniae* producing an Acc-1 class C β–Lactamase. Antimicrob. Agents Chemother. 45(10):2971-2972.
3. Podschun, R. and Ullmann, U.(1998). *Klebsiella spp* . as Nosocomial Pathogens: Epidemiology , Taxonomy , Typing Methods , and Pathogenicity Factors.clinical Microbiology Reviews. 11(4) : 589 – 603.
4. Gundestrup S, Struve C, Stahlhut SG.(2014). First Case of Liver Abscess in Scandinavia Due to the International Hypervirulent *Klebsiella pneumoniae* Clone ST23. Open Microbiol. 8: 22-24.
5. Brisse S, Fevre C, Passet ,. (2009).Virulent clones of *Klebsiella pneumoniae*: identification and evolutionary scenario based on genomic and phenotypic characterization. PLOS One; 4:4982.
6. Yu VL, Hansen DS, Ko WC. (2007). Virulence characteristics of *Klebsiella* and clinical manifestations of *K. pneumoniae* bloodstream infections. Emerg Infect Dis; 13: 986-993.
7. Wu JH, Wu AM, Tsai C. (2008). Contribution of fucose-containing capsules in *Klebsiella pneumoniae* to bacterial virulence in mice. Exp Biol Med ; 233: 64-70.

8. Mohammad S. Abdul-Razzaq, Jawad K. Tarrad Al-Khafaji1, and Esraa H. Khair-allah Al-Maamory.(2014). Molecular characterization of capsular polysaccharide genes of *Klebsiella pneumoniae* in Iraq, Int. J. Curr. Microbiol. App. Sci, Volume 3 Number 7 , pp. 224-234.
9. Majid H. Al-Jailawi, Tamara H. Zedan, Kifah A. Jassim.(2014). Multiplex-PCR Assay for Identification of *Klebsiella pneumoniae* , Int. J. Pharm. Sci. Rev. Res., 26(1), Pages: 112-117.
10. Shaima Basil Salman and Harith Jabbar Fahad Al-Mathkhury (2016). Molecular Detection of *Klebsiella pneumoniae* serotype K2 Isolated Clinically, Iraqi Journal of Science,Vol. 57, No.1A, pp: 89 -103.
11. Akeel M.Hamza AL-Hamdawee and Abdul-Jabbar K.Hassoon AL-Zeydi (2019). Diagnosis of *Klebssiella pneumonia* Isolated from Clinical Cases of Hospital - Acquired Infection in Al-Dewaniyah Teaching Hospital, AL-Qadisiyah Medical Journal, Vol.15, No.1, pp: 52-60.
12. O. N. Flaih, L. M. Najeb and R. K. Mohammad (2016). Molecular Detection of Serotypes K1 and K2 of *Klebsiella pneumonia* , Anbar Journal of Veterinary Science, Vol.9, No.1, pp: 1-7. Isolated Form Wound and Burn Infections
13. Evrard,B. , Balestrino,D. , Dosgilbert, J. L. , Gachancard,J. B., Charbonnel, N. , Forestier,C. , Tridon ,A. (2010) . Roles of Capsule and Lipopolysaccharide O Antigen in Interactions of Human Monocyte-Derived Dendritic Cells and *Klebsiella pneumoniae* .INFECTION AND IMMUNITY, Jan. 2010, p. 210–219. Vol. 78, No.
14. March C, Cano V, Moranta D. (2013).Role of bacterial surface structures on the interaction of *Klebsiella pneumoniae* with phagocytes.
15. Hsieh PF, Lin TL, Yang FL. (2012). Lipopolysaccharide O1 antigen contributes to the virulence in *Klebsiella pneumoniae* causing pyogenic liver abscess.
16. Mhammad S. Abdul Razzaq , Jawad Kadhim Trad and Esraa H. Ker-Alla Al-Maamory.(2013). Genotyping and Detection of Some Virulence Genes of *Klebsiella pneumonia* Isolated from Clinical Cases, Medical Journal of Babylon-Vol. 10- No. 2.
17. Fresno S, Jimenez N, Canals R. (2007). A second galacturonic acid transferase is required for core lipopolysaccharide biosynthesis and complete capsule association with the cell surface in *Klebsiella pneumoniae*. J. Bacteriol.189(3), 1128–1137.
18. March C, Moranta D, Regueiro V. (2011). *Klebsiella pneumoniae* outer membrane protein A is required to prevent the activation of airway epithelial cells. *J. Biol. Chem.* 286(12), 9956–9967.
19. Padilla E, Llobet E, Domenech-Sanchez A, Martinez-Martinez L, Bengoechea JA, Alberti S. (2010). *Klebsiella pneumoniae* AcrAB efflux pump contributes to antimicrobial resistance and virulence. *Antimicrob. Agents Chemother.* 54(1), 177–183.
20. Rafal M. Abdal Jabar and Athraa H. Hassoon (2019). The expression of efflux pump AcrAB in MDR *Klebsiella pneumoniae* isolated from Iraqi patients, J. Pharm. Sci. & Res. Vol. 11(2),423-428.
21. Majida M. Meteab Alshammari and Hussein Ali Al-Skhattat (2015). Detection of Plasmid-Mediated Quinolone Resistance Genes in Clinical and Environmental Hospital Isolates of *Klebsiella pneumoniae* in Al-Najaf City pneumoniae Klebsiella, Kufa Journal For Nursing Sciences Vol.5 No. 2,pp: 1-9.
22. Siham Sh. AL-Salihi , Yusra AR. Mahmood and Ali S. Al-Jubouri (2012). Pathogenicity of Klebsiella pneumoniae isolated from diarrheal cases among children in Kirkuk city, Tikrit Journal of Pure Science, Vol. 17(4), 17-25.
23. Ali Hussein Alwan and NoorNaeemKhwen (2017). DetectionOf genes Responsible for BiofilmsFormedby Klebsiella pneumoniaeandEsherichia coliand their effect on innate immunity, AJPS, Vol. 17, No.1, 192-203.
24. Ahmed Abduljabbar Jaloob Aljanaby and Alaa Hassan Abdulhusain Alhasani (2016). Virulence factors and antibiotic susceptibility patterns of multidrug resistance *Klebsiella pneumoniae* isolated from different clinical infections, African Journal of Microbiology Research, Vol. 10(22), pp. 829-843.
25. Yao J, Moellering R. (2011). Antibacterial Agents. In: Versalovic J, Carroll K, Funke G, eds, Manual of clinical microbiology. . 10th edn. Washington DC, ASM Press. p. 1043-1081.
26. Djahmi N, Dunyach-Remy C, Pantel A, Dekhil M, Sotto A, Lavigne JP.(2014). Epidemiology of carbapenemase-producing Enterobacteriaceae and Acinetobacter baumannii in Mediterranean countries. Biomed Res Int:305784.
27. Abbas Atyia Hammoudi1 and Azhar N. Hussein (2018). Antibiotic resistance of *Klebsiella pneumoniae* isolates from in patients with burn infections, Wasit Journal for Science & Medicine, Vol. 11(1): (133-145 ).
28. Fatima Moeen Abbas and Eman Mohammad Jarallah (2017). Detection of OXA-23 among Carbapenem Resistant Clinical Isolates of Klebsiella pneumoniae in Hilla, Journal of Babylon University/Pure and Applied Sciences/ No.(2)/ Vol.(25), 435-440.
29. Noor Salman Kadhim Al-Khafaji1, Hasanain Khaleel Shareef and Hussein Oleiwi Muttaleb Al-Dahmoshi (2015). Analysis of β-lactamases Among Multi Drug Resistant *Klebsiella pneumoniae* in Hilla city-Iraq, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 6(4) ,903-907.
30. Saade Abdalkareem Jasim, Mohammed Nadhir Maaroof and Najwa Shihab Ahmed(2017). Detection of polymorphism in $bla_{KPC2}$ of local *K. pneumoneiae*

isolation from Iraq patient, Journal of Biotechnology Research Center, 11(1), 26-33.

31. Saade Abdalkareem Jasim, Mohammed Nadhir Maaroof and Najwa Shihab Ahmed(2018). Detection of *bla*$_{KPC1}$ gene in *Klebsiella pneumoniae* isolated from Iraqi patients, American Research Foundation.
32. Abdulkadir Kareem Rhumaid and Harith J.F. Al-Mathkhury(2015). Detection of blaKPC Gene in Some Clinical Klebsiella pneumoniae Isolates in Baghdad, Iraqi Journal of Science, Vol 56, No.4A, pp: 2853-2861.
33. Samah Ahmed Kadhum (2018). Antibiotic sensitivity tests of *Klebsiella pneumonia* isolated from different clinical specimens in hilla city, Biochem. Cell. Arch. Vol. 18, Supplement 1, pp. 1351-1355.
34. Adnan H. Al-Hamadani,Adel M. Al-Rikabi and Atheer F. Al-Fatlawi. Detection of TEM and SHV genes in *Escherichia coli and Klebseilla* species isolated from cancer patients in Al-Diwaniya Governorate, QMJ VOL.9 No.16, 22-39.
35. Ahmed Abduljabbar Jaloob Aljanaby, Nabil S.S. Tuwaij and Huda J.B. Al-khilkhali (2018). Antimicrobial susceptibility patterns of *Klebsiella pneumoniae* isolated from older smokers and non-smokers of inpatients in intensive care unit infected with chronic pneumonia in AL-Najaf hospital, Iraq, J. Pharm. Sci. & Res. Vol. 10(5), 2018, 1093-10970.
36. Anwar Ali Abdulla, Hussein Oleiwi Muttaleb Al-Dahmoshi, Thikra A. Abed and Wurood Hamzah Muttaleb (2016). Characterization of Multidrug Resistant Carbapenemases-Producing *Escherichia coli and Klebsiella pneumoniae* Isolates from Urinary Tract Infection, Journal of Chemical and Pharmaceutical Sciences, Vol. 9 Issue 3, 1116-1120.
37. Abdulelah A. Almayah , Awatif H. Issa and Hanaa k. Ibrahim (2017). Virulence factors and antibiotic susceptibility patterns of *Klebsiella pneumonia* strains Histamine producing bacteria isolated from sputum, Scientific Journal of Medical Research Vol. 1, Issue 4, pp 103 – 109.
38. Israa AJ. Ibrahim, Tuqa A. Kareem, Yaseen M. Azeez andHawraa K. Falhi (2019). Phylogenetic tree analysis based on the 16S sequence alignment for *Klebsiella* spp. isolated from different sources, Iraqi Journal of Science, Vol.60, No.12, pp: 2618-2628.