Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Navigating The Landscape of Klebsiella Pneumoniae : Virulence, Pathogenicity and Antibiotic Resistance- A Comprehensive Review

Majeed ali MD[1], Arumugam Suresh*[2], Natarajan Muninathan[2], Kuppusamy Baskaran[2], Venugopal Gopikrishnan[3], Kamalakar Sarva[2]

[1]Research Scholar, Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram, Tamil Nadu, India

[2]Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute, Meenakshi Academy of Higher Education and Research, Kanchipuram, Tamil Nadu, India

[3]Centre for Drug Discovery and Development, Sathyabama Institute of Science and Technology, Chennai, India.

(Received: 02 September 2023 Revised: 14 October Accepted: 07 November)

KEYWORDS
Klebsiella pneumoniae, Phenotypic and Genotypic Virulence factors, Antibiotic Resistance patterns.

ABSTRACT:

Klebsiella pneumoniae, a prevalent gram negative opportunistic pathogen within the Enterobacteriaceae family, is responsible for wide spectrum of human infections. It's pathogenicity and antibiotic resistance are attributed to the presence of various virulence factors, including serum resistance, hyper-mucoviscosity and biofilm formation. Non- hypervirulent strains are primarily associated with nosocomial infections and exibit heightened antibiotic resistance, where as hypervirulent strains are more susceptible and cause invasive infections in healthy individuals. The pathogenicity of K.pneumoniae bolstered by an array of virulence factors, such as adhesions, siderophores, endotoxins, and capsule. The global dissemination of multidrug resistant strains is driven by plasmid mediated Extended Spectrum Beta-Lactamase activity. Biofilm formation enhances K.pneumoniae's persistence on epithelial tissues and medical devices by shielding it from antibiotics and host immune responses. Detecting and inhibiting the rapid spread of highly resistant strains, necessitating continuous monitoring for specific serotypes of Carbapenemase producers and addressing the challenges posed by strains that rapidly disseminate and produce biofilms is imperative. Further research into natural anti-biofilm agents, such as Phytochemicals, Biosurfactants, Antimicrobial peptides, and micrfobial enzymes, holds promise for eliminating biofilm formation and curtailing the pathogen's spread within healthcare settings.

1. Introduction:

K.pneumoniae is a Gram Negative, Non-Motile, opportunistic, facultative anaerobe, able to colonize, invade, and spread diseases at various sites in the human body. In immune compromised patients, such as those with diabetes or cancer. *K.pneumoniae* is an opportunistic pathogen that can cause a variety of diseases, such as pneumonia, bacteremia, and meningitis. It has been identified as one of the pathogens in the ESKAPE group and possesses the ability to escape or evade the action of Antimicrobial agents. Due to the presence of virulence factor genes, serum resistance, hyper-mucoviscosity, and the capability to form biofilms which confers pathogenicity and antibiotic resistance. WHO enlists K.*pneumoniae* as one of the organisms with high priority research in promoting new antibiotics due to the rapid emergence of antibiotic resistance (1,4). There are two phenotypic strains of *K.pneumoniae* "Classic" and Hypervirulent (hvKP). The Classic non-virulent strains of producing Extended Spectrum Beta Lactamases are mostly associated with Nosocomial infections with increased antibiotic resistance. The Global spread of MDR strains is due to plasmid mediated Extended Spectrum hydrolytic activities, Whereas invasive infections are associated with Hyper virulent strains in healthy individuals and are mostly antibiotic susceptible. The majority of risk factors for mortality in BSI patients include the production of Carbapenemases of, Amber moleculer class A – K.*pneumoniae* Carbapenemase (KPC), class B- Verona integron metallo-betalactamases (VIM), Imipenemase

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

(IMP), New Delhi metallo-betalactamases (NDM), and class D oxacillinase-48 (OXA-48) types. Infections by carbapenem-resistant hypervirulent strains are recently increasing where 50% of bacteremia cases could reach mortality (2,3,4). Improper and Inadequate antibiotic usage K. *pneumoniae* continues to acquire Antibiotic Resistant Genes (ARGs) encoded by plasmid, leading to the formation of Extremely Resistant Strains (XDR) with "super resistone" (5). Prematurity, an immature immune system, leangthy stays in the intensive care unit, mechanical ventilation, and use of intravenous and urinary catheters are the main risk factors for cKP infections in newborns. The role of hvKP in neonates is unknown(6). Presently, Pili, Capsule, Lipopolysaccharide (LPS) and iron carriers have been identified as virulence factors (5). In this review, we summarize the mechanism of convergence of antibiotic resistance and virulence factors of cKp and hvKP.

2. Materials & Methods:

In order to fulfill the objective of this review, we searched the literatures in the scholarly sites including Pubmed, Scopus and Google scholar. The search key words are 'Klebsiella *pneumoniae*, 'Phenotypic and Genotypic Virulence factors', 'Antibiotic Resistance patterns', Only articles written in English language were selected for this review.

3. Virulence factors:

To accomplish the infection K.*pneumoniae* must overcome the Barriers, both chemical and mechanical, as well as the humoral and cellular immune system of the host. Upon entry into the host the invasive organisms are recongnised by immune cells with a specific pattern called PRR(pattern recognition receptors) and signals body to produce various immune mediators. To establish the infection *K.pneumoniae* needs to overcome host's cellular and humoral immune systems. It is described as four virulent factors, Pili, Capsule, Lipo polysaccharides, and iron carriers, Type 1 and 3 pili are used for adhesion to epithelial, immunological, and antibiotic surfaces. The Capsule helps to protect from the immune responses of the host. In fact the LPS modifications prevent identification by the host cells. The production of Capsular polysaccharides is mediated by the plasmid-located RmpA gene. hvKP phenotype with high capsule production often bears the RmpA gene and magA gene associated with hyper mucoviscosity mostly involved in invasive purulent tissue infections such as a liver abscess. *K.pneumoniae* protected by the capsule from host immune responses, Virulence and other factors may also contribute to the pathogenicity of the organism. Importantly, numerous studies have revealed a substantial association between the K1 and K2 serotypes and hvKP. The modification in LPS in specific sites facilitates *K. pneumoniae* not being identified by the host immune cells while some other strains might conceal the LPS in the capsule to prevent being detected by Toll-Like receptor4 (TLR4). *K. pneumoniae* has the four iron-absorbing molecues: Salmochelin, enterobactin, yersiniabactin, and aerobactin present in both classical and hypervirulent strains. Enteromycin is thought to be the primary mechanism for iron absorption because of its strong affinity for iron. Yersinide and Gastrin are more common in hvKP in contrast to enteromycin in cKP. hvKP strains produce a large amount of activated iron-absorbing molecules which confers higher virulence and pathogenicity comparing to cKP strains. Salmochelin is linked to invasive diseases and aerobactin for highly virulence is frequently seen in strains of the extremely virulent hv*K. pneumoniae* that cause serious infections in the community, like pneumonia and liver abscess (5).

The pathogenesis of *K.pneumoniae* is greatly aided by the expression of a wide range of acridity factors, such as adhesins, siderophores, endotoxins, and capsule. The capsule is a key contributor to acridity and is engaged in at least two pathogenic mechanisms, namely the direct inhibition of the vulnerable host response and the protection of bacteria from phagocytosis. Many capsule types (K), including K1, K2, K54, K57, K20, and K5, are frequently linked to the occurrence of invasive pyogenic liver abscesses in the community, septicemia, and pneumonia. Moreover, experimental infections in mice are mostly detrimentally affected by K1, K2, K20, K54, and K57, and severe infections in people are usually linked to these proteins (7). In addition, hvKP strains are associated with good prognoses in Blood Stream Infection patients, specifically harboring pks gene cluster which produces colibactin and can be used as a significant marker of early mortality(3). Adhesins are bacterial components or cell surface elements that make it easier for bacteria to adhere to or attach to other cells or shells, usually on the host where they dwell or infect. To create an infection or to colonize a new host, adhesion is a necessary step in their pathogenesis. For the prevention or treatment of bacterial infections, bacterial adhesions are important targets.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Fimbriae bonds, also known as fimbriae or pili, are structural proteins that assist bacteria in locating particular host kerchief shells. *K. pneumoniae* has different forms of fimbriae i.e., 1, 3. Type 1 fimbriae are projections that resemble thin, stiff hairs on the surface of bacterial cells. Intercellular routes and chaperones collect them, and the FIM gene cluster decodes them (8). The LPS, also known as an endotoxin conforming to the three corridors of antigen O core oligosaccharides, and lipid A, is a crucial component of Klebsiella's exterior membrane. The gene groups wb, waa, and lpx contain the genes required for their conformation. These bacteria's acridity is greatly influenced by lipopolysaccharide, where *K.pneumoniae* can change lipid A and deactivate the seditious response. (9)

4. Biofilm

The pathogenesis of K.*pneumoniae* includes colonization and formation of bacterial biofilm involving a complex process involving attachment of bacteria to the solid surface, micro-colony production, mature-colony formation, and release of free planktonic bacteria from biofilm. The Importance of biofilm is it protects the bacteria from host defence mechanism, and anti microbials making the bacterial community more resistant. The biofilm matrix constitutes dense matrix of proteins, polysaccharides, and DNA which prevents the exposure of bacteria to the antimicrobials (12). The multidrug-resistant *K. pneumoniae* produces a biofilm. Fimbriae affect adhesion stability, Capsular Polysaccharides (CP) affects cell-to-cell communication, the structure of the biofilm. To produce biofilm shape and a range of stimulants from the terrain, the bed cell must be able to carry out rapid-fire and extensive alterations in gene expression. Only a portion of the biofilm's susceptible defenses are guarded against by *K. pneumoniae* cells. The matrix reduces or suppresses the efficiency of complement and phagocytosis as well as prevents antimicrobial peptides and antibodies from reaching the bacterium (10).

The capacity of *K. pneumoniae* to form biofilm increases the pathogen's persistence on epithelial tissues and medical device surfaces by shielding it from antibiotics and host immune responses (11). Antibodies and antimicrobial peptides cannot penetrate the matrix, and complement and phagocytosis are less effective as a result (12). The bactreria growing deep within biofilms multiply at a slower rate than the bacteria present close to the surface making them less susceptible to the antibiotics. The genetic material transfer is much higher in biofilm bacteria thus leading to transfer of genes carrying drug resistance (46,47,48). The capsular production helps the bacteria to maintain shorter distance between the bacterial cells making it more compact within the biofilm. It is also found that capsule production interferes with adhesin function. Cellulobiose is another important factor that aids in biofilm formation (49,50). hvKP factors that contribute to the intestinal colonization and invasion are Capsular polysaccharides, Lipopolysaccharides, fatty acids, Outer membrane proteins(OMP) and DNA folding proteins, Protein sysnthesis elongator factor, an aerobic-anaerobic metabolism regulator, hypothetical proteins (51). The genes associated are *pks gene* cluster,*kpc-2* for enhancement of virulence, *bla*NDM-1 large virulent plasmid, *fab*Z, *lpx*C for biofilm homeostatis, *yfg*L for biofilm formation and expression of type1 pili, kpOmpA aids in cell to cell recognition, adhesion, and immune response (5).

5. Serum Resistance :

After the initiation of inflammation, K.*pneumoniae* invades and meet the cellular and humoral bactericidal components of the innate immune system. The ability to resist host's first line defense which includes bactericidal effect of serum which is mediated primarily by complement proteins. The Lipopolysaccharide(LPS) is the major component that confers bacteria to resist serum bactericidal activity by the host. There are nine different LPS serotypes (O antigens) described and the 01 serotype by the most common O antigen found in most clinical isolates (52). The ability of K.*pneumoniae* to resist the bactericidal potency of human serum is assessed in several studies. There were more than 50% of strains were found to be highly resistant to serum, and there was no correlation between serum resistance and the other characteristics like biofilm formation, hypermucoviscosity, antimicrobial resistance classification, or the presence of virulence genes(1). 69.7% of strains were highly resistant to serum and mostly associated with virulence K serotype, hvKP phenotype, rmpA, rmpA2, and aerobactin genes (27).

6. Antimicrobial Resistance:

The definitions for MDR (Multi Drug Resistant), XDR (Extensive Drug Resistant), and PDR (Pan Drug Resistant) were suggested by the European Centre for Disease Prevention and Control (ECDC) as PDR if the isolate is

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Resistant to all listed antimicrobial agents, XDR if it is resistant to at least one agent in all but two or fewer antimicrobial categories, and MDR if it is resistant to at least one agent in at least three antimicrobial categories (1).The genes associated with Aminoglycoside resistance namely plasmid mediated *aac* , *ant*, *aph* families, Efflux pump mediated *AcrAB-TolC, kpnEF*, *KpnO*. Quinolone resistance genes *OmpK36*, *acrAB*, kdeA are associated with cell permeability, *OqxAB* gene for Efflux pump plasmid mediated quinolone resistance, qnr encoding family of proteins that protect DNA gyrase and Topoisomerase from Quinolone activity, *aa(6')-Ib-cr* gene for quinolone modification. Beta Lactam resistance genes *bla*SHV-1, *blaTEM-1* for Penicillin resistance, *bla*SHV-2 for ESBL, *bla*TEM-3 for Plasmid mediated ESBL variant, *bla*CTX-M for iatrogenic outbreaks, *bla*OXA, *bla*GES, *bla*SFO, *bla*PER, *bla*TLA, *bla*VEB, *bla*KLUC-5. Polymyxin resistance genes *lmpX* for maturation of LipidA, *ramA* for neutralization of LipidA, *pbgP* , *pmrE* for amino arabinose combination, *pmrC* for phosphoethanolamine combination, *pagP* for Palmitate combination, *phoPQ, pmrA, pmrD, mgrB* for LPS modification gene regulators, *RarA* for high expression of efflux pumps *AcrAB-TolC* and *KpnEF*, *mcr-1* encoding family of phosphoethanolamine transferases that can bind to phosphoethanolamine. Tigecycline resistance genes *AcrAB-Tol*, *OqxAB* for over expression of Efflux pump, *RarA, RamA, RamR, AcrR* for efflux pump regulation, *Lon*, *rpsj* for encoding ribosome S10, *OmpK35K* of which decresed transcript level may enhance resistance, *tetA* encoded tetracycline resistant efflux pump(5).

K.pneumoniae strains express chromosomal penicillinase and sulfhydryl variable (SHV1), demonstrating inherent resistance to ampicillin, carbenicillin, and ticarcillin. *K.pneumoniae* is efficient for its ability to collect resistance plasmids and became an indicator species for plasmids encoding extended-spectrum beta-lactamases (ESBLs), which confer cephalosporin resistance. The plasmids containing components that confine resistance to aminoglycosides, tetracyclines, and trimethoprim-sulfamethoxazole initially contained both Temoniera (TEM)- and SHV-type ESBLs. The leading ESBL family today, cefotaximase (CTX-M), first appeared in the 1990s and gives resistance to extended-spectrum cephalosporins and penicillins, but is ineffective against carbapenems. Due to the questionable clinical efficacy of penicillin-inhibitor combinations and the fact that a sizable portion of these isolates have developed resistance to fluoroquinolones and other antibiotics, carbapenems have replaced them as the first-line treatment for MDR ESBL-*K. neumoniae* infections. The extensive use of carbapenems led to the rapid emergence and spread of carbapenemase-producing *K. pneumoniae* (CP-Kp) strains. The most prevalent kinds of *K. pneumoniae* carbapenemases are Verona integron-encoded metallo-lactamases (VIM) and *K. pneumoniae* carbapenemases (KPCs), which range from KPC-2 to KPC-13, (IMP) imipenemase, oxacillinase (OXA)-type enzymes (primarily OXA-48) and New Delhi metallo-lactamase (NDM) types. Colistin and polymyxin B, these two polymyxins, are thought to be among the most effective agents against XDR CP-Kp. To ensure optimal medication exposure, colistin must first be given as a loading dose and then as necessary maintenance doses, To promptly attain the desired serum concentration. Aminoglycosides like Gentamicin and Amikacin have an excellent susceptibility profile to some CP-Kp, so this class of drugs could be used to treat CP-Kp infections (11). Except for trimethoprim-sulphamethoxazole and ampicillin, all antimicrobial drugs showed significantly lower resistance rates in HvKP than in cKP (13). Because hvKp strains have not developed antimicrobial resistance determinants as quickly as cKp strains, it has been hypothesized that plasmid incompatibilities, a physical barrier brought on by capsule over expression, and CRISPR systems may be important causes. The uptake and incorporation of antimicrobial resistance determinants from an ICE element into an hvKp strain's chromosome or virulence plasmid is the second mechanism. The third mechanism is chromosomal gene disruption or mutation (for example, genes for outer membrane proteins [OMPs]). Increased expression levels of AmpC beta-lactamases provide resistance to the same substrates as ESBLs do, plus to the cephamycins (e.g., cefoxitin and cefotetan). The last line of defense against strains that produce metallocarbapenemases at the moment is polymyxins (e.g., NDM-1). Thus, it is very alarming that the polymyxin resistance gene mcr-1 has just appeared on a stable, transferable plasmid. Increased expression of the PhoP-PhoQ-Arn pathway is another mechanism underlying polymyxin resistance. A strain of cKp resistant to Tigecycline transformed into a hvKP strain by acquiring a piece of a hvKp virulence plasmid has been found. (14).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

7. The Covergence of Antimicrobial Resistance and virulence genes:

It is found that a significant relationship between the strains with iucA, rmpA, and uge genes are mostly susceptible, and non ESBL producing, Similarly the strains with irp2, ybtS and fyuA were higher prevalent in ESBL production (1). It is unknown what medium of exchange exists between antibiotic resistance and acridity in K.pneumoniae. *K.pneumoniae* is frequently linked to nosocomial infections (15). The most common Antimicrobials for which resistance was found were Nitrofurantoin (68%), Trimethoprim-Sulfamethoxazole (73%), and Ciprofloxacin (75%). EntB (80%), traT(62%), ybts(75%), magA(5%), iucC(30%), htrA(72%), and rmpA(48%) were the percentages of virulence genes associated in resistant strains. For each of the examined isolates, the prevalence of the genes associated with biofilm formation mrkA, fimH, and mrkD was 88%. Furthermore, efflux pump genes for AcrAB(41%), TolC(33%), and mdtK(26%) were discovered. High expression of efflux pump and biofilm genes in MDR strains are significantly statistically associated. For resistance to various antimicrobials *K. pneumonia* has evolved several mechanisms. Efflux pump systems and biofilm forming capability are two key processes for the development of the MDR. Protein-based structures called efflux pumps can expel many harmful chemicals from cells. The Resistance Nodulation Divisions's (RND) AcrAB efflux pump system plays a significant role in the evolution of MDR strains of K. pneumoniae. The AcrAB-TolC efflux pump is made up of an outer membrane compartment, an inner membrane transporter(AcrB), and a component found in the periplasm (AcrA)(TolC). In MDR strains K. pneumonia, the AcrAB-TolC efflux pump is crucial for resistance to a variety of antibiotics, including Flouroquinolones, Tetracyclines, and Chloramphenicol (4,16,17,18). K. pneumoniae has the ability to build biofilm that shields strains from the host immune system and antibiotics in MDR isolates. Several biofilm-related genes, such as mrk(type 3 fimbriae) and fimH-1 (type 1 fimbrial adhesion) are implicated in the production of biofilms (19). The fimD, fimH, mrkC, and mrkD genes are found in almost all the strains. The virulence genes prevalent as uge (73.23%), irp2(41.73%), ybtS(40.94%), fyuA(40.16%), iucA(11.02%), rmpA(7.09%), ironN(5.51%), clbA(1.57%), and clbQ(1.57%) with the highest presence of uge gene in urinary isolates which significantly shows that strains with iucA,rmpA,iron lack in biofilm producers (1). It has been eshtablished that the production of biofilms and antibiotic resistance are both significantly influenced by efflux pumps. In some investigations, the ability of *K. pneumonia* to form biofilms and its antibiotic resistance with the efflux pump were significantly correlated (20). Some virulence associated genes play a significant role in the pathogenicity of *K. pneumonia* strains, including those that code for the outer membrane protein-coding gene(traT), the regulators of mucoid phenotype A (rmpA), the enterobactin biosynthesis gene(entB), the yersiniabactin biosynthesis gene (ybts), the mucoviscosity-associated gene A (magA) and the iron siderophores aerobactin (21). To restrict nosocomial infections in the hospitals molecular methods will be most rapid and furthermore, in finding the dominant genotype among isolates can be crucial for figuring out the origin of the infection and using preventive measures (16,22). The link between the integron 1 gene, which is the major concern for antibiotic resistance and the *K. pneumoniae virulence genes* wcaG and rmpA. Attributed that the genes may be encoded on the same transferable genetic elements, there is also a link between phenotypic extended-spectrum beta-lactamase and carbapenemase resistance and virulence genes. Genes associated virulence and infection outcome were correlated (23)

There were several resistance profiles found, including pan-drug resistance (PDR; 5%), extended drug resistance (XDR; 35%), and multidrug resistance (MDR; 42.5%). In addition, the selected genes in isolates identified are CTX-M-1(70%), TEM(30%), qnrS(60%), and qnrA(30%). There were spectral β-lactamases (ESBLs) Producers. Interestingly, all these ESBL producers showed the class 1 integrase gene (Intl1), whereas 60% of ESBL producers contained both CTX-M-1 and TEM-I. All isolates tested were encapsulated and 87.5% were biofilm producers. Pili were detected in 90% of the isolates tested (all were biofilm producers and positive for the type 3 pilus adhesion gene [mrkD]). OXA-48, qnrS, and Intl1 sequence analysis indicated 100% similarity to known sequences, whereas sequencing of the qnrA, OmpK-35, and iron-regulated protein (irp2) genes revealed 100% identity. Minor discrepancies were shown in the form of no more than one single nucleotide Polymorphism (24).

CRKP(Carbapenem- resistant *K. pneumoniae)* have become more widely reported. The primary factor causing the high virulence of hvKP is aerobactin. The

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

iucABCDiutA locus is located on the virulence plasmid and codes for aerobactin and its corresponding receptor. According to published research, The virulence plasmids or virulence plasmid-specific loci such as iucABCDiutA and rmpA/rmpA2 have been used to identify hvKP strains. The most common CRKP clones in America and Southern Europe are ST258 and its descendant ST512. 12% of CRKPs in Europe are caused by the single locus variant ST11, which is substantially more common than ST258 or ST512. However, in China, ST11 is the only CRKP clone that has gained dominance (25,26). *K. pneumoniae* strains are often divided into clone complexes (CCs) based on the sequence types (STs) that are determined by the nucleotide sequences at seven loci (mdh, infB, tonB, gapA, phoE, pgi, and rpoB) (27). Uniplex or multiplex polymerase chain reactions (PCR) were used to detect the presence of various resistance-associated genes in the tested *K.pneumoniae* isolates. ESBL (CTX-M-1, TEM), carbapenemase (imipenemase [IMP], OXA-48), quinolone resistance genes (qnrA, qnrB, qnrS, aac(6')-Ib-cr, and qepA), as well as aminoglycoside resistance genes (aacA4 and aacC1) and class 1 integrase gene (Intl1), PCR was performed using various primers (24).The over expression of extended-spectrum lactamases (ESBLs) and AmpC Cephalosporinase is one mechanism that contributes to carbapenem resistance in K. pneumoniae, along with Decreased expression or loss of outer membrane protein (OMP), Activation of efflux pumps, and other mechanisms. The primary mechanism is the synthesis of carbapenemases (28). The most frequent class A carbapenemase causing CRKP is *K. pneumoniae* carbapenemase (KPC) (29). Despite the identification of 54 KPC variants, KPC-2 and KPC-3 are the most common KPCs globally. Transposon Tn4401 frequently carries the blaKPC-2 or blaKPC-3 genes, and ISKpn6 and ISKpn7, two unrelated inserts, surround the blaKPC gene. (30). Zinc is necessary for Class B metallo-lactamases to have an active site. NDM-1, first identified in *K. pneumoniae* in New Delhi India in 2008, has now spread throughout the world(31). The recruitment of blaNDM is linked to ISABa125 upstream and bleMBL downstream (bleomycin resistance gene) (32). OXA-48 was first identified in *K. pneumoniae* epidemic that occurred in Turkey in 2001, followed by an increase in reports (33). Compared to other carbapenemases, OXA-48 hydrolyzes carbapenems to a lesser degree, often associated with other mechanisms of resistance to carbapenems (34). Surprisingly, there are increasing reports of CRKP strains that co-produce multiple types of carbapenemases (35). In addition to carbapenemase, several non-carbapenemase mechanisms also lead to carbapenem resistance. Impairment or deficiency of OmpK35 and OmpK36 is associated with decreased susceptibility to carbapenems (36). This is primarily caused by decreased membrane permeability, and carbapenem resistance is also brought about by the excessive mechanism of efflux pumps (37). Efflux pumps and OMP inactivation often interact synergistically with ESBL or AmpC-β-lactamase Overexpression. Although less studied, CRKPs that do not produce carbapenemase are as important as those that produce carbapenemase (38). Genetic components of colistin resistance mcr-1 and mcr-2 genes were found in 12% and 9%, respectively (39).

8. Conclusion :

In this comprehensive review, we aim to provide a thorough analysis of antibiotic resistance patterns, as well as the phenotypic and genotypic virulence factots associated with K.*pneumoniae*. The global dissemination of highly resistant and pathogenic K.*pneumoniae* strains is a significant and growing concern in the field of healthcare.

a. **K.*pneumoniae*'s Global Impact** : The worldwide prevalence of K.*pneumoniae* has been marked by its highly resistant and pathogenic nature. Among the various strain, the hypervirulent strains stand out due to its ability to cause disseminating infections, including endophthalmitis and meningitis. These infections are primarily community acquired, further emphasizing their potential for harm.

b. Resistance Profiles : Multidrug resistance is a recurring issue, especially in classical K.*pneumoniae* strains found in healthcare settings. The nosocomial multidrug resistant strains including carbapenem resistant variants are primarily classical in type and are often associated patients who have underlying health conditions and comorbidities.

c. **Rapid Outbreaks :** The rapid emergence and spread of such Multidrug resistant strains are exacerbated by plasmid mediated genetic exchange. This genetic mobility poses substantial challenges in healthcare settings, making it difficult to address these issues promptly and effectively.

d. Challenges In Treatment and Prognosis : The treatment and prognosis of K.*pneumoniae* infections, especially caused by highly resistant strains, are often sluggish, and the outcomes are frequently unfavourable.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Colistin is the only antibiotic effective against Carbapenem resistant strains, highlighting the critical need for new treatment options.

e. Biofilm Formation : K.*pneumoniae*'s ability to form biofilms on epithelial tissues and medical devices is another pressing concern. These biofilms serves as protective barriers against both immune responses and antibiotics. Moreover, there have been alarming cases of such strains being detected in ready to eat vegetables, which raises significant food safety issues.

f. Continuous surveillance : *To combat this growing threat of highly resistant K.pneumoniae, continuous surveillance is essential. A combination of conventional phenotypic and genotypic rapid point of care methods should be employed to detect these strains promptly. This will enhance the limiting their dissemination within healthcare facility and the broader community.*

g. Exploring Natural Alternatives : Given the the challenges posed by highly resistant strains of K.pneumoniae, there is growing intrest researching natural antibacterial compounds and anti biofilm compounds such as phytochemicals, biosurfactants, antimicrobial peptides, and microbial enzymes are great choices. These compounds can interfere with quorum sensing, bloch adhesisns, alter cell permeability, and disrupt the electron transport system and there by inhibiting colonization and biofilm formation, potentially preventing serious life threatening infections in healthcare setting.

In summary, the relentless rise of antibiotic resistant K.*pneumoniae* strains, along with their virulence and biofilm forming abilities, pose a substantial threat to public health, addressing this issue requires a multi faceted approach that includes surveillance, the development of novel treatments and research into natural compounds to combat these highly resilient pathogens.

9. Acknowledgement :

It is acknowledged that all the authors contributed in designing, drafting and reviewed this article.

10. Conflict of intrest :

There is no conflict of interest between the authors.

11. Funding :

None.

Table - 1 The Percentage of the relationship between *K. pneumoniae* Antimicrobial Resistance, associated *ESBL and* virulence genes.

Reference	Isolate Resource	Antibiotic Resistance (%)	Antimicrobial Resistance genes (%)	Virulence genes (%)
Ballén et al 2021 [1]	127 isolates from Different Clinical specimens	39.17% Susceptible to all microbial agents 18.9% Resistant to one or two categories 40.16% MDR 1.57% XDR 41.0% Ciprofloxacin 39.0% Amoxycillin /clavulanic acid 35.0% Trimethoprim/sulfamethoxazole 37.0% Ceftazidime 2.0% Colistin 13% Chloramphenicol 11% Imipenem 14% Fosfomycin 17.0% Gentamycin 24.0% Cefipime	85.45% *blaSHV-1* 78.95% *blaCTX-M1* 71.93% *blaTEM-1* 76.92% *blaOXA48* 38.46% *aac-(6)-Ib-cr* 51.92% *qnrB* 13.64% *sul1* 65.91% *sul2*	Fimbriae associated 98.43% (*fimD,fimH,mrkC,mrkD*) Capsule associated 73.23% *uge* 7.09% *rmpA* Siderophores 41.73% *irp2* 40.94% *ybtS* 40.16% *fyuA* 11.02% *iucA* 5.51% *iroN* Colibactin 1.57% *clbA* 1.57% *clbQ*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

		21.0% Piperacillin/ Tazobactam		
Albasha et al 2020 [4]	60 isolates from different clinical specimens	35.0 % MDR 7.0% XDR 30.0% Ciprofloxacin 38.3% chloramphenicol 40.0% Gentamycin 8.3% Imipenem 70.0% Ceftazidime	68.3 % *blaOXA48* 10% *blaNDM* 8.3% *blaKPC* 3.3% *blaIMP*	93.3% *entB* 78.3% *mrkD* 60.0% *kfu* 18.3% *magA* 5.0 % *rmpA*
Mirzaie, A, Ranjbar et al 2021 [16]	100 isolates from different clinical specimens	92% MDR 75% Ciprofloxacin 73% timethoprim/sulfamethozoxazole 68% Nitrofurantoin 48% Imipenem 72% Streptomycin 92% All betalactams	---------	Virulence related 80% *entB* 62% *tratT* 75% *ybtS* 30% *iucC* 72% *htrA* Mucoviscosity 5% *magA* 48% *rmpA* Biofilm-associated 88% mrkA, fimH,mrkD Efflux pump 41% *AcrAB* 33% *TolC* 26% *mdtK*
El-Domany RA, et al 2021 [20]	40 isolates from different clinical specimens	42.5% *MDR* 35.0% *XDR* 5.0% *PDR*	70.0% *CTX-M-1* 30.0% *TEM* 60.0% *qnrS* 30.0% *qnrA*	100 % *fimH* 50% *mrkD* 40% *irp2* 40% *kfu*
Imtiaz W et al 2021 [39]	200 isolates from different clinical specimens	36% MDR-CRKP 38% Carbapenem 55% Gentamycin 53% Ciprofloxcin 59% Aztreonam 22% Fosfomycin 15% Colistin 7% Combined resistance to carbapenems and colistin	46% *blaCTX-M-15* 39% *blaNDM* 24% *blaOXA-48* 12% *mcr-1* 9% *mcr-2*	Mucoviscosity 35.5% rmpA Adhesins 19% fimH 18% mrkD 22% ycfM Porins 56% ompK35 55% ompK36 16% bss polysaccharide regulator gene
Ku YH, Chuang YC et al 2017 [41]	33 isolates from non metastatic meningitis in children	27.3 % Broad spectrum Cephalosporins	18.2% *blaSHV-5* 6.0% *blaCMY-2* 6.0% *blaDHA-1* 3.0% blaTEM-1B	69.7% rmpA 60.6% rmpA2 6.1 % c-rmpA2 30.3% kfu 15.6% alls(associated with allantoin

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

				metabolism) 66.7% aerobactin
Li Y, Li D, Xue J et al 2021 [42]	94 invasive isolates from different clinical specimens in children	30.85% HV-CRKP 37.23%Gentamycin 2.13% Amikacin 29.79% Tobramycin 12.7%Meropenem 12.7% Imipenem 12.7% Ertapenem 46.81% Cefuroxime 46.81% Cefozolin 38.30% Cefotaxime 43.62% Ceftriaxone 23.40%Ceftazidime 21.28% Cefipime 26.60% Ceftizoxime 18.09% Cefoperazone /Sulbactam 12.77% Piperacillin/ Tazobactam 27.6%Ciprofloxacin 4.26% Levofloxacin 18.09% Aztreonam	ESBL genes 19.15% blaTEM-1 86.17% blaSHV-11 48.94% bla-CTX-14 6.38% blaVEB-1 0% blaPER Amp-C genes 70.21% blaACT-1 31.91% blaDHA-1 86.17% blaFOX-1 0 % blaCMY, 0% blaMOX, 0% blaACC, 0% blaCIT, 0% blaABC Carbapenemase genes 10.64% blaKPC-2 5.32% blaOXA-1 19.15 blaNDM-1 13.83 blaVIM-1 0% blaIMP 0% blaAIM 0% blaGIM 0% blaSIM 0% blaSPM 0% blaBIC 0% blaDIM Colistin genes 0% mcr-1 0% mcr-2	Hypervirulent genes 13.83% iucA 30.85% rmpA 2.13% rmpA2 34.04% peg-344 0% terB 86.17% iroB 0% irp2 Other genes 11.7% ybtS 98.94% mrkD 21.28 entB 50.0% kfu 17.02% alls 2.13% iutA 4.26% k2A 100 % wabG 88.3% Uge 95.74% fimH 24.47% wcaG 53.19% kpn 96.81% ycfM 28.72% iron 0% Hly 0% cfn-1
Rastegar S, Moradi M et al 2021 [13]	146 isolates from different clinical specimens	97.6% Ampicillin 66.1% Cefotaxime 63.7% Ceftriaxone 63.7% Ceftazidime 62.1% Aztreonam	-------	2.7 % rmpA 26.7 % kfu 24.8 %fimH 94.5% mrkD

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

		54.8% trimethoprim/sulfamethoxazole 52.4% Gentamycin 50.0% Nalidixic acid 45.2% Tetracycline 38.7% Amikacin 32.3% Ofloxacin 37.9% Imipenem 25.0%Ciprofloxacin		4.1 % alls 5.4% iutA 2.0 % magA 95.8 % entB 58.9% ybtS
Shadkam S et al 2021 [43]	100 isolates from different clinical specimens	67% MDR 11% XDR 52% trimethoprim/ Sulfamethoxazole	7.0% blaVIM 11.0% blaIMP 5.0% blaNDM 28.0% blaOXA-48	Biofilm forming genes 98% luxS 96% treC 34% wza
		51% Cefotaxime 43% Cefipime 43% Ceftriaxone		
Sahoo RK et al 2019[19]	227 isolates from different clinical specimens, And only 20 Isolates for ESBL and Virulence genotyping	31.7% ESBL 31.7% MDR 22.58% Amikacin 70.96% Amoxycillin/ Clavulanate 35.48% Cefixime 22.58% Co-trimoxazole 83.87% Cefuroxime 41.93% Ceftriaxone 25.8% cefotaxime 6.4% Colistin 64.51% Levofloxacin 6.4% Meropenem 83.87% Ofloxacin 22.58% Piperacillin/ Tazobactam	100% blaTEM 85% blaSVH 50% blaCTX-M	Virulence factors 70% fimH 50% mrkD 65% entB 25% irp 25% K1 20% K2
Di Domenico EG et al 2020 [44]	86 CRKP isolates from oncological patients	88% Amikacin 100% Amoxycillin/ clavulanic acid 100% Cefipime 100% Cefotaxime 100% Ceftazidime 15% Ceftazidime/ Avibactam 98% Ciprofloxacin 33% Colistin 100% Imipenem 100% Meropenem	Carbapenemase genes 96.5% KPC 2.3% OXA-48 1.2% VIM	---

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

		100% Ertapenem 89% Tigecyline 80% Trimethoprim/sulfamethoxazole 85% Gentamycin		
Harada S et al 2019 [45]	26 isolates of HVKP from BSI of total 102 isolates of K.*pneumoniae*	Resistant to third generation cephalosporins. 46.2% ESBL	19.23% blaSHV 15.38% blaCTX-M 3.80% blaIMP-6 3.80% blaGES-4	84.6% rmpA and/or rmpA2 100% iroBCDN 88.5% iucABCD 8.5% iutA Capsular genes 26.9% K1 23.0 % K2 2.60% K20 11.5% K57 15.4% K62

TABLE – 2 The percentage of phenotypic characteristics of K.*pneumoniae*

Reference	Isolate Resource	Hypermucoviscosity Producing strains (%)	Biofilm Producing strains (%)	Strains showing Serum Resistance(%)
Ballén et al 2021 [1]	Different Clinical specimens	13.39%	27.55% as weak 33.07%as moderate 19.69% as strong	50%
Mirzaie, A, Ranjbar et al 2021 [16]	100 isolates from different clinical specimens	----	14% as weak 20 % as moderate 71% as strong	----
El-Domany RA, et al 2021 [20]	40 isolates from different clinical specimens	----	87.5%	-----
Imtiaz W et al 2021 [39]	200 isolates from different clinical specimens	22.0%	----	-----
Ku YH, Chuang YC et al 2017 [41]	33 isolates from non metastatic meningitis	66.7%	-----	69.7%
Li Y, Li D, Xue J et al 2021 [42]	94 invasive isolates from different clinical specimens in children	92.55%	-----	------
Rastegar S,	146 isolates	15.1%	-----	------

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Moradi M et al 2021 [13]	from different clinical specimens			
Shadkam S et al 2021 [43]	100 isolates from different clinical specimens	----------	31% as weak 19 % as moderate 25% as strong	-------
Sahoo RK et al 2019[19]	20 Isolates of ESBL producers	---------	15% as weak 40 % as moderate 30% as strong	
Di Domenico EG et al 2020 [44]	86 CRKP isolates from oncological patients	22.1%	55.8% strong	--------
Harada S et al 2019 [45]	102 isolates from BSI	18.6%	--------	---------

Table – 3 Prevalence of hvK.*pneumoniae* and Antimicrobial resistance

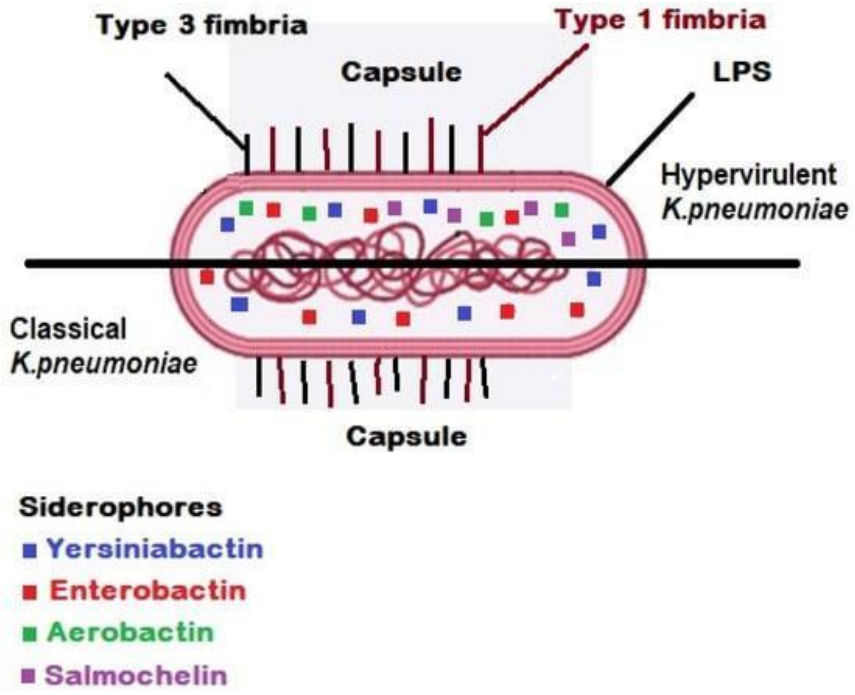
Location	Year	Sample Size	Prevalence of Hypervirulent K. *pneumoniae*	Prevalence of Antimicrobial Resistant hvK. *Pneumoniae*	Reference
Taiwan	2004-2005	11	100%	0%	[51]
China	2007-2008	41	80.50%	95.10%	[52]
Singapore	2008-2011	20	75%	100%	[53]
South Korea	2011-2012	136	11.80%	66.90%	[54]
United States	2011-2013	10	100%	90%	[27]
Thailand	2011-2013	116	6.90%	34.50%	[55]
India	2016-2017	40	22.50%	95%	[56]
India	2018-2019	50	30%	78%	[57]
China	2019	42	97.60%	92.90%	[58]
Spain	2019	15	40%	100%	[59]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Fig 1:



Virulence Factors of *Klebsiella pneumoniae* (Karampatakis T et.al) [60]

Bibliography

1. Ballén V, Gabasa Y, Ratia C, Ortega R, Tejero M, Soto S. Antibiotic Resistance and Virulence Profiles of *K. pneumoniae*Strains Isolated From Different Clinical Sources. *Front Cell Infect Microbiol*. 2021;11:738223. Published 2021 Sep 1. doi:10.3389/fcimb.2021.738223
2. https://doi.org/10.3389/fmed.2018.00225
3. https://doi.org/10.1093/jac/dky397
4. Albasha AM, Osman EH, Abd-Alhalim S, Alshaib EF, Al-Hassan L, Altayb HN. Detection of several carbapenems resistant and virulence genes in classical and hyper-virulent strains of *K. pneumoniae*isolated from hospitalized neonates and adults in Khartoum. *BMC Res Notes*. 2020;13(1):312. Published 2020 Jul 1. doi:10.1186/s13104-020-05157-4
5. Wang G, Zhao G, Chao X, Xie L, Wang H. The Characteristic of Virulence, Biofilm and Antibiotic Resistance of *Klebsiella pneumoniaeKlebsiella pneumoniae*. *Int J Environ Res Public Health*. 2020;17(17):6278. Published 2020 Aug 28. doi:10.3390/ijerph17176278
6. Khaertynov KS, Anokhin VA, Rizvanov AA, et al. Virulence Factors and Antibiotic Resistance of *K. pneumoniae*Strains Isolated From Neonates With Sepsis. *Front Med (Lausanne)*. 2018;5:225. Published 2018 Aug 14. doi:10.3389/fmed.2018.00225
7. Clegg S, Murphy CN. Epidemiology and Virulence of *Klebsiella pneumoniaeKlebsiella pneumoniae*. *Microbiol Spectr*. 2016;4(1):10.1128/microbiolspec.UTI-0005-2012. doi:10.1128/microbiolspec.UTI-0005-2012
8. Llobet E, Martínez-Moliner V, Moranta D, et al. Deciphering tissue-induced *K. pneumoniae*lipid A structure. *Proc Natl Acad Sci U S A*. 2015;112(46):E6369-E6378. doi:10.1073/pnas.1508820112
9. Hughes KA, Sutherland IW, Jones MV. Biofilm susceptibility to bacteriophage attack: the role of phage-borne polysaccharide depolymerase. *Microbiology (Reading)*. 1998;144 (Pt 11):3039-3047. doi:10.1099/00221287-144-11-3039
10. Calbo E, Freixas N, Xercavins M, et al. Foodborne nosocomial outbreak of SHV1 and CTX-M-15-producing *Klebsiella pneumoniaeKlebsiella pneumoniae*: epidemiology and control. *Clin Infect Dis*. 2011;52(6):743-749. doi:10.1093/cid/ciq238
11. Vuotto C, Longo F, Pascolini C, et al. Biofilm formation and antibiotic resistance in *K.*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

*pneumoniae*urinary strains. *J Appl Microbiol*. 2017;123(4):1003-1018. doi:10.1111/jam.13533

12. Piperaki ET, Syrogiannopoulos GA, Tzouvelekis LS, Daikos GL. *Klebsiella pneumoniaeKlebsiella pneumoniae*: Virulence, Biofilm and Antimicrobial Resistance. *Pediatr Infect Dis J*. 2017;36(10):1002-1005. doi:10.1097/INF.0000000000001675
13. Rastegar S, Moradi M, Kalantar-Neyestanaki D, Ali Golabi D, Hosseini-Nave H. Virulence Factors, Capsular Serotypes and Antimicrobial Resistance of Hypervirulent *K. pneumoniae*and Classical *K. pneumoniae*in Southeast Iran [published online ahead of print, 2019 Sep 25]. *Infect Chemother*. 2019;10.3947/ic.2019.0027. doi:10.3947/ic.2019.0027
14. Russo TA, Marr CM. Hypervirulent *Klebsiella pneumoniaeKlebsiella pneumoniae*. *Clin Microbiol Rev*. 2019;32(3):e00001-19. Published 2019 May 15. doi:10.1128/CMR.00001-19
15. Mahajan R. International Journal of Applied and Basic Medical Research: Decade-Old Journey of Journal. *Int J Appl Basic Med Res*. 2021;11(2):63. doi:10.4103/ijabmr.ijabmr_191_21
16. Mirzaie, A., Ranjbar, R. Antibiotic resistance, virulence-associated genes analysis and molecular typing of *K. pneumoniae*strains recovered from clinical samples. *AMB Expr* **11**, 122 (2021). https://doi.org/10.1186/s13568-021-01282-w
17. Yoon EJ, Oh Y, Jeong SH. Development of Tigecycline Resistance in Carbapenemase-Producing *K. pneumoniae*Sequence Type 147 via AcrAB Overproduction Mediated by Replacement of the *ramA* Promoter. *Ann Lab Med*. 2020;40(1):15-20. doi:10.3343/alm.2020.40.1.15
18. Xu Q, Jiang J, Zhu Z, et al. Efflux pumps AcrAB and OqxAB contribute to nitrofurantoin resistance in an uropathogenic *K. pneumoniae*isolate. *Int J Antimicrob Agents*. 2019;54(2):223-227. doi:10.1016/j.ijantimicag.2019.06.004
19. Sahoo RK, Das A, Gaur M, et al. Genotypic validation of extended-spectrum β-lactamase and virulence factors in multidrug resistance *K. pneumoniae*in an Indian hospital. *Pathog Glob Health*. 2019;113(7):315-321. doi:10.1080/20477724.2019.1705020
20. Subramanian P, Shanmugam N, Sivaraman U, Kumar S, Selvaraj S. Antiobiotic resistance pattern of biofilm-forming uropathogens isolated from catheterised patients in Pondicherry, India. *Australas Med J*. 2012;5(7):344-348. doi:10.4066/AMJ.2012.1193
21. Alcántar-Curiel MD, Blackburn D, Saldaña Z, et al. Multi-functional analysis of *K. pneumoniae*fimbrial types in adherence and biofilm formation. *Virulence*. 2013;4(2):129-138. doi:10.4161/viru.22974
22. Mukherjee S, Bhattacharjee A, Naha S, et al. Molecular characterization of NDM-1-producing *K. pneumoniae*ST29, ST347, ST1224, and ST2558 causing sepsis in neonates in a tertiary care hospital of North-East India. *Infect Genet Evol*. 2019;69:166-175. doi:10.1016/j.meegid.2019.01.024
23. Zaki AOBAMES. Molecular Study of *K. pneumoniae*Virulence Genes from Patients with Hospital Acquired Sepsis. *Clin Lab*. 2019;65(1):10.7754/Clin.Lab.2018.180709. doi:10.7754/Clin.Lab.2018.180709
24. El-Domany RA, Awadalla OA, Shabana SA, El-Dardir MA, Emara M. Analysis of the Correlation Between Antibiotic Resistance Patterns and Virulence Determinants in Pathogenic *K. pneumoniae*Isolates from Egypt. *Microb Drug Resist*. 2021;27(6):727-739. doi:10.1089/mdr.2020.0236
25. Lan P, Jiang Y, Zhou J, Yu Y. A global perspective on the convergence of hypervirulence and carbapenem resistance in *Klebsiella pneumoniaeKlebsiella pneumoniae*. J Glob Antimicrob Resist. 2021 Jun;25:26-34. doi: 10.1016/j.jgar.2021.02.020. Epub 2021 Mar 2. PMID: 33667703.
26. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. *J Infect Dis*. 2017;215(suppl_1):S28-S36. doi:10.1093/infdis/jiw282
27. Paczosa MK, Mecsas J. *Klebsiella pneumoniaeKlebsiella pneumoniae*: Going on the Offense with a Strong Defense. *Microbiol Mol Biol Rev*. 2016;80(3):629-661. Published 2016 Jun 15. doi:10.1128/MMBR.00078-15
28. Daikos GL, Tsaousi S, Tzouvelekis LS, et al. Carbapenemase-producing *K. pneumoniae*bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. *Antimicrob Agents Chemother*. 2014;58(4):2322-2328. doi:10.1128/AAC.02166-13
29. Di Domenico EG, Cavallo I, Sivori F, et al. Biofilm Production by Carbapenem-Resistant *K.*

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

*pneumoniae*Significantly Increases the Risk of Death in Oncological Patients. *Front Cell Infect Microbiol*. 2020;10:561741. Published 2020 Dec 10. doi:10.3389/fcimb.2020.561741

30. https://doi.org/10.1016/j.cmi.2014.08.001
31. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *K. pneumoniae*sequence type 14 from India. *Antimicrob Agents Chemother*. 2009;53(12):5046-5054. doi:10.1128/AAC.00774-09
32. Dortet L, Nordmann P, Poirel L. Association of the emerging carbapenemase NDM-1 with a bleomycin resistance protein in Enterobacteriaceae and Acinetobacter baumannii. *Antimicrob Agents Chemother*. 2012;56(4):1693-1697. doi:10.1128/AAC.05583-11
33. Poirel L, Héritier C, Tolün V, Nordmann P. Emergence of oxacillinase-mediated resistance to imipenem in *Klebsiella pneumoniaeKlebsiella pneumoniae*. *Antimicrob Agents Chemother*. 2004;48(1):15-22. doi:10.1128/AAC.48.1.15-22.2004
34. Jacobson, Rachael & Manesen, Mohnamed & Moodley, Clinton & Smith, Mariette & Williams, Seymour & Nicol, Mark & Bamford, Colleen. (2015). Molecular Characterisation and Epidemiolgical Investigation of an Outbreak of blaOXA-181 carbapenemase-producing isolates of *K. pneumoniae*in South Africa. South African Medical Journal. 105. 1030-1035. 10.7196/SAMJ.2015.v105i12.9926.
35. Gao H, Liu Y, Wang R, Wang Q, Jin L, Wang H. The transferability and evolution of NDM-1 and KPC-2 co-producing *K. pneumoniae*from clinical settings. *EBioMedicine*. 2020;51:102599. doi:10.1016/j.ebiom.2019.102599
36. Uz-Zaman, Taher & Aldrees, Mohammed & Al Johani, Sameera & Alrodayyan, Maha & Aldughashem, Faizah & Balkhy, Hanan. (2014). Multi-drug carbapenem-resistant *K. pneumoniae*infection carrying the OXA-48 gene and showing variations in outer membrane protein 36 causing an outbreak in a tertiary care hospital in Riyadh, Saudi Arabia. International Journal of Infectious Diseases. 28. 10.1016/j.ijid.2014.05.021.
37. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. *Clin Microbiol Rev*. 2015;28(2):337-418. doi:10.1128/CMR.00117-14
38. Su CF, Chuang C, Lin YT, et al. Treatment outcome of non-carbapenemase-producing carbapenem-resistant *K. pneumoniae*infections: a multicenter study in Taiwan. *Eur J Clin Microbiol Infect Dis*. 2018;37(4):651-659. doi:10.1007/s10096-017-3156-8
39. Imtiaz W, Syed Z, Rafaque Z, Andrews SC, Dasti JI. Analysis of Antibiotic Resistance and Virulence Traits (Genetic and Phenotypic) in *K. pneumoniae*Clinical Isolates from Pakistan: Identification of Significant Levels of Carbapenem and Colistin Resistance. *Infect Drug Resist*. 2021;14:227-236. Published 2021 Jan 25. doi:10.2147/IDR.S293290
40. Wu X, Shi Q, Shen S, Huang C, Wu H. Clinical and Bacterial Characteristics of *Klebsiella pneumoniae* Affecting 30-Day Mortality in Patients With Bloodstream Infection. Front Cell Infect Microbiol. 2021 Sep 16;11:688989. doi: 10.3389/fcimb.2021.688989. PMID: 34604103; PMCID: PMC8482843.
41. Ku YH, Chuang YC, Chen CC, Lee MF, Yang YC, Tang HJ, Yu WL. Klebsiella pneumoniae Isolates from Meningitis: Epidemiology, Virulence and Antibiotic Resistance. Sci Rep. 2017 Jul 26;7(1):6634. doi: 10.1038/s41598-017-06878-6. PMID: 28747788; PMCID: PMC5529541.
42. Li Y, Li D, Xue J, Ji X, Shao X, Yan J. The Epidemiology, Virulence and Antimicrobial Resistance of Invasive *Klebsiella pneumoniae* at a Children's Medical Center in Eastern China. Infect Drug Resist. 2021 Sep 14;14:3737-3752. doi: 10.2147/IDR.S323353. PMID: 34548798; PMCID: PMC8449645.
43. Shadkam S, Goli HR, Mirzaei B, Gholami M, Ahanjan M. Correlation between antimicrobial resistance and biofilm formation capability among Klebsiella pneumoniae strains isolated from hospitalized patients in Iran. Ann Clin Microbiol Antimicrob. 2021 Feb 15;20(1):13. doi: 10.1186/s12941-021-00418-x. PMID: 33588850; PMCID: PMC7885248.
44. https://www.frontiersin.org/articles/10.3389/fcimb.2020.561741/full
45. Harada S, Aoki K, Yamamoto S, et al. Clinical and Molecular Characteristics of Klebsiella pneumoniae Isolates Causing Bloodstream Infections in Japan: Occurrence of Hypervirulent Infections in Health

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(4), 671-686 | ISSN:2251-6727

Care. *J Clin Microbiol*. 2019;57(11):e01206-19. Published 2019 Oct 23. doi:10.1128/JCM.01206-19

46. Lazăr V, Chifiriuc MC. Medical significance and new therapeutical strategies for biofilm associated infections. *Roum Arch Microbiol Immunol*. 2010;69(3):125-138.
47. Hennequin C, Aumeran C, Robin F, Traore O, Forestier C. Antibiotic resistance and plasmid transfer capacity in biofilm formed with a CTX-M-15-producing Klebsiella pneumoniae isolate. *J Antimicrob Chemother*. 2012;67(9):2123-2130. doi:10.1093/jac/dks169Long dy
48. Favre-Bonte S, Joly B, Forestier C. Consequences of reduction of Klebsiella pneumoniae capsule expression on interactions of this bacterium with epithelial cells. *Infect Immun*. 1999;67(2):554-561. doi:10.1128/IAI.67.2.554-561.1999Wu MC
49. Shon AS, Bajwa RP, Russo TA. Hypervirulent (hypermucoviscous) Klebsiella pneumoniae: a new and dangerous breed. Virulence. 2013 Feb 15;4(2):107-18. doi: 10.4161/viru.22718. Epub 2013 Jan 9. PMID: 23302790; PMCID: PMC3654609.
50. Sahly H, Aucken H, Benedí VJ, et al. Increased serum resistance in Klebsiella pneumoniae strains producing extended-spectrum beta-lactamases. *Antimicrob Agents Chemother*. 2004;48(9):3477-3482. doi:10.1128/AAC.48.9.3477-3482.2004
51. Yeh KM, Lin JC, Chang FY, et al. Epidemiology of Klebsiella pneumoniae bloodstream infections in a teaching hospital: factors related to the carbapenem resistance and patient mortality. Clin Infect Dis. 2007;45(3):312-4. doi: 10.1086/519265
52. Zhang R, Lin D, Chan EW, et al. Emergence of Carbapenem-Resistant Serotype K1 Hypervirulent Klebsiella pneumoniae Strains in China. Lancet Infect Dis. 2016;16(2):161-8. doi: 10.1016/S1473-3099(15)00446-3
53. Koh TH, Sng LH, Wang GC, et al. Klebsiella pneumoniae necrotizing fasciitis associated with diabetes mellitus. Emerg Infect Dis. 2012;18(9):1489-92. doi: 10.3201/eid1809.120232
54. Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH. Global Dissemination of Carbapenemase-Producing Klebsiella pneumoniae: Epidemiology, Genetic Context, Treatment Options, and Detection Methods. Antimicrob Agents Chemother. 2017;61(9):e00694-17. doi: 10.1128/AAC.00694-17
55. Wilasrusmee C, Paitoonpong L, Sribenjalux P, Jirawatnotai S, Tancharoen S. Risk factors and clinical outcomes of carbapenem-resistant Klebsiella pneumoniae infections in a tertiary care hospital in Southern Thailand. Infect Drug Resist. 2018;11:529-37. doi: 10.2147/IDR.S161883
56. Khanna V, Khanna S, Mukherjee A, et al. Rising trend of antibiotic resistance in Klebsiella pneumoniae. J Glob Antimicrob Resist. 2019;17:305-6. doi: 10.1016/j.jgar.2019.02.017
57. Mohanty S, Singh P, Dhawan B, Das BK, Kapil A. Phenotypic characterization and colistin susceptibilities of carbapenem-resistant Klebsiella pneumoniae strains from India. Infect Drug Resist. 2021;14:3273-82. doi: 10.2147/IDR.S332870
58. Chen Y, Fang CT, Lai SY, et al. Klebsiella pneumoniae Genotypes Carrying blaCTX-M-15 and blaDHA-1 and Antimicrobial Resistance in Taiwan. Front Cell Infect Microbiol. 2020;10:160. doi: 10.3389/fcimb.2020.00160
59. Mora-Rillo M, Arsuaga M, Ramírez-Olivencia G, et al. Nosocomial transmission of hypervirulent Klebsiella pneumoniae producing KPC-3 in a general hospital. Emerg Infect Dis. 2019;25(6):1056-7. doi: 10.3201/eid2506.181791
60. Karampatakis T, Tsergouli K, Behzadi P. Carbapenem-Resistant *Klebsiella pneumoniae*: Virulence Factors, Molecular Epidemiology and Latest Updates in Treatment Options. *Antibiotics*. 2023; 12(2):234. https://doi.org/10.3390/antibiotics12020234