

## REVIEW ARTICLE

# An Updated Outline of *Klebsiella pneumoniae* Resistance: Mechanisms and Treatments

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## ABSTRACT

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*Klebsiella pneumoniae* (*K. pneumoniae*) is the most prominent type of *Klebsiella* spp. *K. pneumoniae* has become a worldwide health threat nowadays due to the emergence of hypervirulence and the extended-spectrum  $\beta$ -lactamases (ESBLs) producing strains that lead to the etiologies of hospital-acquired infections (HAI) and community-acquired infections (CAI). To survive within the host, the bacterium acquires virulence traits and techniques to resist antibiotics and the immune system response, hence it gradually becomes multidrug-resistant (MDR). Consequently, more antibiotics are rendered ineffective and thus inappropriate, causing more deteriorating clinical conditions, leading to a high mortality rate. While the vaccine of *K. pneumoniae* is still in progress, and since we are long past the beginning of antibiotic use, new concepts came to play to fight the bacterial infection such as the use of bacteriophage to destroy the prokaryotic cell and enhancement of the immune system. This article covers the most common genetic and structural mechanisms of resistance by which *K. pneumoniae* exhibits its resilience against the defense system and various antibiotics. It also reviews the epidemiology, the leading sites of infections, and possible treatment options for future use.

## INTRODUCTION

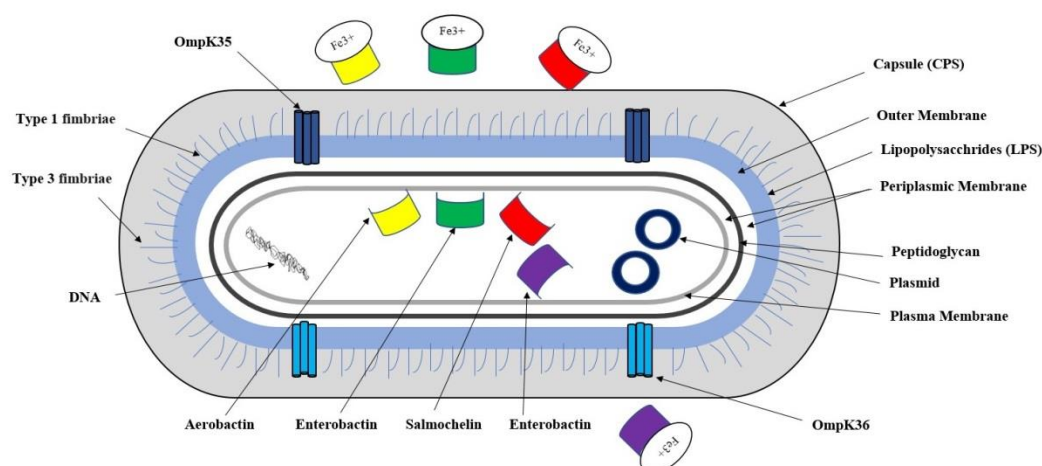
*Klebsiella* spp. are non-motile, encapsulated Gram-negative bacilli. They are facultative anaerobes and may remain viable for many weeks at room temperature with simple nutrition. *Klebsiella* spp. are one of the most ubiquitous organisms, living on the water surface, soil, and sewage<sup>(1)</sup>. As an opportunistic free-living organism, *K. pneumoniae* can be isolated from medicinal products, normally colonizing plants such as tea leaves. *Klebsiella* can be referred to as enteric, as it is a member of the family *Enterobacteriaceae*, which mostly reside in the intestinal tract of humans and most animals where they form part of the normal microbiota<sup>(2)</sup>.

Over the years, *K. pneumoniae* developed various genetic and structural modifications to survive the attack of antibiotics, due to overconsumption of

antibiotics along with inappropriate use such as self-medication without prescription.

*Klebsiella* spp. are a member of the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and extended-spectrum  $\beta$ -lactamase-producing strains of *Escherichia coli* and *Enterobacter* species) which normally colonize the surface of normal flora in humans, since they "escape" the antibiotics attack, hence the expression<sup>(3)</sup>.

There are main 4 virulence factors by which *K. pneumoniae* resist the defense system and antimicrobials, and also compose the structural integrity of the outer membrane of *K. pneumoniae* which are: capsular polysaccharides (CPS), lipopolysaccharide (LPS), fimbrial adhesins and siderophores; they primarily contribute and determine in the extent of virulence of *K. pneumoniae* (fig 1).



**Fig 1. The main 4 structural elements of virulence of *K. pneumoniae***

The virulence factors which also form the structure of the outer membrane: the capsule (CPS), lipopolysaccharides (LPS), the outer membrane proteins (OMPs), and the siderophores (iron chelators). In case of hvKp, the capsule is thicker and the siderophores are released more than the cKp.

### The Virulence Factors:

#### The Capsule:

Until lately, about 80 capsular K antigen serotypes of *K. pneumoniae* have been discovered, but only some cause the pathogenesis<sup>(4)</sup>, specifically K1 and K2 serotypes.

Encoding both of *magA* and *rmpA* (regulator of mucoid phenotype) genes regulate the production of the CPS, and they are usually detected by PCR in hypervirulent strains of *K. pneumoniae*<sup>(5)</sup>. Hypermucoviscous/hypervirulent phenotypes are characterized by increased production of the CPS.

#### Lipopolysaccharides (LPS):

LPS are a crucial component of the bacterial cell wall of *K. pneumoniae*. There are two main virulent components of the LPS: lipid A, the endotoxin, and O-antigen, which is resistant to heat degradation. Lately, at least 12 different serotypes of O-antigens (O1-12) were identified within pathogenic *K. pneumoniae*, but only serotypes O1, O2, O3, and O5 predominant in the strains of MDR-Kp strains<sup>(6)</sup>. The modifications of lipid A contribute to the resistance against AMPs, one of the main weapons of the innate immune system<sup>(7)</sup>.

#### Outer Membrane Proteins (OMPs):

OMPs act as porins or channels that allow the influx of nutrients including iron. They also support the structural integrity of the outer membrane and the overall endurance. OmpK35 and OmpK36 are the most frequent porins present on the outer surface of *K. pneumoniae*.

Downregulation of OMPs can be a beneficial aspect for the bacterial cell in two ways. First, it can help in the stealth movement by low activation of the immune system; second, it minimizes the risk of antibiotic

susceptibility due to the low influx of antibiotics used in the treatment of the infection.

#### Fimbriae:

Bacterial fimbriae (also called pili), a string of protein subunits, are shorter and thinner than the flagella, but unlike flagella, the main function of the fimbriae is adhesion to the surface of host cells and to abiotic surfaces including urinary catheters. Adhesion is the major step for the bacteria to initiate pathogenesis. Fimbriae have the ability to form biofilms, i.e. bacterial clusters that are attached to themselves for protection against the immune system and antibiotics.

There are 2 major types of fimbriae that *K. pneumoniae* possesses, type 1 and type 3 fimbriae. The function of type 1 fimbriae is mainly adhesion especially in UTI, while type 3 fimbriae are necessary for biofilm formation. Type 1 fimbriae contain an adhesin molecule (FimH) that binds to bladder cells surface<sup>(8)</sup>, as a result, the uropathogen replicates intracellularly effortlessly.

#### Iron Acquisition:

Iron is a prominent element for bacterial growth and enhancing the virulence of *K. pneumoniae*. To meet the requirement of iron, most strains of *K. pneumoniae* secrete siderophores (specific ferric iron chelators). The most widely distributed siderophores among clinical isolates of *K. pneumoniae* are aerobactin, salmochelin (also enterochelin), and yersiniabactin. Microcin E492, another siderophore (also one of the bacteriocins, proteins produced by *K. pneumoniae* as enteric bacteria to kill closely related strains, was found to be highly associated with liver abscess caused by the hypermucoviscous *K. pneumoniae*<sup>(9)</sup>.

## Immune System: Response and Resistance

In the perspective of basic immunology, infection is a process by which the microbe enters into a relationship with the host by penetrating through the gastrointestinal tract (GIT), respiratory tract,

genitourinary tract, skin, and mucous membrane. The immune system is complicated, but generally, there are two arms of the immune system, the innate/ native immunity and the adaptive/ specific immunity as (fig 2) shows the classification of each arm.

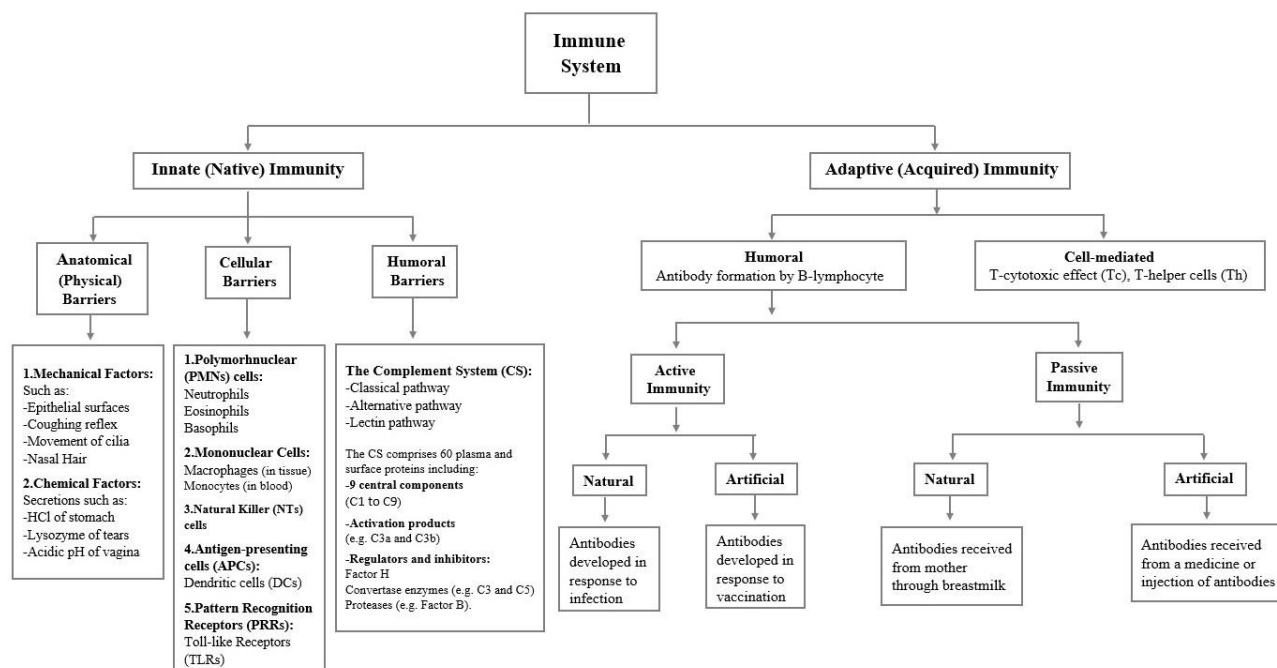


Fig 2. The main components of the human immune system

Studies showed that neutrophils, macrophages, and the complement system are important weapons against *K. pneumoniae* infection; as the murine models proved the role of alveolar macrophages in the course of *K. pneumoniae* infection is crucial regarding the phagocytosis and recruitment of PMNs<sup>(10)</sup>.

The CPS provokes the production of antibodies that induce the serum complement and other phagocytes, thereby, the encapsulated strains of *K. pneumoniae* are more resistant than the unencapsulated *K. pneumoniae* ones to be killed by the phagocytes.

Considering that the lung collectins SP-A and SP-D (i.e. surfactant proteins and activators of phagocytosis) can bind to the LPS<sup>(11)</sup>, the CPS acts as a protective shield for the LPS, hence minimizing bacterial susceptibility.

Upon infection, Toll-like Receptors (TLRs), a fundamental component of the pattern recognition receptors are activated, thereby initiating an innate immune response by inducing cytokines and reactive oxygen species (ROS), leading to phagocytosis that may help in the overall survival of the host against the infection of *K. pneumoniae*. The TLRs are exhibited in immune cells including the dendritic cells (DCs), one of the antigen-presenting cells (APCs) initiating the adaptive immune response, macrophages, as well as in

non-immune cells such as epithelial cells. TLR-4 have a pivotal part role in the induction of innate immunity during the infection of *K. pneumoniae*.

Other virulence factors rather than the CPS contribute in the stealth characteristics without recognition of the immune system including the LPS and OMPs, as previously mentioned, thus counteracting the immune inflammation, hindering stimulation of TLRs, even though the CPS may trigger the activation of TLRs<sup>(12)</sup>.

The adaptive immune response is activated in various ways such as the DCs that capture and present the antigens to lymphocytes. *Klebsiella* interference in the processing of presentation of antigen-derived peptides to T cells is still a question to be investigated.

### The Complement:

Only two pathways of the complement system are involved in the bactericidal activity which are: the classical pathway and the alternative pathway. In both pathways, C3b specifically enables the opsonization of bacteria by binding to the pathogen surface initiating the membrane attack complex (MAC), the result component of the cascade of the alternative pathway activation, which can either cause direct lysis of bacterial membrane or label bacteria for phagocytosis.

The MDR-Kp have several mechanisms to resist complement, for instance, the thick peptidoglycan layer located in the periplasmic space in between the inner and outer membranes, may protect against lysis by the MAC with the help of the CPS that restrict the insertion of MAC in the outer membrane<sup>(13)</sup>.

“Smooth LPS” is a term referred to the LPS which can alter modification of the composition of the O-antigen to adapt with the action of the complement system, unlike the rough LPS which appeared to be more sensitive than the smooth LPS. The modifications also result in C3b deposition further away from the surface, preventing the proper deposition of the MAC, featuring a decrease in the bactericidal activity.

Host-directed therapy (HDT) is a new approach that basically depends on improving innate immunity. It has already proven to be effective such as interferon-beta (IFN- $\beta$ ) as approved antivirals for the treatment of hepatitis B and C, as well as enhancing the phagocytic ability of macrophages against tuberculosis (TB).

More studies need to be done for the HDT efficacy against *K. pneumoniae* infection, given the high diversity of genetics among the different strains is a challenge as some strains may evade this particular approach.

#### There are 2 Types of Pathogenic *K. pneumoniae*: Hypervirulent *K. pneumoniae* (hvKp):

The hvKp can be identified by two features including the hypermucoviscous capsule which is thicker than cKp, and greater extent of production of siderophore than cKp, aerobactin in particular, which contributes to hypervirulence and pathogenesis. *RmpA*-carrying strains were significantly associated with a high-mucus phenotype of the hvKp, and with purulent tissue infection such as pyogenic liver abscess (PLA).

Evidence shows that the string test may help to detect the hvKp, but it is inferior to values of genotypic biomarkers evaluated such as *p-rmpA*, and *iucA* (i.e. the gene that encodes aerobactin siderophore), as it may give a false negative result<sup>(14)</sup>.

A novel virulence factor discovered, type VI secretion system (T6SS), which the hvKp encodes to inject the competing host cells with enzymes and toxins. It also elevates the potential of resistance of the bacteria by stimulating biofilm-formation to combat against wide spectrum antibiotics such as  $\beta$ -lactams and fluoroquinolones<sup>(15)</sup>.

#### Classical *K. pneumoniae* (cKp):

##### $\beta$ -lactamase enzymes:

Due to multiple mechanisms of resistance of the GNB against  $\beta$ -lactam antibiotics such as production of enzymes that destroy the active site (e.g.  $\beta$ -lactamase or penicillinase), the primary mechanism, and alteration of penicillin-binding protein (PBP) receptors. However, penicillin and cephalosporins may render ineffective against GNB (*Enterobacteriaceae* in particular) due to the releasing of the plasmid-mediated hydrolyzing resistant enzymes, besides the presence of the OMPs which provide permeability barrier, and overexpression of efflux pump systems (AcrAB-ToiC in case of *K. pneumoniae*)<sup>(16)</sup>. Moreover, the bacterial cell wall can slow the growth rate which deactivates the cell wall targeting antibiotics as a tolerance mechanism.

Due to the extensive usage of penicillin antibiotics,  $\beta$ -lactamase enzymes have been introduced as an evolution to hydrolyze them, and gradually extended to resist more antibiotics with a wider spectrum and introduced as extended spectrum  $\beta$ -lactamases (ESBLs).

As (fig 3) illustrates there are 4 classes of  $\beta$ -lactamase enzymes: class A, B, C, and D<sup>(17)</sup>.

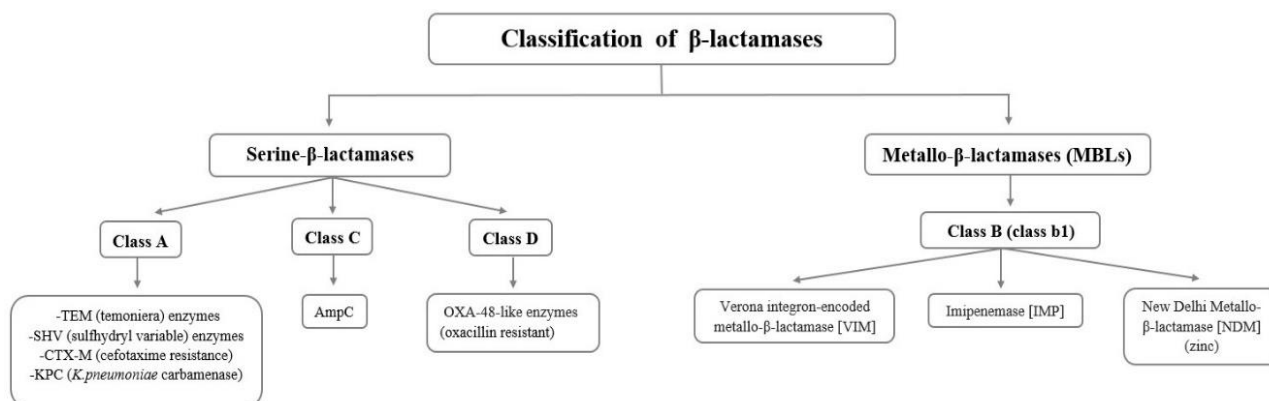


Fig. 3. Illustration of classification of  $\beta$ -lactamase enzymes with clinical relevance



**Class A  $\beta$ -lactamase:**

TEM-1 enzyme is the first enzyme of class A discovered and the most common  $\beta$ -lactamase disseminated among *K. pneumoniae*, then a phenotype TEM-2 was identified clinically, a long before TEM-3 (CTX-M). Although the SHV enzymes were discovered earlier, they did not become prevalent until the 1980s. There are numerous genotypes of TEM and fewer of SHV and CTX-M enzymes, encoded by  $bla_{TEM-1}$ ,  $bla_{SHV-1}$ , and  $bla_{CTX-M}$  genes respectively.

Accordingly, ESBLs, the  $\beta$ -lactamases with resistance to the first three generations of cephalosporins and  $\beta$ -lactamase inhibitors (BLIs) (clavulanic acid, tazobactam, and sulbactam), have emerged and the first line of treatment was the carbapenems including meropenem and imipenem.

$\beta$ -lactam resistance is mediated by ESBLs, which resulted from mutational development of more limited spectrum  $\beta$ -lactamases such as mutational development of TEM and SHV to be ESBLs enzymes resulted in altered their binding capacities to allow the larger cephalosporins to enter and be broken down.

***K. pneumoniae* Carbaminase (KPC):**

Carbapenem-resistant *K. pneumoniae* (CR-Kp) tops the list of the urgent antibiotic-resistant threats, most recently documented by the CDC<sup>(18)</sup>.

By studying the bacterial genetics using the accumulation of multiclass antimicrobial resistance (AMR), it was found that there is a potential hvKp transfer of  $bla_{KPC}$ -plasmids, meaning that the resistance is transferred genes from one strain to another, as demonstrated in ST258 and ST11 strains that contain hypervirulent capsule type K1 and type K2 and are considered as a CR-Kp<sup>(19)</sup>. CR-Kp strains have been specifically linked to a major sequence type (ST258), which was reported in several countries.

**Class C  $\beta$ -lactamases:**

Historically, AmpC  $\beta$ -lactamase of *Escherichia coli* (*E. coli*) is the first bacterial enzyme that destroyed the penicillin in 1940, but it was not named yet then. Although it is expressed in a lower extent than the other ESBLs, it is still threatening in hospitals due to prevalence of its expression by *K. pneumoniae* as much as *E. coli*.

It is widely distributed among the members of *Enterobacteriaceae*, but it is prominent in *K. pneumoniae*. This enzyme is resistant to the penicillins, BLIs, and broad-spectrum cephalosporins including carbapenems<sup>(20)</sup>.

**Class D  $\beta$ -lactamases:**

As for sub-classification of OXA enzymes, there are over 750 types of OXA  $\beta$ -lactamases that have been described but mainly OXA-48 and OXA-181, a variant of OXA-48 enzyme, are the most common enzymes identified among the OXA-48 group. The class D  $\beta$ -lactamase was first described in *Enterobacteriaceae*,

predominantly *K. pneumoniae*, in India then it was sporadically detected in France<sup>(21)</sup>.

**Class B Metallo  $\beta$ -lactamase (MBLs):**

Class B is divided into 3 groups (b1, b2, and b3), but only the b1 class is the most prevalent with clinical importance. The b1 class is subdivided into 3 groups of enzymes as (fig 3) shows. MBLs are resistant to  $\beta$ -lactam antibiotics, including carbapenems and BLIs but not against aztreonam.

The NDM-1 enzyme was first detected in 2008 in a patient who was infected with *K. pneumoniae* and *E. coli* who returned to Sweden from India<sup>(22)</sup>.

A recent in-vitro study suggests that (ceftazidime/avibactam + aztreonam) and (imipenem/relebectam + aztreonam) are more potent than (meropenem/vaborbactam + aztreonam), recommending aztreonam in the combination therapy against MDR CR-Kp strains that harbor MBLs and other  $\beta$ -lactamases<sup>(23)</sup>.

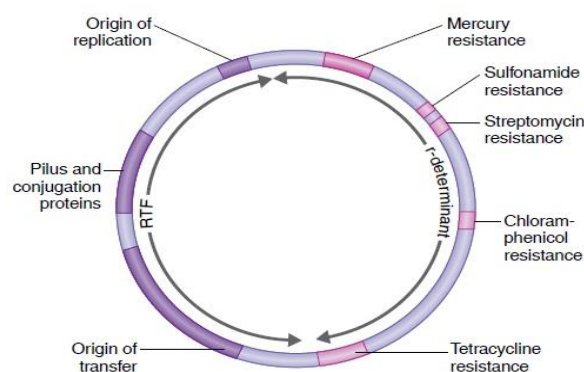
**Antibiotic Resistance:**

Unfortunately, due to the misuse and overuse of antibiotics, the bacterial resistance elevates gradually year after year since the 1980s through the 1990s until now due to ESBLs development.

In the 1950s after several epidemics, the researchers discovered the resistance factors (R factors) which are resistance genes-carrying plasmids. They are composed of 2 parts, the resistance transfer factor (RTF) which includes genes for plasmid replication and conjugation; and the

r-determinant that contains the resistance genes by which the bacteria acquire the resistance against specific antibiotics and toxic substances<sup>(24)</sup>.

Fig 4 illustrates plasmid R100 which can be transferred among *Escherichia*, *Klebsiella*, and *Salmonella*.



**Fig 4. A genetic map of the 2 parts of the R100 plasmid.**

The RTF (segment carrying replication genes), and the r-determinant (segment carrying antibacterial genes)<sup>(24)</sup>.

**Fluoroquinolone Resistance:**

Although *K. pneumoniae* may resist the quinolones by structural modifications, the more crucial mechanism of resistance is gene remodeling. For instance mutations of the *gyrA* gene, which encodes the GyrA subunit of the DNA gyrase which is the target of quinolones, took place due to alteration of amino acid sequence in the resistance region in the plasmid.

Another mutation of Qnr proteins which belongs to pentapeptide repeat, proteins that protect the gyrase from toxins, which is encoded by the genes *qnr*<sup>(25)</sup>.

**Ceftazidime-avibactam (CAZ-AVI) Resistance:**

The FDA approved ceftazidime-avibactam combination for the treatment of complicated

UTI-mediated CPE. As the combination has showed potential for the treatment of the CPE infection. Avibactam is a new BLI that inactivates the main enzymes of class A  $\beta$ -lactamases, class C, and class D-lactamases, yet ineffective against class B<sup>(26)</sup>.

Later, the resistance to avibactam has been reported in strains carrying SHV and CTX-M-15 but it rendered susceptibility to ceftazidime. In theory, double mutations can hydrolyze the (CAZ-AVI) combination, however, the pathogen may use an efflux pump resistance system in resemblance to *Pseudomonas aeruginosa*<sup>(27)</sup>.

**AGs Resistance:**

When it comes to the resistance of aminoglycoside antibiotics, *K. pneumoniae* primarily produces aminoglycoside modifying enzymes (AMEs) and 16S rRNA methylases<sup>(28)</sup>. Both *armA*, *rmtB* are among the most frequent 16S rRNA methylases expressed against aminoglycosides by clinical isolates of *K. pneumoniae*, which were described worldwide.

When amikacin efficacy was tested against *K. pneumoniae* strains, it result in a high MIC (i.e. minimum inhibitory concentration) of amikacin, but when combined with CAZ-AVI, the MIC lowered, which means the combination may be used in the case of MDR-Kp<sup>(29)</sup>.

A new aminoglycoside came into the market, plazomicin, that when compared to the other members of this class, it showed the highest bactericidal activity against *K. pneumoniae* that it may offer an option of treatment<sup>(30)</sup>.

**Polymyxin Resistance:**

When a bacterium becomes resistant to colistin, it can also simultaneously become impervious to components of the host's defense system, such as lysozymes and cationic antimicrobial peptides (CAMPs), principally as they act on the same target of polymyxins, hence the main mechanism of resistance of *K. pneumoniae* is genetic regulation of LPS formation, particularly lipid A<sup>(31)</sup>.

There are two-component regulatory systems responsible for lipid A biosynthesis gene, PhoP/PhoQ and pmrA/pmrB, both are chromosomally encoded. The

pmrA/pmrB system upregulates the genes involved in LPS modification, which leads to polymyxin B resistance.

The PhoQ component is activated by low concentration divalent cations, caused by the action of polymyxins on the LPS, and by CAMPs; while PhoP has a prominent role in evasion of phagocytosis, since the phagocytosis is activated by CAMPs.

Lately, synthetic CAMPs showed potential interaction with the CPS of *K. pneumoniae* leading to removal of the capsule and disruption of the cell surface<sup>(32)</sup>. They may be used in synergism with polymyxins for MDR-Kp in the future. However, the mechanism of synthetic CAMPs is not fully understood and their bonding is far more complex that requires further investigation.

**Tigecycline Resistance:**

The benefits of tigecycline as one of the last line antibiotics to treat ESBLs producing *K. pneumoniae* strains and CR-Kp have diminished due to progressive resistance.

The mechanism of resistance may be target modification, 30s ribosomal subunit, and/or activation of efflux pump systems (AcrAB-TolC and OqxAB<sup>(33)</sup>).

Since numerous antibiotics fail to treat the MDR CR-Kp and fatal infections, the remaining last line options such as: colistin and tigecycline have shown to be more effective when administered as a combination than monotherapy<sup>(34)</sup>, but even here, the resistance genes against both of them became common and may enhance the resistance among other strains.

**Pathogenesis:****Urinary tract infection (UTI):**

UTI is one the most extensive manifestations affecting renal transplant patients, and most women with an estimation of 60% of all ages. Over the years, it was established that there is an overlap between virulence and antibiotic resistance rate which is higher in HAI than CAI.

A recent study, in Indonesia, established that UTI can be caused by ESBLs-producing *K. pneumoniae* with the highest levels of resistance to common antibiotics<sup>(35)</sup>, including a much higher rate of resistance compared to the isolates from a 2005 study.

**Gastrointestinal tract (GIT) Infection:**

Since many members of GNB colonize all the GIT, it is well-known now that they can play a role in GIT-related diseases such as: inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), and colorectal cancer (CRC). Lately, studies have shown *K. pneumoniae* can progress GIT diseases.

The journey of *K. pneumoniae* through the human body to cause GIT infection starts from the oral cavity evading the physical barriers and the oxidative stress, mediated by the ROS and nitric oxide (NO) used by phagocytes and lung epithelial cells to kill pathogens<sup>(36)</sup>. When it comes to gastric acids, the role of thick capsule

comes to play specifically K1 and K2 type capsules of the hvKp as they attach to the mucosal surface by type 1 and type 3 fimbriae.

By secreting siderophores to chelate the host's iron and colibactin, a genotoxin that causes DNA damage and cell cycle disruption, *K. pneumoniae* can confer the colonization of the GIT, and therefore there may be a link between *K. pneumoniae* and the CRC.

#### **Pyogenic Liver Abscess (PLA):**

Several cases of liver abscess-mediated *K. pneumoniae* were described in Europe and the USA. Even though *K. pneumoniae* is transmitted mostly by personal contact or medical equipment, it can be transmitted by the fecal-oral route, reaching the liver through the portal vein and causing liver abscesses.

The treatment of this type of infection includes early antibiotic treatment, ultrasonography-guided puncture aspiration or draining, and open surgical drainage of the liver abscesses<sup>(37)</sup>.

KPLA may induce a rare but devastating ocular infection, Endogenous Endophthalmitis (EE). Mostly the prognosis of EE is poor even if appropriate diagnosis and treatment are given.

#### **Bloodstream Infection (BSI):**

BSIs can be caused by CR-Kp or ESBLs-producing *K. pneumoniae* and associated with more invasive procedures leading to high mortality rate. In addition, *K. pneumoniae* induces sepsis in neonates and in adults, as a bloodborne pathogen, it may cause the infection of the nervous system after penetrating endothelial tight junctions which may lead to meningitis. In addition, endotoxins can cause septic shock upon lysis of the cell, thereby severe drop in blood pressure.

#### **Meningitis:**

Meningitis mediated-*K. pneumoniae* may complicate the treatment of liver abscess, elevating the mortality rate despite the timely adequate antibiotic therapy. Although neonatal meningitis is rare, some cases were reported in Europe<sup>(38)</sup>. Prematurity can predispose meningitis regardless of the type of pathogen, in addition, congenital anomalies of the urinary tract can predispose leading to developmental delays.

#### **Bacteriophage:**

Bacteriophage (also known as phage or bacterial virus) is simply a virus that infects or parasitizes the prokaryotic cell by either lytic cycle (i.e. the virulent cycle) or the lysogenic cycle (i.e. avirulent cycle). The lytic cycle is the one on which the idea of phage therapy (PT) is based.

The proposal of the PT started over a century ago, but there were some drawbacks of the early clinical use as the antibacterial such as lack of interpreting the phage-bacterial strain specificity (i.e., only one phage would work on a single type of bacteria), and the varying routes of administration and doses of phages.

In addition, the discovery of penicillin started a new era of medicine, the antibiotics, which led to suspension

of the phage use, even though the research continued in some countries. Now, because of the urgent need for a new line of treatment for the AMR and the decline of formulation of new antimicrobials over the years, the studies renewed the interest in PT.

Due to the high therapeutic effects and low adverse effects (toxicity), the PT may be used as an alternative for CR-Kp and hvKp as in the post-antibiotic era with the appropriate use.

To give an instance, a recent clinical study has demonstrated the efficacy of the PT in the treatment of prosthetic joint infection, one of the most difficult infections to treat, suggesting that the PT can be used as an add-on with the available antibiotics<sup>(39)</sup>.

Unfortunately, mutant strains are reported to resist the bacteriophage<sup>(40)</sup>, mainly by impairing the adsorption by altering the receptors of bacteriophage of the surface structure (CPS, LPS, and OMP). But, because they can be used in critical resistant infections, we need to implement effective strategies such as using a cocktail of either 2 phages specific to 2 different host receptors (of the cell surface structure) which reduced the resistance compared to using 2 phages for the same receptor, or combining antibiotics with phages with to enhance its efficacy, since phage-resistant strains exhibit more sensitivity to antibiotics.

## **CONCLUSION**

*K. pneumoniae* is a global risk that can be transmitted easily causing severe infections using multiple adaptation strategies in compliance with the surrounding environment within the host either by genetic or structural modifications. The distribution of resistance genes among strains of *K. pneumoniae* or even the members of the family of *Enterobacteriaceae* is concerning as the multiple gene mutations and variations are linked to more persistent resistance to antibiotics even the ones in the last line of treatment!

Coupled with the fact that, the prospects for producing new antibiotics look bleak, and the gradual loss of antibiotic options; some alternatives arose including phage therapy, new combinations of antibacterials, and enhancement of the immune system. Since there are plenty of gaps that still need more investigations regarding the synthetic CAMPs and HDT, and until an effective vaccine becomes available, healthcare professionals need to follow hand hygiene rules and the stewardship programs which include rational, optimal use of antimicrobials to maintain infection control, only then we might stand a chance against the slow-motion catastrophe of antibiotic resistance.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media.

I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

#### Author Contribution:

Antony S. Soliman researched data for the article, wrote the original draft, reviewed and presented the published work.

Mina N. Agban critically supervised, reviewed, and edited the manuscript.

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