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REVIEW ARTICLE

An Overview on Klebsiella Pneumoniae Resistance to Antibiotics

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ABSTRACT:

Background: Klebsiella pneumoniae is an opportunistic bacteria linked to a range of infections. Klebsiella pneumoniae is a gram-negative bacterium that can colonize, invade, and cause infections in several parts of human body. The rise of hypervirulent pathotypes, its capacity to elude the immune system, and rising antibiotic resistance have made it a significant challenge in the medical industry. In this study, virulence factor gene presence and the antibiotic resistance mechaisms that have been used by k.pneumoniae to tolerate used antibiotics were reviewed.

Keywords: K. pneumoniae; Resistance; Antibiotics.

INTRODUCTION:

K. pneumoniae is clinically the most important member of genus Klebsiella that belong to the Enterobacteriaceae family which is a class of gram-negative bacterium that can be found in the environment and mucosal surfaces in animals . In humans, K. pneumoniae colonises mainly the gastrointestinal tract, and nasopharynx, through which it can enter the tissues or circulation, and then cause infection. It has been identified as an important common pathogen which causes many diseases worldwide including community acquired pneumonia which remains one of the major causes of mortality even in developed countries. It is also a major nosocomial pathogen causing pneumonia, burn, wound infections, septicemia and urinary tract infections [1].

The prevalence of K. pneumoniae resistant to multiple drugs (MDR) has increased as a result of the greater utilization of antibiotics, resulting in more challenges and roadblocks for clinical treatment. The World Health Organization views K. pneumoniae that produces β-lactamase (ESBL) and is resistant to carbapenem as a serious public health concern [2].

Aminoglycosides and cephalosporins are commonly used to treat K. pneumoniae. The patient's overall health, medical history, and severity of illness all have a role in the choice of antimicrobial agent. [3].

Because combination therapy uses numerous modes of action at once to boost the Antibiotics' pharmacodynamic killing action, it can postpone the establishment of resistance [4].

Due to K. pneumoniae's high degree of antimicrobial resistance (AMR) and the increasing prevalence of carbapenem-resistant K. pneumoniae (CRKP), combination therapy—which comprises carbapenems, tetracyclines, polymyxins, and fosfomycin—is advised and frequently utilized. Recurring exposure to a broad range of antimicrobial agents can give rise to novel MDR phenotypes. The frequency of K. pneumoniae infection as an opportunistic pathogen is consistently rising in clinical practice because of widespread misuse of carbapenems and β-lactam medicines [5].

The development of K. pneumoniae's biofilms, increased antibiotic efflux pump expression, inactivation and modification, changing of antibiotic targets, and loss or mutation of porins are the main causes of antibiotic resistance .fig (1) [3].

In this study, virulence factor gene presence and the antibiotic resistance mechaisms that have been used by k.pneumoniae to tolerate used antibiotics were reviewed.

Mechanisms of k. pneumoniae antibiotic resistance

Enzymatic antibiotic inactivation and modification

One significant resistance mechanism is β-lactamase, which hydrolyzes the β-lactam's β-loop. They are separated into three categories: carbapenemases, cephalosporinases (AmpC), and extended spectrum βlactamases (ESBLs) **[6].**

The production of these enzymes confers resistance to carbapenems, cephalosporins, and penicillins in K. pneumoniae. After the first identification of penicillin resistance in K. pneumoniae in the 1960s, over 200 ESBLs have been identified. Most of these ESBLs are capable of breaking down β-lactam through serine residues, but a few of them use zinc ions for this purpose [7].

One kind of ESBL is carbapenemase, which is the most prevalent way that mediate K. pneumoniae resistance to carbapenem drugs. At the moment, carbapenemases are mostly separated into Groups A, B, and D. Both class A and class D are serine carbapenemases; class A includes KPC, SME, and SPM; class B includes metallo-β-lactamases such as NDM, VIM, and IMP; class D's major component is OXA. Most carbapenemase-encoding genes are located on plasmids, and propagate horizontally, making nosocomial infection outbreaks an easier consequence [8].

The AmpC enzyme has more than 40 genotypes which can mediate resistant to cephalosporins, cephalomycin, and combinations of β-lactam - β-lactamase inhibitors either chromosomally or by plasmids and it can be transmitted by plasmids in between strains[6].

ESBLs

Plasmid-based antibiotic resistance mechanisms are known as ESBLs. Germany was the first country to identify the blaSHV-2 (ESBL) gene in K. pneumoniae [9]. France was the next country to detect the blaTEM-3 ESBL mutant gene in a viral vector [10].

The ESBL genotype CTX-M is gradually replacing TEM and SHV as the most common one because plasmids and transposons that produce these ESBLs are easily accessible (blaCTX-M) [11].

Many ESBL genotypes, including blaOXA in K. pneumoniae, and other ESBL genes, such as bla GES, bla SFO, bla PER, bla TLA, bla VEB, and bla KLUC-5, were acquired more easily as a result of horizontal gene transfer. ESBL-producing K. pneumoniae is now a common pathogen in infection outbreaks in hospitals, with endemic rates reaching 50% in certain areas [11].

Carbapenemase genes

Due to the widespread use of carbapenems as a therapy medicine, K. pneumoniae is among the most common carbapenem-resistant Enterobacteriaceae (CRE) of ESBL-producing bacterial infections. The plasmid-mediated carbapenem enzymes remain the predominant mechanism of multidrug resistance. The carbapenemase produced by K. KPC, also referred to as K. pneumoniae, is a serine-based class β-lactamase that is the most common and most deadly carbapenemase found in K. pneumoniae. [12].

In addition to being found in a particular Tn4401 transposition form, Bla KPC genes are integrated onto several plasmids and undergo clonal dissemination, which facilitates the gene's propagation to other individuals [13]. K. pneumoniae also has the carbapenemase genes Blame NDM, blame VIM, blame IMP, blame OXA [13].

Presence of these resistance genes makes a significant number of Enterobacteriaceae that produce carbapenemase (CPE) resistant to several commonly used therapeutic antibiotics, difficult to be treated clinically and having a high death rate. Traditional β-lactamase inhibitors typically do not work on KPCs, which poses a therapeutic challenge [14].

Because K. pneumoniae plasmids have translocated their carbapenemase-encoding genes onto chromosomes, these resistances are nearly impossible to control [12].

BlaNDM

The majority of β-lactams, including carbapenems, can be hydrolyzed by, New Delhi metallo-β lactamase (NDM), a subtype of metallo-β lactamase (MBL), with the exception of monobactams [15]. blaNDM-1 was discovered for the first time in a Klebsiella pneumoniae UTI isolate from a Swedish patient visiting New Delhi, India, [16].

The NDM enzyme has three turns, nine helices, and seventeen strands. There are two zinc ions at the active site of the 270 amino acids in the NDM, and substitution has been observed at 17 distinct locations. Normally, one to five amino acids are substituted in these variations. Out of the 28 NDM variations, M154L is the most frequently reported substitution. The main distinction between NDM-1 and NDM-18 is the five amino acid tandem repeat (QRFGD) seen in NDM-1 from positions 44 to 48 [17].

The absence of effective antibiotics, failure to identify high frequency of asymptomatic carriers,

the absence of a standard phenotypic test for the detection of metallo-beta-lactamase (MBL), and plasmid-borne MBL that can rearrange and spread horizontally are among the factors that make NDM-1 producing strains highly resistant [18]. The presence of blaNDM-1 on the Kp chromosome was just reported by Sakamoto et al. [19, 20].

NDM-1 and its variations are present in about 58.15% of the Asian subcontinent, with China, Bangladesh, Sri Lanka, and India having the highest prevalence. On the other hand, NDM-1 and its variation are detected in 16.8% abundance in European nations. According to reports, the USA and Africa account for over 10.8% of the world's NDM-1 production, with Australia providing 1.6% of the reservoir [21].

Antibiotic targets alteration

Klebsiella pneumoniae induces drug resistance through alterations in the target gene or methylation of certain bases, thereby impeding the binding of suitable antimicrobial drugs to the intended location. For example, lipid A alteration is typically a part of K. pneumoniae's resistance mechanism to polymyxin. [22].

Porin loss or mutation

Trimeric transmembrane proteins expressed on the outer membranes of Gram-negative bacteria are called porins, also known as outer membrane proteins (OMPs), are extensively generated. [23].

Bacterial drug resistance may develop as a result of a mutation that lowers the quantity of outer membrane pore proteins in the bacteria, hence reducing the amount of antimicrobial medication molecules that may enter the bacterium [24].

The two primary nonspecific porins are OmpK35 and OmpK36 linked to AMR in K. pneumoniae. Additional porins that contribute to intrinsic resistance include LamB, OmpK26, PhoE, and KpnO [25].

Increased efflux pump expression of the antibiotic

Efflux pumps, membrane proteins responsible for expelling substances out side cells so it can lower intracellular drug levels by releasing antimicrobial molecules outside the cell, hence reducing sensitivity to different antibiotics [26].

K. pneumoniae efflux system (OqxAB and AcrAB-TolC systems) belongs to Resistance nodulation cell division (RND) family. The AcrAB-TolC active efflux system has the ability to expel a wide range of antibiotics such as tetracycline, macrolides, fluoroquinolones and β-lactams resulting in emergence of MDR K. pneumoniae. [27].

Biofilm formation

Biofilms including proteins, extracellular DNA and extracellular polysaccharides, make the organisms resist antimicrobial medication and evade immune reaction by helping organisms' attachment to microbial communities on both living and non-living surfaces, which create a protective environment for bacteria [28].

Biofilms exhibit resistance to antimicrobial drugs and possess osmotic barrier qualities. A study revealed that K. pneumoniae biofilms lowered susceptibility to ciprofloxacin, ampicillin, and gentamicin [29]. Biofilm development has also been connected to Colistin resistance [30].

Quinolone resistance

Quinolone antibiotics prevent DNA replication by interfering with bacterial topoisomerases. Bacterial resistance to flouroquinolones has been observed as a result of the widespread usage of these antibiotics [31]. One of the following processes causes K. pneumoniae resistance to fluoroquinolones, including changes to target proteins, MDR efflux pump development, and target gene mutation. [32].

The main mechanism of resistance is a mutation of topoisomerase IV (parC-parE subunit) and DNA gyrase (gyrA-gyrB subunit). [33].

Alterations in the permeability of K. pneumoniae cells, such as the deficit of OmpK36, the overexpression of the multidrug efflux pump gene acrAB, and the lack of changes in kdeA, are also linked to resistance to Quinolones [34].

In K. pneumoniae, the OqxAB efflux pump plays a critical role in plasmid-mediated quinolone resistance (PMQR). Additionally, the efflux pump regulator plays a role in mediating quinolone resistance in K. pneumoniae. [35].

The QNR gene, which was discovered on the K. pneumoniae plasmid for the first time in the USA in 1994 is one of the fluoroquinolone resistance genes found in K. pneumoniae's PMQR determinant. [36].

Aa(6\)-Ib-cr is another PMQR gene that mediates aminoglycoside resistance and is in charge of quinolone modification in K. pneumoniae [37].

Tigecycline resistance

Since 2005, tigecycline, the original glycylcycline, has demonstrated potential in treating infections with K. pneumoniae, including strains that produce ESBL. However, a K. pneumoniae MDR strain with decreased tigecycline sensitivity was discovered in a hospital shortly after the first use [38].

The chromosomally encoded tigecycline resistance mechanisms encompass variations to the targets.

The changes include adjustments to the permeability of the cell and to the 30S and 16S ribosomal subunits. Tigecycline resistance is a result of changes in the expression of the efflux pumps AcrAB-TolC and OqxAB as well as changes in the levels of their regulators, RamA, RamR, RarA, and AcrR. [39].

A ramR mutation causes AcrAB efflux to be overexpressed, which in turn causes tigecycline resistance [40]. Reduced transcript levels of porin ompK35K and the Lon and rpsJ genes are linked to tigecycline resistance in K. pneumoniae [41].

Resistance to tetracycline

TetA, TetB, and class-1 integrons are the mechanisms that mediate resistance to tetracycline [42, 43]. Tetracycline-responsive repressor (TetR) is tightly regulated by tetA expression, and TetR in turn controls the energy-dependent efflux pump TetA. As a result, tetA mutations activate TetA, which causes tetracycline resistance [44].

Likewise, tetB is an essential tetracycline efflux protein that confers resistance against tigecyclines but not against tetracyclines. [45].

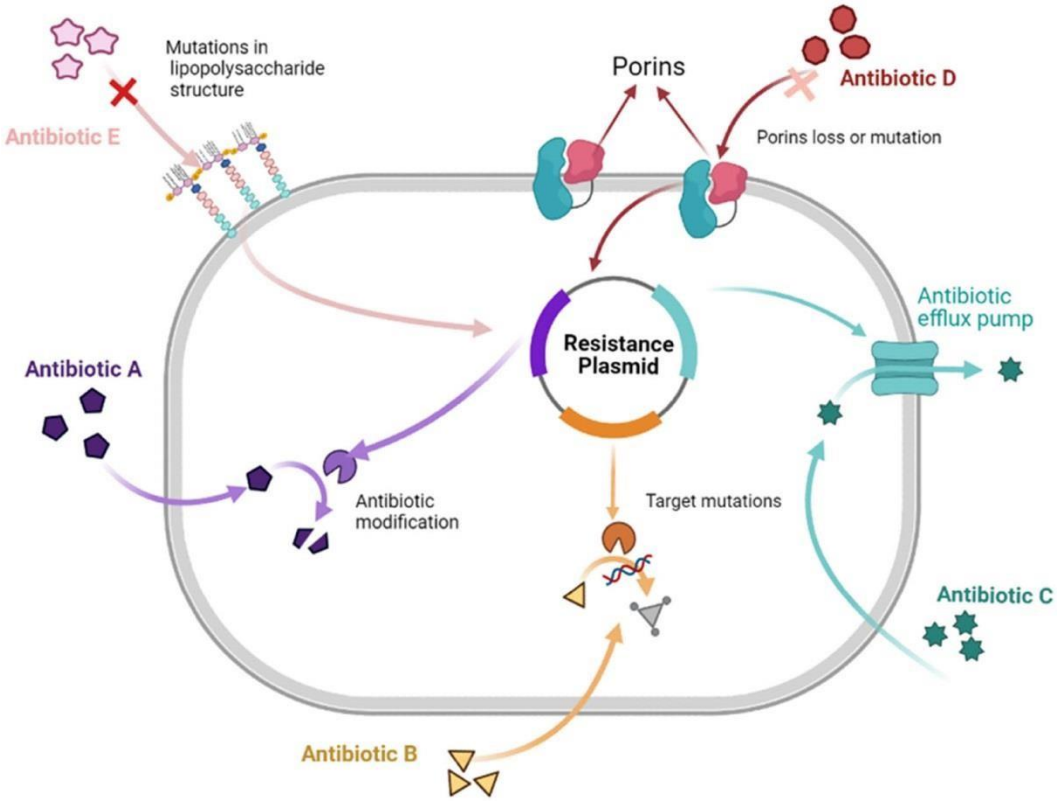

Figure 1 : Various mechanisms conferring antibiotic resistance to K. pneumoniae , Quoted from [5**].**

CONCLUSION

In this study we review that K. pneumoniae possesses different mechanisms and genes by which it can resist antibiotics . The mechanisms of antibiotic resistance in K. pneumoniae are multible and complex. Until now the resistance mechanisms are not completely obvious. This resistance mechanisms must be studied from different aspect and in wide range as it is an important step for the design of treatment and prevention strategies against this organism which in turn may alleviate sufferring of people with diseases caused by K. pneumoniae .

Conflict of interest

The authors declare that they have no competing interest**s**

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