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The Looming Threat of Antimicrobial Resistance: A Global Health Crisis

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ABSTRACT: Antimicrobial resistance (AMR) in Klebsiella pneumoniae is a major global health threat, with the bacterium developing resistance to last-resort antibiotics like carbapenems and colistin. K. pneumoniae causes a range of serious infections including pneumonia, sepsis, and meningitis, with mortality rates up to 50% even with antibiotic treatment. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) K. pneumoniae strains is a major concern, especially in healthcare settings where it is a leading cause of hospital-acquired infections. In India, over 70% of K. pneumoniae isolates are resistant to fluoroquinolones and 3rd-gen cephalosporins, with 56.6% resistant to carbapenems. K. pneumoniae has a high capacity to accumulate resistance genes through horizontal gene transfer, with key mechanisms including production of enzymes like extended-spectrum β-lactamases (ESBLs) and carbapenemases. It is considered a 'canary in the coalmine' for AMR, with new resistance genes often first detected in this species before spreading to other Gram-negatives. The COVID-19 pandemic has exacerbated the AMR crisis, with high rates of resistance in K. pneumoniae isolates from ICU patients co-infected with SARS-CoV-2. Urgent action is needed to develop new antibiotic combinations to treat MDR K. pneumoniae infections while novel antibiotics are in development

Keywords: Klebsiella pneumoniae, Antimicrobial Resistance, Combination Therapy, Global Burden

I. INTRODUCTION

The critical emergence and spread of the antimicrobial resistance (AMR)is threatening the world with possibility of occurrence of another pandemic due to the critical rise of AMR against the last resort antibiotics, which may lead the world to pre-antibiotic era. It is estimated that AMR will lead to 10 million deaths per year and loss of US$100 trillion by the year 2050 (1). Antimicrobial resistance (AMR) is the condition where the pathogens develop the resistance to the antimicrobials that agents formerly could kill the pathogens. The antibiotic era ranged from 1930s to 1960s that give rise to many new antibiotics. As the researchers were unable to uphold the rapidity of the antibiotic discovery as well as due to the lack of support from the major pharmaceutical industries, the antibiotic era diminished. The lack of new antibiotic discovery and development and the non-judicious use of the existing antibiotics led to the emergence of antibiotic resistance globally (figure 1) (2).

World's foremost organizations such as World Health Organization (WHO), Centres for Disease Control and Prevention (CDC), World Economic Forum and Infectious Diseases Society of America have declared the antimicrobial resistance as the global public health concern (3). The slogan given by the WHO for World Antimicrobial Awareness Week has also been changed in 2020 from "Antibiotics: Handle with Care" to "Antimicrobials: Handle with Care" due to the enlarged span of the resistance of drugs (4).

The discovery and subsequent clinical use of antimicrobials saved millions of lives and

International Journal of Pharmaceutical Research and Applications
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changed the therapeutic concepts. But the increasing rate of antimicrobial resistance in common pathogens like Klebsiella pneumoniae is now a global matter of concern due to the high mortality in critically ill patients. Even in 1945, in the New York Times the discoverer of the first antibiotic, Alexander Fleming commented – "the microbes are educated to resist

penicillin and a host of penicillin fast organisms is bred out which can be passed to other individuals and from them to others until they reach someone who get a septicaemia or a pneumonia which penicillin cannot save" (5). That has been proved as we did not pay attention to his words of warning and are now experiencing the consequences (2). The clinical implications associated with K. pneumoniae and the options and status of the treatment is given in figure 2.

Klebsiella pneumoniae (K. pneumoniae)being encapsulated bacteria was already a problem in healthcare settings which became a global threat due to the antimicrobial resistance (AMR) to the existing antimicrobials used to treat the infections caused by this pathogen. K. pneumoniaeis one of the clinically important organisms that have attained public health concern to a large extent. It is a Gram-negative, lactose fermenting, non-motile and encapsulated bacterium of Enterobacteriaceae family. Being an opportunistic pathogen, it affects generally those who are already enfeebled by the other infections or with the conceded immune systems. K. pneumoniae is associated with a broad spectrum of diseases like urinary tract infections (UTI), lung infections, sepsis, wound infections, diarrhoea, upper respiratory tract infections and meningitis (6), (7), (8).

K. pneumoniae is associated with both community acquired infections (CAI) as well as hospital acquired infections (HAI). The mortality rate is high in hospital acquired infections (32%) as compared to community acquired infections (16%) (9). Infectious Diseases Society of America (IDSA) recognized six pathogens, ESKAPE (E. faecium, S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa and Enterobacter) as the most significant and treacherous cause of drug-resistant health resort infections. The infections of K. pneumoniae have a high mortality rate of approximately 50% even with antimicrobial therapy and for the persons with bacteraemia and alcoholism the mortality rate approaches 100% (1). K. pneumoniae has been included in the critical priority list of MDR pathogens by the World Health Organization (WHO, 2017) and it needs to be addressed on priority (10).

K. pneumoniae has become a major cause of threat for neonates also as this is the common pathogen responsible for the sepsis in neonates. The neonatal period is very crucial for the new-born babies as about four million neonates die every year out of 130 million births. Low and middle income countries put in about ninety nine percent to the fatality of neonates (11). One of the leading causes of these neonatal deaths is sepsis caused by the pathogens. Neonatal sepsis is classified as early-onset sepsis (EOS) and late-onset sepsis (LOS) on the basis of the infection arises within or after seven days, respectively. Generally, the early-onset sepsis is well thought-out as a maternal genital tract infection and hence the maternally-acquired and late-onset is generally considered to originate from either of the community or healthcare environment (12). The neonatal sepsis symptoms are imprecise. The most common symptoms encompass fever, feeding difficulties, respiratory distress, exhaustion or tetchiness, deprived perfusion, swollen fontanel, seizure, bleeding problems, abdominal tightness, inexplicable jaundice, or more crucially, "just not looking right" (13). Neonatal sepsis is a major global concern due to its high rate of morbidity and mortality (14),(15),(13). According to the world health organization (WHO) in the first month of life 2.5 million children died, approximately 7000 new born deaths per day amounting to 47% of all child deaths globally were due to the sepsis (16). K. pneumoniae being an opportunistic pathogen (17) is a main threat to the neonates being more immunocompromised because numerous components of the immune system are not completely developed at birth (14), (18), (19).

Antimicrobial resistance (AMR) has become a matter of global concern as it has caused a worldwide health threat (20) and economic threat also as the estimated cost of infections caused by resistant strains to be tens of billions of dollars (21). Multidrug resistance in gram-negative pathogens is emerging rapidly and became a cause of high morbidity and mortality in immunocompromised patients (22). According to the Scoping Report on Antimicrobial Resistance in India, 2017, India has been reported some of the highest antimicrobial resistance rates in the pathogens causing the infections in community as well as hospital settings. The rate of resistance in K. pneumoniae to the broad spectrum antibiotics as fluoroquinolones and third-generation cephalosporins was more than 70% and for carbapenems it was second highest (56.6%) after

International Journal of Pharmaceutical Research and Applications
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A. baumannii(67.3%). Among Indian patients, K. pneumoniae was found associated with blood stream infections with the 69.3% mortality due to the dual resistance to both carbapenem and the colistin (the last line of treatment) (23). The "National Programme for Containment of Antimicrobial resistance" synchronized by National Centre for Disease Control (NCDC) in its five year plan (2012-17) reported the K. pneumoniae as the second most prevalent pathogen with a high resistance towards cephalosporins (approx.. 80%), ciprofloxacin (65%) and carbapenems (approx.. 50%) (24). The annual report of National Antimicrobial Resistance Surveillance Network (NARS-Net India), 2019 also reported the K. pneumoniae (22%) as the second most common pathogen after E. coli (33%). The most frequently isolated pathogen in the ICU was Klebsiella spp. (25).

Treatment of the infection caused by K. pneumoniae has become a challenge due to the prevalence of antimicrobial resistant strains which have been shown resistance against the penicillin, monobactams, carbapenems, aminoglycosides, third & fourth generation cephalosporins, and broad spectrum fluoroquinolones. Recently, studies in India have reported carbapenem resistant multi drug resistant (MDR) strains to be resistant to both tigecycline and colistin (26). According to the ICMR report (2017) K. pneumoniae (56.6%) comes at the second place after Acinetobacter baumannii (70.09%) in the list of carbapenem resistance incidence (27).

Antimicrobial resistance in K. pneumoniae poses problems in the treatment of infections (28). According to a review on AMR the death rate by 2050 can reach up to 10 million deaths per year if the resistance rate will keep growing with the present rate. K. pneumoniae is highlighted by World Health Organization (WHO) as the key AMR alarm mainly due to their effects on the public health problems e.g. K. pneumoniae with HIV (Human Immunodeficiency Virus) (29). Multidrug resistance in K. pneumoniae has become a perturbing concern that is progressively more experiential in human but also in veterinary medicine globally. K. pneumoniae is intrinsically susceptible to few clinically relevant antimicrobial agents, but these bacterial species have a great capacity to accumulate resistance genes, mostly through horizontal gene transfer (HGT). The most challenging system in these pathogens correspond to the attainment of genes coding for the enzymes conferred resistance to the antimicrobials such as extended-spectrum β-lactamases (ESBLs) to broad-spectrum cephalosporins, carbapenemases to carbapenems, 16S rRNA methylases to aminoglycosides, plasmid-mediated quinolone resistance genes to (fluoro)quinolones, and mcr genes to polymyxins (28). According to a recent retrospective study of MDR (multi-drug resistance) and XDR (extensive-drug resistance) prevalence in Enterobacteriaceae the E. coli (51.4%) was followed by K. pneumoniae (33%) (30).

The contribution of K. pneumoniae to the whole AMR calamity is not possible to enumerate, existing evidences advised that this pathogen has an extensive ecological distribution. Also, has considerably more varied DNA composition, larger antimicrobial resistance gene variety and a higher plasmid burden than other Gram-negative pathogens. K. pneumoniae plays a key role in spread of different antimicrobial resistance from ecological bacteria to clinically significant pathogens as shown in the figure 3 (31).

Mechanism of resistance vary with the antimicrobials and bacterial strains such as resistance due the presence of antibiotic inactivating enzymes like β-lactamases, aminoglycoside modifying enzymes, chloramphenicol acetyl transferase etc., changes in porins may interfere with antibiotic transport, efflux pump, alteration of the target, development of an alternate metabolic pathway, point mutation, horizontal gene transfer (HGT) and the most important plasmid mediated resistance. Due to the increasing occurrence of hospital out breaks and deaths associated with the AMR replica producing the K. pneumoniaecarbapenemase (KPC), it has become a significant threat to global public health and the centre point for the researchers of the World Health Organization (WHO), Centres for Disease Control and Prevention (CDC), European Union (EU), and other organisations. K. pneumoniae is also considered as the 'canary in the coalmine' as it is the organism in which the most recent AMR genes were detected for the first time before spreading in other Gram-negative pathogens including the extended-spectrum beta-lactamase (ESBL) forms of SHV and CTX-M; the carbapenemases KPC and NDM; and most recently MCR-1, the first plasmid-borne gene to be associated with colistin resistance (8).

As we all are aware to the present pandemic situation due to the Coronavirus Disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS Cov2). Globally, by the end of June, 2021 this disease has infected 185.2million people and 4.01million deaths have

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

been reported. In India also the situation is worst as by the end of June, 2021 the total infections and deaths were reported as 30.7million and 0.4 million, respectively (COVID-19 pandemic in India. Available from: https://covid19.who.int/region/searo/country/in).
The co-infections in the COVID-19 patients with bacterial infections have also reported where the antimicrobial resistance played a major role in the mortality. According to a recent India based study K. pneumoniae being an ICU prevailing pathogen, have been isolated most commonly from the COVID-19 patients admitted in hospital ICUs. These isolates of K. pneumoniae were the highly resistant strains which showed rate of resistance against ceftriaxone, fluoroquinolones, piperacillin/tazobactam and cefoperazone-sulbactam as (91.7%), (82%), (79.2%) and (76.4%) respectively. For the carbapenems the rate of resistance was also high like ertapenem (79%), meropenem (72%) and imipenem (66.8%) (32).

As the last resort (carbapenems) and last line (polymyxins) of treatment for the Gram-negative bacteria has also reported increasing rate of resistance, so, there is an urgent need to come up with a solution that can be provided in time of immediate need. To develop the novel antibiotic and make available for the public typically takes an extensive route and period henceforth there is an urgent need to come up with the suitable and effective combinations of the existing antimicrobials so that it can reach to the society in a less time. So, this review is mainly focussed on the antimicrobial resistance in K. pneumoniae and the reported studies to combat the infections caused by such MDR strains by using the combinations of the different drugs.

Enterobacteriaceae are a large family of Gram-negative bacteria that comprises a number of pathogens as Escherichia coli, Klebsiella, Enterobacter, Shigella, Salmonella, Serratia, Proteus and other species. The pathogens of Enterobacteriaceae are commonly present in the gut flora and in the human intestinal tract. These pathogens are a frequent cause of diverse types of infections and can be a cause of life-threatening complication if spread to the bloodstream. Like all other bacteria Enterobacteriaceae can develop resistance to antimicrobial agents like carbapenems and referred as the carpenemase-producing Enterobacteriaceae (CPE) (33).

Klebsiella pneumoniae

K. pneumoniae belongs to the Enterobacteriaceae family and Klebsiella genus which consists of non-motile, encapsulated rods that can grow well on an ordinary media. It forms the dome-shaped mucoid colonies of varying degrees of stickiness. These are non-motile, short, plump, straight rods of about 1-2 X 0.5-1.8 μm in size. This capsule is often prominent and can be made out even in Gram-stained smears as haloes around the bacilli and the bacterium comes under gram-negative microorganisms. These are widely distributed in nature occurring both as commensals in the intestines and as saprophytes in the soil and water.

K. pneumoniae also known as Friedlander's bacillus or Bacillus mucous capsulatus was first isolated by a German microbiologist and pathologist Friedlander in 1882 from the lungs of the patients died from fatal pneumonia (34), (9).

II. CLINICAL IMPLICATIONS AND EPIDEMIOLOGY

K. pneumoniae is responsible for the one third of all the infections caused by Gram-negative pathogens for instance pneumonia, septicaemia, urinary tract infections (UTI), cystitis, surgical wound infections, and endocarditis (35). Other infections are also caused by the bacteria like pyogenic liver abscesses, necrotizing pneumonia and endogenous endophthalmitis (6). K. pneumoniae being an opportunistic bacterium targets majorly the immunocompromised patients like old, neonates and patients with diabetes, liver or kidney ailments or other infections. The mortality rate is very high in these immunocompromised patients and alcoholics.

Klebsiella pneumoniae is associated with both community as well as hospital acquired/nosocomial infections. Cheol-In Kanget al., reviewed and analysed the high mortality rate of hospital acquired infections (32%, HAI) as compared to community acquired infections (16%, CAI) (7). The patients that required supportive instrumentations like catheter, ventilators etc. during the hospitalisation period are at high risk. Several studies have been reported the transmission of K. pneumoniae in the hospital through the person to person contact between healthcare workers patients and the contaminated instrumentation and surfaces (36), (37). The most common infections associated with K. pneumoniae are as given below:

International Journal of Pharmaceutical Research and Applications
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Pneumonia

Pneumonia can be categorised as hospital acquired (HAP) and community acquired (CAP) pneumonia. Approximately 3% to 5% of all CAP in the western society is associated with the infection caused by K. pneumoniae, whereas in the developing countries as in Asia and Africa, it is responsible for approximately 15% of all cases of pneumonia (9). F. Paganinet al., analysed the K. pneumoniae (22%) as the second most common bacteria after Streptococcus pneumoniae (33%) in the patients admitted in tertiary health care centre with severe CAP and was the independent risk factor for mortality in severe CAP (38). According to the John V. Ashurst, 2020 approximately 11.8% of all the HAP in the world is caused by Klebsiella pneumoniae with the range of 8-12% who are on ventilator and 7% who are not ventilated. The death rate goes up to 50-100% in the patients with diabetes and alcoholics. Due to the colonization and biofilm formation by the multidrug resistant bacteria in hospital settings it is more difficult to cure the HAP than the CAP. Symptoms of pneumonia due to K. pneumoniae are like fever, nausea, vomiting, tachycardia and most importantly cough up a "currant jelly" like sputum. The characteristic of the sputum is due to the inflammation and necrosis of the surrounding tissues during the infection (9).

Urinary Tract Infection (UTI)

UTI is also associated with both of thesettings i.e. community and hospital acquired, caused by the multiplication of microbes in one or more structures of the urinary tract. Every year about 150 million people worldwide are prone to the UTI and 95% of these cases are due to the bacteria (39). Several studies reported the prevalence of K. pneumoniae as the second most etiological agent involved in UTI (40). The common symptoms of the UTI are like low back pain, hesitancy, dysuria, urgency and suprapubic discomfort. Starting with the bladder infection, UTI often leads to influence the kidneys and eventually may cause renal failure, bacteraemia, severe sepsis and even death (41).

Septicaemia

Septicaemiacan take place as a result of the community acquired as well as nosocomial infections mainly pneumonia (42), (43) UTI and other intra-abdominal infections. Due to this host-pathogen interactions the body manifests an early release of proinflammatory cytokines and anti-inflammatory response with excessive inflammation resulting in cell damage, dysfunction of organs and ultimately death (42), (44). This is a global public health problem as approximately 5 million deaths out of 30 million total cases of sepsis worldwide have been reported (45), (46). Kristina E Rudd, estimated 48.9 million cases of sepsis and 11 million deaths due to sepsis were recorded worldwide (47). K. pneumoniae is the second leading cause of blood stream infections with a high mortality rate (48), (49), (50), (51).Sepsis is a medical emergency. However, because of the characteristics of sepsis as a disease condition with multiple causative organisms and its evolving nature over time, people with sepsis can present various signs and symptoms at different times. Warning signs and symptoms include fever or low temperature and shivering, altered mental status, difficulty breathing/rapid breathing, increased heart rate, weak pulse/low blood pressure, low urine output, cyanotic or mottled skin, cold extremities, and extreme body pain or discomfort (https://www.who.int/news-room/fact-sheets/detail/sepsis).

Neonatal sepsis

Neonatal Sepsis caused by the K. pneumoniae is the major concern worldwide. According to the world health organization (WHO) in the first month of life 2.5 million children died, approximately 7000 new born deaths per day amounting to 47% of all child deaths globally were due to the sepsis (WHO, Sept., 2019). K. pneumoniae being an opportunistic pathogen (17) is a main threat to the neonates as they are theoretically immunocompromised because numerous components of the immune system are not completely developed at birth (14), (18), (19).

Other diseases

Other diseases like liver abscess, meningitis, wound infections etc. are the most common diseases caused by the K. pneumoniae.

Liver abscess is usually a polymicrobial infection that has ascended from the gastrointestinal tract and K. pneumoniae can cause pyogenic liver abscess (PLA) in the absence of hepatobiliary disease. The diabetics are at the highest risk of this infection. Community acquired liver abscess in Asia accounting for 80% of all the cases (52),(53),(54).

Although meningitis due to K. pneumoniae is uncommon but in Taiwan this is the leading causative pathogen of meningitis with the prevalence rates about 25% to 40% and a high mortality rate (48.5%-66%). An infection of the meninges (the protective layers around the brain) can cause headaches, neck and/or back pain, fevers,

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

a stiff neck, and fatigue. In rare instances, meningitis can cause seizures (55),(56),(57),(58).

Wound infections can be of many types like burn, fracture, ulcers, surgical site infections etc. Pathogens can invade whole body and attach to the cells and proliferate. In some of the cases these pathogens cannot be prevented by the immune system. Normally, Klebsiella pneumoniae enters and causes infections due to the injuries. The skin wounds are the direct cause that guides pathogens to make a way into circulatory system and generally arise with shock and ulcers for instance the diabetic foot gangrene (59). Several studies have reported Klebsiella pneumoniae as the most prevalent (60),(61) second most prevalent (62) pathogen in wound infections that can result in delayed wound healing, redness, pus, fevers and pain.

III. ANTIMICROBIALS AND THE TREATMENT

Subsequent to the identification of bacteria by van Leeuwenhoek in the 1670s and the concept of correlation of bacteria and diseases latter in the 19th century attracts the researchers to study about the mystery of the infectious diseases and to find out the substance that can kill or slow down the growth of the bacteria causing the disease. The answer for the problem was the discovery of antibiotics which started with the accidental finding of "penicillin" in 1928 from Penicillium notatum by Sir Alexander Fleming (63).

Vuillemin in 1890 coined the term antibiosis which comes from the French word, antibiose. Later on the founder of streptomycin, Selman Waksman, the microbiologist used the noun "antibiotic" for the first time in 1943 (64). Several definitions were given by the experts to describe the antibiotics from 1947 to the 21st century. According to Waksman (1947), the definition of antibiotics was- ''an antibiotic is a chemical substance, produced by micro-organisms, which has the capacity to inhibit the growth of and even to destroy bacteria and other microorganisms (65).

The action of an antibiotic against micro-organisms is selective in nature, some organisms being affected and others not at all or only to a limited degree; each antibiotic is thus characterized by a specific antimicrobial spectrum. The selective action of an antibiotic is also manifested against microbial vs. host cells. Antibiotics vary greatly in their physical and chemical properties and in their toxicity to animals. Because of these characteristics, some antibiotics have remarkable chemotherapeutic potentialities and can be used for the control of various microbial infections in man and in animals'' (65).

The latest definition of antibiotics was given by Forsdyke in 2000- ''an antibiotic is a chemical (of natural or synthetic origin) which (usually at low concentrations) inhibits microorganisms of some type within a host organism, while not unacceptably interfering with life of that organism'' (64).

Now, there are several identified and FDA approved antibiotics which are in use to treat the infections caused by the pathogens like K.pneumonae. Antibiotics have been classified in different classes on the basis of their sources, types of action, spectrum, mode of action and chemical structures. Flow chart of antimicrobials is given in figure 4.

Different antibiotics have been approved by FDA against Gram-negative bacterial infections. The modes of action of these different antimicrobials on the bacteria are also different (table 1).

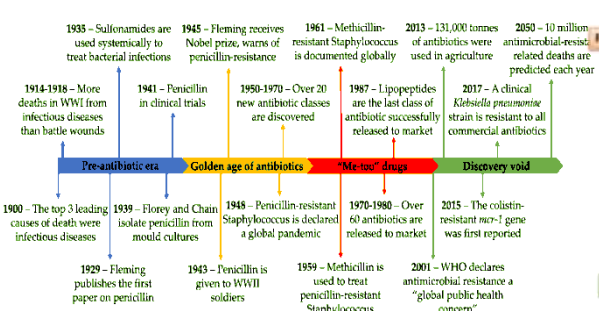

Figure 1

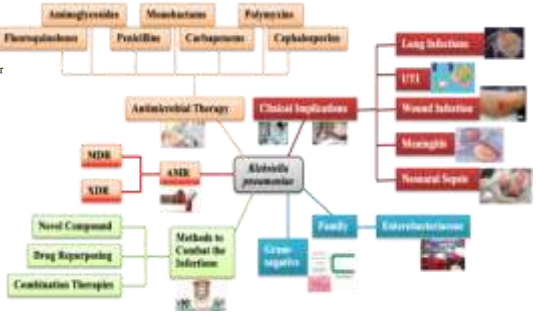

Figure 2

Figure 1 An outline of the proceedings in the antibiotic resistance timeline (source: Katrina Browne et al., (2)). *WHO- World Health Organization, WWI/II- World War I/II

Figure 2 The clinical implications of the K. pneumoniae and the treatment options/status

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

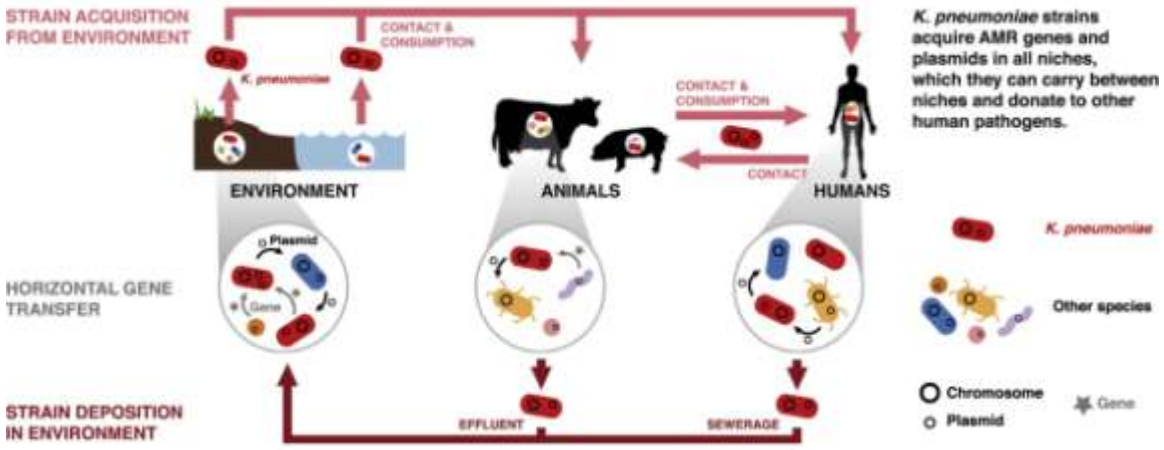

Figure 3 Representation for antimicrobial gene and plasmid trafficking (source- Kelly L.Wyreset al., (31))

IV. ANTIMICROBIAL RESISTANCE (AMR)

Antimicrobial resistance defined as the capability of microorganisms to stay alive and viable under the pressure of antimicrobial agents (66). According to the GLASS (Global Antimicrobial Resistance and Use Surveillance System) the common bacterial infections treatment is difficult due to the lack of effectual antimicrobials. For instance, UTI caused by Klebsiella pneumoniae showed the 4.1%-79.4% resistance rate to the commonly used antibiotics. Also, the resistance in K. pneumoniae to the last line of treatment i.e. carbapenems and colistin has been extended globally (67).

Klebsiella pneumoniae being encapsulated bacteria was already a problem in healthcare settings which became a global threat due to the antimicrobial resistance to the existing antimicrobials used to treat the infections caused by this pathogen (table 2). The mechanism of resistance towards different antimicrobials is shown in figure 5.

AMR is a complex process that is associated with multiple factors. From the bacterial point of view the antimicrobial resistance replicates evolution in deed. Due to the persistent exposure of the antibiotics the evolvement of various genetic mechanisms takes place as a result of selective pressure that leads to the emergence of multidrug resistance (MDR) and extensively resistant (XDR) strains of Enterobacteriaceae(68).

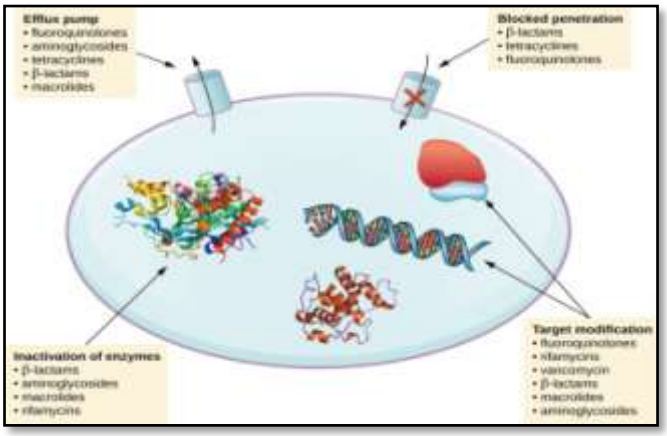

Figure 5 Mechanism of resistance (source: Gerard D Wright)

Table 2 Mechanism of resistance to different antimicrobials commonly used against K. pneumoniae infections

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

Types of Resistance Mechanism	Innate or acquired	Examples of Resistance Mechanism	Class of Antibiotics	Ref.
Restrictive Uptake of Antibiotics	Mostly Innate	Due to the structure and functions of the LPS layer in gram negative bacteria provides a barrier to certain types of molecules	Aminoglycosides	(69)
		Porins Loss (OmpK35 and OmpK36	Cephalosporins Carbapenems	
		Biofilm formation	Beta-lactams Cephalosporins	
Target Modification	Acquired	PBPs target modification	Beta-lactams	(70)
		Ribosomal mutation	Aminoglycosides	
		Ribosomal subunit methylation	Aminoglycosides	
		Ribosomal protection	Tetracyclines	
		Modifications in DNA Topoisomerases	Fluoroquinolones	
		Mutations in enzymes (DHPS, DHFR)	Sulfonamides-DHPS, Trimethoprim-DHFR	
Antibiotic inactivation	Intrinsic and/or acquired	Degradation of the drug by the production of resistance genes in bacteria e.g β-lactamases, ESBLs, carbapenemase	Beta-lactams Carbapenems	(70)
		Transfer of a chemical group	Aminoglycosides Fluoroquinolones	
Active efflux	Intrinsic and/or acquired	Flush out of the drug e.g.,AcrAB efflux pump	Tetracyclines Beta-lactams Aminoglycosides Fluoroquinolones	[45] (71)
Horizontal Gene Transfer (HGT)	Acquired	Acquisition of foreign DNA material through HGT	Beta-lactams Colistin	(72) (73)

*LPS- Lipopolysaccharide, Omp- Outer membrane protein, PBPs- Penicillin-binding proteins, DHPS- Dihydropteroate synthase, DHFR- Dihydrofolate reductase, ESBLs- Extended beta-lactamases

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

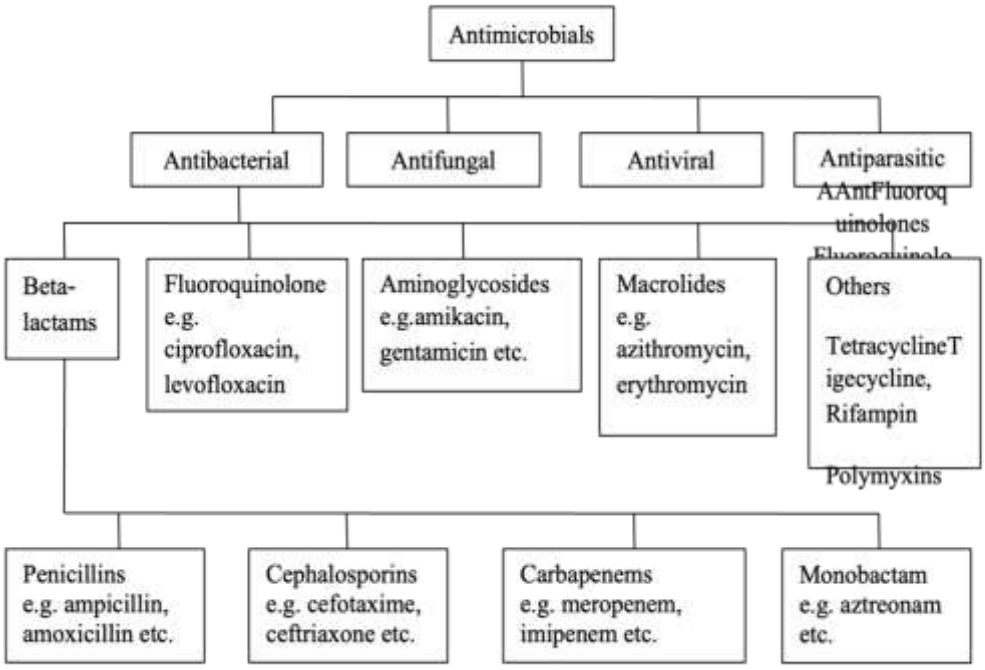

Figure 4 Flow chart of different classes of antimicrobials

Table 1 FDA approved Antibiotics commonly used to treat the infections caused by Gram-negative bacteria like Klebsiella pneumoniae

Class of Antibiotics	**Examples**	**Spectrum/Type of Action**	**Mode of Action**
Penicillins	Amoxicillin	Broad/Bactericidal	Inhibition of cell wall synthesis by inactivation of the enzyme required for the synthesis of peptidoglycan. Act by inhibiting the synthesis of the peptidoglycan layer of bacterial cell walls. The final transpeptidation step in the synthesis of the peptidoglycan is facilitated by DD-transpeptidases, also known as penicillin binding proteins (PBPs). PBPs vary in their affinity for penicillin and other β-lactam antibiotics. (74)(75)(76)
	Piperacillin		
Cephalosporins			
1st Generation	Cephalothin	More effective to gram-positive than gram-negative bacteria/ Bactericidal (77)	
	Cephazolin		
2nd Generation	Cefoxitin	Broad/Bactericidal	
	Cefuroxime		
3rd Generation	Ceftriaxone	Mainly active against Gram-negative bacteria/Bactericidal	
	Ceftazidime		
4th Generation	Cefepime		
	Cefpirome		
Carbapenems	Meropenem	Broad/Bactericidal	
	Imipenem		
	Ertapenem		
	Doripenem		
Monobactams	Aztreonam	Only against Gram-negative bacteria/Bactericidal	

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin Norfloxacin Amikacin	Broad/Bactericidal	Inhibits the activity of the two types of the Topoisomerases and hence the synthesis of bacterial DNA (78)(79)
Aminoglycosides	Gentamicin Kanamycin Neomycin Tobramycin	Broad/Bactericidal	Inhibition of the protein synthesis in bacteria by binding to the 16S rRNA and by disturbing the cell membrane integrity (80)
Tetracyclines	Tetracycline Tigecycline	Broad/Bacteriostatic	Inhibition of the protein synthesis in bacteria by binding to the 16S rRNA (30S ribosomal subunit) and inquisitive aminoacyl-transfer RNA (tRNA) docking (81)
Polymyxins	Polymyxin E (Colistin) Polymyxin B	Only against MDR Gram-negative bacteria/Bactericidal	Binds to LPSs and phospholipids in the outer cell membrane of Gram-negative bacteria and disrupts the cell membrane (82)

V. RESISTANT KLEBSIELLA PNEUMONIAE: AN ESCALATING MENACE

Resistance to the ampicillin is intrinsic to the K. pneumoniae due to the presence of bla-SHV resistance gene in the chromosomal DNA (83). Antibiotic era started with the discovery of penicillin and the resistance in K. pneumoniae also started with the resistant to penicillin as the very first beta-lactamases that showed resistance to penicillin were SHV-1 and TEM-1 reported in 1960s. The first ESBL (extended spectrum beta-lactamase) SHV-2 gene in K. pneumoniae was recovered from a patient in ICU from Germany (1) and then TEM-3 in France (1). Other beta-lactamases further reported in K. pneumoniae like blaCTXM, blaOXA type resistance genes (1).

After penicillin the first, second and third generation of cephalosporin came into the picture but due to the transferable plasmid genes and the ability of K. pneumoniae to incorporate and spread of the beta-lactamase genes, the plasmid–mediated AmpC-like cephalosporins were also stretched (84),(85). The gene families in the Klebsiella pneumoniae plasmid-mediated bla-AmpC belongs mostly to the DHA, MOX, FOX and CMY and the blaCMY-2 was the first chromosomal AmpC gene reported in this species identified in 2009 (86).

The increasing rate of the multidrug resistance in ESBL-producing K. pneumoniae strains directed to the increased use of carbapenems that are last resort for such type of MDR strains. This wide-ranging use of the carbapenems resulted in the development of carbapenemase enzyme that hydrolyses the beta-lactam ring in all the beta-lactam antibiotics. This enzyme was also plasmid mediated (87),(88). The Imipenem was the first carbapenem used to treat K. pneumoniae infections (1) and the first carbapenemase recovered in Japan from the clinical strain of K. pneumoniae in 1991 was IMP-1 (89). Later on the first K. pneumoniae

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

carbapenemase (KPC) was reported in 1996 that became the most common carbapenemase in United States (90) and spread worldwide. Poirelet al., reported another type of carbapenemase in K. pneumoniae i.e. blaOXA-48 (91). In 2008, NDM-1 metallo-beta-lactamase gene was identified in a patient infected with K. pneumoniae and had a recent travel history to India (92). This enzyme spread to various plasmids and to other bacteria of the Enterobacteriaceae family (93).

K. pneumoniae harbour the multi-beta lactamase encoded genes for instance Lee et al., in 2016 reported all types of the beta-lactamase genes in a single strain of this pathogen (94) and also Molandet al., in 2017 depicted the occurrence of 10 beta-lactamase genes including blaSHV, AmpC and blaKPC(1). The presences of copy of blaOXA-232 and NDM-1 on two different plasmids have also been reported (95).

The alteration in the chromosomal AcrAB-TolC and kpnEF efflux pumps in the K. pneumoniae and loss of the alleged porin, kpnO exhibit resistance to the different aminoglycosides (96). The resistance to the quinolones and fluoroquinolones were reported only a few years later to their clinical use. The first quinolone, nalidixic acid was used (1) against K. pneumoniae in 1963 and developed resistance in 1969 (97). Similarly, the first fluoroquinolone used (98) against K.pneumoniae was norfloxacin and this species developed resistance to this drug in1994 (99).

Due to the prevalence of the resistance to antibiotics that were used as the empiric treatment options as well as the last resort of the treatment (e.g. carbapenems) to the infection caused by K. pneumoniae, the old drug polymyxins were selected as the last line of treatment. Although, Davis et al., in 1969 reported the first colistin resistant isolate of K. aerogenes that later on classified as K. pneumoniae during the first period of its usage. In 2004 there was a hospital outbreak of colistin-resistant MDR K. pneumoniae in Greece (100).

Livermore in 2005 reported the first glycylcycline, tigecycline against the K. pneumoniae(101) and in 2005 only there was a report that stated the presence of intermediately resistant strains to the tigecycline (102).

The transfer of the resistance genes mostly takes place by horizontal gene transfer (HGT) mechanism. Other mechanisms of resistance can be the mutations in the bacterial genes, mobile gene transfer and expression of the efflux pump in bacteria (Table 4.2).

VI. DRUG COMBINATION STRETEGIES TO COMBAT THE AMR

Multidrug resistance have become a global threat as maximum of the antimicrobials that are considered as the empirical options for treatment of the infections caused by the resistant bacterial strains. Monotherapy could not help in such types of infections. It takes quite long time to discover and develop a new antibiotic hence the combination studies have been done to combat the infection. For instance in 1995, Jean-Luc Fournier et al., studied the in vivo efficacies of ticarcillin plus clavulanic acid and piperacillin plus tazobactam and found almost 4 $\log_{10}$ units decrease in the bacterial count (103).

Jiang et al., reviewed the meropenem based combination studies against Acinetobacter baumannii where it was stated that the meropenem showed synergy when combined with polymyxin B (37.0%), rifampicin (56.3%) in checkerboard method. The synergy rate with colistin and sulbactam was modest and no synergy with ciprofloxacin (104). Whereas, Pankey and Ashcraft studied the combination of polymyxin B with rifampicin and polymyxin B with meropenem against 14 genetically unique clinical Klebsiella pneumoniaecarbapenemase-producing K. pneumoniae by using time kill kinetics assay (105).

Investigation of Lan Yu et al., suggested the in vitro synergistic activity of colistin with amikacin or meropenem against the carbapenem-resistant Klebsiella pneumoniae (CRKP). This study suggested that the colistin in combination with either amikacin or meropenem could be an applicable remedial choice against colistin-resistant and carbapenem-resistant Klebsiella pneumoniae infection (106). In the similar way Jernigan et al., tested the combination of colistin, doripenem, doxycycline and gentamicin against the carbapenemase-producing K. pneumoniae isolates by time kill assay. According to their study the combination of the carbapenem (doripenem) and colistin also showed the more significant synergy rather that the other combinations used in the study (107). Likewise, Tasciniet al., evaluated the synergy of ten antibiotic combinations against the 13 colistin-resistant KPC-producing K. pneumoniae. Their data suggested that the colistin with rifampin showed the most consistent synergistic combinations against carbapenemase-

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

producing Klebsiella pneumoniae clinical strains including the colistin resistance strains. The combinations of the other antimicrobials with carbapenems, tigecycline, and gentamycin showed the variable synergistic results (108). Also, Deriset al., investigated the bacterial killing with doripenem and colistin mono- and combination therapy for infection caused by multidrug-resistant K. pneumoniae and appearance of colistin resistance (109).

Yimet al., evaluated the Time-kill synergy studies of tigecycline with ciprofloxacin, imipenem and amikacin for 35 clinical isolates of K. pneumoniae and 8 E. coli clinical isolates, where tigecycline with imipenem showed synergy against 18 K. pneumoniae and 3 E. coli isolates, tigecycline with amikacin showed synergy against 8 K. pneumoniae and 3 E. coli isolates and tigecycline with ciprofloxacin against 7 K. pneumoniae and 2 E. coli isolates (110).

Laishram et al., studied the combination of meropenem, colistin and sulbactam against the hundred clinical isolates of Klebsiella pneumoniae that are carbapenem resistant by using checkerboard assay and time kill assay (TKA). This showed the significant bactericidal activity against MDR strains of K. pneumoniae(111). Kadar et al., studied the combination of different drugs like ceftriaxone, ceftazidime, cefotaxime, imipenem, ertapenem, ciprofloxacin, levofloxacin, ampicillin, tobramycin, moxifloxacin, amikacin, rifampicin, colistin and polymyxin B against the colistin-sensitive and colistin-resistant KPC-2 producing MDR strain of K. pneumoniae by using the checkerboard method. Colistin (0.25 μg/ml) together with rifampicin (1 μg/ml), polymyxin B (0.25 μg/ml) plus rifampicin (1 μg/ml) and tobramycin (2 μg/ml) plus meropenem (1 μg/ml) showed the synergistic activity (112).

Fosfomycin is the potential last-resort option for the treatment of certain MDR gram-negative bacteria. Samoniset al., evaluated the double combinations of fosfomycin with colistin, doripenem, meropenem, imipenem, tigecycline and netilmicin against the hundred multidrug resistant clinical strains of Klebsiella pneumoniae, E. coli and P. aeruginosa by using the Etest method. Fosfomycin with all of the three carbapenems used in this study showed synergy for 70-74% of clinical isolates. Synergy of fosfomycin with Colistin, netilmicin and tigecycline was observed for 36.0%, 42.0%, and 30.0% of the isolates, respectively (113). Kastoriset al., reviewed and evaluated the existing published data about the in vitro synergistic activity of fosfomycin with the other antimicrobials against Gram-negative and Gram-positive pathogens. Fosfomycin showed significant synergistic activity against gram negative bacteria with ceftazidime, cefepime, gentamicin, levofloxacin, amikacin, aztreonam and ciprofloxacin and against gram positive bacteria imipenem, ceftriaxone, rifampicin, cefamandole, cephazolin and ciprofloxacin (114). In a recent study of Chukamnerd and Pomwised also fosfomycin showed synergistic activity with gentamicin (115).

As, polymyxins comes under the few antibiotics that keep the dependable action against the carbapenemaseKlebsiella pneumoniae so many studies have been done by using the polymyxin in combination with the other antimicrobials. The increasing rate of multidrug resistance and extensively drug resistant pathogens has imposed the therapeutic use of polymyxins (colistin and polymyxin B). On the other hand, the treatment disappointments with the monotherapy of polymyxin due to the emergence of the polymyxin resistance have catalysed the use of polymyxins in combination. Like, Elemam, Rahimian and Doymaz investigated the synergy of polymyxin B with numerous antimicrobials i.e ceftriaxone, cefazolin, cefepime, imipenem, tigecycline, doxycycline, rifampin and gentamicin against the KPC positive Klebsiella pneumoniaeclonical isolates by using the checkerboard assay. In the combination with doxycycline and rifampin there was a 4-fold decrease in the MIC of polymyxin B. Whereas with tigecycline it showed the less prominent synergy and no synergy with the other remaining antimicrobials (116).

Lenhard, Nation and Tsuji reviewed the in vitro and in vivo studies related to the polymyxins (colistin and polymyxin B) combination studies performed during 2011-2016 against Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa. Polymyxins B with meropenem, imipenem, doripenem, chloramphenicol, rifampicin, fosfomycin, gentamicin, doxycycline or tigecycline were the main combinations used during the given period. Out of all of the combinations carbapenems, rifampicin and chloramphenicol showed the synergy in maximum MDR strains of Klebsiella pneumoniae(117). According to the review study of Rahim et al., polymyxin B showed improved bactericidal activity in combination with chloramphenicol against the NDM producing

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

multidrug resistant strains of Klebsiella pneumoniae(118).

Carbapenems are known as the last line of treatment against the gram negative multidrug resistance pathogens. But as we all know about the global threat due to the spread of the carbapenemase positive clinical strains which are an ultimate cause of the resistance to the carbapenems. Hence, many double and triple combination studies have been conducted to combat the infection caused by these types of MDR clinical strains. Jacobs et al., reviewed the triple combination antibiotic therapy against the carbapenemase- producing Klebsiellapneumoniae. The most common combinations being used were polymyxin (colistin or polymyxin B, 86.8%), tigecycline (73.6%), carbapenem (43.4%) or aminoglycoside (43.4%). But there was also a mortality rate of 35.8% for the patients that are treated with the triple combination therapy (119).

Pournaraset al., studied the tigecycline based combinations against the Klebsiellapneumoniae carbapenemase producing pathogens by using the time kill kinetics assay. They studied the combination of tigecycline with colistin and meropenem and found the synergistic activity only with the colistin but not with the meropenem (120). Also, Yimet al., evaluated the combinational activity of tigecycline with amikacin, ciprofloxacin and imipenem against the clinical isolates of MDR Klebsiella pneumoniae and E. coli that co-producing ESBL and acquired AmpC beta-lactamase. The most potent combination of tigecycline was with imipenem and amikacin and ciprofloxacin also shows synergistic and indifference activities but not antagonistic (110). Yee-Huang Ku et al., compared the synergistic activity of tigecycline, colistin and fosfomycin against the carbapenem resistant ESBL-producing K. pneumoniae clinical isolates and found colistin plus tigecycline as the most effective combination (121).

Ni Wentaoet al., assessed the synergy study of minocycline with the aminoglycosides (amikacin and gentamicin) against the 70 KPC-producing K. pneumoniae by using checkerboard and time kill assay. The finding of their study suggests the synergistic activity of the minocycline and aminoglycoside only against the aminoglycoside susceptible clinical strains and no synergistic activity against the aminoglycoside resistant strains (122).

Due to the high level increase in the rate of resistance of carbapenems and polymyxins the dual carbapenem combination can also be a choice of treatment for MDR Klebsiella pneumoniae infections. Oliva et al., evaluated the synergistic activity of the ertapenem with the meropenem in a series of patients that are infected by the hospital acquired carbapenemase producing Klebsiella pneumoniae. This double carbapenem combination (ertapenem plus meropenem) showed synergy in 11 (78.6%) out of 15 patients with sepsis (123).

Hirsch investigated the in vitro and in vivo efficiency of combinations of numerous antimicrobials against the KPC producing Klebsiella pneumoniae. Six possible double combinations of doripenem, amikacin, rifampin and levofloxacin were assessed by using time-kill studies. Doripenem plus amikacin were found as the most potent synergistic combination while levofloxacin plus amikacin showed the antagonistic activity (124).

Bacterial resistance turn out to be as the widespread and to the maximum of the antimicrobials. The natural bioactive compounds playing an important role for treating the bacterial infections. Turmeric is the well antibacterial agent. Many studies have been done with curcumin, a bioactive compound from turmeric. Kali evaluated the in vitro combination study of curcumin with ciprofloxacin, erythromycin, penicillin and vancomycin against Gram-positive strains and curcumin with ceftriaxone, ampicillin, amikacin, meropenem, imipenem and gentamicin against gram negative bacterial isolates. For gram-positive bacteria the combination of curcumin with ciprofloxacin showed synergy in the maximum number of clinical isolates and for gram-negative gentamicin, cefepime and amikacin showed synergy with curcumin (125).

High mortality rate (43%-53%) due to the KPC-producing K. pneumoniae infection has become a major global health problem because of the limited and expensive options of treatment. So, the study of Fu, Mu, Jiang and Yu explored a novel treatment for the KPC-producing K. pneumoniae infected patients by using the cefepime and amoxicillin/clavulanic acid combination therapy (126).

Krohn and Kirby took the pan-drug resistant strain AR-0636 isolated from a woman in Nevada who died due to the infection caused by pan-drug resistant strain of Klebsiella pneumoniae also harbouring NDM-1 enzyme and studied the colistin based combinations against the respective clinical strain. Colistin was combined with the Doxycycline, Minocycline, Tigecycline,

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1168-1188 www.ijprajournal.com ISSN: 2456-4494

Eravacycline, Clindamycin, Fusidic acid, Linezolid, Chloramphenicol, Azithromycin, Levofloxacin, Trimethoprim-sulfamethoxazole, Rifampin, Meropenem, Ceftazidime-avibactam, Amikacin, Apramycin, Spectinomycin and Vancomycin in double combination. All of the combinations showed synergistic activity except with amikacin, meropenem, apramycin, spectinomycin and vancomycin and no combinations confirmed antagonism (127).

Tängdén tested the effectiveness of the double- and triple-antibiotic combinations of colistin, aztreonam, meropenem, ciprofloxacin, tigecycline, vancomycin, fosfomycin, rifampin, telavancin, and daptomycin against the metallo-beta-lactamase producing Klebsiella pneumoniae. Surprisingly, this study found non-synergistic activity of meropenem-fosfomycin, tigecycline-colistin and meropenem-colistin combinations whereas in many other studies these antimicrobial combinations proved effective. According to this study colistin-rifampicin-meropenem was the most successful combination (128).

Ojdanaet al., evaluated the synergy between tigecycline, ceftazidime-avibactam, ertapenem and fosfomycin against the clinical strains of carbapenemase producing K. pneumoniae by using the E-test method. They observed that all of the combinations (except the combination of ceftazidime-avibactam with tigecycline) were synergistic against the blaOXA-48 producing bacterial isolates and the most effective combinations for NDM and KPC were ceftazidime-avibactam plus fosfomycin and ceftazidime-avibactam plus ertapenem, respectively (129).

Recently, Firmoet al., investigated the in vitro action of polymyxin B with amikacin, gentamicin and meropenem against the clinical isolates of K. pneumoniae consisting of blaNDM-1, blaKPC-2 enzymes and resistant to polymyxin-B by using checker-board assay. Out of these antimicrobial combinations polymyxin-B plus meropenem and polymyxin-B plus amikacin were showed the synergistic activity against MDR strains of K. pneumoniae(130).

Chang et al., in their repositioning study of Azidothymidine in combination with colistin found the synergistic activity of both of the drugs against colistin- and carbapenem-resistant strains of Klebsiella pneumoniae(131).

Hickman et al., tested and found the highly synergistic activity of the double and triple combinations of fosfomycin plus aztreonam and fosfomycin plus aztreonam plus mecillinam, respectively against the MDR strains of Klebsiella pneumoniae and E. coli(132).

Stein et al., performed a three-dimensional synergy study to assess the activity of a triple combination of meropenem, tigecycline and colistin against 20 K. pneumoniae isolates harbouring different β-lactamases. They suggested in their study that the colistin based studies were found synergistic in double combination itself and the addition of the third antimicrobial could not result any significant or high decrease in the FIC value in triple combination (133).

VII. CONCLUSION

Klebsiella pneumoniae is a highly problematic pathogen that has become a major global health threat due to its increasing antimicrobial resistance. This Gram-negative bacterium is a common cause of various serious infections including pneumonia, urinary tract infections, septicemia, and neonatal sepsis.K. pneumoniae has an extensive ecological distribution and exhibits a high degree of antimicrobial resistance, with varied DNA composition, a large repertoire of antimicrobial resistance genes, and a high plasmid burden compared to other Gram-negative pathogens. It plays a key role in the spread of resistance genes from environmental bacteria to clinically important pathogens. The mechanisms of resistance in K. pneumoniae are complex and multifactorial, involving intrinsic and acquired resistance to various antibiotic classes such as beta-lactams, aminoglycosides, fluoroquinolones, and polymyxins. Resistance is mediated by mechanisms like restrictive uptake of antibiotics, target modification, antibiotic inactivation, active efflux, and horizontal gene transfer. With the increasing prevalence of resistance to commonly used antibiotics and even last-resort drugs like carbapenems and polymyxins, there is an urgent need to develop novel treatment strategies against K. pneumoniae infections. Combination therapy using synergistic combinations of existing antibiotics, such as colistin with amikacin, meropenem, doripenem, doxycycline, gentamicin, or rifampin, has shown promising results in vitro and may provide a viable option for combating multidrug-resistant K. pneumoniae infections.

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