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THE LOOMING THREAT OF ANTIMICROBIAL RESISTANCE: A GLOBAL HEALTH CRISIS

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ABSTRACT

Antimicrobial resistance (AMR) in *Klebsiellapneumoniae* poses a significant global health threat, characterized by its resistance to critical antibiotics such as carbapenems and colistin. This bacterium is responsible for severe infections like pneumonia, sepsis, and meningitis, with mortality rates reaching 50% even with antibiotic treatment. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of K. pneumoniae is particularly alarming, notably in healthcare settings where it is a leading cause of hospital-acquired infections. In India, over 70% of K. pneumoniae isolates exhibit resistance to fluoroquinolones and third-generation cephalosporins, while 56.6% are resistant to carbapenems. K. pneumoniae has a remarkable ability to acquire resistance genes through horizontal gene transfer, facilitated by enzymes such as extended-spectrum β-lactamases (ESBLs) and carbapenemases. Often considered a harbinger of AMR trends, new resistance genes frequently emerge in K. pneumoniae before spreading to other Gram-negative pathogens. The COVID-19 pandemic has exacerbated this crisis, with high rates of resistance observed in K. pneumoniae isolates from ICU patients co-infected with SARS-CoV-2. Urgent measures are essential to develop novel antibiotic combinations for combating MDR K. pneumoniae infections, particularly while new antibiotics are under development.

KEYWORDS:
Klebsiellapneumoniae, Antimicrobial Resistance, Combination Therapy, Global Burden.
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INTRODUCTION

The escalating threat of antimicrobial resistance (AMR) presents a critical global challenge, potentially pushing humanity toward a pre-antibiotic era with the emergence of resistance against last-resort antibiotics. It is projected that by 2050, AMR could cause 10 million deaths annually and lead to a staggering economic loss of US$100 trillion (1). AMR occurs when pathogens acquire resistance to antimicrobial agents that were previously effective against them. The antibiotic era, spanning from the 1930s to the 1960s, saw the discovery of numerous antibiotics. However, the pace of new discoveries slowed due to insufficient research efforts and diminishing support from major pharmaceutical industries, leading to a decline in antibiotic development. The misuse and overuse of existing antibiotics further accelerated the global emergence of antibiotic resistance (Figure 1) (2).

Leading global organizations such as the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), World Economic Forum, and Infectious Diseases Society of America have declared AMR a major public health concern (3). In recognition of the expanding scope of drug resistance, WHO changed the slogan for World Antimicrobial Awareness Week in 2020 from “Antibiotics: Handle with Care” to “Antimicrobials: Handle with Care” (4).

***Klebsiellapneumoniae* (K. pneumoniae)**, an encapsulated bacterium, has long been a concern in healthcare settings, but its global impact has intensified due to antimicrobial resistance (AMR) against current treatment options. This Gram-negative, lactose-fermenting, non-motile member of the Enterobacteriaceae family poses significant public health challenges. As an opportunistic pathogen, it primarily affects individuals already weakened by other infections or compromised immune systems. K. pneumoniae is associated with a wide range of diseases including urinary tract infections (UTIs), pneumonia, sepsis, wound infections, diarrhea, upper respiratory tract infections, and meningitis (6), (7), (8).

Both community-acquired infections (CAI) and hospital-acquired infections (HAI) are linked to K. pneumoniae. Mortality rates are notably higher in HAI (32%) compared to CAI (16%) (9). The Infectious Diseases Society of America (IDSA) identifies K. pneumoniae as one of the ESKAPE pathogens (E. faecium, S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa, and Enterobacter), notorious for causing drug-resistant infections in healthcare settings. Mortality rates from K. pneumoniae infections can reach approximately 50% even with antimicrobial therapy, and they approach 100% for patients with bacteremia and alcoholism (1). Recognizing its severity, K. pneumoniae has been placed on the critical priority list of multidrug-resistant (MDR) pathogens by the World Health Organization (WHO, 2017), demanding urgent attention (10).

Treatment of infections caused by K. pneumoniae has become increasingly challenging due to the widespread prevalence of antimicrobial-resistant strains. These strains exhibit resistance to a range of antibiotics including penicillin, monobactams, carbapenems, aminoglycosides, third and fourth generation cephalosporins, and broad-spectrum fluoroquinolones. Recent studies from India have identified carbapenem-resistant multi-drug-resistant (MDR) strains that are also resistant to tigecycline and colistin (26). According to the Indian Council of Medical Research (ICMR) report in 2017, K. pneumoniae ranks second after Acinetobacterbaumannii in carbapenem resistance incidence, with a rate of 56.6% (27).

Antimicrobial resistance in K. pneumoniae significantly complicates the treatment of infections (28). Projections indicate that by 2050, if current resistance rates continue to rise, global deaths attributable to antimicrobial resistance could reach up to 10 million per year (28). K. pneumoniae has been singled out by the World Health Organization (WHO) as a major concern in the context of antimicrobial resistance, especially in scenarios such as co-infection with HIV (Human Immunodeficiency Virus) (29). The emergence of multidrug-resistant strains of K. pneumoniae is increasingly observed in both human and veterinary medicine globally. While inherently susceptible to few clinically relevant antimicrobial agents, these bacteria possess a high capacity for acquiring resistance genes, primarily through horizontal gene transfer (HGT).

The acquisition of genes encoding enzymes such as extended-spectrum ß-lactamases (ESBLs), carbapenemases, 16S rRNAmethylases, plasmid-mediated quinolone resistance genes, and mcr genes confers resistance to a wide array of antimicrobials, including broad-spectrum cephalosporins, carbapenems, aminoglycosides, (fluoro)quinolones, and polymyxins (28). A recent retrospective study on the prevalence of MDR and XDR (extensively drug-resistant) strains among Enterobacteriaceae highlighted that after E. coli (51.4%), K. pneumoniae accounted for 33% of cases (30).

Klebsiellapneumoniae belongs to the *Enterobacteriaceae* family within the *Klebsiella* genus, characterized by non-motile, encapsulated rods that thrive on standard growth media. It forms dome-shaped, mucoid colonies varying in stickiness. These bacteria are non-motile, short, plump rods, typically measuring about 1-2 X 0.5-1.8 µm in size. The capsule is often prominent and visible in Gram-stained smears, appearing as halos around the bacilli, classifying it as a gram-negative microorganism. *K. pneumoniae* is widely distributed in nature, found both as commensals in the intestines and as saprophytes in soil and water.

K. pneumoniae, also known as *Friedlander's bacillus* or *Bacillus mucous capsulatus*, was initially isolated by the German microbiologist and pathologist Friedlander in 1882 from the lungs of patients who succumbed to severe pneumonia.

Klebsiellapneumoniae

Klebsiellapneumoniae, belonging to the Enterobacteriaceae family and Klebsiella genus, is characterized by non-motile, encapsulated rods that thrive on standard media. These bacteria form mucoid, dome-shaped colonies of varying stickiness levels. Microscopically, they appear as non-motile, short, plump rods measuring approximately 1-2 µm in length and 0.5-1.8 µm in width. The prominent capsule can be observed even in Gram-stained smears as halos surrounding the bacilli, identifying them as gram-negative microorganisms. They are widely distributed in nature, acting as commensals in the intestines and saprophytes in soil and water environments.

CLINICAL IMPLICATIONS AND EPIDEMIOLOGY

Klebsiellapneumoniae accounts for approximately one-third of all infections caused by gram-negative pathogens, including pneumonia, septicemia, urinary tract infections (UTI), cystitis, surgical wound infections, and endocarditis (35). Additionally, it causes other serious infections such as pyogenic liver abscesses, necrotizing pneumonia, and endogenous endophthalmitis (6). K. pneumoniae primarily targets immunocompromised patients, including the elderly, neonates, and individuals with diabetes, liver or kidney diseases, or other infections, resulting in significantly high mortality rates, especially among alcoholics.

Both community-acquired and hospital-acquired (nosocomial) infections are associated with Klebsiellapneumoniae. Studies, such as those by Cheol-In Kang et al., have highlighted a higher

mortality rate associated with hospital-acquired infections (32%) compared to community-acquired infections (16%) (7). Patients requiring invasive medical devices like catheters and ventilators during hospitalization are particularly at risk. Numerous studies have documented the transmission of K. pneumoniae within healthcare settings through person-to-person contact among healthcare workers, patients, and contaminated instruments and surfaces (36), (37). Common infections linked with K. pneumoniae include:

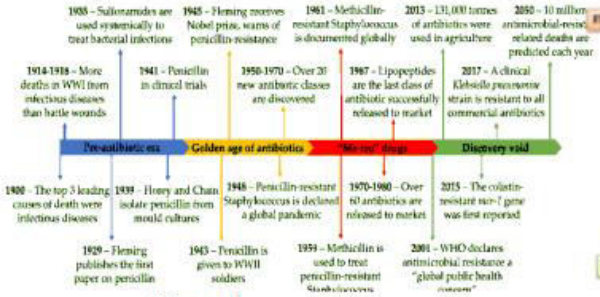

Figure 1

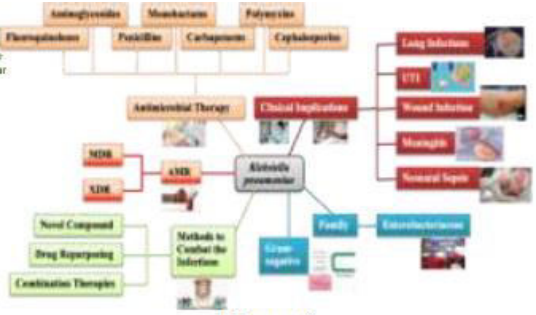

Figure 2

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.

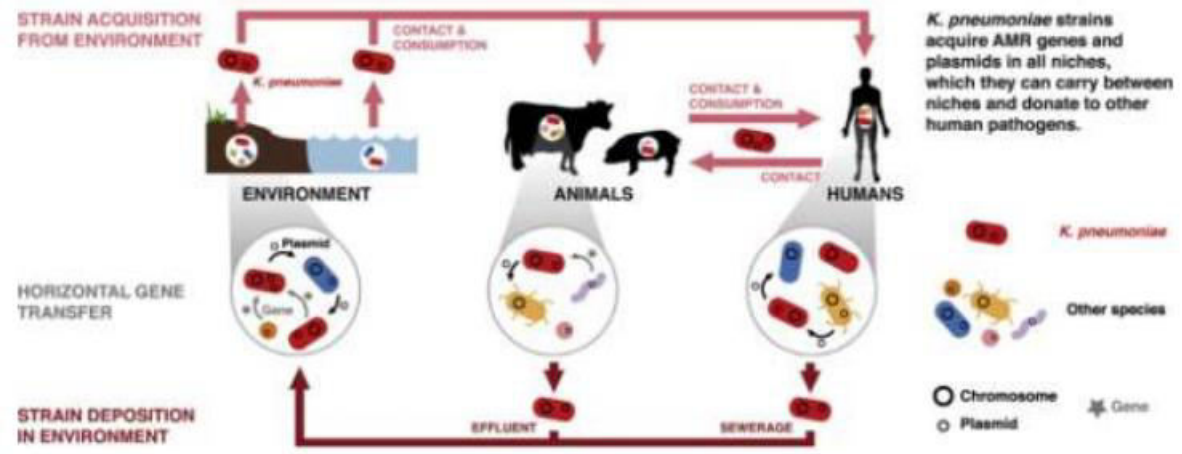

Figure 3 Representation for antimicrobial gene and plasmid trafficking (source- Kelly L.Wyreset al.,

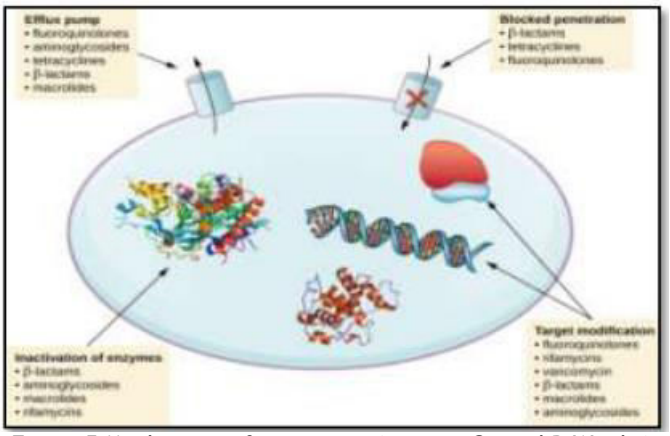

Figure 5 Mechanism of resistance (source: Gerard D Wright)

CONCLUSION

Klebsiellapneumoniae represents a significant global health challenge due to its escalating antimicrobial resistance. As a Gram-negative bacterium, it frequently causes severe infections such as pneumonia, urinary tract infections, septicemia, and neonatal sepsis. K. pneumoniae exhibits widespread ecological distribution and demonstrates high levels of antimicrobial resistance, characterized by diverse genetic makeup, extensive antimicrobial resistance genes, and a substantial plasmid load compared to other Gram-negative pathogens. It plays a critical role in disseminating resistance genes from environmental bacteria to clinically relevant pathogens.

The mechanisms underlying K. pneumoniae resistance are multifaceted and complex, encompassing both inherent and acquired resistance mechanisms against various antibiotic classes including beta-lactams, aminoglycosides, fluoroquinolones, and polymyxins. Resistance mechanisms include restricted antibiotic uptake, target site modifications, antibiotic degradation, active expulsion, and horizontal gene transfer.Given the rising resistance to commonly used antibiotics and even last-resort options like carbapenems and polymyxins, urgent measures are needed to develop novel therapeutic strategies for treating K. pneumoniae infections. Combination therapy involving synergistic combinations of existing antibiotics, such as colistin paired with amikacin, meropenem, doripenem, doxycycline, gentamicin, or rifampin, has demonstrated promising efficacy in vitro and represents a potential approach to combatting multidrug-resistant K. pneumoniae infections.

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