International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Antimicrobial Resistance in Klebsiella pneumoniae: A Comparative Analysis of Resistance Mechanisms and Clinical Outcomes

Gadipally Anudeep Shankar[1], Konjeti Hampi[2]

[1]M.Sc Microbiology
[2]Bachelor of Medicine, Bachelor of Surgery (MBBS)

Abstract

Introduction

Klebsiella pneumoniae is a leading cause of nosocomial infections, including pneumoniae, bloodstream infections and urinary tract infections. Klebsiella pneumoniae demonstrates considerable antimicrobial resistance, predominantly attributed to the synthesis of extended spectrum beta-lactamases (ESBLs) and carbapenemase enzymes leading to multidrug resistance and posing extensively drug-resistant (XDR) strains has significantly challenged treatment outcome and clinical managements. Beyond its rising resistance, K. Pneumoniae plays a pivotal role in antimicrobial gene dissemination through horizontal gene transfer (HGT), enabling the transmission of resistance elements to other microbial populations.

Methods

This review synthesizes data from the recent studies to compare various antimicrobial resistance (AMR) mechanisms in K. pneumoniae, including beta-lactamase production, efflux pumps and target site modifications. Furthermore, clinical implications and therapeutic strategies are analysed to provide insights into the global AMR burden.

Results

Predominant resistance mechanisms include, Beta-lactamases, particularly extended-spectrum beta-lactamases (ESBLs) and carbapenemases. Further contribution of resistance against multiple antibiotic resistance classes caused by efflux pump overexpression and porin loss. MDR and XDR correlate with higher mortality, prolonged hospitalisation and limited treatment options.

Discussion

The escalation of antimicrobial resistance underscores the urgency for innovative treatment modalities, such as beta-lactam/beta-lactamase inhibitor combinations. Polymyxins and emerging options like phage therapy and CRISPR-Cas9 driven interventions. Infection control measures and molecular surveillance are critical to mitigating resistance spread.

Conclusion

AMR in K. pneumoniae poses a significant clinical challenge, requiring urgent global attention, leading to increased morbidity and mortality and economic burden novel drug development and enhanced surveillance to combat MDR and XDR strains. Nevertheless, broader adoption of these strategies hinges on comprehensive research and robust clinical trials to establish efficacy and safety. A collaborative, multidisciplinary effort is required to mitigate the impact of AMR in K. pneumonia and safeguard the efficacy of existing and future antimicrobial agents.

Keywords: Klebsiella pneumoniae, Antimicrobial resistance, ESBL (Extended-Spectrum Beta-Lactamase), Carbapenemase, Multidrug resistance, Efflux pump, Clinical management.

1. Introduction

Klebsiella pneumonia cause wide range of infections, including pneumonia, urinary tract infection, bacteraemia, and liver abscesses. Klebsiella pneumonia due to its rise in several infections and the increased scarcity of treatment has gained notoriety as an infectious agent [1]. It is a Gram-negative, encapsulated, non-motile bacterium residues in environmental sources, including in soil and surface water, plants and medical devices [2] [1]. The isolates from humans/environment and other sources carried identical genes responsible for cephalosporin resistance, but they carried on distinct plasmids [3]. Ability of K. pneumoniae to acquire resistance determinants through horizontal gene transfer (HGT), including plasmid exchange and transposon mobility, has contributed to its rapid adaptation to antimicrobial pressure. The increasing prevalence of Klebsiella pneumonias strains with both hypervirulent (hvKp) and antimicrobial resistance (AMR) traits, particularly carbapenem-resistance K. pneumoniae (CRKP), has complicated clinical management and led to higher mortality rates [4]. The accessory genome in Klebsiella pneumoniae consists of genes that differ among bacterial of the same species. These genes can be found both within the chromosome and in mobile genetic elements. Notably, the majority of the K. pneumoniae genome comprises accessory genes, which play a crucial role in distinguishing different strains and pathotypes. In a clinical setting, these pathotypes can be classified into opportunistic strains, carbapenem-resistant Enterobacteriaceae (CRE), or hypervirulent (hv) variants [5] [6]

Key factors contributing to AMR in K. pneumoniae

Widespread use of antibiotics in hospitals, livestock and agriculture. On the other hand, horizontal gene transfer (HGT) is facilitating the spread of resistance gene and Plasmid-mediated resistance mechanisms allowing bacteria to acquire resistance traits. Selective pressure from antibiotics, leading to dominance of resistance strains.

In K. pneumoniae, the hypermucoid (HMV) phenotype has traditionally been linked to the rmpA gene, although the precise molecular mechanisms underlying this phenotype remain unclear [7]. rmpADC enhances capsules synthesis, leading to a hydermucoid phenotype that protects K. pneumoniae from the host immune responses and antimicrobial agents. Klebsiella pneumoniae produces extended-spectrum beta-lactamases (ESBLs) and carbapenemases (eg., KPC, NDM, OXA-48-like enzymes), which hydralyze

beta-lactam antibiotics, leading to resistance against pencillins, cephalosporins and carbapenems. The global rise of multidrug-resistant Klebsiella pneumoniae (MDRKP) in recent decades present a critical public health threat. Its increasing prevalence highlights the urgent need for immediate intervention and strategic measures to mitigate its impact on healthcare systems worldwide [8] [9].

2. Antibiotic Resistance in Klebsiella pneumoniae

Klebsiella pneumoniae, like several other high-priority pathogens, is experiencing a significant rise in antibiotic resistance, largely driven by genetic modifications that enhance its survival against antimicrobial agents. Over the past few decades, K. pneumoniae has became one of the most concerning multidrug-resistant (MDR) pathogens due to its ability to acquire and disseminate resistance genes. Antimicrobial resistance is an ancient phenomenon, arising naturally from the continuous interaction between microorganisms and their environment. Since many antimicrobial compounds are naturally produced by microbes, coexisting bacterial have evolved diverse mechanisms to counteract their effects, ensuring their survival and adaptation over time [10]. Klebsiella pneumoniae primarily resides within the human population, with studies indicating that 5% to 38% of individuals carry it in their stool, while 1% to 6% harbor it in the nasopharynx [11].

3. Epidemiology and Clinical Disease Data

Table-I. Epidemiological and Clinical Data of pVir+-KPC-kp Infection (Eastern China, 2014-2018) [12]

Parameter	Finding
Antibiotic resistance (higher in pVir+)	Aminoglycosides, cefepime, trimethoprim-sulfamethoxazole
Antibiotic resistance (higher in pVir+)	Ceftazidime-avibactam
Dominant virulence gene combinations	rmpA, aerobactin (iuc), yersiniabactin (ybt) and salmochelin (iro)
Outcomes	Though early (7 day) mortality showed slight difference, 28-day mortality rates were not significantly different between pVir+ and pVir$^-$ - KPC – producing isolates. However, the high prevalence of virulence and resistance determinants raises concerns about treatment failures and outbreaks.

Evidence from Eastern China highlights the simultaneous emergence of antimicrobial resistance and virulence traits in K. pneumoniae, particularly within ST11 clones, which are increasingly recognized as globally dominant high-risk lineages.

4. Resistance mechanisms in Klebsiella pneumoniae

Extended-spectrum β-lactamases (ESBLs) represent a critical resistance mechanism in Klebsiella pneumoniae, enabling the hydrolysis of a broad range of β-lactum antibiotics, including penicillins and third-generation cephalosporins such as cefotaxime and ceftazidime [13]. The predominant ESBL families

identified in this species include TEM, SHV and the increasingly widespread CTX-M enzymes, these resistance genes are commonly located on conjugative plasmids that also carry other antibiotic resistance determinants, facilitating rapid horizontal gene transfer and the emergence of multi-drug resistance strains [14]. High-level aminoglycoside resistance in Klebsiella pneumoniae has been increasingly attributed to the acquisition of 16S rRNS methyltransferase genes, particularly armA, which methylate the aminoglycoside binding site on the 16S rRNA, thereby rendering these antibiotics ineffective [15]. Carbapenem resistance in K. pneumoniae is primarily mediated through the production of carbapenemases, such as KPC, NDM and OXXA-48. These enzymes hydrolyze carbapenems, rendering them ineffective [16].Colistin, which is often used as a final treatment option for multidrug-resistant Gram-negative bacteria, is showing declining efficacy against K. pneumoniae Resistance to colistin is often due to mutations in the mgrB gene, which encodes a negative regulator of the PhoPQ two component system [16].

5. Therapeutic challenges and Clinical outcomes

Antibiotic resistance profile

ESBL-producing K.pneumonia strains were significantly more common in patients who developed bloodstream infections (85.2%) compared to those with pneumoniae alone (29.6%). [17]. XDR K. pneumoniae showed near-total resistance to most antibiotic, including carbapenems, cephalosporins, aminoglycosides and fluoroquinolones [18].

A total of 7,536 respiratory samples positive for Klebsiella pneumoniae were screened, from which 409 eligible patients were included after exclusions of these 274 had KP pneumoniae alone, while 135 developed secondary bloodstream infection (KP-pneumoniae), enabling a comparative analysis of clinical outcomes and therapeutic challenges [17].

Empirical Therapy Challenges

A significant therapeutic challenge observed was the high rate of inappropriate empirical antibiotic therapy, reported in 80.5% of patients with XDR K.pneumoniae bloodstream infections [18]. This often resulted from delayed identification of resistance patterns, leading to the initial use of ineffective β-lactams or carbapenems. The limited availability of effective antimicrobial options further complicated treatment, with only colistin and tigecycline retaining partial susceptibility. However, tigecycline monotherapy was associated with higher clinical failure and mortality rates, particularly among critically ill ICU patients [19].

The overall ICU mortality rate was 51.3%, indicating a significant burden of carbapenem-resistance K.pneumoniae (CR-KP) in critical care settings and 14 days clinical failure was observed in 45.2% of patients despite active antimicrobial treatment [19].

6. Conclusion and Future Directions

Antimicrobial resistance in Klebsiella pneumoniae remains a pressing clinical and public health concern, driven by diverse resistance mechanisms including extended-spectrum β- lactamases, carbapenemases, porin mutations and efflux pump overexpression. These molecular features have contributed to the

emergence of MDR and XDR strains, significantly limiting therapeutic options and compromising clinical outcomes, particularly in ICU and bloodstream infections.

Despite the availability of last resort agents like colistin and tigecycline, treatment failure rates remain high, especially when inappropriate empirical therapies are initiated. The complexity of resistance patterns, frequency co-infections and patients -related risk factors (e.g. age, immune status).

To combat this evolving threat future research should focus on the development of novel antimicrobial agents, combination regiments and alternative approaches such as bacteriophage therapy, CRISPR-Cas9 based interventions and antimicrobial peptides. Additionally, investment in rapid molecular diagnostics, real time surveillance and global antimicrobial stewardship programs is essential. A collaborative, multidisciplinary approach integrated clinical, microbiologist and public health strategies is vital to preserve existing antibiotics and reduce the global Amr burden.

Reference:

1. Susan T, Bagley, "Habitat association of Klebsiella species. Infect Control," pubmed, 1985.
2. Michelle K. Paczosa., Joan Mecsas, "Klebsiella pneumoniae: Going on the Offense with a Strong Defense," Microbiology and molecular biology review, 2016.
3. Catherine Ludden, et al., "A One Health Study of the Genetic Relatedness of," Oxford University Press for the Infectious Diseases Society, p. 8, 2019.
4. Min Xu et al.,, "Epidemiology and clinical significance of pLVPK-like virulence plasmid in KPC-2-producing Klebsiella pneumoniae infections in eastern China: a preliminary exploration," Research square, 2020.
5. Celeste Moya and Sergi Maicas, "Antimicrobial Resistance in Klebsiella pneumoniae Strains: Mechanisms and Outbreaks," in Proceedings, 2020.
6. Martin, R.; Bachman, M, "Colonization, infection, and the accessory genome of Klebsiella pneumoniae. Front.," in Infect. Microbio, 2018.
7. Margaret M.C. Lam et, al.,, "Genomic and functional analysis of rmp locus variants in Klebsiella pneumoniae," in bioRxiv, 2024.
8. World Health Organisation, "Global Action Plan on Antimicrobial Resistance," 2015.
9. T. A. T. N. e. a. Sharma A, "Changing Trend in the Antibiotic Resistance Pattern of Klebsiella Pneumonia Isolated From Endotracheal Aspirate Samples of ICU Patients of a Tertiary Care Hospital in North India," in Cureus, 2023.
10. Jose M. Munita, Cesar A. Arias, "Mechanisms of Antibiotic Resistance," in Microbial Spectrum, 2016.
11. Sona P. H. et,al.,, "Emergence of High-Level Antibiotic Resistance in Klebsiella pneumoniae: A Narrative Review," in South Asian Journal of Research in Microbiology, 2024.
12. Min Xu, et al.,, Epidemiology and clinical significance of pLVPK-likevirulence plasmid in KPC-2-producing Klebsiella pneumoniae infections in eastern China: a preliminary exploration, 2020.
13. Bradford, P. A., Extended-spectrum β-lactamases in the 21st century: Characterization, epidemiology, and detection of this important resistance threat., Clinical Microbiology Reviews, 2001.
14. Paterson, D. L., & Bonomo, R. A., Extended-spectrum β-lactamases: a clinical update, Clinical Microbiology Reviews, 2005.

15. Yu-Kuo Tsai, Chang-Phone Fung et, al, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2011.
16. Mathers AJ, Peirano G, Pitout JDD, The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug resistant Enterobacteriaceae, Clin Microbiol Rev, 2015.
17. Chen J, Li J, Huang F, Fang J, Cao Y, Zhang K, Zhou H, Cai J, Cui W, Chen C, Zhang G., Clinical characteristics, risk factors and outcomes of Klebsiella pneumoniae pneumonia developing secondary Klebsiella pneumoniae bloodstream infection, BMC Pulmonary Medicine., 2023.
18. Andreatos N, Zacharioudakis IM, Zervou FN, Tsueng G, Mylonakis E, Clinical characteristics and outcomes of 56 patients with pneumonia caused by carbapenem-resistant Klebsiella pneumoniae, J Glob Antimicrob Resist., 2021.
19. Kontopidou F, Plachouras D, Papadomichelakis E, Poulakou G, Tropayiannis E, Papafragas E, et al, Infections caused by carbapenem-resistant Klebsiella pneumoniae among patients in intensive care units in Greece: a multi-centre study on clinical outcome and therapeutic options, J Antimicrob Chemother, 2011.