NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY

Prevalence and Antibiotic Resistance Rates of *Klebsiella pneumoniae* Isolates Recovered from Urinary Tract Infections at The Near East University Hospital, during 2022-2024

M.Sc. THESIS

Rifgah Abdalrhman Mohamed Ali ALMAKKI

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Approval

We certify that we have read the thesis submitted by Rifgah Abdalrhman Mohamed Ali Almakki titled **"Prevalence and Antibiotic Resistance Rate of *Klebsiella pneumoniae* Isolates Recovered from Urinary Tract Infections at The Near East University Hospital, during 2022-2024"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Rifgah Abdalrhman Mohamed Ali Almakki

19/6/2025

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Rifgah Abdalrhman Mohamed Ali Almakki

Abstract

Prevalence and Antibiotic Resistance Rates of *Klebsiella pneumoniae* Isolates Recovered from Urinary Tract Infections at The Near East University Hospital, during 2022-2024

Rifgah Abdalrhman Mohamed Ali Almakki

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June, 2025

Objective:

Klebsiella pneumoniae is an important pathogen implicated in urinary tract infections (UTIs), particularly in healthcare settings. The emergence of antibiotic-resistant strains poses a major clinical challenge. This retrospective study aims to assess the prevalence and antibiotic resistance patterns of *K. pneumoniae* isolates recovered from UTI cases.

Methods:

This retrospective study was conducted using microbiology laboratory records and patient data from the Near East University Hospital database. VITEK-2 automated system was utilized for bacterial identification and antimicrobial susceptibility testing for *K. pneumoniae* isolates obtained from urine samples between January 2022 and December 2024. Susceptibility and resistance were determined according to the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Resistance rates were calculated and analyzed to assess trends over the study period.

Results:

A total of 42, 54 and 70 UTI cases caused by *Klebsiella pneumoniae* were detected in 2022, 2023 and 2024, respectively. In 2022, both outpatient and inpatient isolates showed complete (100.0%) resistance to ampicillin. Additionally, amoxicillin-clavulonate (42.9% and 37.5%), cefuroxime (41.2% and 50.5%) and piperacillin-tazobactam (33.3% and 47.8%) resistance rates were notable among outpatients and inpatients, respectively. The rates of ESBL-positive strains were 22.2% for outpatients and 33.3% for inpatients. In 2023, 81.8% of outpatient isolates were resistant to ampicillin. The percentage of ESBL-positive cases among outpatients was 36.4%, while this rate was 69.7% for the inpatients. In 2024, the highest resistance rates were recorded against ampicillin (%83.3) and cephalosporins (varying between 62.5% and 81.8%) among

inpatient isolates. The percentages of ESBL-positive cases were 9.8% and 42.4% among outpatient and inpatient isolates, respectively.

Conclusion:

In the present study, high resistance rates were detected against beta-lactam and cephalosporin antibiotics, while these percentages remained relatively low for carbapenems and fosfomycin among *K. pneumoniae* isolates. The number of cases with ESBL-positive strains increased over time, and higher ESBL levels were detected in the isolates recovered from inpatients. Our study findings suggest that continuous monitoring of antibiotic resistance rates should be maintained to control antibiotic resistance in the healthcare facilities.

***Key Words**:* Antibiotic resistance, *Klebsiella pneumoniae*, urinary tract infections

Özet

2022–2024 Yılları Arasında Yakın Doğu Üniversitesi Hastanesi'nde İdrar Yolu Enfeksiyonlarından İzole Edilen *Klebsiella pneumoniae* Suşlarının Prevalansı ve Antibiyotik Direnç Oranları

Rifgah Abdalrhman Mohamed Ali Almakki

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Danışman: Prof. Dr. Emrah Ruh

Haziran, 2025

Amaç:

Klebsiella pneumoniae, özellikle sağlık hizmeti ortamlarında, idrar yolu enfeksiyonları (İYE) ile ilişkili önemli bir patojendir. Antibiyotiklere dirençli suşların ortaya çıkması, ciddi bir klinik sorun teşkil etmektedir. Bu retrospektif çalışmanın amacı, İYE vakalarından izole edilen *K. pneumoniae* suşlarının prevalansı ve antibiyotik direnç oranlarının değerlendirilmesidir.

Yöntem:

Bu retrospektif çalışma, Yakın Doğu Üniversitesi Hastanesi'nin mikrobiyoloji laboratuvar kayıtları ve hasta verileri kullanılarak gerçekleştirilmiştir. Ocak 2022 ile Aralık 2024 tarihleri arasında idrar örneklerinden elde edilen *K. pneumoniae* izolatlarının tanımlanması ve antibiyotik duyarlılık testleri için VITEK-2 otomatik sistemi kullanılmıştır. Duyarlılık ve direnç oranları EUCAST kılavuzlarına göre değerlendirilmiştir.

Bulgular:

2022, 2023 ve 2024 yıllarında sırasıyla 42, 54 ve 70 *Klebsiella pneumoniae* kaynaklı İYE vakası tespit edilmiştir. 2022 yılında hem ayaktan hem de yatan hastalardan elde edilen izolatlar ampisiline karşı tamamen (%100) dirençli bulunmuştur. Ayrıca, amoksisilin-klavulonat (sırasıyla %42,9 ve %37,5), sefuroksim (%41,2 ve %50,5) ve piperasilin-tazobaktam (%33,3 ve %47,8) direnç oranları da yüksek bulunmuştur. ESBL-pozitif suşların oranı ayaktan hastalarda %22,2, yatan hastalarda ise %33,3 olarak belirlenmiştir. 2023 yılında ayaktan hastalardan elde edilen izolatların %81,8'i ampisiline dirençliydi. ESBL-pozitif oranları ayaktan hastalarda %36,4, yatan hastalarda ise %69,7 olarak saptanmıştır. 2024 yılında, yatan hastalardan elde edilen izolatlarda en fazla direnç ampisilin (%83,3) ve sefalosporinlere (%62,5 ile %81,8 arasında değişen oranlarda) karşı

tespit edilmiştir. ESBL-pozitif vaka oranları ayaktan hastalarda %9,8, yatan hastalarda ise %42,4 olarak kaydedilmiştir.

Sonuç:

Bu çalışmada, *K. pneumoniae* izolatlarında beta-laktam ve sefalosporin grubu antibiyotiklere karşı yüksek direnç oranları gözlenmiştir. Buna karşın karbapenem ve fosfomisin antibiyotiklerine karşı direnç oranları nispeten düşük bulunmuştur. ESBL-pozitif suşların sayısı zamanla artmış ve bu izolatlara yatan hastalarda daha sık rastlanmıştır. Elde edilen bulgular, sağlık hizmeti sunulan alanlarda antibiyotik direncini kontrol altına alabilmek için direnç oranlarının düzenli olarak izlenmesi gerektiğini göstermektedir.

***Anahtar Kelimeler*:** Antibiyotik direnci, *Klebsiella pneumoniae*, idrar yolu enfeksiyonları

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List of Abbreviations

UTI: Urinary tract infection

ESBL: Extended-spectrum beta-lactamases

UPEC: Uropathogenic *Escherichia coli*

GBS: Group B *Streptococcus*

PAIs: Pathogenicity islands

IBCs: Intracellular Bacterial Communities

QIRs: Quiescent Intracellular Reservoirs

BECs: Bladder Epithelial Cells

TMP/SMX: Trimethoprim/sulfamethoxazole

VRE: Vancomycin-Resistant *Enterococci*

BSBL-KP: Broad-Spectrum Beta-Lactamase-producing *Klebsiella pneumoniae*

PDT: Photodynamic Therapy

ATP: Adenosine triphosphate

DNA: Deoxyribonucleic acid

RNA: Ribonucleic acid

tRNA: Transfer ribonucleic acid

mRNA: Messenger ribonucleic acid

TH4: T Helper 4 Cells

PABA: Para-Aminobenzoic Acid

TetX: Tetracycline-inactivating enzyme

KPC: *Klebsiella pneumoniae* carbapenemase

PO: Orally administered

MSSA: Methicillin-Sensitive *Staphylococcus aureus*

PBPs: Penicillin-Binding Proteins

WHO: World Health Organization

CRAB: Carbapenem-Resistant *Acinetobacter baumannii*

CA: Community-Acquired

HA: Hospital-Acquired

blaTEM: Beta-lactamase TEM gene

blaSHV: Beta-lactamase SHV gene

blaCTX-M-15: Beta-lactamase CTX-M-15 gene

CLED: Cystine Lactose Electrolyte-Deficient agar

MEM: Meropenem

CN: Gentamicin

CTX: Cefotaxime

DO: Doxycycline

CIP: Ciprofloxacin

SXT: Trimethoprim-Sulfamethoxazole

MIC: Minimum Inhibitory Concentration

MDR: Multidrug-Resistant

fimH: Fimbrial Adhesin H gene

sat: Secreted Autotransporter Toxin

papEF: P fimbriae Adhesion Proteins EF

afa: Afimbrial Adhesin

vat: Vacuolating Autotransporter Toxin

XDR: Extensively Drug-Resistant

PDR: Pandrug-Resistant

AST: Antimicrobial Susceptibility Testing

EUCAST: European Committee on Antimicrobial Susceptibility Testing

PCR: Polymerase Chain Reaction

SD: Standard Deviation

CRKP: Carbapenem-Resistant *Klebsiella pneumoniae*

CHAPTER I

Introduction

Urinary tract infections (UTIs) represent one of the most widespread types of bacterial infections encountered worldwide, impacting an estimated 150 million individuals annually (Wagenlehner et al., 2020). UTIs can affect various parts of the urinary system: infections limited to the lower tract typically involve the bladder (cystitis) or urethra (urethritis), whereas upper tract infections may extend to the kidneys (pyelonephritis). Symptoms often include loin pain, the presence of pus cells in urine (pyuria), fever, chills (rigors), painful urination (dysuria), haematuria, and in some cases, bacteremia. The likelihood of infection rises significantly in cases of urinary retention (Mulvey et al., 2017).

Despite significant advancements in diagnostic and therapeutic methods, UTIs remain a frequent clinical issue. Their recurrent nature, especially in vulnerable groups, poses a substantial challenge in the context of rising antibiotic resistance (Mulvey et al., 2017).

UTIs can affect individuals of any age or gender, but they occur more frequently in women, with over 10% affected compared to roughly 3% of men. This gender disparity is primarily attributed to the anatomical structure of the female urinary tract, particularly the shorter urethra. Additionally, both symptomatic and asymptomatic UTIs are common during pregnancy (Cheesbrough, 2006).

While UTIs caused by viral or fungal pathogens are rare, they can be life-threatening. Bacterial infections, however, are the most commonly reported, with *Escherichia coli* being the leading causative agent (Demili et al., 2012). *Klebsiella pneumoniae* also plays a significant role as an opportunistic pathogen, contributing not only to UTIs but also to pneumonia, bloodstream infections, wound and soft tissue infections, and osteomyelitis (Ngwai et al., 2023). Indeed, *Klebsiella pneumoniae* is recognized as the second most common causative agent of urinary tract infections, following *Escherichia coli* among Gram-negative uropathogens (Hao et al., 2022).

The clinical management of infections caused by *K. pneumoniae* typically involves antibiotic therapy. These resistant strains reduce treatment efficacy and are associated with longer durations of illness (Karaiskos et al., 2014).

The growing resistance of urinary tract infections (UTIs) to commonly prescribed antibiotics poses a significant threat to our ability to manage not only these infections but also other microbial diseases. As antibiotic resistance increases driven by bacteria adapting to medications previously effective against them several standard treatment options for UTIs have lost their efficacy. This trend contributes to more complicated health, this has led to adverse consequences such as prolonged hospitalization, higher risk of death, and escalating healthcare expenses (Karaiskos & Giamarellou, 2014). While antibiotic resistance can develop naturally, its acceleration has largely been attributed to improper and excessive antibiotic usage in both human medicine and animal husbandry. The types of uropathogens involved and their resistance patterns tend to differ based on geographic and healthcare settings. Therefore, understanding the prevalence of specific causative agents and their antibiotic sensitivity profiles is essential. In light of this, the present retrospective study was conducted over one year in a tertiary care hospital to assess the bacterial agents responsible for UTIs and their resistance characteristics (Somashekara et al., 2014).

Aims of The Study

The primary aim of this study is to determine the prevalence and antibiotic resistance profiles of *Klebsiella pneumoniae* isolates recovered from urinary tract infections (UTIs) at the Near East University Hospital between 2022 and 2024.

Seeks for assess the occurrence rate of *K. pneumoniae* among UTI-causing pathogens during the study period.

To Evaluate the antimicrobial susceptibility patterns of *K. pneumoniae* isolates against commonly used antibiotics .

CHAPTER II

Literature Review

2.1 General Characteristics

Urinary tract infections (UTIs), including cystitis or bladder infections, refer to infections affecting any part of the urinary system. The infections can result from a range of pathogens, Gram-negative and Gram-positive bacteria (Jawetz et al., 2013). These infections are typically divided into uncomplicted and complicated types. Uncomplicated UTIs most often occur in otherwise healthy individuals with structurally and functionally normal urinary tracts, particularly healthy, sexually active women. These infections are frequently due to common pathogens such as *Klebsiella pneumoniae* and typically respond well to first-line oral antibiotics (Flores-Mireles et al., 2015).

On the other hand, complicated UTIs arise in patients with abnormalities in urinary tract structure or function, or in those with weakened immune responses. Contributing factors include urinary tract obstructions, kidney stones, indwelling catheters, diabetes, and advanced age. These infections often involve a broader spectrum of pathogens, including antibiotic resistant strains, and may require more intensive treatment approaches, including intravenous antimicrobial therapy (Hooton, 2012). The clinical spectrum of UTIs ranges from asymptomatic bacteriuria to severe infections such as pyelonephritis. While uncomplicated UTIs are typically manageable with appropriate antibiotics in otherwise healthy women and some men, complicated infections can affect both sexes and often require a more comprehensive treatment strategy (Hooton, 2012).

2.2 Bacteria that Can Cause UTI

Urinary tract infections (UTIs) represent a significant public health concern and are attributed to a broad spectrum of pathogenic organisms. Both Gram-negative and Gram-positive bacteria are responsible for causing these infections (Flores-Mireles

et al., 2015). According to a study conducted in 2019, over 92% of UTI-causing bacterial strains exhibited resistance to at least one commonly prescribed antibiotic, while nearly 80% showed resistance to two or more antibiotics. This escalating trend of antimicrobial resistance has serious implications for UTI management. The treatment of UTIs accounts for a substantial proportion of antibiotic prescriptions, and over time, urinary pathogens have altered their susceptibility patterns. This shift has led to a marked rise in resistance against frequently administered antibiotics (Magalit et al., 2001).

Among the various microorganisms implicated in UTIs, uropathogenic Escherichia coli (UPEC) is the predominant causative agent in both uncomplicated and complicated forms of the infection. In cases of uncomplicated UTIs, other notable pathogens include, in descending order of prevalence: *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B *Streptococcus* (GBS), *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and Candida species. For complicated UTIs, the list of common pathogens varies slightly, with *Enterococcus* species following UPEC in frequency, and further including *K. pneumoniae*, Candida spp., *S. aureus, P. mirabilis, P. aeruginosa*, and GBS (Flores-Mireles et al., 2015).

Klebsiella pneumonia has increasingly been widely acknowledged as a significant infectious agent, especially in healthcare-associated environments, where it frequently contributes to urinary tract infections (UTIs). It is a common cause of hospital-acquired UTIs, with its prevalence influenced by regional variations in antibiotic resistance patterns. For example, research conducted in Burkina Faso indicated that *Klebsiella* species were responsible for 7.18% of UTI cases, highlighting its clinical relevance in certain geographic areas (Filev et al., 2025). The clinical significance of *K. pneumoniae* extends beyond UTIs; it is also involved in causing a diverse array of other infections, including pneumonia, bloodstream infections, osteomyelitis, as well as soft tissue and wound infections, further demonstrating its role as a versatile and opportunistic pathogen (Martin & Bachman, 2018; Ngwai et al., 2023). Among Gram-negative bacteria, *K. pneumoniae* ranks as the second most commonly detected pathogen in clinical samples, following *Escherichia coli* (Tantry & Rahiman, 2021; Hao et al., 2022).

Managing of urinary tract infections caused by *Klebsiella pneumoniae* has become progressively more challenging due to the bacterium's increasing reduced susceptibility to numerous commonly used first-line antibiotics, particularly fluoroquinolones and β-lactam antibiotics (Filev et al., 2025). The rise and widespread dissemination of extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* strains have significantly limited therapeutic options, as these enzymes confer resistance to critical antibiotics such as third-generation cephalosporins (Filev et al., 2025). Consequently, clinicians face considerable difficulties in selecting effective treatments. Of particular concern is the rising resistance to carbapenems, which are often considered the final-line antibiotics used to treat severe infections (Filev et al., 2025).

In a 2022 study, ciprofloxacin was demonstrated to be the most effective antibiotic in inhibiting the growth of both *K.pneumoniae* strains that produce extended-spectrum beta-lactamases (ESBL) as well as those that do not, outperforming alternatives such as cotrimoxazole and doxycycline (Setiawan et al., 2022). The study also showed a concentration dependent inhibitory effect, where higher concentrations of ciprofloxacin resulted in greater bacterial growth suppression, underscoring its potential role as a valuable therapeutic agent against *K. pneumoniae* infections (Setiawan et al., 2022).

***Escherichia coli* (UPEC)** is recognized as the primary agent responsible for urinary tract infections (UTIs) in the community, accounting for approximately 80–90% of these cases (Flores-Mireles et al., 2015). Within UPEC, four principal phylogenetic groups have been identified A, B1, B2, and D based on the presence of genomic Pathogenicity Islands (PAIs) and the expression of various virulence factors. These virulence factors include adhesins, toxins, surface polysaccharides, flagella, and iron-acquisition systems, all of which contribute to the pathogenic potential of UPEC strains (Bien et al., 2012). Generally, the successful establishment of UPEC infection in the urinary tract depends on the coordinated action of many of these virulence determinants (Hannan et al., 2012).

The colonization process of UPEC begins with its attachment to the periurethral and vaginal areas, followed by ascension through the urethra into the bladder lumen. In the urine, UPEC can grow as planktonic cells, adhere to bladder surfaces, and

interact with the bladder epithelium's defense mechanisms. Additionally, UPEC forms biofilms and invades bladder epithelial cells, where it replicates by creating intracellular bacterial communities (IBCs). This intracellular lifestyle allows the formation of quiescent intracellular reservoirs (QIRs) within the underlying urothelium, which contribute to persistent infections. From the bladder, the bacteria may ascend to the kidneys, leading to tissue damage and increasing the risk of bacteremia and septicemia (Maria E Terlizzi et al., 2017).
The natural flushing action of urine removes many bacteria that invade, together with shed bladder epithelial cells (BECs) filled with UPEC. Despite this, UPEC's multiple virulence factors enable it to colonize the bladder effectively, playing critical roles in the pathogenesis of UTIs (Kaper et al., 2004).

Certain UPEC strains have developed resistance to commonly used antibiotics. The two most frequently prescribed antibiotics for *E. coli* induced UTIs are trimethoprim/sulfamethoxazole (commonly known as Bactrim or Sulfatrim) and nitrofurantoin (Macrobid). Other oral antibiotics that may be used include ciprofloxacin (Cipro), ampicillin, fosfomycin (Monurol), amoxicillin-clavulanate (Augmentin), cephalexin (Keflex), cefdinir, and levofloxacin (Levaquin) (Mayo Clinic Staff, 2023).
A 2022 study suggests that consumption of D-mannose may aid in preventing UTIs by passing through the kidneys and attaching to *E. coli* bacteria, thereby reducing bacterial adherence and infection risk (Christiano, 2024).

Staphylococcus saprophyticus ranks as the second most frequent cause of UTIs following *E. coli*, responsible for up to 42% of all such infections (Natsis NE et al., 2018). It is a Gram-positive, coagulase-negative, non-hemolytic coccus commonly implicated in uncomplicated UTIs, particularly affecting young, sexually active women. Less frequently, it can cause complications such as acute pyelonephritis, urethritis, epididymitis, and prostatitis. *S. saprophyticus* is a normal part of the human flora, colonizing areas including the perineum, rectum, urethra, cervix, and gastrointestinal tract (Sarah Ehlers et al., 2023).
This organism can form biofilms, which enhances its virulence, especially in catheterized patients. Once biofilms are established, antibiotic resistance becomes

more pronounced. In such cases, *S. saprophyticus* may show resistance to vancomycin and may only be effectively treated with linezolid (Sarah Ehlers et al., 2023). It is also characteristically resistant to novobiocin. Like other uropathogens, *S. saprophyticus* produces urease to generate ammonia but, unlike some others, it cannot reduce nitrate. The antibiotics of choice for treating infections caused by S. saprophyticus are nitrofurantoin and trimethoprim-sulfamethoxazole (TMP-SMX) (Sarah Ehlers et al., 2023).

Enterococcus faecalis is the predominant pathogen within the genus *Enterococcus*, responsible for about 95% of enterococcal infections, including UTIs. It is a Gram-positive spherical bacterium that typically appears in pairs also short chains, generally non-capsulated and mostly non-motile. Its hemolytic activity varies, with strains exhibiting alpha or beta hemolysis or none at all. E. faecalis is an aerobic organism capable of growth over a broad temperature range (10–45°C) and ferments lactose. It also grows in the presence of 6.5% sodium chloride and 40% bile salts (Stephanie Watson, 2023).
Ampicillin remains the preferred antibiotic for treating infections caused by *E.faecalis* can also be treated with alternative therapeutic agents such as daptomycin, gentamicin, linezolid, nitrofurantoin, streptomycin, tigecycline, and vancomycin. However, some *E. faecalis* strains have developed resistance to vancomycin; such strains are termed vancomycin-resistant enterococci (VRE). In these cases, linezolid or daptomycin are considered suitable treatment options (Stephanie Watson, 2023).

Staphylococcus aureus is implicated in only 0.5% to 6% of UTIs, but if untreated, infections can progress to severe, life-threatening conditions (Yousefi M et al., 2016). UTIs caused by *S. aureus* are often associated with risk factors such as urinary catheterization, prolonged hospitalization, or complicated UTIs. Trimethoprim-sulfamethoxazole is commonly used to treat *S. aureus* UTIs. Notably, *S. aureus* UTI may signal more invasive infections like bacteremia, making clinical evaluation and source identification crucial to ensure effective treatment and prevent further complications (Alshomrani MK et al., 2023).

Proteus mirabilis accounts for 1% to 2% of all UTIs and represents around 5% of hospital-acquired UTIs. The association is even stronger in complicated UTIs, such

as those related to catheter use, where *Proteus* infection rates range from 20% to 45% (Jamil et al., 2023). It is a Gram-negative facultative anaerobe characterized by swarming motility, self-elongation, and secretion of polysaccharides that allow it to adhere to and migrate across surface such as catheters (Jamil et al., 2023).
For uncomplicated UTIs caused by *P. mirabilis*, empirical outpatient treatment typically involves a 3-day course of trimethoprim/sulfamethoxazole (TMP/SMZ) or an oral fluoroquinolone such as ciprofloxacin (Pelling H et al., 2019). In inpatient settings, intravenous antibiotic therapy options include ceftriaxone, gentamicin, fluoroquinolones, gentamicin combined with ampicillin, or aztreonam until fever resolves (Duarte MJ et al., 2018).

Pseudomonas aeruginosa is estimated to cause 7% to 10% of UTIs. Isolates from UTIs often demonstrate higher levels of antibiotic resistance compared to *K.pneumoniea* (Bayyiğit et al., 2023). This opportunistic Gram-negative pathogen is frequently isolated from UTIs in elderly and catheterized patients and is linked to unfavorable clinical outcomes due to ineffective antibiotic treatments (Newman et al., 2022). Phenotypic variation and bacterial cell invasion can further complicate treatment in some cases (Newman et al., 2022).
Recommended antibiotics for *P. aeruginosa* include ciprofloxacin or levofloxacin with levofloxacin preferred combined with antipseudomonal beta-lactams such as piperacillin-tazobactam, cefepime, imipenem, or meropenem (Dainyal et al., 2025).

Group B *Streptococcus* (GBS) or *Streptococcus agalactiae* is a frequent contributor to UTIs, responsible for approximately 1%–2% of all monomicrobial cases. It is a Gram-positive, beta-hemolytic, chain-forming coccus (Mohanty et al., 2021). While generally sensitive to penicillin and ampicillin, resistance to penicillin and other beta-lactams has been increasingly reported (McCartney et al., 2024).

2.3 Extended-Spectrum Beta-Lactamase (ESBL)

Among *Klebsiella pneumoniae* strains, those producing extended-spectrum β-lactamases (ESBL-Kp) are recognized as significant nosocomial pathogens due to their ability to cause serious infectious diseases including bacteremia and pneumonia. Recently, the emergence of multi-drug-resistant *K. pneumoniae* strains

has posed a severe challenge to healthcare systems worldwide, resulting in infections that are increasingly difficult or even impossible to cure. The appearance of extended-spectrum β-lactamase (ESBL)-producing bacterial strains has complicated the treatment of urinary tract infections (UTIs), as these enzymes render many β-lactam antibiotics ineffective (Fils et al., 2021).

Resistance to antimicrobial drugs is no longer a recent development. The identification of β-lactamase enzymes in the two Gram-positive and Gram-negative bacteria can be traced back to the initial years of 1940s, which was before the widespread clinical use of penicillin (Bayraktar et al., 2019). These β-lactamase enzymes confer resistance by hydrolyzing the β-lactam ring structure of β-lactam antibiotics through cleavage of the amide bond, which disables the antibiotic's ability to inhibit bacterial cell wall synthesis (Amer et al., 2019). This enzymatic degradation is one of the primary mechanisms by which bacteria evade the action of β-lactam antibiotics.

The development of extended spectrum β-lactamases (ESBLs), which are plasmid-mediated enzymes, has further complicated treatment options. ESBLs can hydrolyze a broad range of β-lactam antibiotics, including penicillins, oxyimino-cephalosporins, extended-spectrum cephalosporins, and aztreonam, thereby significantly limiting therapeutic alternatives for UTIs caused by *E. coli* and *K. pneumoniae*. Moreover, ESBL-producing organisms frequently exhibit resistance to other antibiotic classes such as aminoglycosides, tetracyclines, trimethoprim/sulfamethoxazole, and quinolones, making infections caused by these bacteria particularly difficult to treat (Logan et al., 2014; Al-Sarraj F, 2021).

To counteract β-lactamase activity, β-lactamase inhibitors such as sulbactam, tazobactam, and clavulanic acid have been developed. These inhibitors bind irreversibly to the active site of β-lactamases, thereby protecting β-lactam antibiotics from enzymatic degradation and restoring their antibacterial activity. Consequently, strains producing β-lactamases become susceptible to combinations of β-lactam antibiotics with β-lactamase inhibitors (Al-Sarraj F, 2021).

A study conducted in 2021 demonstrated that *K. pneumoniae* strains producing ESBL showed higher adherence to urothelial cells compared to ESBL-negative strains, suggesting a potential role in bacterial colonization and infection severity. Interestingly, non-ESBL-producing strains exhibited greater bacterial cytotoxicity.

The same study also found that photodynamic therapy (PDT) was highly effective in eradicating most bacterial strains responsible for UTIs, including ESBL producers, indicating a promising alternative or adjunctive treatment option for resistant infections (Al-Sarraj F, 2021).

2.4 Antibiotics Mechanism of Action

Antibiotics exert their effects through six major mechanisms of action include: (1) disruption of cell wall formation, (2) suppression of protein production, (3) hindrance of nucleic acid replication and transcription, (4) blockage of essential metabolic pathways, (5) compromise of membrane integrity, and (6) inhibition of ATP synthase activity (Kırmusaoğlu et al., 2019).

2.4.1 Blockers of Cell Wall Biosynthesis bacterial cells are enclosed by a rigid cell wall primarily composed of peptidoglycan, which is essential for maintaining cellular integrity and shape. The biosynthesis of peptidoglycan is critical for cell wall formation and bacterial survival. Several antibiotics target this process by inhibiting enzymes involved in the synthesis of peptidoglycan, thereby compromising the cell wall's structural integrity and causing bacterial cell lysis. Since mammalian cells lack peptidoglycan, these antibiotics exhibit selective toxicity against bacteria without harming the host's cells (Kırmusaoğlu et al., 2019).

2.4.2 Blockers of Protein Biosynthesis Protein synthesis in bacteria is a highly intricate process involving the ribosome, composed of the 30S and 50S subunits. Many antibiotics inhibit bacterial protein synthesis by binding to one of these subunits, thereby interfering with the translation process. For example, tetracyclines, including doxycycline, inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the A site of the 30S ribosomal subunit. Notably, these antibiotics can inhibit protein synthesis in both prokaryotic (70S) and eukaryotic (80S) ribosomes, though with different affinities and clinical implications (Kırmusaoğlu et al., 2019).

2.4.3 Blockers of Membrane Function the bacterial cytoplasmic membrane is essential for maintaining selective permeability, homeostasis, and energy

metabolism. Certain antimicrobial agents disrupt bacterial membranes by interacting with their lipid components, leading to structural damage and loss of membrane function. Such agents target both Gram-positive and Gram-negative bacteria and impair essential processes like nutrient transport and energy transduction, ultimately resulting in bacterial death (Kırmusaoğlu et al., 2019).

2.4.4 Inhibitors of DNA Formation Several antibacterial agents disrupt the DNA generation by targeting enzymes involved in DNA replication or transcription. Quinolones, for instance, inhibit bacterial DNA gyrase and topoisomerase IV, enzymes crucial for DNA replication and supercoiling. Second-generation quinolones such as levofloxacin, norfloxacin, and ciprofloxacin have broad-spectrum activity against both Gram-negative and Gram-positive bacteria. Additionally, some antibiotics interfere with RNA synthesis by inhibiting RNA polymerase, like doxorubicin and actinomycin D (dactinomycin). These agents, however, also affect mammalian cells and are primarily used as antineoplastic drugs targeting rapidly dividing cells (Kırmusaoğlu et al., 2019).

2.4.5 Inhibitors of Metabolic Pathways antibiotics that inhibit bacterial metabolic pathways primarily target essential biosynthetic processes such as nucleic acid and amino acid synthesis. A crucial coenzyme in these pathways is tetrahydrofolic acid (TH4), which is required for the synthesis of nucleic acids and certain amino acids across all living organisms. Unlike humans, who acquire folic acid through their diet, folic acid is generated by bacteria de novo initiated from para-aminobenzoic acid (PABA) during the biosynthetic pathway . Antibiotics that inhibit bacterial metabolism disrupt the synthesis of TH4, thereby blocking critical metabolic functions needed for bacterial growth and survival. By interfering with these pathways, these antibiotics effectively reduce bacterial proliferation and facilitate infection control (Kırmusaoğlu et al., 2019).

2.4.6 Blockers of ATP Synthase ATP synthase is a fundamental enzyme complex responsible for the generation of ATP, the universal energy currency in all living organisms, including bacteria and vertebrates. This enzyme catalyzes ATP production through oxidative phosphorylation in respiratory chains or through

photophosphorylation in photosynthetic organisms. Through either substrate-level phosphorylation involving fermentable carbon compounds or oxidative phosphorylation, pathogen can produce cellular energy molecule that depends on ATP synthase activity. Certain Research indicates that antibiotics can interfere with the function of Primary energy currency of the cell synthesis enzyme, thereby disrupting bacterial energy metabolism. By impairing the production of ATP, these inhibitors deprive bacteria of the energy necessary for survival, ultimately leading to bacterial death (Kırmusaoğlu et al., 2019).

2.5 Antibiotics mechanism of resistance

Bacteria become resistant to antibiotics when they acquire the capability to survive their effects antibiotics designed to kill them or halt their growth. This adaptation occurs through various mechanisms and represents a significant global ecological and public health threat, particularly as resistant strains spread and compromise the effectiveness of existing treatments (Habboush & Guzman, 2023).

2.5.1 Intrinsic Resistance Intrinsic resistance is the natural, inherent ability of certain bacteria to resist specific antibiotics due to their structural or functional characteristics. This type of resistance is not acquired through genetic mutation or horizontal gene transfer but is a result of the bacteria's evolutionary adaptations. For example, antibiotics like penicillin, which target bacterial cell wall synthesis, are ineffective against bacteria that naturally lack a cell wall, such as Mycoplasma species. This intrinsic resistance underscores the importance of understanding bacterial physiology when selecting effective antimicrobial treatments (Habboush & Guzman, 2023).

2.5.2 Acquired Resistance Acquired resistance occurs when bacteria that were previously susceptible to an antibiotic develop mechanisms to survive exposure. This can happen through spontaneous mutations that alter antibiotic targets or through the acquisition of resistance genes from other bacteria. Such genetic changes enable bacteria to neutralize or evade the antibiotic's effect. A notable example is Mycobacterium tuberculosis, which can develop resistance to rifamycin antibiotics

through mutations that alter the drug-binding site, making treatment challenging (Habboush & Guzman, 2023).

2.5.3 Genetic Change Bacterial DNA mutations can lead to altered production or structure of proteins, receptors, or enzymes targeted by antibiotics, rendering the bacteria less susceptible or resistant. These genetic modifications can significantly change bacterial components, preventing the antibiotic from binding effectively. Furthermore, bacteria sharing the same environment can harbor intrinsic resistance genes that, through genetic recombination or mutation, change their genomic landscape and resistance profiles. Examples include *Escherichia coli* and *Haemophilus influenzae*, which have developed resistance to trimethoprim through such genetic alterations (Habboush & Guzman, 2023).

2.5.4 DNA Transfer horizontal gene transfer is a major route for spreading antibiotic resistance among bacterial populations. Through this process, bacteria can share genetic material, including resistance genes, across different species and strains. The three primary mechanisms of horizontal gene transfer are transformation, where bacteria uptake naked DNA from their environment; transduction, involving bacteriophage-mediated gene transfer; and conjugation, which requires direct cell-to-cell contact. This gene sharing accelerates the dissemination of antibiotic resistance, complicating infection control efforts worldwide (Habboush & Guzman, 2023).

2.5.5 Resistance by targeting the drug molecule: one common resistance strategy involves the bacterial production of enzymes that chemically modify or destroy antibiotic molecules, rendering them ineffective. The most well-known example is β-lactamases, enzymes that hydrolyze the β-lactam ring a core structure in penicillins and cephalosporins essential for their antibacterial activity. By cleaving the amide bond in the β-lactam ring, β-lactamases neutralize the antibiotic's ability to inhibit cell wall synthesis, thus conferring resistance to these antibiotics (Christy Cheung, 2020).

2.5.6 Drug inactivation bacterial inactivation of antibiotics occurs mainly through two mechanisms: enzymatic degradation of the drug or chemical modification by adding functional groups. β-lactamases represent a broad family of enzymes that hydrolyze β-lactam antibiotics, leading to drug inactivation. Additionally, tetracycline resistance can occur through enzymatic hydrolysis mediated by the tetX gene (Reygaert, 2018). Another common inactivation method involves the transfer of chemical groups such as acetyl, phosphoryl, or adenyl groups onto the antibiotic molecule. Acetylation is widely used by bacteria against various antibiotic classes, including aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones. Phosphorylation and adenylation mainly target aminoglycosides. The wide variety of transferase enzymes contributes due to the swift appearance of bacterial strains that resist multiple types of antibiotics, complicating treatment options significantly (Reygaert, 2018).

Beta-lactam Antibiotics remain among the most widely prescribed drug classes due to their broad spectrum of clinical applications (Pandey et al., 2023). Biochemically, these agents share a common structural feature a highly reactive, a beta-lactam structure made up of a four-membered ring that includes three carbon atoms and a single nitrogen atom. This ring are essential for the antibacterial effectiveness of the drug (Pandey et al., 2023).

Role of Beta-lactamase Inhibitors are compounds designed to neutralize beta-lactamase enzymes, which are produced by certain bacteria especially gram-negative organisms to degrade and inactivate beta-lactam antibiotics (Pandey et al., 2023). These inhibitors fall into two major categories: the first-generation blockers, like clavulanic acid, sulbactam, and tazobactam, and newer agents like avibactam and vaborbactam, which are effective against more resistant strains, including those producing *Klebsiella pneumoniae* carbapenemase (KPC) (Pandey et al., 2023).

Emergence of Beta-lactam Resistance the rise in resistance to beta-lactam antibiotics presents a significant public health concern (Pandey et al., 2023). Notably, pathogens such as *Streptococcus pneumoniae* and gram-negative bacilli

like *Klebsiella pneumoniae* have developed mechanisms to evade the effects of these drugs. These mechanisms include:
Enzymatic degradation via beta-lactamase production. Reduced antibiotic penetration due to alterations in porin channels. Active efflux of the drug through specialized pump systems (Pandey et al., 2023).

Clinical Uses of Beta-lactam Antibiotics the therapeutic applications of beta-lactam antibiotics vary based on the specific subclass. For instance: Beta-lactamase-resistant penicillins, such as oxacillin, nafcillin (IV), and dicloxacillin (PO), are primarily embloyed to manage infections caused by gram-positive organisms and remain effective against methicillin-susceptible *Staphylococcus aureus* (MSSA), despite growing resistance in staphylococcal strains (Pandey et al., 2023). Aminopenicillins, including ampicillin and amoxicillin, possess effective against a range of gram-positive bacteria as well as certain gram-negative bacteria, especially those belonging to the Enterobacteriaceae family. These are often combined with beta-lactamase inhibitors to broaden their effectiveness (Pandey et al., 2023). Ureidopenicillins, such as piperacillin, exhibit efficacy against organisms resistant to aminopenicillins, these are typically co-administered with beta-lactamase inhibitors for enhanced coverage (Pandey et al., 2023).

Cephalosporin Generations and Spectrum of Activity cephalosporins are classified into several generations based on their antimicrobial activity: First-generation: Includes cefazolin (IV), cephalexin (PO), and cefadroxil (PO), mainly targeting gram-positive bacteria (Pandey et al., 2023). Second-generation: Covers cefuroxime, cefoxitin, cefaclor, and others, with improved gram-negative activity. Third-generation: Offers even broader gram-negative coverage and includes ceftriaxone, cefotaxime, cefpodoxime, and cefixime, commonly used in systemic infections (Pandey et al., 2023).
Beta-lactam antibiotics function by targeting bacterial cell wall synthesis. The structural target is peptidoglycan a critical component of the cell wall that confers mechanical integrity. In gram-positive bacteria, peptidoglycan is thick and multilayered, while gram-negative bacteria possess a much thinner layer (Pandey et al., 2023).

The structure of peptidoglycan consists of repeating subunits of N-acetylglucosamine and N-acetylmuramic acid, which are connected together with peptide chains. Beta-lactams inhibit the final stage of peptidoglycan by attaching to penicillin-binding proteins (PBPs), they interfere with the biosynthesis process, which are essential for cross-linking peptide strands. This binding halts the transpeptidation reaction, ultimately leading to bacterial cell lysis via autolytic enzymes (Pandey et al., 2023).

Carbapenems as a subclass of beta-lactam antibiotics, carbapenems are defined by their unique chemical structure that includes a beta-lactam ring, these bacteria that possess an external structure known as the cell wall, which serves as a protective barrier. Similar to other beta-lactam antibiotics, carbapenems act by disrupting the construction of this cell wall, ultimately leading to bacterial cell death. (Catreina et al., 2022).

Widely recognized as the frontline therapy for treating infections caused by highly drug resistant pathogens, including members of the Enterobacteriaceae family, such as *Klebsiella pneumonia* (Catreina et al., 2022). Carbapenems are broad-spectrum antibiotics, include Ertapenem, Imipenem, Meropenem, Tebipenem (Catreina et al., 2022). However, the growing global prevalence of antimicrobial resistance poses a significant threat to public health. In response to this urgent issue, the World Health Organization (WHO) in 2017 released a list of twelve priority antibiotic resistant pathogens to steer global research efforts (Catreina et al., 2022). Among the most critical on this list was carbapenem-resistant Acinetobacter baumannii (CRAB), highlighting the pressing need for the development of new antibiotics and alternative therapeutic strategies (Catreina et al., 2022).

Aminoglycosides belong to a group of antimicrobial agents that are primarily active against Gram-negative aerobic pathogens. These agents exert their bactericidal effect by interaction to the 30S subunit of the microorganism ribosome, it disrupts bacterial growth by hindering the attachment of mRNA and tRNA to their respective sites, which interferes with protein synthesis and leads to the formation of dysfunctional or harmful peptides (Werth B.J 2024). A key structural feature of aminoglycosides is

the presence of an amino-modified glycoside (sugar) moiety, which contributes to their antimicrobial activity. Commonly used aminoglycosides include amikacin, gentamicin, kanamycin, neomycin, plazomicin, streptomycin, and tobramycin. While they are potent against Gram-negative aerobes, their effectiveness is generally limited against Gram-positive organisms and anaerobic Gram-negative bacteria (Werth B.J 2024). Due to the emerging resistance to aminoglycosides, treatment protocols have evolved. In some clinical settings, fluoroquinolones may be considered as alternatives in empiric therapy, particularly when local antimicrobial susceptibility data indicate a higher sensitivity to fluoroquinolones. (Werth B.J 2024).

A study carried out in Ankara, Turkey, from September 2014 to April 2016 assessed the antibiotic resistance trends among urinary tract pathogens in a pediatric population. *Klebsiella pneumoniae* was identified in 14.9% of the isolates. Notably, amikacin demonstrated the highest effectiveness among the antibiotics tested, with a resistance rate as low as 0.1%. These findings support the continued use of amikacin as a reliable treatment option for UTIs caused by *K. pneumoniae* in children (Ulu et al., 2018).

Fluoroquinolones are a group of broad-spectrum antibiotics commonly utilized for managing infections of both respiratory and urinary tract infections (Katzung et al., 2021). These agents exhibit strong antimicrobial acts against a diverse group of aerobic gram-positive and gram-negative bacteria. Their primary mechanism involves disrupting bacterial DNA replication and transcription by inhibiting type II DNA topoisomerases, such as DNA gyrase (Katzung et al., 2021). Importantly, these antibiotics exhibit minimal interference with human cellular enzymes, contributing to their favorable safety profile (Katzung et al., 2021).

Examples of fluoroquinolones include ciprofloxacin, levofloxacin, norfloxacin, moxifloxacin, ofloxacin, and gemifloxacin. They are efficiently absorbed when administered orally and are generally well tolerated with limited side effects (Katzung et al., 2021).

A study carried out in a tertiary medical facility in Western Romania tracked antibiotic resistance trends in *Klebsiella pneumoniae* isolated from urinary tract infections over a six-year period (2018–2023) (Popescu et al., 2023). The

researchers noted a significant rise in resistance to ciprofloxacin, with rates climbing from 34.7% at the beginning of the study to 64.9% by its conclusion. This increasing resistance pattern highlights a concerning reduction in ciprofloxacin's effectiveness against K. pneumoniae UTIs in that region (Popescu et al., 2023).

Nitrofurantoin is a broad-spectrum antibiotic that continues to be effective against many drug-resistant uropathogens, making it a commonly prescribed option for urinary tract infections (UTIs) (Mahdizade Ari et al., 2023). Its use has significantly increased following recent guideline updates that recommend it as a first-line treatment for uncomplicated lower UTIs (Mahdizade Ari et al., 2023).
A study in 2023 highlights the clinical benefits and risks of nitrofurantoin, particularly in long-term use (Mahdizade Ari et al., 2023). While the antibiotic remains highly effective for acute UTIs, especially in younger populations, the study advises caution when considering prolonged use, particularly in elderly patients. Long-term prophylactic treatment is not recommended, and its use in chronic cases should be carefully regulated through strict prescription criteria and clinical oversight (Mahdizade Ari et al., 2023).

2.6 Recent Relevant Studies Related to The Topic

2.6.1 A study in Portugal (2019) Klebsiella pneumoniae is recognized as a significant pathogen in both community-acquired (CA) and hospital-acquired (HA) urinary tract infections (UTIs), with notable differences in antibiotic resistance and virulence profiles between these settings. A retrospective multicenter study conducted in Portugal by Caneiras et al. (2019), published in PubMed, analyzed 81 K. pneumoniae isolates 50 from CA-UTIs and 31 from HA-UTIs to assess their resistance genes and virulence traits (Caneiras et al., 2019). The results showed that all HA-UTI isolates were extended-spectrum β-lactamase (ESBL) producers and exhibited multidrug resistance, in contrast to CA-UTI isolates, which were primarily resistant to ciprofloxacin, levofloxacin, tigecycline, and fosfomycin (Caneiras et al., 2019). The study further identified β-lactamase genes like blaTEM, blaSHV, and blaCTX-M-15, with CTX-M-15 being associated with the globally prevalent ST15 clone. Despite the presence of this successful clone in both hospital and community

settings, the virulence profiles differed significantly between them (Caneiras et al., 2019). Hospital-acquired strains *of K. pneumoniae* show a correlation between virulence and multidrug resistance, a pattern not typically observed in community-acquired isolates. These observations emphasize the significance of sustained genomic surveillance in healthcare environments to monitor and control the spread of resistant and virulent K. pneumoniae pathogens (Caneiras et al., 2019).

2.6.2 A study in Pakistan (2021 to 2023) based on a current piece of research conducted by Zeeshan Khan et al. (2023), the patterns of concerning antimicrobial resistance and the genetic profiling of virulence factors in *Klebsiella pneumonia* isolates from urinary tract infection (UTI) patients were examined at Khyber Teaching Hospital, Peshawar, from October 2021 to January 2023 (Zeeshan Khan et al., 2023). This hospital-based investigation aimed to assess both the rate of resistance to multiple antibiotics and the genetic determinants associated with pathogenicity (Zeeshan Khan et al., 2023). Out of numerous clinical samples analyzed using culture-based methods (including MacConkey, nutrient agar, and CLED media) and further confirmed with API 20E kits and molecular techniques, a total of 215 (3.85%) K. pneumoniae isolates were identified. The data revealed a higher infection rate among female patients (4.35%) compared to males (3.26%), with the 21–40-year age group being the most affected (52.55%) (Zeeshan Khan et al., 2023). Infections were slightly more common among inpatients (55.35%) than outpatients (44.65%), highlighting the significance of nosocomial acquisition (Zeeshan Khan et al., 2023).

Antibiotic susceptibility testing indicated to disturbing resistance rate toward commonly utilized antibiotics like trimethoprim/sulfamethoxazole (93%) and colistin (79.07%), the latter of which is often considered a last-resort treatment. Encouragingly, tigecycline and cefepime demonstrated the highest susceptibility rates (90%) (Zeeshan Khan et al., 2023). Minimum inhibitory concentration (MIC) testing confirmed elevated resistance levels against a broad spectrum of drugs including cefotaxime (CTX), meropenem (MEM), gentamicin (CN), amikacin (AK), doxycycline (DO), ciprofloxacin (CIP), and sulfamethoxazole-trimethoprim (SXT) (Zeeshan Khan et al., 2023). Molecular analysis provided further insight into the virulence potential of the isolates. The most frequently detected virulence gene was

fimH (80%), which plays a crucial role in adhesion and colonization. Other detected genes included sat (65%), papEF (49%), afa (29%), and vat (16%). Sequence analysis revealed mutations in fimH and papEF, suggesting adaptive genetic mechanisms potentially contributing to antimicrobial resistance and increased virulence. Statistical evaluation using the Chi-square test confirmed significant associations between virulence gene presence and patient demographics, with p-values ≤ 0.05. This study emphasized the clinical threat posed by MDR K. pneumoniae, not only due to its resistance also due to its capacity to harbor multiple virulence determinants, reinforcing the urgent need for active surveillance, updated therapeutic protocols, and investment in molecular diagnostics across healthcare institutions in Pakistan (Zeeshan Khan et al,. 2023).

2.6.3 A study in Nigeria (2024) Ashefo Daniel Paul and Dr. Habibu Tanimu conducted a comprehensive study on the incidence and resistance to antimicrobial agents profile of *Klebsiella pneumoniae* obtained from urine samples of patients attending Primary Health Care Centers in Lafia Metropolis, Nasarawa State, Nigeria. P ublished in the Journal of Health Systems, the study involved 266 urine samples collected from four primary healthcare facilities: Isa Mustapha Agwai 1 Polytechnic Clinic, Comprehensive Healthcare Center in Kwandere, Primary Health Care Center in Assakio, and Primary Health Care Center in Adogi (Ashefo et al,. 2024). The overall incidence of K. pneumoniae was 12.78%, with a marked gender disparity showing higher prevalence in females (11.88%) than males (6.14%) (Ashefo et al,. 2024). Location-wise, Isa Mustapha Agwai 1 Polytechnic Clinic exhibited the highest prevalence (19.14%), while outpatients had a notably higher incidence (14.72%) compared to inpatients (7.25%) (Ashefo et al. 2024). Age-related analysis revealed the highest infection rates in the 25–34 years' group (11.82%), and strikingly high positivity in individuals aged 75 years and above (21.62%). The study's antimicrobial susceptibility testing revealed high resistance levels to several frontline antibiotics: Ampicillin (91.18%), Gentamicin (76.47%), and Streptomycin (55.88%) (Ashefo et al. 2024). Multi-drug resistance (MDR) was prevalent in 67.65% of isolates, with 44.11% showing extensive drug resistance (XDR), reflecting significant treatment obstacles. The absence of pan-drug resistant (PDR) strains was a positive finding, yet the authors emphasized the necessity for targeted

antibiotic stewardship programs and surveillance to curtail the rise and dissemination of antibiotic resistant *K. pneumoniae* strains in this Nigerian region (Ashefo et al,. 2024). This study contributes valuable epidemiological data relevant to urinary tract infections caused by *K. pneumoniae* in primary healthcare settings, highlighting the urgent need for localized treatment guidelines and resistance monitoring. (Ashefo et al,. 2024)

2.6.4 A study in India (2025) In a 2025 retrospective observational study, Sahoo et al. assessed the prevalence as well as the antimicrobial resistance exhibited by *Klebsiella pneumoniae* in urinary tract infections (UTIs) patients at the largest hospital in eastern India (Sahoo et al., 2025). The study involved 500 screened urine samples collected from July 2020 to November 2022, of which 250 were confirmed UTI cases (Sahoo et al., 2025). *K. pneumoniae* was the predominant Gram-negative pathogen isolated, responsible for 122 cases, with *Escherichia coli* being the next most frequent isolate (74), Pseudomonas aeruginosa (45), and Acinetobacter baumannii (9) (Sahoo et al., 2025). A key finding in this research was the identification of ten K. pneumoniae isolates classified as multidrug-resistant (MDR), showing resistance to five major antibiotic classes: β-lactams, aminoglycosides, fluoroquinolones, tetracyclines, and polymyxins (Sahoo et al., 2025). High resistance rates were observed against piperacillin/tazobactam, ceftazidime, aztreonam, and imipenem antibiotics frequently used in hospital settings highlighting the increasing treatment challenges posed by K. pneumonia (Sahoo et al., 2025). Even alternative antibiotics such as gentamicin, levofloxacin, minocycline, fosfomycin, and colistin showed reduced effectiveness, though with comparatively lower resistance rate s (Sahoo et al., 2025). The authors concluded that continuous antimicrobial resistance surveillance is essential to inform clinical decision making and reduce the risk of nosocomial contagions. The research supports the urgent need for targeted antibiotic stewardship, particularly in high-burden regions, to address the growing threat of drug-resistant K. pneumoniae in UTIs (Sahoo et al., 2025).

CHAPTER III

Methodology

3.1 Study Design

This study was modelled based on the pattern of a retrospective, cross-sectional study aimed at investigating the prevalence and antibiotic resistance profiles of *Klebsiella pneumoniae* isolates recovered from urinary tract infections (UTIs). The study utilized laboratory and clinical data obtained from Near East University Hospital, a major tertiary care facility located in Nicosia, Northern Cyprus. Data were collected from the hospital's microbiology laboratory and patient records, including both outpatient and inpatient cases, over a three-year period (January 2022 – December 2024). The data analysis phase of the study was conducted from March to June 2025.

3.2 Participants/Population and Sample

A total of 166 urine samples that tested positive for *Klebsiella pneumoniae* were included in this study. These samples were collected from patients of both sexes and all age groups (0–92 years old) who were clinically diagnosed with UTI. Both inpatients and outpatients were included to assess prevalence across hospital settings.

3.2.1 Inclusion criteria:

- Patients with clinical symptoms of UTI.
- Laboratory-confirmed *K. pneumoniae* in urine culture.
- Both male and female outpatients, inpatients.
- All age groups (0–92 years).

3.2.2 Exclusion criteria:

- Patients with incomplete laboratory or clinical data.
- Urine samples that did not yield *K. pneumoniae*.

- Cases of polymicrobial infections where *K. pneumoniae* was not the predominant pathogen.

3.3 Sample Collection and Processing

Urine samples were collected using standard aseptic procedures, including midstream clean-catch and catheter-derived methods, depending on patient condition and clinical necessity. Samples were promptly transported to the microbiology laboratory and processed according to hospital protocols for urine sample handling. Each sample was inoculated on Cystine Lactose Electrolyte Deficient (CLED) agar, MacConkey agar, blood agar, and chocolate agar as per routine practice. Plates were incubated at 37°C for 18–24 hours under aerobic conditions. Culture positivity and colony morphology guided further identification and testing.

3.3.1 Bacterial Identification

Isolates identified as *Klebsiella pneumoniae* were confirmed using the VITEK-2 automated identification system (bioMérieux), which utilizes a comprehensive biochemical profile for species-level identification. All isolates were subjected to standardized quality control procedures.

3.3.2 Antibiotic Susceptibility Testing (AST)

Antimicrobial susceptibility testing was performed using the VITEK-2 automated system, following the interpretative criteria established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Resistance rates were monitored and analyzed to assess temporal and drug-specific trends over the study period.

The antibiotics tested included:

Beta-lactams: Amoxicillin-clavulanate, Ampicillin, Cefuroxime, Cefixime, Ceftriaxone, Ceftazidime, Cefepime, Cefoxitin, Piperacillin-tazobactam.

Carbapenems: Imipenem, Meropenem, Ertapenem.

Aminoglycosides: Amikacin, Gentamicin.

Fluoroquinolones: Ciprofloxacin.

Others: Nitrofurantoin, Fosfomycin, Trimethoprim-sulfamethoxazole.

Results were interpreted as susceptible, intermediate, or resistant.

Although no molecular testing (e.g., PCR for ESBL or carbapenemase genes) was performed, resistance was inferred phenotypically through the VITEK-2 system. The study focused on analyzing resistance rates to key antibiotics and monitoring patterns suggestive of ESBL production based on beta-lactam resistance profiles.

3.4 Data Collection Tools/Materials

Study Location: Near East University Hospital, Nicosia, Northern Cyprus.
Study Population: A total of 166 outpatients and inpatients (male and female, aged 0–92 years) with confirmed urinary tract infections caused by Klebsiella pneumonia
Study Period: Clinical data from January 2022 to December 2024; analysis conducted March–June 2025

3.5 Data Analysis Procedures

Data were compiled and analyzed using Microsoft Excel. Descriptive statistics such as frequencies, percentages, means, standard deviations (SD), minimum and maximum values were calculated to summarize demographic characteristics and antimicrobial resistance profiles. The results were presented using tables and graphs to illustrate patterns across age groups, gender, inpatient vs. outpatient status, and over the study years.

3.6 Ethical Considerations

Ethical approval for the study was obtained from the Near East University Scientific Research Ethics Committee (Project No: NEU/2024/129-1921). All patient information was collected in accordance with institutional data protection policies. Although the dataset included identifying variables such as patient name, age, gender, hospital number, and date of sample collection, data confidentiality and anonymity were maintained during analysis and reporting. Since the study used pre-existing laboratory and clinical records without direct patient contact, informed consent was waived as per ethical guidelines.

3.7 Study Plan

Prevalence and Antibiotic Resistance Profiles of *Klebsiella pneumoniae* Isolates Recovered from Urinary Tract Infections at Near East University Hospital, 2022–2023. The study will provide up-to-date information on the prevalence and resistance trends of *K. pneumoniae* in UTIs at our institution. Findings may help guide empirical treatment choices and inform antimicrobial stewardship policies.

CHAPTER IV

Result

This is a retrospective analysis of *Klebsiella pneumoniae* isolates recovered from urinary tract infections (UTIs) between 2022 and 2024 at Near East University Hospital. A total of 166 clinical urine samples were included in the study, all of which tested positive for *K. pneumoniae*. The results are organized to reflect patient demographics, setting of infection (inpatient vs. outpatient), and antibiotic resistance patterns over the three-year period.

4.1 Patient Demographics

Out of the 166 patients included in the study, 111 (66.9%) were female and 50 (30.1%) were male. Patient ages ranged from newborn (0 years) to 92 years, indicating that *K. pneumoniae* UTIs affected all age groups.
Inpatients accounted for 89 cases (53.6%), including 28 males and 61 females. Outpatients represented 77 cases (46.4%), comprising 27 males and 50 females. These results show that *K. pneumoniae*-related UTIs were more prevalent among hospitalized female patients, possibly reflecting more severe or complicated infections requiring inpatient care.

4.2 Antibiotic Resistance Patterns

The antibiotic susceptibility results were evaluated and grouped according to outpatient and inpatient isolates for each year from a three-year period (2022–2024).

4.3.1 Beta-Lactam and Cephalosporin Resistance

Ampicillin resistance remained extremely high (100%) in both patient groups and across all years, indicating its complete ineffectiveness against *K. pneumoniae* in this setting. Amoxicillin-clavulanate resistance increased sharply in outpatients (from 42.9% in 2022 to 57.9% in 2023), before dropping to 30.4% in 2024. A similar trend was observed in inpatients.

Cefixime and ceftriaxone showed notably high resistance rates among inpatients, reaching 81.3% and 76.7%, respectively, in 2024. Cefuroxime-axetil and ceftazidime resistance exceeded 70% in inpatients, showing widespread cephalosporin resistance. This widespread resistance to beta-lactams and cephalosporins strongly suggests the prevalence of ESBL-producing strains, particularly in hospital settings.

4.3.2 Carbapenem Resistance

Carbapenems (Ertapenem, Imipenem, Meropenem) remained among the most effective agents, but signs of increasing resistance were noted: Imipenem resistance increased from 5.6% to 18.2% in inpatients. Ertapenem resistance in inpatients ranged from 33.3% to 50% by 2024. Meropenem also showed a rise in resistance, though data were incomplete for 2023. Although still relatively effective, these findings highlight an emerging threat of carbapenem-resistant *K. pneumoniae* (CRKP).

4.3.3 Other Agents

Fosfomycin had relatively low resistance rates in outpatients (down to 7.7%) but increased in inpatients (up to 33.3%). Nitrofurantoin showed moderate resistance, especially in inpatients (41.7% in 2024). Piperacillin-tazobactam resistance remained high among inpatients (71.4% in 2024). Trimethoprim-sulfamethoxazole showed a steep rise in inpatient resistance to 56.5% in 2024.

4.4 Comparison Over Time

4.4.1 Outpatient Trends (2022–2024)

Resistance increased significantly in 2023 for nearly all antibiotics, suggesting either overuse of common drugs or increased community-acquired resistance. Some antibiotics, such as amoxicillin-clavulanate and ceftazidime, showed decreased resistance in 2024, possibly reflecting antimicrobial stewardship efforts or changes in prescribing practices.

4.4.2 Inpatient Trends (2022–2024)

Resistance levels in inpatients were consistently higher than in outpatients. Antibiotics like cefepime, cefixime, ciprofloxacin, and carbapenems all showed significant resistance increases over time. Higher resistance among inpatients may reflect frequent use of broad-spectrum antibiotics, underlying comorbidities, and prolonged hospital stays.

Table 4.1 Inpatients and Outpatients population.

Patient Group	Total	Male	Female
Inpatients	89	28	61
Outpatients	77	27	50

4.5 ESBL-Producing *K. pneumoniae* Strains

4.5.1 In inpatients (2022–2024):

The prevalence of ESBL-producing *Klebsiella pneumoniae* among inpatients showed a fluctuating but generally high pattern. In 2022, 33.3% of inpatient isolates were ESBL-positive. This rate nearly doubled in 2023, reaching a peak of 69.7%. In 2024, the rate decreased to 42.4%, but remained significantly higher than in 2022, indicating that antibiotic resistance in hospital settings continues to be a major concern.

4.5.2 In outpatients (2022–2024):

Among outpatients, the ESBL positivity rate started at 22.2% in 2022 and increased to 36.4% in 2023, reflecting a growing problem of community-acquired resistant strains. However, a notable decline was observed in 2024, with the rate dropping to 9.8%. Despite this decline, continuous monitoring remains essential to prevent resurgence.

High resistance to third-generation cephalosporins and beta-lactams strongly suggests the prevalence of ESBL-producing strains, especially among inpatients. These strains were responsible for high resistance to ceftriaxone, ceftazidime, and cefotaxime. Reduced susceptibility to beta-lactam/beta-lactamase inhibitor combinations. ESBL prevalence appeared to rise over time, suggesting the need for routine ESBL screening in UTIs.

4.6 Discussion of Key Results

Klebsiella pneumoniae is a prominent cause of UTIs, particularly among hospitalized and female patients. The organism showed extensive resistance to most first-line antibiotics, including beta-lactams and fluoroquinolones. Carbapenems and fosfomycin remained effective options, though increasing resistance trends were noted. The study strongly supports ESBL-producing isolates, particularly in inpatient settings. These findings are in line with regional and global studies that have noted similar patterns of *K. pneumoniae* resistance. The continued evolution of resistant strains underscores the need for strict antimicrobial stewardship, infection control, and timely microbiological testing.

Table 4.2 Characteristics of the study population Inpatients.

Year	Males	Females	Mean age ± Standard deviation	Median age (minimum - maximum)	Total Cases
2022	4 (16.7%)	20 (83.3%)	68.83 ± 18.27	74.00 (21.00 – 88.00)	24
2023	12 (37.5%)	20 (62.5%)	73.72 ± 17.72	75.00 (0.00 – 92.00)	32
2024	12 (36.4%)	21 (63.6%)	17.59 ± 17.59	77.00 (19.00 – 92.00)	33

Table 4.3 Characteristics of the study population Outpatients.

Year	Males	Females	Mean age ± Standard deviation	Median age (minimum - maximum)	Total Cases
2022	6 (33.3%)	12 (66.7%)	59.33 ± 21.36	65.50 (4.00 – 86.00)	18
2023	6 (27.3%)	16 (72.7%)	57.95 ± 23.04	66.00 (10.00 – 86.00)	22
2024	15 (40.5%)	22 (59.5%)	57.43 ± 22.95	53.00 (8.00 – 91.00)	37

Table 4.4 Antibiotic resistance rates of *Klebsiella pneumoniae* isolates recovered from urinary tract infections in inpatients, 2022-2024.

Antibiotic	Resistance rates among inpatient isolates (%)		
	2022	2023	2024
Amikacin	12.5	26.7	13.0
Amoxicillin-Clavulanate	37.5	69.7	19.0
Ampicillin	100	97.1	83.3
Cefepime	-	81.3	72.7
Cefixime	68.8	78.8	73.1
Cefoxitin	20.8	59.1	62.5
Ceftazidime	47.6	77.3	73.1
Ceftriaxone	41.7	77.3	76.7
Cefuroxime	50.5	78.8	81.8
Ciprofloxacin	37.5	78.8	76.9
Ertapenem	33.3	51.5	50
Fosfomycin	33.3	22.2	33.3
Gentamicin	83.3	39.4	39.1
Imipenem	16.7	10.0	18.2
Meropenem	25.0	34.5	-
Nitrofurantoin	41.7	53.1	47.1
Piperacillin-Tazobactam	47.8	72.7	71.4
Trimethoprim-Sulfamethoxazole	33.3	0.0	56.5

Table 4.5 Antibiotic resistance rates of *Klebsiella pneumoniae* isolates recovered from urinary tract infections in outpatients, 2022-2024.

Antibiotic	Resistance rates among outpatient isolates (%)		
	2022	2023	2024
Amikacin	-	5.3	8.0
Amoxicillin-Clavulanate	42.9	57.9	30.4
Ampicillin	100	81.8	84.0
Cefepime	0.0	22.2	27.3
Cefixime	35.3	55.6	26.9
Cefoxitin	16.7	28.6	16.7
Ceftazidime	27.8	57.1	24.2
Ceftriaxone	31.3	42.9	23.5
Cefuroxime	41.2	52.6	50.0
Ciprofloxacin	27.8	63.2	52.0
Ertapenem	5.9	15.8	4.0
Fosfomycin	12.5	33.3	7.7
Gentamicin	22.2	19.0	21.4
Imipenem	5.6	8.3	0.0
Meropenem	5.6	5.3	4.2
Nitrofurantoin	17.6	27.3	24.3
Piperacillin-Tazobactam	33.3	35.7	11.5
Trimethoprim-Sulfamethoxazole	-	31.8	.32.0

Table 4.6 Extended-spectrum beta-lactamase (ESBL) positive and negative *Klebsiella pneumoniae* strains isolates recovered from urinary tract infections in inpatients, 2022-2024.

	ESBL +ve		ESBL-ve		Total	
	N	%	N	%	N	%
2022	8	33.3	16	66.7	24	100
2023	23	69.7	10	30.3	33	100
2024	14	42.4	19	57.6	33	100

Table 4.7 Extended-Spectrum beta-lactamase (ESBL) positive and negative *Klebsiella pneumoniae* strains isolates recovered from urinary tract infections in outpatients, 2022-2024.

	ESBL +ve		ESBL- ve		Total	
	N	%	N	%	N	%
2022	4	22.2	14	77.8	18	100
2023	8	36.4	14	63.6	22	100
2024	14	42.4	19	57.6	33	100

CHAPTER V

Discussion

This study examined the prevalence and antibiotic resistance profiles of *Klebsiella pneumoniae* isolates from urinary tract infections (UTIs) at Near East University Hospital between 2022 and 2024. Our findings show a concerning trend of increasing antibiotic resistance, particularly among inpatient isolates, highlighting the critical importance of ongoing surveillance and responsible antibiotic use in healthcare settings. Across the three years, a total of 166 UTI cases caused by *K. pneumoniae* were recorded. Resistance to ampicillin was consistently high among both outpatient and inpatient isolates, reaching 100% in 2022 and remaining above 80% in the following years. Similarly, resistance to amoxicillin-clavulanate, cefuroxime, and piperacillin-tazobactam was notable, especially among inpatients. The detection of ESBL-producing K. pneumoniae increased over time, with inpatient isolates showing higher rates than outpatients rising from 33.3% in 2022 to 42.4% in 2024. These findings indicate a growing challenge in managing UTIs effectively, particularly within hospitalized populations where multidrug resistance is more prevalent. When comparing these results with previous research, our findings are consistent with global trends.

A retrospective multicenter study conducted in Portugal analyzed 81 *K. pneumoniae* isolates 50 from community-acquired UTIs (CA-UTIs) and 31 from hospital-acquired UTIs (HA-UTIs). All HA-UTI isolates were extended-spectrum β-lactamase (ESBL) producers and exhibited multidrug resistance. Community-acquired strains, however, were more susceptible to agents like ciprofloxacin, levofloxacin, tigecycline, and fosfomycin. The study emphasized the genetic differences between isolates from hospital and community settings, aligning with our findings that inpatient isolates tend to harbor higher resistance rates (Caneiras et al., 2019).

A study from Pakistan assessed the antibiotic resistance patterns of *K. pneumoniae* UTI isolates between 2021 and 2023. Zeeshan Khan et al. reported alarming resistance rates to antibiotics such as trimethoprim-sulfamethoxazole (93%) and colistin (79.07%), with a majority of infections being hospital-acquired.

Furthermore, molecular analysis revealed a high frequency of virulence genes, including fimH (80%) and sat (65%), which compound the challenges posed by resistant strains (Zeeshan Khan et al., 2023).

A study in Nigeria similar trend was observed. Ashefo Daniel Paul and Dr. Habibu Tanimu investigated the prevalence and resistance profiles of *K. pneumoniae* in patients attending primary healthcare centers. They found an overall incidence of 12.78%, with resistance rates of 91.18% to ampicillin and 76.47% to gentamicin. Importantly, 67.65% of isolates were classified as multidrug-resistant, and 44.11% exhibited extensive drug resistance. These findings strongly advocate for antibiotic stewardship interventions in local healthcare systems (Ashefo, D. P., & Tanimu, H., 2024).

A study in India, by Sahoo et al. (2025) analyzed 250 UTI cases and *identified K. pneumoniae* as the most frequently isolated Gram-negative pathogen. Of these, ten isolates were multidrug-resistant, showing resistance to β-lactams, aminoglycosides, fluoroquinolones, tetracyclines, and polymyxins. The researchers stressed the growing treatment challenges and called for region-specific antimicrobial resistance monitoring systems (Sahoo, M., et al., 2025).

One reassuring aspect of our study is the relatively low resistance to carbapenems and fosfomycin. However, this finding must be interpreted cautiously. While these antibiotics remain effective treatment options, their overuse could quickly lead to the emergence of resistance, as seen in other settings. Therefore, clinicians must be judicious in prescribing these agents, reserving them for cases where other options have failed or are contraindicated.

Our findings also reinforce the need for continuous local surveillance and the development of tailored antibiotic stewardship programs. Hospitals must invest in regular microbial resistance tracking and update their treatment guidelines accordingly. Additionally, infection control protocols should be strengthened, especially in inpatient wards, to limit the spread of resistant strains.

CHAPTER VI

Conclusion and Recommendations

Conclusion

This study set out to determine the prevalence and antibiotic resistance profiles of *Klebsiella pneumoniae* isolates recovered from urinary tract infections at Near East University Hospital between 2022 and 2024. The research aimed to assess not only how widespread *K. pneumoniae* infections were during this period but also how resistant the isolates had become to commonly used antibiotics, including beta-lactams, cephalosporins, aminoglycosides, carbapenems, and others. By distinguishing between outpatient and inpatient isolates, the study also sought to highlight any differences in resistance patterns linked to the healthcare setting.

The findings clearly indicate a progressive rise in resistance rates, particularly among inpatient isolates. Ampicillin showed consistently high resistance across all three years, while other antibiotics such as amoxicillin-clavulanate, cefuroxime, and piperacillin-tazobactam also displayed alarming resistance levels. Notably, the prevalence of ESBL-producing *K. pneumoniae* increased over the study period, with the highest rates observed in 2024. These results underscore a growing challenge in the treatment and management of UTIs caused by *K. pneumoniae*, especially in hospital settings.

One encouraging observation was the relatively low resistance rates to carbapenems and fosfomycin, which still appear to retain therapeutic effectiveness against *K. pneumoniae* in this hospital. However, this advantage must be preserved through cautious and rational antibiotic prescribing, as overreliance on these agents could lead to the emergence of carbapenem-resistant strains, which would significantly limit future treatment options.

Recommendations

Enhance Antibiotic Stewardship Programs: There is an urgent need to strengthen antimicrobial stewardship at Near East University Hospital. This includes implementing updated treatment guidelines that reflect current resistance trends and promoting the judicious use of broad-spectrum antibiotics, especially in inpatient care.

Routine Surveillance of Resistance Patterns: Regular microbiological surveillance should be institutionalized to monitor shifts in resistance profiles. This data should inform both empirical treatment protocols and infection control policies.

Catheter-related UTI focus: Considering that catheter-associated urinary tract infections (CAUTIs) represent a significant risk factor for hospital-acquired infections, especially among inpatients, it is recommended that further large-scale prospective studies be conducted to specifically evaluate the impact of urinary catheterization on the incidence and antibiotic resistance patterns of *Klebsiella pneumoniae* in UTIs. Such studies would help to identify preventable factors, improve infection control practices, and guide targeted antimicrobial stewardship interventions in hospital settings.

Limit Use of High-Risk Antibiotics: Given the high resistance to ampicillin, cephalosporins, and beta-lactam/beta-lactamase inhibitor combinations, these antibiotics should be reserved or used only after sensitivity results confirm their effectiveness. Carbapenems and fosfomycin should be considered only when necessary, with strict criteria for use.

Strengthen Infection Control Practices: Hospital-acquired infections pose a significant risk for the spread of multidrug-resistant *K. pneumoniae*. Enhanced hygiene protocols, isolation of infected patients when appropriate, and regular staff training are essential to prevent cross-transmission.

Educate Healthcare Professionals: Continuous education and training for physicians, nurses, and pharmacists on resistance mechanisms, appropriate prescribing, and the interpretation of antibiograms are critical to combatting antimicrobial resistance.

Encourage Further Research: More in-depth molecular studies are recommended to identify the specific genes responsible for resistance and virulence in *K. pneumoniae* at this hospital. Additionally, further research should focus on patient outcomes, risk factors for infection with resistant strains, and the cost burden of resistance.

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