FATIMA MANASSRA

Intensive Care Unit: A Retrospective Study from a University Hospital in Northern Cyprus

MASTER THESIS

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NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

Department Of Medical Microbiology and Clinical Microbiology

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June 2025

Approval

We certify that we have read the thesis submitted by Hussein Hadi titled by "**A Psychoanalytic Exploration of Mad Love and Obsession in Emily Brontë's *Wuthering Heights***" and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of English Language and Literature.

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STATEMENT (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.

FATIMA MANASSRA

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FATIMA HUSSIEN SHEHDA MANASSRA

Ozet

Yoğun Bakım Ünitesinde Hastane Kaynaklı Enfeksiyonların Değerlendirilmesi: Kuzey Kıbrıs'taki Bir Üniversite Hastanesinden Retrospektif Bir Çalışma

Fatima Hussein Shehda Manassra

Yüksek Lisans, Tıbbi Mikrobiyoloji ve Klinik Mikrobiyoloji Anabilim Dalı

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Haziran 2025, 51

Giriş:

Yoğun bakım ünitelerinde (YBÜ), ciddi şekilde hasta olan hastalar düzenli olarak invaziv cihazlara ve geniş spektrumlu antibiyotiklere maruz kalmaktadır. Klebsiella pneumoniae, hastane kaynaklı enfeksiyonların (HAE) başlıca nedenlerinden biridir. Biyofilm oluşturma ve çoklu ilaç direnci kazanma eğilimi morbiditeyi, mortaliteyi ve sağlık hizmeti maliyetlerini artırmaktadır. Bu retrospektif çalışma, 2024 yılında Yakın Doğu Üniversitesi Hastanesi YBÜ'sünde HAE tanısı alan hastalardan izole edilen K. pneumoniae'nın prevalansını ve antibiyotik direnç paternlerini kapsamlı şekilde değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem:

Bu retrospektif analiz, Kuzey Kıbrıs'ta bulunan Yakın Doğu Üniversitesi Hastanesi'nin veri tabanından elde edilen mikrobiyolojik veriler ve ilgili hasta bilgileri kullanılarak gerçekleştirilmiştir. Klinik örnekler, 2024 yılı boyunca hastane kaynaklı enfeksiyon (HAE) tanısı konmuş yoğun bakım ünitesi (YBÜ) hastalarından alınmıştır. Klebsiella pneumoniae izolatlarının tanımlanması ve antimikrobiyal duyarlılık testleri VITEK-2 otomatik sistemi kullanılarak yapılmıştır. Antimikrobiyal duyarlılık yorumları, Avrupa Antimikrobiyal Duyarlılık Testi Komitesi'nin (EUCAST) belirlediği kılavuzlara sıkı sıkıya uyularak gerçekleştirilmiştir. Direnç profilleri, izolatlar arasında antimikrobiyal direnç prevalansını ve dağılımını belirlemek amacıyla değerlendirilmiştir.

Bulgular:

Çalışmaya, K. pneumoniae ilişkili hastane kaynaklı enfeksiyon tanısı konmuş 35 yoğun bakım ünitesi hastası dahil edilmiştir. Hastaların %42,9'u kadın, %57,1'i erkek olup ortalama yaş 63,3 yıl olarak saptanmıştır. En sık alınan örnekler kan

kültürleri (%27,1) ve aspirat kültürleri (%33,3) olmuştur. Antibiyotik duyarlılık testlerinde seftriakson (%97,8), siprofloksasin (%93,6), meropenem (%80,4) ve imipenem (%73,8) gibi önemli antibiyotiklere karşı yüksek direnç oranları tespit edilmiştir. Analiz edilen 47 K. pneumoniae izolatının %36,17'sinde genişlemiş spektrumlu beta-laktamaz (GSBL) üretimi ve karbapenem direnci (CRKP) saptanmıştır.

Sonuç:

Bu retrospektif çalışma, 2024 yılında Yakın Doğu Üniversitesi Hastanesi YBÜ'sünde HAE'ye neden olan K. pneumoniae'nın önemli prevalansını ve antimikrobiyal direnç yükünü ortaya koymaktadır. Bulgular, seftriakson (%97,83), siprofloksasin (%93,62), meropenem (%80,43) ve imipenem (%73,81) gibi kritik antibiyotiklere karşı endişe verici derecede yüksek direnç oranlarını göstermiştir. İzolatların toplam %36,17'si genişlemiş spektrumlu beta-laktamaz (GSBL) üretimi, karbapenem direnci (KrbR) veya her ikisini birden sergilemiştir. Bu bulgular, çoklu ilaca dirençli K. pneumoniae'nın yayılmasını yavaşlatmak için yoğun bakım ünitelerinde enfeksiyon kontrol önlemlerinin ve hedefe yönelik antimikrobiyal yönetim stratejilerinin geliştirilmesinin kritik önemini vurgulamaktadır.

Anahtar Kelimeler: Hastane kaynaklı enfeksiyonlar, Klebsiella pneumoniae, yoğun bakım ünitesi, çoklu ilaç direnci, antimikrobiyal yönetim, Kuzey Kıbrıs.

Abstract

Evaluation of Hospital-Acquired Infections in the Intensive Care Unit: A Retrospective Study from a University Hospital in Northern Cyprus

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June 2025, 51

Introduction:

In intensive care units (ICUs), where severely ill patients are regularly exposed to invasive devices and broad-spectrum antibiotics, *Klebsiella pneumoniae* is a top cause of hospital-acquired infections (HAIs). Its propensity to create biofilms and acquire multidrug resistance raises morbidity, mortality, and the cost of healthcare. This retrospective study aims to thoroughly assess the prevalence and antibiotic resistance patterns of *K. pneumoniae* isolated from ICU patients with HAIs at Near East University Hospital in 2024.

Materials and Methods:

This retrospective analysis utilized microbiological data and corresponding patient information retrieved from the database of Near East University Hospital, located in Northern Cyprus. Clinical specimens were obtained throughout the year 2024 from patients in the intensive care unit who were clinically diagnosed with hospital-acquired infections. Identification of *K. pneumoniae* isolates, as well as their antimicrobial susceptibility testing, was carried out using the VITEK-2 automated system. Antimicrobial susceptibility interpretations were performed in strict accordance with the guidelines established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The resistance profiles were then assessed to determine the prevalence and distribution of antimicrobial resistance among the isolates.

Results:

The study included 35 intensive care unit patients who had been diagnosed with *K. pneumoniae* related hospital-acquired infections. Patients were 42.9% female and 57.1% male, with an average age of 63.3 years. blood cultures (27.1%) and aspirate cultures (33.3%) were the most commonly obtained samples. High resistance rates to a number of important antibiotics, such as ceftriaxone (97.8%), ciprofloxacin (93.6%), meropenem (80.4%), and imipenem (73.8%), were found by antibiotic susceptibility testing. Extended-spectrum beta-lactamase (ESBL) production and carbapenem-resistant *K. pneumoniae* were detected in 36.17% of the 47 *K. pneumoniae* isolates that were analyzed.

Conclusion:

This retrospective study highlights the significant prevalence and antimicrobial resistance burden of HAIs caused by *K. pneumoniae* among ICU patients at Near East University Hospital in 2024. The results showed concerningly high rates of resistance to important antibiotics, alarmingly high resistance rates were detected, including ceftriaxone (97.83%), ciprofloxacin (93.62%), meropenem (80.43%), and imipenem (73.81%).A total of 36.17% of the isolates exhibited either extended-spectrum beta-lactamase (ESBL) production, carbapenem resistance (KrbR), or both.. In order to slow the spread of multidrug-resistant *K. pneumoniae* these findings emphasize the critical need for improved infection control procedures and focused antimicrobial stewardship strategies in intensive care units.

Keywords: Hospital-acquired infections, *Klebsiella pneumoniae*, intensive care unit, multidrug resistance, antimicrobial stewardship, Northern Cyprus.

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List of Abbreviations

%: Percent sign

AMR: antimicrobial resistance

ASTs: Antibiotic susceptibility tests

CDC: Centers for Disease Control and Prevention e.g.: For Example

ESBL: Extended-Spectrum Beta-Lactamase

ESBLs: Extended-Spectrum Beta-Lactamases

ESCMID: European Society of Clinical Microbiology and Infectious Diseases

ESICM: European Society of Intensive Care Medicine

ESKAPE: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species

et al.: And others.

EUCAST: The European Committee for Antimicrobial Susceptibility Testing

HAIs: Hospital-Acquired Infections

ICU: Intensive care unit

IDSA: Infectious Diseases Society of America

IV: Intravenous

KrbR : carbapenem-resistant *K. pneumoniae* (KrbR)

MDR: Multi-Drug Resistant

MDROs: Multidrug-Resistant Organisms

MIC: Minimum inhibitory concentration

MRSA: methicillin-resistant Staphylococcus aureus

PBPs: penicillin-binding proteins

PCR: Polymerase chain reaction

PDR: Pan-Drug Resistant

S: Susceptible

SD: Standard Deviation

SPP: Several Species

TRNC: The Turkish Republic of Northern Cyprus

XDR: Extensively-Drug Resistant

CHAPTER I

Introduction

The term Hospital-acquired infections (HAIs), refer to infections that are acquired after 48 hours of hospital admission (Ashokka et al., 2020), remain a major concern for hospitalized patients worldwide and are also among the avoidable morbidity and mortality causes (Sheikh Omar et al., 2023). Intensive care unit (ICU) patients are the most vulnerable (Aiesh et al., 2023). Recent studies have highlighted the significant threat that HAIs pose to global public health, impacting both developing and developed countries (European Centre for Disease Prevention and Control., 2024). In the European Union (EU), it is estimated that over 3 million patients are impacted by HAIs each year, also its are responsible for more than 90,000 deaths. The burden of HAIs exceeds that of other infections, such as influenza and tuberculosis, underscoring the critical need for effective prevention and management strategies. (Healthcare-Associated Infections, 2023).

Patients are prone to develop several infections while receiving healthcare for another ailment in any healthcare department (Haque et al., 2018). Despite the continuous development and progression in hospital care, the increase in infections continues (Revelas, 2012).

Every day, one in every 31 hospitalized patients suffers from a HAIs (CDC, 2024). Various microbes can cause HAI, which might cause a wide range of diseases, such as bloodstream infections (BSIs), surgical site infections (SSIs), urinary tract infections (UTIs), respiratory tract infections (RTIs), and skin and soft tissue infections (SSTIs) (Liu & Dickter, 2020), (Baviskar et al., 2019).

The primary cause of HAIs in ICUs is the frequent use of invasive medical devices, which provide pathogens with direct entry points. Examples include urinary catheters, mechanical ventilators, and central venous catheters (Khan et al., 2017). Additional contributing factors are inadequate hand hygiene practices among healthcare workers, environmental contamination of equipment and surfaces, and the prevalence of multidrug-resistant organisms due to antibiotic overuse. Critically ill patients are particularly vulnerable because of their weakened immune systems, prolonged hospital stays, and need for complex medical procedures (Khan et al., 2015).

Despite the fact that the majority of enteric Gram-negative bacilli are susceptible to common disinfectants and cannot survive on the dry surfaces of medical equipment or in ICUs, biofilm-forming bacteria, like *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are extremely resilient to these harsh conditions and are closely linked to HAIs through contaminated medical devices and other hospital environmental equipment (Weinstein & Hota, 2004) . Common bacterial pathogens that cause HAIs, including *Staphylococcus aureus*, *Escherichia coli*, coagulase-negative Staphylococci, Enterococcus species, Candida species, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Bacteroides species, Enterobacter species, and Proteus species (Tolera et al., 2018).

The Gram-negative, encapsulated bacterium *K.pneumoniae* has become a major cause of HAIs globally, especially in critically ill patients admitted to ICUs (Navon-Venezia, Kondratyeva, & Carattoli, 2017). Bloodstream infections, pneumonia, wound infections, and urinary tract infections are among the severe infections that *K. pneumoniae* can cause (Martin & Bachman, 2018). Its pathogenicity is increased by its capacity to form biofilms, elude host immune responses, and acquire multiple antibiotic resistance determinants, including carbapenemases and extended-spectrum beta-lactamases (Martin & Bachman, 2018; Pitout, Nordmann, & Poirel, 2015), Because of these traits, *K. pneumoniae* has become one of the most worrisome multidrug-resistant (MDR) pathogens in medical settings, especially ICUs , where invasive devices and compromised immune systems are common (Navon-Venezia et al., 2017) . Thus, *K. pneumoniae* was chosen as the study's focus organism in order to gain a better understanding of its impact on patient outcomes, antibiotic resistance profiles, and role in ICU-related HAIs. In order to lessen the threat posed by this extremely resistant pathogen, the results highlight the urgent need for strong antimicrobial stewardship programs and efficient infection control measures (Pitout et al., 2015).

The consequences of HAIs extend beyond health outcomes, as they increase hospital stays, necessitate additional medical interventions, and diminish the overall quality of life for patients. Economically, these infections place a heavy burden on healthcare systems (Asegu et al., 2024). In the EU, HAIs cost more than €7 billion annually,

while the financial impact in the United States ranges from $10 billion to $33 billion each year (Szabó et al., 2022).

Understanding the microbiological characteristics of the pathogens responsible for HAIs in ICUs is crucial for developing effective preventive strategies. By identifying the epidemiology of these infections and the patterns of this antimicrobial resistance, healthcare providers can implement targeted infection control measures, enhance antimicrobial stewardship programs, and improve patient outcomes (Custovic et al., 2014; Ghashghaee et al., 2018).

Currently, there is a lack of epidemiological studies on HAIs in Northern Cyprus (NC). Addressing this gap, our study will retrospectively analyze data collected from the ICU of a Near east hospital in Cyprus over the period of one-year 2024. This ICU was selected due to its high prevalence of HAIs and significant burden of antimicrobial resistance, largely attributed to patients' critical conditions, frequent exposure to invasive devices, and high rates of antibiotic use.

Limitation:

There are various limitations to our study. First off, because this study was carried out at a single location, the microbiological profile found there is unique to that setting and cannot be generalized to other healthcare facilities. Additionally, the study's scope was limited to a single medical ICU at our hospital, which excluded patients from other ICUs like the pediatric and surgical units. Second, the current study did not include all antibiotics used in routine medical practice. Thirdly, the study was hampered by the lack of clinical data required to distinguish between genuine infections and colonization, as well as between infections obtained in the community and those obtained in a hospital setting. Finally, because it is not always easy to distinguish between infection and contamination, secondary infection rates might be overestimated.

CHAPTER II

Literature Review

2. General Information

2.1. Risk Factors Associated with Hospital-Acquired Infections (HAIs)

HAIs are infections that occur during hospitalization but were neither incubating nor present upon the patient's admission to the hospital. These infections usually occur within 10 days of discharge and between 48 and 72 hours after hospital admission. (Collins, n.d). HAIs pose a serious risk to patients while they are in medical facilities. Effective prevention and management of these infections rely on identifying the major risk factors, which include patient characteristics, medical procedures, environmental factors, and elements of the healthcare system (Magill et al., 2018).

Patient-Related Factors

After exposure to a pathogenic organism, individuals' susceptibility to infection can vary based on their immune defenses. Some people may have natural immunity against certain microbial virulence factors, allowing them to resist infection without developing symptoms (National Research Council, 2004). Others may form a commensal relationship with the microorganism, becoming asymptomatic carriers (colonization) without experiencing illness. However, some individuals exposed to the same pathogen may develop active disease (Choiński et al., 2024).

Patients are particularly at risk for HAIs due to intrinsic factors. Those who are immunocompromised—such as older adults, neonates, or individuals with underlying medical conditions, severe illnesses, or those on immunosuppressive treatments (including medications or surgeries)—are more vulnerable to infections (National Research Council, 2004).

Certain individuals have impairments in their immune responses, including deficits in humoral immunity, phagocytosis, or cellular immune function, making them more susceptible to infections. For example, patients with primary immunodeficiencies (e.g., anemia or autoimmune diseases), as well as those undergoing chemotherapy, taking corticosteroids, or managing chronic conditions like diabetes or leukemia, are more prone to infections caused by common, less virulent pathogens, opportunistic fungi, and viruses (National Institute of Child Health and Human Development, 1999).

HAIs rates are notably higher in ICUs due to the severity of patients' conditions and

the presence of multiple risk factors. In fact, ICU patients experience infection rates that are approximately three times higher than those in other hospital areas, affecting both adults and pediatric populations (Weinstein, R. A., 1998).

Procedural Factors

Two important procedural factors that raise the risk of HAIs are invasive procedures and the duration of hospital stay. Research indicates that invasive procedures, like surgery, catheterization, or interventional radiology, interfere with the body's natural defenses, allowing pathogens to more easily enter and spread infection (Alamer et al., 2022). For instance, there is a direct connection between increased rates of HAIs and the use of medical devices such as respiratory equipment, IV cannulas, and urinary catheters (Department of Health, Victoria State Government, 2023). Likewise, an extended hospital stay is linked to a higher chance of contracting HAIs. According to studies, patients who stay in the hospital for longer than four days are much more likely to get these infections (Tolera et al., 2020). This is partly because extended hospital stays increase the risk of invasive procedures and prolonged exposure to the hospital environment, which may contain infectious agents (Jeon et al., 2012).

Environmental Factors

HAIs arise from a variety of factors, including overcrowded hospital environments, frequent patient transfers between units, and the concentration of patients who are particularly vulnerable to infection, such as newborns, burn victims, and those in intensive care (Sikora, A. and Zahra, F., 2022). Microbial flora can contaminate medical tools, materials, and other items that come into contact with patients' sensitive body areas. Furthermore, new infections caused by bacteria, including aquatic bacteria (such as atypical mycobacteria), as well as viruses and parasites, continue to emerge (MTC, 2022).

Health Care Worker (HCWs) -related factor

Nosocomial infections (NIs), otherwise known as Hospital-Acquired Infections, are contaminations that patients or HCWs contract while they are in the hospital or while they are performing their daily duties (Mayhall, 2012; Curtis et al., 2013) If an infection manifests 48 to 72 hours following hospitalization or within 10 days following discharge, it is deemed nosocomial (Meena & Gaurav, 2016). HCWs contract these infections when collecting specimens, processing, and discarding medical equipment, as well as when they directly interact with patients during

examinations (Mortell et al., 2013). Urinary tract infections, surgical site infections, lower respiratory tract infections, bloodstream infections, and other non-bacterial infections are frequently caused by nosocomial infections, Nonetheless, surgical-site infections were the most commonplace healthcare-associated infection in low- and middle-income nations (World Health Organization, 2011). Furthermore, NI is a serious public health issue that causes extended hospital stays, permanent disability, and even fatalities (Uwaezuoke & Obu, 2013).

HCW hand hygiene practices are crucial in reducing the incidence of HAIs. Vaccinating healthcare workers against diseases that can be prevented by vaccination, practicing good hand hygiene, preventing sick HCWs from caring for patients, cleaning the environment, and isolating patients who have been infected or colonized with specific organisms (such as methicillin-resistant *Staphylococcus aureus* or *Clostridium difficile*) are all effective ways to prevent infections linked to healthcare (Edmond, Michael & Wenzel, Richard, 2005). The implementation of these measures is crucial to their efficacy. For instance, less than 50% of HCW practice proper hand hygiene, despite the fact that it is believed to be the most effective strategy to prevent NI (Curtis et al., 2013b).

2.2. Pathogenesis and common types of Hospital Acquired Infection

HAIs come in a broad variety of forms. Central line-associated bloodstream infections (CLABSI) are among the most common ones. which involve a catheter placed into a big vein that can become the entry point for bacteria into the bloodstream, thus resulting in CLABSI infections (Flores-Mireles A, 2019). Hospitals frequently use central lines to deliver blood products, medications, and fluids, Serious CLABSIs can result in organ failure, sepsis, and even death (Naj et al., 2024).

Another major HAI Catheter-related urinary tract infections (CAUTI), Catheters, which are tubes that are placed into the bladder, can allow bacteria to enter the urinary tract and cause CAUTIs. Urine is frequently drained from the bladder in hospitals using catheters. Serious CAUTIs have the potential to cause sepsis, renal failure and even death (Habboush Y, 2023).

Surgical site infections (SSI), which are infections at the spot of a surgical incision, SSIs account for about 22% of all HAIs. Incision wounds may be impacted by SSIs. Deeper tissues, organs, and even surgical implants (such as pacemakers or artificial joints) may be impacted (Cleveland Clinic, 2023).

Pneumonia is said to be hospital-acquired if it manifests at least 48 hours after being admitted to the hospital. Many microorganisms can cause HAP, including *Staphylococcus aureus, Streptococcus pneumoniae*, and *Escherichia coli.* Severe outcomes from HAP include sepsis, respiratory failure, and even mortality (Naj et al. , 2024).

Ventilator-associated pneumonia (VAP) is a form of pneumonia that manifests more than 48 to 72 hours after endotracheal intubation, a treatment that involves inserting a tube into the trachea to aid breathing (Stiller A. 2017). Many bacteria, including *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and Staphylococcus aureus, can induce VAP (Singh AK, 2022 and Young PY 2044). Respiratory failure, sepsis, and even death can result from severe VAP.

An infection caused by the bacterium *Clostridium difficile* is known as a *Clostridium difficile* infection (CDI) (Sydnor ER, 2011). The delicate balance of bacteria in the stomach can be disrupted by antibiotic usage, which can cause CDI. Fever, abdominal pain, and diarrhea are all signs of CDI. Severe CDI can cause sepsis, organ failure, and even death (Singh AK, 2022).

The Microbial Agent

The patient is exposed to a variety of microorganisms while they are in the hospital. Contact between a patient and a bacterium does not always result in clinical disease. Numerous factors influence the type and frequency of NI (Alp et al., 2014). The characteristics of the microorganisms, such as intrinsic virulence, resistance to antimicrobial agents, and quantity (inoculum) of infectious material, have an impact on the likelihood that exposure will lead to infection (Litwin et al., 2020). Numerous bacteria, viruses, fungi, and parasites can cause NI. Endogenous infections can be caused by the patient's flora or from a bacterium that was transferred from another patient to the hospital (cross-infection). Inanimate objects or materials that have recently been contaminated by human activity (environmental infection) can harbor certain organisms (Bonadonna et al., 2017).

2.3. Epidemiology of Hospital Acquired Infection in ICUs

ICU patients can be especially prone to infections caused by pathogens that are resistant to several antibiotics (Brusselaers et al., 2011). (HAIs) are thought to affect 9–20% of patients in ICUs, and the ICU accounts for half of all hospital-acquired infections (Magill et al., 2014). Furthermore, 45–51% of them get infected in some way (Litwin et al., 2020b). A continued increase in HAIs is expected due to factors

such as population aging, the expansion of medical and caregiving interventions, the higher prevalence of chronic conditions, and the ongoing dissemination of MDR pathogens (Dimopoulos et al., 2013). The extensive use of broad-spectrum antibiotics is likely to contribute to antimicrobial resistance, with projections estimating over 10 million deaths related to drug-resistant infections within the next three decades (Meyer et al., 2010).

Gram-negative bacteria have gained increasing relevance in the development of drug-resistant infections. These include VRE, MRSA, beta-lactamase-resistant Enterobacter spp., Citrobacter spp., Proteus mirabilis, MDR Escherichia coli, ESBL-producing strains, and K. pneumoniae. Furthermore, attention should also be given to fungal pathogens and anaerobic infections caused by Clostridium difficile spp. (Brusselaers et al., 2011).

2.4. Important Types of Bacteria Detected in the Intensive Care Unit

MDR bacteria are defined as strains resistant to three or more classes of antibiotics (Masters, 2016). MDR comprises methicillin-resistant *Staphylococcus aureus*, CRE (carbapenem-resistant Enterobacterales), VRE (vancomycin-resistant Enterococcus), and ESBL-producing Enterobacterales (Siegel et al., 2007). While PDR (pan-drug-resistant) describes resistance to all agents in all categories, XDR (extensively drug-resistant) is resistance to at least one agent in all but two or less antimicrobial types (Siegel et al., 2007).

P. aeruginosa, *Acinetobacter spp*., ESBL-producing *Enterobacteriaceae,* MRSA, and CRE are among the frequent MDR pathogens found in intensive care units.

2.5.Antimicrobial Resistance Patterns of HAIs

The ecological issue of antimicrobial resistance (AMR) is defined by intricate interactions between different microbial populations that impact the environment, animal health, and human health. In animals, humans, and the environment, the majority of bacteria and their genes can spread readily (Mouiche et al., 2019 Collignon & McEwen, 2019). An increasing threat to healthcare systems, AMR is leading to higher rates of morbidity and mortality as well as decreased effectiveness of antimicrobial therapy. According to estimates, AMR results in 8 million days of inpatient admission and 21–34 billion dollars in health care costs annually in the USA (CDC, 2019).Bacteria have become resistance to the majority of clinically useful antibiotics in recent decades (Chamoun et al., 2016). In the United States and England, nearly all *Staphylococcus aureus* isolates are resistant to penicillin, and in

certain populations, resistance to methicillin exceeds 50%. By taking the right actions in the 2000s, MRSA and VRE growth was controlled globally (Tseng et al., 2012). On the other hand, Gram-negative AMR is increasing, particularly in HAIs, which demand immediate attention (Ziakas et al., 2013). The overuse of antibiotics is one of the main factors contributing to AMR (Aslam et al., 2018).

Basic precaution like hand washing is still disregarded in many centers, even with the increased awareness of AMR. Let detection and high costs make it inefficient to isolate patients with resistant organisms (Siddiqui & Koirala, 2023). another element that contributes to the spread of resistant between nations is health tourism.

2.6.Morbidity and Mortality of HAIs in ICUs

HAI occurring in intensive care units are an important risk factor for mortality and morbidity. HAI are classified into Device Associated Infections (DAIs) and non-device associated (I. D. Khan et al., 2022).

HAI such as pneumonia, urinary infections, bloodstream infections, wound infections, bacteremia, surgical-site infections, and sepsis. Prolonged morbidity, mortality, hospitalization, and healthcare expenses are significantly influenced by DAIs, including Catheter-Related Bloodstream Infection, Pneumonia Associated with Ventilators, Infections of the Bloodstream Associated with Central Lines, and Urinary Tract Infections Associated with Catheters (Kumar et al., 2018).

Significant mortality and morbidities are linked to HAIs. Numerous studies have measured these, but the case mix is probably going to have an impact on the mortality impact. According to a U. S. study (Klevens et al. , 2007), the case fatality rates for CLABSI were 12. 3%, VAP 14. 4%, CAUTI 2. 3%, and SSI 2. 8%. According to a study conducted in a surgical intensive care unit, 35% of fatalities were caused by CLABSI .Since it is challenging to link infection to death in patients with multiple cofactors in ICUs , it was suggested that more research is necessary to ascertain the attributable mortality for the majority of HAIs (Umscheid et al., 2011). VAP and CLABSI are linked to the greatest number of avoidable deaths among all HAIs (Al-Tawfiq & Tambyah, 2014). According to calculations, between 5,520 and 20,239 lives have been saved in the US as a result of fewer cases of CLABSI, and 13,667 to 19,782 lives have been saved as a result of VAP (Umscheid et al., 2011).

2.7. Economic Impact of HAIs

HAIs are a major public health concern as a result of their influence on the safety of admitted patients and the occupational hazards they present to healthcare professionals. These infections are acquired during medical care and are associated with a higher incidence of adverse events, contributing significantly to morbidity and mortality. As a result, HAIs negatively influence patient safety and compromise the overall quality of healthcare services (Cavalcante et al., 2019)

Like in other parts of the world, HAP and VAP are serious public health concerns in Asian nations. NI rates have been reported by point-prevalence studies to range from 6.1% to 15% globally. In Asia, rates appear to be especially high. According to a recent Malaysian study, pneumonia accounted for 21% of NI , which affected 14% of hospitalized patients (Hughes et al., 2005). As a result, ICUs are highly technologically complex settings that are considered to be crucial for patient instability and have a high risk of developing HAIs. Accordingly, HAIs are defined as infections contracted while receiving care in a hospital or other care facility. They are regarded as a serious health issue since they lead to high mortality, extended hospital stays, and the spread and selection of multi-resistant microbes (Jeôncio jm, et al., 2019; Garbuio dc, et al. , 2022). Nevertheless, patients who contract these HAIs incur higher medical costs than those who do not have the illness.Numerous studies demonstrate that HAIs is a serious health concern that can have a significant financial impact, especially in ICUs . These extra expenses are linked to the treatment's complexity and, in turn, the lengthier hospital stays. In this sense, HAIs directly affects patient care and raises hospital expenses because they use a lot of potentially costly medications, require a more specialized team relative to the amount of beds, necessitate more recurrent test requests, and ultimately have a significant financial impact, especially ICUs (Cavalcante efo, et al., 2019; Machado lg, et al., 2022; Osme sf, et al., 2022). In this regard, given that they involve governments, patients, and healthcare facilities, cohort studies or even the use of a database are required for the analysis of costs associated with HAI. In addition to hospitals using various approaches, which can increase the variability and discrepancy of the data, the cost estimation process generally adheres to protocols that concentrate primarily on the direct ones, which are challenging to define (Ramirez k, 2018; Benenson S, et al., 2020; Gomes hms e Gasparetto v, 2021). Therefore, one of the factors

influencing the high cost of treating HAIs is antimicrobial therapy, particularly when it comes to treating infections brought on by agents resistant to antimicrobials. Assessing the cost of HAIs is a crucial first step in putting programs in place that can address this issue. By calculating the benefit-cost ratio, the best use of resources can be allocated to the most successful interventions. It's obvious that hospital service quality improvement and cost reduction should always be discussed, but these two approaches are obviously diametrically opposed (Barroso et al., 2023).

The immune systems of ICU-admitted patients are altered and rendered vulnerable to HAIs by factors such as the severity of their illness, physiological and psychological stress, sleep deprivation, advanced age, longer hospital stays, and malnutrition. All nations' health systems bear a heavy clinical and financial burden from HAIs. In US hospitals, HAI has resulted in 16 million additional hospital days and yearly direct medical costs between $28.4 to $33.8 billion (Zolfaghari et al., 2024). Less research has been done on the prevalence of HAIs in developing nations. The estimated extra expense for VAP in Argentine ICUs is $2,255 (Rosenthal et al., 2005). Iran has an 8.8% prevalence of HAIs, according to WHO data, and a 14.8% mortality rate from these infections. Iranian patients are thought to spend $4.74 million a year on HAI-related expenses (Plowman, 2002).

2.8. Prevention from Hospital Acquired Infection

Serious complications like sepsis, organ failure, and even death can result from HAIs. Nonetheless, there are several steps that can be taken to stop HAIs,

Washing one’s hands is the top crucial strategy to stop the spread of infection. Before and after interacting with each patient (Metersky ML, 2017)., healthcare personnel must thoroughly wash their hands with soap and water. Additionally, they should wash their hands before eating, after handling contaminated materials, and after using the restroom (Naj et al., 2024b).

Hand Hygiene , most people agree that the best way to prevent HAIs is to practice good hand hygiene, which reduces the spread of pathogens. Prior to patient contact and following exposure to bodily fluids, among other important patient interaction points, the WHO "Five Moments for Hand Hygiene" model encourages hygiene. High hand hygiene compliance dramatically lowers infection rates, according to numerous studies. For instance (Pittet et al., 2000), a study showed that a hospital-wide hand hygiene campaign increased compliance from 48% to 66% and resulted in a 41% reduction in HAI (Alnadawy et al., 2024). supported these findings, further

demonstrating the ongoing relevance of hand hygiene interventions. However, sustaining high compliance remains a challenge, particularly in high-pressure healthcare environments. Therefore, fostering a culture of safety and continuous education is essential to ensure long-term adherence and protection against HAIs (Erasmus et al., 2010).

Applying sterile methods, healthcare professionals should use sterile techniques whenever they are inserting medical devices, such as central lines and catheters, to avoid introducing bacteria into the patient's bloodstream (Patel AR, 2019). This calls for rigorous protocols and the use of brand-new, sterile equipment (Magill SS, 2014).

Disinfecting the hospital environment: to get rid of bacteria that could lead to infections, the environment must be cleaned and sanitized on a regular basis. This entails sanitizing and cleaning rooms, surfaces, and equipment (Naj et al., 2024).

Antibiotic stewardship, to stop the emergence of antibiotic resistance, antibiotics should be used sparingly. This entails using antibiotics only when absolutely required and for the shortest amount of time at the lowest effective dose (Magiorakos AP, 2012).

2.8.1 Methods for Preventing and Minimizing the Spread of Infections Caused by Multidrug-Resistant Pathogens

It highlights the most important medical procedures for preventing the spread of drug-resistant bacteria. These include recognizing possible routes of infection transmission, using antibiotics judiciously and appropriately, and diagnosing infections (Brusselaers et al. , 2011). It is essential to establish effective infection treatment and antibiotic management strategies in hospital buildings. They should be based on staff training, prospective audits, feedback, clear guidelines, and molecularly based microbiological research and testing technologies (Habboush & Guzman, 2025). The Infectious Diseases Society of America (IDSA) discusses key elements of proper antibiotic treatment. These include: establishing specialized permits and assigning responsible people to implement them in order to lower antibiotic usage; developing clinical and therapeutic pathways based on patterns of resistance and local microbiota; and involving the doctor throughout the therapeutic process by soliciting input and feedback; enhancing and de-escalating therapy to eliminate needless combination therapy; optimizing antibiotic dosages taking into account the drug's pharmacodynamics, pharmacokinetics, and infection site; and creating clinical pathways that permit, if feasible, the conversion of parenteral

medications to oral medications (Habboush & Guzman, 2025).

2.8.2. Restricting the Spread of Antibiotic-Resistant Bacteria in the ICU Setting

Given the serious threat posed by multidrug-resistant bacteria in intensive care units (ICUs), it is crucial to ensure that all medical equipment used with patients is thoroughly disinfected, or alternatively, replaced with single-use items. Special attention must be given to equipment that has been in contact with patients infected with antibiotic-resistant organisms, as these items may serve as potential sources of transmission (Strich & Palmore, 2017).

Research has shown that Klebsiella *pneumoniae* may live for five to six days on plastic and steel surfaces , emphasizing the need for strict hygiene protocols within hospital settings. Awareness of how long resistant bacteria can persist on surfaces reinforces the importance of comprehensive antiseptic measures (Strich & Palmore, 2017).

Advanced methods of disinfection, such ultraviolet (UV) radiation and hydrogen peroxide vapor , have demonstrated promising results in ICU settings by reducing microbial contamination. These technologies are particularly useful for sanitizing areas that are difficult for healthcare workers to reach during routine cleaning (Otter et al., 2016).

Additionally, attention should be given to the role of hospital plumbing systems as possible reservoirs for resistant bacteria like Aeromonas, Pseudomonas, and Sphingomonas. Although the evidence is not yet conclusive, replacing or routinely maintaining these systems may help reduce the risk of transmission within critical care environments (Williams et al., 2013).

2.9.The Prevalence of *Klebsiella Pneumoniae* in HAIs

K. Pneumoniae are common rod-shaped bacteria that are commonly found in plants, water, and soil. Some Klebsiella strains are believed to be a typical part of people's gastrointestinal tract and nasopharynx flora. These microorganisms are facultative anaerobic gramme negative bacilli (GNB) and members of the Enterobacteriaceae family, according to microbiological classification (Conlan et al., 2016). Most of these bacteria are immobile and contained in a unique capsule made of polysaccharides. *K. pneumoniae* is the most important species that affects humans. It causes a variety of severe, potentially fatal diseases, including pneumonia, septicemia, urinary tract, nosocomial, and opportunistic infections (Bi et al., 2015).

The bacterium *K. pneumoniae* has a variety of physiological functions. It is commonly found in soil and water and inhabits ecological settings (Ahmadi et al., 2022). *K. pneumoniae* absorbs atmospheric nitrogen gas and converts it to ammonia and amino acids through metabolic nitrogen fixation pathways. Because oxygen can harm some of the nitrogenase enzyme, *K. pneumoniae* only uses nitrogen fixation in anaerobic conditions (Martin & Bachman, 2018b).

A noticeable polysaccharide capsule may help the bacterium protect itself from phagocytosis, increasing its virulence and potential for harm. This bacterium is isolated in a hospital setting from sources such as tainted cleaning supplies, contaminated bar soaps, contaminated sink handles and drains, and contaminated medical equipment (Gray & Omar, 2013). Typical biochemical characteristics of this bacterium include lactose fermentation, lysine decarboxylation, nitrate reduction, a positive urea hydrolysis test, a negative oxidase test, and a positive citrate utilization test. *K. pneumoniae* is the most common bacterium in a number of nosocomial and community-acquired illnesses (Cubero et al., 2016). This bacterium causes an extensive range of nosocomial infections, such as UTIs, pneumonia, wound infections, intraabdominal infections, bactremia, and neonatal septicemia. In addition to being a nosocomial pathogen, Klebsiella species has been connected to invasive and systemic illnesses such as liver abscess, meningitis, endophthalmitis, and septic arthritis in diabetics and immunocompromised individuals (Gaonkar et al., 2023). The association between drug resistance and hospital-acquired *K. pneumoniae* infections is often stronger. This bacterium demonstrates acquired, adaptive, and intrinsic antibiotic resistance mechanisms. Intrinsic resistance results from the antibiotic's inability to build up in the cell, whereas acquired and adaptive resistance are brought on by modifications to the antibiotic's target sites or enzymatic inactivation of the drug. For a while, carbapenems were the preferred drug for treating MDR infections. Inappropriate initial empirical therapy is a major contributor to treatment failure, which raises mortality rates (Gaonkar et al., 2023).

2.9.1 Mechanisms of Antibiotic Resistance in *Klebsiella pneumoniae* Associated with Hospital-Acquired Infections

A major nosocomial pathogen, *K. pneumoniae* causes a variety of HAIs, including urinary tract infections , bloodstream infections, and pneumonia. After *Escherichia coli*, it is acknowledged as the second most frequent cause of gram-negative BSIs

(Alfaifi et al., 2025). The bacterium demonstrates a broad spectrum of resistance mechanisms, with one of the most notable being the production of β-lactamase. These include carbapenemases, AmpC β-lactamases, and extended-spectrum β-lactamases , which can hydrolyze a variety of β-lactam antibiotics and counteract their effects(Huy, 2024).

Since carbapenems are frequently used as last-resort treatments, carbapenem resistance is especially concerning. The main way that resistance arises is through:

Carbapenemase synthesis (KPC, NDM, and OXA-type enzymes)

Mechanisms that combine several resistance pathways (Shettar et al., 2025), Furthermore, *K. pneumoniae* actively extrudes antibiotics from the cell using efflux pump systems, which reduces the intracellular concentration and effectiveness of the antibiotics. This mechanism helps to create resistance to a variety of antibiotic classes including β-lactams, macrolides, and fluoroquinolones (Huy, 2024).

Target site modifications, such as changes in penicillin-binding proteins (PBPs), which lower antibiotic binding affinity, further increase resistance. By restricting drug entry into the bacterial cell, changes in membrane permeability—specifically due to the loss or alteration of outer membrane porins like OmpK35 and OmpK36—also increase resistance (Martin & Bachman, 2018).

K. pneumoniae demonstrates several genetic adaptations that promote resistance. Because colistin is used as a last resort, it is particularly concerning that colistin resistance has been linked to mutations in particular regulatory genes, such as mgrB (Kidd et al., 2017).The organism's accessory genome is essential for the horizontal acquisition of resistance genes, which are frequently transmitted by mobile genetic elements like transposons and plasmids(Martin & Bachman, 2018).

The ability of *K.pneumoniae* to create biofilms on medical equipment further enhances its resistance by protecting bacterial communities from antibiotics and host immune responses.Additionally, integrons and plasmids facilitate horizontal gene transfer,

which increases the rate at which resistance genes spread among bacterial populations in healthcare facilities (Gaonkar et al. , 2023).

2.9.2.Patterns of Antibiotic Resistance in *Klebsiella pneumoniae* in Hospital-Acquired Infections from General Infection and ICU Cases

One of the primary causes of HAIs , especially in adult patients, is the Gram-negative opportunistic pathogen *K. pneumoniae*. Urinary tract infections, pneumonia,

surgical site infections, and bloodstream infections are frequently linked to it. *K. pneumoniae* is clinically significant because of its growing capacity to become resistant to several antibiotic classes, which makes treatment more difficult and raises healthcare expenses and mortality rates (Podschun & Ullmann, 1998; Patel et al., 2020).

The production of ESBLs , carbapenemases, and other enzymatic mechanisms that hydrolyze beta-lactam antibiotics, such as penicillins, cephalosporins, and carbapenems, is the primary cause of antibiotic resistance in *K. pneumoniae* (Nordmann, Naas, & Poirel, 2017). Carbapenem-resistant *K. pneumoniae* (CRKP) strains are a grave concern, particularly in ICUs , where patients frequently have compromised immune systems and undergo invasive treatments like central venous catheterization and mechanical ventilation (Tamma et al., 2019). MDR is more common in *K. pneumoniae* isolates from ICUs than in general hospital wards, according to studies. Lengthier hospital stays, increased broad-spectrum antibiotic use, and more exposure to invasive devices in ICUs are some of the factors contributing to this discrepancy. These factors promote nosocomial transmission and selection pressure for resistant strains (Navon-Venezia, Kondratyeva, & Carattoli, 2017). Additionally, MDR bacteria are more likely to colonize ICU settings, which acts as a reservoir for horizontal gene transfer and speeds up the spread of resistance (Munoz-Price & Weinstein, 2008).

Regular monitoring is essential to guide empirical treatment and infection control efforts due to geographic and institutional differences in the epidemiology of *K. pneumoniae* resistance. In order to prevent the spread of antibiotic-resistant *K. pneumoniae* strains, strict infection prevention measures and efficient antimicrobial stewardship programs are essential (David et al., 2021). Additionally, knowing the molecular mechanisms behind resistance in local isolates can help customize treatment plans and guide public health initiatives meant to lower the number of HAIs this pathogen causes.

CHAPTER III

Materials and Methods

3.1. **Study Design and Period**

A retrospective study utilizing record-based data from clinical microbiology laboratory was conducted over a one-year period, from December 2023 until December 2024, at Near East University Hospital in Nicosia, North Cyprus. This hospital is an academic institution that serves as a teaching hospital. Within its facilities, a team of dedicated intensivists provide round-the-clock care to patients in the ICUs.

3.2. **Study Participants**

Adult patients (≥18 years old) admitted to Near East University Hospital's medical (ICU) in 2024 made up the study population.

All patients in the study who spent more than 48 hours in the intensive care unit were found to have HAIs. The study only included patients whose clinical samples, such as blood, aspirates, urine, catheter tips, or other sterile bodily fluids, contained *K. pneumoniae* isolates that were confirmed by culture. Clinical assessment and microbiological results were used to diagnose HAIs, and all infections were categorized as ICU-acquired.

3.3. **Data Collection Tools**

The clinical specimens were received by the hospital microbiology laboratory and subsequently subjected to standard procedures for the identification and isolation of potential pathogens.The KirbyBauer disk diffusion test, which was carried out on MuellerHinton agar in accordance with the standards set forth by the European Committee for Antimicrobial Susceptibility Testing (EUCAST), was used to determine antimicrobial susceptibility.

Data was gathered regarding demographic variables, including age and gender, sample types such as aspirate cultures blood cultures. Additional information included hospitalization date, sample date and the microbiological data involved the identification of isolated cultures as well as the results of antimicrobial susceptibility resistance testing.

3.4 Data Analysis Procedures

The patient data were recorded and organized using Microsoft Excel. Retrospective statistical analysis, including frequency distributions and percentage calculations, was performed using Excel to summarize demographic data, sample types, and antimicrobial resistance patterns.

3.5 Study Plan

This study represents the first evaluation of MDR *K. pneumoniae* infections among ICU patients at Near East University Hospital.In 2024, 35 clinical samples from adult ICU patients who had been diagnosed with HAIs were analyzed. The distribution of specimens included aspirates, blood cultures, urine, catheter tips, and other sterile body fluids.

The isolated K. pneumoniae strains were subjected to a thorough examination of their antimicrobial resistance profiles and prevalence.

CHAPTER IV

Results

4.1. **Patient Demographics**

The study involved 35 patients ,15were female (42.86%) with average age of 60 years, and 20 were male (57.14%) with an average age of 62 years (Figure1).

The intensive care unit staff collected a total of 47 *K. pneumoniae* isolates from 35 patients over the research period (December 2023, to December, 2024). Clinical samples were sourced from various origins, predominantly aspirate culture (33.33%), followed by aerobic blood culture (27.08%), urine cultures (14.58%), catheter culture (14.58), Samples from cerebrospinal fluid (CSF), sputum, and thoracentesis constituted only a small fraction is (2.08) of cases (Figure2).

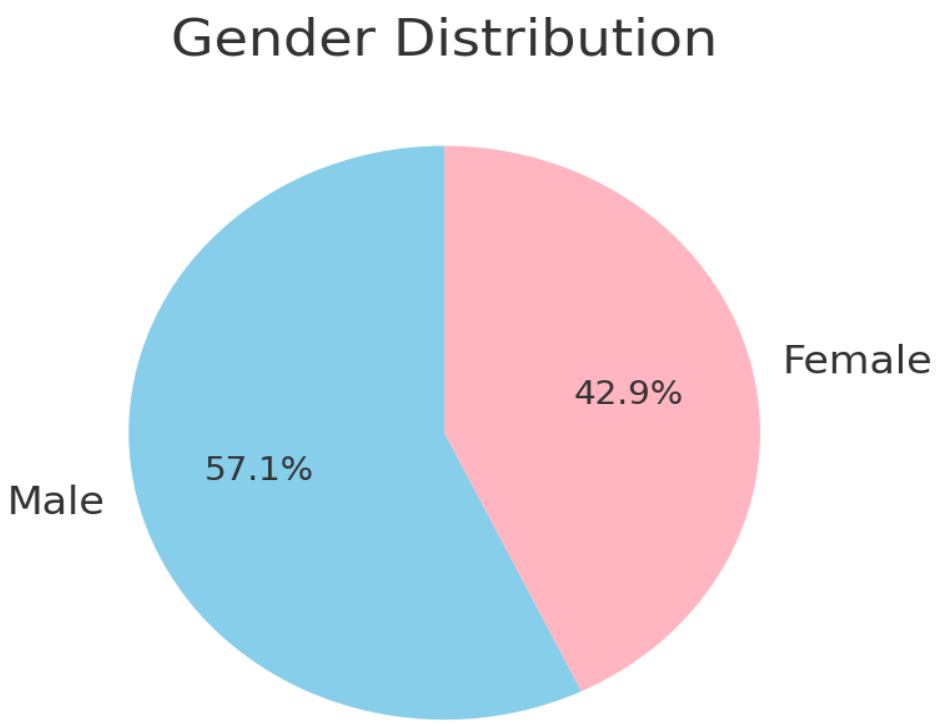

Figure 1: Gender distribution of ICU patients with *Klebsiella pneumoniae* infections.

Table 1: The percentages of each biological sample type used for detection of *Klebsiella pneumoniae* infection**.**

Biological sample (Test)	% of biological sample
Aerobic Blood Culture	27.65 %
Urine Culture	14.89 %
Aspirate Culture	34.04 %
Catheter Culture	14.89 %
Sputum Culture	2.12 %
Cerebrospinal Fluid (CSF) Culture	2.12 %
Thoracentesis Culture	2.12 %
Total	97.83 %

Note: percentages were calculated as (n/total*100)and rounded to two decimal places. therefore, the total may not be exactly100%.

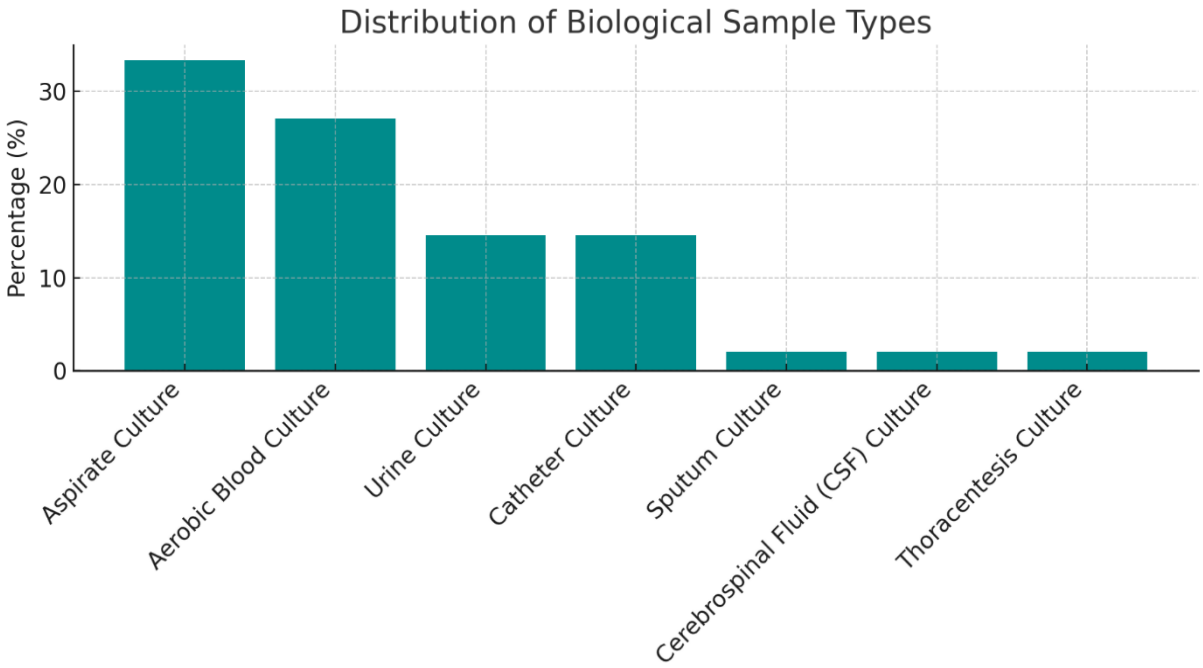

Figure 2. Bar chart showing the percentage distribution of biological sample types.

4.2. **Antibiotic Resistance Rates of** *Klebsiella Pneumoniae* **Isolates:**

The rates of resistance of the *K. pneumoniae* isolates to various antibiotics were calculated as the percentage of isolates classified as "Resistant" according to the test results.

Table 2: Antibiotic Resistance Rates of *Klebsiella Pneumoniae*

Count of Result	Result				
Antibiotic	less sensitive	Sensitive	Resistant	Resistance Rate (%)	Grand Total
Amikacin	2	15	25	59.52%	42
Amoxicillin			1	100.00%	1
Amoxicillin/Clavulanate	1		42	97.67%	43
Ampicillin		1	38	97.44%	39
Ampicillin/Sulbactam			1	100.00%	1
Aztreonam			5	100.00%	5
Cefepime		5	32	86.49%	37
Cefixime		1	6	85.71%	7
Cefotaxime			1	100.00%	1
Cefoxitin			22	100.00%	22
Ceftazidime	3	9	31	72.09%	43
Ceftriaxone		1	45	97.83%	46
Ceftriaxone/Clavulanate			1	100.00%	1
Cefuroxime – axetil		1	28	96.55%	29
Ciprofloxacin		3	44	93.62%	47
Colistin	6	15	2	8.70%	23
Ertapenem		1	47	97.92%	48
Fosfomycin	1	3		0.00%	4
Gentamicin		13	14	51.85%	27
Imipenem	2	9	31	73.81%	42
Levofloxacin		5	13	72.22%	18
Meropenem	3	6	37	80.43%	46
Nitrofurantoin			8	100.00%	8
Piperacillin/Tazobactam	2	1	35	92.11%	38
Teicoplanin		1		0.00%	1
Tigecycline		15	1	6.25%	16
Trimethoprim/Sulfamethoxazole		8	36	81.82%	44
Grand Total	20	113	547	80.44%	680

The accompanying tables provide a summary of the resistance rates of 47 *K.pneumoniae* isolates to the tested antibiotics. The number of isolates designated as "Resistant" during antimicrobial susceptibility testing served as the basis for defining resistance.

K.pneumoniae showed 100% resistance to cefotaxime; however, this result was based on a single isolate and may not be statistically significant. More reliable indicators of high resistance were observed for ceftriaxone (97.83%), amoxicillin/clavulanate (97.67%), and ampicillin (97.44%). The prevalence of ESBL-producing strains among the isolates is indicated by the strong resistance to third-generation cephalosporins, such as ceftriaxone and cefixime.

The exceptionally high carbapenem resistance rates of 73. 81%, 80. 43%, and 97. 92% for imipenem, meropenem, and ertapenem, respectively, demonstrated considerable resistance to even these last-resort antibiotics. This shows that carbapenem-resistant *K. pneumoniae* (KrbR) strains are common in the ICU.

K.pneumoniae isolates in intensive care units typically exhibit the MDR pattern seen here. Amoxicillin, ampicillin, and their inhibitor combinations (such as amoxicillin/clavulanate) were among the beta-lactam antibiotics with the highest levels of resistance. With the presence of ESBL producers, third-generation cephalosporins like cefotaxime, ceftazidime, and ceftriaxone also showed startlingly high resistance rates.

The effectiveness of these alternate treatment options is compromised by the similarly high resistance found for aminoglycosides (gentamicin showed 51.85% resistance) and fluoroquinolones (ciprofloxacin and levofloxacin showed 93.62% and 72.22% resistance, respectively).

Among the tested isolates, Fosfomycin showed no resistance; however, this result is constrained by the small number of isolates assessed using this agent, so it should be interpreted with caution. Similarly, Teicoplanin did not exhibit any resistance; however, considering its primary use against Gram-positive pathogens and the limited testing conducted in this study, its clinical relevance against *K. pneumoniae* is limited.

Overall, these results show that the *K. pneumoniae* isolates in this ICU have important resistance mechanisms that limit treatment options and make clinical management more difficult.

4.3. **Analysis of Antibiotic Resistance Mechanisms**

Resistance mechanisms were identified by examining resistance to key antibiotic groups associated with each mechanism. An isolate was classified as positive for a given mechanism if it exhibited resistance to at least one representative antibiotic from the corresponding group .

Among the 47 *K. pneumoniae* isolates , 36.17% were identified as both ESBL producers and KrbR , confirming the coexistence of these two major resistance mechanisms. Theses isolates displayed extremely high resistance to third-generation cephalosporins, such as ceftriaxone, cefotaxime, and ceftazidime, with resistance rates greater than 95%. Additionally, these isolates demonstrated significant resistance to these antibiotics. the same group showed significant resistance to carbapenems , with 97.92% resistance to ertapenem, imipenem 73.81% , and meropenem 80.43%.

No isolates were found to be positive for other resistance mechanisms such as monobactam resistance (MR), glycopeptide resistance (VanR), inhibitor-resistant beta-lactamases (IBL), or phenotypically confirmed AmpC beta-lactamase production (AmpC-R). However, the high levels of resistance to beta-lactam/beta-lactamase inhibitor combinations suggest that undetected mechanisms such as AmpC or porin loss may still play a role and warrant further molecular investigation.

These findings highlight ESBL and carbapenemase production as the predominant resistance pathways in ICU-acquired *K. pneumoniae* isolates in this study. The simultaneous presence of both in over one-third of the isolates poses serious clinical challenges, limiting treatment options and emphasizing the urgent need for targeted surveillance and antimicrobial stewardship programs.

CHAPTER V

Discussion

Due to its clinical significance as a leading cause of HAIs, particularly in ICUs, *K.pneumoniae* was the focus of this study.The pathogen is well known for its ability to MDR and induce possibly deadly illnesses such as pneumonia, urinary tract infections, and bloodstream infections. It belongs to the ESKAPE group of pathogens, which are notorious for avoiding hospital infection control and antibiotic treatments (Boucher et al., 2009). Because of its rising incidence in nosocomial settings, especially in our area, and the dearth of adequate local surveillance data describing its resistance patterns, *K.pneumoniae* was chosen as the focus of this investigation. The above-mentioned study sought to decipher The frequency and trends of antimicrobial resistance in *K.pneumoniae* collected from ICU patients at Near East University Hospital in 2024.

Out of 47 isolates, 36.17% were carbapenem resistant and produced ESBL, indicating a high level of MDR. This is a clinical concern because dual resistance severely limits treatment options, especially in critically ill patients who frequently require broad-spectrum antibiotics.

Although cefotaxime showed 100% resistance, this was based on a single isolate, making it statistically unreliable. More meaningful indicators of high resistance were observed with ceftriaxone (97.83%), amoxicillin/clavulanate (97.67%), and ampicillin (97.44%). These results align with the enzymatic degradation properties of ESBLs, which inactivate many β-lactam antibiotics (Rawat and Nair, 2010). The detection of ESBL-producing strains (36.17%) in this particular study is in line with rates reported in other regions, including 40.3% in Saudi Arabia (Alshehri et al., 2024) and widespread ESBL activity in Egyptian ICU settings (Taha et al., 2023).

Carbapenem resistance was also significant, with resistance rates of 73.81% for imipenem, 80.43% for meropenem, and 97.92% for ertapenem. These findings confirm the presence of carbapenem-resistant *K. pneumoniae* phenotypically in over one-third of isolates. Comparatively, a Turkish study reported resistance rates of 98% to meropenem and 94% to imipenem among ICU isolates (Köse et al., 2023).

This study did not confirm the existence of other resistance mechanisms, such as porin loss (e. g. , OmpK35 and OmpK36) or AmpC βlactamase production, but their potential role in β-lactam and carbapenem resistance cannot be discounted. Several studies have shown that these mechanisms are significant in *K. pneumoniae* multidrug resistance, particularly in isolates that do not produce ESBLs but have high resistance rates (Jacoby, 2009; Codjoe and Donkor, 2017; Zhou et al., 2018). Therefore, molecular characterization is warranted in future studies to elucidate the full spectrum of resistance determinants present in ICU-acquired strains.

In Turkey, a nationwide ICU surveillance study found that more than half of *K. pneumoniae* isolates were carbapenem-resistant, with meropenem and imipenem resistance being especially prevalent (Kose et al., 2023). High resistance was also seen against fluoroquinolones and aminoglycosides, consistent with the broad MDR profiles observed in our study.

Northern Cyprus had slightly lower resistance rates. For example, a study conducted from 2016 to 2022 found a 42.6% resistance rate to piperacillin/tazobactam among *K. pneumoniae* isolates from ICU settings, whereas non-ICU settings had significantly lower rates (Ciftci et al., 2022). This indicates that ICU environments play a significant part in resistance development, most likely due to factors such as prolonged hospital stays, increased antibiotic pressure, and frequent invasive procedures.

Longitudinal surveillance studies in Southern Cyprus and Greece have shown that resistance is steadily increasing. A study conducted in Crete (Greece) found that fluoroquinolone resistance among *K. pneumoniae* urinary isolates increased from 33.7% in 2017-2019 to 47.8% in 2020-2022. Similarly, resistance to amoxicillin/clavulanic acid and tigecycline increased significantly (Tsivitanidou et al., 2021).

These regional comparisons emphasize the urgent need for collaborative efforts in antimicrobial surveillance and stewardship. Differences in resistance patterns may stem from variations in antibiotic prescribing, infection control practices, hospital infrastructure, and diagnostic capacity. For example, more rigorous antimicrobial stewardship programs in Southern Cyprus may explain their relatively lower carbapenem resistance rates compared to Turkey. Northern Cyprus, where this study

was conducted, may be undergoing transitional challenges in implementing such policies.

From a clinical standpoint, the high resistance rates to third-generation cephalosporins and carbapenems are particularly alarming, as these antibiotics are typically used for severe infections. Their ineffectiveness necessitates the use of last-resort drugs such as tigecycline and colistin, which are associated with greater toxicity and emerging resistance. The detection of ESBL and carbapenemase-producing *K. pneumoniae* strains in ICU settings underscores the need for comprehensive infection control, molecular diagnostics, and continuous local surveillance.

The overall results show that the MDR profile of *K. pneumoniae* strains acquired in ICUs is alarming. These trends are in line with international reports, like the ECDC's 2022 surveillance, which found that carbapenem resistance was rising throughout Europe, especially in ICUs (ECDC, 2022). A major clinical challenge is the co-occurrence of ESBL and KrbR in more than one-third of isolates, which reduces treatment efficacy, raises healthcare expenses, and requires longer hospital stays.

CHAPTER VI

Conclusion and Recommendations

K.pneumoniae has become one of the most highly dangerous MDR pathogens in critical care units during the last ten years. According to the results of this study, which was conducted in 2024 in the ICU of Near East University Hospital, 47 clinical isolates showed significant resistance rates to fluoroquinolones, aminoglycosides, third-generation cephalosporins, and even carbapenems. Of these isolates, 36.17% showed ESBL activity, and the same percentage showed resistance linked to the production of carbapenemase.

These findings point to a pattern of localized resistance that is primarily caused by enzymatic processes, significantly reducing the range of treatment alternatives. This resistance burden is probably exacerbated by the extensive and frequently uncontrolled use of broad-spectrum antibiotics, particularly in critical care units. The ICU is a hotspot for the emergence and spread of resistance due to its high antibiotic pressure and susceptible patient populations.

The findings underscore the urgent need for medical decisions to be guided by local antimicrobial susceptibility testing. Reliance on microbiological data that reflects the specific resistance landscape within individual hospitals or units can inform more effective empirical therapy and reduce the risk of inappropriate antibiotic use. Therefore, it is crucial to strengthen antimicrobial stewardship programs tailored to ICU settings, implement strict infection control protocols, and promote molecular diagnostic tools to rapidly detect resistance genes such as ESBL and carbapenemases. Furthermore, Northern Cyprus would benefit significantly from the establishment of a comprehensive national antimicrobial resistance monitoring system that ensures timely, accurate, and hospital-specific data. Encouraging continuous medical education and awareness among healthcare professionals, along with public health campaigns to reduce unnecessary antibiotic use, are essential components of a multi-faceted strategy to mitigate the impact of antimicrobial resistance and improve outcomes for critically ill patients.

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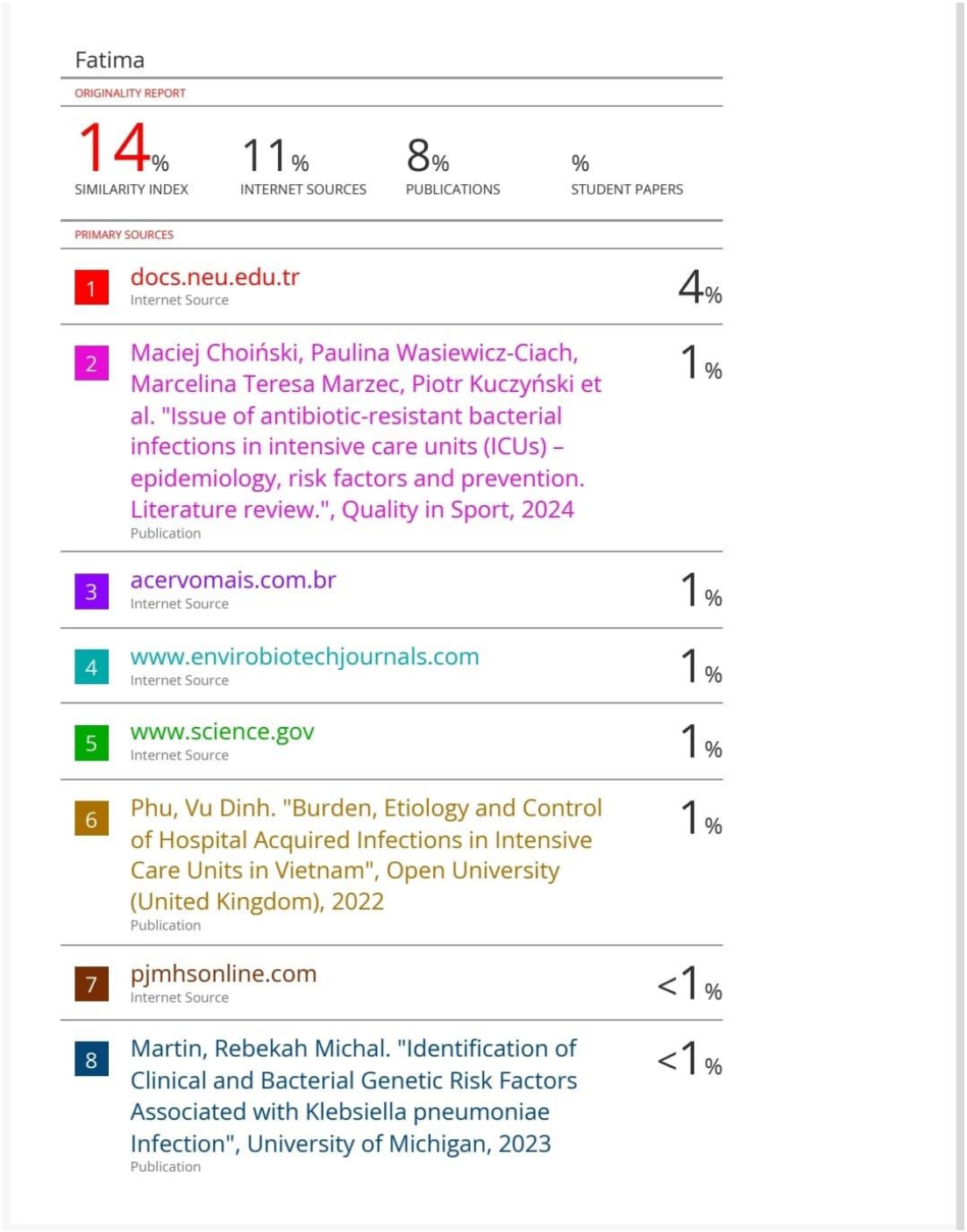
Appendix A



Fatima

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Appendix B

CURRICULUM VITAE

1. PERSONAL INFORAMTION

Name	Fatima Hussien Shehda Manassra
Date of Birth	17/8/1991
Place of Birth	Hebron /Palestine
Nationality	Palestinian
Tel	+972597045857
E-mail	hussien.manasra@yahoo fatimamanasra936@Gmail.com

2. EDUCATION

Degree	Name of the Institution	Graduation year
High school	Bani Naim Girls' Secondary School, Palestine	2009
Undergraduate bachelor's degree MBBCH.	Birzeit University, Ramallah, Palestine	2014
Masters	Near East University, Northern Cyprus	2025

3. WORK EXPERIENCE

Duty	Institution	Year
Filed Observer	Palestinian Central Election Commission, Palestine	2017-2018
Science Teacher	High schools Ramallah, Palestine	2018-2020
Administrative Assistance	Dar Al-Marefa Office Ramallah, Palestine	2020-2022

4. MASTER'S THESIS

Thesis Title	**Evaluation of Hospital-Acquired Infections in the Intensive Care Unit: A Retrospective Study from a University Hospital in Northern Cyprus**
Supervisor	Asst. Prof. Dr. Umut Gazi

5. FIELD OF INTERESTS

E.g., Clinical Microbiology	bacteriology, antibiotics resistance, multidrug resistance bacteria

Appendix C

Ethical approval

NEAR EAST UNIVERSITY
SCIENTIFIC RESEARCH ETHICS COMMITTEE

RESEARCH PROJECT EVALUATION REPORT

Meeting date :30.01.2025
Meeting Number :2025/130
Project number :1919

The project entitled "Evaluation of hospital-acquired infections in the intensive care unit: a retrospective study from a university hospital in Northern Cyprus" (Project no: NEU/2025/130-1919), which will be conducted by Assoc. Prof. Dr. Umut Gazi has been reviewed and approved by the Near East University Scientific Research Ethical Committee.

Prof. Dr. Şanda Çalı
Near East University
Head of Scientific Research Ethics Committee

Committee Member	Role	Meeting Attendance *Attended(✓)/Not attended(X)*	Decision *Approved(✓)/Rejected(X)*
1. Prof. Dr. Şanda Çalı	Head	✓	✓
2. Assoc. Prof. Dr. Gulifeiya Abuduxike	Rapporteur	✓	✓
3. Prof. Dr. Tamer Yılmaz	Member	✓	✓
4. Prof. Dr. Şahan Saygı	Member	✓	✓
5. Prof. Dr. İlker Etikan	Member	✓	✓
6. Assoc. Prof. Dr. Dilek Sarpkaya Güder	Member	✓	✓
7. Prof. Dr. Burçin Şanlıdağ	Member	✓	✓
8. Prof. Dr. Nerin Bahçeciler	Member	✓	✓