An-Najah National University

Faculty of Graduate Studies

EPIDEMIOLOGY OF *ACINETOBACTER BAUMANNII* INFECTIONS AMONG PATIENTS ADMITTED TO THREE INTENSIVE CARE UNITS IN PALESTINE: A RETROSPECTIVE CHART REVIEW STUDY

By

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Dedication

I gratefully dedicate this thesis to my family, whose unwavering support and encouragement have been my greatest strength throughout this journey.

To my supervisors and advisors, thank you for your guidance, wisdom, and belief in my work. Your insights and encouragement have been invaluable.

To my friends and colleagues, whose camaraderie and shared passion have made this research both enjoyable and rewarding, your support has been greatly appreciated.

And to all the patients and healthcare professionals who have faced the challenges posed by *Acinetobacter baumannii*, this work is a tribute to your resilience and dedication.

Shaden Arjan

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Shaden Arjan

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

EPIDEMIOLOGY OF *ACINETOBACTER BAUMANNII* INFECTIONS AMONG PATIENTS ADMITTED TO THREE INTENSIVE CARE UNITS IN PALESTINE: A RETROSPECTIVE CHART REVIEW STUDY

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Shaden Soleman Arjan

Signature: [signature]

Date: 31/10/2024

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Abstract

Background: Multidrug-resistant (MDR) strains of *Acinetobacter baumannii* pose significant treatment challenges. This study aimed to evaluate the sociodemographic and clinical characteristics of patients with *A. baumannii* infections in medical intensive care units (ICUs) across three hospitals in the West Bank, Palestine. It also sought to determine the prevalence of multidrug-resistant and extensively drug-resistant strains and assess patient survival and mortality rates.

Methods: A retrospective cohort design was conducted from 2019 to 2020, spanning a period of two years, and including patients from adult medical ICUs from three hospitals of the north (NICU), the center (CICU), and the south (SICU) of in the West Bank, Palestine. Data on infections acquired during ICU stays or present at admission were analyzed using patient medical records, where sociodemographic, clinical, and treatment-related information, including comorbidities, infection history, diagnostic results, therapies, device usage, and outcomes such as ICU length of stay and mortality, were collected, and prevalence was calculated.

Results: The study encompassed 231 patients, with 136 (58.9%) from CICU Hospital, 56 (24.2%) from SICU Hospital, and 36 (16.9%) from NICU Hospital. The median patient age was 63 years. Prevalence rates of *A. baumannii* infections were (11.5%) at CICU Hospital, (6.5%) at NICU Hospital, and (5.3%) at SICU Hospital, with an overall rate of (8.2%). Of the patients, 46 (19.9%) had infections upon admission, while 185 (80.1%) developed infections during their ICU stay. The isolates included 154 (66.7%) extensively drug-resistant (XDR), 61 (26.4%) multidrug-resistant (MDR), and 16 (6.9%) non-resistant strains. Factors associated with increased mortality included recent ICU admission (2.65 times more likely), heart failure (4.95 times more likely), and central line catheter use (3.46 times more likely). Higher white blood cell counts, lower platelet counts, longer ICU and mechanical ventilation durations, and shorter hospital stays, shorter therapy were linked to survival.

Conclusions: This study provides a comprehensive understanding of *A. baumannii* infections in the medical ICUs, highlighting the critical need for multidisciplinary infection control, especially for critically ill patients with comorbidities. The rise of drug-resistant bacteria underscores the importance of antimicrobial stewardship and infection control. Findings suggest a need for ongoing research and collaboration to address this growing hospital-acquired issue effectively.

Keywords: *Acinetobacter* species, *A. baumannii*, Intensive care unit, infection, Hospital

Chapter One

Introduction and Theoretical Background

1.1 Theoretical basis

A. baumannii is a gram-negative bacterium that pertains to the family *Moraxellaceae* (1). This bacterium is known to withstand harsh environmental conditions like survival for extended period over dry surfaces and human skin (2). These abilities potentiate its persistence and wide spread in hospitals and other healthcare facilities (3, 4). Over the years, misuse of antibiotics and poor management measures have contributed to the appearance of strains including *A. baumannii* strains that exhibit significant resistant to different antibiotics (5, 6). Therefore, the Centers for Disease Control and Prevention (CDC) have recognized *A. baumannii* as an important source of epidemics and outbreaks because of its mounting resistance to many of the available antibiotics (7). Additionally, *A. baumannii* was shown to cause life-threatening infections, including urinary tract infections, meningitis, bloodstream infections, pneumonia, and skin/wound infections (8).

1.2 Problem statement

It is well-established that multidrug resistant strains of *A. baumannii* are difficult to treat. MDR refers to bacteria that are resistant to at least one antibiotic in three or more different classes of antibiotics. Therefore, infections with multidrug resistant strains of *A. baumannii* present a major challenge to providers of healthcare for hospitalized patients, notably, those admitted to the intensive care units. Because patients in the intensive care units are fragile, they could be at higher risk for increased morbidity and mortality in case they acquire *A. baumannii* (9-11).

Lately, description of epidemiology of hospital infections have received considerable attention. In a previous epidemiological analysis of sepsis syndrome among patients in an intensive care unit in Palestine, *Acinetobacter* species caused the majority of the hospital-acquired infections (12). In another respective analysis, medical records of intensive care unit patients with *A. baumannii* infections at An-Najah National University Hospital who were admitted between the year 2015 and 2017 were reviewed for sensitivity tests (13). The analysis was a single center study, included a small number of cases (99 cases), was conducted over a span of 3 years, and did not include analysis of clinical manifestations and survival/mortality rates. Additionally, the previous study did not classify the patients using sequential organ failure assessment score, a tool used to evaluate the extent of organ dysfunction or failure in critically ill patients. Moreover, the study did not include some variables like white blood cells count, platelets count. Similarly, the study did not collect data on the use of corticosteroids, use of antibiotics, immunosuppressant drugs, continuous renal replacement therapy and/or mechanical ventilation. Information of placement of devices like inserted central venous catheter, inserted urinary catheter, and inserted nasogastric tube were not collected. The duration of mechanical ventilation, length of stay in the intensive care unit, length of stay in the hospital, duration of antibiotic therapy, mortality at discharge were also not included in the analysis.

Little research was conducted on the epidemiology of *A. baumannii* infections, specifically among patients admitted to the intensive care units in Palestine. Additionally, little is known on the survival/mortality among patients with *A. baumannii* infections in the Palestinian intensive care units. Furthermore, there is a notable lack of research on extensively drug-resistant (XDR) *A. baumannii*, which refers to strains resistant to at least one agent in all but two or fewer antibiotic categories, complicating treatment options significantly. Therefore, an epidemiological analysis of these infections using recent data would be interesting and informative to the infectious diseases practice in Palestine.

1.3 Study questions/general aims

The research questions of this thesis were posed in the context of the Palestinian healthcare system in the West Bank. This thesis attempted to answer the following research questions:

- What were the sociodemographic and clinical variables of the patients admitted with *A. baumannii* infections or acquired during ICU stay in the medical intensive care units in three different hospitals in the West Bank of Palestine?
- What was the prevalence of multidrug resistant and extensive drug-resistant *A. baumannii* strains in the medical intensive care units in three different hospitals in the West Bank of Palestine?

- What were the clinical manifestations of *A. baumannii* infections among the patients admitted to in the medical intensive care units in three different hospitals in the West Bank of Palestine in relation to their sociodemographic and clinical variables?
- What were the survival/mortality rates among patients with *A. baumannii* infections in the medical intensive care units in three different hospitals in the West Bank of Palestine and what are the predictors of higher survival/mortality?

1.4 Objectives

The study was conducted with the following objectives:

- Assess the sociodemographic and clinical variables of the patients who acquired *A. baumannii* infections in the medical intensive care units in three different hospitals in the West Bank of Palestine.
- Assess the prevalence of multidrug resistant and extensive drug-resistant *A. baumannii* strains in the medical intensive care units in three different hospitals in the West Bank of Palestine.
- Describe the clinical manifestations of *A. baumannii* infections among the patients admitted to in the medical intensive care units in three different hospitals in the West Bank of Palestine in relation to their sociodemographic and clinical variables.
- Determine the survival/mortality rates among patients with *A. baumannii* infections in the medical intensive care units in three different hospitals in the West Bank of Palestine and what are the predictors of higher survival/mortality.

1.5 Importance of the study

In 2019, an outbreak of a novel coronavirus that caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. Later, the virus spread globally and led the World Health Organization (WHO) to declare this global widespread of the virus as COVID-19 pandemic (14). Patients who experienced severe symptoms and manifestations of COVID-19 required admissions to the intensive care units. During the pandemic, the numbers of admissions to the intensive care unit skyrocketed in all healthcare systems around the globe. Patients admitted to the intensive care units often received empiric broad-spectrum antibiotics and other drugs that reduce cytokines (15). The use of empiric broad-spectrum antibiotics and cytokines reducing agents increased the risk of superinfections that are caused by multi-drug-resistant bacteria (15). Infections caused by *A. baumannii* represent a major health concern in patients admitted to the intensive care units. Infections causes by multi-drug-resistant strains were shown to be associated with high mortality rates among patients admitted to the intensive care units. Description of the epidemiology of *A. baumannii* infections among patients admitted to the intensive care units in Palestine could be informative to the clinicians, intensivists, infectious diseases specialists, epidemiologists, and other healthcare professionals and decision makers who might be involved in developing national and local protective measures and antimicrobial use policies.

1.6 Literature review

Acinetobacter species are ubiquitous environmental bacteria that are non-fermentative, aerobic, gram-negative coccobacilli (16). The majority of infections caused by *Acinetobacter* species are opportunistic and mostly affect patients with severe underlying diseases who need prolonged treatment with mechanical ventilation and antimicrobials while staying in the intensive care unit (17). In managing patients with *A. baumannii* in intensive care units, the key controllable factor is antimicrobial treatment. It's essential to avoid unnecessary antibiotics to reduce resistance. Transmission of *A. baumannii* is commonly associated with ventilatory equipment and can be facilitated by contaminated hands of nursing and respiratory staff (16).

The epidemiology of nosocomial respiratory infections with *A. baumannii* has become complex due to the presence of both epidemic and sporadic cases from different strains. This complexity underscores the importance of using molecular typing techniques to identify and control microepidemics early. Nosocomial infections caused by *Acinetobacter* species are associated with high fatality rates, ranging from (30%) to (75%), with the highest mortality observed in ventilator-dependent patients. (18). Like other gram-negative bacilli that take advantage of opportunities, the growing resistance to antibiotics has made it difficult to effectively treat nosocomial infections caused by *Acinetobacter* species.

Usually species of the *Acinetobacter* genus are often found in the soil, water, and animals. *A. baumannii* is mostly discovered in the hospital setting, namely in critical care units (19). In veterinary practice, very ill animals in clinics and intensive care units are increasingly observed to become infected and colonized by *A. baumannii*. Although there are occasional reports of *A. baumannii* in nonhuman sources such as animals, lice, vegetables, aquaculture, and soil, it remains unclear whether these findings are due to environmental contamination from hospital reservoirs or if they point to alternative natural reservoirs for the bacterium (20). This requires further investigation.

The significance of *A. baumannii* in clinical settings has significantly grown since the late 1980s due to the appearance and widespread transmission of three dominant clones (referred to as international clonal lineage) that have the ability to cause hospital outbreaks globally (21). Among these clones, international clonal lineage 1 and international clonal lineage 2 are multidrug-resistant. Currently, the multilocus sequence typing of *A. baumannii* reveals around 400 MLST sequence types. A recent investigation has shown the presence of at least six significant international clonal lineages that are spread throughout different continents globally (21). The six international clonal lineages consist of the three primary outbreak clones that were first detected, and they indicate the concerning appearance of additional epidemic clones. The developing population structure is believed to be caused by a low initial phylogenetic diversity of *A. baumannii*, followed by a fast dissemination after a severe evolutionary bottleneck (21, 22).

A. baumannii is a widely distributed bacterium that thrives in both hospital and community settings, making it a significant nosocomial pathogen. Known for its resistance to last-resort antibiotics such as colistin, tigecycline, and carbapenems, it is a major concern for public health, as highlighted by the WHO and CDC. Its ability to form biofilms, survive harsh conditions, and resist host defenses underscores its persistence and virulence. The plasticity of the bacterium's genome leads to an increased genetic diversity within its strains, which is a major problem in the study and management of this organism. This combination of special features makes *A. baumannii* a dangerous global disease occurrence that needs further, close surveillance (23).

Traditional paradigm regards *A. baumannii* as a Gram-negative bacterium that possesses all of the exhaustion factors as such but very few of the classic virulence determinants. It has been elucidated quite a number of these bacterial structures and more so its mechanisms of surface coating. This paper contains a survey of immune responses elicited to *A. baumannii*, outlines the current status of the problem and gap which exists, and evaluates the current state of different animal models utilized in the exploration of *A. baumannii* (24).

Acinetobacter species especially *A. baumannii* are highly prevalent in the hospitals as well as normal skin, throat and rectal flora or even in food and lice. Since they are often found in intensive care units, they can also transmit from one patient to another through surfaces, equipment and even through wounds. Even though *A. baumannii* is extensively harboring in many patients, invasive pathologies like ventilator-associated pneumonia and bacteremia do occur. Multidrug resistance particularly towards the carbapenems and cephalosporins derives its root from the mechanisms of β-lactamase production, membrane protein alterations, and efflux proteins (25).

A. baumannii is successful multicultural boreal or very poorly acid ecology shape out, undergoes evolution to the harsh test of loyalty through fierce battles of change in surrounding environment.

A. baumannii causes severe hospital-acquired infections like pneumonia and bloodstream infections, especially in patients with preexisting conditions or significant surgery. Infections are linked to prolonged hospital stays and are more common in older males. (10).

A. baumannii can cause community-acquired infections like pneumonia, which constitutes (85%) of such cases, as well as bacteremia, skin infections, and secondary meningitis. These infections are more common in older males with underlying conditions such as diabetes and COPD. Community-acquired pneumonia is often severe, with rapid progression and fatality rates up to (60%), predominantly reported in tropical and subtropical regions during summer (1, 26).

Recent developments link *A. baumannii* infections to injuries in conflict zones and natural disasters, such as the Marmara earthquake. Data suggest that morphine, often used for pain management in these situations, might worsen *A. baumannii* infections due to its immunosuppressive effects. Additionally, the high demand on emergency units during crises can compromise infection control, leading to rapid *A. baumannii* spread and outbreaks, although this is not always a direct cause (27).

The severity of *A. baumannii* infections varies widely, with fatality rates averaging between (8%) and (35%) depending on the strain and infection type (16, 28, 29). Studies using mouse models have shown significant differences in pathogenicity among strains. For example, a multidrug-resistant strain from a blood culture caused an (80%) mortality rate in mice, while a strain causing meningitis resulted in only a (13%) mortality rate. Additionally, strains from international clone 1 and sporadic isolates showed higher virulence compared to those from international clone 3. Variations in mortality rates are linked to different virulence factors; for instance, a mucoid strain had a (48%) mortality rate in a pneumonia model, while a nonmucoid strain had a (19%) rate, despite having the same PFGE profile.

1.6.1 Prevalence of *A. baumannii*

In a retrospective study, *A. baumannii* infections were analyzed over a period of 3-years (2015-2017) (13). The medical records of intensive care unit patients in a single tertiary hospital in Palestine were reviewed for culture and sensitivity test results. The study included 99 patients with a mean age of 59.9 ± 18.8 years. Of the patients, (58.6%) were male and Colistin was the most effective antibiotic. The study did not identify any significant relationships between sensitivity profiles and age, gender, and number of comorbidities.

Ayobami et al. (2019) have also undertaken a detailed systematic review and a meta-analysis of the incidence and prevalence of *A. baumannii* nosocomial infections across Africa, Eastern Mediterranean and Europe. In particular, they underlined the threat these infections cause to health, especially those achieving resistance to carbapenem antibiotics. Moreover, analyzing 24 studies (total, 3,340 records), they demonstrated that *A. baumannii* ICU-associated infections were at 56.5 cases per 1000 young patients and 4.4 cases per 1000 patient-days. It was also reported that rates of healthcare-associated bloodstream infections were between 0.85 and 5.6 cases per 1000 patients. Data on the pre-occupying issue of *A. baumannii* emerged from infection by carbapenems was presented as 41.7/1000 patients and 2.1/1000 patient-days. While *A. baumannii* were responsible for (20.9%) of all infections ‘picked up’ hospital and (13.6%) of carbapenem resistant strains were identified as the causative agent. These results highlight the continuing relevance of *A. baumannii* infections in clinical practice today, especially in hospital settings (18).

Alotaibi et al. (2021) evaluated *A. baumannii* infection in ICU patients accorded at King Fahad University Hospital in Saudi Arabia from the years of 2013 to 2017. Of the 198 patients assessed, the infection had a (3.37%) prevalence with a (40.8%) mortality rate. Most of the patients were male in the mean age of 49 years and younger in the average age of survivors. Therapy was different: 65 patients were on colistin treatment, 22 were on combined treatment with carbapenems and colistin and 18 on carbapenems only. A greater percentage of patients treated with carbapenems survived. The study noted the still great problem how to treat patients with multi-drug-resistant *A. baumannii* as it was health care associated complication with high mortality and long ICU care (30).

Uwingabiye et al. (2017) conducted a study in Morocco regarding *A. baumannii* infections of the Intensive Care Unit patients at a teaching hospital between January 2015 to July 2016. Another retrospective cohort study by Seng et al. conducted within 964 invasive ICU patients reported that 81 (8.4%) of the subjects were found to have *A. baumannii* infections. Several factors responsible for prolonged ICU stay were identified and especially included central lines, mechanical ventilation and prior use of antibiotics, operative room admissions were however beneficial. High mortality rate due to *A. baumannii* infections was (74.1%). Moreover, multivariate analysis has shown higher risk of death associated with septic shock (OR=19.2) and elderly patients aged ≥65 years (OR=4.9). The study concludes that reducing length of stay at the ICU, better use of medical apparatus and correct prescriptions of antimicrobials may reduce infection rates and improve the overall outcome (31).

In another study, El Kettani et al (2017) conducted a study on the detection of *A. baumannii* from blood cultures and its patterns of antibiotics resistance in the intensive care unit of Ibn Rochd University Hospital in Morocco (Casa Blanca). A distinct but complementary design was longitudinal retrospective in nature and it involved the abstraction and analysis of blood cultures from all critical care units at Ibn Rochd University Hospital from 2010 to 2014. Out of the 4232 samples sent to the laboratory, 2402 was found positive for the test. Most of the *A. baumannii* strains that were identified in this study were resistant to the majority of antibiotics tested which include but are not limited to imipenem (75.7%), ceftazidime (85.4%), cefotaxime (98.6%), gentamicin (78.1%), amikacin (63.5%), and finally ciprofloxacin (88.2%) (32).

A study in Tehran, Iran, from July 2005 to November 2006 (33), examined the prevalence of resistant *Acinetobacter baumannii* in a large hospital. Out of 88 strains recovered, most were from respiratory specimens. The bacterium showed high resistance to several antibiotics, including ceftriaxone, piperacillin, ceftazidime, amikacin, and ciprofloxacin. Imipenem was the most effective, with a low resistance rate of (4.5%), while tobramycin had a (44.3%) resistance rate. The study found a correlation between patient demographics, such as age and hospital stay, and the level of antibiotic resistance.

A retrospective study in Turkey from 2003 to 2007 (34), analyzed imipenem-resistant *A. baumannii* (IRAB) infections. Out of 720 patients with 925 infections, most cases were in critical care units, with an occurrence rate of 6.2 per 1000 admissions. Pneumonias and bloodstream infections were most common. The prevalence of imipenem resistance increased significantly from (43.3%) to (72.9%) over the study period. Factors linked to higher mortality included imipenem resistance, extended ICU stays, female gender, older age, and pneumonia. Infections were notably associated with hemodialysis, malignancy, and mechanical ventilation. Strains from pneumonia patients had higher imipenem resistance. Cefoperazone-sulbactam and netilmicin were the most effective treatments. The study highlighted a rising trend in *A. baumannii* infections and imipenem resistance, emphasizing the need for vigilance in patients with specific risk factors.

1.6.2 Antimicrobial resistance and treatment options

A. baumannii poses significant treatment challenges due to its ability to endure in various environments and cause severe healthcare-associated infections. The rise in antimicrobial resistance, particularly to carbapenems, limits treatment options. Addressing this issue requires developing new therapies, evaluating current treatments, and enhancing infection prevention strategies in healthcare settings (35).

The prevalence of certain *A. baumannii* lineages has been associated with the multidrug-resistant phenotype of the infecting strains (11, 34, 36, 37). Currently, it’s unclear if multidrug resistance is a factor in the epidemic spread of *A. baumannii* or a trait of specific strains. Since the 1970s, antimicrobial resistance has increased, with up to (70%) of isolates being multidrug-resistant by 2007, including resistance to carbapenems, affecting both military and civilian settings.

Colistin seems to be the most consistently successful antibiotic in laboratory tests against multidrug-resistant *A. baumannii* (38). However, the use of colistin is linked to various adverse effects and is not appropriate for treating all kinds of infections. There are already global reports of colistin resistance, leading to the development of strains that are resistant to all known antibiotics in some regions. Concerningly, there are indications that resistance is becoming more widespread throughout the population. There have been reports of *Acinetobacter* species that are resistant to carbapenem in cattle and other animals, as well as in the Seine River in Paris, France.

In recent decades, *A. baumannii* has developed resistance to a wide range of antimicrobials (4). The ability of this bacteria to acquire resistance genes, sometimes by horizontal gene transfer, largely determines it’s potential. Recent research indicates that the development of the multidrug-resistant phenotype is a crucial aspect in the success of *A. baumannii* as a pathogen in healthcare settings.

A. baumannii is often seen in ICU patients and those with weakened immune systems. It causes severe infections like ventilator-associated pneumonia and bloodstream infections, leading to higher mortality and longer hospital stays. Key risk factors include previous antibiotic use and prolonged ICU stays. Research is ongoing into new treatments to address its resistance. (2).

A study by Abbo et al. (2005) investigated multidrug-resistant *Acinetobacter baumannii* using epidemiologic methods and PFGE. Analyzing 118 patients across 27 wards, the study identified clusters of infections and ten PFGE clones, with two being most common. Key risk factors included male gender, cardiovascular disease, mechanical ventilation, and metronidazole use, while penicillins provided some protection. The study underscores the challenges in managing *A. baumannii* due to its complex epidemiology and resistance patterns. (9).

The "antibiotic era" may be approaching its end in the near future. The early and apparently unstoppable triumph of antibiotics, a product of human ingenuity, has been met by an increase in resistance mechanisms in bacteria. This situation has been characterized as a "unwinnable conflict". The monitoring efforts have yielded data that demonstrate the rise of several species of bacteria that exhibit resistance to all antibiotics. The genus *Acinetobacter* exemplifies this pattern and warrants further scrutiny. *Acinetobacter* species exhibit resistance mechanisms against all currently available classes of antibiotics, and possess a remarkable ability to acquire novel resistance determinants. The increasing success in treating multidrug-resistant *A. baumannii* in the clinical setting is a daunting truth (39).

A. baumannii infections mainly affect patients with weakened immune systems, severe illnesses, and those with recent invasive procedures or broad-spectrum antibiotic use (34). Therefore, *A. baumannii* infections are prevalent in critical care units, causing ventilator-associated pneumonia, urinary tract infections, and bacteremia. They can also lead to complex skin, soft tissue, gastrointestinal, and central nervous system infections. Recently, *A. baumannii* has emerged as a significant pathogen in conflict-related wounds, with ongoing research focusing on factors influencing its colonization, pathogenicity, and invasion.

Distinguishing between infection and colonization by *Acinetobacter baumannii* can be challenging, and there is ongoing debate about the clinical significance of its presence. Some physicians view the detection of *A. baumannii* in hospitalized patients as an indicator of severe illness, with a fatality rate around (30%). Recent studies, including cases from northern Australia and southern Asia, have reported high fatality rates for community-acquired pneumonia caused by *A. baumannii*. Many patients in these studies also experienced severe complications such as bacteremia, acute respiratory distress syndrome, and disseminated intravascular coagulation. These findings suggest that some strains of *A. baumannii* may have developed enhanced virulence traits, distinguishing them from other *Acinetobacte*r species (4, 11, 18, 28, 29).

Acinetobacter species, particularly *A. baumannii*, have developed resistance to multiple classes of antibiotics. These bacteria are notable for their high capacity for genetic exchange and are classified as "naturally transformable," with *A. baylyi* strain ADP1 showing exceptionally high natural competence and homologous recombination abilities. Strains lacking the mutS gene, which helps repair DNA mismatches, exhibit increased mutation rates. The presence of competence genes such as comFECB and comQLONM aids in the efficient uptake of external DNA. It remains unclear whether other *Acinetobacter* species, including *A. baumannii*, naturally acquire foreign DNA or if environmental factors could be exploited to enhance their pathogenicity and resistance (6, 10, 11, 15, 19, 29, 34).

Recent research analyzing the genome sequences of both susceptible *SDF* and resistant *AYE A. baumannii* isolates has uncovered a high prevalence of resistance genes in the bacterium. The study identified the AbaR1 resistance island in the multidrug-resistant *AYE* isolate, which contains 45 resistance genes, including major beta-lactamases (VEB-1, AmpC, OXA-10), aminoglycoside-modifying enzymes, and tetracycline efflux pumps. This resistance island features mobile genetic elements like transposons and genes previously associated with other bacterial species such as *Pseudomonas, Salmonella*, and *E. coli*. In contrast, the susceptible *SDF* strain had a 20-kb genomic island at the same location, but it lacked resistance genes. The distribution and presence of this extensive resistance region across different multidrug-resistant *A. baumannii* strains remain unclear (4, 27, 37).

A different modern study presents the examination of the *A. baumannii* ATCC 17978 genomic sequence (40). Researchers combined sequencing, insertional mutagenesis, and *C. elegans* virulence tests to create a new pathogenicity assay using *Dictyostelium discoidium*. They found that a 1951 genome sample had 3.98 million base pairs with 3,830 open reading frames, (17%) of which were from potential foreign DNA. Many genes were part of pathogenicity islands, including one similar to type IV secretion systems in *Legionella* and *Coxiella burnetii*. Six of these foreign islands' pathogenic features were confirmed in *C. elegans* using insertional mutagenesis.

A sequence with a similar insertion pattern was identified. The resistance island had a length of 13,277 base pairs and consisted of nine genes. It was situated between the 5′ and 3′ ends of the presumed ATPase gene. Remarkably, just a single gene associated with drug resistance, sulI, was discovered inside this specific region of genetic insertion. *A. baumannii* ATCC 17978 isolate has 74 putative drug resistance genes, which consist of 32 efflux pump genes, 11 permease genes, and 26 genes that encode resistance to heavy metals (41, 42). These results suggest that genes have inserted into this organism in locations other than the specified "hot spot". Due to the unavailability of the whole sequences of the two French isolates, it is currently not possible to compare the resistance and pathogenicity islands.

Resistance to beta-lactams in *A. baumannii* involves multiple mechanisms: beta-lactamases hydrolyze the antibiotics (1). Changes in penicillin-binding proteins (PBPs) hinder their action, structural changes in porin proteins limit antibiotic entry, and efflux pumps expel antibiotics from the cell. Notably, class A extended-spectrum beta-lactamases (ESBLs), such as PER-1, are newly identified in *A. baumannii*, conferring resistance to penicillins and cephalosporins but not to carbapenems. PER-1 is prevalent in Turkey, Korea, France, Belgium, and Bolivia, and was recently reported in the U.S. Other ESBLs found in *A. baumannii* include VEB-1 (in France and Belgium), SHV-12 (in China and the Netherlands), TEM-92 (in Italy), and CTX-M-2 (in Japan and Bolivia), though the spread of CTX-M-2 is less extensive compared to Enterobacteriaceae (43). Clinical identification of ESBLs is challenging due to the presence of chromosomal cephalosporinases and the variability in clinical standards (39, 44).

1.6.3 Prevalence of *A. baumannii* infection in ICU:

A recent study (2019-2021) in an ICU examined multi-drug-resistant *A. baumannii* strains among patients with COVID-19 and other conditions. It found that *A. baumannii* colonization, high serum lactate levels, and steroid use were linked to increased risk of infection and 30-day mortality in COVID-19 patients (45).

In another study, the demographic characteristics, clinical variables, and outcomes of the patients who had *A. baumannii* infections in the intensive care units in Indian were described (46). It was a retrospective study of *A. baumannii* infections in ICU patients from January to December 2009 identified 108 infections in 94 patients, with (76.9%) affecting the respiratory tract. The study found that medical patients were more prone to these infections than surgical patients were, with (63.8%) acquired in the ICU. Infected patients had longer intubation durations, and (70%) of the infections were from multidrug-resistant strains. The overall mortality rate exceeded (70%), linked to improper antimicrobial use and prolonged intubation

In Poland a 6-years single-center retrospective study was conducted to investigate *A. baumannii* infections among patients admitted to the intensive care unit (29). The study also aimed to investigate how the susceptibility of *A. baumannii* to antimicrobials changed over the 6 years period. During the study, there were 183 *A. baumannii* infections. The incidence of *A. baumannii* infections was amounted to 6.4/1000 patient-days. The study showed increase in the percentages of *A. baumannii* infections over the years from 2011 to 2016. The respiratory tract was the primary site of *A. baumannii* infections and the most common infections (73.8%) involved ventilator-associated pneumonia. The majority of *A. baumannii* were considered multidrug-resistant. All *A. baumannii* strains were susceptible to colistin. On the other hand, susceptibility percentages to imipenem, meropenem, amikacin, and ciprofloxacin were (12.3%), (11.5%), (10.7%), and (2.4%).

Chapter Two

Methods

2.1 Study design and settings

This study was conducted in a retrospective cohort design. Patients admitted to the adult medical ICUs at three major governmental hospitals in the north, center, and south of the West Bank of Palestine with *A. baumannii* infections and who acquired infection during ICU stay, (defined as an infection that occurs 48 hours or more after a patient has been admitted to the Intensive Care Unit) were included. The data were collected from three governmental hospitals, south hospital (SICU), center hospital (CICU), and north hospital (NICU).

2.2 Study period

In this study, the files of the patients admitted to the medical intensive care units in the three hospitals in the period between January 2019 and December 2020 were reviewed. This time frame allowed to compare *A. baumannii* infections before and during the COVID-19 pandemic. Also, to assess the impact of the pandemic on ICU infection rates, as the COVID-19 crisis resulted in significant changes to healthcare systems, infection control practices, and the prevalence of hospital-acquired infections, including *A. baumannii***.** In Palestine, the first case of COVID-19 was diagnosed on March 5, 2020. Therefore, the period from the beginning of 2019 up to March 2020 was considered "period before COVID-19" and the period from then until the end of 2020 was considered "period during COVID-19".

2.3 Population

The study population was adult patients (> 18 years) admitted to the medical intensive care units in the three hospitals in the period from the beginning of January 2019 and end December 2020 with *A. baumannii* infections whether admitted with the infection or acquired during the intensive care units stay.

2.4 Selection of the patients and antimicrobial resistance

Adult patients with *A. baumannii* infections admitted with the infection or acquired during the intensive care units stay were included in this study. Clinical presentation of *A. baumannii* infections were considered only if confirmed by a positive culture. Multidrug resistant (MDR) *A. baumannii* strains were considered when the isolates were resistant to three classes or more of antimicrobials: 1) penicillins/cephalosporins, 2) aminoglycosides, and 3) fluoroquinolones (47, 48). Extensively resistant (XDR) *A. baumannii* strains were considered when the isolates were resistant to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories) (49). Resistance to carbapenems was also investigated in this study.

2.5 Sample size and sampling method

In this study, a purposive total population sampling method was used. This means that all patients who were admitted to the medical intensive care units in the three hospitals in the study period were selected. The inclusion and exclusion criteria were applied on the total population of the patients.

2.5.1 Inclusion criteria

The inclusion criteria were:

All adult patients (> 18 years) who were admitted to the medical intensive care units in the three hospitals and had *A. baumannii* infection confirmed by a positive culture either admitted with the infection or acquired during ICU stay regardless of the reason for admission to the intensive care units.

2.5.2 Exclusion criteria

Patients with incomplete files were excluded from this study.

2.6 Data Collection and study tools

The data collection form was developed to collect the following information:

1. Sociodemographic data of the patients like age and gender.
2. Clinical data of the patient,

a. History of hospitalization, hospital to which the patient was admitted, history of admission to the intensive care unit, reason for admission to the intensive care unit.
b. Presence of comorbidities like cardiovascular disease, heart failure, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, chronic liver disease, neurological disease, respiratory disease, COVID-19, cancer.
c. History of infections like previous infection with *A. baumannii,* multidrug-resistant, bloodstream infections, sepsis, other infections and also source of infection and site of infection and *A. baumannii* colonization.
d. Scoring and test results like sequential organ failure assessment score, white blood cells count, platelets count, results of culture and susceptibility tests.
e. Drug use and therapies like chronic use of corticosteroids, use of antibiotics, use of immunosuppressant drugs, continuous renal replacement therapy, use of mechanical ventilation
f. Placement of devices like inserted central venous catheter, inserted urinary catheter, inserted nasogastric tube.
g. Duration of mechanical ventilation, length of stay in the intensive care unit, length of stay in the hospital, duration of steroidal therapy, duration of antibiotic therapy, mortality at discharge from ICU.

2.7 Microbiological methods

In the South Hospital, microbiological samples for culture testing were processed manually. The method involved the direct inoculation of clinical samples, such as blood, urine, sputum, and wound swabs, onto various types of agar plates (e.g., MacConkey agar, Blood agar, and Chocolate agar). The plates were then incubated at specific temperatures based on the suspected organism, and colonies were examined for growth. Bacterial identification was performed through colony morphology, Gram staining, and biochemical testing, which included catalase, oxidase, and urease tests, among others. This traditional method relies heavily on the experience of microbiologists for accurate interpretation of results.

In contrast, the North and Center Hospitals uses the Vitek system for microbiological testing. The Vitek 2 Compact System is an automated microbiological identification and susceptibility testing system that provides faster and more accurate results. After inoculating the clinical samples into specialized Vitek cards, which contain a series of wells with substrates for biochemical reactions, the system performs the tests automatically. The Vitek machine measures changes in the color of the wells, corresponding to bacterial metabolism, and uses this information to identify the microorganism and its antibiotic susceptibility profile. This method significantly reduces the turnaround time for results and increases diagnostic accuracy, compared to manual testing.

2.8 Analysis plan

The data were tabulated using MS Excel and were then entered into IBM SPSS v.22.0. Descriptive statistics and cross-tabulations were used. The data were assessed for normality of distribution using Kolmogorov–Smirnov test. Because the data were not normally distributed, nonparametric tests were used. Categorical data were presented as frequencies (n) and percentages (%). On the other hand, continuous data were expressed using the median with the interquartile range (IQR = Q1, Q3). Distribution of the categorical variables were compared using Chi-square tests or Fisher's exact tests, as appropriate. The variables that were significantly associated in the Chi-square tests or Fisher's exact tests were included in a multivariate analysis to calculate the odds ratios with their (95%) confidence intervals (95% CI).

On the other hand, continuous data were compared using Mann-Whitney U tests or Kruskal-Wallis tests, as appropriate. The variables that were significantly associated in the Mann-Whitney U tests or Kruskal-Wallis tests were included in a multiple linear regression model. A p value of < 0.05 was considered as statistically significant.

Chapter Three

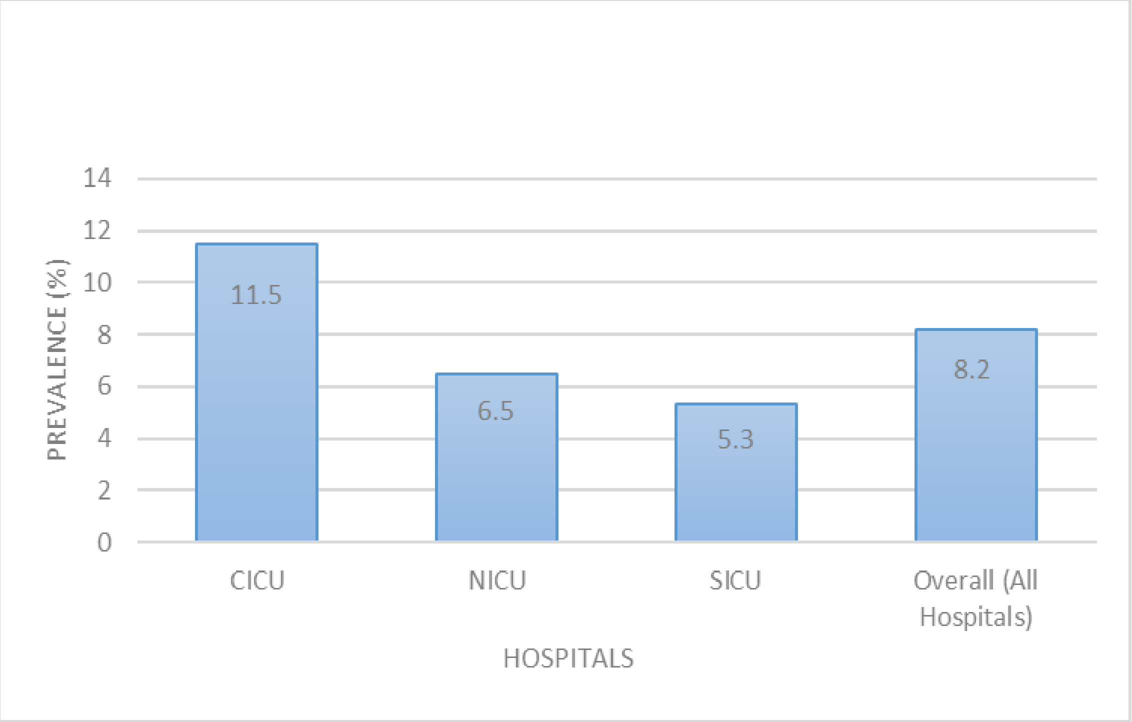
Results

3.1 Prevalence of *A. baumannii* infections in the different study hospitals

The total number of admitted patients to medical ICU in the three hospitals was 2832. Among these patients, 231 patients met the inclusion criteria and their data were analyzed. The overall prevalence rate across all hospitals was (8.2%) (231/2832) (Figure 1). The prevalence rates of *A. baumannii* infections at the CICU was (11.5%) (136/1187), at the NICU was (6.5%) (39/598), and at the SICU was (5.3%) (56/1047).

Figure 1

Prevalence of A. baumannii infections in the different three major governmental hospitals in the north, center, and south of the West Bank of Palestine

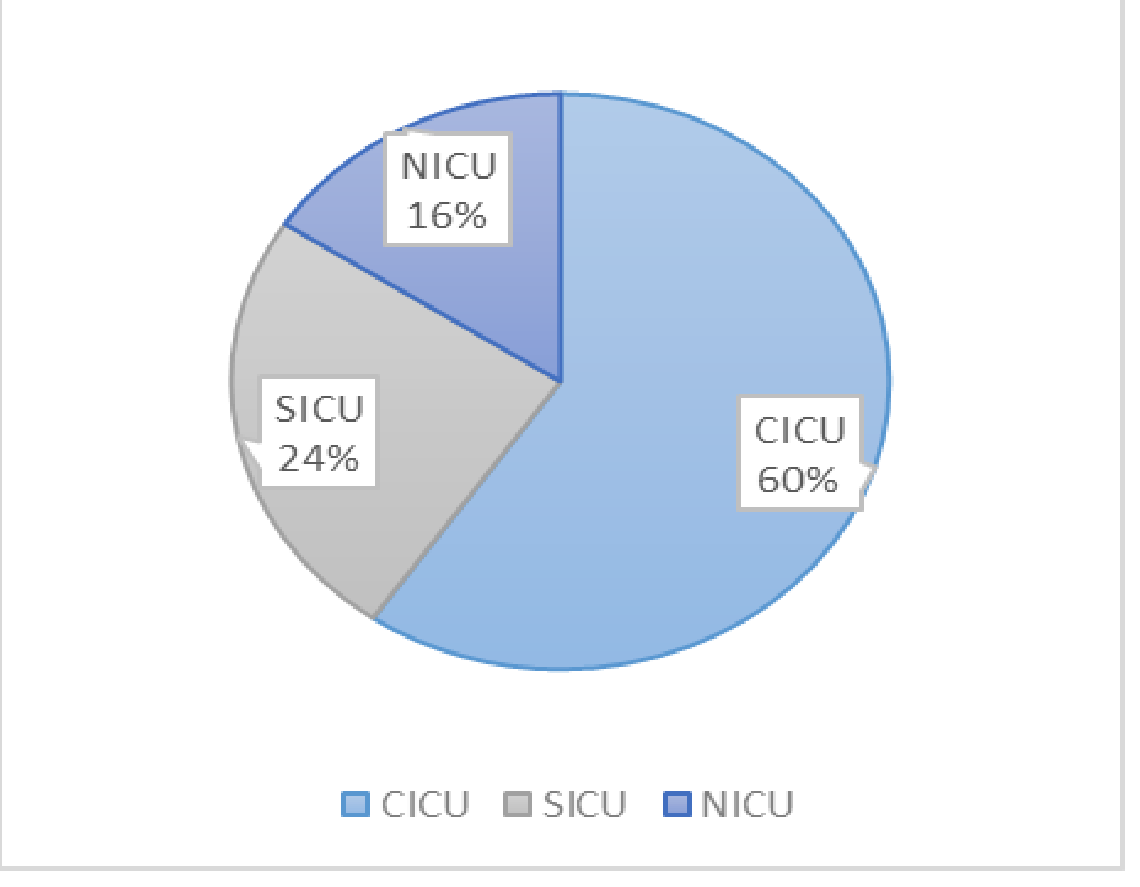


3.2 Demographics and clinical variables of the patients who acquired *A. baumannii* infections

The total number of patients from the different ICUs was 231 patients. Patients from CICU presented (58.9%) (136) of the patients, while (24.2%) (56) were from SICU and (16.9%) (39) were from NICU (Figure 2).

Figure 2

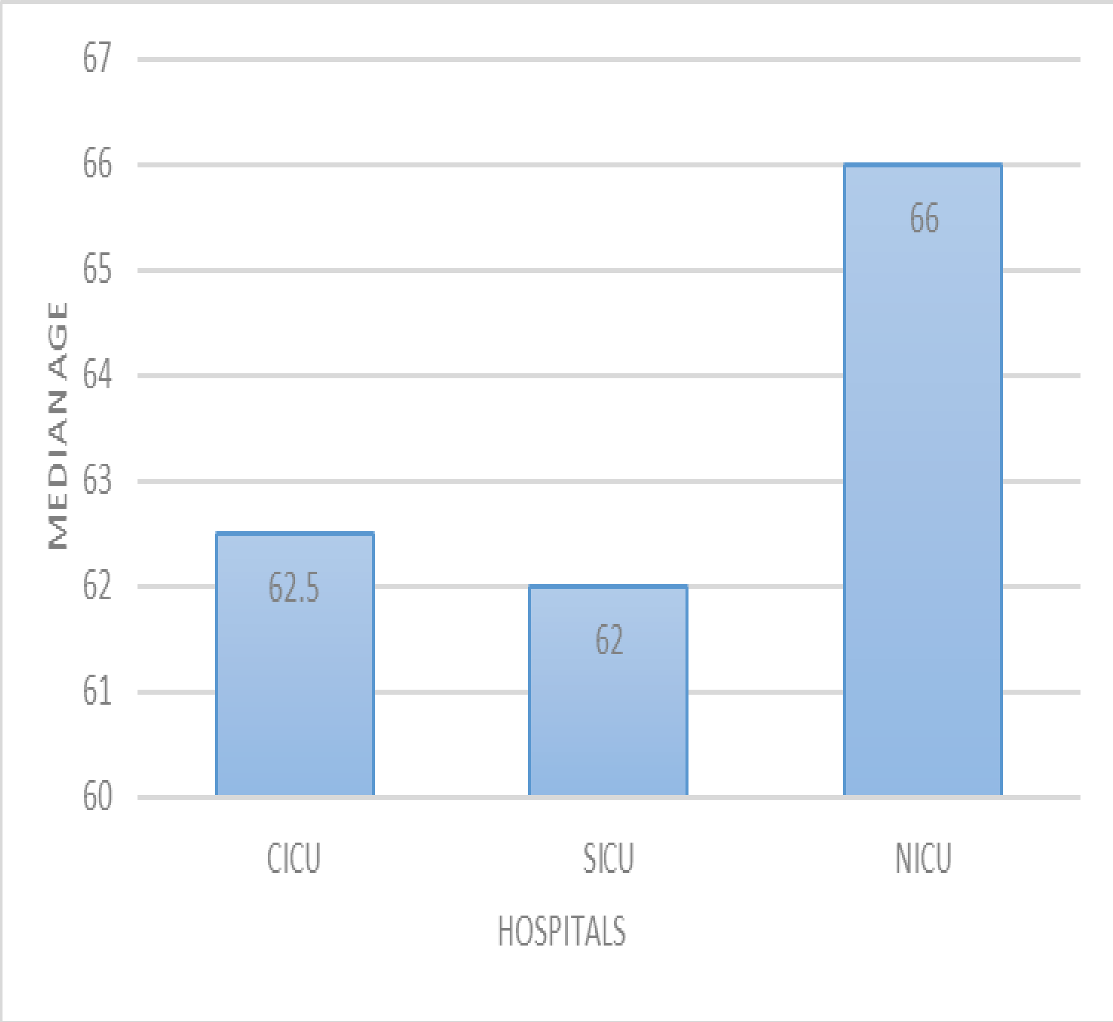
Hospital distribution of the patients with A. baumannii infections



The median age of the patients was 63.0 [IQR = 52.0, 75.0] years. There was no statistical difference (p = 0.769) between the age of the patients who were included from CICU, SICU, and NICU Hospital (62.5 [IQR = 54, 73], 62 [IQR = 37.5, 75.5], and 66 [IQR = 48, 75], respectively). Of the patients, 148 (64.1%) were males, 83 (35.9%) were females, and 87 (37.7%) were smokers (Table 1) (Figure3).

Figure 3

Age distribution of the patients with A. baumannii infections



The majority of the patients suffered from comorbidities, including hypertension (n = 166, 71.9%), hyperlipidemia (n = 150, 64.9%), diabetes mellitus (n = 136, 58.9%), heart failure (n = 105, 45.5%), neurological diseases (n = 80, 34.6%), and respiratory diseases (n = 91, 39.4%). Corticosteroids were administered to 91 (39.4%) patients. The details of the comorbidities that the patients had are shown in Table 1 and Figure 4.

Figure 4

Comorbidities of the patients with A. baumannii infections

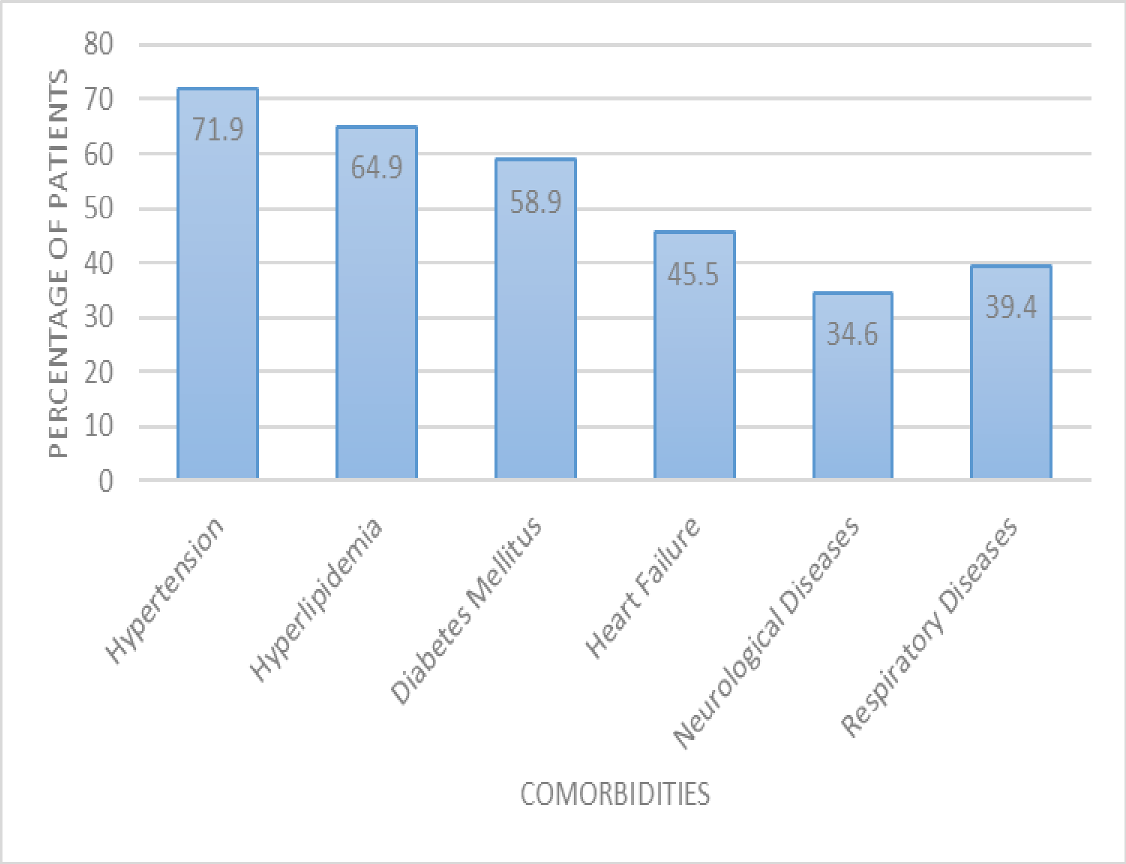


Table 1

Demographics, comorbidities, and use of medications

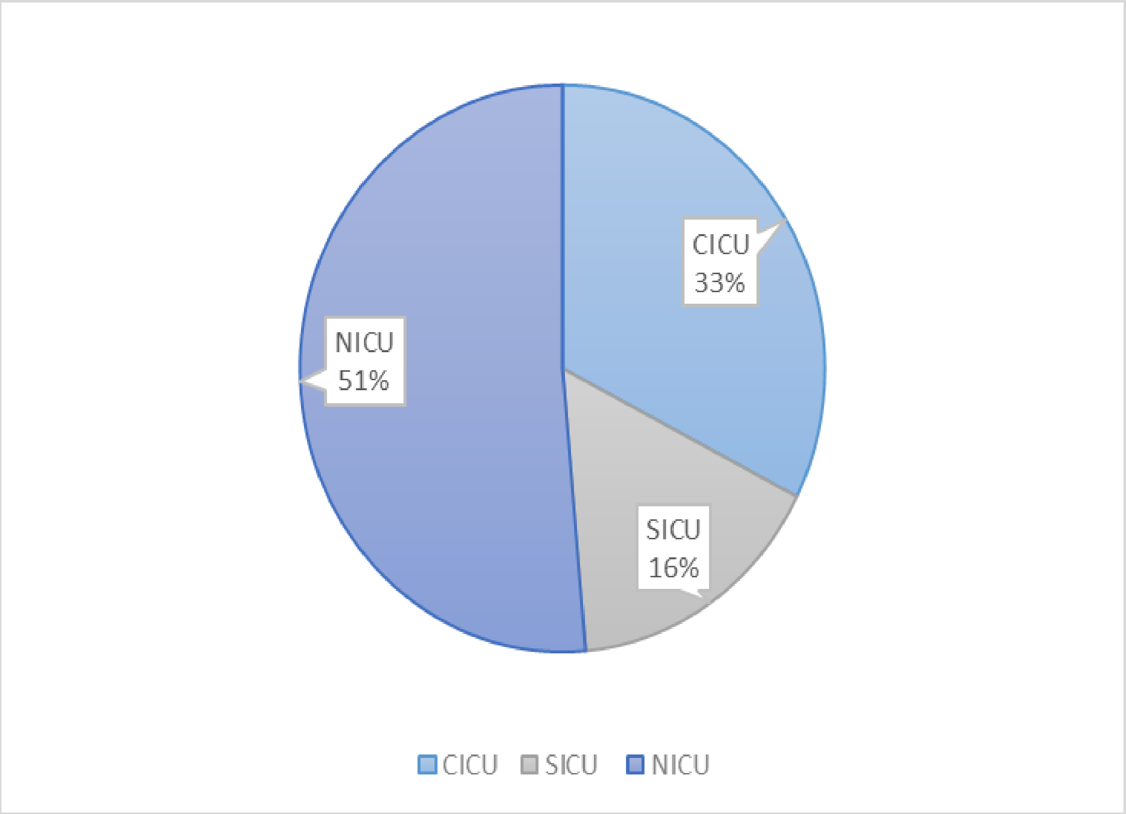
Hospital	CICU (n = 136)	SICU (n = 56)	NICU (n = 39)	Total (n = 231)	p*
Variable					
Gender					
Male	91 (66.9)	32 (57.1)	25 (64.1)	148 (64.1)	0.439
Female	45 (33.1)	24 (42.9)	14 (35.9)	83 (35.9)	
Smoking status					
No	79 (58.1)	37 (66.1)	28 (71.8)	144 (62.3)	0.239
Yes	57 (41.9)	19 (33.9)	11 (28.2)	87 (37.7)	
Comorbidities					
Coronary artery disease	41 (30.1)	17 (30.4)	14 (35.9)	72 (31.2)	0.783
Heart failure	62 (45.6)	24 (42.9)	19 (48.7)	105 (45.5)	0.852
Hypertension	97 (71.3)	37 (66.1)	32 (82.1)	166 (71.9)	0.229
Hyperlipidemia	93 (68.4)	33 (58.9)	24 (61.5)	150 (64.9)	0.408
Diabetes mellitus	79 (58.1)	35 (62.5)	22 (56.4)	136 (58.9)	0.804
Chronic kidney disease	26 (19.1)	11 (19.6)	8 (20.5)	45 (19.5)	0.981
Chronic liver disease	20 (14.7)	4 (7.1)	6 (15.4)	30 (13)	0.325
Neurological disease	48 (35.3)	18 (32.1)	14 (35.9)	80 (34.6)	0.902
Respiratory disease	44 (32.4)	9 (16.1)	20 (51.3)	73 (31.6)	0.001
COVID-19	6 (4.4)	5 (8.9)	6 (15.4)	17 (7.4)	0.136
Cancer	12 (8.8)	3 (5.4)	3 (7.7)	18 (7.8)	0.717
Chronic use of corticosteroids	60 (44.1)	17 (30.4)	14 (35.9)	91 (39.4)	0.184
Use of immunosuppressant drugs	21 (15.4)	5 (8.9)	4 (10.3)	30 (13)	0.396
Continuous renal replacement therapy	21 (15.4)	12 (21.4)	4 (10.3)	37 (16)	0.330

Note**.** COVID-19: Coronavirus disease, CICU: center intensive care unit, NICU: north intensive care unit, SICU: south intensive care unit, *Chi-square/Fisher's exact test

The patients included from the different hospitals were not different in terms of demographics, comorbidities, and use of medications, except for the prevalence of respiratory disease among the patients. The patients who were included from NICU Hospital had significantly more respiratory diseases compared to those included from the other two hospitals (Table 1 and Figure 5).

Figure 5

Prevalence of respiratory disease among the patients who admitted to the three hospitals

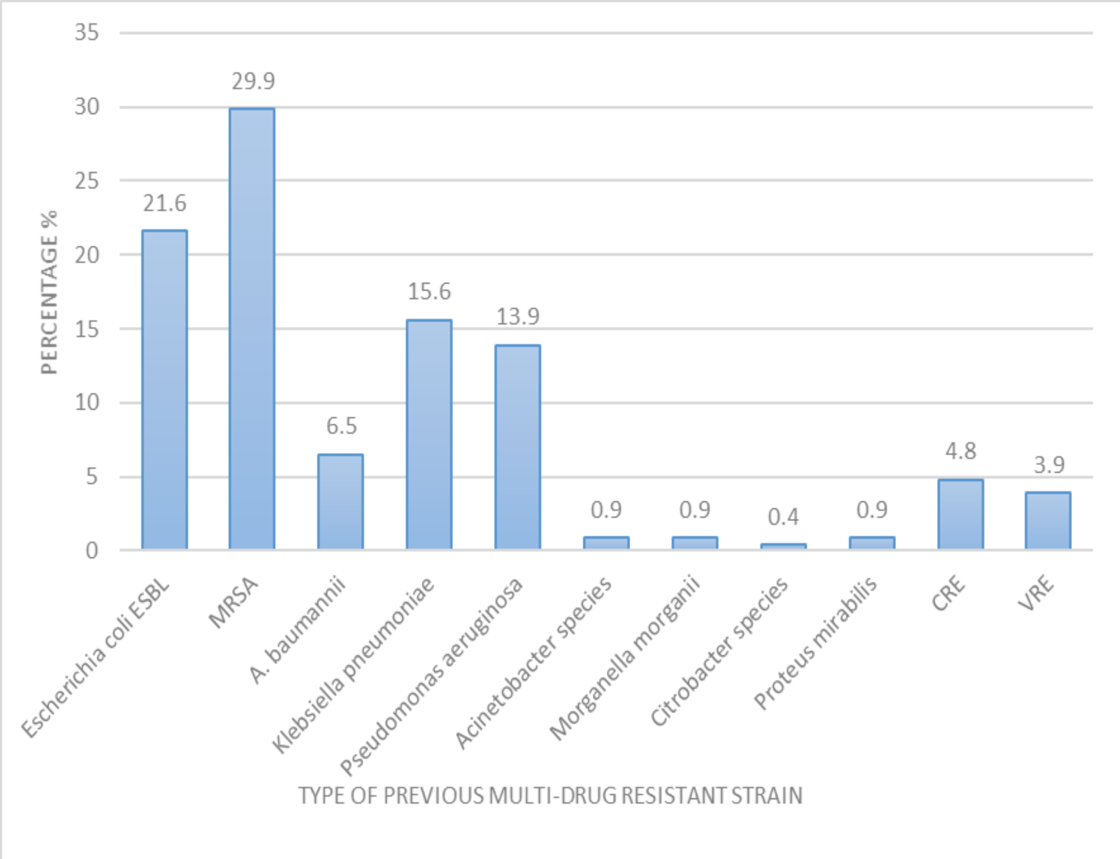


3.3 Use of antibiotics, previous infections with MDR strains, hospitalization, and intensive care unit admission

Of the patients, 156 (67.5%) had used antibiotics in the last 90 days whether intravenous or oral antibiotics and 133 (57.6%) had previous infections with multidrug-resistant strains. There were no statistical differences in the use of antibiotics and having previous infections with multidrug-resistant strains between the patients who were included from the different hospitals (Figure 6).

Figure 6

Percentages of patients with previous infections with multidrug-resistant strains bacteria in Intensive care units



Of the patients, 64 (27.7%) were given previously vancomycin and 40 (17.3%) used piperacillin/tazobactam. The patients from SICU Hospital had received previously (before infection with *A. baumannii)* significantly more piperacillin/tazobactam compared to those from the other two hospitals. On the other hand, the patients who were included from NICU Hospital had used previously colistin, linezolid, and rifampicin (rifampin) compared to those who were from the other two hospitals. Of the patients, 149 (64.5%) were hospitalized in the last 90 days and 56 (24.2%) were admitted to the intensive care unit in the last 90 days, primarily due to infection-related issues. The patients who were included from NICU Hospital had significantly more previous admission to the intensive care unit compared to those who were included from the other two hospitals. There was no statistically significant difference between the intensive care unit admission rates before and after COVID-19. These details are shown in Table 2 and Table 3.

Table 2

Use of antibiotics, previous infections with MDR strains, and intensive care unit admission

Hospital	CICU (n = 136)	SICU (n = 56)	NICU (n = 39)	Total (n = 231)	p*
Variable					
Use of antibiotics in the last 90 days	89 (65.4)	36 (64.3)	31 (79.5)	156 (67.5)	0.214
Previous infection with multidrug-resistant strains	82 (60.3)	35 (62.5)	16 (41)	133 (57.6)	0.069
Type of previous multidrug-resistant strain					
Escherichia coli ESBL	29 (21.3)	15 (26.8)	6 (15.4)	50 (21.6)	0.410
MRSA	42 (30.9)	20 (35.7)	7 (17.9)	69 (29.9)	0.163
A. baumannii	9 (6.6)	4 (7.1)	2 (5.1)	15 (6.5)	0.922
Klebsiella pneumoniae	23 (16.9)	6 (10.7)	7 (17.9)	36 (15.6)	0.507
Pseudomonas aeruginosa	20 (14.7)	10 (17.9)	2 (5.1)	32 (13.9)	0.190
Acinetobacter species	1 (0.7)	1 (1.8)	0 (0)	2 (0.9)	0.631
Morganella morganii	1 (0.7)	1 (1.8)	0 (0)	2 (0.9)	0.631
Citrobacter species	1 (0.7)	0 (0)	0 (0)	1 (0.4)	0.704
Proteus mirabilis	2 (1.5)	0 (0)	0 (0)	2 (0.9)	0.494
CRE	7 (5.1)	4 (7.1)	0 (0)	11 (4.8)	0.260
VRE	6 (4.4)	2 (3.6)	1 (2.6)	9 (3.9)	0.862
Antibiotics used in previous three months					
Penicillin					
Ampicillin	1 (0.7)	0 (0)	0 (0)	1 (0.4)	0.704
Beta-lactams inhibitors					
Piperacillin/tazobactam	24 (17.6)	14 (25)	2 (5.1)	40 (17.3)	0.041
Cephalosporin					
Ceftazidime	14 (10.3)	6 (10.7)	0 (0)	20 (8.7)	0.108
Cefuroxime	1 (0.7)	2 (3.6)	0 (0)	3 (1.3)	0.212
Carbapenems					
Meropenem	13 (9.6)	4 (7.1)	6 (15.4)	23 (10)	0.407
Fluoroquinolones					
Levofloxacin	1 (0.7)	1 (1.8)	0 (0)	2 (0.9)	0.631
Ciprofloxacin	4 (2.9)	1 (1.8)	0 (0)	5 (2.2)	0.525
Aminoglycosides					
Amikacin	15 (11)	4 (7.1)	2 (5.1)	21 (9.1)	0.446
Gentamicin	0 (0)	0 (0)	1 (2.6)	1 (0.4)	0.084
Tetracyclines					
Doxycycline	0 (0)	1 (1.8)	0 (0)	1 (0.4)	0.208
Tetracycline	1 (0.7)	0 (0)	2 (5.1)	3 (1.3)	0.063
Tigecycline	1 (0.7)	0 (0)	0 (0)	1 (0.4)	0.704
Others					
Vancomycin	42 (30.9)	17 (30.4)	5 (12.8)	64 (27.7)	0.074
Trimethoprim/sulfamethoxazole	4 (2.9)	3 (5.4)	0 (0)	7 (3)	0.324
Colistin	2 (1.5)	0 (0)	5 (12.8)	7 (3)	< 0.001
Linezolid	3 (2.2)	0 (0)	6 (15.4)	9 (3.9)	< 0.001
Nitrofurantoin	1 (0.7)	0 (0)	0 (0)	1 (0.4)	0.704
Rifampicin (rifampin)	0 (0)	0 (0)	2 (5.1)	2 (0.9)	0.007
Clindamycin	0 (0)	0 (0)	1 (2.6)	1 (0.4)	0.084

Note**.** CICU: center intensive care unit, NICU: north intensive care unit, SICU: south intensive care unit, CRE: Carbapenem-resistant *Enterobacteriaceae*, ESBL: Extended-spectrum beta-lactamases, MRSA: Methicillin-resistant *Staphylococcus aureus*, *Chi-square/Fisher's exact test

Table 3

Hospitalization and intensive care unit admission reason

Hospital	CICU (n = 136)	SICU (n = 56)	NICU (n = 39)	Total (n = 231)	p*
Variable					
Previous hospitalization in the last 90 days					
Hospital admission	89 (65.4)	32 (57.1)	28 (71.8)	149 (64.5)	0.319
ICU admission	33 (24.3)	12 (21.4)	11 (28.2)	56 (24.2)	0.750
Reason for ICU admission					
Infectious cause	88 (64.7)	27 (48.2)	36 (92.3)	151 (65.4)	< 0.001
Post operation	11 (8.1)	10 (17.9)	0 (0)	21 (9.1)	
Burn	0 (0)	6 (10.7)	0 (0)	6 (2.6)	
Other medical reason	37 (27.2)	13 (23.2)	3 (7.7)	53 (22.9)	
ICU admission year					
2019- march 2020 (before COVID-19)	92 (67.6)	33 (58.9)	26 (66.7)	151 (65.4)	0.505
March 2020 (COVID-19)	44 (32.4)	23 (41.1)	13 (33.3)	80 (34.6)	

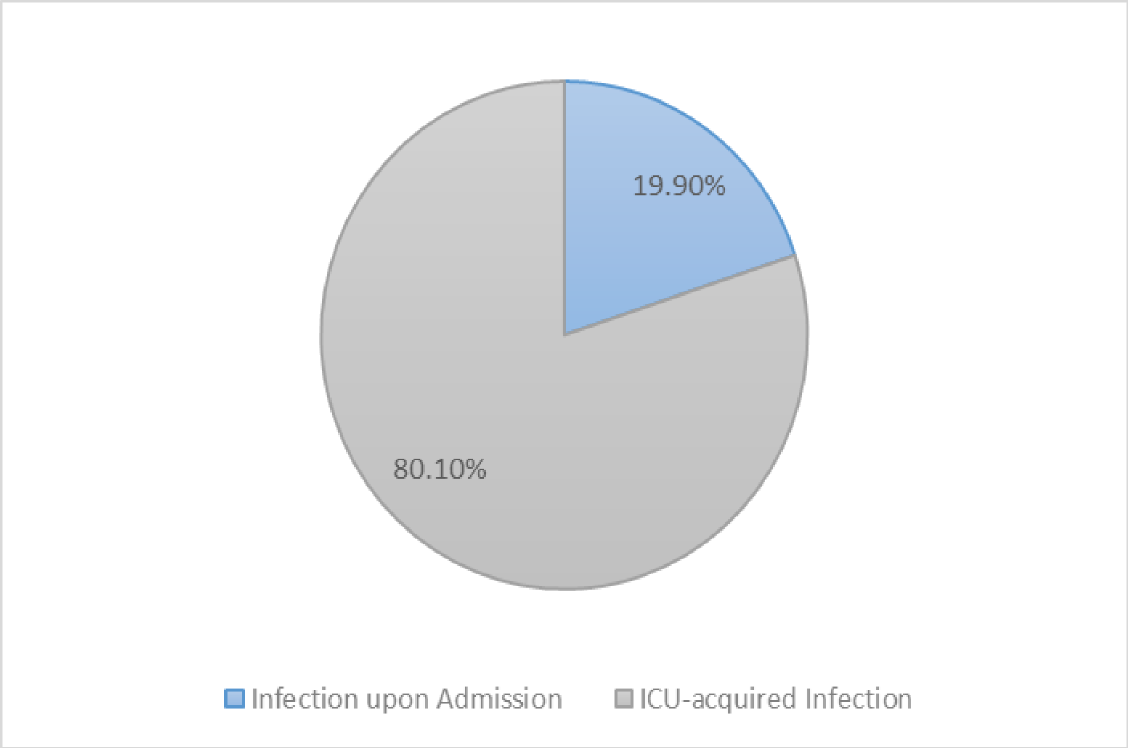
Note. CICU: center intensive care unit, NICU: north intensive care unit, SICU: south intensive care unit, *Chi-square/Fisher's exact test. COVID-19: Coronavirus disease

3.4 Onset of infection, source, susceptibility/resistance pattern, treatment, and outcomes of the patients

In this study, 46 (19.9%) patients had *A. baumannii* infection upon admission and 185 (80.1%) patients had ICU-acquired. *baumannii* infection (Table 4, Table 5, and Figure 7).

Figure 7

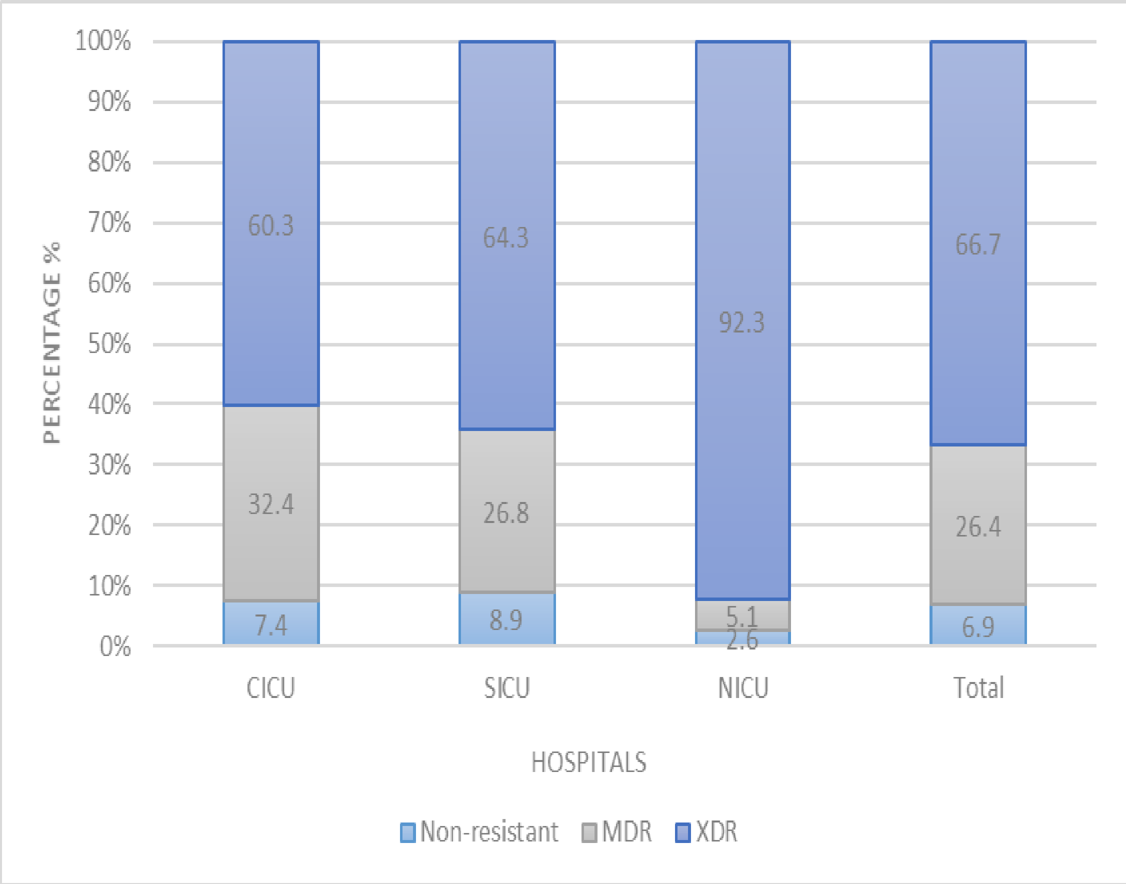
Proportion of A. baumannii Infections: Admission vs. ICU-acquired



Percentage of sputum, wound, urine, and blood cultures were the most common sources of *A. baumannii* isolates. Of the isolates, 154 (66.7%) were XDR, 61 (26.4%) were MDR, and 16 (6.9%) were non-resistant to commonly used antibiotics. The strains isolated from the patients who were included from NICU Hospital were significantly more XDR compared to those who were included from the other two hospitals (Figure 8).

Figure 8

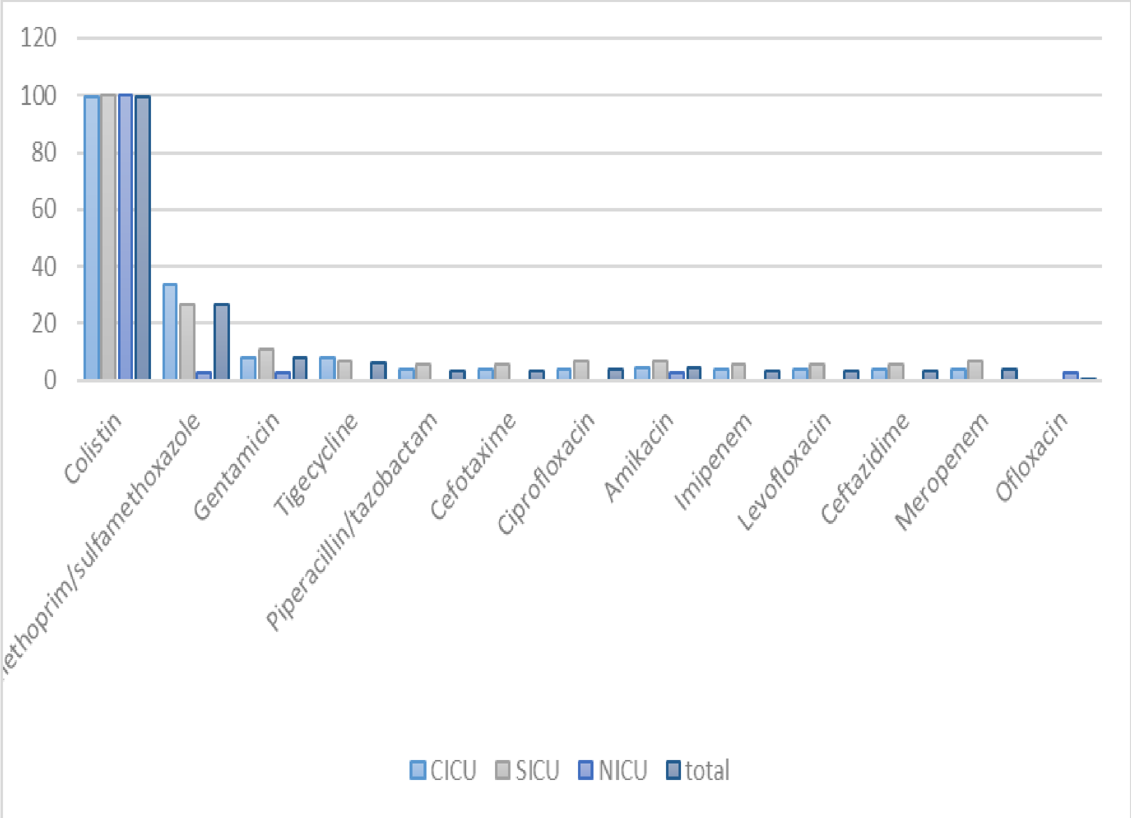
Antibiotic Resistance Type Across Hospitals



The vast majority of the patient's culture results (99.6%) susceptible to colistin and 62 (26.8%) susceptible to trimethoprim/sulfamethoxazole. The patients who were included from NICU Hospital susceptible significantly less trimethoprim/sulfamethoxazole compared to those who were included from the other two hospitals (Figure 9).

Figure 9

Frequency of Antibiotic susceptibility for A. baumannii Patients at SICU, NICU, CICU Hospitals



The patients received antibiotics for a median duration of 9 [IQR = 4, 14] days. There was no significant difference (p = 0.206) between the duration of antibiotic therapy received by the patients who were included from CICU, SICU, and NICU Hospital (10 [IQR = 4, 14], 7.5 [IQR = 2, 13.5], and 8 [IQR = 1, 17], respectively).

Of the patients, 161 (69.7%) received mechanical ventilation. Of the patients, 198 (85.7%) had a central venous catheter inserted. The vast majority of the patients (98.3%) had a urinary catheter inserted. Of the patients, 164 (71.0%) had a nasogastric tube inserted. Significantly, more patients who were included from CICU received central venous catheters, urinary catheters, and nasogastric tubes compared to those who were included from the other two hospitals.

The patients received mechanical ventilation for a median duration of 8 [IQR = 0, 17] days, stayed in the intensive care unit for a median of 15 [8, 23] days, and stayed in the hospital for a median of 18 [IQR = 12, 26] days. The patients who were included from CICU received mechanical ventilation for a significantly (p = 0.006) longer period compared to those who were included from SICU and NICU (10 [IQR = 1.5, 18] vs 4.5 [IQR = 0, 10] and 4 [IQR = 0, 22], respectively). On the other hand, the patients who were included from SICU Hospital stayed in the intensive care unit for shorter durations ($p < 0.001$) compared to those who were included from CICU and NICU hospital (9 [IQR = 6, 16] vs 16 [IQR = 10, 24] and 16 [IQR = 7, 27.5], respectively). Similarly, the patients who were included from SICU Hospital also stayed in the hospital for shorter durations ($p = 0.023$) compared to those who were included from CICU and NICU hospital (16 [IQR = 9.5, 21] vs 19 [IQR = 13, 26.5] and 20 [IQR = 11.5, 28], respectively).

During their stay, the median sequential organ failure assessment score was 12 [IQR = 10, 12]. The patients who were included from SICU Hospital had a significantly lower ($p = 0.006$) sequential organ failure assessment score compared to those who were included from CICU and NICU hospital (11 [IQR = 8, 12] vs 12 [IQR = 11, 12] and 12 [IQR = 11, 13], respectively). The median white blood cells count was 16.5 [IQR = 11.2, 21.7]. The patients who were included from NICU Hospital had a lower white blood cells count ($p = 0.001$) compared to those who were included from CICU and SICU hospital (11.2 [IQR = 8.4, 16.4] vs 16.8 [IQR = 12.9, 21.7] and 17.7 [IQR = 10.6, 25.5], respectively). The median platelets count was 180 [IQR = 120, 266]. There were no statistically significant differences ($p = 0.100$) in the platelets counts between the patients who were included from the different hospitals (185.5 [IQR = 131.5, 267] vs 213 [IQR = 112.5, 265.5], and 158.5 [IQR = 79, 220], respectively). Of the patients, 163 (70.6%) survived and were discharged alive and 68 (29.4%) died in the intensive care unit (Figure 10).

Figure 10

Patient Outcomes for A. baumannii Infections Across Hospitals

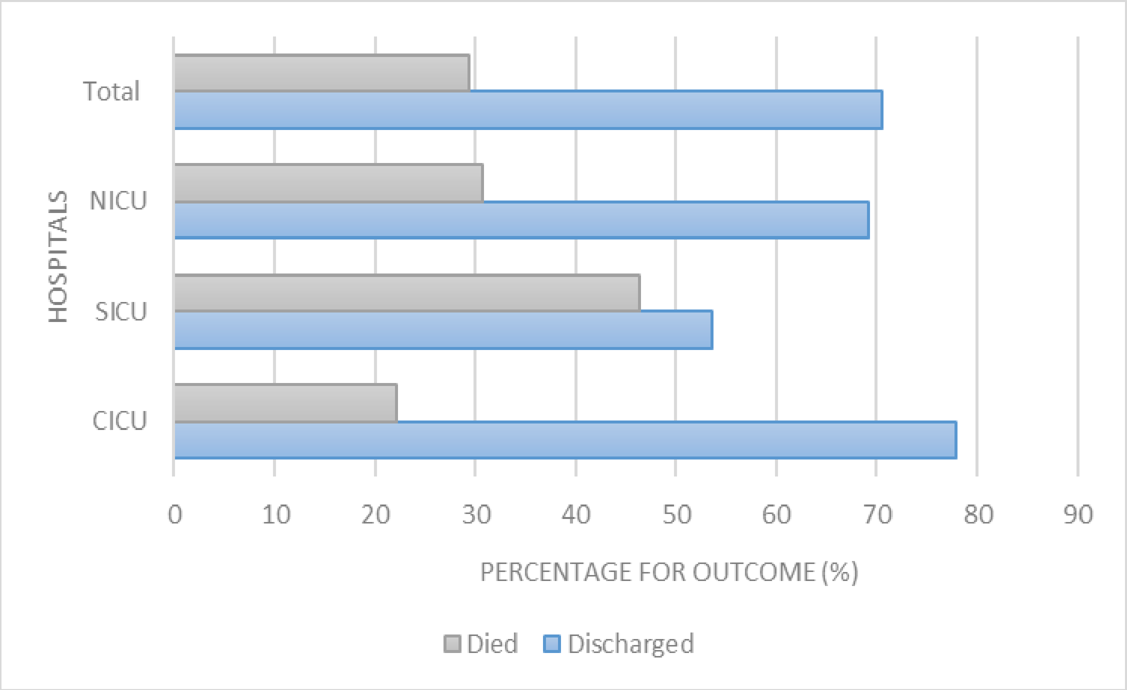


Table 4

Onset of infection, source, and type pf colonization

Hospital	CICU (n = 136)	SICU (n = 56)	NICU (n = 39)	Total (n = 231)	p*
Variable					
Onset of infection					
Present on admission	22 (16.2)	15 (26.8)	9 (23.1)	46 (19.9)	0.213
ICU-acquired	114 (83.8)	41 (73.2)	30 (76.9)	185 (80.1)	
Sources of *A. baumannii* isolated from patients					
Nasal swab colonization	22 (16.2)	9 (16.1)	1 (2.6)	32 (13.9)	0.026
Rectal swab colonization	16 (11.8)	7 (12.5)	1 (2.6)	24 (10.4)	
Vaginal swab	1 (0.7)	0 (0)	0 (0)	1 (0.4)	0.702
Throat swab	0 (0)	3 (5.4)	0 (0)	3 (1.3)	0.009
Sputum culture	88 (64.7)	19 (33.9)	18 (46.2)	125 (54.1)	< 0.001
Urine culture	22 (16.2)	16 (28.6)	7 (17.9)	45 (19.5)	0.145
Blood culture	23 (16.9)	5 (8.9)	15 (38.5)	43 (18.6)	0.005
Wound culture	32 (23.5)	19 (33.9)	7 (17.9)	58 (25.1)	0.173
PEG tube culture	0 (0)	0 (0)	1 (2.6)	1 (0.4)	0.085
Central line culture	0 (0)	0 (0)	1 (2.6)	1 (0.4)	0.085
Missing data	88 (64.7)	33 (58.9)	37 (94.9)	158 (68.4)	
Type of colonization (Swabs done upon admission to ICU)					
Nasal	22 (16.2)	9 (16.1)	1 (2.6)	32 (13.9)	0.026
Rectal	16 (11.8)	7 (12.5)	1 (2.6)	24 (10.4)	

Note**.** CICU: center intensive care unit, NICU: north intensive care unit, SICU: south intensive care unit, MDR: Multi-drug resistant, XDR: extensively drug-resistant, *Chi-square/Fisher's exact test

Table 5

Susceptibility/resistance pattern, treatment, and outcomes of the patients

Hospital	CICU (n = 136)	SICU (n = 56)	NICU (n = 39)	Total (n = 231)	p*
Variable					
Susceptibility/Resistance to antibiotics					
Non-resistant	10 (7.4)	5 (8.9)	1 (2.6)	16 (6.9)	
MDR	44 (32.4)	15 (26.8)	2 (5.1)	61 (26.4)	0.005
XDR	82 (60.3)	36 (64.3)	36 (92.3)	154 (66.7)	
Antibiotics susceptibility for patients with *A. baumannii*					
Beta-lactams					
Beta-lactamase Inhibitors					
Piperacillin/tazobactam	5 (3.7)	3 (5.4)	0 (0)	8 (3.5)	0.365
Cephalosporin					
Cefotaxime	5 (3.7)	3 (5.4)	0 (0)	8 (3.5)	0.365
Ceftazidime	5 (3.7)	3 (5.4)	0 (0)	8 (3.5)	0.365
Carbapenems					
Imipenem	5 (3.7)	3 (5.4)	0 (0)	8 (3.5)	0.365
Meropenem	5 (3.7)	4 (7.1)	0 (0)	9 (3.9)	0.204
Aminoglycosides					
Gentamicin	11 (8.1)	6 (10.7)	1 (2.6)	18 (7.8)	0.339
Amikacin	6 (4.4)	4 (7.1)	1 (2.6)	11 (4.8)	0.562
Fluoroquinolones					
Ciprofloxacin	5 (3.7)	4 (7.1)	0 (0)	9 (3.9)	0.204
Levofloxacin	5 (3.7)	3 (5.4)	0 (0)	8 (3.5)	0.365
Ofloxacin	0 (0)	0 (0)	1 (2.6)	1 (0.4)	0.084
Others					
Colistin	135 (99.3)	56 (100)	39 (100)	230 (99.6)	0.704
Trimethoprim/ sulfamethoxazole	46 (33.8)	15 (26.8)	1 (2.6)	62 (26.8)	0.001
Tigecycline	11 (8.1)	4 (7.1)	0 (0)	15 (6.5)	0.190
Inserted devices					
Use of mechanical ventilation	103 (75.7)	32 (57.1)	26 (66.7)	161 (69.7)	0.035
Inserted central venous catheter	122 (89.7)	44 (78.6)	32 (82.1)	198 (85.7)	0.104
Inserted urinary catheter	136 (100)	54 (96.4)	37 (94.9)	227 (98.3)	0.046
Inserted nasogastric tube	107 (78.7)	32 (57.1)	25 (64.1)	164 (71)	0.007
Outcome					
Discharged	106 (77.9)	30 (53.6)	27 (69.2)	163 (70.6)	0.003
Died	30 (22.1)	26 (46.4)	12 (30.8)	68 (29.4)	

Note**.** CICU: center intensive care unit, NICU: north intensive care unit, SICU: south intensive care unit, MDR: Multi-drug resistant, XDR: extensively drug-resistant, *Chi-square/Fisher's exact test

3.5 Risk of death among the patients

Significant associations between smoking status, intensive care unit admission within the last 90 days, coronary artery disease, heart failure, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, liver disease, and respiratory disease were more likely to die compared to the other patients (Table 6). Similarly, the isolation of *A. baumannii* from sputum and wound culture, continuous renal replacement therapy, hospitalization for infection, mechanical ventilation, a central catheter, and a nasogastric tube significantly correlated with increased mortality. Table 6 displays these details.

Table 6

Univariate analysis of associations between survival/mortality outcomes with the other variables of the patients

Variable	Category	Outcome: Survived n (%)	Outcome: Died n (%)	p*
Smoking	No	109 (47.2)	35 (15.2)	0.028
	Yes	54 (23.4)	33 (14.3)	
Admission to ICU in the last 90 days	No	117 (50.6)	58 (25.1)	0.029
	Yes	46 (19.9)	10 (4.3)	
Coronary artery disease	No	100 (43.3)	59 (25.5)	< 0.001
	Yes	63 (27.3)	9 (3.9)	
Heart failure	No	71 (30.7)	55 (23.8)	< 0.001
	Yes	92 (39.8)	13 (5.6)	
Hypertension	No	38 (16.5)	27 (11.7)	0.012
	Yes	125 (54.1)	41 (17.7)	
Hyperlipidemia	No	47 (20.3)	34 (14.7)	0.002
	Yes	116 (50.2)	34 (14.7)	
Diabetes mellitus	No	59 (25.5)	36 (15.6)	0.018
	Yes	104 (45)	32 (13.9)	
Chronic kidney disease	No	124 (53.7)	62 (26.8)	0.008
	Yes	39 (16.9)	6 (2.6)	
Liver disease	No	137 (59.3)	64 (27.7)	0.038
	Yes	26 (11.3)	4 (1.7)	
Respiratory disease	No	105 (45.5)	53 (22.9)	0.044
	Yes	58 (25.1)	15 (6.5)	
Sputum culture	No	64 (27.7)	42 (18.2)	0.002
	Yes	99 (42.9)	26 (11.3)	
Wound culture	No	128 (55.4)	44 (19)	0.023
	Yes	34 (14.7)	24 (10.4)	
Continuous renal replacement therapy	No	130 (56.3)	64 (27.7)	0.007
	Yes	33 (14.3)	4 (1.7)	
Reason for hospital admission	Infection (sepsis)	118 (51.1)	33 (14.3)	< 0.001
	Post operation	7 (3)	14 (6.1)	
	Burn	1 (0.4)	5 (2.2)	
	Other medical cause	37 (16)	16 (6.9)	
Mechanical ventilation	No	31 (13.4)	39 (16.9)	< 0.001
	Yes	132 (57.1)	29 (12.6)	
Central catheter	No	12 (5.2)	21 (9.1)	< 0.001
	Yes	151 (65.4)	47 (20.3)	
Nasogastric tube	No	31 (13.4)	36 (15.6)	< 0.001
	Yes	132 (57.1)	32 (13.9)	

Note**.** ICU: intensive care unit, *Chi-square/Fisher's exact test

The variables that were significantly associated in the univariate analysis were included in a multivariate logistic regression model (Table 7). The model showed that being admitted to the intensive care unit in the last 90 days was 2.65-times (95% CI = 1.00 to 7.03) more likely to die compared to the patients who were not admitted to the intensive care unit in the last 90 days. In addition, the patients who had heart failure were 4.95-times (95% CI = 1.64 to 14.97) more likely to die compared to the patients who did not have heart failure. Moreover, the patients who received central line catheter were 3.46-times (95% CI = 1.03 to 11.61) more likely to die compared to the patients who did not receive central line catheter.

Table 7

Multivariate logistic regression analysis of associations between survival/mortality outcomes with the other variables of the patients

Variable	Category	β	S.E.	Wald	p	OR	95% C.I. for OR Lower	Upper
Smoking	No	Reference category						
	Yes	-0.45	0.41	1.23	0.268	0.64	0.29	1.42
Admission to ICU in the last 90 days	No	Reference category						
	Yes	0.98	0.50	3.85	0.050	2.65	1.00	7.03
Coronary artery disease	No	Reference category						
	Yes	0.34	0.62	0.31	0.576	1.41	0.42	4.73
Heart failure	No	Reference category						
	Yes	1.60	0.56	8.04	0.005	4.95	1.64	14.97
Hypertension	No	Reference category						
	Yes	-0.25	0.75	0.11	0.740	0.78	0.18	3.37
Hyperlipidemia	No	Reference category						
	Yes	0.44	0.71	0.39	0.530	1.56	0.39	6.23
Diabetes mellitus	No	Reference category						
	Yes	0.19	0.48	0.16	0.692	1.21	0.47	3.10
Chronic kidney disease	No	Reference category						
	Yes	-0.36	1.12	0.10	0.747	0.70	0.08	6.24
Liver disease	No	Reference category						
	Yes	1.23	0.74	2.77	0.096	3.43	0.80	14.63
Respiratory disease	No	Reference category						
	Yes	-0.21	0.49	0.18	0.669	0.81	0.31	2.11
Sputum	No	Reference category						
	Yes	0.13	0.48	0.08	0.782	1.14	0.45	2.92
Wound	No	Reference category						
	Yes	0.12	0.56	0.05	0.825	1.13	0.38	3.39
Continuous renal replacement therapy	No	Reference category						
	Yes	1.10	1.31	0.71	0.398	3.02	0.23	39.04
Reason for hospital admission	Infection	Reference category						
	Post operation	-0.34	0.51	0.44	0.507	0.71	0.27	1.93
	Burn	1.24	0.82	2.26	0.133	3.45	0.69	17.36
	Other medical cause	1.80	1.30	1.90	0.168	6.03	0.47	77.51
Mechanical ventilation	No	Reference category						
	Yes	1.43	1.01	2.01	0.156	4.19	0.58	30.34
Central catheter	No	Reference category						
	Yes	1.24	0.62	4.03	0.045	3.46	1.03	11.61
Nasogastric tube	No	Reference category						
	Yes	0.38	0.96	0.16	0.693	1.46	0.22	9.60

Note**.** ICU: intensive care unit

On the other hand, the patients who died were significantly younger, had lower SOFA score, lower WBCs, higher platelets, and received treatment for a longer period. These details are shown in Table 8.

Table 8

Univariate analysis of associations between survival/mortality outcomes with age, WBCs, platelets, duration of hospitalization, and length of treatment

Variable	Survival/Mortality	Median [Q1, Q3]	p*
Age	Survived	66 [55, 75]	< 0.001
	Died	55 [35, 69]	
SOFA	Survived	12 [11, 13]	< 0.001
	Died	8 [7, 10]	
WBCs	Survived	16.8 [12.2, 22.7]	0.005
	Died	12.9 [9.6, 20]	
Platelets	Survived	166 [98, 231]	< 0.001
	Died	261 [183, 299]	
Duration of mechanical ventilation (days)	Survived	11 [4, 20]	< 0.001
	Died	0 [0, 7]	
Length ICU stay (days)	Survived	16 [10, 24]	0.002
	Died	10 [6, 19]	
Length of hospital stay (days)	Survived	18 [12, 26]	0.779
	Died	19 [12, 26]	
Duration of therapy (days)	Survived	8 [3, 14]	0.047
	Died	12 [7, 14]	

Note**.** SOFA: sequential organ failure assessment score, WBCs: white blood cells, ICU: intensive care unit, Q1: first quartile, Q3: third quartile, *Mann-Whitney U test

Similarly, the variables that were significantly associated in the univariate analysis were included in a multiple linear regression model (Table 9). The model showed that survival was significantly associated with higher SOFA, higher WBCs, lower platelets, longer duration of mechanical ventilation, duration of intensive care unit stay, shorter duration of therapy.

Table 9

Multiple linear regression analysis of associations between survival/mortality outcomes with age, WBCs, platelets, duration of hospitalization, and length of treatment

Variable	Unstandardized Coefficients	S.E.	Standardized Coefficients	t	p
Age	0.00	0.00	-0.07	-1.67	0.097
SOFA	-0.14	0.01	-0.66	-14.70	< 0.001
WBCs	-0.01	0.00	-0.09	-2.24	0.026
Platelets	0.00	0.00	0.10	2.37	0.019
Duration of mechanical ventilation	0.00	0.00	-0.22	-3.16	0.002
Length ICU stay	-0.01	0.00	-0.43	-2.28	0.024
Duration of therapy	0.01	0.00	0.22	3.44	0.001

Note: SOFA: sequential organ failure assessment score, WBCs: white blood cells, ICU: intensive care unit, SE: standard error, t: t-statistics, outcome: mortality

Chapter Four

Discussion

Acinetobacter baumannii is one of the most important threats in ICUs, especially for immunocompromised and critically ill patients. Its ability to survive in healthcare environments and increasing multidrug resistance, including pandrug-resistant strains, has been associated with increased transmission and high mortality rates. With the limited availability of treatment options, combination therapies are generally recommended, which further increases the need for better infection control and therapeutic strategies (50).

The results show an overall incidence of *A. baumannii* infections of (8.2%) in medical ICU patients in three major governmental hospitals located in the West Bank of Palestine. This prevalence is significantly higher than the (3.37%) rate reported in a study from Saudi Arabia, indicating a public health concern in the region (51, 52).

Incidence rates of infection varied between hospitals: (11.5%) at CICU, (6.5%) at NICU Hospital, and (5.3%) at SICU Hospital. This may be attributed to differences in infection control practices, the populations served, or the resources available to the hospitals. One study done in Taiwan found that ICU admission rates may vary between hospitals due to variations in infection control practices (53).

The median age of the patients with the infection was 63 years; (64.1%) of them were men. This is in agreement with reports from other countries' current research that reveal older individuals and males get affected more due to *A. baumannii* (51).

Hypertension was the most frequent comorbidity among the patients (71.9%), followed closely by hyperlipidemia (64.9%) and diabetes mellitus (58.9%). A very well-known risk factor for *A. baumannii infections*, and consequently for acquiring this disease, is the presence of multiple comorbidities, since these diseases can compromise the immune system and lead to susceptibility (54).

The findings concerning the use of antibiotics, previous infections caused by multidrug-resistant (MDR) strains, and episodes of hospitalization reveal important determinants related to the development of *A. baumannii* infections in critically ill patients. A significant number (67.5%) of the subjects in this study had used antibiotics in the previous 90 days, and (57.6%) had previous infections caused by multidrug-resistant strains. The findings are in the line with the known association between recent antibiotic exposure and the risk of developing multidrug-resistant infections. Previous antibiotic therapy is known to disrupt the normal flora, hence predisposing to the colonization of resistant species, including *A. baumannii* (55, 56).

Another important finding that can be drawn from the data is the increased use of certain antibiotics in patients across different healthcare settings. In contrast, patients from SICU Hospital had much exposure to piperacillin/tazobactam, while patients from NICU had more frequent exposure to colistin, linezolid, and rifampicin. This present finding signifies that regional differences in antibiotic usage may be the major cause resulting in resistance to *A. baumannii*. From literature, it is enlightened that *A. baumannii* develops resistance to commonly used antibiotics, specifically piperacillin/tazobactam. Also, treatment with colistin and rifampicin has been reported to have efficacy against the multidrug-resistant strains; however, resistance to these drugs is increasing at the same time (57, 58).

The high percentages of previous hospitalization (64.5%) and intensive care unit admissions (24.2%) underlined the fact that critically ill patients were easily afflicted with infections due to *A. baumannii*. Nosocomial infections, particularly those caused by multidrug-resistant organisms, are more likely to develop in patients hospitalized and in the ICU, especially those with prolonged stays (59). The results are in line with previous studies showing that patients in the ICU are more prone to acquiring *A. baumannii* infections because of invasive procedures, prolonged antibiotic use, and frequent contacts with healthcare staff (60).

Although there were no significant differences in antibiotic use rates or preceding MDR infections between hospitals, differences in specific antibiotic use and ICU admissions suggest that hospital-specific factors may influence the prevalence and spread of *A. baumannii* and suggests discrepancies in hospital antibiotic policies through the implementation of Antibiotic stewardship program. These findings strongly support the need for hospital-level infection control measures and tailored antibiotic stewardship programs to limit the spread of resistance organisms (61).

This will bring out critical results in relation to the challenges encountered in the treatment of such infections in ICUs. The majority of the infections, (80.1%), are acquired in the ICU setting; hence, it poses a very high risk of nosocomial infections in critically ill patients, especially for those who require longer ICU stays, more invasive procedures, and mechanical ventilation. This is consistent with other studies showing that ICU-acquired infections are more likely to be caused by MDR organisms, including *A. baumannii* (62).

The most frequent sites of infection were sputum, wound, urine, and blood cultures. This was similar to the previous study of *A. baumannii* is often associated with respiratory infections, bloodstream infections, and wounds, especially in mechanically ventilated patients and those receiving invasive medical devices (63). The high rate of extended drug-resistant (XDR) strains, (66.7%) of the isolated samples, is of great concern. In relation, the rise in XDR *A. baumannii* has been linked to inadequate treatment options, thus placing a rising threat to health globally (64).

The study has also demonstrated important diversities in resistance patterns across the hospitals. Indeed, patients in NICU Hospital showed a significantly higher proportion of XDR strains compared with the rest of the hospitals. This is indicative of the need for more localized epidemiological surveillance and specific infection control strategies in preventing the spread of resistant strains (61). This presents the variation in susceptibility to trimethoprim/sulfamethoxazole with the most striking finding from NICU, showing reduced susceptibility, and thus perhaps geographical differences in resistance findings possibly related to antibiotic stewardship strategies and the selection pressure from previous antibiotic treatments.

Most patients were treated with an antibiotic average duration of 9 days; however, no significant difference was observed among the different institutes in the length of treatment. Although the causes of mechanical ventilation, central venous catheters, and urinary catheters were similar, their incidence was higher in patients treated at CICU, hence explaining the higher duration of mechanical ventilation in this group. The length of both ICU and hospital stays was longer at CICU compared with those at SICU and NICU Hospitals, reflecting the complex clinical course that developed in patients with

A. baumannii In general, *A. baumannii* infections and the intensity of pre-existing comorbid conditions usually require longer periods of critical care intervention (65).

These findings underline the importance of good infection control practices, appropriate use of antibiotics, and close monitoring of critically ill patients in order to prevent *A. baumannii* infections. The geographic differences in resistance mechanisms and therapeutic strategies further underline the need for institution-specific approaches to fight the spread of resistant *A. baumannii* strains.

The clinical and demographic variables that were found to have a significant influence on mortality risk among patients with *Acinetobacter baumannii* infections included smoking, recent ICU hospitalization, and comorbidities like coronary artery disease, heart failure, diabetes mellitus, and chronic kidney disease. The risks of invasive interventions, such as central venous catheterization, nasogastric tube insertion, and mechanical ventilation, showed an increased mortality rate, which corroborated previous studies from Europe and the Middle East that identified these as prominent risk factors (66, 67). Multivariate analysis showed that ICU admission in the last 90 days was an independent predictor of mortality (OR: 2.65), along with heart failure (OR: 4.95) and use of central line catheter (OR: 3.46), underlining the strong influence of ICU-related exposures and pre-existing cardiovascular conditions on outcomes (68, 69).

Younger patients with low SOFA scores and WBC counts but high platelet levels had high mortality, which was contrary to the prediction and may reflect complexity in disease progression and challenges in treatment. The relationship between longer ICU stays and mechanical ventilation underscores the importance of increased critical care, whereas the relationship between longer antibiotic use and increased mortality points to the need for preventing complications such as drug toxicity and resistance (70, 71).

These findings flag the need for focused infection control measures, especially in institutions with a high prevalence. Implementation of strict infection control measures, including hand hygiene practices, environmental sanitation, and antimicrobial stewardship, will be needed to decrease *A. baumannii* infections (61). The results also have brought into the forefront the real need use invasive devices judiciously, and tailor therapeutic strategies to reduce mortality risks in patients with MDR *A. baumannii* infections at both regional and global levels.

4.1 Strengths of the study

This study had several important strengths. The retrospective cohort design is an appropriate method for analyzing the results of a study conducted over a certain time period, as it enables researchers to use previously collected data to investigate the development and effects of *A. baumannii* infections over time. Additionally, the inclusion of three large public hospitals from different regions of the West Bank—north, center, and south—adds diversity to the patient group and enhances the generalizability of the results.

The study spans two years, from January 2019 to December 2020, providing a thorough understanding of *A. baumannii* infections before and after the COVID-19 pandemic. This timeframe offers valuable insights into how the pandemic influenced infection rates and outcomes. The inclusion and exclusion criteria are clearly defined, ensuring that the patient group is well-defined and relevant to the research.

The data collection form is comprehensive, incorporating a wide range of sociodemographic, clinical, and treatment-related factors. This thorough approach enables an in-depth examination of the elements that influence *A. baumannii* infections and patient outcomes. The use of reliable statistical methods, such as Chi-square, Fisher's exact test, Student t-test, analysis of variance, Pearson's correlations, logistic regression models, and linear regression models, ensures that the findings are robust and trustworthy.

The study specifically focuses on the challenging area of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *A. baumannii.* This is important for understanding resistance patterns and the effectiveness of treatments. Analyzing data from multiple hospitals also allows the identification of variations in infection rates, treatment approaches, and outcomes, which can guide hospital-specific actions and policies.

By considering comorbidities and medication usage, such as corticosteroids and antibiotics, the study enhances its understanding of the underlying factors that affect patient outcomes and the complexity of treating A. baumannii infections. Furthermore, the research distinguishes between infections that were present at the time of admission and those that developed during the hospital stay, which is crucial for understanding the epidemiology and transmission dynamics of *A. baumannii.*

Finally, the study provides precise outcome indicators, such as the length of ICU and hospital stays, the duration of mechanical ventilation, and death rates. These indicators offer a comprehensive view of the impact of *A. baumannii* infections on both patient health and healthcare system resources

4.2 Limitations of the study

This study presents several limitations that should be considered. One of the potential issues is related to the inclusion criteria, which might unintentionally exclude significant cases, such as patients with incomplete medical records, or include cases that do not entirely reflect the target population, like patients who were admitted to the ICU but died on the same day. This could lead to selection bias, which in turn might affect the generalizability of the results.

Another limitation is the study’s limited geographical scope. Although the research incorporates data from three hospitals in different parts of the West Bank, it may not fully represent other geographical regions or healthcare systems. This could restrict the ability to apply the findings to broader settings, particularly those with different healthcare infrastructures or patient populations.

The quality and completeness of the data is another concern, as the study relies heavily on hospital records. This dependence on existing records may result in missing or incomplete data, which could compromise the reliability of the findings and lead to potentially skewed conclusions. Furthermore, despite employing statistical methods to control for various factors, there may still be unmeasured confounders influencing the results, such as differences in healthcare practices, environmental factors, or patient behaviors.

Changes over time also present a challenge. The study was conducted between January 2019 and December 2020, a period during which medical practices, antibiotic resistance patterns, and healthcare regulations likely evolved. These changes could affect the comparability of data collected at different points in time, making it difficult to draw consistent conclusions across the entire study period.

The generalizability of the study's findings may also be limited. Given that the data comes from hospitals in the West Bank, it might not be directly applicable to other regions or countries with different healthcare systems, patient demographics, or local strains of *A. baumannii.* Additionally, there could be biases in how certain factors, such as comorbidities or medication usage, are reported in hospital records, leading to inaccurate data or omissions.

The study also faces challenges in measuring outcomes. For example, the presence of an *A. baumannii* infection is not the only factor influencing outcomes such as the duration of mechanical ventilation or ICU stay. Other variables could affect these outcomes, making the interpretation of the data more complex. Moreover, pinpointing the exact source of infection can be difficult, particularly in cases where there are delays in diagnosis or incomplete infection control data.

The timing of the research is another limitation. Conducted during the COVID-19 pandemic, the study was influenced by significant changes in hospital operations, patient demographics, and infection control measures. This complicates the ability to distinguish the specific effects of *A. baumannii* infections from the broader impacts of the pandemic.

Another potential issue is the risk of overfitting in the statistical models used. With multiple models applied, there is a possibility that the results could be overfitted, particularly if the sample size is too small relative to the number of variables being analyzed. Finally, the variability of resistance patterns poses a limitation. Since resistance patterns can fluctuate over time and vary across locations, the study's findings regarding MDR and XDR *A. baumannii* may not be applicable to other regions or future periods where these patterns could be different

4.3 Recommendations

A multifaceted approach is essential to address all risks related to *A. baumannii* infections. Strengthening infection control measures should be a priority, including strict hand hygiene, a clean environment, implementation of sterilization techniques, and isolation procedures for patients affected by multidrug-resistant organisms. Furthermore, promotion of antimicrobial stewardship by judicious use of antibiotics, monitoring of prescribing patterns, and adjustment of guidelines according to local resistance data is of the essence to contain the development of resistance. A multifaceted approach may also include the reduction in device use to minimize infection risk by avoiding central lines, catheters, and mechanical ventilation when not strictly indicated, as well as timely removal when unnecessary. It includes tailoring treatment modality, for example, combination antibiotic therapy based on susceptibility profiles and exploring alternative options in the case of XDR strains. This will require continuing surveillance of resistance trends at the hospital and regional levels, along with exploration into new therapeutic options, to provide information necessary for intervention strategies. Equally important is the need for professional education in infection control, antimicrobial resistance, and judicious antibiotic use, with increased collaborative multidisciplinary efforts to provide more complete and effective care for patients.

4.4 Conclusion

Infections caused by *A. baumannii* are a serious problem, especially in intensive care units, due to the antibiotic resistance of this pathogen, its environmental tenacity, and also due to an association with a high mortality rate. This study shows an alarming infection rate of (8.2%) of the ICU patients admitted to three West Bank hospitals, which is higher compared to neighboring countries. Principal risk factors, including comorbidities, recent ICU hospitalization, invasive procedures, and antibiotic exposure, make the management of critically sick patients a quite complex task. Geographic variations of resistance patterns therefore indicate the importance of targeted epidemiological monitoring in developing customized treatments.

List of Abbreviations

Abbreviation	Meaning
A. baumannii	*Acinetobacter baumannii*
ADP1	*Acinetobacter baylyi* strain ADP1
β-lactamase	Beta-lactamase
CDC	Centers for Disease Control and Prevention
COPD	Chronic Obstructive Pulmonary Disease
comFECB	Competence genes
CT	Clinical Trials
COVID-19	Coronavirus Disease 2019
CI	Confidence Interval
CRE	Carbapenem-resistant Enterobacteriaceae
ESBLs	Extended-Spectrum Beta-Lactamases
ICU	Intensive Care Unit
IQR	Interquartile Range
IRAB	Imipenem-Resistant *Acinetobacter baumannii*
IQR	Interquartile Range
MDR	Multi Drug-Resistant
MLST	Multi-Locus Sequence Typing
MS Excel	Microsoft Excel
MRSA	Methicillin-Resistant *Staphylococcus aureus*
OR	Odds Ratio
PFGE	Pulsed-Field Gel Electrophoresis
PBPs	Penicillin-Binding Proteins
SOFA	Sequential Organ Failure Assessment
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
VEB-1	Verona Extended Spectrum Beta-Lactamase 1
v.22.0	Version 22.0
WBCs	White Blood Cells
WHO	World Health Organization
XDR	Extensively Drug-Resistant
NICU	North Intensive Care Unit
SICU	South Intensive Care Unit
CICU	Center Intensive Care Unit

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Appendices

Appendix A

Data collection form

Patient Data Collection Form

1. Patient Information

- File Number: ___________________________________
- Hospital: ______________________________________
- Gender: ☐ Male ☐ Female
- Age: ____
  - If in days or months, specify: _______________

2. Medical History

- Smoking Status: ☐ Yes ☐ No
- Previous Hospitalization in the Last 90 Days: ☐ Yes ☐ No
- Previous Admission to the Intensive Care Unit (ICU) in the Last 90 Days: ☐ Yes ☐ No
- Reason for Admission to the ICU: _______________________________________
- Date of Current ICU Admission: ____

3. Health Conditions

- Coronary Artery Disease: ☐ Yes ☐ No
- Heart Failure: ☐ Yes ☐ No
- Hypertension: ☐ Yes ☐ No
- Hyperlipidemia: ☐ Yes ☐ No
- Diabetes Mellitus: ☐ Yes ☐ No
- Chronic Kidney Disease: ☐ Yes ☐ No

- Chronic Liver Disease: ☐ Yes ☐ No s
- Neurological Disease: ☐ Yes ☐ No
- Respiratory Disease: ☐ Yes ☐ No
- COVID-19: ☐ Yes ☐ No
- Date of COVID-19 Confirmation (if applicable): ___________________________
- Cancer: ☐ Yes ☐ No
- Chronic Use of Corticosteroids: ☐ Yes ☐ No
- Use of Antibiotics in the Last 90 Days: ☐ Yes ☐ No
- Previous Infection with *A. baumannii*: ☐ Yes ☐ No
- Infection with Multidrug-Resistant Strains: ☐ Yes ☐ No

4. Infection Details

- Type of Multidrug-Resistant Strain: _____________________________________
- Type of Antibiotic Used: ____
- Suspected Clinical Source of Infection with *A. baumannii*: _________________
- Site of Infection with *A. baumannii*: _____________________________________
- *A. baumannii* Colonization: ☐ Yes ☐ No

5. Diagnostic Data

- Sequential Organ Failure Assessment (SOFA) Score: ______________________
- White Blood Cells Count: _________________________
- Platelets Count: __________________________________
- Susceptibility Tests (details): ____

6. Treatments and Procedures

- Use of Immunosuppressant Drugs: ☐ Yes ☐ No
- Continuous Renal Replacement Therapy: ☐ Yes ☐ No

- Use of Mechanical Ventilation: ☐ Yes ☐ No
- Inserted Central Venous Catheter: ☐ Yes ☐ No
- Inserted Urinary Catheter: ☐ Yes ☐ No
- Inserted Nasogastric Tube: ☐ Yes ☐ No

7. ICU and Hospital Stay

- Duration of Mechanical Ventilation: ____
- Length of Stay in the Intensive Care Unit (ICU): ______________________________
- Length of Stay in the Hospital: ____

8. Antibiotic Therapy

- Patient was Started on (treated) by Susceptible Antibiotic (mainly Colistin):

  ☐ Yes ☐ No

- Duration of Antibiotic Therapy: ____

9. Discharge Information

- Mortality at Discharge: ☐ Alive ☐ Dead

Additional Notes: ____

Appendix B

Study approval 1

جـــامـعـة النـجـــاح الـوطـنـيـة
An-Najah National University
مكتب نائب رئيس الجامعة للشؤون الأكاديمية
Vice President for Academic Affairs Office

الرقم: ن ك ص/ 13ش/2023
التاريخ: 2023/2/12

حضرة الدكتور عبد الله القواسمي المحترم
مدير عام التعليم الطبي- وزارة الصحة

تحية طيبة وبعد،

الموضوع: تسهيل مهمة

نهديكم أطيب التحيات ونعلمكم بأن **شادن سليمان جمعه عرجان** طالبة ماجستير تخصص مكافحة وضبط العدوى وهي بصدد اعداد أطروحة الماجستير الخاصة بها والتي بعنوان " **وبائيات عدوى بكتيريا البوماني بين المرضى الذين تم إدخالهم إلى وحدتين للعناية المركزة في نابلس: تحليل بأثر رجعي بإستخدام الملفات الطبية**" ولإتمام الرسالة تحتاج الطالب إلى الاطلاع على ملفات المرضى في المستشفيات التالية والذين أدخلو إلى العناية المكثفة في العناية المكثفة في عام 2019 2020، مستشفى الوطني – نابلس، مجمع رام الله الطبي – رام الله، مستشفى عاليه – الخليل، علما بأن المعلومات ستستخدم لإغراض البحث العلمي فقط وسيتم المحافظة على السرية التامة للمعلومات.

شاكرين لكم تعاونكم ومساعدتكم للعملية التعليمية.

مع وافر الاحترام والتقدير

نائب الرئيس للشؤون الأكاديمية

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Appendix C

Study approval 2

عطوفة الوكيل المساعد المدير التنفيذي لمجمع فلسطين الطبي المحترم،،،

ق. أ. الوكيل المساعد لشؤون المستشفيات والطوارئ المحترم،،،

الاخ مدير عام الادارة العامة لتكنولوجيا المعلومات المحترم

تحية واحترام-

الموضـــوع: تسهيل مهمة بحث

يرجى تسهيل مهمة الطالبة: شادن سليمان جمعة عرجان- برنامج ماجستير الامراض المعدية- جامعة النجاح، في عمل بحث بعنوان:

" وبائيات عدوى بكتيريا البوماني بين المرضى الذين تم ادخالهم الى وحدتين للعناية المركزة في نابلس: تحليل بأثر رجعي باستخدام الملفات الطبية "

حيث سيتم جمع معلومات من ملفات المرضى الذين ادخلوا الى العناية المكثفة في العام 2019-2020، علما ان البحث تحت اشارف د. رشا الخياط ود. هادي ربيع، وذلك في:

- مستشفى الوطني - مستشفى عالية
- مجمع فلسطين الطبي

على ان يتم الالتزام بأساليب واخلاقيات البحث العلمي، وعدم التعرض للمعلومات الشخصية للمرضى.

على ان يتم تزويد الوزارة بنسخة PDF من نتائج البحث.

مع الاحترام...

وزارة الصحة / الإدارة العامة لتكنولوجيا المعلومات
الرقم: GD-IT 790
التاريخ: 31/6/2023
وارد

د. عبد الله القواسمي

رئيس وحدة التعليم الصحي والبحث العلمي

نسخة: نائب الرئيس للشؤون الاكاديمية المحترم/ جامعة النجاح

جامعة النجاح الوطنية
كلية الدراسات العليا

وبائيات عدوى بكتيريا البوماني بين المرضى الذين تم إدخالهم إلى ثلاث وحدات للعناية المركزة في فلسطين: تحليل بأثر رجعي بإستخدام الملفات الطبية

إِعداد
شادن سليمان جمعة عرجان

إشراف
د. رشا خياط
د. هادي ربيع

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في مكافحة وضبط العدوى، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس – فلسطين.

2024

وبائيات عدوى بكتيريا البوماني بين المرضى الذين تم إدخالهم إلى ثلاث وحدات للعناية المركزة في فلسطين: تحليل بأثر رجعي بإستخدام الملفات الطبية

إِعداد

شادن سليمان جمعة عرجان

إشراف

د. رشا خياط

د. هادي ربيع

الملخص

خلفية الدراسة: من الثابت أن السلالات المقاومة للأدوية المتعددة من الراكدة بومـــاني يصـــعب علاجهـــا. أجريت الدراسة لتقييم: 1) المتغيرات الاجتماعية والديموغرافية والسريرية للمرضى الذين أصيبوا بعـــدوى Acinetobacter baumannii في وحدات العناية المركزة في ثلاثة مستشفيات مختلفة في الضفة الغربيـــة في فلسطين ، 2) انتشار سلالات مقاومة للأدوية المتعددة ومقاومة للأدوية واسعة النطـــاق ، و 3) تحديـــد معدلات البقاء على قيد الحياة / الوفيات بين المرضى.

منهجية الدراسة: أجريت هذه الدراسة في تصميم أترابي بأثر رجعي. تم تضمين المرضى الذين تم إدخالهم إلى وحدات العناية المركزة الباطنية للبالغين في ثلاثة مستشفيات حكومية رئيسية في شمال ووسط وجنـــوب الضفة الغربية في فلسطين المصابين بعدوى الراكدة باوماني. تم جمع البيانات من ثلاثة مستشفيات حكومية من الشمال(العناية المكثفة الشمالية)، الوسط (العناتية المكثفة الوسطية)، والجنوب (العناية المكثفة الجنوبية).

نتائج الدراسة: في هذه الدراسة ، تم تضمين ما مجموعه 231 مريضا. ومن بين هؤلاء، تـــم إدراج 136 (58.9٪) من العناتية المكثفة الوسطية ، و 56 (24.2٪) من العناية المكثفة الجنوبية ، و 36 (16.9٪) من العناية المكثفة الشمالية. كان متوسط عمر المرضى 63.0 [IQR = 52.0، 75.0] سنة. في هذه الدراسة ، كان 46 مريضا (19.9٪) مصابين بعدوى *Acinetobacter baumannii* عند القبـــول و 185 (80.1٪) مريضا يعانون من عدوى *A. baumannii* في المستشفى. من بين العزلات ، كان 154 (66.7٪) XDR

، و 61 (26.4٪) من MDR ، و 16 (6.9٪) غير مقاومة. كان الدخول إلى وحدة العناية المركـــزة فـــي آخر 90 يوما أكثر عرضة للوفاة بمقدار 2.65 مرة (95٪ CI = 1.00 إلى 7.03) مقارنة بالمرضى الذين لم يتم إدخالهم إلى وحدة العناية المركزة في آخر 90 يوما. بالإضافة إلى ذلك ، كان المرضى الذين يعانون من قصور القلب 4.95 مرة (95٪ CI = 1.64 إلى 14.97) أكثر عرضة للوفاة مقارنة بالمرضى الذين لم يكن لديهم قصور في القلب. علاوة على ذلك ، كان المرضى الذين تلقوا قسطرة الخـــط المركـــزي أكثـــر عرضة للوفاة بمقدار 3.46 مرة (95٪ CI = 1.03 إلى 11.61) مقارنة بالمرضى الذين لم يتلقوا قســـطرة الخط المركزي. ارتبط البقاء على قيد الحياة بشكل كبير بارتفاع SOFA ، وارتفاع كرات الدم البيضــــاء ، وانخفاض الصفائح الدموية ، ومدة أطول للتهوية الميكانيكية ، ومدة أطول للإقامة في وحدة العناية المركزة ، ومدة أطول للإقامة في المستشفى ، ومدة أطول للعلاج.

إستنتاجات الدراسة: بشكل عام ، يقدم هذا البحث فهما شاملا لخصائص السكان ، والسمات الطبية ، وطرق العلاج ، ونتائج المرضى الذين يعانون من عدوى *A. baumannii* في مرافق الرعاية الصحية المختلفـــة. تؤكد نتائجنا على الحاجة إلى استخدام تقنيات متعددة التخصصات في السيطرة على العدوى ، خاصـــة فـــي المرضى المصابين بأمراض خطيرة والذين يعانون من أمراض مصاحبة. ويمثل ظهور البكتيريا المقاومـــة للأدوية على نطاق واسع مشكلة كبيرة، تتطلب اهتماما دقيقا بالإشراف على مضادات الميكروبات وأساليب مكافحة العدوى. علاوة على ذلك ، تؤكد النتائج التي توصلنا إليها على العلاقة بين بعض عوامـــل الخطـــر والعلاجات مع الوفيات ، وتزويد الأطباء بمعلومات حول التشخيص وتوجيه العلاجات المركزة لتعزيز نتائج المرضى. باختصار ، تضيف هذه الدراسة إلى الأدبيات الموجودة حول عـــدوى *A. baumannii* ، ممـــا يسلط الضوء على الحاجة إلى البحث المستمر والمبادرات التعاونية للحد من تأثير مرض شائع بشكل متزايد مكتسب من المستشفى.

الكلمات المفتاحية: *A. baumannii*، وحدة العناية المركزة، العدوى، مستشفى.