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NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

THE SPREAD OF *ACINETOBACTER* SPECIES IN NEAR EAST UNIVERSITY HOSPITAL

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20169017

MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY
MASTER THESIS

SUPERVISOR
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NICOSIA
2019

ACKNOWLEDGMENTS

I would like to start by appreciating my supervisor Assoc. Prof.Dr. Kaya SÜER from theInfectious Diseases and Clinical Microbiology, Faculty of Medicine, Near East University.You are also a mentor and a role model to me, thank you for impacting me with so much knowledge and for your time and support.

I would like to thank the entire staff of the Department of Medical Microbiology and Clinical Microbiology, Faculty of Medicine, Near East University. I am grateful to the Head of Department, Prof.Dr.Turgut İMİR for his support.

I would like to thank MSc EmrahGüler for his assistance and support during this study. I would like to thank the entire laboratory staff for their assistance and support during this study.

To my lovely family for all their support and prayers during my study, I am saying a big thank you.

ABSTRACT

Hospital-acquired infections are mostly caused by Gram-negative organisms and are one of the major issues in patient safety. These infections are often associated with the medical processes of hospitals such as invasive medical devices and various surgical procedures. Gram-negative organisms account for most infections in the hospital environment because of their ability to acquire resistant against multiple antibiotics. Among all Gram-negative bacteria, *Acinetobacterbaumannii* is an emerging pathogen that accounts for about 80% of all reported infections. *Acinetobacter* is non-motile, obligate aerobic Gram-negative coccobacillus and are ubiquitous free-living saprophytes. It is commonly transmitted through medical devices such as ventilators, urinary catheters and other invasive devices in hospitals, but its ability to colonize on the skin of individuals often increases the rate of transmission through person to person contact. Patients admitted to Intensive Care Unit (ICU) are at the major risk of getting infected by *A. baumannii* and these include pneumonia, bloodstream infections, wound abscesses, urinary tract infections, etc.

ÖZET

Sağlık Hizmeti ile ilişkili enfeksiyonlar çoğunlukla gram negatif organizmalardan kaynaklanır ve hasta güvenliğindeki en önemli konulardan biridir.Bu enfeksiyonlar sıklıkla invaziv cerrahi prosedürler,çeşitli tıbbi cihaz kullanımı gibi hastanelerin tıbbii şlemleriyle ilişkilidir.Hastane ortamında,birçok antibiyotiğe karşı direnç kazanma yeteneğine sahip Gramnegatif organizmal ar,çoklu antibiyotik dirençli enfeksiyondan sorumludur.Tüm Gram negatif bakteriler arasında *Acinetobacter baumannii* bildirilen tüm enfeksiyonların yaklaşık %80'ini oluşturan yeniden or tayaçıkan bir patojendir.*Acinetobacter baumannii* hareketsiz,zorunlu aerob Gram (-) kokobasildir ve heryerde serbest yaşayabilen saprofitlerdir.Genellikle ventilatasyon cihazları, idrar sondaları ve hastanelerdeki diğer invaziv cihazlar gibi tıbbi cihazlar yoluyla bulaşır,anca k bireylerin cildinde kolonizasyon kabiliyeti çoğu zaman kişiden kişiye bulaşma oranını arttırı r.Genel Yoğun Bakım Ünitesine (YBÜ) başvuran hastalar pnömoni,kan dolaşımı enfeksiyonları,ürinersistemenfeksiyonlarıgibienfeksiyonlarayolaçabilenA. Baumanniiileenfekteolmariskialtındadır.

TABLE OF CONTENTS

CHAPTER ONE

INTRODUCTION

1.1.Introduction

The genus *Acinetobacter* is gram negative coccobacilli, non-motile, catalase positive and oxidase negative bacteria. *Acinetobacterbaumanniiis* one of the established bacteria among nosocomial infections caused by gram negative bacteria, and are predictable opportunistic bacteria in immunocompromised patients. Until a few years back, *Acinetobacter spp.* had been considered as a harmless bacteria with very little clinical relevance, if any and these bacteria were susceptible to commonly used antibiotics so that infections caused by these organisms were treated relatively easily. Recently, *Acinetobacter* infections have increased and gained more attention because of its prolonged environmental survival and tendency to develop drug resistance. *A.baumannii* is ranked second after *Pseudomonas aeruginosa* among the nosocomial pathogens of non-fermentative gram negative bacilli. However, in many clinical laboratories the Non Fermentative Gram Negative Bacilli (NFGNB) other than *Pseudomonas aeruginosa* is not taken as a serious pathogen (Veenu Rama and Arora, 1999).

1.2. Pathogenicity

These bacteria have a range of fermenting agents (factors that make bacteria capable of causing the disease) that qualify them to cause various diseases. For example, they have the ability to stick to hard and dry surfaces. They can get low-concentration nutrients such as iron with high efficiency, adhesion and cell destruction. The ability of some strains to produce digestive enzymes for different gelatin and proteins, thus facilitating the destruction of infected tissues, their ability to colonize the skin of both healthy and sick people. It also has the unique ability to form biofilms,so it is making disposal very difficult. *Acinetobacter* bacteria can infect blood, soft tissue, respiratory tract and urinary tract. Any of the previous infections can lead to septicemia, meningitis, endocarditis and pneumonia.So, it is very dangerous for patients with immunodeficiency.

These bacteria are important in wound infections and burns in particular, which often lead to complicationthat are difficult to control and may lead to death.The most important characteristic of the *Acinetobacterbaumannii* is that it has multipleresistance to antibiotics, making it a challenge in treating patients and in control of infection in hospitals and nursing homes.

According to the World Health Organization (WHO) 2017, *Acinetobacterbaumannii*topped the list of resistant to carbapenems. They were the leading list of pathogens that pose a threat to human health, which require the urgent search for antibiotics.

Death rate and complications of infection and the absence of solutions with available antibiotics make them top of the list.

These bacteria are often not very dangerous in societies, while they are of paramount importance in health care homes, hospitals and clinics. Several studies have shown that the

following groups are more susceptible than others to infection with *Acinetobacterbaumannii:*

a. Severe latent disease, especially cancers of the blood.

b. Patients with serious illnesses who have been admitted to the intensive care unit (ICU).

c. Patients received long-term antibiotic treatment, especially Broad-spectrum antibiotic.

d. Infection or colonization of the respiratory, urinary tract, and digestive system.

e. Burn injuries and surgical wounds (that caused by surgical operations).

f. Patients with diabetes.

g. Patients with chronic lung disease.

h. Transfusion of blood.

i. Intestinal nutrition and contaminated solutions.

j. Conditions of hospitalization.

k. Preterm infants.

1.3.Antibiotics

Antibiotics are the agents that either kill or inhibit the growth of bacteria and they are also called antibacterials. Antibiotics are usually taken orally; however, they can also be administered by injection or applied directly to the affected parts of the body, the antibiotics work against bacteria. A broad-spectrum antibiotic can be used to treat many infections.

More than 25 years ago, it was found that *Acinetobacter* began to resist some antibiotics, including aminopenicillin, the first and second generation of cephalosporin, aminoglycosides, cephamycin, chloramphenicol, and tetracycline. These bacteria were able to keep up with developments through antibiotic resistance, which has been newly developed and has increased in hospitals. According to CDC (CentersOf Disease Control) 63% of *Acinetobacter*bacteria are resistant to multiple antibiotics (and a recent study of 74% of isolates was resistant to many antibiotics). The shortcut term(XDRAB) "intensively drug-resistant *A. baumannii" i*s defined as *A.baumannii* that is resistant to all antibiotics except for polymyxinand tigecycline.

The results of several studies also indicated resistance to carbapenem, the most famous members of carbapenem is imipenem and meropenem. This has caused epidemiological concern because of the importance of this group of antibiotics, which have been considered as a last resort.

1.4. Ongoing problem

Currently one of the most serious problem in modern medicine is facing the continuous rise of bacteria that are resistant to different antimicrobials. It has long been recognized and is apparently increasing. The increasing antimicrobial resistance (AMR) presents a major threat to public health because it reduces the effectiveness of antimicrobial treatment leading to increased morbidity and mortality and health care expenditure. The excessive or over use of antibiotics by humans to treat infections and livestock breeding has led to a large output of resistant bacteria into the environment where resistant bacteria and their genes can spread. World Health Organization(WHO) (Bassetti et al., 2011) has identified antimicrobial resistance as one of the three most important problems facing human health.The most common and serious Multiple Drug Resistance(MDR) bacterial species have been *Enterococcus faecium, Staphylococcus aureus, Klebsiellapneumoniae, Acinetobacterbaumannii, Pseudomonas aeruginosa and Enterobacter spp.*

Acinetobacterbaumannii is one of the sophisticated nosocomial weapons among the *Acinetobacter* species in the health care setting of 21st century. This is because of its multi-drug resistant (MDR) genetic determinates, tolerance to wide range of pH, salinity, humidity and its unique ability to survive on almost all nutrient sources. Although it has been mostly associated with colonization of hospital patients and responsible for nosocomial infection such as bacteremia, urinary tract infection, secondary meningitis, surgical site infection, burn or wound infection and nosocomial and ventilator-associated pneumonia, especially in patients admitted to intensive care units (ICUs) . Several species of microorganisms have

been isolated from different hospitals across the world *A. baumannii*accounts for 2-10% of nosocomial infections in hospital based intensive care units (ICUs).

The β-lactam groups of antibiotics are most frequently prescribed antibiotics in the ICUs throughout the world to treat the gram negative bacterial infections which are favoured because of their efficacy, broad spectra and low toxicity.

The *Acinetobacter*members have an ability to acquire resistance to considerably major classes of antibiotics including newer β lactams. The β lactamase production is the major defense mechanisms in the gram negative bacteria. In early 1970s, the *Acinetobacter* bacterial infection was treated with either alone or in combination with gentamicin, minocycline, nalidixic acid, ampicillin and carbaniciilin. During 1971-1974, these strains became resistant to antibiotics whereas in early 1990s, they were multidrug resistant conferring resistance to penicillins, narrow spectrum to extended spectrum cephalosporins (cephalothin, cefamandole, cefoxitin, cefotaxime and ceftazidime), amino-glycosides, chloramphenicol, tetracycline and fluoroquinolones. Carbapenems are the remaning drug of choice to treat this superbug in late 1990s but carbapenem resistant clones have already emerged.
A public health surveillance study at 40 centers in 12 countries detect that significantly increased in resistance rate in *Acinetobacter* species for meropenem (43.4%) and imipenem (42.5%), (Turner,2008). Theprevalence of imipenem resistance in these species isolated from a burn unit of United States of America was found to be 87% (Sareek et al., 2012). In India, it has been documented that approximately 35% are found to be resistant to carbapenems and these resistance is increasing prominently (Sinha et al., 2007; Uma Karthika et al., 2009).

However the rifampicin was introduced in clinical practice in combination with carbapenems, sulbactam and colistin (Pachon-Ibanez et al., 2010) but resistance is already demonstrated

leaving the only hope of treatment by tigecycline, polymyxin B and colistin. Resistance to these drugs has also been demonstrated and today this pathogen is enormously drug resistant. The rapid spread of multidrug resistant *A. baumannii* (MDRAB) in clinical setting has made choosing an appropriate antibiotic to treat these infections difficult for clinicians.

1.5 Aim and Objectives

The spread of *Acinetobacter spp*. in the Near East University Hospital, Northern Cyprus.

The Aim of this study is to determine the spread of *Acinetobacter spp.*

Objectives:

(i) To determine the spread among male and female patients

(ii) To determine the spread among different age group.

(iii) To determine the outcome of *Acinetobacter spp*. Infection among patients

(iiii) To determine the most place in hospital can infect patients with *Acinetobacter spp.*

CHAPTER TWO

Literature Review

2.1 Epidemiology

Multidrug-resistant *Acinetobacterbaumannii* is a rapidly emerging pathogen in the health care setting where it causes infections that include bacteremia, pneumonia, meningitis, urinary tract infection, and wound infection. The organism's ability to survive under a wide range of environmental conditions and to persist for extended periods of time on surfaces make it a frequent cause of outbreaks of infection and an endemic health care–associated pathogen. In addition to transmission, the emergence of resistance appears in the context of selective pressure of broad-spectrum antimicrobial therapy, such as therapy involving carbapenem or cephalosporin of the third generation.In many health care institutions, *Acinetobacter* infection is endemic and multidrug-resistant, complex epidemiological features and co-existence ofmultiple strain types(Appo et al,2005).

Multi-drug resistant *Acinetobacter* infection has been reported to be among patients residing in rehabilitation and long-term care facilities, as well as in acute care hospitals. Several factors work together to maintain the presence of multidrug resistant *Acinetobacter*species in the health care setting, including the presence of susceptible patients, already colonized or infected with the organism and incomplete compliance with infection control procedures.

The molecule-based PFGE strain (it is a technique used to produce a DNA fingerprint for a bacterial isolate) or other methods can be used to identify outbreaks and control the

transmission ofmultidrug resistant *Acinetobacter* species between institutions, regions and countries.

In Czech Republic(Nemec A,2004), the study used ribotyping and amplified fragment–length polymorphisms to prove the genetic relationship of *Acinetobacter* isolates in western Europe. The researchers used PFGE to demonstrate spread among institutions ofcarbapenem-resistant*Acinetobacter*infection between acute care hospitals in locales including New York, Argentina, the United Kingdom, and the Iberian Peninsula. While a study in Latin America used PFGE to demonstrate the spread of epidemic *Acinetobacter* clones between Brazil and Argentina.

Multidrug-resistant *Acinetobacter* deep wound infections, osteomyelitis, respiratory infections, and bacteremia have been reported among military personnel who suffered painful injuries during the conflicts in Iraq and Afghanistan. Theories that former colonial soldiers are autoinoculated or that *Acinetobacter* species from local soil or water are introduced during traumatic injury have not been supported by cultures of specimens obtained from healthy soldiers, soil samples, water samples, or samples from fresh wounds. Current literature indicates that these injuries are associated with health care and are obtained by soldiers in medical facilities during the process of stabilization, emergency treatment, and evacuation through the military medical system. The possibility of introducing new drug-resistant strains of *Acinetobacter* in hospitals through the return of soldiers is a concern that requires ongoing monitoring and careful attention to infection control measures.

2.2 Impact on Patient Outcome

Because *Acinetobacter* MDR infection usually occurs in patients with severe diseases in the intensive care unit, the associated crude mortality rate is high, ranging from 26% to 68%. However, it has been proven difficult to determine the mortality attributable to these infections, regardless of the underlying disease. Recent studies and systematic reviews(Appo A,2007) have showed that *Acinetobacter*infection or colonization is associated with increased mortality. Many of these studies were limited to small sample sizes, methodologicaldifferences, and failure to adequately control the severity of disease for patients. Other studies showed that Strict control for severity of illness did not find *Acinetobacter* infection to be independently associated with increased mortality.The alternative explanation is that*Acinetobacter* infection is a sign of increased mortality in patients with severe primary disease but not an independent mortality indicator.

Mortality may be related to antimicrobial resistance, efficacy of experimental therapy, and the availability of definitive therapeutic options. A recent matched cohort study from Korea (Kwon KT,2007) found that administration of ineffective empirical antimicrobial therapy for *Acinetobacter* bacteremia was an independent predictor of 30-day mortality. However, other studies have found apoor correlation between patient mortality and experimental selection of antimicrobial agents that had *Acinetobacter* infection resistant.

Acinetobacter infection is associated with increased morbidity and a prolonged length of hospital stay. Retroactively, matched cohort study found that patients with *Acinetobacter* bacteremia had a 5-days excess length of mechanical ventilator

dependence and ICU stay, compared with critically ill patients without *the infection of Acinetobacter(*Blot,Vandewoude,&Colardyn,2007).

Multidrug-resistant *Acinetobacter* infection was found to significantly prolong the stay of the intensive care unit 6-days and the median duration of hospitalization 18-days (Sunenshine,Wright&Maragakis,2007). However, another study by (Garnacho et.al.,2003)found no evidence of a prolonged length of ICU stay for patients with *Acinetobacter* ventilator-associated pneumonia, So the impact on length of stay may depend on the type of infection and the extent of antimicrobial resistance.

2.3 Antimicrobial Resistance

Antimicrobial resistance among *Acinetobacter* species has increased in the past decades. The capacity of *Acinetobacter* species for extensive antimicrobial resistance may be due in part to the organism's relatively impermeable outer membrane and its environmental exposure to a large reservoir of resistance genes(Bonomo&Szabo,2006), the most common definition of multidrug resistance is carbapenem resistance(Falagas,Koletsi&Bliziotis,2006). Some strains are susceptible only to polymyxins-peptide antibiotics that are not routinely used because of earlier reports about toxicities. Strains that show resistance to all antimicrobial agents, including polymyxins, have also been reported in the literature, making treatment of these infections difficult and in some cases impossible(Gales,Jones&Sader,2006).

2.4 Mechanisms of Resistance

Resistance mechanisms for *Acinetobacter* species are similar to those for *Pseudomonas*species. The mechanisms of resistance generally fall into 3 categories:

1- Antimicrobial-inactivating enzymes;

2-Reduced access to bacterial targets; or

3- Mutations that change targets or cellular functions.

Acinetobacter species can acquire resistance genes from other organisms, mutations leading to resistance can develop over time in *Acinetobacter*strains, or sub-populations with previous resistance, may appear and become dominant under selective antimicrobial pressure. The appearance of antimicrobial *Acinetobacter* species is due to both the selective pressure of broad-spectrum antimicrobial use and the transmission of strains between patients, although the relative contributions of these mechanisms are not yet know(Harris,McGregor&Furuno,2006).

2.5Treatment

A.baumannii is considered by the Infectious Diseases Society of America as one of the ‘’red alert” pathogens that significantly threaten the effectiveness of our current antibacterial armamentarium(Peleg et al.,2008), a few antimicrobials can be reliably used for effective treatmentofMDR *Acinetobacter* infections. Since few antimicrobials remain consistently effective in the treatment of nosocomial *Acinetobacter* infections, the search for new drugs and there-evaluation of older agents have become a priority.

Drug of Choice:Drugs of choice and dosage recommendations are not based on rigorous clinical trials but based on in vitro susceptibility surveys. The spread and persistence in geographical locations of particular epidemic lineages of *A. baumannii* means that knowledge

of the prevalent local susceptibility pattern is essential when selecting antibiotic therapy for *Acinetobacter* infection. If susceptible, *A. baumannii* could be readily treated with conventional antibiotics, including 3rd or 4th generation cephalosporins, carbapenems, or fluoroquinolones. Although aminoglycosides may show moderate activity against *A. baumannii* in vitro and in vivo, their use is generally described in combination with other classes of antimicrobial agents for the treatment of bacteremia or meningitis. Some clinical and experimental supports the use of tetracyclines for the treatment of *A. baumannii* infections.

It is important to emphasize that clinical isolates of *A. baumannii* are now frequently MDR, and that some isolates are non-susceptible to all conventional antimicrobial agents. So, full laboratory susceptibility testing is required in order to identify the optimal drug or combination of drugs. In the absence of susceptibility data, a carbapenem had been the empiric drug of choice fortreating *A. baumannii* infection for the past 20 years. However, recent years have seen the emergence and worldwide spread of epidemic lineages with diminished susceptibility to carbapenems. A carbapenem, in combination with another antibiotic class (polymyxins, sulbactam or tigecycline), is probably a better choice for empiric therapy of patients with suspected *A. baumannii* infections before the identification and susceptibility is available. For the treatment of isolates non-susceptible to all conventional antibiotics, the following agents, either alone or in combination, have been used with some success.

a. *Carbapenems* : Increasing antimicrobial resistance leaves few therapeutic options, and there are no well-designed clinical trials to compare treatment regimens for multidrug resistant *Acinetobacter* infection. Available data are from in vitro, animal, and observational studies. Carbapenems remain the treatment of choice if isolates retain susceptibility to this antimicrobial class.

b. Lactamase inhibitors: Particularly sulbactam, have activity against many *Acinetobacter* strains, The presence of β-lactam agent (e.g., ampicillin) in combination with the β-lactamase inhibitor does not appear to contribute activity(Brauers et.al., 2005).
c. Tigecycline:A relatively new glycylcycline agent has bacteriostatic activity against multidrug-resistant *Acinetobacter* species. High-level resistance to tigecycline has been detected among some multidrug-resistant *Acinetobacter* isolates, and there is concern that the organism can rapidly evade this antimicrobial agent by upregulating chromosomally mediated efflux pumps(Navon-Venezia, Leavitt &Carmeli,2007).
d. Aminoglycoside agents such as tobramycin and amikacin are therapeutic options for infection with multidrug-resistant *Acinetobacter*isolates that retain susceptibility. These agents are usually used in conjunction with another active antimicrobial agent.
e. Polymyxin therapy : Given limited therapeutic options, clinicians have returned to the use of polymyxin B or polymyxin E (colistin) for the most drug-resistant *Acinetobacter* infections, Colistin is bactericidal against *Acinetobacter* species, and its effect is concentration dependent(Li J, Nation RL,2006). Resistance to polymyxins has been reported, possibly as a result of outer cell membrane alterations or an efflux pump mechanism (Li J, Nation RL,2006).

Observational studies have reported rates of cure or improvement for colistin of 57%–77% among severely ill patients with multidrug resistant *Acinetobacter* infections, including pneumonia, bacteremia, sepsis, intra-abdominal infection, and Central nervous system infection (KallelH, Bahloul M,2006). A rate of 67%, Levin et al., (1999) found a lower response rate of 25% for patients with pneumonia due to multidrug-resistant who were treated with parenteral colistin. While other studies have reported more favorable clinical response rates (56%–61%) for parenteral colistin treatment of multidrug-resistant *Acinetobacter* ventilator-associated pneumonia(Linden PK, Paterson DL,2006).

There are case reports of successful treatment of multidrug-resistant *Acinetobacter* meningitis with parenteral colistin, but its efficacy for this condition remains unclear (Katragkou A,2005). Several case reports and case series report the use of intraventricular or intrathecal polymyxin therapy, with or without parenteral therapy, for the treatment of gram-negative bacterial meningitis (Ng J, Gosbell IB,2006). A review of 31 reports involving 64 episodes of gram-negative bacterial meningitis found a cures rate of 80%, including cure for 10 (91%) of 11 patients with *Acinetobacter* meningitis (Falagas ME,2007). The majority of patients received systemic antimicrobial therapy in addition to local administration of polymyxin. Neurologic toxicity occurred primarily in reports published before 1970, and the most common manifestation was meningeal irritation, which was apparently dose-dependent and reversible(Falagas ME,2007). Overall, there is insufficient evidence to draw conclusions regarding the efficacy, safety, or pharmacokinetic properties of colistin for treatment of CNS infection, although it remains an important option for salvage therapy (Katragkou A,2005).

Combination therapy - Combination antimicrobial therapy is frequently used in *Acinetobacter* infections as a strategy to increase the likelihood of adequate empiric antibiotic coverage before drug susceptibility testing results are known, to decrease the risk of emergent resistance, and to improve outcomes in multidrug or extensively drug-resistant infections, but there are no definitive clinical data to support its use for these purposes. Nevertheless, because of the excess mortality rate associated with inappropriate empiric antibiotic therapy and with drug-resistant infections, we use a combination antimicrobial regimen for empiric therapy of *Acinetobacter* infections when local rates of resistance to the chosen antibiotic are high and for directed therapy in the setting of infection with extensively drug-resistant isolates.

Vaccines:

There are currently no vaccines for use in humans available against *A. baumannii* or other members of the genus *Acinetobacter*.

2.6. Infections with *Acinetobacterbaumannii*:

Most infections with *A. baumannii* involve organ systems that contain high levels of fluids. Such systems include among others the urinary and respiratory tract, peritoneal cavity, and are linked to indwelling devices.The difference between the infectionand colonization with *A. baumannii* is difficult to differentiate. It is believed that the retrieval of *A. baumannii* in the hospitalized patient is a sign of severe illness, with a related mortality of about 30% (Jung and Park, 2015).

2.6.1.Hospital-acquired *Acinetobacter* pneumonia

The majority of *A. baumannii* pathogens are isolated from the respiratory tracts of hospitalized patients and it is very difficult to differentiate between upper airway colonization from true pneumonia. The incidence of this microorganism varies from one site to another. However, it is the second most common etiologic agent among all the Gram-negative bacteria(Luna and Aruj, 2007). Nosocomial pneumonia occurs in intensive care units (ICUs) with a frequency of 3–5% and with crude death rates of 30–75% being reported (Doughari et al., 2011).

2.6.2.Community-acquired *Acinetobacter* pneumonia

Acinetobacter easily inhabit tracheostomy sites and result in community acquired bronchiolitis and tracheobronchitis in healthy children and in immuno-compromised adults but rarely cause community-acquired pneumonia and sepsis (Whitman et al., 2008). However, community-acquired pneumonia due to *A. baumannii* has been identified in tropical

regions of Australia and Asia during the rainy season in people who have a history of alcohol abuse or have chronic obstructive pulmonary disease (Peleg et al., 2008, Whitman et al., 2008).

2.6.3.Bacteremia (bloodstream infection)

Bacteremia by *A. baumannii* is most commonly caused by intravascular and respiratory tract catheter. The origin from surgical wounds, burns, and the urinary tract is less encountered and is infrequent from endocarditis. The origin of the bacteremia is unknown in about 21–70% of the episodes (Cisneros and Rodriguez-Bano, 2002).

2.6.4 Trauma and other wound infection

A. baumannii can be the cause of skin or soft tissue infections outside of the military population, it led to 2.1% of ICU-acquired skin/soft tissue infections. Moreover, *A. baumannii* isolated from combat casualties in Iraq or Afghanistan was the most frequently isolated organism (32.5% of cases) from battle victims with open tibia fractures (Falagas et al., 2015).

2.6.5. Urinary tract infection

A. baumannii is an infrequent cause of UTI (Peleg et al., 2008, Falagas et a., 2015), it is responsible for only 1.6% of ICU-acquired UTIs. This organism is usually linked to catheter-associated infection or colonization. It is unusual for *A. baumannii* to cause complicated UTI in outpatients.

2.6.6. Meningitis

Nosocomial post neurosurgical meningitis, caused by multidrug-resistant *A. baumannii*, is an increasingly important issue (Doughari et a., 2011, Basri et al., 2015). In a number of acute

bacterial meningitis in adults, *Acinetobacter* was responsible for around 10% of Gram-negative bacillary and 4% of all nosocomial meningitides. Mortality may be as high as 70%, although the reason is often difficult to distinguish (Peleg et al., 2008, Basri et al., 2015).

2.7Mode of transmission by Air:

In a tertiary care hospital conducted surveillance a study for 8 months, 186 air samples were taken from 2 ICU's . They compared the clonal characteristics of air isolates with the prospective clinical strains and the previously isolated strains of ICU patients over a 23 months period. They found that 26(11.4%) from total air samples yielded *A.baumannii*, of which 24(92.3%) isolates were carbapenem-resistant(Yakupogullari Y, Otlu B, Ersoy Y, Kuzucu C, Bayindir Y, Kayabas U, Togal T, Kizilkaya C,2016).

The highest concentration of *Acinetobacter* was in bedside sampling areas of infected patients. In 13 genotypes air isolates were clustered and 7 genotypes (including 18 air strains) were clonally related to the clinical strains of 9 patients from ICU.

Over 27 days in ICU air 1 clone continued to be cultured, air isolates can be relatively correlated with clinical strains for 7 weeks and approximately 15 weeks.

The results of this study suggested that infected patients can deploy large amounts of *Acinetobacter* in the ICU air. These strains can survive in the air for several weeks, and may still infect new patients after a few months. Special measures may be needed to combat the airborne spread of *Acinetobacter*in intensive care units.

2.8 *Acinetobacter*Infection in Animals

'' *Acinetobacter* in veterinary medicine, focusing on *Acinetobacterbaumannii* ''

Nowadays *A.bumannii* represents an important veterinary nosocomial pathogen. It seems that the majority of infections caused by *A. baumannii* in veterinary medicine are from hospitals, These isolates have been associated with several types of infections, such as: canine pyoderma, feline necrotizing fasciitis, UTI, equine thrombophlebitis and lower respiratory tract infection, foal sepsis, pneumonia in mink, and cutaneous lesions in hybrid falcons. Given the potential multi-drug resistance of *A. baumannii*, the treatment of diseased animals is often based on the results of an antimicrobial sensitivity test in vitro. It should be noted that animal isolates show a large genetic diversity and are generally characterized in their serial types and patterns of resistance to those in humans. However, it cannot be ruled out that animals may sometimes play a role as a reservoir of *A.baumannii*. Thus, it is important to implement infection control measures in veterinary hospitals to avoid nosocomial outbreaks through the use of multidrug-resistant *A.baumanniii.*

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Design

This study was conducted at Near East University Hospital. Data was obtained for 63 patients suffering from *Acinetobacter spp.* infection in the intensive care unit (ICU) and in the rest of the patient hospital rooms.

We conducted a retrospective matched cohort study in which all ICU patients with microbiologically documented *one of Acinetobacter spp.* were defined as cases. The study covered data obtained for the period between 2015 and 2018.

3.1.1 Study Population

1-Adults who were less than 30 years

2-Middle ages adult (30-59 years)

3-Old ages 60 years and above

3.2 Data Collection

The research instrument used for this study was the hospital laboratory data and nursing unit gave us the part of infected patients inside the hospital.

3.3 Data Analysis

After data collection was completed, the data was analysed using Statistical Package for the Social Sciences (SPSS) version. A total of 63 patients were entered which included outpatients and patients outcome (Dead or Alive).

CHAPTER FOUR

DATA ANALYSIS AND RESULTS

Table 1: Socio-Demographic Characteristics of the Patient Status (n=63)

	Variable	n (%)
Gender	Male	42(66.70)
	Female	21(33.30)
Age	Less than 30 years	3(4.80)
	30-59 years	19(30.20)
	60 years and above	41(65.10)
Patient Outcome	Dead	26(41.30)
	Alive	37(58.70)

Table 2: Patients Attendance at Different Unit Locations of Hospital

(Attendance Hospital Frequencies)

Hospital Location	N	Response Percent (%)	Percent of cases (%)
4 East	5	4.90	7.90
5 East	11	10.70	17.50
4 West	20	19.40	31.70
5 West	25	24.30	39.70
ICU	39	37.90	61.90
Outpatient	3	2.90	4.80
Total	103	100.00	163.50

The table above shows that 61.90% patients were found to be admitted into the intensive care unit (ICU) which indicate more patients were found to be admitted into this unit than every other unit in the hospital. This was followed by 5 West wing of the hospital with 39.70% of the patients while the 4 West wing had 31.70%. The 5 East wing and the 4 East wing location recorded 17.50% and 7.90% of the patients respectively while 4.80% of the patients were attended to as an outpatient.

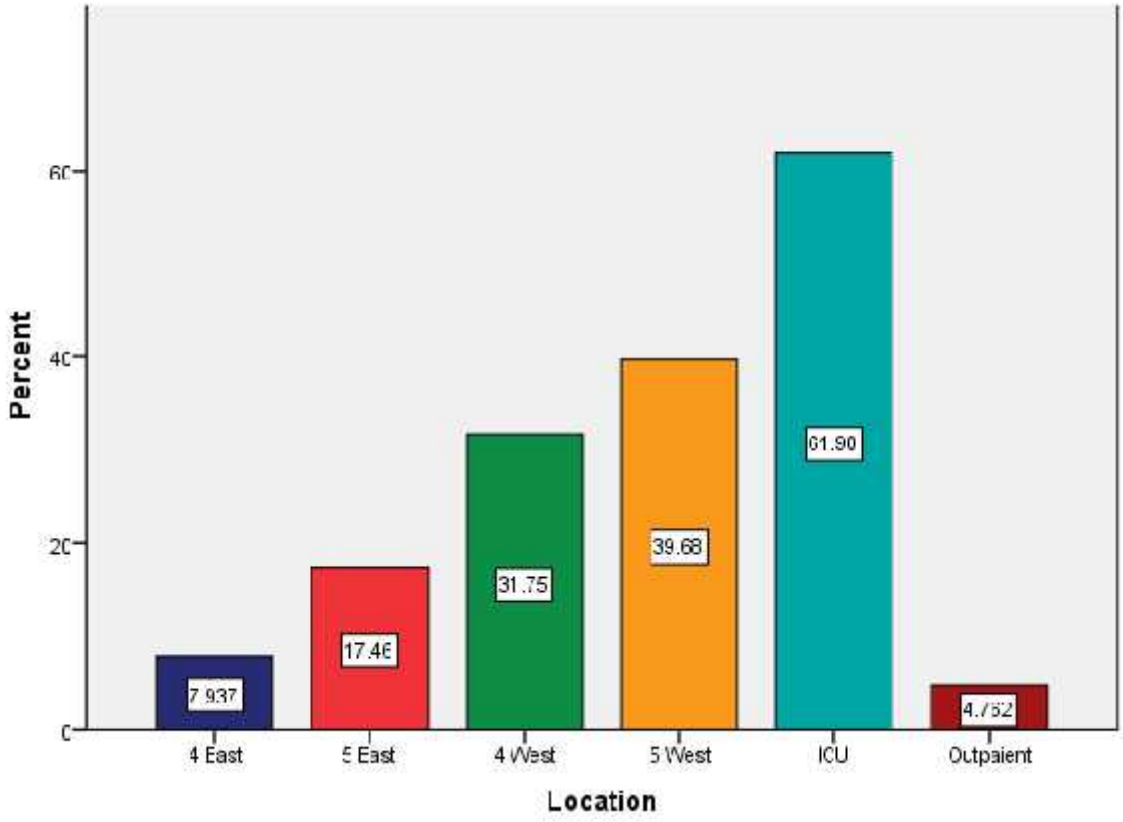

Figure 1: Patients Attendance at Different Unit Locations of the Hospital.

Table 3**:** Day Duration of Patients According to Hospital's Location.

Location	Mean±SD	Median	Min.	Max.
4 East	11.50±8.84	10.00	4.00	28.00
5 East	76.63±104.44	43.50	14.00	330.00
4 West	43.06±55.77	27.00	3.00	232.00
5 West	46.68±116.70	12.00	1.00	624.00
ICU	28.23±40.57	10.00	1.00	161.00

Table 3 shows the descriptive measure on the days spent by patients at different location units of the hospital. The highest median days[43.50(14.00-330.00)] spent by the patients was at the 5 East wing of the hospital followed by the 4 West wing of the hospital with a median of [27.00(3.00-232)] days. The least number of days were spent at the 4 East win [10.00(4.00-28.00)] days and the ICU with [10(1.00-161.00)] days respectively.

Table 4: Total Day Duration of Patients in the Hospital.

Total Duration	Mean±SD	Median	Min.	Max.
	63.67±102.39	29.00	2.00	655.00

The median day spent by patients relative to the total numbers of days spent by the total number of patients was[29.00(2.00-655.00)] days.

Table 5: Patients Gender Relative to Total Days Spent in the Hospital.

Patients Gender	Mean±SD	Median	Min.	Max.
Male(n=42)	52.78±73.57	25.00	4.00	384.00
Female(n=21)	85.45±143.86	34.50	2.00	655.00

In order to evaluate if there is any significance difference in patients gender relative to total days spent in the hospital, a normality test was conducted.

Table 6: Patient Statues relative to total Days spent in hospital

Patient Status	Mean±SD	Median	Min	Max
Alive (n=37)	11.50 ± 8.84	10.00	4.00	28.00
Dead (n=26)	76.63 ±104.44	43.50	14.00	330.00

In order to evaluate if there is any significance difference in Patient status relative to total days spent in the hospital, a normality test was conduct.

CHAPTER FIVE
Discussion and Conclusion

5.1 Discussion

Our data revealed that (61.90%) of patients were admitted into intensive care unit(ICU) and indicates more patients were found to admitted into this unit than every other units in hospital. However, since the mortality relative to the number of days that spent inside the hospital was high (41.30%), we conclude that mortality in the cases is due to severe infections, complications and non-response to antibiotics.

In addition to an increase in mortality, an excess entry to the (ICU) for more than once and staying for long was observed and it's representing an important economic burden.

In (60 years and above) age group they have the highest rates of infection due to antibiotic resistance. Also the study indicates that males are more susceptible to *Acinetobacter* infection.

There is a clear correlation between an excess length of stay in hospital and the presence of infection. The highest median days {43.50(14.00-330)} spent by patients was at 5 East wing of the hospital.

The number of patients in the study were small and therefore these results are difficult to interpret.

5.2 Conclusion:

Acinetobacter has been known as a major cause of nosocomial infections worldwide and have shown a broad spectrum of resistance toward commonly used antimicrobial agents. In view of this, control measures need to be implemented to control the spread of this organism in the hospital environment. It is advisable that healthcare facilities should implement proper safety programs to limit the spread of these bacteria as well as other hazardous bacteria. Research should focus on identifying novel agents with lower resistance. Multidrug-resistant *Acinetobacter* infection poses a formidable threat to patients. The cause of many outbreaks, this organism is increasingly endemic in the health care setting. Antimicrobial resistance is increasing, likely as a result both of the emergence of resistance in the context of antimicrobial pressure and of health care–associated transmission of drug-resistant strains. Multidrug-resistant *Acinetobacter* infections have an extremely high crude mortality rate and occur most frequently in severely ill patients. Although the attributable mortality of multidrug-resistant *Acinetobacter*infections is debatable, these infections are clearly associated with increased time in the ICU, and in the hospital. Treatment options are severely limited, no controlled trials to guide therapeutic choices. Carbapenems and colistin are the agents of choice for the most drug-resistant infections. The role of other agents and combination therapy remains unclear. More data are needed on the pharmacokinetics, pharmacodynamics, and appropriate dosing of colistin, especially in light of the discovery of heteroresistance. Given the lack of good therapeutic options, the development of new therapies, well-controlled clinical trials of existing regimens and antimicrobial combinations, more research, and greater emphasis on the prevention of health care-associated transmission of multidrug-resistant *Acinetobacter* infection are essential.

5.3 Summery and Recommendation

Acinetobacter has the ability to develop resistance through several diverse mechanisms, leading to the emergence worldwide of drug-resistant strains, which are more difficult to treat and are associated with a higher mortality than susceptible strains. Health care exposures, including prior antibiotic receipt (particularly carbapenems and fluoroquinolones), are associated with colonization and infection due to drug-resistant isolates.

Most support for the use of various antibiotics for *Acinetobacter* infections is based upon in vitro data and observational series. Few trials have evaluated the efficacy and safety of different antimicrobial regimens for *Acinetobacter* infections. When infections are caused by antibiotic-susceptible *Acinetobacter* isolates, there may be several therapeutic options, including a broad-spectrum cephalosporin (ceftazidime or cefepime), a combination beta-lactam inhibitor, or a carbapenem (imipenem, meropenem). In the setting of resistance to the above agents, therapeutic options are polymyxins and possibly tigecycline.

Empiric antibiotic therapy for *Acinetobacter*, before results of antimicrobial susceptibility testing are available, should be selected based on local susceptibility patterns. In general, it should consist of a broad spectrum cephalosporin, a combination beta-lactam inhibitor, or a carbapenem. For empiric therapy of patients with *Acinetobacter* infection in a location where resistance to the chosen antibiotic is high, it id suggested to add a second agent pending susceptibility results. An antipseudomonal fluoroquinolone, an aminoglycoside, or colistin are second agent options.

Adequate management of *Acinetobacter*infections also includes removal of associated foreign material, such as urinary or venous catheters. In patients who have *Acinetobacter* pneumonia

resistant to beta-lactams and carbapenems and thus receive an alternate intravenous antibiotic, inhale colistin as adjunctive therapy.

Prevention of drug-resistant *Acinetobacter* depends on early recognition, aggressive control of spread,and preventing establishment of endemic strains. Drug-resistant *Acinetobacter* remains largely susceptible to disinfectants and antiseptics.

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Appendix

Tests of Normality

	Status	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Total_Days	Dead	.275	26	.000	.648	26	.000
	Alive	.292	34	.000	.523	34	.000

a. Lilliefors Significance Correction

Tests of Normality

	Status	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Total_Days	Dead	.275	26	.000	.648	26	.000
	Alive	.292	34	.000	.523	34	.000

a. Lilliefors Significance Correction

Since the P-value <0.05 using kolmogorov-simirnov test of normality, it entails that the data are not normally distributed. Hence, the Mann-whitney test which is a non-parametric test will be used.

Ranks

	Status	N	Mean Rank	Sum of Ranks
Total_Days	Dead	26	31.69	824.00
	Alive	34	29.59	1006.00
	Total	60		

The rank table indicated that patients that died had a higher rank of days spent in the hospital while those that were alive had a lower rank of days spent.

Test Statistics[a]

	Total_Days
Mann-Whitney U	411.000
Wilcoxon W	1006.000
Z	-.463
Asymp. Sig. (2-tailed)	.644

However from the Mann-whitney U test, it can be concluded that there was no statistically significant difference between the number of days spent by those that were alive and those that died (U=411.00, p=0.644).

Tests of Normality

	Gender	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Total_Days	Male	.255	40	.000	.634	40	.000
	Female	.281	20	.000	.550	20	.000

a. Lilliefors Significance Correction

Since the P-value <0.05 using the kolmogorov-Smirnov test of normality, it entails that the data are not normally distributed. Hence, the Mann-whitney test which is a non-parametric test will be used.

Ranks

	Gender	N	Mean Rank	Sum of Ranks
Total Days	Male	40	29.50	1180.00
	Female	20	32.50	650.00
	Total	60		

The Ranks table above indicated that patients female had a higher rank of days spent in the hospital while those that were male had a lower rank of days spent.

Test Statistics[a]

	Total Days
Mann-Whitney U	360.000
Wilcoxon W	1180.000
Z	-.627
Asymp. Sig. (2-tailed)	.530

a. Grouping Variable: Gender

However from Mann-Whitney U test, it can be concluded that there was no statistically significant difference between the number of days spent by the male and female patients(U=360.00, p=0.530).