T.C.
TOKAT-GAZİOSMANPAŞA ÜNİVERSİTESİ
Graduate Education Institute
Department of Medical Microbiology
Master's Program with Thesis

Investigation of antibiotic susceptibility rate of *Acinetobacter baumannii* isolates identified from blood cultures

Master Thesis

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TOKAT – 2022

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TOKAT GAZİOSMANPAŞA UNIVERSITY

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With this document, I declare that the Master's thesis named “Investigation of *Acinetobacter baumannii* strains and their antibiotic susceptibility isolated from blood cultures” is an original work which I prepared in accordance with the guidelines of Tokat Gaziosmanpaşa University - Institute of Graduate Studies and under the consultancy of Doç. Dr. Umut Safiye ŞAY COŞKUN. And i hereby declare that all the information in the current thesis have been gathered and presented in line with academic rules and ethical principles, and as a prerequisite for these rules and principles, I have cited all data, thoughts, and results that do not belong to me.

(21/12/2022)

The Student Who Prepared the Thesis

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JURY ACCEPTANCE AND APPROVAL

The defense examination of the thesis study titled “Investigation of antibiotic susceptibility rate *of Acinetobacter baumannii* isolates identified from blood cultures’’ which was prepared by **ZAID FARIS HASAN** was held on --/--/2022. It was accepted by the jury members of that session as a Master Thesis at Tokat Gaziosmanpaşa University, Institute of Graduate Studies, Department of Medıcal Microbiology.

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CONFIRMATION

21/12/2022

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ACKNOWLEDGMENTS AND FOREWORD

God is to be praised for granting us peace, prosperity, and all the possibilities that have helped to illuminate our path.

We like to thank our supervisor **Doç. Dr. Umut Safive ŞAY COŞKUN**, who helped us with this project, for his assistance.

I would like to express our appreciation for the efforts put out by our department head **(Prof. Dr. Yunus BULUT)** and the academic staff members of the college and hospital.

ABSTRACT

Investigation of antibiotic susceptibility rate
of *Acinetobacter baumannii* isolates identified from blood cultures

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Thesis supervisor: **Doç. Dr. Umut Safiye ŞAY COŞKUN**

Acinetobacter baumannii is one of the major bacteria that lead to nosocomial infections, particularly in intensive care units, with relatively high mortality. *Acinetobacter baumannii* has emerged as the most common cause of bloodstream infections in hospitalised patients. Bacterial resistance and virulence are the main factors linked to high mortality in patients with bloodstream infections. *Acinetobacter baumannii* have a lot of acquired and intrinsic resistance against to many antibiotics. The aim of this study is to evaluate the prevalence of *Acinetobacter baumannii* strains and their antibiotic susceptibility isolated from blood cultures. A total of 117 isolates identified from blood cultures between January 2018 and December 2019 from the Microbiology Laboratory of Tokat Gaziosmanpaşa University Research and Application Hospital were evaluated retrospectively. Blood culture samples were incubated in BACT / ALERT 3D automated system (bioMérieux, Marcy I'Etoile, France). Identification and antibiotic susceptibility of microorganisms were done with VITEK 2 (bioMérieux, France). Multidrug-resistant was defined as acquired resistance to at least one antimicrobial agent from three or more antimicrobial categories. *Acinetobacter baumannii* were detected from patients of which 59.8% (70 cases) were males (sex ratio = 1.9) and 40.2% (47 cases) were female. The patient's median age was 67.31 ± 15.11 years. The majority of *Acinetobacter baumannii* positive blood culture samples (90.6%) were obtained from the intensive care unit. Multidrug-resistant isolates were identified from 88.9% of the samples. The highest antibiotic resistance rate was seen to meropenem with 55% and to imipenem (79.5%). The resistance rate to colistin was 17.1%. All of the isolates were susceptible to tigecycline. Gender, age, and type of clinic had no significant relationship with the prevalence of MDR strains ($p>0.05$). Tigecycline and colistin may be the first choice to treat infections caused by *Acinetobacter baumannii* in this geographic area. Because of the increasing antibiotic

resistance, analyzing epidemiological data for each center regularly should be useful for the development of rational antibiotic use policies.

ÖZET

Kan kültürlerinde üreyen *Acinetobacter baumannii* izolatlarının antibiyotik duyarlılıklarının araştırılması

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Acinetobacter baumannii, özellikle yoğun bakım ünitelerinde hastane enfeksiyonlarına yol açan ve yüksek mortalite neden olabilen önemli bakterilerden biridir. *Acinetobacter baumannii* hastanede yatan hastalar arasında kan dolaşımı enfeksiyonlarının önde gelen nedeni haline gelmiştir. Bakterilerin yüksek direnci ve virülansı, kan dolaşımı enfeksiyonu olan hastalarda yüksek mortalite ile ilişkili ana faktörlerdir. *Acinetobacter baumannii*, birçok antibiyotiğe karşı çok fazla kazanılmış ve içsel dirence sahiptir. Bu çalışmanın amacı, *Acinetobacter baumannii* suşlarının prevalansını ve kan kültürlerinden izole edilen antibiyotik duyarlılıklarını değerlendirmektir. Tokat Gaziosmanpaşa Üniversitesi Araştırma ve Uygulama Hastanesi Mikrobiyoloji Laboratuvarına Ocak 2018- Aralık 2019 yılları arasında gönderilen kan kültürlerinden tespit edilen toplam 117 izolat etken olarak retrospektif şekilde değerlendirildi. Kan kültürü örnekleri BACT / ALERT 3D otomatik sistemde (bioMérieux, Marcy I'Etoile, Fransa) inkübe edildi. Mikroorganizmaların tanımlanması ve antibiyotik duyarlılıkları VITEK 2 (bioMérieux, Fransa) ile yapıldı. Çoklu ilaca dirençli, üç veya daha fazla antimikrobiyal kategoriden en az bir antimikrobiyal ajana karşı kazanılmış direnç olarak tanımlandı. *Acinetobacter baumannii* izolatlarının %59.8'i (70) erkek ve %40.2'si (47) kadın hastalarda tespit edildi. Hastaların ortanca yaşı 67.31 ± 15.11 yıl olarak saptandı. İzolatların %90.6'sının yoğun bakım ünitesinden gelen örneklerden üretildiği görüldü. Örneklerin %88.9'unda çoklu ilaca

dirençli izolatlar tespit edildi. Antibiyotiklere karşı en yüksek direnç oranı %55 ile meropeneme ve imipeneme (%79.5) karşı saptandı. Kolistine karşı direnç oranı %17.1 idi. İzolatların tamamı tigesikline duyarlıydı. Çoklu ilaç direnci olan suşlar ile çoklu ilaç direnci olmayan suşlar arasında cinsiyet, yaş ve klinik tipinin ile anlamlı bir ilişkisi yoktu ($p>0.05$). Bu çalışmada *Acinetobacter baumannii* izolatlarının daha çok yoğun bakımda yatan hastalardan gönderilen kan kültürü örneklerinde ürediği tespit edildi. Bölgemizde *Acinetobacter baumannii*'nin neden olduğu enfeksiyonların tedavisinde tigesiklin ve kolistin ilk seçenek olabilir. Artan antibiyotik direnci nedeniyle, her merkez için epidemiyolojik verilerin düzenli olarak analiz edilmesi akılcı antibiyotik kullanım politikalarının geliştirilmesi için faydalı olacaktır.

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SYMBOLS AND ABBREVIATIONS

ICU: Intensive care units

IDSA: Infectious Diseases Society of America

MDR: Multidrug-resistant

HAIs: Hospital-acquired infections

NHSN: National Healthcare Safety Network

BSI: Bloodstream infections

HAP: Hospital-acquired pneumonia

OMP: Outer membrane proteins

MIC: Minimum inhibitory concentrations

LPS: Lipo polysaccharide

PL: Phospholipase

OMVs: Outer membrane vesicles

AMR: Antimicrobial resistance

CRAB: Carbapenem-resistant A. baumannii

XDR: Xtend drug resistant

DNA: Deoxyneuclotidic acid

QRDRs: Qinolone resistance determining regions

PBP: Penicillin-binding protein

RPO: Recruitment Process Outsourcing

RND: Resistance-nodulation-division

WHO: World Health Organization

1.Introduction

Acinetobacter species are a group of gram-negative, aerobic, and oxidase-negative coccobacilli capable of causing infection in social and hospital environments ((Doi et al., 2015; Viehman & Nguyen, 2014). So far, 73 species of *Acinetobacter* have been discovered. However, in the *Acinetobacter* species *baumannii* (*A. baumannii*) complex, a group of organisms is responsible for the majority of clinical infections. Four species are included in this collection: (i) *Acinetobacter baumannii* (*A. baumannii*), (ii) *A. nosocomialis*, (iii) *A. pittii*, and (iv) *A. calcoaceticus*; the final one is a non-clinical environmental organism. The most widespread genome species around the globe is *A. baumannii*, and it is connected to increased mortality and antibiotic resistance more than other species (Lynch III et al., 2017; Viehman & Nguyen, 2014). Among all Acinetobacter species, *A. baumannii* is responsible for many human illnesses, involving meningitis, urinary tract infection, skin infections, bloodstream infections, and ventilator-associated pneumonia (Dijkshoorn et al., 2007; Parte et al., 2020). One of the primary culprits behind nosocomial infections, particularly in intensive care units (ICU), is this organism (Garnacho-Montero et al., 2015; Vazin et al., 2017). However, *A. baumannii* cannot be differentiated from other *Acinetobacter* species using commonly molecular identification techniques in clinical microbiology labs (Viehman & Nguyen, 2014). The mortality rate associated with infection of *A. baumannii* has been informed to be up to 50%, based on the infection's kind (Cornejo-Juárez et al., 2020). This pathogen can survive as biofilms or live planktonic cells under a wide variety of pH, temperature and humidity conditions (Espinal et al., 2012). In addition, it uses several sources of energy and carbon for survival. The spread and persistence of *A. baumannii* in the hospital setting are facilitated by these traits (Abbo et al., 2005).

A. baumannii shows a lot of acquired resistance and intrinsic against many antibiotics (Lynch III et al., 2017; Olaitan et al., 2014). *A. baumannii* is one of six troublesome multidrug-resistant (MDR) organisms in hospitals, according to the Infectious Diseases Society of America (IDSA) around the globe (Boucher et al., 2009). To all of the existing antimicrobial medications, *A. baumannii* has effectively developed resistance, even against colistin as the last line of treatment (Lin & Lan, 2014). The increase in *Acinetobacter* resistance to antibiotics is caused by

various techniques like the development of broad-spectrum beta-lactamases, aminoglycoside modifying enzymes, carbapenemases, and changes in outer membrane proteins or overexpression of active efflux pumps and penicillin-binding proteins (Doi et al., 2015; Talbot et al., 2006; Wong et al., 2017). Many isolates of *A. baumannii* are currently resistant to all fluoroquinolones, cephalosporins, and aminoglycosides. Additionally, there is a rise in resistance to combinations of -β-lactam/beta-lactamase inhibitors like ampicillin-sulbactam and carbapenems (Talbot et al., 2006; Wong et al., 2017). *A. baumannii* is thought to have an advantage in colonization and the development of chronic infections that are resistant to antimicrobial drugs and present difficulties in treatment because of its capacity to build biofilms on medical equipment and in the hospital environment (Pompilio et al., 2021). Patients who are undergoing major surgery or who have an underlying condition are more likely to get *A. baumannii* infection. Through open wounds, mechanical ventilators, and intravenous catheters, these bacteria may easily infiltrate the body. Longer hospital stays are specifically linked to *A. baumannii* infections (Peleg et al., 2008), particularly among older and male people (Wisplinghoff et al., 1999).

A. baumannii can frequently lead to infections that are acquired in the community, including pneumonia (85% of reported community-acquired infections due to *A. baumannii*) and bacteremia. Skin, soft tissue, eye, endocarditis, secondary meningitis, and other community-acquired infections are also common (Falagas et al., 2007). There are more cases of these illnesses in men and are linked to chronic obstructive lung disease, alcoholism, diabetes mellitus, heavy smoking, age, and kidney and chronic obstructive pulmonary disease. More risky than nosocomial pneumonia, community-acquired *A. baumannii* pneumonia often has a fatality rate of up to 60% and is fulminant (eight days after diagnosis, the patient passes away). In tropical and subtropical climes, summer is when community-acquired pneumonia cases are most prevalently reported (Falagas & Rafailidis, 2007).

About 2% of hospital-acquired infections in Europe and the US are caused by *A. baumannii*, with twice that rate occurring in the Middle East and Asia (Lake et al., 2018; Lob et al., 2016). Drug resistance to all known antibiotics has been reported because of the widespread usage of antibiotics. If efforts are not made toward new therapeutic strategies, this bacterium will soon revert to the pre-antibiotic period (Falagas et al., 2008).

Although the infection rate by *A. baumannii* compared to further gram-negative bacteria is substantially lower, multidrug-resistant phenotypes are alarmingly compared to different types of gram-negative bacteria like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*; their levels are four times greater (Harding et al., 2018). Carbapenem sensitivity was first observed in *A. baumannii* isolates. But reports suggest that up to 90% of cases of *A. baumannii* are carbapenem-resistant (Organization, 2016). Carbapenem-resistant *A. baumannii* infection and *A. baumannii* infection, respectively, accounted for 13.6% and 20.9% of nosocomial infections, according to research conducted in Africa, the Eastern Mediterranean, and Europe (Ayobami et al., 2019).

A. baumannii is notable for being ubiquitous, occurring in various places (such as the skin of humans), and surviving on dry inanimate surfaces for long periods (such as side rails). It can swiftly acquire antibiotic resistance, as was previously indicated. The combination of these elements, the final two, in particular, facilitates the multidrug-resistant (MDR) spread of *A. baumannii* infection in ICUs, physical therapy clinics, and other hospital wards (Consales et al., 2011; Maragakis et al., 2004).

Over 50% of pathogenic *A. baumannii* strains recovered from persons in China are frequently drug-resistant (PDR) strains (Wu et al., 2018). Furthermore, *A. baumannii* as demonstrated to increasingly promote survival, immune evasion, and other virulence characteristics through a number of virulence determinants relating to capsules, outer membrane proteins, biofilms, siderophores, etc. (Harding et al., 2018; Wong et al., 2017). Because of limited treatment alternatives, patients frequently receive improper care, which has a severe impact on their health results (Russo et al., 2019).

Bloodstream infection by hospital-acquired *A. baumannii* is more resistant to several drugs than the community-acquired type. Chen et al., in their study, reported more than double this ratio (Chen et al., 2018). Some *A. baumannii* infections are related to very rapid clinical progression and a high rate of mortality, whereas other infections with this pathogen initially show relatively poor clinical progression, with patients having relatively mild but sometimes mild symptoms. They cause unresolvable sepsis (Chopra et al., 2013; Fishbain & Peleg, 2010). Rich media standard bottles have been created for both aerobic and anaerobic growing environments. They are made to hold 10 mL of blood maximum. However, particular pediatric blood bottles have been created for the culture of quantities 3 mL due to the difficulties in getting high volumes of blood. Specific

bottles have been designed with charcoal or resins to neutralize antibiotics administered before sampling.(Baron et al., 2005) When lytic agents are introduced to some growth conditions, organisms that have been endocytosed by phagocytes are helped to recover and proliferate. 5 days is the typical incubation period, which is long enough for the majority of organisms to recover.(Petti et al., 2006). Blood cultures are crucial in the assessment of feverish patients (Wilson et al., 2000). Clinicians have been urged to collect blood samples for culture from feverish patients due to the 200,000 occurrences of bacteremia that occur annually and the related death rate of 40%–50%. The criteria for collecting blood samples for culturing are ambiguous and general (Jacobs et al., 1998). Clinical factors by themselves have not proven effective in predicting bacteremia and as a result are not reliable indicators of which patients should have blood samples taken for bacterial culture. Given that their blood culture yield is lower than that of individuals who are not getting antibiotics, the problem is made worse for patients who are already taking antibiotics (Mead et al., 1999).

Determining the prevalence of positive blood culture cases for *A. baumannii* when ICU patients are admitted to hospitals can provide important information about the level of compliance with health precautions in these departments and the level of risk of hospital infection that critically ill patients face. In addition, examining bacterial sensitivity and identifying the best antibiotics to treat these infections can help doctors to select appropriate antibiotics. The study aims to evaluate antibiotic susceptibility rate of *A. baumannii* isolates identified from blood cultures

1.1. Characteristics of *A. baumannii*

A. baumannii is a member of the Moraxellaceae family and the order Pseudomonadals in the Gammaproteobacteria class, branch Proteobacteria of Eubacteria (Bouvet & Grimont, 1986; Rossau et al., 1991). In the last ten years, molecular techniques have improved the ability to identify different Acinetobacter species. Species with clinical associations are mostly limited to the ACB complex, which includes *A. baumannii*, *A. calcoaceticus*, *Acinetobacter pittii*, *Acinetobacter nosocomialis*, and many new species that have lately been added (MarÝ-Almirall et al., 2017; Nemec et al., 2011; Parte, 2018). Nevertheless, due to its frequent participation in nosocomial outbreaks, *A. baumannii*, among the ACB complex, is particularly significant. This pathogen especially affects sick and immunocompromised people (Dijkshoorn et al., 2007; Peleg

et al., 2008). In addition, The ESKAPE group consists of six bacterial pathogens (Enterobacteriaceae, Pseudomonas aeruginosa, faecium, *Acinetobacter baumannii*, *Enterococcus*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*) that are the main contributors to antibiotic-resistant infections, and several agents that provide virulence (Rice, 2008). *A. baumannii* is a Gram-negative, oxidase-negative, non-motile, catalase-positive, non-fermentative, and strictly aerobic bacterium (Dijkshoorn et al., 2007).

A. baumannii is an opportunistic and essential bacterium that has a big impact on human pathogenesis and most commonly affects seriously ill patients. In long-term care facilities, this bacterium has been isolated from 54% to 92% of human nasal samples, indicating its distinct preference for nasal mucosa (Liu et al., 2018). In addition, It can easily survive adversity for extended periods of time and adhere to surfaces in the environment of a hospital. Nevertheless, *A. baumannii* is the reason for serious hospital-acquired infections that patients have experienced at a number of different anatomical sites, especially those hosted in intensive care units (ICU) (Bialvaei & Samadi Kafil, 2015; Mullié et al., 2017). Therefore, it is crucial to establish the processes for assessing infection risk and microbial ecology in the (ICU) through behavioral observation of medical staff, testing for bacterial isolates, and active environmental microbiological surveillance (Migliara et al., 2019). For susceptible patients, the mortality rate from *A. baumannii* is 60% (Blanchard et al., 2014; Leylabadlo et al., 2015). Pneumonia and bacteremia are among the general clinical symptoms (Karageorgopoulos & Falagas, 2008). A survey of US hospitals found that the bloodstream (23.9%), skin or wounds (9.1%), and respiratory tract (57.6%) accounted for the majority of *A. baumannii* isolates (Queenan et al., 2012). Interestingly, *A. baumannii* may be a component of the skin's bacterial microbiota. According to research, more than 40% of healthy adults can show this bacteria on the mucous membranes and skin, mostly in moist places like the groin and between the toes; In addition, among hospital employees, this rate is higher (Marchaim et al., 2007; Morgan et al., 2010).

1.2 Clinical importance

A. baumannii is primarily well-known and responsible for a variety of hospital-acquired infections (HAIs) involving meningitis, tract infections, wound infections, urinary, bacteremia, and pneumonia (Eliopoulos et al., 2008). More than 1,000,000 *A. baumannii* infections are

estimated to occur annually worldwide, with 50% of those infections being carbapenem-resistant in nature, according to a previous study (Spellberg & Rex, 2013). *A. baumannii* was discovered in surgical site infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, and central line-associated bloodstream infections, according to National Healthcare Safety Network (NHSN) data for 2009–2010 (Sievert et al., 2013). These *A. baumannii* infections may have a significant mortality rate of 8 to 35% (Falagas & Rafailidis, 2007). Ventilator-associated pneumonia and bloodstream infections are the most serious and have the highest rates of mortality from these nosocomial infections (Dijkshoorn et al., 2007). There are several risk factors for infections with *A. baumannii*, like previous colonization, older age, nursing home stay, previous hospitalization, previous use of antimicrobial agents, presence of previous invasive devices or procedures, intensive care unit admission, and long-term hospitalization (Jang et al., 2009; Kaye & Pogue, 2015; Zhou et al., 2019).

Despite the fact that *A. baumannii* is a significant nosocomial pathogen that can reason for a number of illnesses, community-acquired infections caused by this microbe (pneumonia and bacteremia) are less frequent but are still linked to a high mortality rate (Chusri et al. al., 2019). In most cases, there have been reports of infection from the community in Asia and the Pacific: Australia (Anstey et al., 2002; Davis et al., 2014), Hong Kong (Leung et al., 2006), India (Sharma et al., 2005). Singapore (Ong et al., 2009), Korea (Oh et al., 2013) and Taiwan (Chen et al., 2001). smoking, excessive alcohol consumption, diabetes mellitus, kidney disease, and chronic obstructive pulmonary disease are *A. baumannii* infection risk factors that are acquired in the community (Dexter et al., 2015). Earlier studies have also discussed the connection between *A. baumannii* infections and wounds sustained during the war and natural disaster victims (Falagas & Karveli, 2007).

1.2.1 Bacteremia

In the strictest definition, bacteremia refers to live bacteria in the blood. Asymptomatic bacteremia can develop during routine everyday tasks like brushing your teeth and following minor medical treatments. These clinically benign infections are transitory and have no lasting effects in healthy individuals. (Butler-Laporte et al., 2018) . However, when immune response mechanisms fail or become overwhelmed, bacteremia becomes a bloodstream infection that can evolve into many clinical spectrums and is differentiated as septicemia. Untreated and clinically significant

bacteremia progresses to systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multiple organ dysfunction syndrome (MODS).(Dagasso G et al., 2018).

1.2.2 Clinical findings

Clinical manifestations of bloodstream infections caused by *A. baumannii* may range from benign transient bacteremia to fulminant disease and septic shock associated with an overall mortality (crude mortality rate) of up to 46% (Jang et al., 2009). The incidence of septic shock in patients with bacteremia caused by *A. baumannii* between 45.8% and 61.4% (Xu et al., 2022). Compared to hospital-acquired *A. baumannii* infections, the community-acquired variant causes a distinct clinical syndrome characterized by a fulminant and severe infection. Severe community-acquired pneumonia is the most common manifestation of *A. baumannii* infection, characterized by the sudden onset of fever, respiratory distress, septic shock, multiorgan failure, and possible death. Common symptoms include a productive cough that is often purulent or bloody, shortness of breath, drowsiness, or pleuritic chest pain (Chen et al., 2001; Falagas et al., 2007). Chest radiographs usually show lobar consolidation (Lee et al., 2012). An Australian study found that 80% (41/33) of CA-Ab infection cases presenting to emergency departments require intensive care unit admission (Dexter et al., 2015). Mortality from *A. baumannii* pneumonia has been reported to range from 11% (Davis et al., 2014) to 64% (Anstey et al., 1992), which often occurs within the first 48-72 hours after hospital admission (Ong et al., 2009). Apart from acute pneumonia and blood infections caused by *A. baumannii*, a number of other infections have been reported in the last 30 years, including chronic pneumonia, meningitis, soft tissue infections, normal valve endocarditis, and urinary tract infections (Dexter et al., 2015).

1.3 Epidemiology

Generally, More than 12% of hospital-acquired bloodstream infections (BSI) are caused by *A. baumannii* in the intensive care unit. This disease is common in South America, Asia, Middle Eastern countries, and Southern Europe, while it is rare in Australia and Northern European countries (Tabah et al., 2012). ICU-acquired pneumonia, particularly late-onset pneumonia, is frequently caused by *A. baumannii* (Koulenti et al., 2017). The predominant pathogen is isolated from patients with hospital-acquired pneumonia (HAP). In countries where *A. baumannii* is

spreading. In fact, more than 36% of HAP cases in Asia may be caused by *A. baumannii* (Chung et al., 2011). In addition, in some countries, it only accounts for 1% to 2% of cases of nosocomial pneumonia (Dananché et al., 2018). Also, *A. baumannii* may contribute to the occurrence of healthcare-associated infections outside the hospital. Consequently, a comparison of two main studies of the multicenter cohort showed a dramatic increase in hospital-acquired infections from 1.2% to 14.2% from 2000 to 2010. In contrast, infections with *A. baumannii* in the intensive care unit appear to have decreased recently (Olaechea et al., 2016).

A. baumannii has some important characteristics, such as its increased prevalence due to its resistance to microbes and, on dry surfaces is capable of long-term survival. The healthcare environment, healthcare workers' hands, and contaminated equipment all play a significant influence in the transmission of multidrug-resistant strains of *A. baumannii* outbreaks (Escudero et al., 2017; Munoz-Price et al., 2013). If surfaces around patients are colonized, if there are many patients colonizing the unit together, or if patients are heavily colonized, the risk of cross-transmission rises (Masse et al., 2017).

According to earlier research, patients who are colonized and infected serve as the primary reservoirs for the dissemination and horizontal transmission of *A. baumannii* in the environment of the hospital (da Silva et al., 2018). In addition, the contaminated hands of health care workers may potentially have a significant impact on the transmissions. Thom et al. (2018) discovered that 30% of the time, when caring for patients infected with *A. baumannii*, the healthcare workers had the *A. baumannii* on their gloves or hands when they left the room (Thom et al., 2017). Although the main reservoirs for *A. baumannii* are patients who are infected and colonized, other hospital environmental sources can be used to isolate *A. baumannii*. Various studies that recovered *A. baumannii* isolates have been recorded in the literature from diverse sources: faucets and sinks (Hong et al., 2012), hands of healthcare workers (Enoch et al., 2008), hospital furniture, devices, medicine and gloves (Raro et al., 2017).

1.4 Virulence and pathogenesis factors of *A. baumannii*

Although a number of pathogenicity factors for *A. baumannii* were discovered in recent genomic and phenotypic analyses, *A. baumannii*, in contrast to other Gram-negative pathogens, has had relatively few virulence factors discovered (McConnell et al., 2013).

1.4.1. Purines

The outer membrane protein purines manage the permeability of cells. One of the most prevalent porins in the outer membrane is OmpA is a β-barrel porin. In *A. baumannii*, OmpA is a known virulence factor whose interesting biological properties are defined in vitro models (McConnell et al., 2013; Smith et al., 2007). An investigation indicated that mutant OmpA in *A. baumannii* in human epithelial cells inducing apoptosis is defective (Choi et al., 2005). Purified OmpA binds to host epithelial cells, induces apoptosis by releasing proapoptotic molecules like apoptosis-inducing factor and cytochrome c, and targets mitochondria (Choi et al., 2005; Lee et al., 2005). al., 2010). OmpA interacts with fibronectin to play an important function in epithelial cell adhesion and invasion (Smani et al., 2012) and binds to factor H in human serum (Kim et al., 2009) to allow *A. baumannii* to avoid destruction by complement. The survival of *A. baumannii* in the mouse lung depends on the ompA gene (Wang et al., 2014).

Also the antimicrobial resistance of *A. baumannii* is also influenced by OmpA (Smani et al., 2014). The main porin of *A. baumannii* is OmpA, which has 70-fold lower pore-forming activity than OmpF (Sugawara & Nikaido, 2012). In addition, The minimum inhibitory concentrations (MICs) of some antibiotics (nalidixic acid, chloramphenicol, and azetronam) are reduced significantly by ompA gene disruption, suggesting that OmpA helps to eliminate antibiotics from the periplasmic space. It participates through the coupling with the efflux systems and the outer membrane of the inner membrane (Smani et al., 2014). Via biofilm formation and facilitating surface motility, OmpA increases the persistence and survival of *A. baumannii* (Clemmer et al., 2011; McConnell et al., 2013). Additionally, the biogenesis of outer membrane vesicles regulates OmpA (Moon et al., 2012). A desirable objective for prevention strategies and the creation of new antibiotics is OmpA protein, according to these findings. OmpA is known as a potential applicant for an *A. baumannii* vaccine in two recent studies based on reverse vaccinology and immunoproteomics (Hassan et al., 2016).

1.4.2. Lipopolysaccharides (LPS) and Capsular polysaccharides

Beyond OmpA, many factors are associated with the coat of *A. baumannii* that take part in virulence. Meanwhile, LPS and capsular exopolysaccharides are pathogenic factors of *A. baumannii*. A conserved gene cluster called the K locus is found in several isolates from individuals with *A. baumannii* infection, and it is noteworthy that this gene cluster may control the

formation of surface capsular polysaccharides in these isolates (Geisinger & Isberg, 2015); Hu et al., 2013). The epsA and ptk genes were discovered through a random transposon screen to find genes important for development in an inflammatory exudative fluid. These genes are anticipated to be needed for capsule formation and polymerization (Russo et al., 2010). In capsule production, epsA and ptk mutants are ineffective due to having growth defects in human sera, resulting in a soft tissue infection's survival being greatly reduced (Russo et al., 2010). Additionally, pglL or pglC mutations cause aberrant biofilm formations and lower lethality in the model of mouse septicemia. These genes are responsible for producing the O-pentasaccharide present in capsular polysaccharides and glycoproteins (Iwashkiw et al., 2012). As a result, capsular polysaccharides have been suggested as a target for protective antibody-based interventions (Russo et al., 2013).

Antimicrobial resistance of *A. baumannii* contributes to capsular polysaccharides, according to a study. Mutants lacking capsular polysaccharides have a less inherent resistance to peptide antibiotics. Furthermore, Capsular polysaccharides are produced in excess when antibiotics are present. Antibiotic-induced production of capsular polysaccharides enhances host complement resistance and pathogenicity in a mouse model of systemic infection (Geisinger & Isberg, 2015).

Most Gram-negative bacteria have a significant amount of LPS in their outer membrane leaflets, which, in a Toll-like receptor 4 (TLR4)-dependent way, causes the release of tumor necrosis factor and interleukin-8 from macrophages (Erridge et al., 2007). LPS consists of an oligosaccharide core, an O-antigen, and an endotoxic lipid A moiety (Lee et al., 2013). LPS has a significant impact on the survival and virulence of *A. baumannii* (Lin et al., 2012; Luke et al., 2010). A mutant cell lacking LpsB glycotransferase in a mouse model of soft tissue infection has a very short LPS glycoform with just two carbohydrate residues connected to lipid A, which leads to lower survival and resistance to serum (Luke et al., 2010; McConnell et al., 2013). The lipid A biosynthesis enzyme LpxC is inhibited, but this does not prevent bacterial growth; rather, it prevents LPS-mediated TLR4 activation (Lin et al., 2012).

1.4.3. Phospholipase

An important lipolytic enzyme for phospholipid metabolism is phospholipase, and many bacteria have it as a virulence factor. , including Clostridium perfringens, Legionella

monocytogenes, and P. aeruginosa (Flores-Díaz et al., 2016). By the cleavage site, three classes of phospholipases, including phospholipase D (PLD), phospholipase C (PLC), and phospholipase PLA (A), have been identified. PLC cleaves the phosphorylated head group from the phospholipid, while PLA hydrolyzes fatty acids from the glycerol backbone. A trans phosphatidylase called PLD only cleaves the head group. The host cell membrane stability is impacted by phospholipid degradation, and the truncated group can interfere with cell signaling, changing the host's immune response (Flores-Díaz et al., 2016). *A. baumannii* has been found to contain the virulence factors PLD and PLC (Stahl et al., 2015).

The cytotoxic effect of *Acinetobacter baumannii* on epithelial cells is moderately reduced when the A1S 0043 gene is inactivated in comparison to the parent strain of *A. baumannii* (ATCC17978), which has two PLCs (A1S 2055 and 0043) (Fiester et al., 2016). In accordance with another study, *A. baumannii* ATCC 19606 possesses three PLD genes, all of which are crucial for virulence and coordinated host cell invasion (Stahl et al., 2015). These results demonstrate the crucial role that phospholipase enzymes play in the virulence of *A. baumannii*.

1.4.4. Outer membrane vesicles (OMVs)

The outer membrane of several Gram-negative pathogenic bacteria secretes OMVs, which are 20–200 nm in diameter in the shape of spherical vesicles (Kulp & Kuehn, 2010). They serve as carriers for bacterial agents in host cells and are made up of LPS, phospholipids, periplasmic proteins and outer membrane, and RNA or DNA (Ellis & Kuehn, 2010). Multiple virulence factors are simultaneously delivered into host cells by OMVs, enabling pathogens to interact with the host without having to come into close proximity to the host's cells (Jun et al., 2013). OMVs containing virulence factors, including phospholipases, proteases, and OmpA, are secreted by numerous *A. baumannii* strains (Kwon et al., 2009). OMVs generated from *A. baumannii* interact with host cells, causing cytotoxicity and conveying bacterial agents to host cells by lipid rafts (Jin et al., 2011). Proinflammatory cytokine genes are expressed in epithelial cells by purified OMVs of *A. baumannii* ATCC 19606 in a dose-dependent manner (Jun et al., 2013). OMVs' contribution to the pathogenesis of *A. baumannii* is supported by one research. In comparison to a strain that generates fewer OMVs, an *A. baumannii* strain that produces a lot of OMVs and has more virulence reasons are more cytotoxic and elicits a higher innate immune response (Li et al., 2015).

1.4.5. Iron acquisition system

Iron is one of the items that is greatest prevalent in biological and environmental organizations, Due to its low solubility (17-10 M for ferric iron) in neutral pH and aerobic environments and chelation by low molecular weight compounds like high-affinity iron-binding compounds or heme such as lactoferrin and transferrin, ferric iron is highly soluble and therefore relatively inaccessible to bacteria (Rakin et al., 2012; Saha et al., 2013).

Most aerobic bacteria develop a high-affinity iron chelator known as a siderophore to get around this iron restriction. Siderophores are low molecular weight (400–1000 kDa) substances having a strong affinity for iron (Saha et al., 2013). The most well-known *A. baumannii* siderophore, acintobactin, is an oxazoline ring-derived mixed-type siderophore with an iron siderophore. *A. baumannii* also possesses iron siderophores (McConnell et al., 2013).

The virulence component of *A. baumannii* is acintobactin (Ali et al., 2017). *A. baumannii* ATCC 19606 cells are substantially less able to survive in epithelial cells when acintobactin production and transport processes are disrupted, leading to animal mortality and cell damage (Gaddy et al., 2012).

1.4.6. Protein secretion systems

A. baumannii has been shown to contain many protein secretion mechanisms (Weber et al., 2016). The newest secretion system is type II, found in *A. baumannii* (T2SS) (Johnson et al., 2016). A Multi-protein complex referred to as T2SS shares a lot in common structurally with type IV pili systems, an accessory often seen in Gram-negative bacteria (Korotkov et al., 2012). A large variety of proteins are transported by the T2SS from the periplasm to the extracellular space. A dodecameric outer membrane complex, an inner membrane platform complex, a pseudopilus and a cytoplasmic secretion ATPase are the four subassemblies that make up the T2SS, which is made up of 12 to 15 proteins (Harding et al., 2016; Korotkov et al. ., 2012). There are two steps involved in T2SS secretion. The general secretion system (Sec) or the twin-arginine transport system (Tat) first transports the target proteins to the periplasm, where they are then secreted out of the cell by the T2SS (Korotkov et al., 2012). LipA is a T2SS substrate since its secretion is lost when the T2SS components gspE or gspD are deleted from *A. baumannii* (Johnson et al., 2016). Since long-chain fatty acids are degraded by LipA, which is a lipase, gspD, lipA, and gspE mutant strains

are unable to develop using long-chain fatty acids as the only carbon source, and in vivo growth in the model Bacteremia neutropenic mice is flawed (Johnson et al., 2016). In G. mellonella and mouse lung infection models, the importance of a functioning T2SS for complete *A. baumannii* pathogenicity has been shown (Harding et al., 2016).

1.5. Antimicrobial resistance

Antimicrobial resistance (AMR) has emerged as an important phenomenon worldwide, which is associated with increased costs for health care systems. In recent years, due to hospitalization and long-term treatment, it related to complications, mortality and increased costs. Despite the fact that new antimicrobial medicines have been developed over the past several decades, resistance seems to be an issue that is getting worse with geometric progression. According to data from multicenter studies conducted over the past few decades, the prevalence of elderly individuals with primary or secondary immunodeficiency is rising along with both hospital-acquired and community-acquired AMR (Ayoub Moubareck & Hammoudi Halat, 2020; Vrancianu et al., 2020). The WHO identified Carbapenem-resistant *A. baumannii* (CRAB) as the top priority for the development and research of antibiotics in 2018. Because of the wide range of concomitant resistance to other antibiotic classes that carbapenem resistance is typically linked with, carbapenem was chosen as a marker (Tacconelli et al., 2018).

According to estimates, 79.9% of *A. baumannii* patients have multidrug-resistant strains, with incidence varying from 61.8% in Taiwan and 56.5% in Argentina to 100% in Croatia, Qatar, Lebanon, Pakistan, and Central America, even if its total mortality rate might reach 56.2% (Lim et al., 2019). Patterns of carbapenem resistance vary across Europe and in the Arab League countries. In the eastern Arab Union countries, as well as northern and eastern Europe, an increase in the prevalence of *A. baumannii* isolates resistant to carbapenem has been noted (Iraq, Lebanon, Jordan, Syria, and Palestinian territories) (Moghnieh et al., 2018; Prevention & Control, 2020).

Multidrug-resistant (MDR) *A. baumannii* infections were traditionally treated with carbapenems, but recent usage of these drugs has increased the prevalence of carbapenem resistance (Nordmann & Poirel, 2019). Although they were first avoided because of systemic toxicities, polymyxins are now extensively utilized as the antibiotic of choice for MDR infections brought on by *A. baumannii* (nephrotoxicity and neurotoxicity) (Piperaki et al., 2019). Very

resistant to drugs (XDR) An isolate of bacteria called *A. baumannii* has at least three antibiotics resistance (aminoglycosides, fluoroquinolones, cephalosporins and penicillins, and most often resistant to carbapenems). While *A. baumannii* is an XDR isolate that is multidrug-resistant (PDR), it is also resistant to tigecycline and polymyxins. Drug-resistant isolates have recently sparked the development of novel antimicrobials and treatment strategies (Karakonstantis et al., 2020).

Clinical isolates of *A. baumannii* were discovered to be susceptible to many widespread antibiotics in the 1970s, including nalidixic acid, chloramphenicol, gentamicin, and ampicillin. Nevertheless, this bacterium became a significant nosocomial infection in the late 1970s, mostly due to the introduction of broad-spectrum antibiotics in hospitals (Towner, 2009). The majority of first-line antibiotics are no longer effective against *A. baumannii*. For multidrug-resistant (MDR) *A. baumannii*, Colistin and Tigecycline remain the only antibiotics that are effective against it. Colistin-resistant strains, however, have been discovered in a number of locations worldwide (Cai et al., 2012).

There are a number of causes behind the rising prevalence of antibiotic resistance. Antibiotics usage and the growth of resistant bacteria are directly correlated. When acquired from relatives, mechanisms of resistance can spread from one bacterium to another either longitudinally or horizontally (using plasmids). The latter might result in the spread of resistance among many species (Read & Woods, 2014). Another notable occurrence is improper prescription. Studies have revealed that 30–50% of antibiotic prescriptions are made incorrectly (Luyt et al., 2014). Another significant issue is the extensive use of antibiotics in agriculture, particularly as growth promoters for cattle. Through animal meat consumption, resistant bacteria and antibiotics are transferred to people, increasing the number of antibiotic-resistant strains that cause human diseases. The delayed new antibiotics development is another factor. The pharmaceutical sector has significantly decreased its investment in novel alternatives as a result of the accessibility and affordability of antimicrobials (Bartlett et al., 2013).

A. baumannii clinical isolates were examined in one investigation. More than half (50-70%) of these isolates are resistant to cephalosporins (cefepime and cefazidime), beta-lactam/beta-lactamase inhibitors (tazobactam-piperacillin), and carbapenems (meropenem, imipenem, and duripenem). Quinolones (levofloxacin and ciprofloxacin) account for 73.6% of It should be

highlighted that only 26.7% of the samples had antibiotic tigecycline resistance. There was no evidence of colistin resistance (Chen et al., 2017).

Antibiotic resistance can arise through a number of routes. The most often seen examples, according to Warehan and Gordon, involve abnormalities in target locations, variations in multidrug efflux pumps, perfusion defects, and deficiency in certain degradation enzymes, which are frequently linked to other diseases (Gordon & Wareham, 2010).

1.6. Mechanisms of resistance to different antibiotics

A. baumannii comes in a variety of strains that are endemic to various parts of the world (Woodford et al., 2011). MDR strains escape the effect of antimicrobials by different techniques; each of these is specific against certain classes of medications.

1.6.1. Aminoglycosides

From the 30S ribosomal subunit, aminoglycosides bind to 16S RNA. The development of aminoglycoside modifying enzymes is the approach that makes *A. baumannii* strains the most resistant to this kind of antibiotic. Aminoglycoside acetyltransferases (AAC), such as AAC(60)-Ih, are one of three distinct functional categories of known modifying enzymes (which are also resistant to amikacin and gentamicin) (Landman et al., 2011), APHs (aminoglycoside phosphotransferases), such as APH (3 0)-IA (which imparts gentamicin resistance) (Akers et al., 2010) and ANT (2 0 0)-IA, an aminoglycoside adenylyltransferase (Shaw et al., 1993). A developing method of aminoglycoside resistance is the creation of 16S ribosomal RNA methyltransferases, notably ArmA (the first of its kind to be found in a clinical isolate) (Liou et al., 2006). Highly resistant to tobramycin, amikacin, and gentamicin are *A. baumannii* strains that generate ArmA (Yu et al., 2007).

Additionally, 61 of 75 Acinetobacter isolates from two hospitals in Korea in research by Choy et al. revealed the presence of aminoglycoside resistance genes. The results of this investigation demonstrated that *A. baumannii* isolates containing the genes for the aminoglycoside-modifying enzymes ant(3'')-Ia, aac(60)-Ib, aph(30)-1a, aac(3)-Ia, and aph(30)-VI produced ArmA, making them resistant to tobramycin, amikacin, streptomycin, spectinomycin, gentamicin, and ispamycin (Cho et al., 2009).

1.6.2. Carbapenems

Carbapenems are mostly utilized as a treatment for infections brought on by Gram-negative bacteria and have the greatest scope of all β-lactams (Jeon et al., 2015). Overexpression of carbapenem-hydrolyzing oxacillinase (OXA)-51-like-B-lactammase (Rumbo et al., 2013). Some of the mechanisms underlying carbapenem resistance in *A. baumannii* strains include the ribosomal methyltransferase ArmA RNA 16S (Adams-Haduch et al., 2008). *A. baumannii* has a significant increase in carbapenem resistance, which is mostly caused by the development of Ambler class D -lactams (OXA) (Perez et al., 2007; Zarrilli et al., 2004). A large number of them are discovered as integrons (Poirel et al., 2001). The acquired OXA carbapenemases such as -123-like, -58-like, 24 (OXA-40-like), and OXA-23 all be expressed by *A. baumannii* in addition to the chromosomal OXA-51-like group (Higgins et al. al., 2013). Clinical consequences have been linked to OXA-23's contribution to the spread and growth of carbapenem resistance (Girlich et al., 2010). OXA-24 has mild hydrolytic action against carbapenems, according to studies (Bou et al., 2000).

The chromosomally encoded carbapenemases OXA-51 are constitutively produced by *A. baumannii*; hence it is not the direct source of resistance. However, overexpression starts if ISAba1 or ISAba9 translocation takes place upstream of the OXA-51 group gene (Figueiredo et al., 2009). The OXA group of carbapenemases result in resistance to carbapenems and oxacillin but not to cephalosporins. Furthermore, in the majority of clinical isolates, the presence of blaOXA genes established acquired resistance to carbapenems, whereas resistance to cephalosporins was already present because of other bla-type genes like blaAmpC (Viehman & Nguyen, 2014). *A. baumannii* has also been found to have non-OXA carbapenemases; however, Enterobacteriaceae is where they are most frequently found. Ambler class B metallo-β-lactamases are one type that has been discovered. Imipenmase VIM (Verona imipenmase), IMP (imipenmase), and other metallobetalactamases that are uncommon in *A. baumannii* strains are included in the category of NDM enzymes (New Delhi metallobetalactamase) in this classification (Chen et al., 2011). Reduced expression of penicillin-binding protein (PBP) 2 may also play a significant role in the development of carbapenem resistance, according to Fernández-Cuenca et al. (Fernández-Cuenca et al., 2003).

1.6.3. Fluoroquinolones

Changes in DNA gyrase and DNA topoisomerase IV's quinolone resistance determining regions (QRDRs), which prevent fluoroquinolones from binding to their target proteins, are part of fluoroquinolone resistance mechanism of *A. baumannii* (Adams-Haduch et al., 2008). Increased resistance in strains with changed QRDRs and intermediate resistance on their own can be brought on by overexpression of activated efflux pumps (Coyne et al., 2010).

1.6.4. Cephalosporins

Cephalosporin resistance is common in *A. baumannii* clinical isolates. A novel Ambler class C beta-lactamase, which is also produced in Escherichia coli DH10B, was discovered in a clinical isolate collected from a hospital in Cleveland, USA. When compared to cefepime, this enzyme showed more resistance to ceftazidime and cefotaxime. It was discovered that a distinct class of class C enzymes is characterized after phylogenetic study of this novel enzyme and other class C -lactamases reported in Oligella urethralis, *Acinetobacter pittii*, and *A. baumannii*. As a result, the term "*Acinetobacter*-derived cephalosporinases" was recommended as a standard nomenclature for these cephalosporinases (ADC). Due to the earlier descriptions of six similar cephalosporinases, the new enzyme was given the designation ACD-7 β-lactamase (Hujer et al., 2005).

A. baumannii AmpC ADC-7 cannot be induced by cefoxitin, unlike the majority of chromosomally generated class C β-lactamases (Hujer et al., 2005). Increasing the expression of the ADC gene by inserting the ISAba125 or ISAba1 sequence upstream can result in higher promoter activity than the native promoter activity, according to the study findings by Lopes et al. (Lopes & Amyes, 2012). The minimum inhibitory concentration of different cephalosporins must thus be raised, with the exception of cefepime, which is not a substrate of class C beta-lactamase, which includes ADC. According to reports, some *A. baumannii* strains produce extended-spectrum class C beta-lactamases, like ADC-33, which confer resistance to cefepime and other cephalosporins (Tian et al., 2011).

1.6.5. Sulbactam

According to research, PBP2 (penicillin-binding protein) has the greatest affinity for both beta-lactamase inhibitors and penicillin. Sulbactam acts against the microorganism by attaching to

PBP2 of *A. baumannii* (Urban et al., 1995). Sulbactam resistance in *A. baumannii* is linked to decreased PBP2 expression (Fernández-Cuenca et al., 2003). Additionally, it has been established that sulbactam resistance in *A. baumannii* is influenced by the function of β-lactamase production expressed by the BlaTEM-1 gene (Krizova et al., 2013).

It is significant to remember that sulbactam may have better therapeutic potential than other beta-lactamase inhibitors like tazobactam and clavulanic acid. Despite having intrinsic action, beta-lactamase inhibitors are unable to increase the effectiveness of beta-lactams against *A. baumannii* (Higgins et al., 2004).

1.6.6. Rifampicin

Rifampicin inhibits the process of transcription by binding to the active site of bacterial RNA polymerase. The replacement of amino acids in the β subunit of this target protein serves as the medication's escape mechanism. RpoB mutation is related to an increased minimum inhibitory concentration in *A. baumannii*. Rifampin resistance in *A. baumannii* strains is also a result of enzymatic modification and active efflux by ADP ribosyltransferase rifampicin (ARR-2) (Giannouli et al., 2012).

1.6.7. Tetracyclines

Tetracycline resistance can be achieved in a number of ways, including active antimicrobial agent efflux through resistance proteins in the bacterial cytoplasmic membrane and preventing ribosome and tetracycline binding. The resistance-nodulation-division (RND) efflux pumps produced by the majority of clinical isolates of *A. baumannii* are susceptible to the effects of tigecycline, which is intended to prevent most resistance mechanisms (Coyne et al., 2011). Increased MICs of tigecycline were demonstrated by Hornsey et al. to be related to high expression of adeABC. When their adeB was disturbed, tigecycline-resistant clinical isolates once again showed complete sensitivity to this drug (Hornsey et al., 2010).

1.6.8. Polymyxins

With increasing antibiotic resistance among gram-negative bacteria, especially P. aeruginosa, K. pneumoniae, and *A. baumannii*, effective antimicrobial treatment methods are limited. Colistin is a polymyxin that more than 50 years ago was discovered, and its clinical use is now being explored (Li et al., 2006).

Lipopolysaccharide (LPS) lipid A interacts with colonistin (Polymyxin-E). Its alteration results in acquired polymyxin resistance. The type of modification that has been most often described involves adding a phosphor ethanolamine residue to the heptaacylated version of lipid A. This method removes negative charges and lowers the affinity of LPS for polymyxins (Beceiro et al., 2011). The complete loss of primary LPS is another way that *A. baumannii* acquires such resistance (Moffatt et al., 2010). MDR gram-negative bacteria are being treated with polymyxin-rifampicin combination therapy, according to Biswas et al. Most investigations have demonstrated that the combination of rifampicin and colistin is 100% effective against MDR *A. baumannii* (Biswas et al., 2012).

1.7. Common isolates in blood culture

The prevalence of bacteria isolated from blood samples is different in various places and depends on the studied population. A study in Greece reported *Escherichia coli* as the most common isolate in blood cultures of hospitalized patients with an annual prevalence between 25.3 and 28.1%, followed by *Klebsiella pneumonia (K. pneumonia)* (17.0%), *Staphylococcus aureus* (*S. aureus*) (14.0%), *Pseudomonas aeruginosa (P. aeruginosa)* (9.9%), *Enterococcus faecalis (E.faecalis)* (8.9%), *A. baumannii* (9.0%), *Enterococcus faecium* (*E.faecalis*) (5.6%), *Enterobacter spp.* (4.6%), and *Proteus mirabilis* (4.6%) were the most common blood culture isolates of hospitalized patients. Among the isolates studied from patients admitted to the intensive care unit, *A. baumannii* was the most common bloodstream isolate in each year of the study period with an annual prevalence ranging from 26.1% to 30.9%, followed by *K. pneumonia* (26.1%). The isolates of *P. aeruginosa* (16.0%), *E.faecalis* (8.9%), *E.faecium* (5.3%), and *S. aureus* (4.3%) were in the next ranks (Polemis et al., 2020). Another systematic review evaluated common pathogens in the blood of hospitalized individuals with febrile symptoms in studies conducted in Africa and Asia between 1984 and 2018. The most common pathogen was *Salmonella enterica* (34.8%), which includes typhoid (10.2%) and non-typhoid (23.5%) species, followed by *Escherichia coli* (8.8%) and *Enterobacterales* (3.3%). Only 8 cases (0.2%) of *A. baumannii* were found in this study, indicating a low prevalence of blood infection with this microorganism in febrile patients (Marchello et al., 2019). A study in California, USA, evaluated the blood culture samples of patients from three hospital centers. Among 1225 bloodstream infections, the most common

isolates were *S. aureus*, *E. coli*, *Enterococcus spp.*, *K pneumoniae*, Coagulase-negative *Staphylococcus*, and *Pseudomonas aeruginosa* (Pien et al., 2010).

2. Material and method

2.1. Type of study.
The current study is retrospective.

2.2. Study patients.
Individuals who had positive *A. baumannii* blood culture in the Microbiology Laboratory of Tokat Gaziosmanpaşa University Research and Application Hospital in 2018 and 2019.

2.3. Inclusion and exclusion criteria.
Adults who had positive *A. baumannii* blood cultures in January 2018- January 2019 and had microbial sensitivity results were included in the study. Results with no growth in blood culture and detected the other bacteria growth in blood culture was not included in the study.

2.4. Method.
In this study, with a retrospective design, positive blood culture samples in the records of the Microbiology Laboratory of Tokat Gaziosmanpaşa University Research and Application Hospital were evaluated, and a total of 117 samples with *A. baumannii* positive blood cultures were identified. This study was approved by the Scientific and Ethical Committee of the Tokat Gaziosmanpasa University Clinical Research Ethics Committee (21-KAEK-245).

In several hospital departments, blood samples from the patients were obtained, including the ICU, department, as a routine process for the initial diagnosis of the patients. The each set of bottles sent to the laboratory were examined with the BacT/Alert 3D (bioMerieux, Durham, NC, USA). All bottles were incubated for five days using the dedicated system equipment. Bottles indicated positive growth signal were both gram stained and inoculated in blood and EMB agar.

2.9. Blood agar.
28 g of nutrient agar powder (Himedia, France) was added in 1 litre of distilled water and heated stirring to fully dissolve all components. The dissolved mixture was autoclaved at 121 degrees Celsius for 15 minutes. When the agar has cooled to 45-50 °C, 5% sterile defibrinated blood was added in that has been warmed to room temperature and was mixed.
On blood agar, colonies look like smooth spherical Enterobacterales.

Figure 1: *A. baumannii* on blood agar

2.10. EMB agar

The dehydrated powder components suspended in the water (36 grammes in 1000 ml of purified/distilled water). For a few seconds, the medium was boiled until the ingredients are completely dissolved and sterilized for 15 minutes in an autoclave at 121°C pressure. The medium was cooled to 45-50°C and stir it to oxidise the methylene blue (restore its blue colour) and the flocculant precipitate was suspended. The ingredients of the medium (HiMedia) : Peptone 10.00 g/lt, dipotassium hydrogen phosphate 2.00 g/lt, lactose 5.00 g/lt, saccharose 5.00 g/lt Eosin - Y 0.40 g/lt, methylene blue 0.065 g/lt, agar 13.50 g/lt.

Using EMB agar, *A. baumannii* was cultivated, however because it was unable to digest lactose, a crucial element of this medium, the colonies were colorless.

Figure 2: *A. baumannii* on EMB agar

2.11. Gram-stain procedure

The suspension with bacteriae was prepared on the clean slide with a loopful of sample. After air dried Crystal Violet (Merck) was poured and kept for about 30 seconds to 1 minutes and rinsed with water. Lugol was added for one minute and washed with water. Then 95% alcohol was added for about 10-20 seconds and rinsed with water. The safranin was added for about one minute and washed with water. With the microscope reveal gram negative coccobacilli.

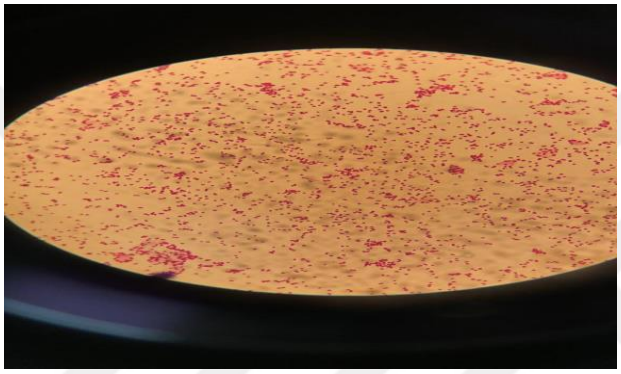

Figure 2: *A. baumannii* Gram-stain

2.12 Procedure of Vitek 2

Using Vitek 2 (bioMérieux, France), the turbidity of the bacterial suspension was modified to match the McFarland standard of 0.5 in 0.45% sodium chloride. For identification the Vitek 2 GN ID card, for antibiotic susceptibility Vitek 2 NF 64 card were used and bacterial suspension was manually added. A sterile swab or applicator stick is used to transfer a sufficient number of colonies of a pure culture and to suspend the microorganism in 3.0 mL of sterile saline (aqueous 0.45% to 0.50% NaCl, pH 4.5 to 7.0) in a 12 x 75 mm clear plastic (polystyrene) test tube. The turbidity is adjusted accordingly and measured using a turbidity meter called the Vitek DensiChek (bioMérieux, France). Identification cards are inoculated with microorganism suspensions using an integrated vacuum apparatus. A test tube containing the microorganism suspension is placed into a special rack (cassette) and the identification card is placed in the neighboring slot while inserting the transfer tube into the corresponding suspension tube.

Vitek 2 automatised system conducted tests on antibiotic susceptibility for ampicillin, amoxicillin, piperacillin/tazobactam, and amoxicillin/clavulanic acid antibiotics, as well as ampicillin/sulbactam, meropenem, ertapenem, gentamicin, ciprofloxacin, tobramycin, levofloxacin, amikacin, tigecycline. Growth-based technology is employed by the automated microbiology system known as Vitek 2 automatised system. This system has colorimetric reagent cards that are incubated and analyzed automatically. AES, which analyzes minimum inhibitory concentration (MIC) patterns and finds phenotypes for the majority of the tested organisms, is a component of the system. Rapid outcomes enable doctors to stop prescribing empiric medicine in favor of tailored therapy, improving patient outcomes and increasing antibiotic stewardship. 64 microwells may be found on the Vitek 2 (bioMérieux, France) card. Each well has a substrate for antibacterial or detecting purposes.

2.5. Statistical analyses

After assigning appropriate codes, the data were entered into SPSS software and analyzed. According to the goals of this investigation, descriptive statistics were used to report the sensitivity of blood infection with *A. baumannii*. Also, age groups were considered in the sample report. Data were analyzed using the Chi-square statistical and an independent t-test with a significance level of 0.05.

3. Results

In this investigation, a total of 117 positive samples of *A. baumannii* were identified during the years 2018 and 2019. 59.8% of the samples belonged to men (Table 1).

Table 1: Gender distribution of the studied samples

gender	Frequency	Percent
Female	47	40.2
Male	70	59.8
Total	117	100.0

The average age of people was 67.31±15.11 years, of which 65.8% of people were 65 years old or older. The majority of *A. baumannii* positive blood culture samples (90.6%) were obtained from patient who were under intensive care unit. The most positive samples were obtained from the departments of internal medicine (29.1%) and neurology (10.3%) (Figure 3).

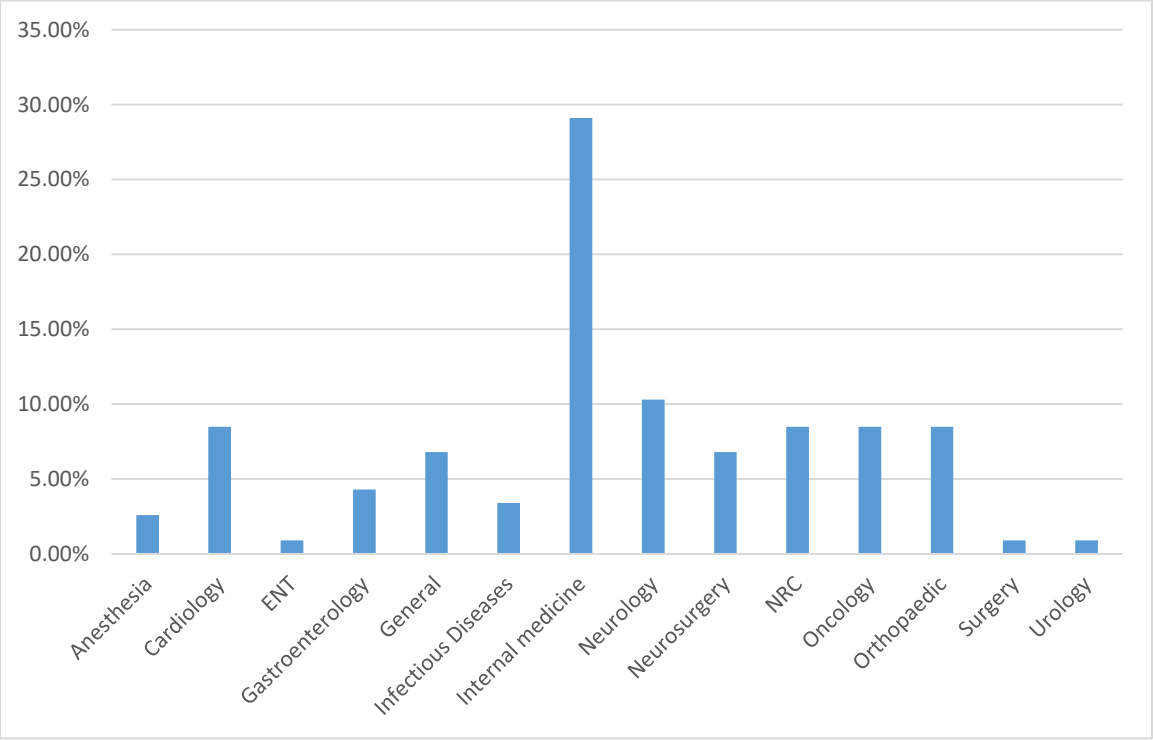

Figure 3: Departments which positive blood culture samples were sent.

MDR species made up 88.9% of the recognized *A. baumannii* species. The samples obtained from different hospital departments had almost the same distribution of MDR species. The majority of MDR *A. baumannii* cases were obtained from patients under intensive care unite (89.4%), but on the other hand, all samples that were not MDR *A. baumannii* were also obtained from these patients. There is not significant difference between the patients who have multidrug-resistant and no multidrug-resistant ($p>0.05$). The amount of *A. baumannii* species identified in blood cultures with multidrug resistance (MDR) by the relevant hospital departments were shown in Table 2.

Table 2: The amount of *A. baumannii* species identified in blood cultures with multidrug resistance (MDR) by the relevant hospital departments

	MDR
	Positive
Anesthesia	2 (66.7%)
Cardiology	9 (90%)
ENT	1 (100%)
Gastroenterology	4 (80%)
General	7 (87.5%)
Infectious Diseases	4 (100%)
Internal medicine	28 (82.4%)
Neurology	11 (91.7%)
Neurosurgery	8 (100%)
Nutrition Rehabilitation Centers (NRC)	10 (100%)
Oncology	10 (100%)
Orthopaedic	8 (80%)

Surgery	1 (100%)
Urology	1 (100%)
Total	104 (88.9%)

The average age of patient who had MDR *A. baumannii* species in blood culture was 66.55±15.37, which was lower than the average age of others. However, the results of the independent T-test showed no difference in the age of people with MDR *A. baumannii* and without MDR *A. baumannii* (P>0.05). The evaluation of the age group demonstrated that there was a greater incidence of MDR in people aged 64 years and younger, and there was no significant difference revealed by the chi-square test findings (P>0.05)

A. baumannii species identified in the blood culture showed the highest antimicrobial resistance to meropenem (99.1%). Resistance to other carbapenems was also high, and the lowest resistance was related to imipenem (79.5%). Three antibiotics, amoxicillin/clavulanic acid, ampicillin and ampicillin/sulbactam, showed the same resistance (90.6%) to *A. baumannii*. Among cephalosporins, cefotaxime and ceftazidime showed the highest sensitivity and the highest resistance, respectively, both of which are third-generation cephalosporins. Resistance to quinolones was also high in the identified species, so that less than 6% of *A. baumannii* identified were sensitive to ciprofloxacin or levofloxacin. Aminoglycoside antibiotics were more effective than quinolones. The resistance rate for amikacin, tobramycin and gentamicin was 74.4%, 82.1% and 87.2%, respectively. Colistin showed almost adequate sensitivity so that only 17.1% of species showed some degree of resistance to this drug. No cases of resistance to tigecycline were reported, and this antibiotic was completely effective against *A. baumannii* strains. All susceptibilities that are all antibiotics have resistance only tigecycline antibiotic that are totally effective to *A. baumannii.* Antimicrobial sensitivity of *A. baumannii* species were shown in Table 3

Table 3: Antimicrobial sensitivity of *A. baumannii* species identified in blood culture

	Sensitive	Resistant
Amoxicillin/clavulanic acid	11 (9.4%)	106 (90.6%)
Ampicillin	11 (9.4%)	106 (90.6%)
Ampicillin/sulbactam	11 (9.4%)	106 (90.6%)
Piperacillin/tazobactam	112 (95.7%)	5 (4.3%)
Cefoxitin	20 (17.1%)	97 (82.9%)
Cefotaxime	22 (18.8%)	95 (81.2%)
Ceftazidime	6 (5.1%)	111 (94.9%)
Cefepime	10 (8.5%)	107 (91.5%)
Gentamicin	15 (12.8%)	102 (87.2%)
Amikacin	30 (25.6%)	87 (74.4%)
Tobramycin	21 (17.9%)	96 (82.1%)
Ciprofloxacin	5 (4.3%)	112 (95.7%)
Levofloxacin	6 (5.1%)	111 (94.9%)
Imipenem	24 (20.5%)	93 (79.5%)
Meropenem	1 (0.9%)	116 (99.1%)
Ertapenem	10 (8.5%)	107 (91.5%)
Tigecycline	117 (100%)	0 (0.0%)
Colistin	97 (82.9%)	20 (17.1%)

4.Discussion

A. baumannii has emerged as the most common cause of bloodstream infections (BSI) in hospitalised patients. Blood culture is one of the most important samples examined by the clinical microbiology laboratory, which is the primary and most sensitive method for diagnosing bloodstream infections (bacteremia, mycosis, and sepsis), and in addition, it also affects the appropriate antimicrobial treatment of patients (Snyde., 2015). Because blood is usually a sterile medium, a positive blood culture with a known pathogen such as A. baumannii generally has a high positive predictive value for infection. Therefore, in the present study, the results of blood cultures from patients were examined.

A. baumannii has become the main cause of bloodstream infections among hospitalized patients (Perez et al., 2010). According to the definition of the American Burn Association for the diagnosis of bloodstream infection, the patient's blood culture must detect a known pathogen in two or more separate samples or in a single sample but with signs of sepsis (Saffle et al., 2007). In the present study, since only one sample from each person was examined and the clinical symptoms related to sepsis were not evaluated in the patients, it was not possible to determine the amount of bloodstream infection. There is limited information on bloodstream infections caused by MDR A. baumannii. A study examining patients with bloodstream infections caused by carbapenem-resistant A. baumannii reported a 30-day mortality rate of 48%. In this study, the severity of the disease and the presence of immunosuppression were the only two predictors of 30-day mortality (Tseng et al., 2007).

In Xie et al.'s study, the incidence of imipenem resistance was discovered by looking at the global prevalence of antibiotic resistance in *A. baumannii* infections. From 2011 to 2016, it was 73.9-77.8%. This resistance rate had increased dramatically compared to 2005-2000 when the resistance was only 23.8% (Xie et al., 2018). In the current research, 79.5% resistance to imipenem was reported, which is consistent with the above results and shows that the resistance of *A. baumannii* strains to imipenem is increasing over time. Of course, a recent study in Jordan reported the *A. baumannii* resistance strains to meropenem and imipenem as 68.9% and 75.1%,

respectively, which is lower than the values obtained in the present research. Geographical differences and the health system of hospitals can be involved in these differences (Al-Tamimi et al., 2022).

The carbapenem-hydrolyzing oxacillinase OXA-51 found in *A. baumannii* only imparts resistance to carbapenems when it is overexpressed. Oxcillinase production of OXA-23, the OXA-58-like, the OXA-235-like, the OXA 24/40-like, or the OXA 143-like by *A. baumannii* is the most commonly acquired method leading to carbapenem resistance (European Center for Disease Prevention Control, 2016). According to a study in Turkey, previous use of carbapenem and aminopenicillin can increase the risk of resistance to carbapenems in *A. baumannii* strains (Aydemir et al., 2012). Studies show that carbapenem resistance is increasing in *A. baumannii*, and in various areas, particularly in the Middle East and Europe, most *A. baumannii* strains are resistant to carbapenems (Lob et al., 2016; Suetens et al. al., 2018). These facts justify the very high prevalence of resistance to ertapenem (91.5%) and meropenem (99.1%) in the present study. tigecycline, Colistin, and more recently, cefiderocol, when available, are the major treatments for *A. baumannii* that is resistant to carbapenems (Piperaki et al., 2019).

Since the initial discovery of colistin resistance in *Acinetobacter* species in 1999 in the Czech Republic, reports from all over the world have risen (Manchanda et al., 2010). In some regions like the United States (5.4%), the United Kingdom (2%), and Jordan (2.3%), the reported resistance rate is low (Al-Tamimi et al., 2022; Henwood et al., 2002; Queenan et al., 2012). However, reports of high resistance of this organism to colistin have been observed in India (53%), Iran (48%), Korea (30%), and Spain (40.7%) (Asif et al., 2018). In the present investigation, the prevalence of resistance to colistin was reported as 17.1%, which is an average number compared to the mentioned values. Colistin is considered as one of the treatments for multi-drug resistant *A. baumannii* infection in many studies. So that a study by examining samples from a hospital in Izmir, Turkey, demonstrated that colistin was effective against all MDR strains (Ece et al., 2014). Therefore, considering that the level of resistance in the present study was not high, it can be one of the treatment options for patients infected with *A. baumannii* who do not respond to common antibiotics. A recent systematic review exploring the colistin resistance pathways in *A. baumannii* strains showed that numerous mutations were detected in the majority of instances in the

chromosomal locus of pmrCAB (mainly pmrB), which lead to the upregulation of pmr genes (Karakonstantis, 2020). This chromosomal locus regulates a phosphoethanolamine transferase (pEtN) encoded by pmrC, which modifies the lipid A component of LPS to reduce its negative charge and subsequently reduce positively charged colistin's binding (Beceiro et al., 2011).

Various studies have used the Vitek 2 system to check antibiotic sensitivity for different bacteria, including *A. baumannii*. The results show that this system is highly accurate and provides antibiotic sensitivity results in a relatively short time (Bobenchik et al., 2015; Dimitriadis et al., 2016; Leal Castro et al., 2010; Sanders et al., 2001). Nevertheless, the Vitek 2 system's ability to precisely identify antibiotic resistance to particular types of drugs, including tigecycline, colistin, and minocycline is debatable because, according to some reports, it may overestimate the resistance to these antibiotics (Dimitriadis et al., 2016; Kulah et al., 2009; Tan et al., 2007).

In addition, discrepancies in the results reported by the disc diffusion test and Vitek2 have been noted for imipenem and meropenem susceptibility.

Similar inconsistencies with the Vitek 2 test have been noted in other investigations, which is more consistent with broth microdilution (Bobenchik et al., 2015; Dimitriadis et al., 2016; Yong et al., 2012). However, this system has a very small error, and in many studies to investigate the antimicrobial sensitivity of *A. baumannii* has been used (Al-Tamimi et al., 2022; Ece et al., 2015). Therefore, in the present study, we used the Vitek 2 system to check antibiotic sensitivity.

Some studies have reported low *A. baumannii* resistance to aminoglycosides. Research in Brazil reported 21.4% resistance of this pathogen to amikacin (Castilho et al., 2017). However, the outcomes of investigations conducted in closer countries are more similar to the outcomes of the current research. A recent study by Al-Tamimi in Jordan showed the resistance of *A. baumannii* strains to aminoglycosides from 37.2% for tobramycin, 37.1% for amikacin to 62.6% for gentamicin (Al-Tamimi et al., 2022). In the present study, resistance to these three antibiotics was also observed, and similarly, the highest resistance was related to gentamicin (¬87.2%). However, the level of resistance to these three antibiotics was much higher than in the above study. On the other hand, Rashvand et al., in a research on 192 *A. baumannii* strains isolated from hospitalized patients in Iran, reported 98.4%, 83.9%, and 97.9% resistance to gentamicin, amikacin, and tobramycin respectively. These values are higher than what was obtained in the

current research. However, the pattern of resistance to aminoglycosides was consistent with the present study, so that the lowest resistance to amikacin and the highest resistance to gentamicin was observed (Rashvand et al., 2021).

In past studies, *A. baumannii* strains have shown relatively strong resistance to cephalosporins. A recent study reported resistance rates for cefoxitin, ceftazidime, and cefepime of 99.5%, 77.9%, and 81.9%, respectively (Al-Tamimi et al., 2022). While in the current research, the resistance rate of these three drugs was reported as 82.9%, 94.9% and 91.5%, respectively. Except for cefoxitin, the rate of resistance was higher in the present study. A study in China mentioned the rate of resistance to cephalosporins is much less than the present study. They reported 61% and 59.6% resistance of *A. baumannii* strains to ceftazidime and cefepime, respectively (Qi et al., 2016). *Acinetobacter*-derived cephalosporinases, which are present in all strains of *A. baumannii* and are relatively comparable to the AmpC enzymes found in Enterobacter and other Enterobacterales are chromosomal AmpC-type enzymes (Bergogne-Berezin & Towner, 1996). Broad-spectrum cephalosporins become resistant to overexpression of these enzymes, however, cefepime and carbapenem antibiotics continue to function. *Acinetobacter* species have a wide range of extended-spectrum beta-lactamases (ESBLs), and these enzymes resemble those found in other Enterobacterales and *Pseudomonas aeruginosa*. Hospital surroundings can be adapted by *Acinetobacter* spp. by horizontally transferring resistance islands containing plenty of resistance genes and rearranging already existing genes (Snitkin et al., 2011).

Fluoroquinolones have demonstrated a good efficacy against isolated *A. baumannii* in the last four decades. Nevertheless, these medications' resistance has quickly evolved (Mohammed et al., 2020). In the current research, the resistance level to fluoroquinolones was very high, so that after imipenem, the highest resistance to ciprofloxacin (95.7%) and levofloxacin (94.9%) was reported. In a study in China, the rate of resistance to ciprofloxacin was informed to be 65.8% (Qi et al., 2016), which was much lower than the outcomes of the present research. The cause for this difference can be associated with the difference in the geographical area. The resistance rate of *A. baumannii* strains in China is lower compared to the Middle East, so that the highest resistance to mezlocillin was reported, which was only 78.3% (Qi et al., 2016). This shows that the reported resistance of ciprofloxacin was almost high in the research area, which is dependable with the pattern of resistance in the present study. Topoisomerase IV and DNA gyrase are two genes in the

quinolone resistance determining region (QRDR) that spontaneously mutate when exposed to fluoroquinolones. High levels of resistance to fluoroquinolones are linked to mutations that limit the drug's capacity to function on its targets, such as topoisomerase IV C (parC) subunits or DNA gyrase (gyrA) (Kakuta et al., 2020).

The first compound in the family of glycylcyclines of antibiotics, gecycline, is effective against infections with *A. baumannii* and exhibits bacteriostatic action through binding to the 30S ribosomal subunit (Anthony et al., 2008; Koomanachai et al., 2009; Pachón-Ibáñez et al., 2004). With some antibiotic classes, such as amikacin, tigecycline has a synergistic effect (Moland et al., 2008) and colistin (Yilmaz et al., 2012). The resistance of *A. baumannii* strains to tigecycline was reported as 7.2% in a study in Jordan (Al-Tamimi et al., 2022). Another study on patients hospitalized in ICU in Brazil also reported a 7.1% resistance of *A. baumannii* strains to tigecycline (Castilho et al., 2017). In comparison, some other studies have reported 20% resistance of this pathogen to tigecycline (Tewari et al., 2018). In the current research, tigecycline presented a much higher sensitivity so that no strain showed resistance to it. Therefore, tigecycline may serve as an alternative drug for the treatment of drug-resistant strains; however, there is disagreement about whether it should be used alone or in addition to other antibiotics. (Hagihara et al., 2014).

In the current research, the resistance of *A. baumannii* strains to piperacillin/tazobactam was very low, so that 95.7% of the strains were completely sensitive to this antibiotic. These findings do not agree with those of earlier investigations. A study in India reported the sensitivity of *A. baumannii* strains to piperacillin/tazobactam as 33.3% (Tewari et al., 2018).

Some other studies also reported the results of high resistance of *A. baumannii* strains to piperacillin/tazobactam (Van et al., 2014). Some studies showed lower resistance. A study in China showed resistance to piperacillin/tazobactam in 48.9% of strains (Qi et al., 2016). However, the values reported in this study show that, unlike previous studies, piperacillin/tazobactam is one of the sensitive antibiotics for treating *A. baumannii* infection, and even its sensitivity was higher than colistin.

A study in Brazil identified 56 *A. baumannii* infections by examining patients in 5 ICUs. According to their review, 91.1% of the identified strains were MDR-type (Castilho et al., 2017).

Research by Tewari et al. informed the prevalence of MDR among *A. baumannii* strains isolated from hospital patient samples in India to be 86.6% (Tewari et al., 2018). Nazmul et al. reported 85% multidrug-resistant *Acinetobacter* isolates (Nazmul et al., 2012), while a study in Iran reported 95% MDR prevalence among *A. baumannii* strains (Vakili et al., 2014). The definition of MDR in the present study was the same as the standard definition, which included non-susceptibility (intermediate susceptibility or resistance) to ≥1 agent in ≥3 antimicrobial classes (Magiorakos et al., 2012). In the current research, the prevalence of MDR isolates was 88.9%, which is very close to the results of the above studies. These findings show that the prevalence of multi-drug resistant *A. baumannii* strains is high in the study area as in other Middle East regions, and finding the most sensitive antibiotic is important to determine an appropriate treatment strategy.

5.Conclusion

A. baumannii isolates in the present research did not show any resistance to tigecycline. In fact, the only drug that showed 100% sensitivity to *A. baumannii* was tigecycline. It seems that using this drug for the treatment of MDR isolates can be a very good option. Since resistance to colistin was lower than other antibiotics in this study, this drug can also be used to treat *A. baumannii* infections. As previously explained, combined treatment with tigecycline and colistin can be more effective than single drug use. Therefore, the use of these two drugs is recommended for the treatment of *A. baumannii* infections.

The new finding of the present study was the high sensitivity of *A. baumannii* isolates to piperacillin/tazobactam. This is while this organism has shown relatively high resistance to piperacillin/tazobactam in other studies. The reason for this high sensitivity in the present study is not clear at all due to the high resistance of the other two combined drugs. But the use of this drug can also be one of the treatment options for MDR cases in the studied geographical area.

The prevalence of MDR strains in the current research was 88.9%, which shows that this organism has high resistance to different antibiotics in the studied treatment center. In general, the pattern of antimicrobial resistance in the examined sample was consistent with previous studies, and previous recommendations that combined treatment with tigecycline and calcitin can be the best choice in cases of treatment-resistant infection with *A. baumannii* were confirmed in the present study.

6.RECOMMENDATION :

Because the vast majority of Acinetobacter baumannii have developed strains resistant to all antibiotics, more research is necessary to find new antibiotics.

To prevent the spread of resistance genes, focus on personal protective equipment and reduce the use of antibiotics at random both inside and outside of hospitals.

The doctor's prescribed antibiotics must be used.

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