Review Article

Acinetobacter baumannii

A multidrug-resistant pathogen, has emerged in Saudi Arabia

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ABSTRACT

بعض الامراض الانتهازية التي تسببها بكترياء ومنها Acinetobacter baumannii (A. baumannii) تطورت المقاومة لمجموعة واسعة من المضادات المكروبات ومنها مضاد carbapenems. في هذه المقالة العلمية، قمنا بتقييم الانتشار وعوامل الخطر والحساسية لمضادات للميكروبات وآليات المقاومة بين A. baumannii في عدة مواقع في المملكة العربية السعودية.ان العدوى المكتسبة من المستشفيات الناجمة عن A. baumannii كانت سائدة في البلاد لأسباب متنوعة ، مثل ارتفاع عدد المرضى المصابين بأمراض خطيرة ، وتكرار التهاب والاستعمار الجهاز الهضمي والاستخدام الواسع النطاق للأدوية المضادة للميكروبات. كانت هناك زيادة في وتيرة A. baumannii وانتاج سلالات مقاومة للعديد من مضادات الميكروبات، بما في ذلك carbapenems. ان المستشفيات هي أرض مناسبة لمقاومة الأدوية المتعددة للبكترياء ونها A. baumannii بسبب الاستخدام الواسع النطاق للمضادات الحيوية، إمكانية انتقال البكتيريا من مريض لآخر وارتفاع مخاطر العدوى أثناء إجراءات في وحدة العناية المركزة، والتردد العالي الذي يخضع به مرضى السكري والسرطان في المستشفيات لإجراءات تشخيصية وعلاجية. تظل مجموعات colistin، tigecycline، مع carbapenems وبعض المضادات الحيوية الأخرى هي أفضل خيار علاجي وهي آمنة نسبيا لعلاج المرضى الذين يعانون من مقاومة الأدوية المتعددة A. baumannii والعدوى، على الرغم من ارتفاع معدل مقاومة هذه الأدوية التي لوحظت في العديد من المستشفيات انتشار A. baumannii المقاوم لمجموعة من الأدوية في المستشفيات السعودية تدعو إلى بحث متعمق في الآليات الجزيئية الأساسية للأدوية المقاومة بالاضافة. فقد تكون افضل لفهم A. baumannii ان أنماط المقاومة وإنشاء بروتوكول علاجي لتخفيف عبئ العدوى في المملكة العربية السعودية يمكن ان تستفيد من تنفيذ قاعدة بيانات محلية للمضادات الحيوية جنبا الى جنب مع برنامج وطني للاشراف على مضادات الميكروبات والوقاية من العدوى.

A significant opportunistic pathogen, *Acinetobacter baumannii* (*A. baumannii*) has evolved mechanisms of resistance to a wide variety of antimicrobials, including carbapenems. In this article, we assessed the prevalence, risk factors, antimicrobial sensitivity, and resistance mechanisms among *A. baumannii* in several locations in Saudi Arabia. Hospital-acquired infections caused by *A. baumannii* were prevalent in the country due to a variety of reasons, such as the high number of critically ill patients, the frequency of gastrointestinal colonization, and the widespread use of antimicrobial medications. There has been an increase in the frequency of *A. baumannii* strains that are resistant to several antimicrobials, including carbapenems. Hospitals are a breeding ground for multidrug-resistant *A. baumannii* due to the widespread use of broad-spectrum antibiotics, the potential for patient-to-patient transmission of the bacteria, the high risk of infection during invasive intensive care unit procedures, and the high frequency with which diabetic and cancer patients in hospitals undergo invasive diagnostic and therapeutic procedures. Combinations of colistin and tigecycline with carbapenems or other antibiotics remain the best treatment option and are relatively safe to treat patients with multidrug resistance (MDR) *A. baumannii* infections, despite the rising incidence of resistance to these drugs observed in many hospitals. The prevalence of multidrug-resistant *A. baumannii* in Saudi hospitals calls for in-depth research into the underlying molecular mechanisms of multidrug resistance. In addition, a better understanding of *A. baumannii* resistance patterns and the establishment of a treatment protocol to reduce the infection burden in Saudi Arabia could benefit from the implementation of a local antibiogram database in tandem with a national antimicrobial stewardship and infection prevention program.

Keywords: revised manuscript multi-drug resistance, risk factors, carbapenem resistance mechanisms, mechanisms of resistance, Saudi Arabia

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Acinetobacter baumannii (*A. baumannii*) is a type of coccobacillus that is gram-negative and aerobic, capable of growing at 44°C. However, extracting the bacteria from the strain can be challenging, leading to it being mistakenly identified as Gram-positive. It is pleomorphic, non-fermentative, non-fastidious, and pH- and temperature-tolerant, with a deoxyribonucleic acid (DNA) G+C composition of 39% to 44%.[1]

To identify *A. baumannii* accurately, several sophisticated molecular diagnostic procedures have been developed, including the analysis of the restriction of the amplified 16S Ribosomal ribonucleic acid (rRNA) gene.[2] Transfer ribonucleic acid (tRNA) spacer fingerprinting, 16S-23S rRNA intergenic spacer restriction analysis, 16S-23S rRNA gene spacer sequence analysis.[3,4] and sequencing of the rpoB (RNA polymerase β-subunit) gene and its flanking spacers.[5]

Epidemiology. The bacteria are capable of surviving on dry surfaces for a period of 5 months, presenting a problem for infection control methods in hospitals.[6] As a result, the microbe is now recognized as a potentially devastating nosocomial disease, which might lead to a pandemic. Although the bacterium is often found in healthcare facilities, the first infection might be spread by individuals admitted from outside facilities.[7] It has been found that the prevalence of *A. baumannii* infection is widespread, and several studies have investigated the factors that lead to multidrug resistance (MDR) *A. baumannii* infections worldwide.[8] A multinational study of intensive care units (ICUs) revealed that the prevalence of *A. baumannii* infection is 14.8% in Africa, 5.6% in Western Europe, 3.7% in North America, 13.8% in Central and South America, 17.1% in Eastern Europe, 4.4% in Oceania, and 19.2% in Asia.[1]

The source contamination of *Acinetobacter* outbreaks, including contaminated respiratory and mechanical ventilators, and cross-infection through contaminated hands of healthcare staff caring for colonized or infected patients, have been implicated as the cause of the epidemic.[9] The numerous risk factors related to the formation or infection by MDR *A. baumannii* include previous exposure to long-term antimicrobial medical aid, mechanical ventilation, length of hospital stay, disease severity, current surgery, and various invasive procedures.[10]

As part of the treatment options for *A. baumannii* infection, carbapenems became imperative in treating the infection before the outbreak of the carbapenem-resistant *A. baumannii*, which emerged around the early 1990s, extending to the Middle East in 2006, and became a serious concern around 2015 in the European Union.[11,12] A recent study by Ibrahim[13] (2019) has demonstrated the outbreak of *A. baumannii* infection in Saudi Arabia, which is an area of interest in this study. According to Ibrahim (2019), the high rates of MDR *A. baumannii* in Saudi hospitals indicate that intense research around this area is required alongside investigations on the current therapeutic effects arising from the increased risk of MDR *A. baumannii* in Saudi Arabia.[13]

Several studies in Saudi Arabia have evaluated the risk factors for infection with *A. baumannii.*[13] A 2001 study reported prevalence of endemic strains of *A. baumannii* in ICU patients on mechanical ventilation and found that tracheal secretions were the site of colonization among these patients.[14] A 2013 study reported that during an epidemic in the adult ICU of a tertiary hospital in Riyadh, *A. baumannii* was also identified and was found extensively in an intensive care unit setting, including on a stethoscope and the computer mouse, increasing the possibility that medical professionals may be responsible for transporting the clones.[15] Another study reported that the presence of additional comorbidities, surgical procedures, and mechanical ventilation were the main risk factors for infection. According to the study, *A. baumannii*, which later developed into MDR bacteria, was caused by a contaminated ventilator. Furthermore, ICU admission is a significant risk factor for ventilator-associated pneumonia caused by *A. baumannii*. It has been noted in the literature that patients over 60 years of age, who used artificial ventilation for an extended period of time, were more likely to develop infections.[16] Moreover, another study found that the risk of infection increased with ICU admission, increase in the patient's age, the use of catheters or intubation, prior surgery, and prolonged hospital admission.[17] *A. baumannii* colonization of the gastrointestinal tract in intensive care unit patients is a significant risk factor for the development of antibiotic resistance, leading to an increase in the severity of the disease and acting as a critical reservoir for clinical infections and hospital outbreaks. Reducing the duration of breathing by utilizing ventilator care packages and encouraging gastro-oral intubation rather than nasogastric intubation are the necessary control

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measures to reduce the risk factors for *A. baumannii* infection.[13] Clinical evidence from Saudi Arabia and other countries across the world has demonstrated that people suffering from diabetes are more likely than the general population to become seriously infected with *A. baumannii*.[18] *Acinetobacter baumannii* is becoming more resistant to several antibiotic classes, according to several key Saudi Arabian investigations. A retrospective investigation at Riyadh Military Hospital from 2005 to 2010 found a rise in multiple-resistant *A. baumannii* blood culture isolates.[19] Establishing routines to improve hand washing, staff education, and environmental decontamination of hospital critical care areas is essential to prevent such epidemics.[15]

Acinetobacter baumannii resistance mechanism. The majority of *A. baumannii* are currently completely resistant to broad-spectrum antibiotics in clinical use. *Acinetobacter baumannii* exhibits several resistance mechanisms that target various classes of antibiotics.[20] The lack of novel antibacterial chemicals and *A. baumannii* poses significant issues for the healthcare sector.[21]

There are several mechanisms of resistance development against antibiotics in *A. baumannii*. The first mechanism is the membrane permeability reduction, therefore increasing the efflux pump and preventing antibiotic access to the target.[22] The overexpression of efflux pumps prevent antibiotics such as tetracyclines from reaching its target. The adeABC efflux system, the mechanism used by *A. baumannii* to eject antibacterial agents from the cell, decreasing antibiotics accumulation.[23]

The second mechanism involves the inactivation of antibiotics directly by modification or hydrolysis, and lastly, bacterial genetic mutation or post-translation can help in the protection of the antibiotic target.[24] *Acinetobacter baumannii* has a remarkable genetic plasticity that allows for rapid genetic mutation and integration of foreign determinants carried by mobile genetic elements.[24] Additionally, *A. baumannii* exhibits a number of resistance mechanisms that impact several antibiotic classes, including changes in proteins in the outer membrane and the formation of β-lactamases, enzymes that change aminoglycosides, permeability issues, and altered target locations *A. baumannii* resistance mechanisms in humans to β-lactams (enzymes that break down β-lactams antibiotics, such as penicillins, cephalosporins, carbapenems, monobactams, and β-lactamase inhibitors.[10] These β-lactamase enzymes are classified into 4 Ambler classes (A-D), which depend on the sequence of amino acids.[25] Ambler class A are the most common source for resistance against β-lactams, both natural and acquired resistance. The most common enzymes are *Klebsiella pneumoniae* carbapenemase (KPC), cefotaximase (CTX-M), temoneira (TEM), and sulfydryl variant (SHV).[26] While Ambler class B enzymes are associated with gene cassettes of integrons.[27] the primary enzymes are New Delhi metallo-β-lactamase (NDM) Verona integron-borne metallo-β-lactamase (VIM), Sao Paulo metallo-beta-lactamase (SPM), and Imipenemase (IMP). Cephalosporin antibiotic resistance is attributed to Ambler class C anzymes. The primary enzyme in this class is Acinetobacter-derived cephalosporinase (ADC).[28] Finally, Ambler class D enzymes, specifically OXA (oxacillinase) are associated with resistance to carbapenems in *A. baumannii*.[25] Modification of targeted mmolecule can lead to resistance such as lipid A structure and downregulation of lipopolysaccharid (LPS) lead to polymyxin resistance. Polymyxin destroy the outer-membrane of the bacteria by interacting with lipid *A. baumannii* to the *lpxA*, *lpxC,* and *lpx* genes affect lipid a synthesis, resulting in increased resistance against polymyxin. Therefore, to avoid treatment failure, a combination therapy of polymyxin with colistin was found to be superior against *A. baumannii*.[25]

In this review, *A. baumannii* mechanisms of resistance to different classes of antibiotics are explored in detail. This aims to aid with future perspectives for the early identification of resistant genes. The antibiotic classes include aminoglycosides (amikacin, gentamycin and tobramycin), carbapenems (imipenem, meropenem), tetracyclines (tetracycline, doxycycline), fluoroquinolones (ciprofloxacin, levofloxacin), macrolides (azithromycin, erythromycin), lincosamides (licomycine, clindamycin), cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime). streptogramin (virginiamycin, pristinamycin), polymyxins (polymyxin b, colistin), and others such as amphenicols, oxazolidinones, rifamycins, fosfomycin, diaminopyrimidines, sulfonamides, glycopeptide, and lipopeptide antibiotics. Modulation of antibiotic transport across bacterial membranes, changes in the antibiotic target site, and enzyme modifications that neutralize antibiotics are all components of antimicrobial resistance. In addition, the review examines virulence variables that influence antibiotic sensitivity and medication resistance. Resistance profiles and MDR genes were analyzed for *A. baumannii* co-infected with SARS-CoV-2 during the COVID-19 pandemic.[1]

Multidrug-resistance. *Acinetobacter baumannii* is a human pathogen that results in a large number of infections and is also known to be multidrug-

resistant (MDR) pathogen associated with hospital-acquired infections.[29] According to the World Health Organization, *A. baumannii* is one of the most resistant organisms, and may develop biofilms on numerous abiotic surfaces, which may help them survive in hospitals and cause healthcare-associated illnesses and outbreaks.[30,31]

Acinetobacter baumannii infections are commonly found in patients with bloodstream infection (BSI), ventilator-associated pneumonia (VAP), severe and invasive (usually nosocomial) infections with significant mortality rates, and nosocomial meningitis.[24] Infections such as hospital-acquired pneumonia and ventilator-associated pneumonia (HAP, VAP), urinary tract infections, meningitis, bacteremia, as well as gastrointestinal and skin/wound diseases, are examples of the wide variety of infections that may occur due to this pathogen.[32] The factors that increase the risk of developing *A. baumannii* infections include previous surgery, immunosuppression, and antibiotic therapy. According to Lockhart et al[33] (2007), *A. baumannii* cases are increasing, which accumulate resistance determinants causing MDR strains and outbreaks due to the bacterium's ability to survive for long periods through the hospital environment. MDR phenomenon has become a serious concern as identified by the World Health Organization (WHO) with regard to nosocomial and community-acquired infections.[34]

Community-based *A. baumannii* infections are spreading worldwide, and the World Health Organization (WHO) has listed Carbapenem-resistant *A. baumannii* (CRAB) as the top priority for antibiotic research and development in 2018. Since carbapenem resistance is often linked with a wide variety of co-resistance to other antibiotic classes, it was employed as a marker for this pathogen.[35] Carbapenem-resistant *A. baumannii* infections are a significant challenge to hospitals due to the difficulty of treatment. Carbapenem-resistant *A. baumannii* infections are mostly found in wounds and respiratory specimens.[36] Its infections are very limited and the treatment profile is limited. Therefore, there is currently no clear establishment of antibiotic treatment protocol or effective comparison research for CRAB infections.[36] The most common therapy for carbapenem resistant Gram negative bacteria is meropenem or Fosfomycin, both have nephrotoxic side-effects.[36] Recently Cefiderocol, a cephalosporin, was found to have lower 30-days mortality rate compared to the control group of hospitalized patients. In addition, cefiderocol was effective in 70% of treated patients, without sever adverse events reported.[37] However, it is necessary to conduct further examination on more diverse group of patients to validate the effectiveness of cefiderocol compared to colistin treatments.

Extreme drug resistant (EDR) *A. baumannii* is a highly resistant pathogen that can cause serious infections such as bacteraemia and ventilator-associated pneumonia in healthcare settings. The increase in infections caused by this organism is due to the inappropriate and excessive use of broad-spectrum antibiotics, which leads to adaptive selection of resistant isolates and horizontal transmission of resistance mechanisms. Treatment options for XDR *A. baumannii* are limited and there are no clear clinical practice guidelines for managing these infections. This poses a significant challenge for clinicians and contributes to the high morbidity and mortality rates associated with XDR *A. baumannii* infections globally.[38]

The aim of this study is to succinctly review recent progress in *A. baumannii* in order to provide the latest data on infectious cases in Saudi Arabia.

Antimicrobial resistance emerging in Riyadh and Buraidah, Saudi Arabia. The emergence of nosocomial MDR *A. baumannii* in several hospitals in Saudi Arabia has become a significant healthcare and economic concern.

Saudi Arabia is split into 5 main regions: Riyadh, Eastern, Northern, Southern, and Western areas. In Riyadh, *A. baumannii* has been evaluated for susceptibility to several antibiotic groups. Research from 2004 to 2009 in the adult ICU of King Fahad National Guard Hospital found the susceptibility of *A. baumannii* to imipenem (55% to 10%), meropenem (33% to 10%), ciprofloxacin (22% to 10%), and amikacin (12% to 6%) was greatly reduced.[39] In another study, 253 *A. baumannii* isolates from patients at King Abdulaziz Medical City Hospital, Riyadh between 2006 and 2008 were assessed. Out of the 253 patients, 92.1% were resistant to meropenem, whereas 79.1% were resistant to imipenem.[40] According to another study, at Riyadh Military Hospital between January to December 2009, the results indicated that 96% of *A. baumannii* cases were resistant to amoxicillin/clavulanic acid, 93% were resistant to piperacillin/tazobactam, and 92% were resistant to ciprofloxacin.[41] Out of the 27 *A. baumannii* isolates from a tertiary hospital from January through December 2010, 78% were resistant to ceftazidime, cefepime, and aztreonam, whereas 24 (89%) were resistant to imipenem and meropenem, 15 (56%) to tigecycline, and 8 (30%) to colistin. This study is the first to find out that GES-5 makes *A. baumannii* resistant to carbapenems.[42] However, colistin and tigecycline combinations with carbapenems and other antibiotics are commonly utilized as the safest and most effective

treatments for MDR *A. baumannii* infections diagnosed today.[43] A 2008 to 2012 study by Al-Sultan[44] assessed the occurrence of multidrug-resistant *A. baumannii* isolates among diabetic patients admitted to King Faisal Specialist Hospital and Research Centre in Riyadh. Of the 64 *A. baumannii* isolates obtained, 54 were resistant to both imipenem and meropenem, and only 4 had complete susceptibility to the antibiotic. However, 57 isolates demonstrated sensitivity to tigecycline and colistin. Resistance was found to be mediated by the β-lactamases blaOXA-23 and blaOXA-24/40.[44] Since Saudi Arabia relies on tigecycline and colistin to treat MDR *A. baumannii* infections, the rate of resistance is concerning.[13] A 2018 to 2019 study investigated the incidence and clinical determinants of *Acinetobacter* infections among patients admitted to ICU at 8 Saudi hospitals located in various regions, including Riyadh, Jeddah, Al Madinah Al Munawwarah, and Makkah.[45] 98.4% of the 124 *Acinetobacter* infections were caused by *A. baumannii*. Moreover, drug-resistant *A. baumanni* was more common in mechanically ventilated patients as well as in patients admitted to military hospitals and in facilities with fewer ICU beds.[45] In another study, Al-Obeid et al[46] assessed the prevalence of carbapenem-resistant *A. baumannii* in hundreds of isolates collected from Security Forces Hospital (SFH) in 3 separate years (2006, 2009, and 2012). Interestingly, they found a decreasing trend in meropenem resistance rates during the 3 years (64%, 34.5%, and 8.3%, respectively), as well as uniform susceptibility to colistin.[46] A similar trend was demonstrated for imipenem resistance (81.2% in 2006 isolates, 45.3% in 2009 isolates, and 11% in 2012 isolates).[46] Aly et al[47] used multilocus sequence typing (MLST) to determine the occurrence of the PER-1 drug resistance gene in 503 random *A. baumannii* isolates from a tertiary facility in Riyadh from n 2006 to 2014.[47] The researchers found that 384 isolates (76.3%) expressed the gene, with clustering into 3 subgroups bearing subtypes of the gene.[47] Some isolates harbored the resistance gene in a concealed form, whereas others bore additional resistance genes, such as TEM. Most of these findings confirmed an increase in *A. baumannii's* resistance to several antimicrobial drugs.

The most important hospitals in the city of Buraidah is located in the Qassim area at King Fahad Specialist Hospital, Buraidah from January to December 2011. *A. baumannii* exhibited high levels of resistance to all of the antimicrobials that were put to the test in a study, including high levels of resistance to ciprofloxacin (90%) and ceftazidime (89%), as well as trimethoprim/sulfamethoxazole (66%).[48] Al-Rass General Hospital in Al-Rass city performed a study from December 2014 to March 2015 to investigate the antibiotic susceptibility of *A. baumannii* clinical isolates. *A. baumannii* isolates were resistant to all antimicrobial drugs tested, including amoxicillin/clavulanic acid (100%), ciprofloxacin (100%), piperacillin (100%), ceftazidime (100%), trimethoprim sulfamethoxazole (100%), gentamicin (90.9%), and amikacin (80%).[49] Alhaggass and Al-Hazzani et al[50] performed genotypic characterization and antibiotic susceptibility analysis of 217 isolates from facilities in the Qassim area collected between March and December 2017. Multidrug resistance was found in 57.7% of isolates, with as much as 56.8% of isolates showing resistance to carbapenems.[50] In addition, nearly 50% of isolates were resistant to cefepime, ceftazidime, and ciprofloxacin. Genotyping using PCR identified the resistance genes blaOXA-23 like gene and ISAba1 in as much as 93% of the isolates with carbapenem resistance.[50]

Antimicrobial resistance emerging in Dammam and Khobar, Saudi Arabia. Dammam and Al Khobar are located in the country's Eastern region. Previous study at tertiary care hospital, King Fahad Specialist Hospital-Dammam, found that among the tested carbapenem-resistant Acinetobacter baumannii (CRAB) isolates, a hundred percent resistance to ciprofloxacin and cefepime was observed, 62.9% resistance to gentamicin, 51.4% resistance to tigecycline, and 40% resistance to amikacin. In addition, compared to carbapenem-susceptible Acinetobacter bacteria, CRAB isolates exhibited significantly higher levels of resistance to cefepime, amikacin, gentamicin, tigecycline, and ciprofloxacin ($p>0.05$). However, no statistically significant difference was observed between CRAB and carbapenem-susceptible isolates with regard to colistin resistance ($p>0.05$) of the intestinal microbiota from the ICU patients tested at 2 hospitals in Dammam and Khobar throughout the months of January - June of 2014.[51] Another research evaluated the prevalence of CRAB isolates from one large hospital from January 2010 until February 2012 and discovered that all *A. baumannii* strains tested (n=141) were sensitive to the antibiotic colistin. Ceftazidime (85.1%), cefepime (73.8%), and ciprofloxacin (69.5%) depicted the greatest rates of resistance among CRAB isolates, totaling to 32.6%. The rates of resistance for imipenem were 32.6%, while meropenem was found to be 33.3%, and piperacillin-tazobactam was 33.3%.[52] A 2014 investigation at King Fahd Hospital of the University assessed the genetic characteristic of MDRAB isolates. The imipenem and meropenem resistance rates in the 60 *A. baumannii* strains obtained were 93.3% and 96.6%. The rate of tigecycline resistance was, however,

much lower at only 6.6%.[53] Genetically, the strains clustered into 4 groups with high similarity. Another study evaluated the distribution of drug-resistant Gram-negative bacilli isolates from 7 facilities in the Eastern province of Saudi Arabia between 2008 and 2012.[54] Twenty-three isolates were obtained from diabetic patients, whereas 60 were nondiabetic patients. 69% of isolates demonstrated carbapenem resistance, while 94% of the isolates expressed the resistance gene blaVIM.[54] A 2019 survey investigated the extent of hospital surface and environmental contamination with CRAB in a 335-bed general hospital in Saudi Arabia's Eastern region.[55] As high as 35.5% of surfaces tested were found to be contaminated with multidrug-resistant isolates. All isolates obtained from the hospital surfaces harbored at least one drug-resistance gene, including blaOXA-66, blaOXA-69, and blaGES-11.[55]

Antimicrobial resistance emerging in Jeddah and Makkah, Saudi Arabia. Jeddah, located in the nation's Western region, is the second-most populous city in the kingdom of Saudi Arabia after Riyadh. A retrospective study was carried out at King Abdulaziz Hospital, Jeddah, over the course of 4 years, beginning in January 2010 and continuing through December 2013, in order to investigate the epidemiology of *A. baumannii* and the patterns of its resistance. The frequency of multidrug-resistant *A. baumannii* was found to be high for the entirety of this research, increasing from 55% in 2010 to 67% in 2013.[49] Another retrospective study by Al-Tawfiq et al[56] analyzed the drug susceptibility of *A. baumannii* isolates collected from 1998 to 2004. In the total of 513 isolates recovered, they demonstrated a high rate of resistance to cefoxitin (89%), nitrofurantoin (89%), and ampicillin (86%).[56] However, only 3% of isolates demonstrated imipenem resistance. The prevalence of multidrug resistance was observed to be between 14% and 35.8%.[5] Compared to other studies, this multidrug resistance rate was minute. A few researchers obtained 361 isolates from environmental surfaces and patients at King Abdulaziz University Hospital in Jeddah in 2015 and conducted a genomic analysis to determine the distribution of resistance genes across bacterial strains.[57] The analysis found similarities between *A. baumannii* strains obtained from the environment and those from clinical settings. Most of the isolated strains expressed the resistance genes blaOXA-66, blaADC-25, as well as blaOXA-23.[57] The findings highlighted the significance of the environmental spread of multidrug-resistant strains of *A. baumannii* in the hospital setting. In a 2018 study, 6840 samples collected from patients in a tertiary facility in Al Madinah Al Munawwarah were screened for *Acinetobacter* to determine antimicrobial resistance patterns.[58] The drug sensitivity analysis identified colistin as the most effective agent against the bacteria, with 76% of isolates being inhibited.[58] Other drug classes tested, including ceftazidime, carbapenems, and trimethoprim-sulfamethoxazole presented sensitivities of less than 15%. The results also indicated a preponderance of the infection in the respiratory system and a higher occurrence during the summer months.[50]

Makkah is the western region's major city. Millions of Muslims from throughout the world visit Makkah for pilgrimage and Umrah from January to June 2015. These huge gatherings might lead to the spread of multi-drug-resistant pathogens worldwide.[59] Clinical isolates of *A. baumannii* were obtained from intensive care unit patients at general hospitals in Makkah between 2012 and 2014, and the vast majority of these strains 94 % were found resistant to the antibiotics cefepime, ceftazidime, and aztreonam, high prevalence of *A. baumannii* ESBL producers.[60] A 2005–2006 research in 2 Makkah tertiary care hospitals (Al-Noor Specialist Hospital, and Hera Hospital). The most prevalent Gram-negative bacteria *A. baumannii* (10.8%), *Klebsiella pneumoniae* (8.3%), *Klebsiella sp.* (6.2%), *Haemophilus influenzae* (3.7%), *Enterobacter* (1.9%), *Proteus* (3.3%), they found that *A. baumannii* was resistant to most antimicrobial drugs at 50-100%. *A. baumannii* presented 15-40% imipenem, piperacillin/tazobactam, and meropenem resistance in this study.[61] Al-Sultan investigated the occurrence of specific genetic fingerprints linked to β- lactamases resistance in *A. baumannii* in the regions of Makkah and Al Madinah Al Munawwarah, which are characterized by large numbers of international visitors.[62] As much as 82.5% of isolates showed resistant to carbapenem and 5% demonstrated tigecycline resistance. However, all isolates susceptible to colistin. The commonest resistance genes in the isolates were blaOXA and blaVIM.[62] In a similar study, from February-April 2011. Khan et al[63] characterized *A. baumannii* resistance patterns in isolates from 72 hospitalized patients (7 different hospitals) in a facility in Makkah. Results indicated high resistance rates to multiple agents, including piperacillin (93.1%), tetracycline (76.4%), aztreonam (80.5%), cefotaxime (75%), and ampicillin (76.4%). The presence of underlying diseases was identified as a significant risk factor for *A. baumannii's* high drug resistance.[63] In January 2012 and 31 August 2012, a matched case-control study was conducted by Al-Gethamy et al. to examine the risk factors conferring multidrug resistance in nosocomial *A. baumannii* isolates obtained from the ICU of Al

Noor Specialist Hospital in Makkah.[64] Similar to other studies, the research highlighted alarmingly high rates of multidrug resistance affecting agents such as ceftazidime (92%), imipenem (83.3%), trimethoprim (83%), gentamicin (72.7%), and amikacin (79%).[64] Another longitudinal study was conducted by Faidah et al[65] at the same hospital between 2012 and 2015, wherein the prevalence of carbapenem resistance was determined. The researchers assessed resistance by multiple gram-negative bacilli, including *A. baumannii*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*. Alarmingly, carbapenem resistance was found to be highest in *A. baumannii* isolates (99.1%), followed by *P. aeruginosa* (62.4%), which is another notoriously drug-resistant nosocomial bacterium.[65] The rate of antibiotic resistance among isolates has been increasing from 2012 to 2015. Considering the large pilgrimage traffic in these areas, the risk of global dissemination of these resistant strains is high.[58]

Antimicrobial resistance emerging in Al Jouf, Saudi Arabia. Al Jouf is located in the nation's Northern region. Hospital-acquired infections caused by *A. baumannii* were investigated at Community Hospital in the Al Jouf area to ascertain their frequency, causative agents, medication susceptibility pattern, and plasmid profile. Some 7.1% of *A. baumannii* isolates were resistant to the most frequently used antibiotics. This as a result of widespread administration of antimicrobial medications in healthcare settings, non-medical uses, and the fact that many antibiotics may be purchased without a prescription. This is a recognized contributor to the spread of resistant strains, along with the increased risk of cross-infection among inpatients (Among the complications of surgical site infection (SSI) are infections with multidrug-resistant pathogens, which are challenging to treat and are associated with a higher mortality rate).[66] In January to December 2019, cross-sectional survey using blood culture data from hospitals in Al Jouf region, Gram-negative bacteria were found to account for 62.2% of bloodstream infections, nearly half of which demonstrated multi-drug resistance. Carbapenem resistance was found in 46% of *K. pneumoniae* and in more than 90% of *A. baumannii* isolates. While *A. baumannii* was resistant to several 1st to 4th generation cephalosporins, 87% of isolates were sensitive to ceftriaxone [67]. The principal mechanism of resistance by *A. baumannii* was production of extended beta lactamase (ESBL), followed by AmpC beta lactamases, and finally carbapenemase production. Among bacterial isolates from urine samples obtained from patients in Prince Mutaib Bin Abdulaziz Hospital in Al Jouf from January 2017 to December 2017, Gram-negative bacteria accounted for 58.5% of the infections, the commonest being *E. coli*.[68] Multidrug resistance, particularly to beta-lactams, was highest in *Acinetobacter* and *Pseudomonas* isolates. In a study utilizing repetitive palindromic (REP) PCR, Selim et al[69] identified 4 genotypic categories of carbapenem-resistant *A. baumannii* isolates. All lineages had the highest resistance to imipenem (89.5% resistance) and were most sensitive to ciprofloxacin.[69] Isolates from genotype A had the highest resistance level to all pharmacologic agents tested.[62]

Antimicrobial resistance emerging in Aseer and Najran, Saudi Arabia. Aseer and Najran regions are located in the nation's Southern region. In the Aseer regions of Saudi Arabia, multidrug-resistant and widely resistant *A. baumannii* strains were isolated and identified in this investigation and 74% of these isolates were multidrug-resistant bacteria.[70] Approximately fifty percent of these MDR bacteria were extensive drug-resistant isolates that were susceptible to colistin; however, they were resistant to all other medicines of choice. This leads to increased worry on this potentially hazardous infection. Susceptible the most effective antibiotic with a broad spectrum for treating *A. baumannii* is colistin (60%), followed by the combination of trimethoprim and sulfamethoxazole (46%). These rates are comparable to those of prior trials.[71] Another study conducted between 2013 and 2014 at tertiary care hospital in the Aseer area found that *A. baumannii* was highly resistant to cefepime (89.8%), ciprofloxacin (82.9%), and gentamicin (81.5%). *A. baumannii* isolates becoming carbapenem-resistant. Class D carbapenemase-encoding genes, notably ISAba1/OXA-23 and ISAba1/OXA-24, are widespread.[72] Similarly, researchers found that *A. baumannii* isolates collected between the months of October 2012 to March 2013 in a 350-bed tertiary care hospital in Najran city were extremely resistant to ceftazidime (91%), trimethoprim/sulfamethoxazole (77.9%), gentamicin (60.3%), and ciprofloxacin (46.4%).[17] Alasmary cultured pathogens in 136 midstream urine samples from patients in multiple public hospitals in Najran were collected between 2013 and 2016.[73] Over 90% of the samples depicted bacterial growth, most of which was *E. coli.*[73] The overall resistance rate against multiple pharmacologic agents was found to be 27.2%, with *P. aeruginosa* depicting the highest multidrug resistance rate.[73] The *A. baumannii* isolates cultured from the urine samples were resistant to ciprofloxacin (75%), imipenem (25%), meropenem (50%), and nitrofurantoin (50%).[73] In a cross-sectional study aimed at estimating the prevalence of *Acinetobacter* infections

Table 1 - Summarize all prevalence, risk factor, ABO genes report from various studies in Saudi Arabia.

Study	City	Period	Prevalence of MDR *A. baumannii*/percentage	Risk Factors	ABO Genes	Ref
King Fahad National Guard Hospital	Riyadh	2004-2009	The susceptibility of *A. baumannii* to imipenem (55% to 10%), meropenem (33% to 10%), ciprofloxacin (22% to 10%), and amikacin (12% to 6%) was greatly reduced.	N/A	N/A	39
King Abdulaziz Medical City Hospital	Riyadh	2006-2008	Resistance against Meropenem (92.1%), Imipenem (79.1%)	N/A	N/A	40
Riyadh Military Hospital	Riyadh	January to December 2009	Resistance against Amoxicillin/clavulanic acid (96), Piperacillin/tazobactam (93), Ciprofloxacin (92)	N/A	N/A	41
Tertiary Hospital	Riyadh	January to December 2010	Resistance against Ceftazidime (78), Cefepime (78), Aztreonam (78), Imipenem (89), Meropenem (89), Tigecycline (56), Colistin (30)	N/A	GES-5 makes *A. baumannii* resistant to carbapenems.	42
King Faisal Specialist Hospital and Research Centre	Riyadh	2008-2012	Resistance against Imipenem and Meropenem (54%), but it was sensitivity to Tigecycline and Colistin (57%).	Diabetic patients	$bla_{OXA-23,}$ $bla_{OXA-24/40}$	44
Multiple hospitals	Various regions including Riyadh, Jeddah, Al Medina Al Munawwarah, and Makkah	2018-2019	N/A	Mechanically ventilated patients, military hospitals, and fewer ICU beds	N/A	45
Security Forces Hospital	Riyadh	2006, 2009, and 2012	Considering years 2006, 2009 and 2012, the susceptibilities to meropenem and imipenem were 64–81.2%, 34.5–45.3%, and 8.3–11%, respectively	N/A	N/A	46
Tertiary care hospital	Riyadh	2006- 2014	The PER-1 locus is highly prevalent among carbapenem-resistant.	N/A	PER-1	47
King Fahad Specialist Hospital	Buraidah	January to December 2011	Resistance against Ciprofloxacin (90%), Ceftazidime (89%), Trimethoprim/ sulfamethoxazole (66%)	N/A	N/A	48
Al-Rass General Hospital	Al-Rass	December 2014 to March 2015	Resistance against Amoxicillin/clavulanic acid (100), Ciprofloxacin (100%), Piperacillin (100%), Ceftazidime (100%), Trimethoprim sulfamethoxazole (100%), Gentamicin (90.9%), Amikacin (80%)	N/A	N/A	49
Territory care hospital in Qassim	Qassim area	March - December 2017	Multidrug resistance (57.7%), Carbapenem (56.8%)	N/A	bla_{OXA-23} like gene and ISAba1	50
King Fahad Specialist Hospital	Dammam	January - June of 2014	Among tested carbapenem-resistant *A. baumannii* (CRAB) isolates: 100% resistance against ciprofloxacin and cefepime, 62.9% resistance to gentamicin, 51.4% resistance to tigecycline, and 40% resistance to amikacin. No significant difference in colistin resistance compared to carbapenem-susceptible Acinetobacter bacteria	ICU patients	N/A	51
Tertiary care hospital	Dammam	January 2010 until February 2012	Sensitive to the antibiotic colistin. Ceftazidime (85.1%), Cefepime (73.8%) Resistance against Imipenem were 32.6%, while Meropenem was found to be 33.3%	ICU patients	Carbapenem resistance came from bla_{OXA-23} at ISAba1.	52

Acinetobacter baumannii: A. baumannii, MDR: multidrug resistance, ICU: intensive care units, Ref: reference, N/A: not applicable

Table 1 - Summarize all prevalence, risk factor, ABO genes report from various studies in Saudi Arabia (continuation).

Study	City	Period	Prevalence of MDR *A. baumannii*/percentage	Risk Factors	ABO Genes	Ref
King Fahd Hospital of the University	Al Khobar	February to September 2014	Resistance against Imipenem 93.3% and Meropenem 96.6%		ERIC-PCR genotyped CRAB	53
seven major hospitals	Eastern Province of Saudi Arabia	2008-2012	69% showed carbapenem resistance,	N/A	Gene bla_{VIM}	54
General hospital	General hospital in Saudi Arabia's Eastern region	N/A	35.5% of surfaces tested were contaminated with multidrug-resistant isolates of carbapenem-resistant *A. baumannii*	Environmental contamination,	$bla_{OXA-66,}$ $bla_{OXA-69,}$ and bla_{GES}	55
King Abdul-Aziz Hospital	Jeddah	January 2010 - December 2013	The prevalence of MDR and PDR *A. baumannii* increased from 55% and 20% respectively in 2010 to 67% and 33% in 2013. Resistance against 100% Ceftriaxone, 92.3 % Gentamycine, Cefepine 88.7%, Levofloxacin 88.5%, Piperacelli/ Tazobactam 88.4%, Ciprofloxacin 88.4%, Meropenem 88.2%, Ceftazidme 88.2%, Imipenem 86.5%, Amikacin 84.6%, Trimethoprim/sulphamethoxazole 69.3%, while Colistin and Tigecycline were with no resistance	N/A	$bla_{OXA-66,}$ $bla_{ADC-25,}$ bla_{OXA-23}	49
N/A	Jeddah	1998-2004	prevalence of multidrug resistance to cefoxitin (89%), nitrofurantoin (89%), and ampicillin (86%), only 3% of isolates demonstrated imipenem resistance	N/A	N/A	56
King Abdulaziz Hospital	Jeddah	2015	N/A	N/A	strains expressed the resistance genes bla_{OXA-66}, $bla_{ADC-25,}$ as well as bla_{OXA-23}	57
Tertiary Hospital	Madinah	2018	Summer had 39.15% of these infections, autumn 28.17%, winter 26.48%, and spring 6.2%.	Respiratory system infection, summer months	N/A	58
Two hospitals	Makkah	January -June 2015	Beta-lactam resistance was high. Ceftazidime was also resistant to *A. baumannii* (n=16, 77%).	N/A	N/A	59
Local hospitals	Makkah	from 2012-2014	High prevalence of A. baumannii ESBL producers 94 % were found to be resistant to cefepime and ceftazidime, and aztreonam	ICU	Bla, TEM, SHV, and CTX-M-group genes 1, 2, 8, 9, and 25 were examined. Additionally, bla_{OXA51}-like and bal_{OXA23}-like genes	60
Al-Noor Specialist Hospital, and Hera Hospital	Makkah	October 2005 to March 2006	The most prevalent Gram-negative bacteria *A. baumannii* (10.8%), *Klebsiella pneumoniae* (8.3%), Klebsiella sp. (6.2%), *Haemophilus influenzae* (3.7%), Enterobacter (1.9%), Proteus (3.3%). 50%-100% resistance to most antimicrobial drugs	N/A	N/A	61

Acinetobacter baumannii: A. baumannii, MDR: multidrug resistance, ICU: intensive care units, Ref: reference?, N/A: not applicable, CRAB: carbapenem-resistant *A. baumannii*

Table 1 - Summarize all prevalence, risk factor, ABO genes report from various studies in Saudi Arabia (continuation).

Study	City	Period	Prevalence of MDR *A. baumannii*/percentage	Risk Factors	ABO Genes	Ref
Different major hospitals	Makkah and Jeddah	N/A	*A. baumannii* isolates showed tigecycline and colistin susceptibility, whereas 81 and 84% were resistant to imipenem and meropenem, respectively.	The presence of underlying diseases was identified as a significant risk factor for *A. baumannii* high drug resistance.	$bla_{OXA,}$ bla_{VIM}, and ISAba1	62
Seven different hospitals	Makkah	February-April 2011	resistance rates to multiple agents, including piperacillin (93.1%), tetracycline (76.4%), aztreonam (80.5), cefotaxime (75%), and ampicillin (76.4%).	N/A	N/A	63
Al Noor Specialist	Makkah	1 January 2012 and 31 August 2012	The study showed that some drugs, like ceftazidime (92%), imipenem (83.3%), trimethoprim (83%), gentamicin (72.7%), and amikacin (79%), have alarmingly high rates of resistance to more than one drug.	Nosocomial infections caused by *Acinetobacter* are linked to being in the ICU and being exposed to invasive treatments.	N/A	64
Al-Noor Specialist Hospital	Makkah	between 2012 and 2015	*A. baumannii* 1710 (99.13%) was carbapenem-resistant.	N/A	N/A	65
Community Hospital	Al Jouf,	N/A	7.1% of isolates were resistant to most commonly used antibiotics	Multidrug-resistant organisms can cause. Surgical site infection and increase mortality.	N/A	66
N/A	Al Jouf,	January - December 2019	Carbapenem resistance shows hospital antimicrobial medication non-compliance. *A. baumannii* was resistant to several 1st to 4th generation cephalosporins, 87% of isolates were sensitive to ceftriaxone	Resistant BSI-causing microorganisms make infection management difficult and complicate treatment,	RFLP patterns	67
Prince Mutaib Bin Abdulaziz Hospital	Al Jouf,	January-December 2017	Carbapenem resistance indicates hospital antimicrobial treatment noncompliance.	Hospitals struggle to handle resistant BSI-causing bacteria,		68
N/A	Aseer	2013-2014	Highly resistant to cefepime (89.8%), ciprofloxacin (82.9%), and gentamicin (81.5%)		ISAba1/$_{OXA-23}$ and ISAba1/$_{OXA-24}$	72
Tertiary care hospital	Najran	October 2012 to March 2013	Highly resistant to ciprofloxacin (75%), imipenem (25%), meropenem (50%), and nitrofurantoin (50%)	the incidence of ESBL development in the region.	N/A	17
King Khalid Hospital	Najran		Cefuroxime was 79%, amikacin was 43%, and colistin was 8%	include old age, chronic diseases, and invasive procedures	N/A	73

Acinetobacter baumannii: A. baumannii, MDR: multidrug resistance, ICU: intensive care units, Ref: reference?, N/A: not applicable, CRAB: carbapenem-resistant *A. baumannii*, BSI: bloodstream infection

in patients admitted to the intensive care unit at King Khalid Hospital, the organism was found in 11.7% of patients.[74] Factors identified as increasing the likelihood of infection include old age, chronic diseases, and invasive procedures. The *A. baumannii* isolates cultured demonstrated multidrug resistance rates comparable to those reported by other studies. For instance, the resistance rate against cefuroxime was 79%, amikacin was 43%, and colistin was 8%.[74] Table 1 is summarize all prevalence, risk factor, ABO genes report from various studies in Saudi Arabia.

In conclusion, the complicated nature of the hospital setting, patient comorbidities, length of hospital stay, intensive care unit complexity, concurrent disease, and antimicrobial agent use all play a significant role in the spread of *A. baumannii* in Saudi Arabia. Many Saudi Arabian tertiary referral hospitals have discovered that *A. baumannii* has become more resistant to many different types of antimicrobial drugs. This issue has been reported in several regions and may provide a challenge to municipal health departments. However, there is a lack of information in certain smaller communities, as well as in the North. The prevalence of *A. baumannii*strains resistant to major classes of antimicrobials necessitate extensive monitoring systems in Saudi Arabia. However, expanding our understanding

of *A. baumannii* resistance patterns may be possible with the support of a national antimicrobial stewardship program and an infection prevention initiative.

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