MULTIDRUG RESISTANCE *ACINETOBACTER BAUMANNII:* AN EMERGING THREAT

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ABSTRACT

Acinetobacter baumannii is a Gram-negative bacillus that is a common pathogen among immunocompromised individuals and is associated with aquatic environments. It has been designated as a "red alert" human pathogen due to its broad antibiotic resistance spectrum. *A. baumannii* is one of the ESKAPE organisms that pose a global threat to human health and a therapeutic challenge due to its emerging and constantly growing resistance. In 2018, WHO ranked carbapenem-resistant *A. baumannii* (CRAB) as the top priority for antibiotic research and development. The virulence potential of *A. baumannii* is based on a "persist and resist" strategy, with the bacteria also resisting oxidative stress and complement-mediated killing. The most significant virulence factors include protein secretion systems, iron-chelating systems, capsular polysaccharides, lipopolysaccharides (LPS), proteases, outer membrane porins, and phospholipases. The pathogen is a common cause of biofilm-related infections, especially ventilator-associated pneumonia and catheter-related infections, making clinical management of these infections extremely difficult.

Keywords: *Acinetobacter baumannii, A. baumannii,* Multidrug resistance, XDR, Nosocomial infections, Biofilm

I. INTRODUCTION

Acinetobacter baumannii is a Gram-negative bacillus that is aerobic, pleomorphic and nonmotile. *A. baumannii*, an opportunistic pathogen, is common among immunocompromised people, especially those who have been in the hospital for more than three months. It is commonly associated with aquatic environments and has been shown to colonize the skin in addition to being isolated in large numbers from infected individuals' respiratory and oropharyngeal secretions. In recent years, it has been designated as a "red alert" human pathogen, causing concern among the medical community, owing to its broad antibiotic resistance spectrum. The genus *Acinetobacter* originated in the twentieth century, when the Dutch microbiologist Beijernick described an organism known as *Micrococcus calcoaceticus*, which was isolated from soil using a medium enriched with calcium acetate. *A. baumannii* is one of the ESKAPE organisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, A. baumannii, Pseudomonas aeruginosa*, and *Enterobacter* spp.) that pose a global threat to human health and a therapeutic challenge as a result of emerging and constantly growing resistance. In 2018, WHO ranked carbapenem-resistant *A. baumannii* (CRAB) as the top priority for antibiotic research and development. Carbapenem was selected as a marker because carbapenem resistance is typically associated with a wide range of co-resistance to other antibiotic classes. Its capacity to create biofilms and withstand desiccation and disinfectants is particularly concerning because these traits enable *A. baumannii* to flourish in hospital environments.

The virulence potential of *A. baumannii* is based on a "persist and resist" strategy, in which the bacteria also resist oxidative stress and complement-mediated killing. This is supported by the antibiotic resistance, environmental persistence, and lack of known host-damaging toxins in its genome. According to genomic and phenotypic studies, the most significant virulence factors are protein secretion systems, iron-chelating systems, capsular polysaccharides, lipopolysaccharides (LPS), proteases, outer membrane porins, and phospholipases. *A. baumannii* is a common cause of biofilm-related infections, especially ventilator-associated pneumonia and catheter-related infections. These infections can be extremely resistant to antibiotic therapy, making clinical management of *A. baumannii*-related biofilm infections extremely difficult. Because of the fast spread of infections linked to medical devices and antibiotic resistance, *A. baumannii* biofilms have emerged as one of the most significant worldwide problems.

II. MULTIDRUG RESISTANCE IN *ACINETOBACTER BAUMANNII*

Amnioglycosides

Amnioglycosides interact with the RNA 16S of the ribosomal 30S subunit. The production of aminoglycoside modifier enzymes is the well-studied mechanism of antibiotic resistance in *A. baumannii* strains. There are three types of modifier enzymes: aminoglycoside acetyltransferases (AAC), such as AAC (6′)-Ih (which also confers resistance to gentamicin and amikacin), aminoglycoside phosphotransferases (APH), such as APH (3′)-IA (which confers resistance to gentamicin), and aminoglycoside adenililtransferases (ANT), such as ANT (2″)-IA. The production of RNA 16S ribosomal methyltransferase, particularly ArmA, the first of its kind found in a clinical isolate, appears to be an emerging mechanism of aminoglycoside resistance. *A. baumannii* strains producing ArmA are highly resistant to tobramycin, amikacin & gentamicin.

Carbapenems

Among all β-lactam antibiotics, carbapenems have the widest spectrum and are primarily used to treat infections brought on by Gram-negative bacteria. Among the mechanisms that give *A. baumannii* strains resistance to carbapenems are over expression of the carbapenem-hydrolyzing oxacillinase (OXA)-51-like-B-lactammase and ArmA RNA 16S ribosomal methyltransferase. Clinical repercussions have been linked to increased carbapenem resistance production and dissemination when OXA-23 is present. OXA-24 has been shown to exhibit moderate hydrolytic activity against carbapenems. Ambler's class B metallo-β-lactamases are one example of the non-OXA carbapenemases that have been reported in *A. baumannii*.

Fluoroquninolones

Substitutions in the quinolone resistance-determining regions (QRDRs) of DNA gyrase and DNA topoisomerase IV are the basis of *A. baumannii's* fluoroquinolone resistance mechanism. These substitutions prevent the fluoroquinolones from binding to their target proteins. In addition to increasing resistance in strains with RDRQ substitutions, over expression of efflux active pumps can also result in moderate resistance on its own.

Tetracyclines

Three primary mechanisms are thought to be responsible for resistance to tetracycline antibiotics: (i) ATP-dependent efflux, (ii) enzyme-mediated tetracycline inactivation, and (iii) ribosomal protection proteins (RPPs). Tetracycline resistance in *A. baumannii* refers to two energy-demanding efflux pump types. Tetracyclines can be efficiently removed by RND pumps, with AdeABC in particular, but they also significantly raise the minimum inhibitory concentrations (MICs) of tigecyline, minocycline, and tetracycline. Tetracycline major facilitator super family (MFS) efflux pumps TetA and TetB are included in the second group. TetA appears to be responsible for the tigecycline's efflux into the periplasm, after which RND pumps push the drug out through the outer membrane.

Polymixins

The lipid A of lipopolysaccharides (LPS) interacts with colistin (Polymyxin-E). Acquired polymyxin resistance is the result of its alteration. By adding a phosphoethanolamine residue to the hepta-acylated form of lipid A, negative charges are eliminated and the affinity of LPS for polymyxins is decreased. This modification technique is the most frequently reported. Complete loss of the

original LPS is another way that *A. baumannii* develops this resistance.

Macrolides

Mutations in the rpoB gene, which codes for the rifamycin-sensitive beta-subunit of RNA polymerase and prevents RNA elongation immediately after the addition of the first nucleotides, have been connected to resistance to rifampin (also known as rifabicin) in A. baumannii infections. RpoB is linked to resistance to all rifamycins, including rifabutin, rifaximin, and rifapentine, in addition to rifampin.

Sulfonamides

Antifolate antibiotics work by preventing the synthesis of DNA and RNA by blocking purine metabolism. Trimethoprim is an inhibitor of dihydrofolate reductase (DHFR), which prevents dihydrofolic acid from forming tetrahydrofolic acid, a crucial stage in the biosynthesis of folate. DfrA1, DfrA5, DfrA7, DfrA10, DfrA12, DfrA14, DfrA16, DfrA17, DfrA19, DfrA20, DfrA27, and DfrB1 are trimethoprim-resistant dihydrofolate reductases that primarily confer resistance against diaminopyrimidines in *A. baumannii* infections.

III. BIOFILM FORMATION IN *ACINETOBACTER BAUMANNII*

Biofilms are bacterial communities that have formed in an extracellular polymeric matrix composed of polysaccharides, lipids, proteins, and nucleic acids. Biofilm development is a complex process in which microorganism cells switch from planktonic to sessile growth, influenced by a variety of environmental factors such as surface porosity, fluid flow, and nutrient availability. Quorum sensing regulates the common stages of biofilm development, which include initial contact or attachment to the biotic and/or abiotic surface, microcolony formation, biofilm maturation and architecture formation, and, finally, biofilm detachment or dispersion. *A. baumannii's* environmental survival is influenced by a number of factors, including its capacity to endure harsh environmental conditions, the dormancy of bacterial cells deep within the biofilm, its resistance to multiple antibiotics, its ability to prolong survival on inanimate objects, and its resistance to environmental stress. As a result, biofilms can cause a variety of sub-acute or chronic infections that are extremely difficult to treat. Compared to other *Acinetobacter* species, *A. baumannii* forms biofilms at the solid-liquid interface at a rate that is at least three times higher. Stronger biofilms can be formed by clinical strains than by environmental strains, and the development of biofilms on surfaces of medical significance influences the strains' resistance to desiccation, stress, nutrition availability, and antimicrobial therapy. Additionally, multidrug resistance and the expression of virulence factors like OmpA, the extracellular polysaccharide poly-β-1,6-N-acetyl glucosamine (PNAG), type I pili, Rec A, Bap, and the Omp CarO are positively correlated with the biofilm process of *A. baumannii* on abiotic surfaces. It requires chaperone-usher pili in order to form biofilm on an animate surface. The ability of *A. baumannii* to adhere to biotic and abiotic surfaces and form biofilms is facilitated by biofilm-related virulence genes and proteins.

Antibiotic resistance is inherent in *A. baumannii*. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria have emerged as a result of the growing use of antibiotics. Consequently, the global spread of *A. baumannii* is turning into a serious issue. One of the main reasons for the high death rate is the appearance of MDR strains. despite the fact that there is ongoing discussion regarding the relationship between antibiotic resistance phenotypes and biofilm production. There is a positive correlation between biofilm formation and multidrug resistance, according to some evidence. Biofilm formers showed greater resistance to ampicillin-sulbactam, amikacin, ciprofloxacin, and ceftazidime than to imipenem and piperacillin.

IV. IMPACTS OF PATHOGEN AND CLINICAL INFECTIONS

Respiratory infections

MDR *A. baumannii*-induced ventilator-associated pneumonia (VAP) continues to be a major cause of high fatality rates in critically sick patients. Red blood cell transfusion and female gender were identified as independent risk factors for mortality in a more recent study from a university hospital. The frequencies of MDR, XDR, and PDR *A. baumannii* recovered from VAP cases were 13.3%,

68.3%, and 18.3%, respectively. *A. baumannii*-induced community-acquired pneumonia (CAP) is a growing issue, despite the fact that VAP caused by this organism seems to favour susceptible people. It primarily affects people with diabetes mellitus, smoking, chronic lung disease, and excessive alcohol use. It is distinguished by a fulminant course, high incidence of bacteremia, and a high fatality rate, particularly in tropical locations.

Blood vascular infections

The death rate from *A. baumannii*-caused bloodstream infections is close to 40%. For four years in a row, *A. baumannii* was the most common pathogen isolated from blood in burn patients admitted to an intensive care unit. The isolates had nearly 100% resistance to various antibiotics, with the exception of a low resistance profile to polymyxin B and minocycline.

Skin and soft tissues infection

Patients with severe burns, wounds, or trauma—such as soldiers hurt in combat or natural disasters—have had *A. baumannii* isolated from their skin and soft tissues on multiple occasions. Over the course of eight years, the percentage of *A. baumannii* isolates in a US military medical center rose from 4% to 55%, with wound isolates making up 24% of all *A. baumannii* specimens. Furthermore, compared to local patients (20%), combat casualties deployed overseas had a higher percentage of MDR *A. baumannii* isolates recovered (52%).

Urinary tract infection

According to one study, A. baumannii was the cause of 1.6% of UTIs acquired in intensive care units (ICUs) and can occasionally cause UTIs, particularly when indwelling urinary catheters are used. In a study examining the traits of A. baumannii isolated from intensive care units in ten Korean hospitals, urinary tract infections were linked to 55.6% of the isolates. Of these isolates, 19.8% exhibited imipenem resistance, 25% maropenem resistance, 13.5% polymyxin B resistance, and 17.7% colistin resistance.

Meningitis

With a mortality rate of nearly 70%, nosocomial meningitis caused by A. baumannii continues to pose a growing threat in intensive care neurosurgery units, particularly for patients undergoing post-operative antibiotic therapy and on indwelling ventriculostomy tubes or cerebrospinal fistulae. According to the largest case series of post neurosurgical A. baumannii meningitis published in 2019, 21% of isolates exhibited an XDR phenotype, meaning they were only sensitive to tigecycline and colistin. A. baumannii-related mortality in the neurosurgical intensive care unit was also associated with comorbidities (diabetes and hypertension), age over 40, the presence of an external ventricular drain, and an elevated white blood cell count in the cerebrospinal fluid.

V. CONCLUSION

A. baumannii is a significant opportunistic and emerging pathogen that can cause serious nosocomial infections. Its pathogenic potential includes the ability to adhere to surfaces, form biofilms, exhibit antimicrobial resistance, and acquire genetic material from unrelated genera, making it a difficult adversary to control and eradicate. *A. baumannii* can acquire antibiotic resistance through a variety of mechanisms, including changing the antibiotic target site, controlling antibiotic passage through its membranes, and enzymatically neutralizing antibiotics. In order to completely adapt to modern healthcare environments, *A. baumannii* has developed three fundamental properties: (i) The capacity to colonize skin, mucous membranes, and devices and to endure in a hospital setting; (ii) the expression of multiple virulence features; and (iii) broad resistance to antimicrobial agents due to antibiotic enzymatic modification, target gene mutation, altered permeability of outer membranes, and up regulated multidrug efflux pumps. The multitude of clinical infections caused by the bacteria and its biofilm formation along with drug resistance mechanisms make it a emerging universal risk for public health.

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