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PATTERN OF ANTIBIOTIC RESISTANCE IN ACINETOBACTER BAUMANNII, REVIEW

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ABSTRACT

Acinetobacter baumannii pathogenesis, including porins, capsular polysaccharides, lipopolysaccharides, phospholipases, outer membrane vesicles, metal acquisition systems, and protein secretion systems. Mechanisms of antibiotic resistance of this organism, including acquirement of b-lactamases, up-regulation of multidrug efflux pumps, modification of aminoglycosides, permeability defects, and alteration of target sites, are also discussed. Lastly, novel prospective treatment options for infections caused by multi-drug resistant *Acinetobacter baumannii* (*A. baumannii*) is a leading cause of nosocomial infections as this pathogen has certain attributes that facilitate the subversion of natural defenses of the human body. *A. baumannii* acquires antibiotic resistance determinants easily and can thrive on both biotic and abiotic surfaces. Different resistance mechanisms or determinants, both transmissible and non-transmissible, have aided in this victory over antibiotics. In addition, the propensity to form biofilms (communities of organism attached to a surface) allows the organism to persist in hospitals on various medical surfaces (cardiac valves, artificial joints, catheters, endotracheal tubes, and ventilators) and also evade antibiotics simply by shielding the bacteria and increasing its ability to acquire foreign genetic material through lateral gene transfer. The biofilm formation rate in A. baumannii is higher than in other species. Some of the properties that make A. baumannii a serious pathogen include its capacity to tolerate high levels of stress and enhanced expression of efflux pumps that enable high degrees of antibiotic resistance.

KEYWORDS: Bacterial infection, Antimicrobial resistance, *Acinetobacter baumannii*, Resistance mechanism, Virulence factor.

INTRODUCTION

A rapid surge in the incidence of multidrug-resistant *Acinetobacter baumannii* infections has become a threat for public health worldwide.[1] *A. baumannii*, opportunistic gram-negative, aerobic, non-motile, coccobacilli, causes nosocomial and community-acquired infections among immune-compromised patients. Its genome plasticity provides an advantage to acclimate various mechanisms of resistance, rendering antibiotics ineffective for treatment.[2] Apart from decking the ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp*.) pathogen list, now WHO has declared *A. baumannii* as Group-1 priority pathogen for which new antimicrobials are urgently required. Among all the 73 species of *Acinetobacter*, *A. baumannii* causes a wide range of infections in humans, including urinary tract infection, ventilator-associated pneumonia, skin, wound infection, bloodstream infection and meningitis. Mortality rates as high as 50% associated with *A. baumannii* infections.[3]

Extensive clinical and animal model studies have clearly established A. baumannii as the most pathogenic bacteria in the genus Acinetobacter.[4] It has become one of the leading causes of nosocomial infections worldwide, including hospital-acquired pneumonia, and skin and urinary tract infections. A. baumannii is highly resistant to multiple antibiotics leading to its classification by the World Health Organization (WHO) as priority one threat to human health worldwide.[5] *A. baumannii* has successfully acquired resistance to all the available antimicrobial drugs, including colistin, the last line of therapy.[6] Its ability to form biofilm in the hospital environment and on medical equipment is advantageous for colonization and persistent infections that are resistant to antimicrobials and imposes challenges in treatment. The pathogen employs various strategies to curb the effects of antibiotics, including expression of b-lactamases, multidrug efflux pumps, and aminoglycoside-modifying enzymes.[7]

ACINETOBACTER BAUMANNII

VIRULENCE FACTORS AND PATHOGENESIS

Although recent genomic and phenotypic analyses of *A. baumannii* have identified several virulence factors responsible for its pathogenicity, relatively few virulence factors have been identified in A. baumannii, compared to those in other Gram-negative pathogens. The proposed A. baumannii virulence factors and antibiotic resistance in figure-1.[8]

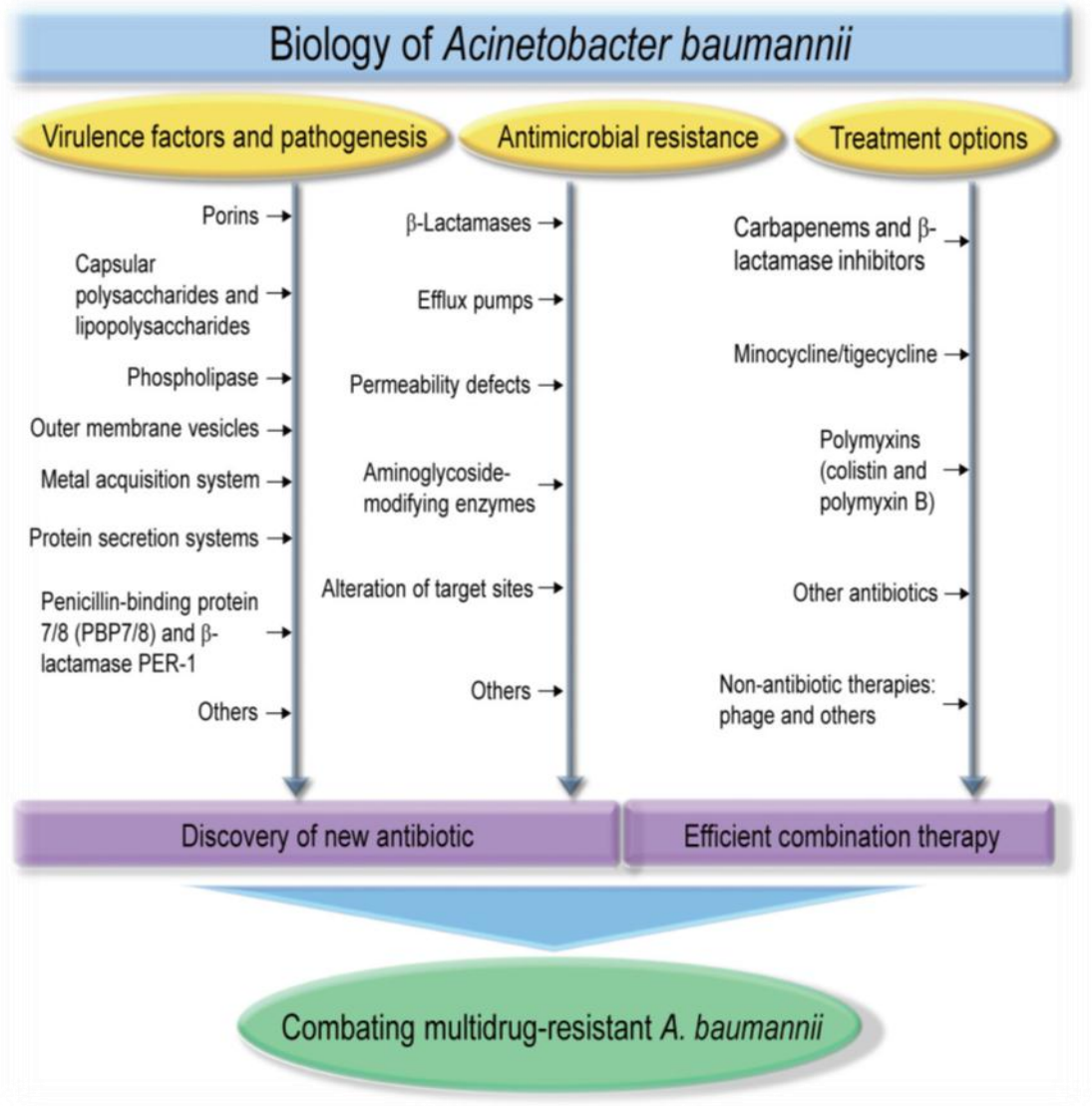

Figure 1: Biology of *Acinetobacter baumannii*. (virulence factors, pathogenesis, antimicrobial resistance).

Porins

Porins are outer membrane proteins associated with modulating cellular permeability. OmpA is a b-barrel porin and one of the most abundant porins in the outer membrane.[9] In A. baumannii, OmpA is the very well-characterized virulence factor with a variety of interesting biological properties identified in in vitro model systems. A randommutagenesis screen showed that the A. baumannii ompA mutant is defective in inducing apoptosis in human epithelial cells.[10] Purified OmpA binds host epithelial cells, targets mitochondria, and induces apoptosis by releasing proapoptotic molecules, such as cytochrome c and apoptosisinducing factor. Another study showed that OmpA translocates to the nucleus by a novel monopartite nuclear localization signal and induces cell death. OmpA also plays a

major role in adherence and invasion of epithelial cells by interacting with fibronectin. and binds to factor H in human serum which may allow A. baumannii to avoid complement-mediated killing.[11]

Capsular Polysaccharides and Lipopolysaccharides (LPS)

Beyond OmpA, the *A. baumannii* envelope is associated with many factors that contribute to pathogenicity. Among these, capsular exopolysaccharides and LPS are A. baumannii pathogenicity factors.[12] Notably, many isolates from patients with A. baumannii infections express surface capsular polysaccharides and contain a conserved gene cluster, called the K locus, which may determine production of capsular polysaccharides. A random transposon screening to identify genes essential for growth in an inflammatory exudative fluid lead to the identification of the ptk and epsA genes, which are predicted to be required for capsule polymerization and assembly.[13] The ptk and epsA mutants are deficient in capsule production and have a growth defect in human serum, resulting in a highly significant decrease in survival in soft tissue infection sites. Mutation in the pglC or pglL gene, which is responsible for synthesis of the O-pentasaccharide found on glycoproteins and capsular polysaccharides, also attenuate lethality in a mouse septicemia model and form abnormal biofilm structures. Therefore, capsular polysaccharides have been proposed to be a target for protective antibody-based interventions.[14]

Outer membrane proteins

Outer membrane proteins (OMPs) of *A. baumannii* such as OmpA, CarO, Omp33 OprD-like, PstS are well-documented to play a role in biofilm formation. Outer membrane receptor proteins were upregulated during biofilm formation when analyzed by two-dimensional gel electrophoresis.[15] Among several identified OMPs, outer membrane protein A (ompA) is a well-characterized virulence factor owing to its diverse key roles in the survival and pathogenesis of *A. baumannii,* including maintenance of cell membrane integrity, mediating drug resistance, modulation of host immune response, initiation of biofilm formation, invasion of host epithelial cells and triggering host cell apoptosis. These characteristics make ompA an ideal drug target for controlling *A. baumannii* infections. OmpA is a beta barrel-shaped monomeric integral outer membrane protein encompassing 8 to 26 antiparallel strands, linked by four loops on the outer membrane surface and three short turns on the periplasmic side.[16]

The role of OmpA in mediating the initial stage of biofilm formation on abiotic surfaces is well defined; besides, it is also required for adhesion to host epithelial cells and facilitates the invasion of *A. baumannii* cells to host epithelial and immune cells. Another study showed that *A. baumannii* cells easily adhered to a 96-well plate coated with fibronectin compared to BSA due to the binding of ompA with fibronectin, suggesting the initial stages of interaction between *A. baumannii* biofilm formation on biotic surfaces. Choi et al. found that a highly invasive *A. baumannii* 05KA103 exhibited reduced adherence and invasion to epithelial cells when pre-incubated with recombinant AbOmpA. Once *A. baumannii* is internalized within the host cells, it migrates to the nucleus based on the nuclear localization signal (KTKEGRAMNRR) presented by OmpA and mediates host cell apoptosis by causing degradation of chromosomal DNA.[17]

A study showed that immunization of diabetic mice with recombinant OmpA improved survival and reduced bacterial load when later administered with lethal *A. baumannii* infection. Another mechanism of host cell apoptosis employed by *A. baumannii* Omp38 targets mitochondria and causes the release of proapoptotic molecules such as cytochrome c and other apoptosis-inducing factors. *A. baumannii* mutants lacking OmpA were comparatively less virulent than wild-type cells showed decreased adherence to human airway epithelium cells, and formed weaker biofilms.[18]

Quorum sensing regulates biofilm formation in *A. baumannii*

Quorum sensing (QS) is the eminent property of bacterial cells that facilitates communication within their microenvironment. QS involves the production of small diffusible signaling molecules termed autoinducers (AI), which interact with the receptors of neighbouring cells and induce the expression of targeted genes to respond to a stimuli in a coordinated way. Three classes of QS systems have been identified in bacteria: 1) luxI/luxR system in Gram-negative bacteria, which involves acyl-homoserine lactone as an autoinducer type I (AI-1); 2) oligopeptide-two-component-type QS identified in Gram-positive bacteria, uses small peptides as signal molecules; 3) luxS system encoding autoinducer 2 (AI-2) quorum sensing molecule found in both Gram-negative and Gram-positive bacteria.[19]

In *Acinetobacter spp*. AI-I acyl-homoserine lactone (AHL) QS system has been identified. The first step in QS involves the synthesis of AHL by AbaI synthase. Medium to long chain AHL (C6-C14) are produced by combining the acyl side chain of a specific acyl-acyl side chain protein (acyl-ACP) from a fatty acid biosynthetic machinery to the homocysteine

moiety of S-adenosine methionine. The intermediate, N-acyl homoserine, lactonizes to produce acyl-HSL, releasing methylthioadenosine. In *A. baumannii* N-(3-hydroxydodecanoyl)-L-HSL (AHL) is produced. In the second and third steps, this signaling molecule diffuses through the membrane in the environment. It interacts with the AHL receptor, abaR, present on the surface of neighbouring bacterial cells. Next, the receptor-signal complex is retrieved from the cell surface, binds to the promoter region, and activates the transcription of pathogenicity and biofilm-related genes.[20]

A study showed increased expression of csu pili and biofilm formation as a result of AHL interaction with the abaR receptor. Recently, the role of abaM in regulating QS-dependent and QS- independent genes in *A. baumannii* 5075 has been identified. Increased levels of N-(3-hydroxydodecanoyl)-L-HSL (AHL) positively activate the expression of abaM, which is a negative auto-regulator and negatively regulates the production of AHL by repressing abaI and abaR expression. abaM mutant showed increased surface motility and biofilm formation by reduced virulence in *Galleria mellonela* compared to wild type.[21]

Efflux pumps

Efflux systems have gained importance as antimicrobial resistance determinants mediating resistance by pumping out the antibiotic and other metabolites and toxins out of the cell. Five major subfamilies of the efflux system have been identified in prokaryotes: ATP-binding cassette (ABC), resistance nodulation division (RND), small multidrug resistance (SMR), major facilitator superfamily (MFS), and multidrug and toxin-compound extrusion (MATE). In *A. baumannii*, families of efflux system identified are MFS, MATE, AbeM, RND, AdeABC, SMR, ABC and MacB. RND efflux pumps in *A. baumannii* are of three types, AdeABC, AdeFGH, and AdeIJK. Investigations on biofilm formation mechanisms are directed towards efflux pumps' involvement in the formation of biofilm. Analyzing the whole transcriptome of *A. baumannii* from biofilm and planktonic conditions showed the overexpression of RND (A1S_0009, A1S_0116 and A1S_0538) and MFS (A1S_1316) efflux genes. Some efflux genes such as A1S_1117, A1S_1751 and adeT were expressed only in cells present in biofilm state and not in planktonic cells. In a clinical *A. baumannii* isolate, AdeFGH efflux pump was overexpressed along with abaI in sessile condition, suggesting its role in the efflux of substrates required for biofilm formation. Targeting RND efflux pump with its inhibitor Phenylalanine-arginine beta-naphthylamide (PaβN) significantly reduced the biofilm formation ability of *A. baumannii* and weakly eradicated preformed biofilm.[22]

Clinical importance of *A. baumannii*

A. baumannii is responsible for causing approximately 2% of nosocomial infections in the United States and Europe, twice the rate in Asia and the Middle East. Due to unrestricted antibiotic overuse, drug resistance against all the available antibiotics has been reported. In no time, the pre-antibiotic era will return if efforts in the direction of novel therapeutic strategies are not made.[23] *A. baumannii* employs various strategies to combat the effect of antibiotics, including production of β-lactamases, aminoglycoside modifying enzymes, modification of the target site, efflux pumps and permeability defects. Although the rate of infection by *A. baumannii* is comparatively low than other Gram-negative bacteria, but phenotypes with multidrug resistance are worryingly four times higher than other Gram-negative bacteria such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Initially, *A. baumannii* isolates were susceptible to carbapenems. However, the rate of carbapenem-resistant *A. baumannii* is reported as high as 90% (Central Asian and Eastern European Surveillance of Antimicrobial Resistance: annual report 2016.World Health Organization). A study conducted in Europe, Eastern Mediterranean and Africa showed that *A. baumannii* and carbapenem-resistant *A. baumannii* accounted for 20.9% and 13.6% of nosocomial infections, respectively. Resistance to antibiotics in *A. baumannii* is contributed by mutability, horizontal gene transfer potential and outer membrane vesicles in the evolution of *A. baumannii* as multidrug resistant (MDR), pan-drug resistant (PDR) and extensively drug resistant (XDR) figure -2.[24]

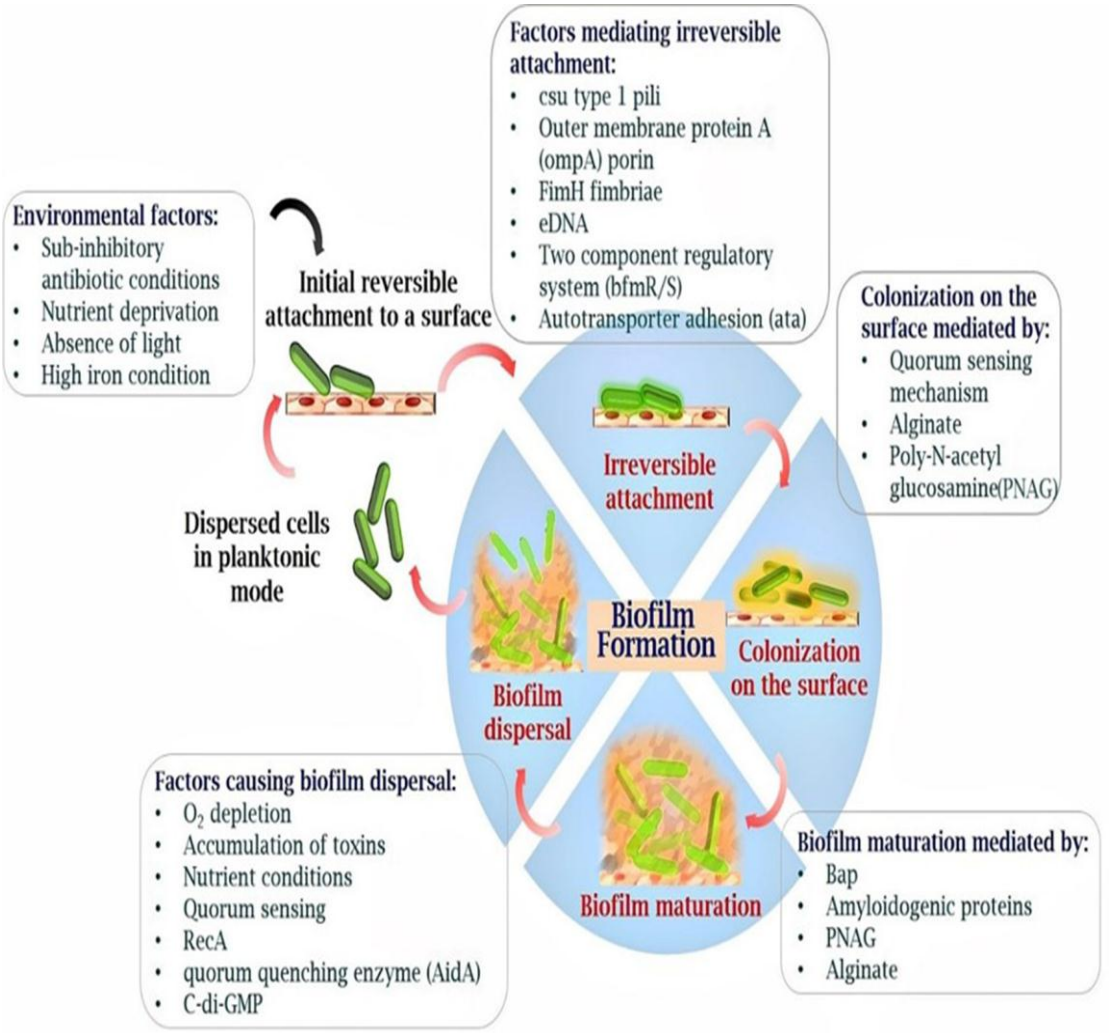

Figure 2: Clinical importance and virulence factors of *A. baumannii.*

CONCLUSION

A. baumannii is responsible for causing wide range of multidrug resistant and biofilm-associated infections in hospitals and community settings. Biofilm formation by *A. baumannii* is a multifactorial process involving various intrinsic and extrinsic factors governed by regulatory mechanisms directing bacterial adhesion, biofilm maturation and bacterial cell dispersal from the biofilm. The emergence of antibiotic resistance and the complex structure of the biofilm matrix render antibiotics ineffective. The determinants that drive any organism to be a successful pathogen are a consequence of several diverse factors. These factors include antibiotic use, infection control practices, climate change, human behavior, deforestation, availability of resources, and several others, that can over the years determine how these pathogens evolve. Future research will increase our understanding of this pathogen.

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