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A LITERATURE REVIEW ON *Acinetobacter baumannii* AND THE CHALLENGES: INSIGHTS INTO VARIOUS CLINICAL AND PATHOPHYSIOLOGICAL CONDITIONS WITH REFERENCE TO BIOFILM FORMATION.

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Abstract
Acinetobacter baumannii is a Gram-negative multidrug-resistant pathogen that poses a significant threat to public health, particularly in healthcare settings. Its ability to resist desiccation, colonize abiotic surfaces, and form biofilms contributes to its persistence in medical environments. This literature review explores the various clinical and pathophysiological challenges posed by *A. baumannii*, with a focus on biofilm formation, surface motility, and virulence factors. The bacterial resistance to common antibiotics, including carbapenems, fluoroquinolones, and cephalosporins, exacerbates its role in nosocomial infections such as pneumonia, catheter-associated bacteremia, and soft tissue infections. Understanding the multifaceted nature of *A. baumannii* virulence can guide future therapeutic strategies aimed at mitigating its impact, particularly in critical care units. The review highlights the need for deeper investigations into virulence mechanisms, biofilm disruption strategies, and iron acquisition systems. Furthermore, it underscores the importance of enhancing infection control measures, improving antibiotic stewardship programs, and developing policies to reduce the incidence of multidrug-resistant infections. This synthesis serves as a guide for researchers, clinicians, and policymakers in addressing the challenges posed by AI. *baumannii* in clinical settings.

Keywords: *Acinetobacter baumannii*, Biofilm formation, Multidrug resistance, Nosocomial infections, Virulence factors, Quorum sensing.
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INTRODUCTION
Acinetobacter baumannii is a Gram-negative, aerobic, coccobacillus exhibiting resistance not only to the carbapenem group of drugs but also to other classes like fluoroquinolones, ampicillin-sulbactam, third-generation cephalosporins, aminoglycosides being multidrug-resistant organism and even can go to the end where it can be resistant to the entire panel of drugs that are being tested during the process of primary culture and sensitivity methodbeing sent from the physician.[1]These characteristics of the bacteria are alarming since it has extensive ability to survive and dominate multiple abiotic surfaces in healthcare facilities. The bacterium is an omnipresent organism but has great colonizing potential. The prevalence of isolation of this bacteria from ICU patients varies in different geographical regions. The nosocomial acquisition of this bacteria in ICU setup is determined by various predisposing factors like length of hospital stay, patient if at all on mechanical ventilation, urinary and IV catheterization, and endotracheal intubations.[2]In the present scenario, the bacteria have immense importance in the medical community because of their association with aspiration pneumonia, catheter-associated bacteremia, soft tissue infection, endocarditis, and lower respiratory tract infection.[3]

Desiccation-resistant phenotypes are an important feature shown by Acinetobacter species. Desiccation is a common ecological pressure that may impose opposition to bacterial cells. Due to water loss the force within a cell that keeps the plasma membrane in contact with the cell wall is lost. Water loss causes low turgor pressure. It also induces biochemical changes that can damage cell membranes and denaturation of intracellular proteins. Thus, desiccation enables *Acinetobacter* species to propagate and produce a huge number of cells that can survive on dry surfaces for an extended period.[4]

On the other hand, *Acinetobacter baumannii* isolated from community settings have been implicated in causing community-acquired pneumonia, community-acquired bacteremia, urinary tract infection, and meningitis. These strains have been found to carry IMP1 metallo- β lactamase. According to Ambler'sclassification, there are four groups of enzymes viz: Class A, B, C, and D. Metallo-β lactamase belongs to group B according to which they carry Zn ion in

The active site.[5] It can cause life-threatening community-acquired pneumonia associated with severe inflammatory reactions (SIR) and disseminated intravascular coagulation (DIC).[6]

Little information about the prevailing existence of potential virulence factors in Acinetobacter species documented so far. Lipopolysaccharide (LPS) plays an important role in mediating such a serious fulminant disease course. The various factors that lead to the development of disease and disorder primarily depend on the activation of innate immune response. When the bacteria come in contact with a damaged host tissue with hemorrhages, they confront blood clots and complements

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as the first line of defense mechanism. However, the macrophages and neutrophils move to the site of infection and mediate adaptive immunity.[7]

Lipopolysaccharides (LPS), an important outer membrane component of Gram-negative bacteria, consist of a hydrophobic lipid core. The lipopolysaccharides in all Gram-negative bacteria are composed of:[8]

1. LipidA: it is an endotoxin and responsible for endotoxic shock
2. O-antigen: the repeating hydrophilic distant oligosaccharide
3. The hydrophilic core polysaccharide [8]

Once the bacteria gain access to the bloodstream, the LPS breaks up from the cell surface and is simultaneously recognized by the complementary receptors on the surface of macrophages and endothelial cells. The sequence of processing of the LPS occurs by binding to LBP in the serum followed by transfer to the CD14 receptor which is present on the cell membrane of the immune cells. It is the responsibility of CD14 to transfer to MD2 which is a non-anchored protein. This in turn interacts with Toll-like receptor-4 (TLR-4). The entire complex of LPS attached to CD14/TLR4/MD2 is found in ample amounts in various cell types viz: monocytes, dendritic cells, macrophages, and B cells. The fate of the complex is decided by the production of various cytokines like TNF, IL-1, IL-6, and IL-8 which in turn stimulate the release of prostaglandins and leukotrienes leading to inflammation and septic shock. The complex further stimulates the complement proteins initiating histamine release and vasodilation with neutrophil imbibition to the infected site. Activation of the blood clotting factors activates the humoral system leading to coagulation, thrombosis, and acute disseminated intravascular coagulation.[8]

Given the increasing incidence of multidrug-resistant A. baumannii infections, there is a pressing need for a comprehensive understanding of its pathogenicity and the mechanisms underlying its resistance. Therefore, this review seeks to address the following key questions:

1. What are the primary mechanisms of virulence and antibiotic resistance in *Acinetobacter baumannii*?
2. How does biofilm formation contribute to the persistence and pathogenicity of this pathogen in clinical settings?
3. What strategies can be developed to effectively manage and control infections caused by *A. baumannii*?

METHODS

The literature search for this review was conducted using a systematic approach to identify relevant studies focusing on *Acinetobacter baumannii*. The search included studies published from 2000 to 2024 to ensure a comprehensive overview of recent advancements and findings related to this pathogen. Only articles published in English were considered to maintain consistency and comprehensibility.

In terms of publication status, both peer-reviewed articles and grey literature—including conference proceedings, theses, and dissertations—were included to provide a broad perspective on the topic. The review encompassed various study designs, including original research articles, systematic reviews and meta-analyses, case studies, clinical trials, and laboratory studies focusing on microbiological characteristics.

To identify relevant literature, a search was conducted across several electronic databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Cochrane Library. The search strategy utilized relevant keywords and Medical Subject Headings (MeSH) terms such as "Acinetobacter baumannii," "biofilm formation," "multidrug resistance," "virulence factors," and "nosocomial infections." Inclusion and exclusion criteria were applied rigorously to ensure that only studies pertinent to the objectives of this review were selected.

DISCUSSION

Various virulence factors of *Acinetobacter baumannii*

One important factor for an organism to establish infection by colonization is by mediating contact with the surface via adhesion before the expression of virulence factors. Depending on the prevailing conditions in the microenvironment Acinetobacter species shows immense capability to transit from planktonic free-living bacteria to surface-oriented forms which currently is said to be the "persist and resist" mode of such pathogenic traits. This combined with the surprising capacity of the organism to survive in adverse conditions makes it a frightening pathogen. [9]

The Genus Acinetobacter (derived from the Greek word *akinetos*, meaning nonmotile or motionless) was established by Brisou and Prevot, in 1954. Correlation between motility and the ability to invade the host tissue has been well established in the case of *Escherichia coli*, and Salmonella but remains controversial in the case of Acinetobacter species which is a non-flagellate organism.[5] However, this organism can still migrate showing two different types of motility viz: twitching motility and surface-associated motility. Twitching motility is an organized complex migration system executed by the process of extension, attachment, and retraction of type IV pili. [10] Type IV pili (T4P) are bacterial accessories made up of protein units called pilins which are co-associated by weak bonds (due to no sharing of electrons) in the spiralform. The existence of type IV pili is common to all Gram-negative aerobic non-flagellated bacteria including *Acinetobacter baumannii*. However, there is heterogeneity in the distribution of amino acids as well as in the glycosylation pattern of type IV pili in other non-flagellated organisms.[11]

Biofilm formation is an important process in twitching motility seen in the case of this organism mediated by the

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expression of genes like *pilA, pilD, and pilT* and the GacS/GacA, a two-component regulatory system. [10,12] On the other hand, surface-driven motility is also a type of accessory-independent form of movement seen in *Acinetobacter baumannii* isolates that occurs due to the secretion of extra-polymeric substances. It is mainly enforced by the synthesis of 1,3- diamino-propane, lipopolysaccharide production, and due to the functioning of some efflux pumps.[13]

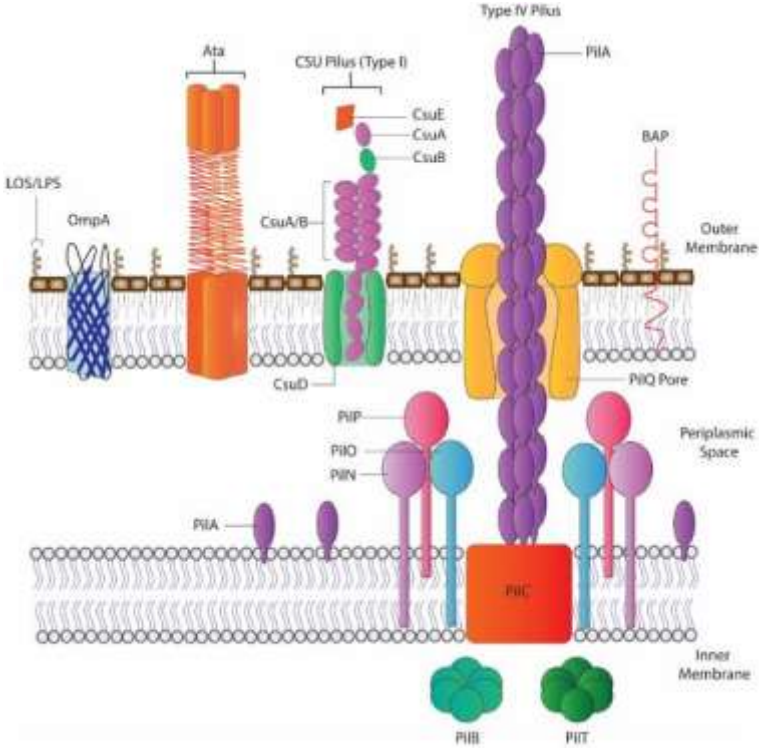

Figure 1: A schematic diagram illustrating the bacterial cell envelope and surface-associated virulence factors primarily involved in motility, adherence, and biofilm formation.

These factors include lip oligosaccharides (LOS) & lipopolysaccharides (LPS), Outer Membrane Protein A, Csu Pili, Type 4 Pili (TFP), Biofilm-Associated Protein (BAP), and the Trimeric Autotransporter (Ata).

One major role that any bacteria have to face to initiate infection is by overcoming the repulsive forces generated from negative charges shared by the host cell surface and the bacteria itself following contact. [14,15] Hydrophobicity or lipophilicity is a measure of the propensity of any substance undergoing analysis (i.e. analyte) to stick to a non-aqueous over an aqueous environment. Cell surface hydrophobicity (CSH) enables an organism to search for carbon sources found on the surface of the cell helping the organism to move from water to the organic phase in a microenvironment it resides in as a survival advantage. Hydrophobic cells tend to adhere more strongly to hydrophobic surfaces, while hydrophilic cells exhibit stronger adhesion to hydrophilic surfaces. The association of various accessories present on the cell surface in recognizing the surroundings makes an organism more competent and survives in extreme conditions by modulating the cell surface hydrophobicity. It is a known fact that Acinetobacter species survive in the hospital environment specifically in the critical care unit because they can adhere to the abiotic surfaces such as metal and plastic found in medical devices[16, 17] An array of expressions of virulence factors like gelatinase, biofilm-associated genes, cell surface hydrophobicity subject to environmental sensing or expression of type IV pili along with the expression of related motility phenotypes have been observed in Acinetobacter species. [18,19]

CLONAL LINEAGES

These strains represent a group that shares common biological and molecular characteristics, all originating from a single ancestor. This has resulted in the global spread of these strains, including international clonal lineages I (IC I) and II (IC II), also referred to as European clones I and II.[20,21] Identified for the first time in the 1970s, these strains have spread across the globe and caused hospital device-related infections and a positive correlation between the hydrophobic character of the organism with biofilm formation was noted. [16,22] Features that delineate IC-II from ICI- is due to its inability to form pellicle Pellicle formation occurs at the air-liquid interface and is composed of cells surrounded

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by exopolysaccharide, lipids, DNA, and protein components. [23,24] ICI-I forms pellicles on medical devices containing liquid and represents an appropriate site for *Acinetobacter baumannii* colonization. [23,24] The clonal complexes can be differentiated based on the secretion of capsular exopolysaccharide (CPS). Studies showed that IC-I strains produced polysaccharides of variable molecular mass. On the other hand, IC-II did give high molecular mass CPS.[25]

Infection by *Acinetobacter baumannii* via attachment and adherence on abiotic and biotic surfaces:

Bacteria have developed techniques to fight out challenges like nutritional deficiency, antagonistic environment, temperature, and pH through adaptation where the bacteria transform from planktonic form to stalkless form in which they remain fixed and attached to a surface. When discussing a notorious and resilient pathogen like *Acinetobacter*, which predominantly inhabits hospital environments, it demonstrates a particular affinity for colonizing medical devices such as breast implants, ventricular shunts, tissue fillers, ventricular-assist devices, contact lenses, catheters, joint prostheses, urinary catheters, orthopedic implants, pacemakers, mechanical heart valves, defibrillators, vascular grafts, endotracheal tubes, and voice prostheses.[31]

Initiation of biofilm formation begins with the attachment of a bacterium to a solid surface where the organisms are loosely attached. The organisms change their position and become organized in a flat position. 3′-5′-cyclic dimeric guanosine monophosphate (c-di-GMP) is an intracellular signaling molecule and plays an important role in irreversible fixation by regulating type IV pili-mediated twitching motility and increasing the biofilm matrix formation.[27]

This is followed by cell division with the formation of a huge number of cells known as microcolonies in the presence of a high conc. of c-di-GMP. These cells coordinate with each other by quorum sensing, cell-to-cell communication, and signaling cascades.[26]

These microcolonies are encased in a matrix composed of polysaccharides, proteins, and DNA. The exopolysaccharide structure of biofilm plays an important role in preserving and maintaining the 3D structure thereby giving a "mushroom" or "tower" shape structure. [28,29,30]

The last step in the life cycle of biofilm formation is dispersion to start a new life cycle again.

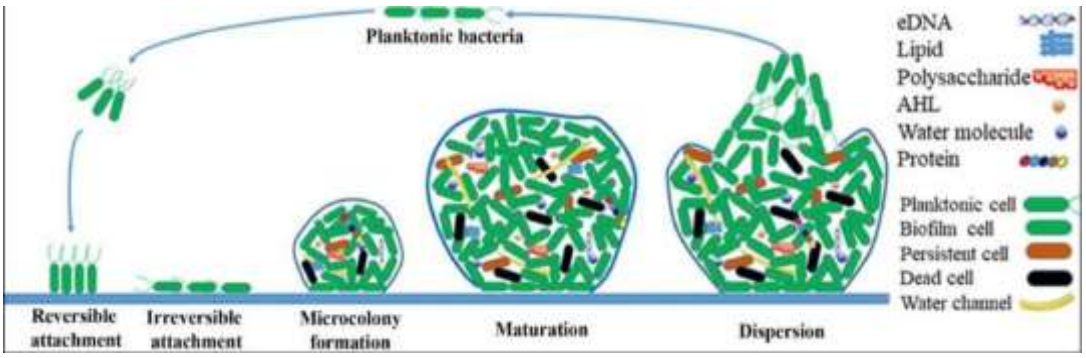

Figure2: Variousstepsin biofilmformation[31]

The initial step of biofilm formation starts with the attachment of planktonic microorganisms to the surface followed by irreversible attachment and development of Microcolonies. On maturation, microcolonies have a specific shape, and composition which is followed by dispersion to repeat the cycle. The various constituents of a mature biofilm are heterogenous in composition being made of planktonic followed by sessile, persistent, and dead bacteria including various signaling molecules like acyl-homoserine lactones (AHL), lipids, polysaccharides, proteins, and extra-cellular DNA (eDNA).[31]

An array of virulence traits leading to the successful establishment of biofilm is due to the expression of biofilm-associated protein encoded by (*bap* gene) which has a positive correlation in increasing the volume and thickness of biofilm. The major outer membrane protein encoded by (*the Omp A* gene) plays an important role in the attachment of bacterial cells to human alveolar epithelial cells.[32] The open reading frame of chaperone usher protein (CSU) encoded by the CsuA/BABCDE- out of which most importantly is *csu E*, the driving force in the formation of biofilm in Acinetobacter species. Results showed that the inactivation of *CSU led* to the abolition of pilin protein formation. The formation of biofilm is further strengthened by the secretion of poly-β-(1-6)-N-acetylglucosamine (PNAG) the formation of which is encoded by the PGA ABCD locus. [33] Communication among the bacterial microcolonies is due to the production of autoinducer molecules like acyl homoserine lactone encoded by *abaI*gene, required for quorum sensing and the later stage of biofilm formation. [32,34]

Identified for the first time in *Escherichia coli* outer membrane protein (OmpA) is a dominant virulence factor in *Acinetobacter baumannii*. OmpA has been found to

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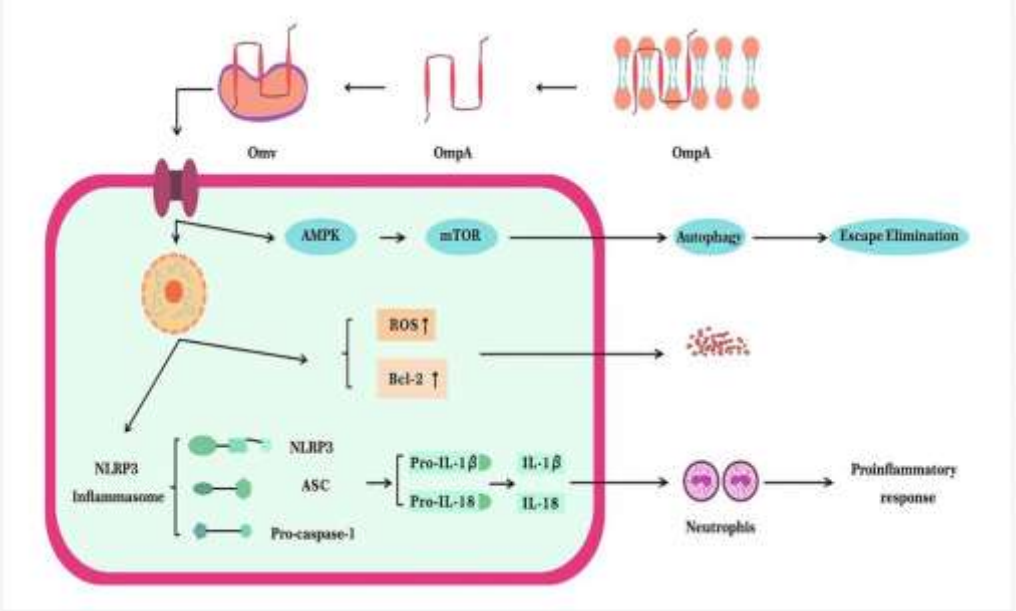
cause apoptosis of the eukaryotic cells by targeting the nucleus and mitochondria resulting in programmed cell death.[34] The OmpA is transported into the target cell by outermembrane vesicles leading to the release of reactive oxygen species breakdown of DNA and activation of NLRP3 inflammasomes. NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) is present inside the cell and detects a broad range of microbial receptors and environmental foreign substances that activate caspase-1 leading to the release of pro-inflammatory cytokines like IL-1β and IL-18. Finally, cell death occurs due to gastrin D- -mediated pyroptotic cell death.[35]

Outer membraneproteins

Omp A can form outer membrane vesicles that in turn are made up of bacterial outer membrane proteins, periplasmic proteins, inner membrane proteins, lipopolysaccharide, peptidoglycan, mRNA, and DNA. Altogether this protein helps in adhesion, invasion release of toxic factors leading to cell death. Autophagy is a process that encapsulates the cytoplasmic organelles and bacterial &viral pathogens. This indirectly leads to neutrophil activation, degranulation, and release of reactive oxygen species. Hence Omp A is a well-deserved target for serotherapy. The entire mechanism of action of this protein is explained in figure 3

Figure 3: Activation of AMPK/mTOR s pathway through autophagy. Activates the NLRP3 inflammasome by the Omp A and release of proinflammatory mediators.[34]



Efforts were made to increase the therapeutic efficacy of developing peptide molecules that target the Omp A of Acinetobacter *baumannii* and prevent the process of complementary fit with the receptor molecules present on the surface of the bacteria. An important protein that inhibits transcription and expression of Omp A is the A1S_0316 protein has been already recognized by Oh et al. 2020. A DNA vaccine targeting OmpA provided significant protection against *Acinetobacter baumannii* infection in a mouse pneumonia model. There remains potential for developing novel compounds that inhibit NLRP3 inflammasome activation, thereby reducing the conversion of pro-IL-18 and pro-IL-1β into their active forms, IL-18 and IL-1β. However, the inhibition of IL-18 and IL-1β release into the extracellular space could be Explored as a future therapeutic strategy, though further comprehensive research is required.[34]

Bacterial capsules

The protective layer of the capsule between the bacterial cell wall and the external environment acts as a barrier to various stress responses. The capsular antigen is demoted by the letter "K" derived from the German word Kapsel. In *Acinetobacter* species nine KL antigens were included (KL-1 to KL-9 antigens). A study conducted by the authors found that patients infected with *Acinetobacter* species possessing the KL2-type capsular antigen exhibited higher rates of drug resistance, more severe infections, and increased mortality compared to those infected with non-KL2 types.[36]

The capsular polysaccharide serves as an avenue to be targeted by a combination therapy of phage and antibiotics making the organism once again to become re-susceptible to the antibiotic therapy. One specific gene that is associated with the expression of capsular polysaccharides is *the wzb* gene which controls transcription and translation of capsular proteins. Hence this particular *WZB* gene can be targeted so that the strain

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no longer produces capsular material and the first line defence mechanism can effectively eliminate the bacteria from the body.[34]

Quorum sensing (QS)

During the process of biofilm formation when planktonic form changes to the sessile form and construct microcolonies, then the cells within the microcolonies communicate with each other subject to the production of extracellular signaling molecules called autoinducers (AI). The secretion of the AI is directly proportional to the bacterial population density. However, the bacterial community keeps an eye on the level of autoinducers to decide on the expression of a specific virulence trait over the other in the prevailing microenvironment.[38] QS is a process that occurs in response to biofilm formation and secretion of other virulence factors.[38] The process of QS starts with the production of AI by the cells right from the beginning when the cell density is low. The AIs produced by Gram-negative bacteria include acyl-homoserine lactone autoinducers that easily move out of the cell wall. The AIs thus produced initially diffuse into the surroundings and cannot be detected as the amount remains below the threshold level of detection. With increasing cell density via logarithmic increase the
Several cells by the process of division, and collective accumulation of AIs lead to local high levels finally hitting a so-called "critical mass". This excess concentration of AI beyond the bacterial cell community makes the situation unfavorable for more accumulation of AI outside the community. Consequently, the intracellular concentration of AI increases which stimulates the binding of AIs by the receptors present on the cell membrane and for further responses to be generated inducing the expression of genes needed for collaborative behavior.[38]

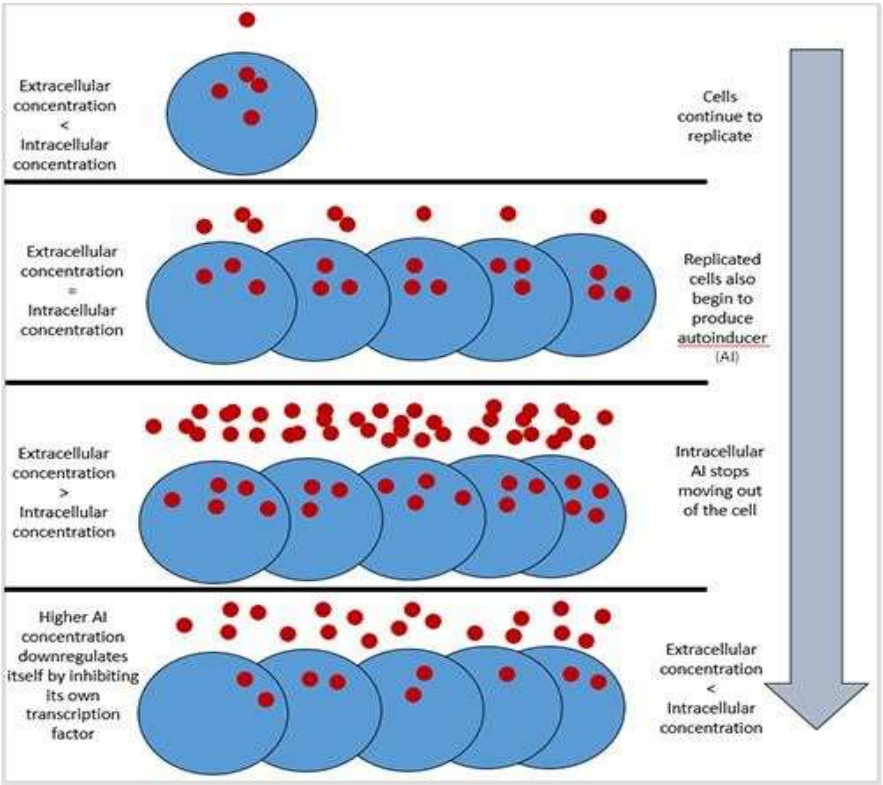

Figure 4: Overview of how quorum sensing works in bacteria.[37]

Quorum sensing (QS) in *Acinetobacter baumannii* is a complex process involving the autoinducer synthase (*aba*), the receptor (*abaR*), signal molecules (AHLs), and target genes. The *bar* gene encodes AHLs, whose concentration rises with increasing bacterial population density. Once a threshold concentration is reached, AHLs bind to *abaR*, triggering signal
Transduction that influences gene expression. The QS system enables *Acinetobacter baumannii* to respond effectively to environmental changes. Quorum quenching occurs when disruptions in the QS system's signaling pathways interfere with these processes.[38]

Effect of secretion system on *Acinetobacter baumannii*: [39,40]

Type I secretion system (T1SS)

Four distinct secretion systems have been identified in *Acinetobacter baumannii*, each contributing to its infectivity. The Type 1 secretion system is composed of three main components: the ATP-binding cassette (ABC)

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located in the inner membrane, which supplies energy to the entire system; the membrane fusion protein (MFP), extending into the periplasmic space; and an outer membrane β-barrel protein.[40]
These components create a transmembrane channel that spans the entire cell envelope of Gram-negative bacteria, facilitating the transport of unfolded protein substrates to the exterior of the cell, as illustrated in the figure below. The primary functions of the Type 1 secretion system include the production of virulence factors such as adhesins, lipolytic and proteolytic enzymes, iron-scavenging proteins, and pore-forming toxins. [39]

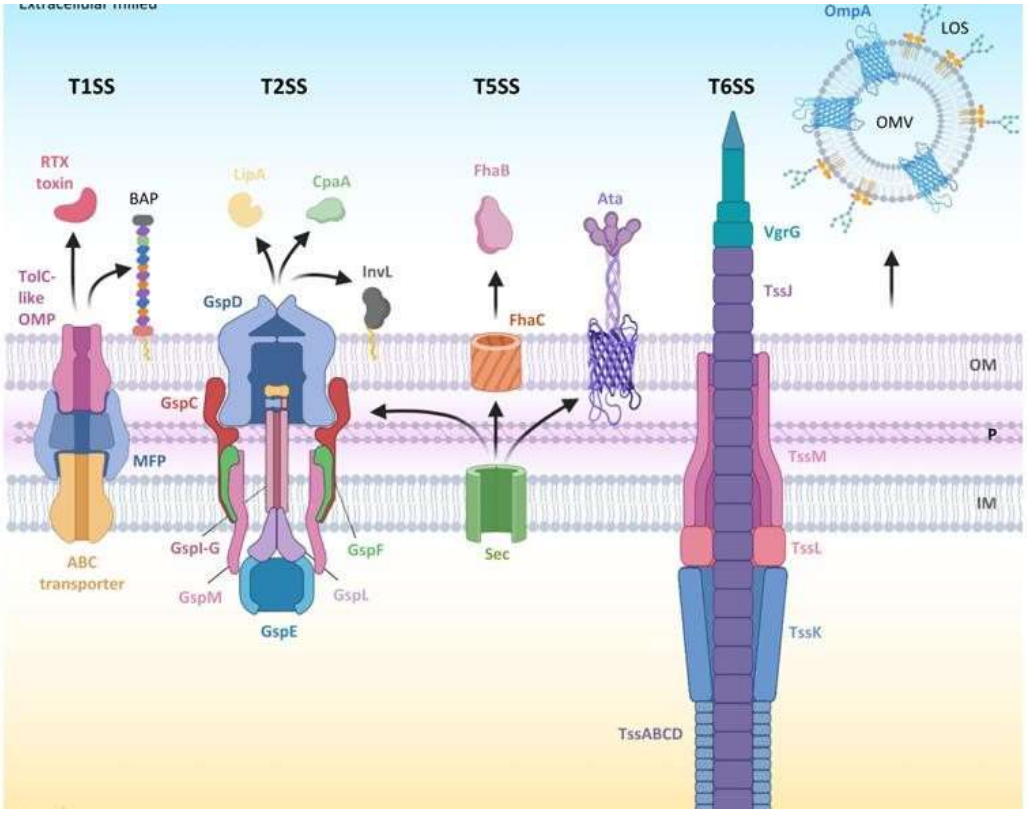

Figure 5: Secretion systemin Acinetobacter baumannii.[39]

The role of TISS in *Acinetobacter nosocomialis* has been investigated and two different effector molecules serralysin-like protein with a repeats-in-toxin (RTX) domain and the biofilm-associated protein BAP, that carry a C-terminal secretion domain have been identified as effector molecule.

Type II secretion system (T2SS)

The T2SS is a complex machinery that helps in the release of protein molecules (toxins, lipases, metalloproteases) by general secretory (Sec) or the twin-arginine translocation (TAT) pathway. T2SS has been found in *Acinetobacter* species like A. *nosocomialis, A. pittii, A. calcoaceticus, and A. junii*. The structural and functional T2SS genes are spread throughout the chromosome rather than being clustered in one locus. The T2SS has been found to bind firmly to the urinary catheters and cause urinary tract infection (UTI) as compared to mutants lacking the T2SS gene and showing a 10fold decreased ability to bind to urinary catheters. Other virulence traits like metallopeptidase CpaA, the lipases LipH and LipAN, and the adhesin InvL are produced and secreted by the T2SS system. Molecular characterization of Cpa A at the molecular level revealed that it is a zinc-dependent metallo-endo-peptidase that breaks down several human glycoproteins involved in complement activation and intrinsic coagulation pathways.[39]

Type V secretion system(T5SS)

The other name of T5SS is an autotransporter system made up of a protein with three regions namely N terminal signal peptide for transportation across the cytoplasmic membrane, extracellular domain, and translocator β shaped domain. The extracellular domainalso known as the passenger domain has various functions like adhesion, cell-to-cell aggregation, biofilm formation, intracellular motility, and enzymatic activities like proteases, lipases, and haemolytic activities. [39]
The autotransporter protein in *Acinetobacter baumannii* is trimeric and is known as Acinetobacter trimeric autotransporter (Ata). The Ata has protein binding activity and can bind to multiple proteins on the host extracellular matrix. Inactivation of ata gene in *Acinetobacter*

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baumannii ATCC 17978 greatly reduced biofilm formation on plastic surfaces and hence the lethal effect did come down in immunocompromised mice.[39]

Most of the *Acinetobacter baumannii*strains express functional contact-dependent inhibition (CDI) systems. CDI is initiated by T5SS and somewhat looks like needle-like structures assembled on a bacterial outer membrane These needle-like structures pierce the target cells to deliver toxic products.[40] The outer membrane pore-forming protein (Cdi B protein) switches the expression of CdiA toxin at the cell surface. In *Acinetobacter baumannii* two types of CDI systems have been identified which differ in CdiA protein structure. Type II CdiA are large proteins with a long array of 20-mer repeats. On the other hand type I CdiA is smaller with a central heterogeneity region.[40]

Outer membrane vesicles (OMVs)

The OmpA porin is the most predominant protein in *Acinetobacter baumannii* OMVs. OmpA is important for OMV generation. It can be delivered by the OMVs into the cytoplasm of host cells causing cytotoxicity. OMV carryantibiotic resistance genes on the plasmids and can very easily get transmitted to other bacterial species.

Iron uptake systems

A group of many genes encoding for iron acquisition has been identified in Acinetobacter species that probably makes the organism more competent to survive in an environment with iron limitation. Iron accession systems found in this bacterium are the Feo system, responsible for the ferrousiron uptake, three siderophore synthesis/transport systems, and two haem uptake systems.[41,42]

The iron accession, usage, and repository system or the Feo system consists of FeoA, a cytoplasmic protein, FeoB, an essential membrane protein that transports Fe 2+ across the inner membrane, and Feo C, a transcriptional repressor.[43] This Feo system has the capability of adhering to the lung epithelial cells as proved in a study where deletion of *feo A* reduces the ability of ATCC 17978 to adhere to human epithelial cells. [44,45]

Siderophores have a strong affinity for iron and form a stable complexon binding with iron from environmental sources. Acinetobactin and baumannoferrinare siderophores were identified in this bacterium. Another gene clusterinvolved in the synthesis and accession of a third

siderophore is called fimsbactin and has been identified in a few *Acinetobacter baumannii* strains, including ATCC 17978. During experimentation, the expression of Acinetobactin gene and its analysis in ATCC 17978 Acinetobacter species proved that the organism was pathogenic and could proliferate in host tissue due to the production and release of acinetobactin. [46,47]

The haemophilin secretion modulator HsmA helps in the translocation of HphA, called the haemophilin secretion modulator. During the process of translocation of haem across the outer membrane haemophilin receptorHph R gets hold of the molecule. The cell's ability to utilize iron is entirely dependent on the acinetobactin cluster, which consists of the *basABCDEFGHIJ* genes for synthesis, *bauABCDEF* for uptake, and *barAB* for siderophore export. The acinetobactin siderophore binds extracellular ferric iron with high affinity and transports it into the cell using the BauA TonB-dependent outer membrane receptor and an inner membrane ATP-binding cassette (ABC) transporter composed of BauC, BauD, and BauE. Additionally, NfuA, a cytoplasmic Fe-S cluster protein, is essential for intracellular iron storage and utilization.[48]

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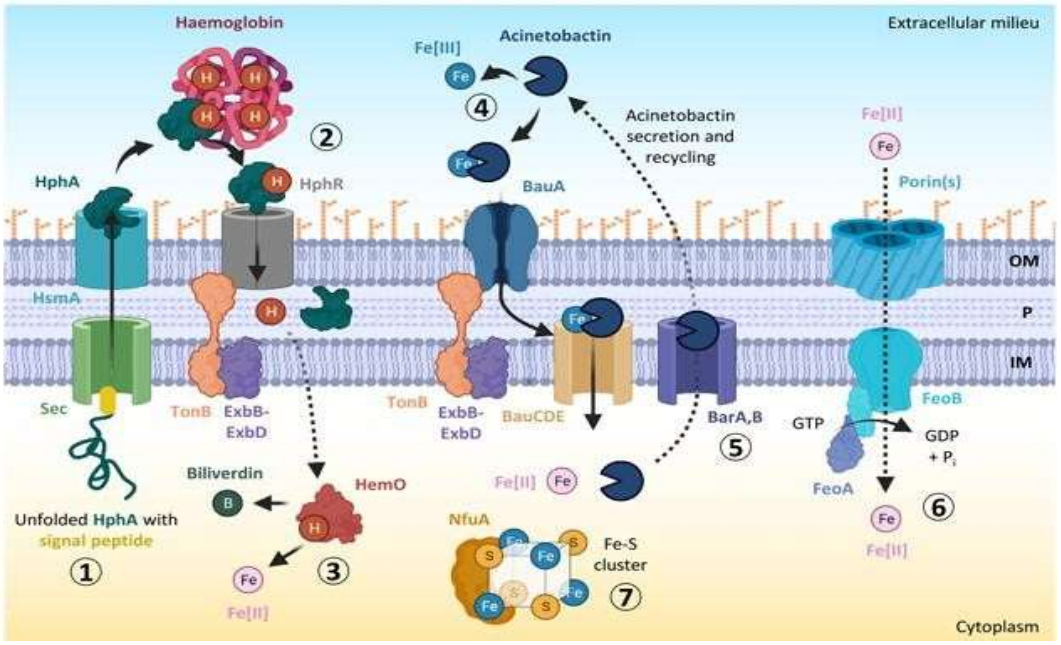

Figure 6: Iron uptake system in Acinetobacter species [48]

The siderophore and haem uptake systems rely on a triple protein complex—TonB, ExbB, and ExbD—located in the inner membrane and extending through the periplasmic space, collectively known as the TonB complex. This complex converts the transmembrane proton gradient into the energy needed to transport the iron carrier into the periplasm. Targeting the TonB system is a promising antimicrobial strategy, as its inhibition would hinder bacterial growth under low iron conditions, such as those encountered during infection.

Phospholipases encoding genes like (plc1 and plc2) have been indirectly found to be involved in iron acquisition by causing lysis of the RBC and release of the haemoglobin. Type D phospholipases namely pld1, pld2, and pld3 are potential virulence factors as the expression of these genes elevate the alveolar basal epithelial cells invasion.[48]

Zinc metabolism

Zinc acts as a cofactor of various proteins that take part in various metabolism like carbon metabolism, and amino acid biosynthesis. Studies using *the Acinetobacter baumannii* ATCC 17978 strain carried out in mammals showed that zinc-binding proteins such as calprotectin tend to accumulate in the lung within 6 hours of infection and disappear only when the foreign bacterial agent is cleared. The genetic locus responsible for zinc uptake includes an operon that encodes the zinc uptake regulator, Zur, the ATPase ZnuC, and the inner membrane transporter ZnuB, along with two monocistronic genes encoding the periplasmic proteinZnuA and the TonB-dependent receptor ZnuD.

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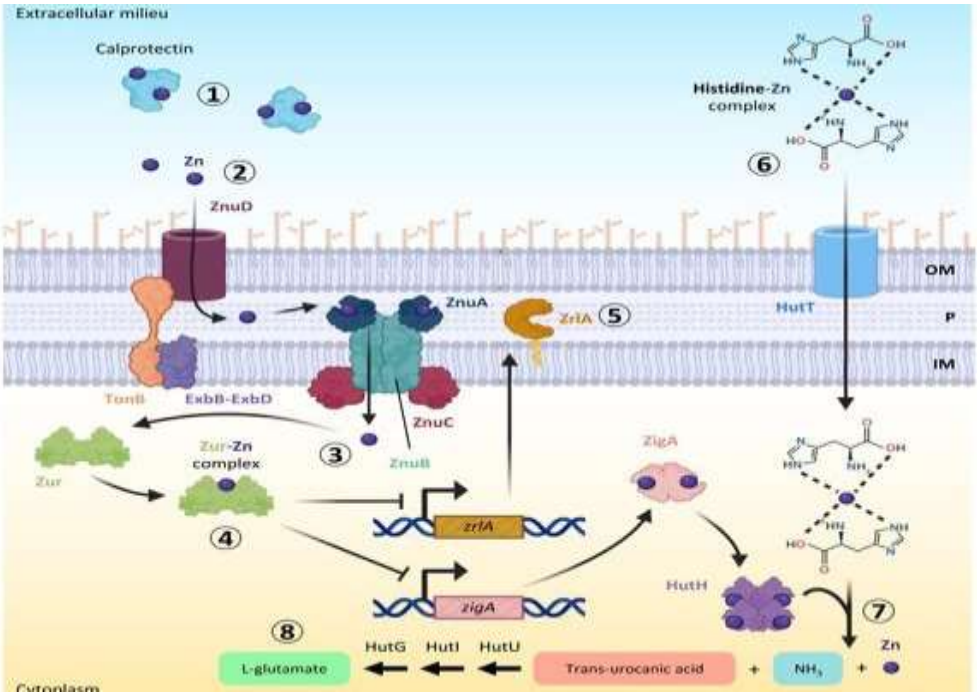

Figure 7: Zinc metabolism in Acinetobacter species[49]

Transportation of free zinc across the outer membrane toward the interior of the cell in the periplasmic mediated by TonB-dependent receptor ZnuD. From the periplasmic space, the zinc is further shifted into the cytoplasm by the ZnuABC system. Within the cytoplasm, zinc binds to intracellular zinc, triggering the expression of zinc-regulated genes *zigA* and *zrlA*. ZrlA is a peptidase involved in peptidoglycan modification and maintaining the cell envelope's shape. The zinc-His complex enters the cell via the Hutt transporter and is cleaved inside the cytoplasm by the Zn-dependent enzyme His ammonia-lyase (HutH) into trans-urocanic acid, ammonia, and zinc. Trans-urocanic acid is then converted into L-glutamate through reactions catalyzed by HutU, HutI, and HutG. [50]

Resistance to xeric stress

Water molecules are the non-volatile solvents in the cells and offer firmness to lipids, DNA, and proteins. Water loss that occurs during desiccation stress leads to total loss of cell wall integrity disrupting the respiratory chain and accumulation of superoxide radicals.

CONCLUSION

Acinetobacter baumannii has emerged as a formidable pathogen, particularly in healthcare settings where its ability to persist on surfaces and resist desiccation allows it to thrive. Its multidrug resistance, biofilm formation, and a wide array of virulence factors, including motility mechanisms and iron uptake systems, contribute significantly to its pathogenicity. These factors not only complicate infection management but also limit therapeutic options, making it a global health challenge. A deeper understanding of its virulence mechanisms, biofilm formation, and resistance pathways is crucial for the development of more effective treatment strategies. Future research aimed at disrupting biofilm formation, quorum sensing, and iron acquisition may hold the key to controlling infections caused by *A. baumannii*, particularly in critical care environments where the pathogen is most dangerous.

Limitations

While this review provides a comprehensive overview of the current understanding of *Acinetobacter baumannii*, several limitations should be acknowledged. The quality of the research included varied significantly, with some studies lacking robust methodologies, small sample sizes, or limited geographical representation, which may affect the generalizability of the findings. Additionally, the reliance on English-language publications may have introduced a publication bias, potentially excluding valuable insights from non-English studies. Furthermore, the dynamic nature of bacterial resistance and virulence mechanisms necessitates ongoing research, as the field is continually evolving. Future studies should aim for standardized methodologies and larger, multi-center trials to enhance the reliability and applicability of findings related to *A. baumannii*.

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List of Abbreviations

A. baumannii: Acinetobacter baumannii
ICU: Intensive Care Unit
MeSH: Medical Subject Headings
QS: Quorum Sensing
LPS: Lipopolysaccharides
OMVs: Outer Membrane Vesicles
TLR: Toll-like Receptor
CPS: Capsular Polysaccharide

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Conflict of Interest

The authors declare that they have no conflicting interests related to this study.

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