

Article Review: *Acinetobacter baumannii*

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ABSTRACT

Acinetobacter baumannii is highly invasive, resistant to multiple drugs bacteria that are primary source of nosocomial illness in the modern hospital systems. It has been linked to a significant death rate or has been identified as a causative of meningitis, pneumonia; a condition called urine tract illnesses, or wound diseases. Many virulence variables, such as porins, capsules, including cell wall a substance called lip digestive enzymes, biofilm formation, movement, or iron-acquisition structures, amongst other people, contribute to severity in *A. baumannii* illnesses. These virulence factors aid in the organism's ability to withstand harsh ecological circumstances also permit the growth of serious diseases. For tandem to the rise for *A. baumannii* diseases, difficult varied resistant pathways for this pathogen are effectively known, leading to the low efficacy of main antibiotics groups. *A. baumannii* has a distinct capacity to sustain a resistant to multiple drugs phenotype via a diverse range of antibiotic-hydrolyzing digestive enzymes, modifications to the efflux pumps, impermeability, or alterations in pharmaceutical targets, making therapy even more intricate. Understanding of *A. baumannii*'s transmissible diseases revolves on a comprehension of the processes underlying illness, pathogenicity, or resistant development. This review's objectives are to emphasize *A. baumannii* illnesses major disease-causing variables while also touching on the processes behind resistant to different antibiotics groups.

Keywords- *Acinetobacter baumannii*, antibiotic, stress, pathogen, infection virulence.

I. INTRODUCTION

Acinetobacter baumannii is a cardiovascular, pluralistic, non-motile gram-negative bacillus. *A. baumannii* is an opportunistic infection that is very prevalent in impaired people, especially those who have had a lengthy inpatient treatment (more than 90 days). It is often found in aquatic settings or had been demonstrated to colonized epidermis[1]. This has also been found to be highly distinct from pulmonary or oral fluids of sick people. Owing to this vast of resistant to antibiotics, it has been classified as a "red alert" humans disease throughout subsequent decades, which had alarmed physicians. The emergence of multidrug-resistant (MDR) bacteria has raised significant concerns about nosocomial illnesses as well as diseases obtained in the society. In fact, among the top three issues affecting human health according to the World Health Organization (WHO) is resistance to antibiotics[2]. The

abbreviation "ESKAPE," which stands for *Enterococcus faecium*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, or *Enterobacter spp.*[7], encompasses some of the most prevalent or dangerous MDR pathogens. *A. baumannii* is assumed to had been susceptible to most medications in the 1970s, but it now seems that the bacterium has significant immunity to the majority of first-line medicines. Throughout more modern times, *A. baumannii* has grown to be a significant source of worry in war areas. Bacterium had becoming especially well-known in the ongoing desert battles in Iraq, where it has earned the nickname "Iraqibacter." For instance, during Operation Iraqi Freedom (OIF), there are emerged indications for an elevated prevalence for MDR bacterial overgrowth (circulation diseases) amongst United States Army combat men[3-4]. During the last fifteen years, the academic society's research has resulted in notable advancements in human comprehension of this creature.

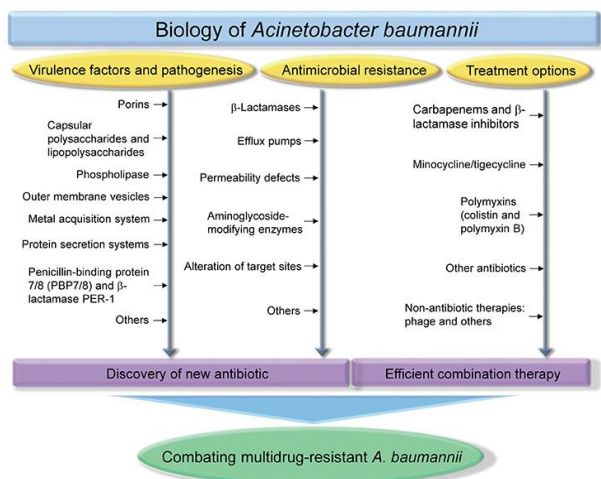


Figure 1. Biology of *Acinetobacter baumannii*' Research on *A. baumannii*'s disease progression, virulence- antimicrobial resistance, as well as available treatments will be crucial in the search for novel antibiotics or effective conjunction therapies—two tactics that are critical in the fight against multidrug-resistant *A. baumannii* illnesses.

II. TAXONOMY AS WELL AS MICROBIOLOGICAL PROPERTIES OF *ACINETOBACTER BAUMANNII*

According to present definitions, the genus *Acinetobacter* is made up of small, pluralistic microorganisms that are inert, exclusively aerobic, catalase-positive, Gram-negative, or oxidase-negative[5]. Their G+C concentration in DNA varies from 39% to 47%. *Acinetobacter* species forms seamless, mucoid, grayish-white colony at 37 °C on solid substrates such tryptic soy gelatin or sheep plasma agar that are frequently utilized in diagnostics[6]. Such diverse family of bacteria had endured an amazing, intricate taxonomy background since it was initially identified around the start of the twentieth century[7]. Improved nomenclature is being revised often since the 1980s, coinciding with the growing awareness or growth of acinetobacters as nosocomial bacteria. *A. baumannii*, *Acinetobacter johnsonii*, *Acinetobacter haemolyticus*, *Acinetobacter junii*, and *Acinetobacter calcoaceticus*, *Acinetobacter species lwoffii* had been among the twelve DNA categories as well as genospecies that were identified by the first, historic categorization of acinetobacters, which was made possible by the efforts of Bouvet as well Grimont. According with 2019, based on a study by Vijayakumar et al., there are 59 species in the genus *Acinetobacter*, of which 11 have identities that are known while 15 have descriptions that are speculative[8-9]. *Acinetobacter calcoaceticus*–*Acinetobacter baumannii* complex (ACB complex) in particular consists of four related organisms which are challenging to differentiate through phenotypic properties: *Acinetobacter calcoaceticus*

(genomic species 1), *Acinetobacter baumannii* (genomic species 2), *Acinetobacter pittii* (which used to be genetic species 3), as well *Acinetobacter nosocomialis* (previously genomic species 13 TU). *Acinetobacter seifertii* or *Acinetobacter species dijkshoorniae* are 2 fresh species that have just been added to the ACB complicated[10]. Therefore, the *Acinetobacter* species *baumannii*, *nosocomialis*, *seifertii*, *pittii*, and *dijkshoorniae*—five that are linked to human diseases—and *Acinetobacter calcoaceticus*, a naturally occurring species that frequently escapes from soil but has not been identified as an individual's pathogen, make up the ACB intricate[11-12]. It is still difficult or hard in identify *Acinetobacter* species-level. By the context of commercially automatic processes, phenotype approaches using development temperatures, hemorrhaging hypoglycemia acidity, or carbon/energy are recommended[13]. An growing number of investigations were using matrix-assisted lasers diffraction ionization-time of flights analytical in flight (MALDI-TOF), 16S rRNA genotyping, including DNA–DNA hybrid for biological taxonomic determination. Furthermore, whole-genome sequencing-based methodologies have supplanted conventional genotyping technique, and these methods are showing promise in the epidemiologic categorization of *Acinetobacter*[14]. The effectiveness of these techniques outperforms traditional classification therefore suggests their beneficial integration in disease management for the years to come, as well as to their present use in epidemiological investigations. The *bla*OXA-51-as a gene, which is chromosomally localized in *A. baumannii*, also but exhibits exceptionally poor carbapenem the process of hydrolysis serves as a valid diagnostic to recognize that organism. Turton as well as others have commented on the use of that locus in differentiating *A. baumannii*, also from the ACB group[15]. *Acinetobacter baumannii*, *A. pittii*, or *A. nosocomialis* were the 3 most therapeutically significant subspecies of *Acinetobacter* which has been linked for a preponderance of invasive or community-acquired illnesses, but they remain hard to recognize exactly in conventional labs. For that reason, each of those kinds shall be referred to throughout this research by the general term *A. baumannii*.

III. RELATED INFECTIONS WITH *A. BAUMANNII*'S THERAPEUTIC EFFECTS

As was already noted, *A. baumannii* has a tendency to withstand adverse circumstances or various medication classes, which allows it to live or proliferate as a nosocomial pathogen. This is especially true for individuals who are severely sick, which raises morbidity or death rates. Numerous risk factors for acquiring *A. baumannii* have been identified in past research[16]. These include extended stays in intensive care units (ICUs), prior healthcare as well as ICU stays,

using mechanically ventilation, prior antimicrobial agents treatment, implanted catheters, which are endotracheal tubes, as well as nasogastric tubes, older individuals age, substantial or emerging surgery, infants with low birth weight along with premature birth, kidney transplantation, as well as continuous administration of intramuscular fatty acids or total parenteral nutrition[17-18].

A. baumannii illnesses affecting the circulation, epidermis or soft tissue of the the bladder, the brain, or pulmonary system have become more troublesome for healthcare facilities in recent decades. The illness load, obstruction, or widespread of *A. baumannii* shown individuals, pets, or the environment are summarized given Figure 2.

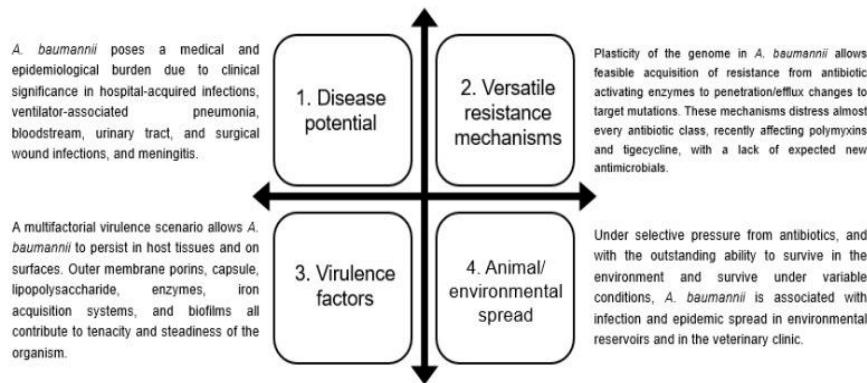


Figure: 2 Because of the interaction between related sickness, a diverse range of virulence variables, a multidrug-resistant the phenotype or dissemination within creatures as well as surroundings, the bacterium *Acinetobacter baumannii* has a dynamic biological character.

IV. PATHOGENIC PROCESSES IN INFLUENZA-RELATED RESPIRATORY CONDITIONS ATTACH AND ADHERE

A. baumannii is able to cling to extracellular matrix (ECM) enzymes including ligands on the epithelial membranes of the alveoli during the early stages of an infection. The variables of virulence listed above are necessary for this mechanism to occur (Figure 3).

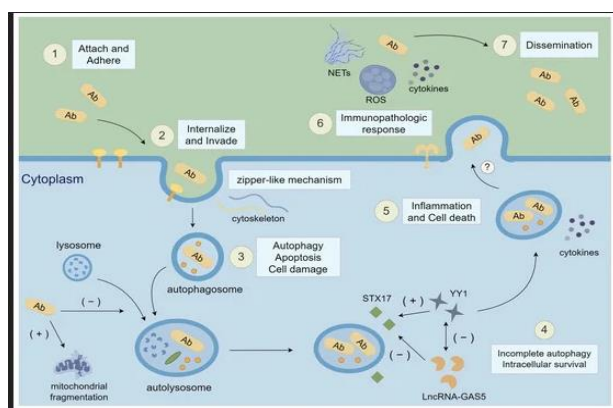


Figure 3. The mechanism of pulmonary disease-causing *Acinetobacter baumannii* infections.

YY1, Yin Yang 1, LncRNA-GAS5, development arrest-specific gene 5, NETs, neutrophil extrinsic devices, ROS, and *Acinetobacter baumannii* are

some of the acronyms used in this sentence. The method is fictitious, demonstrated by the query sign. The general sequence of the incubation procedure is shown by numbers.

4.1 Omps

OmpA is known with directly interface with collagen on the interfaces of the bronchi and pulmonary the epithelium which is important for adhesion to the pulmonary epitheliums. Furthermore, CarO was shown to increase bacterial adherence or colonized in rodents by Labrador-Herrera et al. Humans respiratory epitheliums showed decreased adhesion or invasive capability in variants devoid of CarO[19-20]. Human lung epithelial cellular interface cells expressed ChoP (phosphorylcholine), which ChoP-containing OprD coupled to trigger platelet-activating factor receptor (PAFR) and set off a series of events leading to adhesion to the pulmonary epithelial surface. Additionally, it was discovered that Omp33 or OmpW were implicated in the invading cell death, or adhesion of microbes to human's pulmonary epithelial cells.

4.1.2. Systems of Protein Secretion

As was already noted, AbFhaB(T5bSS) uses the RGD domain to bind with collagen or eukaryotes fibronectin. Adherence was seen to be significantly reduced in *Ata*-deleted mutations using *Galleria mellonella* larvae mice. *Ata*, a member of T5cSS, similarly utilizes the RGD pattern to facilitate bacterial attachment with ECM components[21]. *A. baumannii* T6SS's sticky and aggressive qualities are shown to be diminished with deletion from its *vgrG* a gene, a crucial component, according to a different research.

4.1.3. Variant IV Pili with The pilus Mediated by CsuA/BABCDE

Another experimental investigation has demonstrated that these kinds of IV pili stimulate adherence to pulmonary cancerous cells in the esophagus. Moreover, earlier research shown that *A. baumannii*'s adherence or adherence to bronchi epithelium cells was unrelated to CsuA/BABCDE-mediated pilus[22]. Nevertheless, that Csu pilus was an element to the mannose-sensitive kind I pilus group as well as that it promoted *baumannii* adherence and colony growth. Members of the lytic transglycosylase (LT) family, including MltB, are implicated in the remodelling of the peptidoglycan (PG) surface or the dissolution of pieces from it[23]. According to a research, MltB deactivation compromised the strength of human cellular membrane, which significantly reduced its amount of pili onto bacterium or their penetration of the pulmonary system.

4.1.4. Biofilm-Associated Protein (Bap), Bap-like Protein (Blp), and PstS

The biofilm-associated peptide (Bap) produced by *A. baumannii* enhances the hydrophobic property of the cell's appear, which in turn enhances adherence to epithelium cells. Bap-like proteins (Blp) BLP1 that BLP2, additional auxiliary protein molecules, have recently been discovered to co-express to Bap and share a sequence at the NH₂ terminal with Bap[24-25]. Their *blp1* or *blp2* knock-out mutant showed a significant reduction for adhesive to pulmonary epithelium cells, indicating the synergistic roles of Blp or Bap for adhesion or persistence. Furthermore, it remained noted in Gil-Marqués et al. revealed protein phosphate sensors PstS exhibited a very sticky or aggressive feature; however, it was unclear how specifically this trait affected *A. baumannii*'s pathogenicity.

4.2. Internalize and Invade

A. baumannii connects with platelet-activating factor receptors (PAFRs) via ChoP (phosphorylcholine)-containing OprD towards the start of invading. This interaction sets off a cascading reaction that includes clathrin, β -arrestins, or G protein-coupled phospholipase C (PLC). Cellular morphologies or movement properties were often associated with adhesion impulses sent by receptors on cells[26]. This zipper-like process known as receptor-mediated access is triggered by inside of cells communication routes which are triggered by the attaching of ChoP as well PAFRs or through interactions between the integrins or particular infections adhesion molecules. This process relies on microfilaments as well small tubes leading to in regional actin cytoskeletal reorganization at the invaded site[27-28].

A. baumannii internalization of *Baumannii*. The incorporation mechanism is assumed might be aided by the myosin cytoskeleton's flexibility. Bacteria remain in membrane-bound vacuoles following that. The path in which chambers travel is consequently dictated by proteins such as clathrin or β -arrestin-1/2, that have the

ability to connect *A. baumannii*—which is paired with PAFRs—to the vesicular trafficking mechanism or steer it to certain locations[29]. According to some research, this procedure is necessary for *A. baumannii* to internalize into the pulmonary epitheliums. According with a different research, *A. baumannii* increased bacterial penetration of the cell membranes or internalization inside vacuoles via binding with the humans carcinoembryonic antigen-related cellular adherence molecule (CEACAM) receptor CEACAM1/5/6 (Figure 1).

4.3. Cellular Destruction, Apoptosis, or Autophagy

For order to achieve cells metabolic processes, resistant protection, as well as known as regrowth for limited organelle-like structures autophagy—an vital cells process—cleaves elderly organelle-like structures scathed amino acids, as well as inside cells infectious agents within autophagic Lysosomes that are created by a combination of lysosomes as well as self-destructing. In order to create an environment for its development as well as development while avoiding being eliminated by the body's immune system, *A. baumannii* may diligently cause the autophagy process while also preventing self-destructing in fusing about Lysosomes[30]. This would result in a persistent increase in the release of pro-inflammatory cytokines. OmpA of *A. baumannii* was stimulate the mitogen-activated protein kinase (MAPK)/c-Jun Nterminal kinase (JNK) communication route, which using turn caused decomposition in macrophage with cells of epithelium.

The mammalian target of rapamycin (mTOR) pathway is another route linked to phagocytosis. This is being shown that mTOR plays a significant role for autophagy signal transduction since it combines many vital biological processes information originating forward, including oxidant stages, vitality, or nutrients[31]. It is subsequently shown that OmpA stimulates the mTOR signalling system to increase autophagy. In order that promote autophagy, which OmpA suppresses mTOR function and raises total amount for activating kinases 1 growth regulators (TAK1). Furthermore, TAK1 may stimulate the MAPK pathway, which would result for reduced to p62, which as well as an upsurge for that dissociation of microtubule-associated protein light chain 3 (LC3), consequently promoting autophagy.

Moreover, CEACAM5 or CEACAM6 were shown by Ambrosi et al. to stimulate the c-JNK1/2-Rubicon-NOX2 route, triggering LC3-associated phagocytosis (LAP) or autolysosome development, that in turn resulted in microbiological destruction[32]. However, further research is required to fully comprehend these intricacies of *A. baumannii*'s host-pathogen connections owing to the intricacy of its intracellular respiration process. On stimulating autophagy, OmpA additionally serves a role within DRP1 (GTPase dynamin-related protein 1) triggering, which increases the protein's build-up in mitochondrial

or ultimately leads to cytotoxicity, mitochondrial disintegration, elevated ROS production, including intracellular destruction. The clinically relevant strain AB5075, which produced mitochondria disintegration within human epithelial cells of the lungs A549, was validated by Tiku et al. to have an extended chromosomal separation[33-34]. Such implies therefore this pathogen has clinical significance as well as that the transmissible pathway has been conserved. The process of programmed cell death is known as apoptosis, with caspases are essential for controlling the transmission of apoptotic signals. Rumbo et al. discovered that Omp33 activated caspases and altered autophagy, or increased p62 as well as LC3 to cause mortality in immunological or ligament cells[35-36]. Reactive oxygen species (ROS) are produced by such procedures, while phagocytosis was shown in this research to occur when apoptotic was absent.

Partial Autophagy It is known that in order for microorganisms to survive inside the cells of their hosts, *A. baumannii* inhibits and postpones the integration of phagocytes with lysosomes. The precise chemical process behind imperfect autophagy is yet unknown, nevertheless[37]. Prior research revealed that OmpA was primarily responsible for regulating imperfect autophagy throughout the infectious phase of *A. baumannii*. This was due to OmpA's promotion of the bacteria's colonization in self-destructing which allowed for intracellular development as well as escape from the immune system. The interruption the autophagy occurs by the recently identified LncRNAGAS5/YY1/STX17 biochemical system, which is being clarified subsequently.

Synapsin 17, or STX17, is a critical regulator of the merging of self-destructing with lysosomes. Prior studies have verified that pathogens impeded the production of autophagic lysosomes by degrading STX17 in order to circumvent phagocytic resistance[38-39]. LncRNA-GAS5, or maturation arrest-specific transcription 5, is related to autophagy modulation with STX17 gene expression suppression. Overall zinc-finger transcriptional regulator Yin Yang 1 (YY1) has excellent conservation and upregulates the expression of STX17. An verified that through mutually regulating one another, LncRNA-GAS5 or YY1 preserved the equilibrium of STX17 concentrations. Consequently, there was little change on the levels of inflammatory or apoptosis. When *A. baumannii* suppressed YY1 expression, LncRNA-GAS5 levels increased and STX17 levels sharply decreased[40]. Furthermore, YY1 was blocked by the elevated quantity of LncRNA-GAS5, which significantly reduced STX17 production or STX17 itself. Thus interplay among inflammatory with respiration was upset as a result of such relationships. According to a different research, the transcription factor EB (TFEB) became active for reaction to *A. baumannii* infection of A549 cells[41-42]. This contributed the observation of lysosomal biogenesis, which is autophagy

stimulation, or an upsurge of A549 cell mortality. It has been shown that TFEB is important to *A. baumannii*'s internal transportation or is required for the uptake or viability of the bacterium in human that host it. Its role in reducing lysosomal acidity is one potential explanation[43]. Regulate autophagy by affecting the production of proteins involved in lysosome biosynthesis or decomposition. Bacteria may remain or proliferate within autolysosomes due to imperfect autophagy caused by these mechanisms. Nevertheless, the precise process of exocytosis is yet unknown.

4.4. Cellular Mortality or the Inflammatory Reaction

The buildup of inflammatory chemicals or cellular death is thought to have been primarily caused by *A. baumannii*'s impairment with autophagic elimination. Numerous inflammatory reaction systems have been postulated to far, but a great deal of effort was made to attempt to clarify these precise processes of the communication systems implicated by *A. baumannii*[44]. The pathogenic process of *A. baumannii*. TLR-NF- κ B (Nuclear Factor-Kappa B) Path of Signalling Among most common pathogen-recognizing receptors (PRRs) connected to intrinsic immune response stimulation are toll-like receptors (TLRs). The protective inflammation responses is triggered through its nucleotide-binding oligomerization domain (NOD)-like enzymes NOD1/2, that were PRRs found within organisms that sense peptidoglycan, the particular component of the bacterium cellular wall[45-46]. RIP2 is a protein adapter that carries out intracellular signalling cascades in response to PRRs such as NOD1/2. Receptor interacting protein 2 (RIP2), that has been demonstrated with become essential within NF- κ B activation, is triggered when PRRs, such as TLR2/TLR4, that are found on pulmonary phagocytes as well as bronchial epitheliums, and NOD1/NOD2, that reside inside the cytoplasm, acknowledge the LPS of *A. baumannii*. This starts the typical development of pneumonia. Inducing the inflammatory responses while encouraging neutrophils migration to the lungs, the NF- κ B signaling cascade controls the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-8, as well as IL-6.

Fascinatingly, it has been discovered that IL-33 therapy suppresses TLR4/NF- κ B signaling or lowers IL-8 and TNF- α levels, consequently preventing the *A. baumannii* pneumonia-induced systemic inflammation. Additional research showed that NOD2 induced the production of ROS enhanced initial resistance against *A. baumannii*, while rapid microbial removal helped mitigate the harm that proinflammatory cytokines caused to lung cells throughout the disease. TLR9 is present inside the cell in the endosomes that has been shown with mice lung instances to play a role to the defense towards *A. baumannii* illnesses[47]. *A. baumannii* released a bioactive lipids which linked to TLR2, activating the NF- κ B pathways in both human or rodent macrophages and as discovered subsequently by Tiku et

al. This mechanism activated inflammatory communication, something they are going to discuss about later, along with generated a number of inflammatory substances cytokines that including TNF α , IL-6, or IL-8. It also led to pyroptotic cellular demise[48]. Additionally, its signaling transmission in inflammatory was halted by protease therapy and TLR2 blockade in vitro. But further research is needed to figure out such activated lipid's impact on reality.

Antimicrobial agents 2023, 12, x FOR peer review 13 of 23 discovered that, although it was not necessary to deal in the pressure about AB-19606, a NLRP3 the inflammasome system helped preserve the respiratory tract from diseases triggered by the pathogenic separate AB-8879[49]. This suggests the importance of inflammatory during the medical cause of *A. baumannii*.

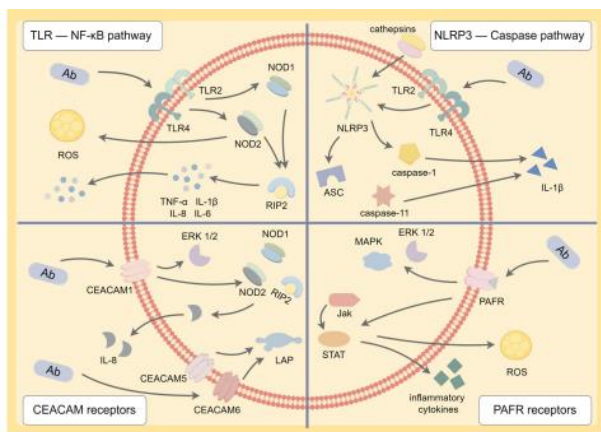


Figure 4: When *Acinetobacter baumannii* is infected, pulmonary epithelial cells or bronchial macrophage become inflamed. Ab is for *Acinetobacter baumannii*. Apoptosis-associated speck-like protein (ASC); ROS, reactive oxygen species; NOD, nucleotide-binding the formation domain-like proteins; RIP2, interface associating protein 2; NLRP3, NOD-like receptors 3; CEACAM, a sort of cell adhesive component linked to carcinoembryonic antigens; Platelet-activating factor receptors (PAFR); extracellular signal-regulated kinase (ERK); LC3-associated phagocytosis (LAP); mitogen-activated protein kinase (MAPK); janus kinase (Jak); STAT, transcription activator or signaling transduction; Figdraw was utilized to create this figure.

4.5 NLRP3 Inflammasome-Caspase Pathway

A protein component called an inflammatory complex is a part of the immune system that is innate. One mostly conventional inflammasome, NOD like receptor 3 (NLRP3), may react to a variety of infectious agents, including *A. baumannii*. Pro-inflammatory cytokines are produced via the NLRP3-ASC-caspase-1/caspase-11 pathway, according to earlier research. The NLRP3 inflammasome within monocytes was first activated by a variety of PRRs, including LPS or

damage-associated biochemical trends, including the ejection of cathepsins[50-51]. Subsequently, the activation through the subsequent cellular adaptor apoptosis-associated speck-like protein (ASC) led to the activation of caspase-1, and this in turn facilitated the development as well as generation of IL-1 β , ultimately causing lung damage.

The NLRP3 inflammasome process has been shown to aid within respiratory defense against diseases triggered by the pathogenic isolate AB-8879, but it was not necessary to deal with the pressure of AB-19606, according to identical research, indicating the importance of inflammasome in the medical pathogenesis of *A. baumannii*. Caspasese-1–NOD-like receptors (NLRs) activation is often referred to as the classic inflammasome pathway. It was shown subsequently that caspase-11, via a mechanism known as the non-canonical the inflammatory process pathway, may stimulate the production of IL-1 β without the need for NLRs[52-53].

According to Wang et al.'s research, a defect in caspase-11 hampered the removal of *A. baumannii* from infected areas, which led to a decline in lung infestations with aggregation. Additionally, as LPS is believed to be a cytosolic receptor for caspase-11, this is recognized being a dominating component in caspase-11 activation in Gram-negative bacteria. The precise chemical process behind the caspase-11-triggered inflammatory reaction is yet unknown, albeit. Furthermore, it is shown that Omps control the synthesis of inflammasomes[54]. It was shown by Li Y. et al. that OmpA blocked caspase-1 degradation, which led to the ejection of the NLRP3 inflammatory, raised inflammation, or worsened cell destruction. It has been demonstrated that Omp33 stimulates the NLRP3 inflammasome on murine monocytes by releasing ROS generated from mitochondria. . Additionally, Li, D. et al. discovered that inhibiting the p38 MAPK signalling cascade facilitated the switch at macrophages mortality from pro-inflammatory this process to non-inflammatory a process called which within turn caused lower to vitro concentrations of both the NLRP3 the inflammasome with IL-1 β . Consequently, there was a reduction in severe pulmonary damage or inflammation of the lungs.(Figure 2).

4.6 CEACAM and PAFR

Human carcinoembryonic antigenrelated cell adhesion molecule (CEACAM) the receptors belong to a class of glycoproteins that are associated with immunoglobulin, or Ig, which are involved in a number of biological processes, including attachment, signaling by cells transmission, as well as inflammatory reaction[55]. It is stated which *A. baumannii* binds to these receptors. When *A. baumannii* interacts with these receptors, two distinct signaling pathways are triggered. In order to enlist immunological system cells towards microbial authorization, *A. baumannii* initially attaches itself by binding to CEACAM1 ligands on pulmonary

tissues, which in turn causes the production of IL-8 via extracellular signal-regulated kinase (ERK)1/2 or NF- κ B activation cascades[56].

A. baumannii-activated CEACAM-5 or CEACAM-6 are additional routes that may facilitate LC3-associated phagocytosis (LAP). The platelet-activating factor receptor (PAFR), which is found on pulmonary epithelium tissues, is the final type of epithelial membrane receptors with which A. baumannii interacts. Research has shown that the collaboration between ChoP-containing OprD as well as PAFRs activates ERK-1/2 or mitogen-activated protein (MAP) kinase, that is associated with subsequent immunological or inflammatory reactions[57]. It has recently been shown that infiltration into the bronchial epithelium by ChoP-PAFR causes oxidant harm, amplification of the Janus kinase (Jak)-signal transducers leading regulator of the transcription (STAT) transmission pathway, or ultimately host cell death. The aforementioned mechanisms finally led to an uncontrollably systemic inflammation reaction[58]. Considering a primary cause for lung damage, A. baumannii viruses induce overwhelming inflammatory or immunological responses that negatively impact respiratory epithelium cells (Figure 2).

V. A. BAUMANNII VIRULENCE FACTORS

Recent approaches combining phenotypic, genomics, or infectious modeling investigations have aided in the discovery of critical virulence determinants for the pathogenesis of A. baumannii. Considering around 16 discovered gene islands involved in virulence, prevailing agreement indicates as multivariable or creative approach, indicating that the microbe dedicates a significant fraction of its genomes to pathogenesis[59]. Comprehensive investigations were unable to pinpoint a specific virulence component that contributed to A. baumannii's therapeutic efficacy.

Substantial evolutionary possibility is highlighted by this viewpoint, which may arise from adjustment to various biological locations or harmful methods, as is the case with other microbes as Legionella and Escherichia coli[60]. A brief overview of the pathogenicity factors that have been found as A. baumannii currently is provided next, with the condensed version illustrated in Figure 5.

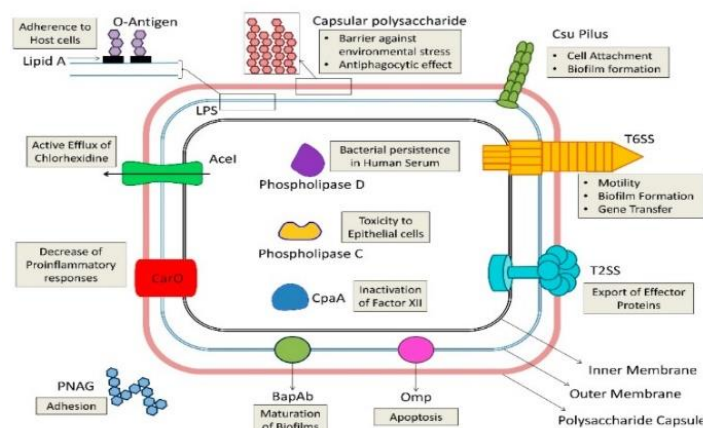


Figure : 5 An illustration of virulence determinants possessed by *Acinetobacter baumannii*.

The rectangular area next to it displays each determinant's functionality. The terms AceI and CpaA refer to glycan-specific adamalysin-like enzyme and chaperon/usher pilus framework, respectively; LPS and Omp stand for lipopolysaccharide and exterior membrane protein, respectively; PNAG and T2SS stand for type II and type VI secretions systems, poly- β -1,6-N-acetylglucosamine and T6SS, respectively.

5.1 Outer Membrane Proteins (Omps)

Since omps, sometimes referred to as porins, play a role in apoptosis, cytotoxicity, blood obstruction, creation of biofilm, and host-cell relationships, it is believed that enzymes were essential to the hazardous growth of A. baumannii[61]. Omps that have been discovered or thoroughly examined so far are OmpA, CarO, Omp33, OprD, or OmpW.

5.2 OmpA

OmpA is a β -barrel-shaped polypeptide with a periplasmic C-terminal region having an opening width of 2 nm. 2 essential peptide acids linked with the peptide g component that covers the cell's membrane assist binding OmpA to the exterior wall[62]. The amino acid sequencing from OmpA, which is regarded as the main significant exterior amino acids, is substantially consistent across medical strains of A. baumannii.

OmpA is involved in a variety of bacterial virulence or pathological activities, such as as infiltration or attachment, activation of autophagy, cellular damage, attachment to the recipient immunological system as well, development of biofilms, or susceptibility to medications. OmpA stimulates several indicate processes, such as the microbial emphasize for

rapamycin, or mTOR, process as well as the mitogenactivated protein kinase (MAPK)/c-339 Jun N-terminal kinase (JNK) signaling route, that can be covered with more detail in their portions follow to cause autophagy process within serve cells throughout the tract of respiration[63]. Additionally, DRP1 (GTPase dynamin-related protein 1) is activated by OmpA, which ultimately results in cytotoxicity or mitochondrial disintegration. Similarly research of Gaddy et al., the OmpA of ATCC 19606 was essential for microbial adherence to A549 alveolar in the lungs as partly contributed to the production of biofilms on biological surfaces.

5.3 CarO

Regarding the Omps of *A. baumannii*, CarO (carbapenem-susceptibility porin) is the 2nd most prevalent enzyme following OmpA. Whenever CarO is eliminated or altered, it may stimulate the inflow of imipenem into the bacterial cell wall, which leads to the development of carbapenem resistance. CarO is currently linked to *A. baumannii* adhesion to cell surfaces including infiltration throughout this bloodstream including several mammalian tissues, according to research conducted employing *A. baumannii* ATCC 196006[64]. The recruitment of neutrophils entering the lung cells as well as reduced the amount for anti-inflammatory mediators found in lung tissue, which led to the growth of microorganisms or worsened bronchitis.

5.4 Omp33

Omp33, an additional significant Omp in *A. baumannii*, serves as a water route. Omp33 was discovered to be important in a prior investigation regarding *A. baumannii*'s adaptation or virulence and including adhesion, encroachment or cytotoxicity of lung epithelial cells[65-66]. Additionally, it was shown that this cytotoxic protein significantly increased virulence by activating caspases, which in turn caused apoptosis in immunological or ligament tissue samples.

5.5 OprD/OccAB1

OprD was shown to be in charge of the transportation of substances including amino acids, carbohydrates, including antibiotic when it was discovered in specimens of *A. baumannii* that were resistance to carbapenem[67-68]. It is subsequently shown that OprD helped its carbapenem-resistant *A. baumannii* clone ST2/KL22 develop significant virulence, whereas pathogenicity was reduced when the oprD chromosome was knocked out. Identified OprD's crystalline structure in 2016, as well as assigned them the new designation OccAB1[69]. Researchers discovered that OccAB1 had a considerable transmit size which made it easier for numerous molecules circulate between them, which may have helped *A. baumannii* survive in vivo or assimilate resources.

5.6 OmpW

OmpW has cytotoxic effect towards cells in the host that is implicated in innate tolerance to different

ecological stressors. *A. baumannii*'s OmpW mutation decreased adhesion production or hindered the bacterium's capacity to attach to as well as invade A549 cell[70-71]. Furthermore, another research utilizing a rodent intraperitoneal septic paradigm found that a deletion in OmpW had no impact in sensitivity to various medications.

Additionally, OmpW was considered to be an iron regulator linked with both *A. baumannii*'s colistin, which affinity or iron absorption[72]. A research that suggested that OmpW reacted with iron or colistin reported generated pathways within synthetic phospholipid of lipids as well as improved virulence of *A. baumannii* into a rodent could not result into colistin resistance[73-74]. CPS, the primary component of bacterial fluid, has been shown to play a role in the development of the mucoid traits, a known hypervirulence aspect in *A. baumannii*. This mucoid appearance forms an obstacle that shields the microorganisms from external emphasizes along with inhibits the ingress of antimicrobial agents towards their cells[75]. Mucoid *A. baumannii*'s pathogenicity was mostly dependent on CPS manufacturing, which was controlled by BfmRS with OmpR-EnvZ.

VI. CONCLUSION

Due to *A. baumannii*'s growing therapeutic significance, there are a disproportionately large amount of investigations on the organism. Significant knowledge on the elements of virulence that are linked to the pathophysiology of *A. baumannii* has been obtained via the implementation of animal models. In particular, certain research on protein secretion mechanisms including absorption of metals is intriguing. The identification of zinc or manganese acquisition mechanisms in *A. baumannii* expands our comprehension of *A. baumannii* pathogenesis in addition to iron systems for acquisition like acinetobactin.

Further comprehensive investigations into the many protein secretion mechanisms found in *A. baumannii* are necessary. Transposon sequencing out *G. mellonella* larval was used to identify around 300 genes necessary for *A. baumannii*'s in vivo viability (Gebhardt et al. To determine if these markers are connected to the pathophysiology of *A. baumannii*, additional thorough investigations are necessary since several of the aforementioned proteins are not previously recognized to be connected with the disease. Transposon analysis in other experimental species will additionally shed new light on the pathophysiology of *A. baumannii*. Understanding for virulent mechanisms that contribute towards the pathogenesis of *A. baumannii* is going to be essential for the development of new antibiotics. For instance, LPS is a significant pathogenicity aspect, but rodents are fully protected against fatal illness by the LpxC inhibitory agents, that suppresses the manufacture of LPS. These findings suggest that preventing the

production of LPS is an effective approach for finding new antibiotics. Nevertheless, the toxicity or pathogenicity of *A. baumannii* is still unknown notwithstanding current, in-depth research regarding the pathological process of the organism.

The main reason for the current surge of interest in *A. baumannii* is its apparently limitless ability to develop resistance to antibiotics. Nearly every microbial susceptibility pathway is present in *A. baumannii*. *A. baumannii* was shown to contain all class β -lactamases, while an elevated incidence of strains resistance to carbapenem as has been observed. Additionally, virtually all *A. baumannii* has enzymes that alter aminoglycosides, including a large number of efflux pumps that confer resistance towards the range of pharmaceutically significant medications has been isolated from *A. baumannii*.

These attributes severely restrict the number of antibiotics that were currently accessible to cure *A. baumannii* illnesses. Because of the extremely tiny probability of obstruction, the drug colistin was utilized solely for an alternative to antimicrobial therapy. But as the drug colistin usage have expanded globally, so too have the creation of colistin-resistant *A. baumannii* strains. Particularly, a number of additional recent research have demonstrated that polymyxin B, another polymyxin antibiotics, may be a useful curative substitute for colistin.

Due to dependent on dose nephrotoxicity, polymyxin B is not considered a successful antibacterial. However, new research indicates that treating carbapenem-resistant *A. baumannii* infections by tigecycline as or carbapenems as an unusual treatment through low doses for polymyxin B may be an effective approach. These findings highlight the need for in-depth research on the polymyxin B's pharmaceutical dynamics when combined treatment.

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