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# Immune Evasion Mechanisms of *Acinetobacter baumannii*: A Narrative Review

**Hafez Mozayyan Esfahani[1*], Arefe Nikmehr[2], Soodabeh Rostami[3]**

[1]Department of Cell and Molecular Biology & Microbiology, Faculty of Biological Science and Technology, University of Isfahan, Isfahan, Iran; [2]Department of Microbiology, Faculty of Basic Sciences, Shahid Ashrafi Esfahani University, Isfahan, Iran; [3]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

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***Correspondence**
**Email**: Hafezmozayyan@gmail.com
**Tel**: +989370566972



**ABSTRACT**

*Acinetobacter baumannii* is a multidrug-resistant, Gram-negative pathogen known for causing severe healthcare-associated infections. This bacterium effectively evades host immune defenses through multiple strategies. It alters surface components such as lipopolysaccharides and capsular polysaccharides to avoid recognition by pattern recognition receptors and resist complement activation. The pathogen also forms biofilms and delivers virulence factors via outer membrane vesicles (OMVs) and a type VI secretion system, and secretes virulence-associated enzymes, including proteases and phospholipases, to enhance survival. The pathogen neutralizes reactive oxygen species via antioxidant enzymes. Furthermore, it degrades neutrophil extracellular traps to escape immune clearance. Some strains can survive intracellularly in macrophages and modulate inflammasome activation, thereby dysregulating innate immune signaling. By integrating these bacterial evasion strategies with the corresponding host defense responses, this review provides a framework for identifying novel therapeutic targets. Understanding this dynamic interplay between bacterial evasion and host defense mechanisms provides a comprehensive framework for developing novel therapeutic strategies.

## INTRODUCTION

*A. baumannii* is a Gram-negative, opportunistic pathogen known for its exceptional ability to resist antimicrobial therapies and evade host immune defenses. As a significant cause of healthcare-associated infections, including ventilator-associated pneumonia, bloodstream infections, and wound infections, *A. baumannii* is linked to high morbidity and mortality rates, particularly in immunocompromised patients [1, 2]. Its success as a pathogen is largely attributed to its diverse immune evasion mechanisms, which allow it to subvert both innate and adaptive immune responses. The World Health Organization (WHO) has designated carbapenem-resistant *A. baumannii* as a critical, high-priority pathogen due to its extensive antimicrobial resistance (AMR) and propensity for rapid adaptation to environmental and therapeutic pressures [3].

Understanding how this bacterium interacts with and evades the host immune system is crucial for developing novel therapeutic approaches. In this review, we briefly introduce the major categories of immune evasion strategies—such as surface modifications, biofilm formation, secretion of proteases and virulence factors, delivery of effector molecules via OMVs, and resistance to oxidative stress—which are discussed in detail in later sections.

This review aims to provide a comprehensive analysis of the immune evasion mechanisms employed by *A. baumannii*, highlighting recent advancements in the understanding of its pathogenesis. Such insights are essential for informing the design of targeted interventions to combat infections caused by this critically resistant pathogen.

## LITERATURE SEARCH STRATEGY

This narrative review was based on a comprehensive literature search conducted in PubMed, Scopus, and Web



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of Science databases up to June 2025. The following keywords and their combinations were used: "*Acinetobacter baumannii*", "immune evasion", "host-pathogen interaction", "complement resistance", "biofilm", "outer membrane vesicles", "inflammasome", "antimicrobial peptides", and "iron acquisition".

Peer-reviewed original research articles and relevant review papers published in English were considered. Studies focusing on molecular mechanisms of immune response and immune evasion were prioritized. No formal PRISMA framework was applied, as this work was designed as a narrative synthesis; however, efforts were made to include the most relevant and up-to-date studies in the field.

## Immune responses against *A. baumannii* infection

### A) Pattern recognition receptors (PRRs)

Pattern recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs) of *A. baumannii*, triggering intracellular signaling cascades that drive the immune response [4]. Toll-like receptors (TLRs) are PRRs, which play a main role in the initiation of innate immunity. Three major TLRs include:

TLR4 recognizes lipopolysaccharides (LPS) on *A. baumannii*, initiating the NF-κB and MAPK pathways. This promotes the production of pro-inflammatory cytokines like IL-6, TNF-α, and IL-12 [4-6]. TLR2 detects bacterial lipoproteins, enhancing the production of IL-8, a chemokine critical for neutrophil recruitment [4, 5, 7]. TLR9 recognizes unmethylated CpG motifs in bacterial DNA [4, 5, 7]. TLR9-deficient mice experience worse infections, with increased bacterial dissemination [8].

Within the cytoplasm, NOD-like receptors (NLRs) are crucial for detecting bacterial peptidoglycan fragments. In particular, NOD1 recognizes peptidoglycan (PGN) fragments characteristic of Gram-negative bacteria like *A. baumannii*. Both NOD1 and NOD2 signal through the serine/threonine kinase RIPK2 (receptor-interacting serine/threonine kinase 2). NOD deficiency increases bacterial invasion in epithelial cells [4, 5].

### B) Neutrophils

Neutrophils are the first responders and play a pivotal role in controlling *A. baumannii* infection [9, 10]. They rapidly recognize, phagocytose, and kill bacteria within the first few hours (typically 1–4 h) of infection, a process facilitated by the extension of large filopodia-like membrane protrusions that improve bacterial capture [11]. Recruitment of neutrophils to the infection site occurs within hours, guided by chemokines such as CXCL1 and CXCL2 (also known as MIP-2 in mice) [12]. Once at the site, neutrophils deploy multiple antimicrobial strategies. These include phagocytosis, the release of antimicrobial peptides (AMPs), and NADPH oxidase–mediated oxidative bursts, which generate reactive oxygen species (ROS) essential for bacterial killing [13, 14]. In addition, gene expression analyses of neutrophils exposed to *A. baumannii* show significant upregulation of pro-inflammatory cytokines such as IL-6, IL-1β, and CXCL8 (IL-8), consistent with activation of a pro-inflammatory transcriptional program [11].

Beyond direct killing, neutrophils release neutrophil extracellular traps (NETs) that ensnare and neutralize bacteria. However, *A. baumannii* has evolved mechanisms to counter these defenses, including inhibition of NETosis (the process of NET formation), degradation of AMPs such as LL-37, and modulation of neutrophil apoptosis. These strategies prolong inflammation and cause tissue damage, which may create nutrient-rich niches and disrupt epithelial barriers, ultimately promoting bacterial persistence [4, 13, 15]. Furthermore, the pathogen can adhere to neutrophils without being phagocytosed, potentially using them as vehicles for dissemination within host tissues [13].

### C) Macrophages and monocytes

Tissue-resident macrophages are among the earliest immune cells to respond, whereas circulating monocytes are subsequently recruited to the infection site and differentiate into macrophages. They phagocytose bacteria and produce cytokines that amplify the inflammatory response and recruit neutrophils to the site of infection [16]. They also play a vital role by recognizing *A. baumannii* through PRRs, particularly TLRs. The interaction between these receptors and bacterial components such as LPS initiates intracellular signaling cascades, leading to the activation of nuclear factor-kappa B (NF-κB) and the production of pro-inflammatory cytokines, which amplify the host's defensive response and recruit additional immune cells to the infection site [13]. During the early stages of infection, cytokines and chemokines such as IL-6, TNF-α, and MIP-2 are released, promoting inflammation and enhancing immune cell recruitment. As the infection progresses, IL-1β continues to drive and amplify the inflammatory response, whereas IL-10 production gradually increases, serving as a key regulatory cytokine that suppresses excessive inflammation and promotes resolution of the immune response [5, 13]. A primary function of activated macrophages is to engulf *A. baumannii* through phagocytosis. Within the phagosome, the bacterium is exposed to ROS and nitric oxide (NO), which are essential for effective bactericidal activity. However, studies have shown that multidrug-resistant (MDR) strains of *A. baumannii* can resist oxidative stress, potentially leading to persistent infections. Furthermore, *A. baumannii* can manipulate macrophage polarization, shifting them toward an anti-inflammatory M2 phenotype, which promotes bacterial survival and dampens the bactericidal M1 response [13]. Macrophages effectively kill phagocytosed bacteria, although at a slower rate than neutrophils. The role of macrophages in defense against *A. baumannii* remains debated. Some studies highlight their contribution



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through phagocytosis, cytokine secretion, and antigen presentation, suggesting they play a substantial role in shaping the immune response. Other reports, however, indicate that neutrophils are the dominant protective cell type, with macrophages playing a comparatively minor role. These discrepancies may arise from differences in experimental models and infection settings: for instance, studies using acute murine pneumonia models often emphasize neutrophil-driven clearance, whereas investigations in systemic or chronic infection models demonstrate more pronounced macrophage involvement. Such variation underscores the context-dependent nature of macrophage function in *A. baumannii* infection [15, 16].

**D) Dendritic cells (DCs)**

Dendritic cells (DCs) are pivotal antigen-presenting cells that bridge innate and adaptive immunity. Upon encountering *A. baumannii*, DCs recognize the pathogen through pattern recognition receptors (PRRs), NOD-like receptors (NLRs), and notably TLRs such as TLR2 and TLR4, which bind to pathogen-associated molecular patterns (PAMPs) such as LPS on the surface of *A. baumannii* [17, 18]. This recognition triggers intracellular signaling cascades, leading to the activation of nuclear factor-kappa B (NF-κB) and the production of pro-inflammatory cytokines and chemokines such as TNF-α, IL-6, IL-12, CCL2, and CCL3. These mediators, in turn, promote the recruitment of neutrophils and macrophages to the site of infection [4]. TLR4, in particular, plays a key role in the recognition of LPS and activates the MyD88 signaling pathway, which leads to the production of inflammatory cytokines [18]. TLR2 is involved in recognizing surface lipoproteins of this bacterium [19]. After recognition, dendritic cells engulf the bacteria and trap them within a phagosome. The phagosome fuses with a lysosome, and the enzymatic complexes degrade the bacteria. During this process, bacterial proteins are proteolytically processed to generate antigenic peptides that enter the antigen-processing pathway. Dendritic cells process antigenic fragments and display them on MHC class II molecules (for $CD4^+$T helper cells) or, through cross-presentation, on MHC class I molecules (for $CD8^+$cytotoxic T cells) [17]. Upon activation, DCs undergo maturation characterized by upregulation of co-stimulatory molecules, including CD80 and CD86, and increased expression of MHC molecules. This maturation is essential for effective antigen presentation to $CD4^+$T helper and $CD8^+$cytotoxic T cells. This maturation enhances their capacity to present antigens to naive T cells, thereby initiating adaptive immune responses. Notably, *A. baumannii* can influence DC function; certain strains have been shown to induce lower expression of the co-stimulatory molecule CD80, which may impair T cell activation and thus serve as an immune evasion strategy. Concurrently, reduced IL-10 expression has been observed, though this would be expected to enhance rather than suppress inflammation, suggesting a complex and potentially strain-dependent modulation of DC responses [19]. By providing co-stimulatory signals and cytokines, DCs both activate T cells and direct their differentiation into specific effector subsets, thus orchestrating the adaptive immune response to *A. baumannii* infection [5, 20]. In summary, DCs orchestrate downstream adaptive responses, including the generation of memory T cells and the provision of T cell help for B cell activation and antibody production [17].

**E) Complement system**

The complement system is a key component of innate immunity that defends the host against *A. baumannii* through opsonization, inflammation, and direct bacterial lysis. Upon infection, *A. baumannii* triggers complement activation primarily via the alternative and lectin pathways, with the classical pathway becoming relevant in the presence of pre-existing antibodies [21, 22]. During primary infection, the alternative and lectin pathways are likely the dominant routes of activation, with classical pathway engagement increasing after the development of specific antibodies.

The complement fragment C3b deposits on the bacterial surface, promoting opsonophagocytosis by neutrophils and macrophages. Furthermore, the assembly of the membrane attack complex (MAC; C5b–C9) can disrupt bacterial membranes and mediate direct killing [23].

However, *A. baumannii* has evolved several strategies to resist complement-mediated killing. For instance, the surface protein CipA binds human plasminogen and facilitates its conversion to plasmin, which degrades complement components including C3b and fibrinogen, thereby inhibiting opsonization and MAC formation [22]. In addition, OmpA and other outer membrane proteins can interact with Factor H, a regulator of the alternative pathway, promoting the decay of C3 convertase and preventing complement activation on the bacterial surface [24, 25]. The bacterial capsule further enhances serum resistance by physically shielding underlying antigens from complement recognition [26].

**F) Antimicrobial peptides (AMPs)**

AMPs are crucial effectors of the innate immune system that provide a first line of defense against *A. baumannii*. They are produced by epithelial cells and immune cells such as macrophages, neutrophils, and dendritic cells [27]. AMPs eliminate bacteria primarily by binding to and disrupting bacterial membranes, leading to leakage of intracellular contents and cell death [28]. Among these, the human cathelicidin LL-37 and β-defensins (hBD-2, hBD-3) exhibit potent bactericidal activity against *A. baumannii* at micromolar concentrations. The mouse ortholog, cathelin-related antimicrobial peptide (CRAMP), has been shown to be critical for host defense



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during pulmonary infection [29]. LL-37 directly interacts with outer membrane protein A (OmpA), promoting bacterial killing [30].

However, *A. baumannii* has evolved several strategies to resist AMP-mediated killing, enabling persistent infection and immune evasion.

First, modification of the lipid A moiety of lipooligosaccharides (LOS) through enzymes such as phosphoethanolamine transferases reduces the negative surface charge, reducing electrostatic attraction between AMPs and the bacterial membrane [31].

Second, efflux pumps—notably the RND and MFS systems—actively export AMPs out of the cell, lowering their intracellular accumulation [15].

Third, the bacterium secretes proteases capable of degrading or inactivating host AMPs, thereby neutralizing their bactericidal activity [32].

Fourth, biofilm formation offers a physical barrier that limits AMP diffusion and protects bacterial communities within host tissues [33].

Collectively, these multifactorial resistance mechanisms enable *A. baumannii* to counteract the antimicrobial activity of host AMPs and sustain chronic or recurrent infections.

**G) Adaptive immunity and antibodies**

While the innate immune response is the primary defense during early infection, the adaptive immune system also contributes to controlling *A. baumannii*. Antibodies directed against surface proteins such as OmpA enhance opsonization and phagocytosis. Experimental studies have further demonstrated the protective potential of OmpA-based immunization strategies in preclinical models, supporting its candidacy as a potential vaccine target [34]. Antibodies contribute to host defense against *A. baumannii* primarily by promoting opsonization and neutralizing virulence factors, while their interaction with complement — through the classical pathway — provides an important link between adaptive and innate immunity. The mechanistic details of complement activation are discussed in the next sections. Through this process, opsonized bacteria are more efficiently cleared by phagocytes [35]. Antibodies can also neutralize specific virulence factors. For example, antiserum against Ata, a trimeric autotransporter protein involved in adhesion to extracellular matrix components, has been shown to inhibit binding to type IV collagen *in vitro* [36].

In addition to antibody-mediated responses, T cells play crucial roles in adaptive immunity against *A. baumannii*. T helper cells regulate immune activity through cytokine secretion: Th1 responses, characterized by IFN-γ production, macrophage activation, and enhanced phagocytosis, are particularly important for host defense. Although the response is predominantly Th1-driven, Th2 cells also contribute by stimulating antibody production and reinforcing humoral immunity [37]. The role of cytotoxic T cells ($CD8^+$ CTLs) in immunity to *A. baumannii* is less clear. CTLs are classically specialized for eliminating host cells harboring intracellular pathogens, including viruses and intracellular bacteria. Although *A. baumannii* is generally regarded as an extracellular pathogen, some studies suggest that certain strains can persist within host cells [38, 39], in which case CTLs may contribute by recognizing infected cells and releasing perforin and granzymes. Nevertheless, CTL-mediated killing is not considered a major mechanism of host defense against this bacterium. Meanwhile, regulatory T cells (Tregs) temper excessive inflammation through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, ensuring that protective responses do not escalate into harmful immunopathology [40]. Collectively, these T cell subsets —including Th1 cells for macrophage activation, Th2 cells for antibody support, and Tregs for inflammation control—illustrate the diverse and complementary functions of the adaptive immune system in the defense against *A. baumannii*.

**H) Cytokine production**

The production of cytokines plays a central role in coordinating the host response to *A. baumannii* infection. These signaling mediators facilitate communication between immune cells and orchestrate both the initiation and regulation of inflammation [19]. Early during infection, innate immune cells such as macrophages and neutrophils recognize pathogen-associated molecular patterns through receptors like TLRs, triggering the release of pro-inflammatory mediators. Among the most important mediators are TNF-α, IL-1β, IL-6, and IL-8, which increase vascular permeability, amplify inflammation, and drive the recruitment of additional phagocytes [41]. IL-17, secreted primarily by Th17 cells, further supports granulopoiesis and chemokine production, thereby enhancing neutrophil mobilization, although it is not universally essential for bacterial clearance [4, 13, 41]. While these cytokines are critical for host defense, their excessive production can lead to a dysregulated hyperinflammatory response (sometimes termed as 'cytokine storm'), characterized by severe inflammation, tissue injury, and in some cases sepsis, which has been associated with increased mortality during severe *A. baumannii* infections [42].

**I) Inflammasome activation**

In *A. baumannii* infection, inflammasome activation occurs predominantly through the NLRP3 pathway. Bacterial components such as outer membrane proteins and LOS provide the priming signal (Signal 1) through TLR-mediated recognition, while subsequent cellular stress signals—including potassium efflux, mitochondrial ROS, and lysosomal destabilization—trigger NLRP3 inflammasome assembly (Signal 2) [15, 43, 44]. Activated caspase-1 processes pro-IL-1β and



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pro-IL-18 into their active forms and cleaves gasdermin D(GSDMD), whose N-terminal fragment oligomerizes to form pores in the plasma membrane, initiating pyroptotic cell death [45]. Ninjurin-1 (NINJ1) functions downstream of GSDMD, mediating the final step of plasma membrane rupture but not pore formation itself [46]. Experimental studies demonstrate that the outer membrane protein A (OmpA) enhances NLRP3 activation and IL-1β release, while strain-to-strain variability in inflammasome activation has been associated with differences in lung inflammation and experimental models [44, 47]. Such differences are thought to reflect strain-specific virulence traits, including variability in outer membrane proteins, secretion systems, or toxin production, which may influence the strength and duration of inflammasome signaling. These observations underscore the complexity of host-pathogen interactions and suggest that inflammasome activation is not uniform across all *A. baumannii* isolates. Although inflammasome activation supports bacterial clearance, excessive or dysregulated responses can cause tissue damage without improving pathogen elimination, thereby contributing to immunopathology [15, 43].

## Immune evasion mechanisms of *A. baumannii*

The remarkable ability of *A. baumannii* to establish persistent infections is largely due to its diverse immune evasion strategies. After encountering multiple layers of host defense—including complement activation, AMPs, phagocytosis, and adaptive responses—this pathogen utilizes a wide array of immune evasion mechanisms that collectively undermine immune clearance. These mechanisms range from structural alterations of surface components (capsule, LPS/LOS, and outer membrane proteins), to extracellular strategies such as biofilm formation, secretion of proteases and OMVs, and the use of type VI secretion systems. In addition, *A. baumannii* employs intracellular survival within macrophages, manipulation of inflammasome pathways, and metabolic adaptations such as iron acquisition and phenylacetic acid catabolism to evade immune surveillance. Efflux pumps, oxidative stress resistance, and quorum sensing further contribute to its persistence and resilience.

Figure 1 and Table 1 provide a consolidated overview of these immune evasion strategies. Together, these mechanisms illustrate how *A. baumannii* orchestrates a multifaceted and context-dependent network to avoid recognition, neutralize host defenses, and promote chronic infection.

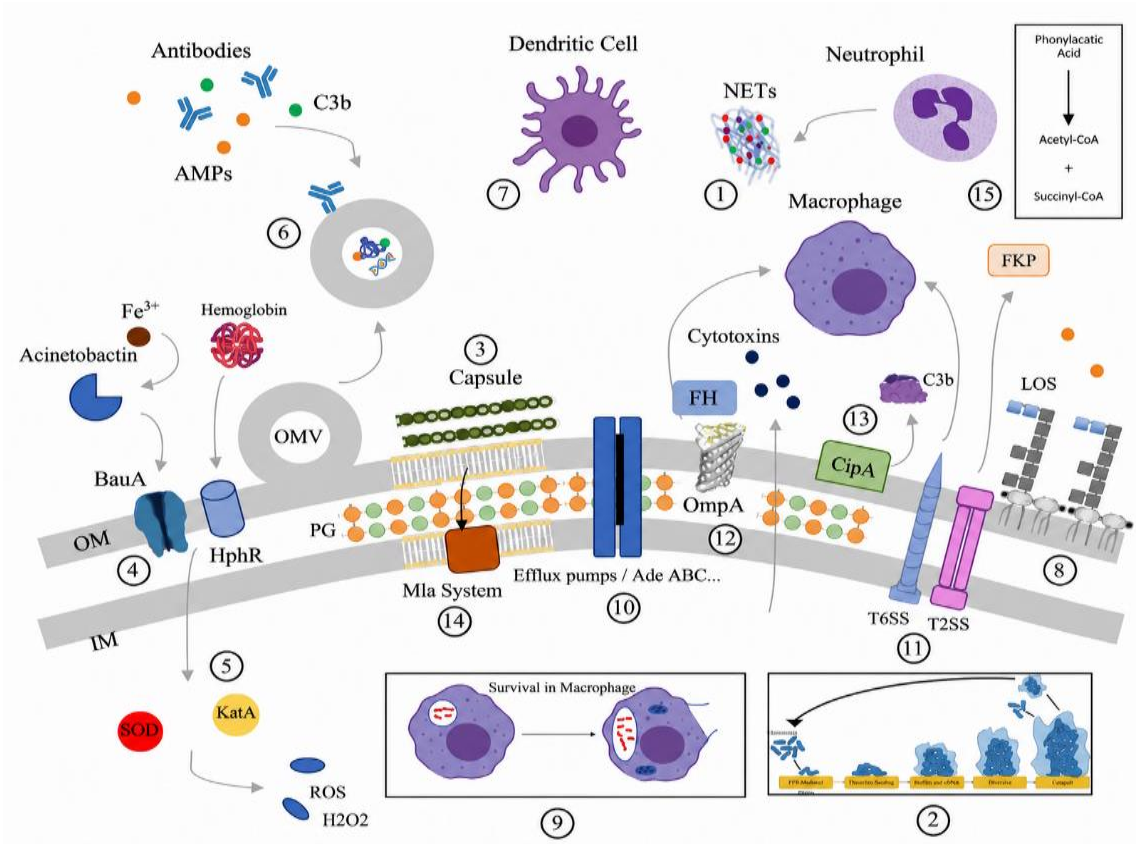


**Fig 1.** Schematic illustration of the major mechanisms used by *A. baumannii* to evade host immune defenses, including surface modifications, biofilm formation, capsule production, secretion of virulence factors, oxidative stress resistance, OMVs, intracellular survival, efflux pumps, secretion systems, and metabolic adaptations. Figure created by the authors using Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).





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Figure 1 shows that *A. baumannii* evades immune responses through multiple mechanisms: (1) Degradation of NETs using nucleases to neutralize their antimicrobial effects, (2) Biofilm formation acting as a physical barrier against immune cells and antimicrobials, (3) Capsule formation preventing complement deposition and opsonophagocytosis, (4) Iron acquisition ensuring bacterial growth and virulence, (5) Resistance to oxidative stress via catalases and superoxide dismutases (SODs), (6) OMVs absorbing AMPs and antibodies, (7) OMVs are proposed to act both as decoys (neutralizing antibodies, AMPs, and complement) and as delivery systems, transferring PAMPs and OmpA to DCs or macrophages to trigger immune responses or apoptosis, (8) Modification of surface components like LPS/LOS to evade immune detection, (9) Intracellular survival within macrophages, (10) Efflux pumps expelling toxic compounds and contributing to multidrug resistance, (11) Type VI secretion system (T6SS) injecting effector proteins into host or competing bacteria, (12) OmpA binding to Factor H to inhibit the alternative complement pathway, (13) CipA degrading complement proteins like C3b to prevent bacterial entrapment, (14) Mla system regulating membrane phospholipids to reduce complement activation and enhance serum resistance, and (15) Phenylacetic acid catabolism: degradation of phenylacetate via the *paa* pathway to reduce neutrophil chemotaxis. These strategies collectively enable *A. baumannii* to evade immune defenses and persist in host environments as follows.

**Table 1.** Summary of major immune evasion mechanisms of *A. baumannii*

| Category | Mechanisms | Details | References |
|---|---|---|---|
| Surface modifications | Capsule formation | Shields against opsonophagocytosis; prevents complement deposition. | [48] |
| | LPS/LOS modifications | Alters recognition by TLR4 to evade immune detection. | [38, 48-50] |
| Biofilm formation | EPS matrix shielding | Protects against immune cell penetration and antimicrobial agents. | [51] |
| | Genes (*e.g.*, *csuC*, *csuD*, *ompA*) | Regulate biofilm formation and maintenance. | [51] |
| Secretion of virulence factors | Proteases and phospholipases | Degrade host proteins; disrupt epithelial barriers. | [52] |
| | Type VI Secretion System (T6SS) | Targets competitors and modulates host immune responses. | [53] |
| Resistance mechanisms | Degradation of NETs | Breaks down DNA scaffolds using extracellular nucleases. | [49, 54] |
| | Oxidative stress resistance | Employs catalases, peroxidases, and superoxide dismutases (SODs) to neutralize ROS. DNA-repair systems (e.g., RecA, MutT), glutathione, and the OxyR regulon protect macromolecules, while molecular chaperones (DnaK, GroEL, ClpB) and proteases maintain protein stability under oxidative and desiccation stress. | [4, 55] |
| | Efflux pumps | Expel antibiotics and AMPs; contribute to resistance. | [10, 56] |
| | complement evasion | Capsule prevents C3b deposition; OmpA interacts with Factor H. CipA degrades complement components like C3b, preventing entrapment in fibrin clots and facilitating bacterial dissemination. CipA also inhibits the alternative complement pathway. The Mla pathway reduces activation of the alternative complement pathway and enhances serum resistance. | [21, 22, 24, 48] |
| | Phenylacetic acid catabolism | Metabolizes phenylacetate via the paa (phenylacetic acid) catabolic pathway, thereby reducing phenylacetate accumulation and decreasing neutrophil chemotaxis/recruitment. | [15] |
| Outer membrane vesicles (OMVs) | Decoy function | Absorb antimicrobial peptides and antibodies. | [57, 58] |
| Iron acquisition | Iron acquisition | Siderophore-mediated iron chelation (acinetobactin), TonB-dependent receptors, OMV-assisted iron scavenging, and direct exploitation of host iron-binding proteins. | [59-62] |
| Intracellular survival | Survival in macrophages | Avoids phagolysosomal fusion; persists within spacious vacuoles. | [38] |
| Quorum sensing and virulence regulation | Virulence factor coordination | Regulates biofilm formation, motility, and iron acquisition based on population density. | [63-65] |
| Host exploitation | Inflammasome modulation | Modulates (suppresses or enhances) NLRP3 activity in a strain-dependent manner, affecting proinflammatory cytokine production. | [15, 26, 66] |
| | Host nutrient utilization | Enhances survival in nutrient-limited environments. | [67] |



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**A) Degradation of NETs**

During infection, activated neutrophils release NETs—fibrous structures composed of chromatin and antimicrobial proteins such as neutrophil elastase and myeloperoxidase (MPO)—that immobilize and neutralize invading pathogens [68]. Although NETs are critical for host defense, their excessive formation can exacerbate inflammation, contribute to autoimmune reactions, and promote thrombosis [69, 70].

*A. baumannii* has evolved several mechanisms to evade and counteract NET-mediated killing. The bacterium secretes extracellular nucleases that degrade the DNA backbone of NETs, thereby dismantling their structure and neutralizing their antimicrobial effects [11, 49, 54]. The degradation of NETs not only facilitates bacterial escape and dissemination but may also release nutrients such as nucleotides and amino acids that could promote bacterial growth [49, 54]. In addition, *A. baumannii* can suppress NET formation by downregulating neutrophil surface molecules such as CD11a, which contribute to adhesion and activation processes that precede NETosis [43, 54]. In addition, some studies suggest that *A. baumannii* may use OMVs to modulate or sequester components of NETs, thereby reducing their antimicrobial activity. However, direct evidence showing that OMVs or secreted enzymes specifically neutralize neutrophil elastase or MPO in *A. baumannii* remains limited and requires further investigation [71].

**B) Biofilm formation**

Biofilm formation is one of the most critical immune evasion strategies employed by *A. baumannii*. Biofilms are structured bacterial communities embedded within an extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, and extracellular DNA. These structures act as physical barriers that protect bacteria from host immune defenses and antimicrobial agents [72].

The process of biofilm development in *A. baumannii* is influenced by multiple bacterial and environmental factors, including adhesins, capsular polysaccharides, surface appendages, and virulence-associated genes. Among the key molecular determinants are biofilm-associated protein (Bap), outer membrane protein A (OmpA), and the Csu chaperone-usher pilus system, which collectively mediate bacterial adhesion, surface attachment, and intercellular aggregation [49-51, 66]. Additional contributors include poly-β-(1,6)-N-acetylglucosamine (PNAG), produced via the *pga* operon in some strains, and the two-component regulatory system BfmS/BfmR, which regulates adhesion and matrix formation. Moreover, certain β-lactamases, such as PER-1, have been associated with enhanced biofilm formation, although the underlying mechanism remains unclear. It has been hypothesized that PER-1 expression may be co-regulated with genes affecting cell surface properties or outer membrane composition, thereby facilitating bacterial aggregation [33, 73, 74].

Biofilm-embedded cells exhibit reduced susceptibility to AMPs and antibiotics, facilitating chronic infection and persistence on both biotic and abiotic surfaces. Furthermore, biofilm formation enhances genetic exchange via horizontal gene transfer, thereby promoting adaptation and resistance development [33, 74].

Collectively, these mechanisms underscore the multifactorial and dynamic nature of biofilm formation in *A. baumannii*, highlighting its central role in immune evasion and antibiotic resistance [75].

**C) Capsule formation**

One of the most important mechanisms by which *A. baumannii* escapes the host immune system is the production of a polysaccharide capsule. This capsule, a dense polysaccharide layer, acts as an effective barrier against multiple immune defenses. It prevents phagocytosis by blocking the access of phagocyte receptors to bacterial surface antigens, thereby reducing uptake and intracellular killing [76]. The polysaccharide capsule interferes with complement activation by sterically hindering the deposition of C3b on the bacterial surface and limiting the assembly and amplification of C3 and C5 convertases. As a result, deposition of the opsonin C3b on the bacterial surface is reduced, and generation of C5b -the initiating component of the membrane attack complex (MAC)- is limited. By blocking these upstream steps, the capsule protects the bacterium from both opsonophagocytosis and complement-mediated lysis [2, 77].

Beyond phagocytosis and complement evasion, the capsule contributes to immune modulation by shielding underlying surface components, thereby reducing host immune recognition and inflammatory responses [78]. In addition, the capsule enhances bacterial persistence by protecting against host immune defenses and promoting survival during interactions with neutrophils and macrophages [76].

The capsule further contributes to persistence by enhancing adhesion to surfaces and promoting biofilm formation, which creates an additional barrier against both antimicrobials and immune clearance. Capsule expression is regulated through phase variation, enabling the bacterium to adjust capsule thickness according to environmental pressures, thereby balancing immune evasion with other survival needs [79]. Moreover, capsular polysaccharides increase tolerance to desiccation, facilitating survival on abiotic hospital surfaces. Studies consistently show that capsule-deficient mutants are more susceptible to phagocytosis and AMPs, underscoring the capsule's essential role in pathogenesis [26, 48]. Thus, the capsule should be regarded as a multifunctional virulence factor: while it promotes



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environmental persistence, its primary contribution during infection is protection against complement-mediated killing and phagocytic clearance.

**D) Iron acquisition mechanisms**

Iron is indispensable for the growth and virulence of *A. baumannii*, but the host limits its availability through nutritional immunity, mediated by proteins such as transferrin, ferritin, and lactoferrin. To overcome this restriction, *A. baumannii* produces siderophores, particularly acinetobactin, which efficiently chelate iron from host proteins. The resulting iron–siderophore complexes are recognized by outer membrane receptors such as BauA and are subsequently imported into the bacterial cell and processed to release iron for metabolism[59-62]. This strategy enables the bacterium to bypass host sequestration systems and sustain its survival under iron-limited conditions.

In addition to siderophores, *A. baumannii* utilizes OMVs as an auxiliary iron-acquisition strategy. OMVs enriched with TonB-dependent receptors scavenge iron from the environment and deliver it to bacterial cells, ensuring survival in iron-limited niches [26, 48, 59, 60]. The bacterium is also capable of directly exploiting host iron- and heme-binding proteins such as hemoglobin, hemopexin, and lactoferrin. For example, outer membrane receptors such as HphR can extract iron from hemoglobin, a process that becomes relevant primarily after red blood cell lysis, while the host restricts iron through sequestration by transferrin, lactoferrin, and ferritin [80, 81].

Furthermore, iron deprivation imposed by the host can trigger oxidative stress. To survive under these conditions, *A. baumannii* upregulates antioxidant defenses, including catalases and superoxide dismutases, while simultaneously enhancing iron uptake pathways [82]. The bacterium also adapts to environmental changes by regulating the expression of iron-related genes. Regulators such as Fur (ferric uptake regulator) play a central role by controlling siderophore biosynthesis and receptor expression in response to iron limitation [83].

Collectively, these multifaceted strategies allow *A. baumannii* to persist in iron-restricted environments such as blood and infected tissues, thereby supporting its pathogenicity and contributing to severe infections.

**E) Resistance to oxidative stress**

Oxidative stress represents one of the primary host defense mechanisms against bacterial infection, where phagocytic cells such as neutrophils and macrophages generate ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals. *A. baumannii* has evolved multiple adaptive strategies to withstand this oxidative assault. The bacterium expresses antioxidant enzymes such as superoxide dismutases (SODs), which convert superoxide anions to hydrogen peroxide, and catalases and peroxidases, which subsequently decompose hydrogen peroxide, collectively neutralizing ROS and preventing cellular damage. Mutants deficient in these enzymes exhibit reduced virulence and survival within inflammatory environments, underscoring their importance in bacterial persistence [4, 15, 55].

Beyond enzymatic detoxification, *A. baumannii* employs DNA repair systems to mitigate oxidative damage. The RecA protein plays a central role in homologous recombination repair and in initiating the SOS response, while MutT hydrolyzes oxidized nucleotides such as 8-oxo-dGTP, converting them to the monophosphate form and thereby preventing their incorporation into DNA and reducing mutagenesis and ensuring genomic stability under stress [15, 60, 84].

Glutathione (GSH) and related thiol-based antioxidant molecules may also contribute to defense against oxidative injury, although canonical glutathione biosynthesis genes are absent in many *A. baumannii* strains. The transcriptional regulator OxyR senses oxidative stress and upregulates genes encoding catalases and SODs, thus coordinating a global antioxidant response [15, 55, 83].

Efflux systems, particularly those belonging to the resistance–nodulation–division (RND) and major facilitator superfamily (MFS), may contribute to the removal of toxic metabolites and by-products of oxidative damage from the cytoplasm, further supporting bacterial survival under oxidative challenge [15, 56].

In addition, *A. baumannii* can benefit from biofilm-associated protection, as the extracellular matrix moderates oxidative damage and supports survival under stress conditions. This protective mechanism, discussed in detail in “Biofilm formation section”, complements other antioxidant defenses and contributes to the bacterium’s persistence within host tissues. Collectively, these multifaceted strategies enable *A. baumannii* to withstand oxidative killing and promote chronic or recurrent infections [15, 33, 73, 74].

**F) Outer membrane vesicles (OMVs)**

OMVs are bilayered structures, typically 20–300 nm in diameter, released from the outer membrane of *A. baumannii*, containing lipids, proteins, and nucleic acids that reflect the bacterial envelope composition. These vesicles play multiple roles in host–pathogen interactions. First, OMVs act as decoys that absorb AMPs and antibodies, thereby reducing their effective concentration near bacterial cells and enhancing survival under immune pressure [57, 58]. Second, OMVs function as delivery systems for virulence factors such as OmpA, which can be translocated into host cells via OMV fusion at cholesterol-rich membrane regions. OMV fusion promotes host cell apoptosis, as demonstrated by the inability of OMVs from *ompA*-deficient mutants to induce macrophage death [85].



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Third, OMVs serve as potent immune modulators by engaging host PRRs, including TLRs. Through this interaction, they can stimulate the secretion of inflammatory cytokines (*e.g.,* IL-1β, TNF-α) or alternatively suppress inflammation via anti-inflammatory mediators such as IL-10, contributing to immune evasion [58]. Additionally, OMVs facilitate horizontal gene transfer and promote biofilm formation, aiding in antibiotic resistance dissemination and persistence within host environments [57, 58]. Collectively, OMVs represent a multifaceted virulence strategy central to *A. baumannii* pathogenesis and immune evasion.

**G) Modification of cell surface components**

One of the most important immune evasion strategies of *A. baumannii* involves remodeling of its cell surface components to avoid recognition by the host immune system, resist complement-mediated lysis, and enhance survival.

Surface modifications in LPS and LOS play a central role in this process. Alterations in lipid A reduce recognition by TLR4, thereby dampening the host's proinflammatory cytokine response and promoting bacterial persistence [18, 66]. Similarly, changes in LOS sugar composition can limit antibody and complement recognition [50]. In some isolates, complete loss of LPS has been observed, representing a radical structural change that alters immune recognition and also confers colistin resistance [86].

In addition to LPS remodeling, *A. baumannii* alters the expression of surface lipoproteins and outer membrane proteins such as OmpA and OmpW. These changes reduce antibody binding, impair macrophage phagocytosis, and modulate inflammatory signaling pathways [87]. While CarO is primarily associated with antibiotic resistance, its potential contribution to cell envelope integrity suggests an indirect role in resisting host environmental stress. Alterations in peptidoglycan structure represent conserved immune evasion mechanisms in multiple bacterial pathogens. O-acetylation of N-acetylmuramic acid residues increases resistance to lysozyme-mediated cleavage, while de-N-acetylation of N-acetylglucosamine similarly reduces susceptibility to hydrolysis. These modifications limit access to the β-1,4-glycosidic bonds targeted by lysozyme, thereby stabilizing the bacterial cell wall against enzymatic degradation [88].

Moreover, regulation of phospholipid content and incorporation of phosphoethanolamine into lipid A by phosphoethanolamine transferases alter surface charge, reducing interactions with host AMPs such as cathelicidins and defensins, and enhancing resistance to both immune defenses and antibiotics [89].

Collectively, these coordinated alterations in the bacterial envelope enable *A. baumannii* to evade immune detection, resist killing, and persist within host tissues.

**H) Intracellular survival in macrophages**

Recent studies demonstrate that MDR clinical strains of *A. baumannii* can persist and replicate within specialized intracellular compartments termed *A. baumannii*–containing vacuoles (AbCVs, also referred to as ACVs in some studies). These vacuoles have been observed in diverse host cell types, including macrophages, epithelial cells (A549), the endothelial cell line EA.hy926, and primary normal human neonatal keratinocyte cells. Their morphology varies by strain and cell type, ranging from single- to double-membrane structures [39].

Within macrophages, certain isolates establish spacious ACVs that prevent phagolysosomal fusion, thereby protecting the bacteria from intracellular killing and enabling long-term persistence [38, 90, 91]. This intracellular niche shields *A. baumannii* not only from host immune clearance but also from certain classes of antibiotics that achieve poor intracellular penetration, representing an important mechanism contributing to chronic infection [15, 84].

While MDR isolates can induce ROS production within macrophages, their mechanisms of oxidative stress resistance—including catalase activity, OxyR regulation, and Fur-mediated control of iron metabolism—are addressed separately in "Resistance to oxidative stress" section. This distinction highlights that intracellular survival relies on both vacuole formation and broader stress adaptation pathways.

Overall, the ability of *A. baumannii* to exploit ACVs illustrates its remarkable capacity to evade host defenses by establishing a protected intracellular niche, which may contribute to dissemination and persistence during infection.

**I) Efflux pumps**

Efflux pumps in *A. baumannii* represent a critical mechanism that enhances both antibiotic resistance and immune evasion. These systems, which belong to families such as RND (Resistance-Nodulation-Division), MFS (Major Facilitator Superfamily), ABC (ATP-Binding Cassette), and SMR (Small Multidrug Resistance), actively expel a wide range of toxic compounds, including host-derived antimicrobial molecules and harmful metabolic byproducts. Prominent efflux pumps such as AdeABC and AdeFGH have been shown to contribute not only to resistance against antibiotics but also to survival under immune pressure, as mutants with impaired efflux activity exhibit reduced persistence in hostile environments [10].

The immune evasion functions of efflux pumps are multifaceted. By exporting cationic antimicrobial peptides (CAMPs) and reactive oxygen species (ROS), these pumps limit intracellular oxidative stress, thereby improving bacterial survival within macrophages [56]. Efflux pumps may potentially influence immune



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recognition by modulating the bacterial cell envelope and reducing the accumulation of immune-stimulatory molecules. For instance, their activity lowers intracellular stress and has been hypothesized to affect the transport of certain metabolites involved in cell surface remodeling, which could potentially attenuate TLR-mediated signaling and cytokine production [92]. Efflux systems also contribute to multidrug resistance by extruding carbapenems, tetracyclines, and other antibiotics [93], which may indirectly reduce the release of immunostimulatory bacterial components that occur during antibiotic-induced lysis, although this hypothesis requires further investigation. Furthermore, efflux pumps contribute to bacterial fitness under stress conditions by reducing the intracellular accumulation of toxic compounds and supporting cellular homeostasis. In *A. baumannii*, multidrug efflux systems such as AdeABC have been implicated in stress responses and virulence, suggesting a potential role in adaptation to hostile host environments [94]. Collectively, these findings highlight efflux pumps as dual-function systems that protect *A. baumannii* from both antimicrobial agents and immune defenses, positioning them as promising therapeutic targets.

**J) Type VI secretion system (T6SS)**

The Type VI secretion system (T6SS) is a contractile nanomachine employed by *A. baumannii* to inject effector proteins into target cells. Structurally resembling to an inverted bacteriophage tail, it consists of conserved components, including the inner tube protein Hcp, the spike protein VgrG, and the contractile sheath components TssB/TssC, which together assemble to form the secretion apparatus. Functionally, the T6SS contributes to both bacterial competition and host interaction.

In interbacterial contexts, the *A. baumannii* T6SS delivers antibacterial effectors such as phospholipases and peptidoglycan hydrolases, allowing the bacterium to eliminate rival microbes and persist within polymicrobial environments [51]. This activity enhances its ability to colonize host tissues and medical devices where microbial competition is intense.

Beyond its antibacterial role, evidence suggests that the T6SS also mediates interactions with eukaryotic cells. Certain effectors can influence macrophage activity and cytokine production, thereby modulating host immune responses and indirectly contributing to immune evasion [90]. Notably, the regulation and activation of the T6SS appear to be strain-dependent, reflecting adaptation to different host and environmental pressures [53].

Together, these findings highlight the multifaceted role of the T6SS in *A. baumannii* pathogenesis, encompassing both interbacterial competition and manipulation of host immune defenses.

**K) Neutrophil evasion mechanisms**

Neutrophils are among the first immune cells recruited to infection sites, where they eliminate pathogens through phagocytosis, the release of reactive oxygen species (ROS), and the formation of NETs. *A. baumannii* employs multiple strategies to resist or exploit neutrophil activity, thereby enhancing its survival and dissemination within the host.

Rather than functioning as independent mechanisms, these strategies integrate processes discussed in earlier sections, including the degradation of NETs, resistance to oxidative stress, and surface remodeling through LPS modification. A particularly notable mechanism involves the ability of *A. baumannii* to transiently associate with activated neutrophils, potentially facilitating bacterial dissemination across tissues [7, 95]. Moreover, metabolic modulation—particularly through the phenylacetic acid (PAA) catabolic pathway—has been shown to influence neutrophil recruitment, linking bacterial metabolism to immune evasion [96].

Collectively, these interconnected processes highlight the multifaceted strategies by which *A. baumannii* undermines neutrophil function, ultimately contributing to persistent infection and immune escape.

**M) Evasion of complement activation**

*A. baumannii* employs multiple strategies to evade complement-mediated killing, ensuring its persistence in host serum. As introduced in before sections, a key mechanism involves the interaction of outer membrane proteins with host complement regulators. In particular, OmpA binds to Factor H, a major inhibitor of the alternative complement pathway, thereby preventing C3 convertase (C3bBb) formation and subsequent C3b deposition. This interference suppresses membrane attack complex (MAC) assembly and protects the bacterium from complement-mediated lysis [22, 24, 97].

In addition to OmpA, the plasminogen-binding protein CipA contributes to complement evasion by converting plasminogen into active plasmin, which degrades fibrinogen and complement components such as C3b. This not only facilitates bacterial dissemination but also reduces complement activity [22].

The maintenance of the lipid asymmetry (Mla) system provides another layer of protection by preventing phospholipid accumulation in the outer membrane, which would otherwise trigger the alternative complement pathway [21]. Finally, the secreted serine protease K–like factor (PKF) has been suggested to participate in complement component degradation, although the specific substrates remain to be identified [13].

Together, these findings reflect the multifaceted strategies of *A. baumannii* to evade complement attack, combining membrane remodeling, host protein



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interaction, and proteolytic degradation to ensure survival within the host.

**N) Quorum sensing and virulence regulation**

Quorum-sensing (QS) systems enable *A. baumannii* to coordinate the expression of virulence factors based on population density. The AbaI/AbaR system, in particular, regulates motility, iron acquisition, and biofilm formation [63-65]. Beyond biofilm regulation, QS controls the expression of virulence-related genes, enhancing the production of enzymes and toxins that facilitate host tissue damage and immune evasion [98]. Interestingly, deletion of QS-related genes such as *abaR* has been reported to increase cytotoxicity [99] and alter bacterial interactions with host immune cells, a finding that may seem counterintuitive given the general role of QS in virulence activation. This paradox likely reflects the dual regulatory function of the AbaI/AbaR system, which not only activates but also fine-tunes the expression of specific virulence genes in a strain-dependent manner. For instance, Sun *et al*. (2021) [99] demonstrated that AbaR can repress the expression of specific virulence-associated cytotoxic genes under specific environmental conditions, suggesting that QS acts as a global modulator rather than a simple activator of virulence. Overall, quorum sensing serves as a central regulatory system that synchronizes multiple immune evasion mechanisms in *A. baumannii*, representing a potential target for novel anti-virulence therapies.

**O) Resistance to host AMPs**

Resistance to host AMPs in *A. baumannii* primarily results from structural remodeling of cell surface components, particularly lipid A of LPS. The addition of phosphoethanolamine and other lipid A modifications reduces the overall negative surface charge, thereby decreasing the electrostatic attraction of cationic AMPs such as LL-37 and limiting their membrane-disruptive activity [50, 100, 101]. These adaptive changes in the outer membrane enhance bacterial resistance to peptide-mediated killing and represent a key mechanism of innate immune evasion.

**P) Horizontal gene transfer and genetic adaptability**

Horizontal gene transfer (HGT) is a major driver of genetic adaptability in *A. baumannii*, facilitating the rapid dissemination of antibiotic resistance and virulence determinants. This process occurs through several mechanisms, including natural transformation, plasmid-mediated conjugation, phage-mediated transduction, and DNA exchange via OMVs.

Natural transformation enables the uptake and integration of exogenous DNA from the environment [63]. Conjugative plasmids promote the horizontal spread of key resistance genes such as *bla(OXA-23)*, *bla(OXA-58)*, and *bla(NDM-1)*, which are frequently associated with IS*Aba1*-linked transposons [93]. Phage-mediated transduction, although less extensively studied, has been identified as a potential route of gene exchange among clinical isolates [101]. Moreover, OMV-mediated transfer facilitates the dissemination of DNA and resistance determinants between bacterial populations, contributing to rapid genetic adaptation [58].

The mobilome of *A. baumannii*—comprising plasmids, genomic islands, integrons, and transposons such as IS*Aba1* and Tn*2006*—acts as a genetic reservoir that accelerates the acquisition and spread of adaptive traits [50, 102]. This extensive network of mobile elements underpins the species' extraordinary genomic plasticity, supporting both antimicrobial resistance and immune evasion in nosocomial environments.

**Q) Resistance to environmental stresses**

Beyond oxidative stress, *A. baumannii* exhibits significant resilience to other environmental challenges that indirectly support immune evasion and persistence.

One important adaptation is desiccation resistance, which allows *A. baumannii* to survive for extended periods on dry hospital surfaces. Capsular polysaccharides play a central role in preventing water loss and maintaining cell surface integrity [26, 48, 76]. In parallel, outer membrane remodeling, including changes in lipid composition and protein architecture, contributes to the structural stability of the cell envelope under dehydration stress [64, 86, 103]. Such persistence facilitates fomite-mediated transmission between hosts and enables the bacterium to re-establish infection, during which its immune evasion mechanisms promote immune escape.

In addition, molecular chaperones—notably DnaK, GroEL, and ClpB—along with ATP-dependent proteases, preserve protein homeostasis during desiccation and temperature stress. These systems protect essential virulence-associated proteins from denaturation, thereby enhancing bacterial survival and immune evasion during host colonization [15, 33, 74].

Collectively, these mechanisms ensure survival under adverse environmental conditions and promote long-term persistence, contributing to immune evasion and infection recurrence.

**X) Exploitation of host nutrient pathways**

To persist within the host, *A. baumannii* must overcome nutritional immunity—the host's defense mechanism that limits the availability of essential metals such as iron and zinc. In addition, the bacterium must acquire carbon sources from the host environment to sustain growth. Instead of relying on a single pathway, *A. baumannii* coordinates several acquisition systems that collectively sustain growth under immune pressure.

Iron uptake is primarily mediated by the acinetobactin siderophore system, which extracts iron from host proteins and is essential for virulence and intracellular survival [61]. Zinc acquisition is primarily mediated by the ZnuABC transport system, which maintains metal homeostasis during host-imposed zinc limitation [104].





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Moreover, the bacterium can utilize host-derived carbon sources such as lactate to persist in inflamed host tissues [67].

These coordinated nutrient acquisition strategies not only sustain metabolic activity but also enhance bacterial tolerance to oxidative and immune stress, supporting long-term persistence within host tissues.

**Y) Inflammasome modulation**

*A. baumannii* modulates inflammasome signaling, affecting host immune responses in a context-dependent manner. Rather than uniformly suppressing inflammation, different strains and virulence factors either inhibit or potentiate inflammasome activation to promote persistence or induce host damage.

During early infection, some strains can transiently suppress inflammasome activity to reduce the production of proinflammatory cytokines such as IL-1β and IL-18, thereby limiting neutrophil recruitment and delaying immune clearance [4, 66].

In contrast, specific Omps enhance inflammasome activation, contributing to tissue injury and dysregulated inflammation. For example, OmpA has been shown to stabilize active caspase-1 by preventing its degradation in a murine pneumonia model, thereby prolonging NLRP3 inflammasome activity and increasing IL-1β release [44]. Similarly, Omp34 triggers NLRP3 activation through mitochondrial ROS generation in RAW264.7 macrophages, amplifying inflammatory signaling *in vitro* [105].

Furthermore, strain-dependent variability in inflammasome activation has been documented, with certain *A. baumannii* isolates inducing stronger NLRP3 responses than others, correlating with differences in disease severity and inflammatory outcomes [46].

Collectively, these findings indicate that *A. baumannii* modulates inflammasome signaling in a dynamic, strain-specific manner—suppressing activation to avoid detection at early stages and promoting hyperactivation later to damage host tissues and facilitate dissemination. Understanding this balance may provide new insights for the development of targeted anti-inflammatory or immunomodulatory therapies.

**Z) Phenylacetic acid catabolism**

The phenylacetic acid (PAA) catabolic pathway represents an important metabolic mechanism linking bacterial physiology with immune evasion. *A. baumannii* utilizes the *paa* gene cluster to degrade phenylacetate, a host-derived metabolite that acts as a chemoattractant for neutrophils. In murine infection models, functional disruption of this pathway results in phenylacetate accumulation, enhanced neutrophil chemotaxis, and increased bacterial clearance, demonstrating its role in immune modulation *in vivo* [96, 106].

Through efficient PAA catabolism, *A. baumannii* limits neutrophil recruitment at infection sites, thereby reducing immune surveillance and tissue inflammation. In addition, the pathway contributes to bacterial adaptation under oxidative and metabolic stress conditions that arise during infection, further supporting bacterial persistence in the host. Collectively, these findings highlight PAA catabolism as a dual-purpose system that integrates metabolic adaptation with immune evasion.

## CONCLUSION

This review synthesizes current evidence to show that the immune evasion of *A. baumannii* is best understood as a multifactorial and interconnected process: multiple virulence and resistance mechanisms operate not in isolation but as an interacting network that maintains the bacterium's fitness in the face of host immunity and antimicrobial therapy. Surface alterations (LPS/LOS remodeling, capsule production) reduce initial recognition and complement activation; extracellular strategies, such as the formation of protective biofilms and the release of OMVs, block immune access; effector proteins delivered by secretion systems and OMV cargo degrade or neutralize host effectors; intracellular persistence and metabolic flexibility sustain growth in hostile niches; and efflux and enzymatic resistance mechanisms further increase tolerance to treatment. Importantly, the functional consequences of any single mechanism are frequently amplified or modulated by others (*e.g.,* capsule presence enhancing biofilm resilience or OMVs facilitating horizontal transfer of resistance and virulence determinants), which may partly explain why targeting single factors has sometimes produced limited clinical benefit. These mechanisms collectively reduce complement activation and facilitate bacterial persistence in serum and tissues. Understanding these interactions between *A. baumannii* and the complement system is essential for developing targeted immunotherapies and vaccine strategies.

Much of the mechanistic literature derives from *in vitro* experiments or a narrow set of laboratory strains; inter-strain heterogeneity and the influence of genetic background on phenotype remain incompletely characterized. In addition, the clinical relevance of some proposed mechanisms (especially OMV-mediated effects and certain putative effectors) requires validation in standardized animal models and human-relevant systems.

Future research on *A. baumannii* immune evasion would benefit from focusing on integrative, multitarget anti-virulence strategies rather than isolated single-factor approaches. Promising directions include the development of inhibitors or neutralizing antibodies targeting conserved nodes of the evasion network—such as major Omps, key secreted effectors, and iron-acquisition systems—that collectively contribute to bacterial persistence.



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Combination therapies also merit systematic evaluation, particularly those that pair conventional antibiotics with immune-modulating agents, such as monoclonal antibodies, complement-potentiating agents, or compounds capable of disrupting biofilms and OMVs, using standardized and reproducible *in vivo* models.

Advanced systems biology and -omics technologies, including comparative genomics, proteomics (notably OMV proteomics), and single-cell transcriptomics, should be leveraged to map the regulatory circuits and biomarkers underlying strain-specific differences in immune evasion and therapeutic response. Establishing standardized models and consensus panels of clinical isolates will further enable reproducible cross-study comparisons and translational validation. Finally, biomarker-guided approaches hold promise for precision therapy—allowing clinicians to tailor interventions based on which immune evasion modules are most active in a given infection. Confronting the clinical threat of *A. baumannii* will require this integrative, systems-level framework that bridges mechanistic insight with translational application, paving the way for more effective therapeutic and preventive strategies.

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## CONFLICT OF INTERESTS

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## DATA AVAILABILITY

Not applicable — this manuscript is a literature review and did not generate new datasets. All information discussed in this article is derived from publicly available, peer-reviewed literature, as cited throughout the manuscript. Additional details regarding specific references or extracted tables are available from the corresponding author upon reasonable request.

## AUTHORS' CONTRIBUTIONS

H.M.E. contributed to conceptualization, literature search strategy, screening, writing – original draft, visualization, and supervision. A.N. contributed to literature search, screening, validation, and writing – review & editing. S.R. contributed to scientific supervision, critical revision, writing, review & editing, and resources. All authors have read and approved the final version of the manuscript.

## ETHICS STATEMENT

Not applicable — this study is a review of previously published literature and did not involve human participants, human tissue, or animals; therefore, no ethics approval or consent procedures were required.

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