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Mechanisms of Virulence, Resistance and Treatment Options for Acinetobacter Baumannii - A Rising Threat in the Resistance Era

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ABSTRACT

***Acinetobacter baumannii* is an opportunistic, ubiquitous pathogen that typically causes healthcare-associated (nosocomial) infections. It is associated with high mortality rates as it can lead to respiratory infections (ventilator-associated pneumonia), bloodstream infections (bacteremia), skin and soft tissue infections (wounds, burns, trauma), urinary tract infections, and meningitis. The pathogenesis of this organism is attributed to a variety of virulence factors such as enzymes, toxins, porins, and biofilm formation, which enable it to withstand extreme conditions and cause life-threatening diseases, thereby posing a significant threat in healthcare settings. The organism has a wide array of resistance mechanisms, and has evolved to become one of the most resilient pathogens in modern medicine. This review aims to explore the numerous virulence factors and antimicrobial resistance mechanisms of *A. baumannii*.**

1. INTRODUCTION:

Acinetobacter baumannii was once considered a low-virulence commensal; however, the World Health Organization (WHO) has classified it under the **critical** group of bacteria **(Chai *et al.*, 2022)** and also as one of the six ESKAPE pathogens **(Boucher *et al.*, 2009)**. It exhibits multidrug resistance due to its ability to evade the effects of various antibiotics **(C. Liu *et al.*, 2018); (Boucher *et al.*, 2009)**. It has also been designated as a **Priority 1** pathogen by the WHO. The Center for Disease Control and Prevention (CDC) has identified *Acinetobacter baumannii* as a "Red Alert" pathogen, emphasizing its increasing importance in clinical settings **(Howard *et al.*, 2012)**. The clinical significance of this organism lies in its remarkable ability to acquire resistance and survive under a wide range of physical conditions by developing adaptive mechanisms.

The *Acinetobacter* genus includes various species such as *Acinetobacter baumannii*, *Acinetobacter pittii*, *Acinetobacter nosocomialis*, *Acinetobacter dijkshoorniae*, and *Acinetobacter seifertii*, among which *A. baumannii* is the most dominant. A study conducted in India in 2017 reported an infection rate of 5.36% for *A. baumannii*, while other *Acinetobacter* species accounted for only 1.07%, underscoring *A. baumannii* as the leading infectious species within the genus**(A. Sharma *et al.*, 2017)**. It is highly clinically significant and well characterized. Species identification can be performed manually or semi-automatically using systems such as VITEK 2, MALDI-TOF, and Microscan WalkAway **(Peleg *et al.*, 2008)**.

HISTORY:

Early in the 20th century, in 1911, Dutch microbiologist Martinus W. Beijerinck published the first description of the genus *Acinetobacter*,

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naming it *Micrococcus calcoaceticus*. The term "*Acinetobacter*" was first introduced by Brisou and Prévot in 1954, derived from the Greek word *akinetos*, meaning "non-motile." *Acinetobacter baumannii* was later named in honor of Paul Baumann, who isolated the bacterium from soil and water **(Baumann, 1968)**. In 1971, the genus *Acinetobacter* was incorporated into the taxonomy of *Moraxella* and allied bacteria **(Lessel, 1971)**. It was subsequently recognized as a separate genus in the 1974 edition of *Bergey's Manual of Systematic Bacteriology*. In 1986, Brisou and Grimont identified 12 distinct species within the *Acinetobacter* genus based on DNA-DNA hybridization studies. Some of the species identified include *A. baumannii*, *A. haemolyticus*, *A. junii*, *A. johnsonii*, *A. calcoaceticus*, and *A. lwoffii*. Whole-genome sequencing of *A. baumannii* (strain ATCC 17978) was first performed by **(S. G. J. Smith *et al.*, 2007) (Ma & McClean, 2021)**

INCIDENCE:
It is estimated that one million people globally have *A. baumannii* infections each year, and that 50% of those cases progress to become resistant to different medications **(Al-Rashed *et al.,* 2023)**. The incidence and prevalence of *Acinetobacter baumannii* increases in ICU compared to general wards in hospitals. In the intensive care unit, *Acinetobacter baumannii* accounted for 2.1% of all bacterial infections **(Asif *et al.,* 2018)**. The prevalence of this organism in the communities outside hospitals is comparatively very low. This organism is present worldwide but the density varies from country to country. The crude mortality ranges from 40-80%. In a study done in India the carbapenem resistance was said to be about 40-75% **(Vijayakumar *et al.,* 2019)**. In Mediterranean regions, the organism found is about 90% resistant to carbapenem. Depending on the kind of sample the organism is isolated from the prevalence of the organism varies. The organism was found the highest in sputum cultures 31% **(Dent *et al.,* 2010)** .The organism's capacity to endure in adverse environments and the rise in antibiotic resistance are the main causes of the sharp rise in prevalence rates in recent years.

PATHOGENESIS:
Acinetobacter baumannii survives under the principle of "persist and resist," and global reports indicate a rising trend of infections among hospitalized inpatients. Transmission is primarily facilitated by extended length of hospitalisation—especially in intensive care units (ICUs)—and invasive medical interventions such as catheterization, mechanical ventilation, surgical wounds, advanced age, immunocompromised conditions, and inappropriate use of antibiotics **(Djordjevic *et al.,* 2016); (Baran *et al.,* 2008); (H.-Y. Lee *et al.,* 2018)**. Mortality among ICU-admitted patients infected with *A. baumannii* may reach up to 43% **(A. Sharma *et al.,* 2017)**

Clinically, infections caused by *A. baumannii* are generally divided into two distinct categories: nosocomial (hospital-acquired) infections and community-acquired infections. Its prevalence in the community is significantly lower compared to that in hospital environments **(Peleg *et al.,* 2008)**. *A. baumannii* is largely restricted to medical settings or groups in close contact with healthcare facilities, and its natural reservoirs remain poorly understood **(Ma & McClean, 2021)**. It is infrequently found as part of the normal skin microflora, with colonization reported in only 3% of the population **(Howard *et al.,* 2012)**. Common colonization sites include the respiratory tract, urinary tract, bloodstream, and pleural fluid.

The organism's ability to survive in highly disinfected environments is attributed to a variety of virulence factors, including biofilm-associated proteins (e.g., Bap, OmpA) and siderophores such as acinetobactin **(Sheldon & Skaar, 2020)**. These factors enable bacterial self-protection, facilitating persistence within the human host and under diverse environmental conditions such as variable pH and temperature. The associated mortality increases from 5% in general hospital wards to as high as 54% in ICUs **(Bianco *et al.,* 2016)**.

INFECTIONS CAUSED:
A.baumannii can cause a variety of infections at various anatomical sites; the rates of infection ranges from 19% to over 50% in Asia **(Lynch *et al.,* 2017)**. India ranks third among the countries with high prevalence of *A. baumanni*, as it hosts about 13% of all strains globally **(R. K. Sharma & Mamoria, 2017)**. The major infections caused by this organism include ventilator-associated pneumonia, Blood stream infections (BSIs), meningitis, SSTIs, and catheter-associated UTIs **(Sievert *et al.,* 2013)**. Of the aforementioned, respiratory tract infections are the most common, and often have a rapidly progressing clinical course with bacteremia and high mortality.

Ventilator Associated Pneumonia (VAP):
A. baumannii is most often associated with pneumonia, which is the most common nosocomial infection in patients admitted to critical care units (ICUs). As mentioned, VAP is strongly correlated with mechanical ventilation because it increased the risk of infection by 3.5 times for patients on ventilators compared to those who were not **(H. Huang *et al.,* 2018) (Zhang *et al.,* 2021)**.

It significantly increases the mortality rate from 45% to 70%. The American Thoracic Society defines VAP as "pneumonia occurring more than 48 hours after the initiation of endotracheal intubation and mechanical ventilation". In two recent Indian studies, the incidence of VAP was approximately 18% **(Kelkar *et al.*, 2021)** and 22.3% **(Goel *et al.*, 2021)**.This high incidence maybe due to the shift in the oral microflora of critically ill patients. Studies suggest that Oral flora can shift to enteric gram-negative bacilli such as *Acinetobacter species* and *Pseudomonas aeruginosa* **(Safdar *et al.*, 2005)**. *A.baumannii* ranks first in the most commonly isolated pathogenic organism in patients with VAP followed by *P.aeruginosa* and *K.pneumoniae* **(Kelkar *et al.*, 2021) (Joseph *et al.*, 2009)**. Findings published from India also found *A. baumannii* to be the most frequent organism isolated from VAP patients **(Dey & Bairy, 2007) (Lakshmi *et al.*, 2006)**. This may be due to three reasons: its lengthened survival on inanimate objects, the presence of the organism in hospital water, and transmission from the hands of healthcare workers to patients or from patient to patient. The ability to colonize highly disinfected environments is linked to a variety of virulence factors, including biofilms (bap,OmpA), siderophores (acetobactin) **(Sheldon & Skaar, 2020)** etc these are used for self-protection of bacteria. This high incidence of *A.baumannii* in VAP patients generally leads to increased use of Carbapenems and colistin as drugs for treatment.

Blood stream infections (BSI):

A.baumannii ranks 10th among the organisms that cause blood stream infections. The origin of the infection is mostly invasive diagnostic procedures, catheterization mostly intravenous catheters linked to respiratory infections **(Motbainor *et al.*, 2020)**. A case control study in India linked the use of intravenous catheters especially central venous catheters to BSI **(Kharduit *et al.*, 2024), (Sawant & Paritekar, 2024)**. It has previously been reported that neonates who were exposed to umblical cord catheters are also more likely to develop BSI **(Brito *et al.*, 2005)**

Hoang-Van Quang noted that gram negative organisms cause higher level of BSI (65.7%) than gram positive organisms (34.3%). BSI was also linked to higher hospitalisation and was found mostly in older patients than in younger ones. The most common sources of infections that lead to BSI are lower respiratory infections and UTI **(Quang *et al.*, 2024)**. Even after proper antibiotic treatment the mortality rate was alarmingly high in BSI (85.7%)**(Chuang *et al.*, 2011)**. Various studies have isolated *A.baumannii* as the top pathogen isolated from blood in ICU. In India, *A.baumannii* is responsible for 10-15% of all the blood stream infections **(Gautam *et al.*, 2023)**. During the COVID 19 pandemic, patients with CRAB BSI and Covid advanced quickly to fulminant septic shock. Patients with COVID-19 had a 3.5-fold increased risk of developing BSI. Additionally, it was discovered that catheter-related BSI accounted for 57.1% of all BSI cases in COVID-19 patients **(J. Y. Kim *et al.*, 2023)** The mortality rate of BSI has been found to be exceeding 50% in most of the studies **(Ulu-Kilic *et al.*, 2018) (Chuang *et al.*, 2011)**. This may be due to the extreme antibiotic resistance found in patients. The T6SS secretion system has been associated in the spread of MDR isolates and patients with those isolates have been reported previously to have diminished response to antimicrobial therapy **(Y. Lin *et al.*, 2023)**. Hence, one of the most effective methods to prevent BSI is to reduce the frequency of invasive procedures.

Meningitis:

A.baumannii is a common nosocomial agent causing meningitis **(Chusri *et al.*, 2018)**. It is isolated in more than 25 % of all pathogens present in the CSF **(Chen *et al.*, 2021)**. Risk factors for *A.baumannii* meningitis [AB meningitis] include emergency neurosurgery procedures, greater than five days of External Venticular Drainage [EVD], CSF leakage, and head trauma **(Cascio *et al.*, 2010; Jimenez-Mejias *et al.*, 1997; Karaiskos *et al.*, 2013) (K.-W. Wang *et al.*, 2005)**. "Post-neurosurgical meningitis" is the term used to describe cases of meningitis that occur within three months after neurosurgery **(Chang *et al.*, 2010)**. In recent years, Post operative meningitis caused by *A.baumannii* has been an increasing factor for concern **(Ni *et al.*, 2015)**. It has been reported that AB meningitis in children has also always been secondary to neurosurgery **(Z. Wang *et al.*, 2024)**. AB meningitis is extremely scarce in children, however the cases diagnosed are extremely fatal in paediatric patients **(Shi *et al.*, 2020)**. *A. baumannii*-caused intracranial infections, such as meningitis and ventriculitis, have proven difficult to treat in neurosurgical settings **(H.-I. Kim *et al.*, 2012) (Giamarellou *et al.*, 2008)**. One of the reasons for this may be the great limitation in the availability of sensitive antibiotics **(Z. Wang *et al.*, 2024)**. In a retrospective study, of post-neurosurgical meningitis isolates from 5 patients in China, 3 patients were developed meningitis with MRAB of which only one patient survived. Post operative meningitis are generally treated with intrathecal or intraventricular polymyxin B **(Ni *et al.*, 2015; Pan *et al.*, 2018).**

Urinary Tract Infections (UTIs):

Urinary tract infection is a common type of infection affecting the urinary bladder, ureter and

kidneys. Among the nosocomial infection it accounts for upto 31% of all infections **(Tolera *et al.*, 2018)**. Hospital-acquired UTIs caused by A. baumannii are typically associated with urinary tract catheterisation or surgery **(Bekele *et al.*, 2015)**. One out of every 5 isolates from urinary sites are reported to be A.baumannii. According to global prevelance studies A.baumannii is responsible for only about 2% of UTIs **(Di Venanzio *et al.*, 2019)**. In a specific study it has been reported previously that nosocomial UTI associated with A.baumannii totally account to 5% of the UTIs **(Motbainor *et al.*, 2020)**. Despite having such low isolation rate, A. baumannii continues to be recognised in certain clinical settings as one of the main causes of catheter-associated UTIs (CAUTI) **(Ding *et al.*, 2018; Kumar *et al.*, 2018)**. In a study characterizing, Antimicrobial resistance in complicated urinary tract infections from North India, the significant bacteriuria rate was found to be 19.1% **(Taneja *et al.*, 2011).**

Skin and Soft tissue infections [SSTI]:
Infections of the skin and soft tissues caused by *A. baumannii* are extremely rare. Invasive medical equipment has been implicated in 35% of *A. baumannii*-associated SSTIs in the past. The common risk factors among patients with SSTI were central venous catheter, total parenteral nutrition, placement of an external orthopaedic fixator. The organism is frequently isolated from combat-related wounds and burns in military personnel following traumatic injuries like gunshot wounds. SSTI was reported to have progressed from an oedematous "peau d'orange" appearance (resembling the skin of orange) to a sandpaper appearance with clear vesicles on surface of the skin accompanied with bacteremia **(Sebeny *et al.*, 2008)**. Immunocompetent individuals have also developed necrotising fasciitis due to *A.baumannii*. The portal of entry has not been reported clearly. Any type of skin breach or laceration, recent surgery, blunt trauma are some of the risk factors attributed to necrotising fasciitis caused by *A.baumannii*. Mortality upto 30% has been associated in cases having atleast one of these conditions namely, underlying comorbidities, bacteremia, Multidrug resistance, presence of co-pathogens and extensive surgical debridement **(Matthews *et al.*, 2019)**.

VIRULENCE FACTORS:
Acinetobacter baumannii has various virulence factors that contributes to the diseases caused by the organism. These virulence factors may involve in the infection process, such as binding to host structures, transmission, invasion and cellular damage. These components also allow the bacteria to exist in highly unfavourable conditions like low temperature, less nutrients, dryness etc. This allows the bacteria swiftly adapt to specific shifts in the demands of their surroundings. Some of the established virulence factors that help in the organism evading the host immune system are pili [aromatic compounds, paaE] **(Cerqueira *et al.*, 2014)** outer membrane proteins [surface antigen protein 1, surA1] **(D. Liu *et al.*, 2016)**, glycoproteins and capsular polysaccharides [O-pentasaccharide, pglC] **(Lees-Miller *et al.*, 2013) (Iwashkiw *et al.*, 2012)**, and extracellular polysaccharide [Phospholipase D, pld]. Bap **(Azizi *et al.*, 2016)**, OmpA (S. G. J. Smith et al., 2007), Omp 33- 36 **(Tomás *et al.*, 2005)** are the adhesin genes which aids the bacteria to attach to the cell membrane of the host. After attachment the bacteria invades the host cell. BasD and BauA are genes that are engaged in the production and movement of siderophores, which are tiny molecules that chelate iron **(Gaddy *et al.*, 2012)**. traT gene provides the bacteria with serum resistance aiding its survival in human serum. The list of these major virulence factors has been given below in Table I

Bacterial adhesion:
Biofilm associated protein (Bap):
The capacity of *Acinetobacter baumannii* to colonize and form biofilms on both biotic and abiotic surfaces is a critical factor contributing to its ability to cause chronic and persistent infections **(Thummeepak & Kongthai, 2016)**. A key genetic determinant of this trait is the *bap* gene, which is homologous to the *bap* gene found in *Staphylococcus* species and is involved in biofilm maturation **((Ghasemi *et al.*, 2018);(Loehfelm *et al.*, 2008))**. The biofilm-associated protein (Bap) is a high-molecular-weight cell surface protein, approximately 854 kDa in size and encoded by a 1449 bp gene ((**Azizi *et al.*, 2016);(Zeighami *et al.*, 2019)**). This protein plays a pivotal role in the production and stabilization of biofilms, which are complex communities of microorganisms attached to various substrates, including living tissues and medical devices **(M.-F. Lin, 2014)**.

Bap also facilitates intercellular interactions within the biofilm matrix **(Chapartegui-González *et al.*, 2018)** and its function is closely associated with pili, which aid in adhesion and biofilm initiation **(Azizi *et al.*, 2016)**. *A.baumannii* exhibits unusually high rate of biofilm formation (80–91%) compared to other bacterial species, which usually range between 5–24% **(Sung, 2018)**. Biofilms formed by *A. baumannii* are categorized based on adhesion properties as strong, moderate, weak, or non-adherent. Among these, strong biofilm formation is predominant, accounting for approximately 35.4% of isolates in one study **(Azizi *et al.*, 2016)**.

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1527-1547
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Notably, strains lacking the *bap* gene failed to form biofilms, underscoring the gene's essential role in this process **(Azizi *et al.*, 2016)**. Several studies have reported that around 75% of *A. baumannii* isolates are capable of producing biofilms **(Zeighami *et al.*, 2019); (Thummeepak & Kongthai, 2016)**

***Acinetobacter* trimeric autotransporter (Ata)**

Acinetobacter trimeric autotransporter (Ata) is a key element in biofilm development, which presents the specific structural properties of trimeric autotransporters (TA): a long N-terminal signal peptide, a C-terminal domain containing four β-strands, and a surface-exposed passenger domain. Ata aids in biofilm formation by facilitating adhesion to components of the basal membrane and extracellular matrix, thus increasing colonization and survival in host tissues.**(Bentancor *et al.*, 2012)**.

Table I: List of major Virulence factors of *Acinetobacter baumannii*

Mechanism	Gene involved	Description	References
Bacterial adhesion	bap	Biofilm associated protein	**(Asaad *et al.*, 2021)**
	Ata	Acinetobacter trimeric autotransporter	**(S. M. Park *et al.*, 2023)**
	blaPER-1	Adherence to respiratory epithelial cells	**(Thummeepak & Kongthai, 2016)**
	EspA	E. coli secreted protein A	**(S. M. Park *et al.*, 2023)**
	chop	C/EBP homologous protein	**(S. M. Park *et al.*, 2023)**
Cellular permeability	Omp A	Outermembrane protein A	**(Asaad *et al.*, 2021)**
	Omp 33-36 kDa	Outer membrane protein 33-36 kilo Dalton	**(Rumbo *et al.*, 2014)**
enzymes	PglC	*O*-linked protein-glycosylation	**(Lees-Miller *et al.*, 2013) (Nothaft & Szymanski, 2010)**
	Pld	Phospholipase D	**(Jacobs *et al.*, 2010)**
Biofilm formation	pbgG	Encodes poly-β-1,6-N- acetylglucosamine synthase an enzyme involved in synthesis of major component of the bacterial biofilm matrix	**(S. M. Park *et al.*, 2023)**
	bfmS/ bfmR	Biofilm formation on polysterene surfaces	**(Thummeepak & Kongthai, 2016)**
	CsgA	Biofilm formation facilitated by curli fibres	**(Darvishi, 2016)**
Host cell death	fhaB	TPS system	**(S. M. Park *et al.*, 2023)**
	abeD	Membrane transporter in bacterial stress response	**(S. M. Park *et al.*, 2023)**
Toxin production	cpaA	Cogulation targeting mettaloendopeptidase	**(Fallah *et al.*, 2017)**
	lipA	T2SS	**(S. M. Park *et al.*, 2023)**
	Cnf1/Cnf2	Cytotoxic necrotic factor	**(Darvishi, 2016)**
Stress response	recA	DNA repair	**(S. M. Park *et al.*, 2023)**
Serum resistance	traT	Survival in Human serum	**(C. Liu *et al.*, 2018)**
Siderophores	basD	Iron uptake from host cell	**(S. M. Park *et al.*, 2023)**
	bauA	Iron uptake from host cell	**(Fiester *et al.*, 2016)**
Cell surface protein	SurA1	Surface antigen protein 1	**(C. Liu *et al.*, 2018)**
Alteration in pathways	paaE	Phenyalanine catabolic pathway	**(C. Liu *et al.*, 2018)**

Cellular permeability: Outer membrane proteins (Omp)

Gram-negative bacteria have major proteins that regulate permeability across the outer membrane; for example, in *Acinetobacter baumannii*, OmpA otherwise known as porins, is a prominent virulence factor. When it binds to host epithelial cells after being purified, it traffics to mitochondria and induces apoptosis by promoting release of pro-apoptotic factors cytochrome c and apoptosis-inducing factor (AIF) **(Choi *et al.*, 2007)**.

Mode of Action:

OmpA interacts with both mitochondria and epithelial cells of the host causing virulence; binding to mitochondria causes them to enlarge and malfunction by releasing cytochrome c, which forms the apoptosome and initiates the intrinsic pathway of apoptosis. OmpA also contains a monopartite nuclear localization signal (NLS) that facilitates its entry into the nucleus where it triggers apoptosis **(Choi *et al.*, 2007)**. Moreover, OmpA bypasses the complement by binding to Factor H in the human serum.**(S. W. Kim et al., 2009)**.

OmpA is also linked to antibiotic resistance, along with its functions in immune evasion and pro-apoptosis. Distruption of the OmpA gene dramatically reduces the MIC range, suggesting a role for this gene in extrusion or decreased absorption of various antibiotics **(C.-R. Lee *et al.*, 2017)**. It is also worth noting that, OmpA is involved in complement resistance and biofilm formation, which may contribute to the pathogenicity and persistence of *A. baumannii.*

Omp33-36 KDa:

The 33–36 kDa outer membrane protein (Omp33-36) predominantly functions as a water channel; interestingly, carbapenem-resistant *A.baumannii*

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1527-1547
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strains lack this porin, indicating that it is involved in antibiotic permeability **(Tomás *et al.*, 2005)**. Besides its structural role, Omp33–36 inhibits autophagy, which promotes intracellular persistence and subsequent cytotoxicity; therefore, strains lacking in Omp33–36 have impaired growth kinetics and severely hinder their ability to adhere and invade to host cells, and cause cytotoxicity, highlighting the relevance of this protein in the fitness and virulence of *A. baumannii*. Overexpression of omp33–36 has shown significant reduction in the MICs of carbapenems like imipenem and meropenem. Because Omp33–36 is involved in both antimicrobial susceptibility and virulence, it represents a potential novel target for new antimicrobials.**(W. Huang *et al.*, 2016)**.

Enzymes: *O*-linked protein-glycosylation (pglC):
PglC is a member of a family of enzymes known as polyisoprenyl-phosphate N-acetylaminosugar-1-phosphate transferases (PNPTs). In *A. baumannii*, PglC activity is essential for the biosynthesis of type I capsular polysaccharide and O-glycoproteins **(Lees-Miller *et al.*, 2013)**. The pglC gene of *Acinetobacter baumannii* is homologous to the enzymes encoding the genes for *Neisseria meningitidis*. The function of glycoproteins is given in Figure I

Figure I: Function of glycoproteins (Iwashkiw *et al.*, 2012)

O glycosylation appears to be widespread in *A.baumannii*. The pglC gene promotes the organism's ability to build biofilms. The development of dense aggregates allows the organism to adhere to abiotic surfaces. The thick aggregates of the biofilm appear to be related to the structure and organisation of the capsular polysaccharide **(Lees-Miller *et al.*, 2013)**. Glycoproteins are typically immunodominant in bacteria, they can serve as the foundation for upcoming vaccine formulations and diagnostic techniques **(Iwashkiw *et al.*, 2012)**. The identification of PglC and the necessity of this gene for the production of the pentasaccharide needed for O-glycosylation could serve as the foundation for the development of novel vaccines directed against *A.baumannii* **(Lees-Miller *et al.*, 2013)**.

Phospholipase D (Pld):
Phospholipids are essential components of biological membranes; they are also highly abundant in the human host and hence ideal candidate for carbon and energy sources **(Stahl *et al.*, 2015)**. In eukaryotic membranes, phosphatidylcholine (PC) is notably abundant, making up 50% of all phospholipids **(Vance, 2008)**. The incidence even rises to 80% in the lungs **(Bernhard *et al.*, 2001)**. Phospholipases (PL) are essential enzymes that are crucial for PC metabolism. Additionally, phospholipases may also impede cellular signalling. In *Acinetobacter baumannii*, there are three phospholipases which exhibit coordinated activity to mediate virulence **(Stahl *et al.*, 2015)**. The three phospholipases and its function are given in Figure II

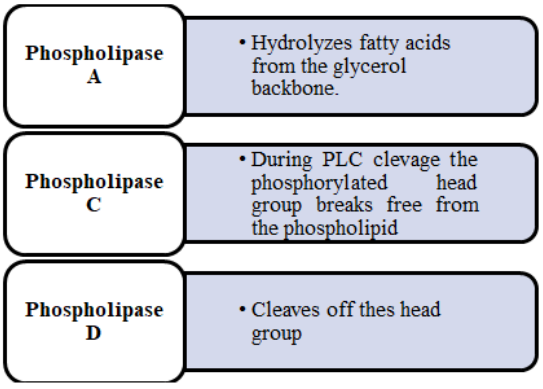

Figure II: Function of the three Phospholipids

PLDs of *A.baumannii* play a significant role in eukaryotic host virulence by mediating invasion. PLD activities hydrolyse phospholipids to produce bioactive compounds like phosphatidic acid, which may potentially impact on eukaryotic signalling cascades. Phospholipase D is subclassified into three types namely PLD1, PLD2, PLD3 **(Camarena *et al.*, 2010)**. The PLD gene disruption in the organism leads to reduction in proliferation in the human serum, reduced ability in invasion and diminished pathogenesis **(Jacobs *et al.*, 2010)**. It has phosphatase activity and hydrolyses polynucleotide backbones **(Selvy *et al.*, 2011)**. These findings prove that Phospholipase D is essential for the organism to thrive in blood and tissues causing bacteremia **(Jacobs *et al.*, 2010)**.

Siderophores:
Iron, one of the most abundant metals in the human body, is essential for the growth and development of bacteria within the host **(Sheldon *et al.*, 2016)**. However, most of this metal is tightly bound by high-affinity chelators, such as transferrin, lactoferrin, and haemoglobin, which the host uses to limit bacterial proliferation **(Bullen *et al.*, 2005;**

Sheldon & Skaar, 2020). This host defense strategy renders iron largely unavailable to invading pathogens. Consequently, the acquisition of iron—a critical micronutrient required by nearly all living organisms—becomes a significant challenge for bacterial pathogens **(Crichton, 2016)**. Siderophores are produced by *A.baumannii* to overcome this limitation. They are low-molecular-weight iron scavengers, that compete with the host for metals required for growth and development **(Sheldon & Skaar, 2020)**. The organism releases siderophores through specific receptors located on its outer membrane, that to bind ferric ions and provide iron available for its growth **(Kumar *et al.*, 2021)**. Among the different siderophores produced by *A. baumannii*, acinetobactin is the most abundant. Acinetobactin inactivation gravely impairs the ability of *Acinetobacter baumannii* to proliferate on human blood, transferrin and lactoferrin progressively compromising the bacterium's capacity to survive **(Sheldon & Skaar, 2020)**.

The proteins BauA and BasD play an important role in the transport and production of acinetobactin. These proteins are crucial for the bacterium to survive on epithelial cells and promote apoptosis in these cells **(Gaddy *et al.*, 2012)**. BauA, an outer membrane receptor protein, is primarily vital for the function of the acinetobactin system, validating its importance in the survival of the bacterium within the human host.

Surface antigen protein 1 (SurA1):
Surface antigen protein SurA1 is a cell surface protein that plays a pivotal role in influencing the virulence of *Acinetobacter baumannii* by modulating bacterial growth and multiplication, which directly impacts the pathogen's pathogenicity **(D. Liu *et al.*, 2016)**. SurA1 significantly affects the bacterium's growth, fitness, and overall virulence. Previous studies have demonstrated that in *A. baumannii*, SurA1 upregulates the expression of genes associated with virulence. Notably, stimulation with low concentrations of alcohol enhances virulence and increases SurA1 expression **(Nwugo *et al.*, 2011)**.

Bacteremia may result from the excessive growth of *A. baumannii*, which leads to cell suppression and impairs normal cellular functions. An increase in bacterial growth in vivo may cause SurA1 to exert more pronounced cytotoxic effects. These cytotoxic effects are dose-dependent, highlighting the variability of SurA1's impact on the host. Furthermore, alterations in antibiotic resistance and pathogenicity can modulate SurA1 expression levels **(D. Liu *et al.*, 2016)**. Some studies suggest that SurA1 may also play a role in serum resistance **(Smani *et al.*, 2011).** Although the exact mechanisms by which SurA1 affects bacterial motility and proliferation remain unclear, it is evident that this protein plays a crucial role in *A. baumannii*'s ability to thrive in hostile environments. Given its central role in virulence, SurA1 represents a promising target for the development of vaccines aimed at combating *A. baumannii* infections.

Alteration of Pathways: Phenylacetic Acid Catabolic Pathway (PaaE)
Aromatic compounds frequently get converted into central metabolic intermediates by a number of peripheral pathways among which PA (phenylacetic acid) is most important. The PA catabolic pathway is utilised by aerobic bacteria via the paa operon. Thirteen genes make up the Paa operon **(Hooppaw *et al.*, 2022)**. They are PaaZ, PaaA, PaaB, PaaC, PaaE, PaaF, PaaG, PaaH, PaaJ, PaaK, PaaY, PaaI and PaaX **(Jiao *et al.*, 2023)**. These gene encode the enzymes required to breakdown phenylacetic acid (Intermediate of the amino acid L-phenyalanine). The Paa pathway of *Acinetobacter baumannii* is the only amino acid catabolic pathway that is consistent and widely controlled over a wide range of conditions **(Hooppaw *et al.*, 2022)**. In *A. baumannii*, the virulence-associated two-component system (TCS); GacS regulates the paa operon. It acts as a global virulence regulator. It regulates PaaA and PaaE genes. PaaE is necessary for the Phenylacetic acid catabolic pathway and for the formation of toxic epoxides needed for pathogenicity of the organism. Epoxides seriously hinder cell growth and damage proteins and DNA **(J.-B. Park *et al.*, 2006)**. *A. baumannii's* capacity to respond to stress was hampered by altering PAA catabolism, which resulted in a reduction in antibiotic tolerance and hydrogen peroxide resistance. PaaE mutant bacteria was unable to survive in animal models. Deletion of PaaE resulted in attenuation of virulence in the bacteria making it a possible target for vaccine production.

Serum resistance (traT):
The complement cascade, which is a first-defense series of serum proteins that, when triggered, adhere to the surface of an invasive bacterial cell in a certain order and ultimately result in lysis and death of the organism. traT is a serum resistance associated outer membrane protein. This shields the bacteria from the host's complement system, which is essential to its survival **(King *et al.*, 2009)**

Secretion systems: Coagulation targeting metallo-endopeptidase of Acinetobacter baumannii (CpaA)
CpaA is a Zinc dependant mettalo-endopeptidase. It

is involved in the impairment of invitro coagulation of human blood. Acting as both an activator and an inhibitor of coagulation, CpaA engages in complex interactions with the coagulation cascade. CpaA hinders antimicrobial therapy's efficacy and encourages resistance. It also stops the immunological response linked to coagulation **(Tilley et al., 2014)**

Other Virulence Factors:
Acinetobacter baumannii's virulence is influenced by a wide variety of genes in addition to the virulence factors mentioned above. The CSU gene cluster **(Eijkelkamp *et al.*, 2014)** is one example of such virulence factors. It is involved in the tight adherence to abiotic, hydrophobic surfaces, and very loose association to hydrophilic surfaces. Another example is secretion systems like T2SS lipase effectors (lipA,lipH) etc. However more thorough research is needed to comprehend the host immune response, the host pathogen interaction, and the targeting of the virulence factors for development of vaccine.

TREATMENT:
Acinetobacter baumannii is inherently resistant to several commonly used antibiotics, including aminopenicillins and first- and second-generation cephalosporins. However, it possesses a remarkable ability to develop resistance to a wide range of additional antibiotics, enabling it to rapidly adapt to changes in environmental conditions. For susceptible strains, first-line treatment typically involves carbapenems such as doripenem, meropenem, or imipenem-cilastatin **(Fishbain & Peleg, 2010)** . Imipenem was historically considered the gold standard for the treatment of ventilator-associated pneumonia (VAP).

Carbapenem resistance in *A. baumannii* has been rising globally, and only a few treatment options are available, which has prompted clinicians to seek alternative therapies. Among the other alternatives, colistin (polymyxin E) is generally employed for the treatment of multidrug-resistant (MDR) *A. baumannii* infections **(Garnacho-Montero *et al.*, 2003)**. But it is not used widely in clinical settings because of poor penetration into lung tissue and higher rates of neurotoxicity and nephrotoxicity. Tigecycline has also been used as an alternative, but it has also shown variable rates of success in treating MDR *A. baumannii* infections **(Y.-T. Lee *et al.*, 2013)**.

The β-lactamase inhibitor, Sulbactam binds naturally to penicillin-binding proteins in *A. baumannii* and can be used for alternative therapy.
Combination therapy is often employed to boost the efficacy of antibiotic treatments for *A. baumannii* infections. Nevertheless, the evidence supporting this from human clinical trials is minimal. Combination therapy is often used to increase treatment efficacy; however, there is limited evidence of this from human clinical trials. Many studies have found that combination therapy (e.g., polymyxin B plus other antibiotics, such as imipenem, meropenem, rifampin, or ampicillin-sulbactam) may lower mortality rates compared to polymyxin B monotherapy, the combination of colistin and carbapenem is the best-supported regimen **(Rigatto *et al*., 2015)**.

ANTIBIOTIC RESISTANCE IN ACINETOBACTER BAUMANNII:
Globally, multiple antibiotic-resistant strains of *A. baumannii* have emerged and led to a reduction in treatment options and an increase in morbidity and mortality; strains resistant to multiple drugs and to all available drugs (multidrug-resistant [MDR] and pan-drug-resistant [PDR]) are now becoming more prevalent.

Resistance has increased for all four major classes of antimicrobials: carbapenems (9–39%), aminoglycosides (19–31%), β-lactams (39–66%), and fluoroquinolones (50–73%) **(Weinstein *et al.*, 2005)**. *A. baumannii* now shows resistance to most first-line antibiotics. Several factors contribute to the increasing prevalence of antibiotic resistance, including increased antibiotic use **("The Antibiotic Alarm," 2013)**, horizontal gene transfer between bacteria(Read & Woods, 2014), and the slow pace in discovery of novel antibiotics **(Bartlett *et al.*, 2013)**.

The most commonly reported mechanisms of antibiotic resistance in *A. baumannii* involve mutations that modify antibiotic target sites, production of degrading enzymes, permeability defects, and changes in multidrug efflux pumps **(Gordon & Wareham, 2010).**

In this section, we will review the molecular mechanisms of the resistance to various antibiotics, focusing on the accumulation of resistance genes and their impact on total resistance and viability of *A. baumannii*.

Table II: Overview of Antibiotic resistance genes in *Acinetobacter baumannii*

Antibiotics	Resistance mechanism	Target	Genes involved	References
β-lactams	β-lactamases	Ambers class A	KPC TEM SHV	**(Ghenea *et al.*, 2022)**
		Ambers class B	NDM	**(Shanthi *et al.*, 2014)**

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1527-1547
DoI-10.004687/1000-9035.2025.198

			VIM IMP SIM GIM SPM	
		Ambers class C	Amp C	**(Rao *et al.*, 2022)**
		Ambers class D	OXA 23 like OXA 24 like OXA 51 like OXA 58 like OXA 123 like	**(Amudhan *et al.*, 2011)**
	Mutations	Penicillin binding proteins	PBP 2	**(Fernandez-Cuenca, 2003)**
	Permeability issues	Loss of porins	OMP 33	**(Depka *et al.*, 2023)**
	Efflux pumps	RND pumps	AdeABC	**(Haeili *et al.*, 2018)**
Colistin	Spontaneous point mutation	Complete loss of Lipid A	lpxA lpxC lpxD	**(Moffatt *et al.*, 2010)**
	Alteration in binding of colistin to cell membrane by addition pEtN	Modification of lipid A component in LPS by PmrCAB operon	PmrA PmrB Mcr-1	**(Farajnia *et al.*, 2022)**
	Efflux pumps	Changes in permeability through reduction in entry channels	emrB	**(Ghahraman *et al.*, 2020)**
Tigecycline	Efflux pumps	Tetracyclines are pumped out of the cell against concentration gradient	AdeABC, AdeIJK Tet A-E and K pumps	**(Haeili *et al.*, 2018)**
	Ribosomal protection		TetO TetM	**(Haeili *et al.*, 2018)**

Beta-Lactam and Carbapenem Resistance

β-lactam antibiotics are widely used as antimicrobials to treat both hospital- and community-acquired infections. **Carbapenems** are a subfamily of β-lactams that are useful in the treatment of severe hospital-acquired infections caused by multidrug-resistant *Acinetobacter baumannii*; carbapenem resistance in this organism is primarily mediated by the production of carbapenemases, mutations in outer membrane proteins (OMPs), increased efflux pump activity, and modifications in penicillin-binding proteins (PBPs) **(Codjoe & Donkor, 2017)**.

Mode of Action:

Carbapenems cannot diffuse readily through the bacterial cell wall; therefore, they must be taken in through porins in the outer membrane of Gram-negative bacteria, where they bind to PBPs 1a, 1b, 2, and 3, with bactericidal activity **(Hoskins *et al.*, 1999)**. PBPs are cytoplasmic membrane proteins that are critical for the synthesis of the peptidoglycan layer of the bacterial cell wall; carbapenems bind to their active sites, inhibiting transpeptidation and other peptidase reactions. As a result, the bacteria lose their ability to construct their cell wall correctly, leading to autolysis and eventual cell death **(Minerdi *et al.*, 2023)**

Mechanisms of Resistance:

Carbapenem resistance in *A. baumannii* is primarily driven by four mechanisms:

1. **Carbapenemases**: These periplasmic enzymes hydrolyse carbapenems, thus inactivating the antibiotic before it can reach its target (PBP).
2. **Efflux Pumps**: Antibiotics are pumped out of the bacterial cell by membrane transporter proteins, lowering intracellular drug concentrations.
3. **Loss of Porins**: Diminished expression of porins reduces the rate at which antibiotics can enter the periplasm.
4. **Penicillin-Binding Proteins (PBPs)**: Mutations in PBPs or downregulation of PBP expression, often resulting in amino acid substitutions, also contribute to carbapenem resistance.

Genes Involved in Carbapenem Resistance:

Class A Carbapenemases:

Class A β-lactamases are associated with resistance to monobactams, carbapenems, cephalosporins and penicillin. Point mutations in Class A enzymes can increase or reduce the spectrum of their activity. Narrow-spectrum β-lactamases display decreased activity to clavulanic acid but are still active against penicillin **(Poirel *et al.*, 2007)**. Extended-spectrum β-lactamases (ESBLs), such as **CTX-M**, **KPC**, **blaTEM-92**, **blaSHV**, and **blaGES-14**, can breakdown extended-spectrum cephalosporins, including **ceftazidime**, **ceftriaxone**, and **aztreonam (Ghafourian *et al.*, 2015; Walther-Rasmussen & Høiby, 2004).**

Class B: Metallo-β-Lactamases (MBLs):

Class B β-lactamases, also known as **metallo-β-lactamases (MBLs)**, contain zinc in their active sites. These enzymes are accountable for *A. baumannii* resistance to cephalosporins and

Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1527-1547
DoI-10.004687/1000-9035.2025.198

carbapenems **(Thomson & Bonomo, 2005)**. The most important class B MBLs include **NDM-1** (New Delhi metallo-β-lactamase), **IMP** (imipenemase), **VIM** (Verona integron-encoded MBL), **SPM**, **GIM**, and **SIM**. MBLs particularly hold importance in the emergence of carbapenem resistance in *A. baumannii*, and strains encoding these enzymes have become widespread in regions like India, with resistance rates surpassing 70% **(Das, 2023) (Saranathan *et al.,* 2014).**

NDM-1 (New Delhi Metallo beta-lactamase)
NDM-1, one of the most clinically significant carbapenemases, was first identified in 2009 in *Klebsiella pneumoniae* and *Escherichia coli* from a Swedish patient who had been previously hospitalized in New Delhi, India **(Das, 2023)**. India remains the epicenter for NDM-1, with prevalence rates up to 90% **(Mohan *et al.,* 2015)**. NDM-1 confers no fitness cost, making it preferred over other MBLs and contributing to its widespread distribution **(López *et al.,* 2019)**

IMP (Imipenemase):
The **IMP-type carbapenemases** were first detected in *Acinetobacter spp*. and *P. aeruginosa* in Japan in the 1990s, and subsequently spread to Asia **(Davoodi *et al.,* 2015)**.The IMP gene is located on plasmids and has disseminated globally in Gram-negative bacteria. In India, IMP has been reported in 31% of *A. baumannii* isolates**(Saranathan *et al.,* 2014)**.

VIM (Verona Integron-encoded MBL)
The **VIM-type MBLs (VIM-1)** were first detected in 1997 from P. aeruginosa in Verona, Italy. In North India, 50% of carbapenem-resistant *A. baumannii* isolates were reported to be positive for VIM**(A. Sharma *et al.,* 2017)**.

Class C Beta-Lactamases:
Class C beta-lactamases, also called as ***Acinetobacter*-derived cephalosporinases (ADC)**, possess chromosome encoded cephalosporinases, found in all *A. baumannii* strains. Overproduction of these lactamases is caused by insertion of sequences (ISAba1 and ISAba125) upstream of the **blaADC** gene, formerly known as **blaAmpC**.
One variant of ADC, **ADC-30**, confers resistance to carbapenems, sulbactam, and cephalosporins **(Kyriakidis *et al.,* 2021)**. In addition, ADC dephosphorylation can lead to imipenem resistance in clinical isolates.

Class D: OXA Beta-Lactamases
OXA β-lactamases were some of the earliest beta-lactamases identified and are known to cause resistance to cephalosporins. Oxacillinases are categorised under **Class D** in **Amber's classification** of beta-lactamases. Beginning in the 1980s, plasmid-encoded β-lactamases became a common characteristic of **Carbapenem-resistant *Acinetobacter baumannii* (CRAB)** isolates **(Paneri *et al.,* 2023)**.

Mechanism of Resistance:
The OXA enzymes that were first characterized were penicillinases that hydrolyse penicillin and oxacillin to confer resistance. They are usually carried by plasmids and have relatively low levels of hydrolysis to carbapenems.**(Evans & Amyes, 2014)**. Therefore, the activity of these enzymes against carbapenems is usually limited, however, these enzymes can increase the minimum inhibitory concentration (MIC) to carbapenems. This results in carbapenem resistance. Since the identification of OXA enzymes, they have been implicated in carbapenem resistance in *A. baumannii*, further elevating the threat posed by this organism and limiting the effectiveness of antibiotics. Moreover, **clonal outbreaks** in ICUs are frequently associated with these enzymes, complicating containment and leading to increased morbidity and mortality.

OXA Genes Involved in Resistance:
Numerous OXA genes have been discovered in *A. baumannii*. Out of which **OXA-23**, **OXA-24**, **OXA-51**, and **OXA-58** are the most predominant.

OXA-23:
OXA 23 was the first class of OXA-type β-lactamases to be documented as carbapenem resistant. In addition to hydrolyse carbapenems OXA 23 enzymes also have the capacity to hydrolyse aminopenicillins, oxyimino cephalosporins, piperacillin, oxacillin, and aztreonam **(Afzal-Shah *et al.,* 2001)**. The turnover rate for imipenem is very high for OXA-23 **(C. A. Smith et al., 2013)**. No other additional resistance mechanisms is needed for strains with OXA-23 to show resistance to carbapenems**(Evans & Amyes, 2014)**.Further demonstration of the role of OXA 23 in making the bacteria resistant to ampicillin/sulbactam, amikacin and Carbapenem was published in 2022.**(Afshar *et al.,* 2022)**

OXA-24:
OXA-24 was the second OXA-type β-lactamase identified, first in isolates from 1997, and later renamed **OXA-40**. OXA-24 exhibits strong activity against carbapenems. An increase in carbapenem sensitivity was observed after the insertional inactivation of the OXA-24 gene, confirming its role in resistance **(Evans & Amyes, 2014).**

OXA-51:
To date, **OXA-51-like β-lactamases** have been identified as the largest category of OXA-type β-

lactamases. OXA-51 was first identified in Argentina in 1996. It is encoded chromosomally and serves as a biomarker for differentiating *A. baumannii* from other *Acinetobacter* species. OXA-51 confers intrinsic resistance to carbapenems **(Paneri *et al.*, 2023)** and interacts most strongly with **ceftazidime (Tiwari *et al.*, 2012)**. A 2020 study of 150 isolates found that all possessed OXA-51**(A. Sharma *et al.*, 2017)** making it a reliable biomarker for identifying *A. baumannii*.

OXA-58:
OXA-58 was first discovered in a multi-drug-resistant clinical isolate of *A. baumannii*. It has the ability to hydrolyse **cefpirome** and **cephalothin**. A mutation in the lysine residue leads to an almost total loss of enzyme function.
The prevalence of OXA genes is given in Table III

Table III: Prevalence of OXA genes

Country	Oxa 23	Oxa 24	Oxa 51	Oxa 58	References
India	47.9	22.9	100	4.2	**(Karunasagar *et al.*, 2011)**
Thailand	68.31	4.92	100	1.09	**(Thirapanmethee *et al.*, 2020)**
Egypt	50%	7.5%	100 %	5%	**(Al-Agamy *et al.*, 2014)**
Iran	82.1 %	36.6 %	100	-	**(Vahhabi *et al.*, 2021)**

Colistin Resistance in *Acinetobacter baumannii*

Colistin, also known as polymyxin E, is a polycationic peptide produced non-ribosomally and belongs to the polymyxin class of antibiotics. Within this class, only **Polymyxin B** and **Polymyxin E** are used clinically **(Cassir *et al.*, 2014)**, and both share a similar structure. After its introduction into clinical practice in the 1950s, colistin was primarily used in human medicine to treat lung infections caused by multidrug-resistant (MDR) Gram-negative bacteria **(Cunningham, 2001)**. Colistin is considered a last-resort antibiotic for treating infections caused by multidrug-resistant *A. baumannii*. The reported resistance rate to colistin in India is approximately **8.2% (Pormohammad *et al.*, 2020)**.

Mode of Action:
Due to its positive charge, colistin interacts electrostatically with the phosphate groups of lipid A (which are negatively charged) in the **lipopolysaccharide (LPS)** component of the outer membrane of Gram-negative bacteria **(Deris *et al.*, 2014)**. This interaction displaces divalent calcium and magnesium cations, which alters the three-dimensional structure of LPS. Subsequently, the hydrophobic terminal acyl fatty chain of colistin inserts into the outer membrane, disrupting and permeabilizing it. This disruption allows colistin to penetrate the inner membrane, damage the phospholipid bilayer, and cause the leakage of intracellular substances, ultimately leading to cell death **(Velkov *et al.*, 2010)**. Therefore, colistin is regarded as a **bactericidal** antibiotic.

Mechanism of Resistance
Several mechanisms of *A. baumannii* resistance to colistin have been documented, including:

1. Total loss of LPS through the inactivation of the biosynthetic pathway **(Olaitan *et al.*, 2014)**
2. Alterations to the target LPS via the insertion of phosphoethanolamine (PEtN) moieties into lipid A, mediated by enzymes encoded by the **eptA** gene and the **pmrCAB** operon **(Adams *et al.*, 2009)**
3. The presence of **mcr genes** encoded by plasmids.
4. Efflux of colistin from the cell.

Total Loss of Lipopolysaccharide (LPS):
The first report of colistin resistance in *A. baumannii* caused by LPS deficiency was reported by **(Moffatt *et al.*, 2010)**. The resistance was due to result from mutations in the first three genes responsible in lipid A synthesis (**lpxA**, **lpxC**, or **lpxD**). Mutations, ranging from single nucleotide changes to large deletions, can cause complete LPS loss leading to formation of frameshifts or truncated proteins, inactivating the lipid A synthesis genes and conferring colistin resistance because of the loss of LPS interaction with the antibiotic.

A. baumannii strains that lack LPS are unable to release of reactive oxygen species (ROS) and pro-inflammatory cytokines, consequently leads to diminished neutrophil activation. Only a few species, such as *A. baumannii*, can survive without LPS. LPS-deficient *A. baumannii* strains may be less virulent due to reduced surface motility, grow poorly under iron limitation, and produce fewer biofilms **(Carretero-Ledesma *et al.*, 2018)**.

Alterations to the LPS Layer
The negative charge of the LPS is decreased by the addition of **PEtN** to the 4′-phosphate or 1-phosphate group of lipid A, which makes it bind more readily with colistin. This modification is facilitated by the **PmrAB two-component system (Olaitan *et al.*, 2014)**. Colistin resistance is adaptive in nature. It is controlled by two-component regulatory systems, namely **pmrA-pmrB (pmrAB) and phoP-phoQ (phoPQ) (El-Sayed Ahmed *et al.*, 2020)**

PmrA-PmrB (pmrAB) System
Modifications in the **pmrCAB** operon are

associated with colistin resistance in clinical isolates of *A. baumannii*. The **pmrC** gene encodes the **PEtN transferase**, whereas the **PmrA** and **PmrB** genes encode the two-component system (TS) tasked with the regulation of this transferase. The coordinated activity of these systems governs the expression of PEtN transferases. Overexpression of **pmrC** due to mutations in the PmrAB TS system leads to lipid A modification with PEtN, conferring colistin resistance. Some colistin-resistant isolates show expression of **pmrA** and **pmrB** genes **(Adams *et al.*, 2009)**.

To confer resistance, **pmrAB overexpression** and at least one mutation in **PmrB** appear to be necessary **(Beceiro *et al.*, 2011)**. Gain-of-function mutations in **PmrB (Ly NS *et al.*, 2021)** can cause constitutive activation of **PmrA**, which elevates **PmrCAB** expression and confers resistance to colistin **(Adams *et al.*, 2009)**. *A. baumannii* can exhibit significantly high colistin resistance (>256 µg/mL or 512 µg/mL) due to certain mutations in **PmrA** alone **(Gerson *et al.*, 2020)**. Laboratory-selected colistin-resistant strains have shown elevated **pmrA** expression **(Beceiro *et al.*, 2011)**.

Mutations frequently occur in the **histidine kinase domain** of **PmrA**, which controls autophosphorylation and the transfer of the phosphoryl group to **PmrA**. Several point mutations have been discovered in **pmrB**, with five distinct types reported by **(Haeili *et al.*, 2018)**, and three in an Iranian study **(Farajnia *et al.*, 2022)**. Other studies have found six mutations in Korea **(Y. K. Park *et al.*, 2011)**, and eight mutations by **(Beceiro *et al.*, 2011)** using strains from various countries.

PhoP-PhoQ (PhoPQ) System

The **PhoP-PhoQ** two-component regulatory system regulates the expression of lipopolysaccharide modification enzymes encoded by the **arnBCADTEF-pmrE** operon, enhancing resistance to polymyxins. The **oprH-phoP-phoQ** operon is autoregulated by the PhoPQ system, a global regulatory system. Autoregulation occurs in the presence of polyamines and when divalent cations are limited, which results in resistance to cationic peptides like colistin **(Beceiro *et al.*, 2011)**. Loss-of-function mutations in **PhoQ** attenuate bacterial virulence, reduce biofilm formation, bacterial motility, and cytotoxicity. Using microarray analysis it was reported that **PhoQ** can modify the regulation and expression of up to 474 genes **(B. Yang *et al.*, 2021)**.

The expression of **pmrA-pmrB** is activated by phosphorylated **PhoP**. At subinhibitory concentrations of colistin, phoP mutants exhibit greater killing activity against wild-type strains.

Prevalence of Colistin Resistance

A systematic review and meta-analysis by **(Bostanghadiri *et al.*, 2024)** reported the following resistance rates in different countries [Table IV]:

Table IV: Resistance rates in different countries

Country	Resistance Rate
India	8.2%
China	12%
United Arab Emirates	50%
USA	5%
Asia	4%
Western Europe	7%

mcr Genes Encoded by Plasmids

The **mcr** (mobile colistin resistance) genes were among the first plasmid-mediated colistin resistance genes identified. The mcr gene was initially discovered in an *Escherichia coli* strain from a pig in China and was later found in human samples collected between 2011 and 2014 **(Rebelo *et al.*, 2018)**. Several **mcr** gene variants have been reported previously, such as **mcr-1**, **mcr-2**, **mcr-3**, **mcr-4**, and **mcr-5**, with **mcr-1** is the most common. The **mcr-1** gene codes for an enzyme known as **phosphoethanolamine transferase**, that alters lipid A in the LPS of the bacterial outer membrane. This change in the lipid A decreases colistin's ability to bind eventually preventing cell lysis **(Rebelo *et al.*, 2018)**

Resistance genes that are plasmid-mediated can spread worldwide, particularly in regions with high levels of antimicrobial resistance, potentially leaving few treatment options for nosocomial settings.

Efflux Pumps

Antibiotic resistance in *A. baumannii* is associated with four major efflux pump families: (i) the **Resistance-Nodulation-Cell Division (RND)** family, (ii) the **Multidrug and Toxic Compound Extrusion (MATE)** family, (iii) the **Small Multidrug Resistance (SMR)** family, (iv) the **Major Facilitator Superfamily (MFS) (Abdi *et al.*, 2020)**. The **RND** class of efflux pumps is the most important in MDR *A. baumannii*, as it has been associated with colistin resistance [Table V] **(Jassim *et al.*, 2016)**.

Table V: Overview of types of Efflux pumps

Efflux pump	Description	Reference
RND efflux pumps	Three major members: AdeABC, AdeFGH and AdeIJK Overexpression of AdeABC contributes to	**(Hornsey *et al.*, 2010);(Yoon *et al.*, 2013)**

Journal of Molecular Science
Journal of Molecular Science
Volume 35 Issue 4, Year of Publication 2025, Page 1527-1547
DoI-10.004687/1000-9035.2025.198

	reduced tigecycline susceptibility	
(MATE) family	AbeM is a member of the MATE transporter family and is an H+-coupled multidrug efflux pump.	**(Su *et al.*, 2005)**
ATP-binding cassette (ABC) transporter	Uses the energy generated by ATP binding and hydrolysis to perform efflux functions MsbA was the first ATP-binding cassette transporter to be crystallized	**(Okada & Murakami, 2022)**
MFS efflux pumps	Proton-dependent antimicrobial drug efflux system TetA is an important member of the MFS family	**(Stephen *et al.*, 2023)**

Tigecycline Resistance in *A.baumannii*

Tigecycline is a broad-spectrum antibacterial drug in the tetracycline class of antibiotics. It was primarily designed to treat multidrug-resistant (MDR) polymicrobial infections, including both Gram-positive and Gram-negative bacteria **(Tasina *et al.*, 2011)**. Tigecycline, a parenteral glycylcycline antibiotic, is bacteriostatic in nature and it is structurally related to tetracycline with about five times its binding affinity **(Ventola, 2015)**. It was first approved for human use by The Food and Drug Administration (FDA) in 2005 **(Stein & Babinchak, 2013)**. Currently, it is licensed by FDA for monotherapy for adults with complicated skin infections. Tigecycline efficiently penetrates bodily fluids and tissues, including the lungs, skin, liver, heart, bones, and kidneys, achieving therapeutic concentrations **(Cai *et al.*, 2016)**. Because of this extensive penetration, it has become extremely beneficial as a last-resort treatment for combating multidrug-resistant bacteria **(Volkers *et al.*, 2011)**. By attaching a glycylamide moiety to the 9-position of minocycline, tigecycline circumvents the primary genetic pathways responsible for tetracycline resistance. The prevalence rate of Tigecycline resistance genes across Asia is shown in Figure III

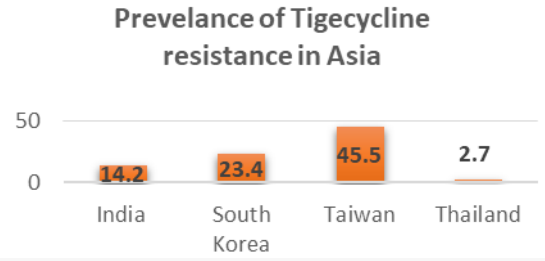

Figure III: Prevalence of Tigecycline resistance in Asia (Taneja *et al.,* 2011)

Mode of Action:

Tigecycline mainly prevents the translation of bacterial proteins. This is achieved by reversibly binding to a helical region (H34) on the 30S subunit of bacterial ribosomes, inhibiting the incorporation of amino acid residues into the elongating peptide chain, eventually halting bacterial protein synthesis and growth **(Stein & Babinchak, 2013)**.

Mechanism of Resistance:

Several mechanisms contribute to the development of resistance to tigecycline in *Acinetobacter baumannii*. These include overexpression of efflux pumps, changes in the permeability of the outer membrane, modifications to the tigecycline binding sites, synthesis of enzymes that inactivate tigecycline, and DNA repair pathways that mediate tigecycline resistance **(Sun *et al.*, 2023)**

In clinical settings, tetracycline resistance is primarily expressed through two mechanisms:

- **Ribosome Protection**
- **Active Efflux**

1. **Ribosome Protection**: In this mechanism, soluble structural homologues of elongation factors are used to weaken the binding between tetracyclines and their target cellular structure-the ribosome.
2. **Active Efflux**: This mechanism involves actively pumping out the tetracycline out of the cell , against the concentration gradient **(W. Yang *et al.*, 2004)**

Active Efflux: AdeABC, AdeFGH, and AdeIJK

The AdeABC efflux pump is the first efflux system that was described in *A. baumannii*, it consists of three proteins: AdeA (major fusion protein), AdeB (multidrug transporter), and AdeC (outer membrane protein) **(Coyne *et al.*, 2011)**.The expression of AdeABC is governed by the two-component system AdeRS, it is composed of a response regulator (AdeR) and a sensor kinase (AdeS). Modifications to the AdeRS lead to overexpression of AdeABC, which frequently leads to decrease in tigecycline susceptibility. Insertional inactivation with ISAba1 a well-known insertion sequence into the sensor kinase (AdeS), enhances the expression of the adeB gene and the formation of AdeS protein which is truncated and soluble in nature. These mutations led to the higher expression of the AdeABC efflux pump, eventually resulting in tigecycline-resistant strains **(Jo & Ko, 2021)**. Deletion of adeRS also leads to loss of adeB expression. These mutations can also significantly increase the activity of the response regulator AdeR by enhancing its phosphorylation ratio or render AdeS more sensitive to external stimuli, which would contribute to resistance to tigecycline **(Lucaßen *et al.*, 2021)**

CONCLUSION

Acinetobacter baumannii is a nosocomial pathogen that poses a significant threat in healthcare settings. It has evolved into one of the most highly resistant nosocomial pathogens. The widespread resistance of this bacterium is primarily attributed to the overuse of antibiotics and poor antimicrobial stewardship. The multidrug-resistant characteristics of *A. baumannii* are further compounded by mechanisms such as modifications in the outer membrane, the activity of efflux pumps, the presence of resistance genes, and the evolution of various virulence factors. The ability to express multiple virulence genes simultaneously allows the organism to thrive in highly sterile environments. A rapid increase in research addressing these determinants is crucial for uncovering and understanding these complex mechanisms. This will be essential for mitigating the impact of *A. baumannii* on human health. A better understanding of its molecular machinery, through innovative research approaches, is anticipated to be a key focus in future studies.

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CONFLICT OF INTEREST

None declared

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