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Acinetobacter baumannii: An Emerging Threat to Public Health – A Review of Literature

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ABSTRACT
Background: *Acinetobacter baumannii* is a microbe that is fast becoming a danger or threat to public health. Studies have described a rapidly changing epidemiology of the opportunistic pathogen and credited it with increasing importance in the community and healthcare-associated infections. The threat of *A. baumannii* is considered to be of public health significance due to its recent association with increased length of hospital admission, increased mortality, and morbidity, particularly among patients in the intensive care units. The objective of this review is to highlight the characteristics of this emergent pathogen to better understand and curtail it.
Methodology: This review comprises a literature search of chapters in books and journals which gives an insight into the peculiarities of *A. baumannii*. It centers on evolving pathogenesis, epidemiology, antimicrobial susceptibility, laboratory investigations, the molecular basis of resistance, and management of infections caused by the pathogen.
Conclusion: Due to the public health significance of the pathogen, there is an urgent call for increased vigilance and improved knowledge/research-driven approaches to the diagnosis and management of *A. baumannii* infections.

KEYWORDS: *Acinetobacter baumannii*, Epidemiology, Healthcare-associated infections, Public health.

INTRODUCTION

Acinetobacter baumannii, named after Paul Baumann, and, the most important representative of the genus *Acinetobacter*, has been reported to be a Gram-negative coccobacillus, a strictly aerobic, non-fermentative and non-motile bacterium. It appears as a coccobacillus when stationary but takes on a rod form during growth. It repulses total decolorization and can swindle as Gram-positive cocci [1]. Acinetobacter is oxygen-intensive and grows at 20–30 °C on common laboratory media. It is catalase-positive, urease-negative, Voges-Proskauer-negative, methyl-red-positive, citrate-positive, nitrate decrease negative, oxidase-negative, indole-negative, and hydrogen sulfide negative. It is a non-fastidious bacterium with a 39% to 47% DNA G-C concentration [2].
When cultured on selective media, such as Leeds Acinetobacter Medium, and, in the presence of a supplement, it produces pink color colonies [3]. Contrary to the ubiquitous nature of different species of Acinetobacter, which are much of the time segregated from the dirt, water, and creatures, *A. baumannii* is tracked down solely in the clinical environment, especially in intensive care units (ICUs) [4].
It is one of the main opportunistic microorganisms with expanding significance in community and healthcare-associated infections. It has a reduced risk for healthy individuals but generally causes diseases in those with compromised immune systems, particularly in patients in intensive care units. It has resulted in different healthcare-associated infections, which include meningitis, ventilator-associated pneumonia, wound sepsis, endocarditis, soft tissue infections, blood infections, skin infections, urinary tract infections, and others that originate from environments in the hospital [5]. Its ability to cause infections in clinical settings may be connected to its resistance to vital antimicrobial disinfectants and drugs and also its capacity to survive in desiccants [3]. *Acinetobacter baumannii* can be secluded from various sources like water, soil, humans, and animals.
The virulence factors possessed by *A. baumannii* contribute to its pathogenesis. These include; phospholipases, porins, metal acquisition capsular polysaccharides, protein secretion systems lipopolysaccharides, and outer membrane vesicles. *Acinetobacter baumannii* is categorized as an "ESCAPE" (*Enterococcus faecium; Staphylococcus aureus; Clostridium difficile; Acinetobacter*

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baumannii; Pseudomonas aeruginosa and *Enterobacteriaceae*) pathogen – a group of microbes that has an increased level of resistance to antibiotics and it is answerable for most nosocomial diseases [6, 7].

The obtainable shreds of evidence suggest that this pathogen is significant and it is rapidly turning into a significant danger to public health. This is because of its high level of antimicrobial resistance, heterogeneity of its environment, desiccation resistance, its affinity to lead to episodes of infection, and the multifaceted nature of epidemiology.

EPIDEMIOLOGY OF *ACINETOBACTER BAUMANNII* INFECTIONS

The epidemiology of *A. baumannii* infection is frequently complicated due to the coexistence of endemic and epidemic infections, the latter of which is frequently prone to an elevated level of antibiotic resistance. The main breakthrough is that *A. baumannii* infections that are potentially serious, for instance, in patients with bacteremia or pneumonia in the emergency unit, and, who are being intubated, are not associated with a greater death rate or a longer stay in the hospital [8].

However, compared to other opportunistic bacteria such as *Pseudomonas aeruginosa (P. aeruginosa), A. baumannii* is significantly less evolved as shown by an inquiry of the Medline data set executed on 1 April 2005, which uncovered 30,247 references for *P. aeruginosa* versus just 703 for *A. baumannii* [8]. In light of the variety of its habitat, how it accumulates antimicrobial resistance components, its resistance to desiccation, its proclivity to result in infection outbreaks, and its epidemiological complexity, *A. baumannii* appears to be a remarkable microorganism.

In a worldwide study in intensive care units (ICUs), the Acinetobacter infections rate was 3.7% in North America; 4.4% in Oceania; 5.6% in Western Europe; 13.8% in Central and South America; 14.8% in Africa; 17.1% in Eastern Europe; 19.2% in Asia [9, 10]. Ntusi *et al*., [11] revealed that the infection rate is 15% in South African patients who are HIV-positive and 13% in burn care units in Canada [11]. The burden of the diseases caused by *A. baumannii* still stays obscure in Africa, because of limited information [12]. In Nigeria, a prevalence of 14% was accounted for in the ICU of a tertiary medical unit in Southwest Nigeria, while none has been reported in Northwestern Nigeria [13]. A fatality rate of 26% with the possibility of an increase to 45% in patients in ICUs [3] has been reported. In Nigeria, it has been reported that *A. baumannii* was associated with catheter- and blood-related infections, with the possibility of the bacteria developing resistance to carbapenem [12].

PATHOGENESIS OF *ACINETOBACTER BAUMANNII*

The pathogenesis of *A. baumannii* has been credited to a blend of factors and a stockpile of virulence factors operating together to cause an infection. It starts with the outer layer of the bacterial cells which is comprised of many molecular components that communicate with the environment [14]. Acinetobacter possesses the ability to create a wide exhibit of virulence factors, however, some are liable for explicit clinical disorders. In contrast with other Gram-negative bacteria, information is scarce as regards the pathogenesis of Acinetobacter.

Current genome sequencing studies including *A. baumannii* have revealed an immense range of antibiotic drug resistance determinants and a large number of pathogenicity islands [15]. Predictable with the role it plays in pathogenesis, a good number of the islands have genes ensnared in virulence which shows the organism dedicates a prominent part of its qualities to pathogenesis. The biggest island contains components homologous to the Legionella/Coxiella Type IV secretion apparatus. This type IV secretion framework was shown to be significant for virulence in different organisms and subsequently probably assist with the pathogenesis of *A. baumannii* [15].

Furthermore, before a bacterium can be attributed to being pathogenic, proximity should initially be made with a specific host surface through adherence before manifesting virulence factors for colonization [16]. After it has adhered to human cells; *A. baumannii* can incite apoptosis through the external film protein. This protein seems to be limited to the mitochondria, prompting both caspase-independent and –dependent pathways of cell death. Quorum sensing which controls a broad array of virulence factors in numerous Gram-negative microbes has been distinguished in Acinetobacter, demonstrating that this might be a focal system for the auto-induction of different virulence factors [17]. It has been perceived that part of the key contributing element to the increase of nosocomial *A. baumannii* originates from its capacity to stick and colonize biotic and abiotic surfaces, utilizing a difference in methodology presently named 'persist and resist' instead of the customary toxin expression of different microorganisms. This, combined with a similarly frustrating ability to get by in negative circumstances makes *A. baumannii* an imposing pathogen [14].

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The investigation of more unambiguous virulence components in *A. baumannii* has zeroed in on biofilm development, siderophore-mediated iron-obtaining systems, the *A. baumannii* Lipopolysaccharide, adherence, and external membrane protein capability. For *A. baumannii* to flourish in the iron-lacking environment of a human host; it produces low molecular mass ferric binding compounds or siderophores. The capacity of *A. baumannii* to stick and form biofilms on lifeless objects and surfaces makes sense for its outcome in the clinic environment. It showed that biofilm development in *A. baumannii* is related to exopolysaccharide creation and pilus arrangement.

Additionally, some ongoing studies have shown the importance of Toll-like receptor (TLR) signaling and the innate immune response to *A. baumannii*. When compared to wild-type mice, TLR4 gene defective mice showed higher bacterial counts, higher bacteremia, worse cytokine/chemokine responses, and delayed onset of lung inflammation. The key immunostimulatory factor was identified as *A. baumannii* lipopolysaccharide. This was further demonstrated by the diminished effects of *A. baumannii* in mice deficient in CD14, a crucial molecule that facilitates LPS binding to TLR4. These findings were confirmed using human cells, however, in contrast to the mouse model, TLR2 was also acknowledged as an important signaling route. Later studies showed the strong endotoxic capability of *A. baumannii* LPS, which invigorated the proinflammatory cytokines interleukin-8 and tumor necrosis factor-alpha. *Acinetobacter baumannii* endotoxin might prompt an intense inflammatory reaction in the course of infection [18].

Acinetobacter disease has also been associated with immunological homunculus, with antibodies directed against LPS's O-polysaccharide and iron-repressable outer membrane proteins. Although recent genomic and phenotypic studies of *A. baumannii* have identified a variety of virulence factors responsible for its pathogenicity, *A. baumannii* has fewer virulence factors established than other Gram-negative microbes [19].

Virulence factors

The genomic and phenotypic analyses of *A. baumannii* have distinguished a few arsenals of virulence factors working concertedly to cause disease [19]. The factors that add to the pathogenesis of *A. baumannii* are phospholipases, porins, capsular polysaccharides, protein secretion system, lipopolysaccharides, outer membrane vesicles, biofilm formation, and metal acquisition system [20].

Porins

Porins are outer membrane proteins (OMPs) that assume a part in cell penetrability regulation. Due to their broad conveyance, practical pertinence, and established role in both antimicrobial obstruction and virulence, the OMPs have generated a lot of interest. The porins of *A. baumannii* incorporate Omp22, OmpA, Omp 33-36 kDa, OprD-like OMPs, CarO, TolB, AbuO, Oma87/BamA, NmRmpM, DcaP, OprF, CadF, and so on [20]. Furthermore, developmental conditions such as temperature, oxygen content, osmolarity, and media components influence the expressions of porins in *A. baumannii* [21].

The outer membrane protein-A (OmpA), which is a Beta barrel porin is also abundant in the external membrane. Outer membrane protein-A is a very much described virulence factor in *A. baumannii*, with various captivating natural properties found in *in-vitro* model frameworks [19]. Besides, OmpA has been associated with the self-death (apoptosis) of epithelial cells via mitochondrial targeting and it is likewise engaged with *A. baumannii* antimicrobial resistance. Disrupting the ompA gene has additionally been displayed to diminish the minimum inhibitory concentrations (MICs) of a few antimicrobials (aztreonam, nalidixic acid, and chloramphenicol), suggesting that OmpA is engaged with the expulsion of antibiotics from the periplasmic space through the external layer and couples with internal membrane efflux systems [22]. Outer membrane protein-A improves *A. baumannii* persistence and survival ingenuity by working with surface motility and biofilm arrangement [19]. It likewise directs the biogenesis of external membrane vesicles, making the OmpA protein a promising target for the improvement of novel antibacterial and preventive procedures [20].

Albeit the commitment of Omp22 to *A. baumannii* pathogenicity is not conclusive, it has been recognized as a comparatively safer antigen for creating viable immunizations against *A. baumannii* diseases [23]. Mice getting both passive and active Omp22 vaccines live longer, have lower bacterial burdens in the peripheral circulation, and have decreased serum levels of inflammatory chemokines and cytokines [23].

The 33-to-36-kDa Omp protein (Omp33-36), which functions as a water entry channel, is another external membrane porin and is associated with *A. baumannii* cytotoxicity. The human lung epithelial cells' adhesion, invasion, and cytotoxicity are all reduced by the omp33-36 deletion strain. Erasure of the omp33-36 quality lowers mortality and bacterial concentration in the lungs and spleen in a murine sepsis model [24]. Omp33-36 and antibiotic resistance are related, and, episomal expression of Omp33-36 lowers the

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MICs of imipenem and meropenem in *A. baumannii* strain JC10/01, which shows resistance to carbapenem antibiotics due to the loss of Omp33-36.

The 8-stranded beta barrel-shaped external membrane channel protein known as carbapenem susceptibility porin (CarO), which is divided into two subtypes called CarOa and CarOb, mediates the in-flow of β lactams (particularly imipenem) into *A. baumannii* but lacks a continuous passage [25]. It was initially discovered in *A. baumannii* isolates that were susceptible to imipenem (IMP) but became resistant after losing a 29 kDa protein. Contrary to these findings, a liposome model framework surrounded with CarO was found to be capable of transporting carbapenem antibiotics but not small amino acids like glycine and ornithine [26].

The OprD is an orthologous protein of a porin involved in the transfer of an important amino acid and the antibiotic imipenem in *P. aeruginosa*. *Pseudomonas aeruginosa* OprD crystallographic studies revealed a monomeric 18-abandoned -barrel structure with very little pore constriction [27]. Its potential capability in *A. baumannii* is supported by the structural domain amino acid structure between *A. baumannii* and *P. aeruginosa* OprD porins. It was discovered for the first time during external membrane analyses of isolates of carbapenem-resistant *A. baumannii* [27].

Lipopolysaccharides (LPS) and Capsular Polysaccharides

The *A. baumannii* envelope is linked to several elements that raise pathogenicity in addition to OmpA. The pathogenicity factors for *A. baumannii* among these components or elements include capsular exopolysaccharides and LPS. The K locus, a maintained gene cluster found in the majority of *A. baumannii* infection isolates from patients, may regulate the formation of surface capsular polysaccharides [28].

A mouse septicemia model shows that mutations in the quality of pglL or pglC, which are responsible for generating the O-pentasaccharide found in glycoproteins and capsular polysaccharides, also reduce lethality and create unique biofilm architectures. Capsular polysaccharides were then proposed as the primary target for preventive antibody-based interventions and passive vaccinations [29]. *Acinetobacter baumannii's* resistance to antimicrobials is related to its capsular polysaccharides. Mutants with reduced typical protection from peptide antimicrobials are missing in capsular polysaccharides. Additionally, the synthesis of capsular polysaccharides is increased by antibiotics [28].

In a mouse model of systemic infection, antibiotic-induced capsular polysaccharide production results in greater protection from extinction by host complement as well as higher pathogenicity. After exposure to an antibiotic, increasing capsule manufacturing depends on transcriptional expansions in K locus gene expression. The two-part regulatory system of the bfmRS regulates this K locus' expression [28]. A gene called bfmR is significant because it is predicted to arise in human ascites, an ex vivo model of infection, and the persistence of the infection in the lungs of mice with pneumonia. Similarly, bfmS which helps biofilms to develop binds to eukaryotic cells and defends against human serum. The bfmR-mediated protection from the complement-mediated bactericidal movement was discovered, as well as its protection from clinically significant antimicrobials, such as meropenem and colistin [29].

Most Gram-negative microbes have a prominent part of the external leaflet of the outer membrane called lipopolysaccharides (LPS), which is an immunoreactive molecule that makes macrophages produce interleukin 8 and tumor necrosis factor in a Toll-like receptor 4 (TLR4)- dependent way. It is made out of an oligosaccharide center, endotoxic lipid-A moiety, and a redundant O-antigen [30]. In *A. baumannii*, LPS assumes a significant part in its survival and virulence. In a rodent model of soft tissue infection, mutant cells lacking LpsB glycosyltransferase possess an exceptionally shortened LPS glycoform encompassing simply 2 carbohydrate residues bound to lipid A, which results in diminished resistance to or protection from human serum [19].

LpxC, a protein involved in lipid-A production, can be suppressed to prevent *A. baumannii* LPS from activating TLR4, although this does not prevent bacterial growth. Limiting LpxC in a mouse model causes *A. baumannii* to survive by improving opsonophagocytic extinction and reducing serum LPS inflammation and concentration, which completely protects animals from lethal infection [30]. These findings suggest that inhibiting LPS synthesis is a useful strategy for discovering novel antimicrobials. Modifying LPS increases antimicrobial resistance [20].

Phospholipase

A predicted lipolytic enzyme for the breakdown of phospholipids is phospholipase. This contributes to the pathogenicity of many bacteria, including *Listeria monocytogenes*, *Clostridium perfringens*, and *P. aeruginosa* [31]. Phospholipase D (PLD), phospholipase C (PLC), and phospholipase A (PLA) are the three different types of phospholipases that have been identified based

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on the cleavage site. Phospholipase A hydrolyzes unsaturated fats from the glycerol spine, whereas PLC removes the phosphorylated head from the phospholipid. Phospholipase D is a transphosphatidylase that selectively divides phosphate molecules at the head group. It is noteworthy that PLC and PLD have been discovered to be virulence factors in *A. baumannii*. Phospholipid degradation affects the stability of host cell layers, and the isolated head group can obstruct cell signaling, altering the host immune response [31].

Outer Membrane Vesicles (OMVs)

Outer Membrane Vesicles (OMVs) are round vesicles, with a width of 20-200 nm emitted by the external layers of different Gram-negative pathogenic microorganisms [29]. They are distinguished as conveyance vehicles for bacterial effectors to host cells and are comprised of phospholipids, LPS, external membranes, periplasmic proteins, and DNA or RNA. It simultaneously circulates an assortment of virulence factors to the inside of host cells, permitting microbes to cooperate with the host not having immediate contact between bacteria and host cells [32].

Numerous *A. baumannii* strains also release OMVs that contain virulence factors such as OmpA, phospholipases, and proteases. *Acinetobacter baumannii's* outer membrane vesicles connect with host cells and deliver bacterial effectors to them through lipid pontoons, which results in cytotoxicity. In epithelial cells, cleaned *A. baumannii* ATCC 19606 OMVs induce the expression of pro-inflammatory cytokine genes in a dose-dependent manner [32]. Proteinase treatment of OMVs has not been shown to significantly increase the expression of pro-inflammatory cytokine genes, suggesting that OMV membrane proteins are responsible for inducing a potent immune response [32]. A few reports have revealed that OMVs from *A. baumannii* could be utilized as an acellular vaccine to support immunity because of the significance of OMVs in *A. baumannii* virulence [20].

Biofilm

Biofilm formation is another capacity of *A. baumannii* which might assume a role during the period of colonization. Biofilm is an aggregate or colony of microorganisms that structure or forms a self-created network of extracellular DNA, polysaccharides, and protein that binds the cells to each other or a surface. The cells that structure the biofilm vary from their planktonic partners concerning morphology, digestion, and physiological qualities. Biofilms help the microorganisms in opposing disinfection while additionally permitting partaking cells to exchange resistance genes, further enhancing the persistence of the microbe [33]. Biofilm development assumes a significant part in avoiding the immune system by *A. baumannii*, and pili are fundamental for *A. baumannii* adherence to and biofilm development on abiotic surfaces as well as virulence. It additionally adds to clinical gadget-related infection. Treatment of the imipenem-resistant *A. baumannii* isolate with imipenem prompts the exhibition of significant genes engaged with type IV pili synthesis, recommending that the capacity to overproduce pili gives a biological benefit to *A. baumannii* [20].

THE MOLECULAR BASIS OF RESISTANCE IN *ACINETOBACTER BAUMANNII*

One of the important issues confronting emergency clinics, clinicians, and military medical care staff concerning *A. baumannii* today is multi-drug resistance (MDR). The Center for Disease Control (CDC) portrays any species resistant to at least 3 classes of antimicrobials as MDR. *Acinetobacter baumannii* has an extraordinary capacity to procure antimicrobial resistance.

World Health Organisation (WHO) to limit the consequences of MDR microorganisms and develop better treatment approaches, its report, “Global Strategy for Containment of Antimicrobial Resistance” described two pillars of action. The first emphasizes preventing the dissemination of bacterial resistance, and the second, avoiding the accelerated emergence of new forms of resistance [34].

A lot of strains of *A. baumannii* are exceptionally impervious to many clinically accessible antimicrobials. Antimicrobial resistance components portrayed for *A. baumannii* are noteworthy, equaling those depicted for other non-fermentative Gram-negative microbes. *Acinetobacter baumannii* has an assortment of antibiotic resistance mechanisms, as well as target destination adjustments, β-lactamases, efflux pumps, aminoglycoside-modifying enzymes, and permeability defects [20]. The fast worldwide rise of *A. baumannii* strains impervious to all β-lactams, including carbapenems, exhibits the organism's capacity to adjust rapidly to variations in particular ecological tension. The rise of resistance mechanisms in *A. baumannii* has progressively diminished the number of antimicrobial classes accessible in clinical practice to treat *A. baumannii* infections [20].

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The capacity to upregulate inborn resistance systems and obtain foreign determinants has procured *A. baumannii* a great deal of regard. An 86-kb resistance island, one of the biggest at any point depicted, was found after entire genome sequencing of a hospital epidemic *A. baumannii* strain was tracked down in France (AbaR1). Of the 88 anticipated open reading frames (ORFs) inside this genomic district, 82 were anticipated to have started from other Gram-negative bacteria, for example, *Pseudomonas sp*., *Escherichia coli*, and *Salmonella sp*. [15].

Additionally, this location's GC content was 52.8% as opposed to the extra chromosome's 38.8%, indicating a plausible unidentified source. Fifty-two resistance genes were generally found, and 45 (86.5%) of these were restricted to the AbaR1 resistance island. Three class 1 integrons, transposons, and insertion sequence (IS) components, among other expansive host-range adaptable hereditary components, were identified as hereditary environmental factors of these resistance determinants, providing additional evidence of genetic wantonness.

Contrasted with an *A. baumannii* strain from a similar geographic district (SDF), a comparable structure was known (AbaG1) in the homologous ATPase-like ORF, however, it was without any trace of resistance determinants [15]. To decide if this problem area is preserved among *A. baumannii* strains, more than 22 clinical strains were screened. Seventy-seven percent had a flawless ATPase ORF yet likewise had a multidrug resistance phenotype, demonstrating that resistance determinants can be embedded into different regions of the genome. It is not unexpected that *A. baumannii* has become impervious to various antimicrobials as it is barraged by drugs and is in close relationship with other Gram-negatives in the clinical setting. Accordingly, it has obtained a great exhibit of resistance components in addition to its characteristic capacities. *Acinetobacter baumannii*, alongside other Gram-negative microbes, can procure newly discovered systems through transposons, integrons, and plasmids. Studies have shown that numerous flare-up strains of *A. baumannii* have a class 1 integron which is responsible for the moving and enrollment of numerous resistance qualities and has been displayed to be available in 88% of biofilm-forming *A. baumannii* strains. A resistance instrument found in *A. baumannii* and other Gram-negative microbes are enzymes, in which the qualities coding for these proteins can be passed from one cell to another. A typical protein is β-lactamase, which hydrolyzes and presents resistance to cephalosporins, penicillins, and carbapenems [35].

Different enzymes *A. baumannii* can secure include acetyltransferases, nucleotidyltransferases, and phosphotransferases which all elevate resistance to aminoglycosides and fluoroquinolones. Genes that are mutated can likewise be obtained from different microbes. Mutations can modify the bacterial focuses of antimicrobials, diminishing their partiality for the microorganisms and raising the MIC for the medication. An illustration of a point mutation would be a transformation in the gyrA and parC qualities. Assuming that there were point mutations in the two genes, the isolate would have a raised MIC for all suitable fluoroquinolones [35].

Acinetobacter baumannii likewise has its very own intrinsic components. These incorporate efflux pumps and porins. Porins are particular OMPs that license the entry of little metabolites like ions, sugar, and amino acids. More porins in the external membrane of a cell enable the cell further penetrability into specific antimicrobials. It is extensively less porous than other Gram-negative microbes, and scientists have recommended that the small number and size of porins in the external membrane could be a justification for the innate resistance that can be attributed to *A. baumannii.* Likewise fascinating is the perception that there are three (3) porins lacking in *A. baumannii* strains impervious to imipenem, a rare example of medications still effective against most strains. Further exploration is expected to explain the importance of backing these various porins and their relationship with antimicrobial resistance (AMR). An additional noteworthy component *A. baumannii* has is the efflux pumps. They can effectively eliminate antimicrobials from the bacterial cell, forestalling the microorganisms' openness to it. The activity of efflux pumps related to porins is accepted to be an extremely strong resistance mechanism [36]. To place these instruments into a better viewpoint, if an *A. baumannii* isolate gained mutations or transformations in both the parC and gyrA qualities and had efflux overexpression as well as a loss of porins, it means that the isolate would be exceptionally impervious to every single accessible medication: the clinicians most dreaded fear.

The table below depicts the antibiotic resistance components and mechanisms involved in *A. baumannii* as detailed by Chakravarty [37].

Resistance mechanisms detected in *Acinetobacter baumannii*

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Mechanism of action	Classification	Classes of antibiotics targeted
Enzymatic modification of antibiotic molecules	Aminoglycoside modifying enzymes	Aminoglycosides
	Ambler β-lactamase enzyme classes:	
	Class A: extended-spectrum beta-lactamases (ESBL)	β-Lactams,carbapenems, cephalosporins, penicillins
	Class B: metallo-beta-lactamases (MBL)	
	Class C: Acinetobacter-derived cephalosporinases (ADC)	β-Lactams,carbapenems, cephalosporins, penicillins
	Class D: carbapenem-hydrolyzing class-D beta-lactamases (CHDL)	
Altering the target sites or cellular functions	Altering the host cell envelope structures: By Phospholipase action	
	Altering lipids and polysaccharides	Aminoglycosides, tigecycline, fluoroquinolones, colistin
	Biofilm generation, surface capsular proteins,	Polymyxin, colistin
	Activating response regulators (TCS): AdeRS, BaeSR, pmrAB, BfmRS, GacSA	
	Activating metal acquisition systems: Iron, Zn, Mn	Aminoglycosides, tigecycline, fluoroquinolones, colistin Polymyxin, colistin
	Altering bacterial targets by point mutations and topoisomerase mutations:	
	Penicillin-binding proteins (PBP)	Imipenem
	DNA gyrase gyrA, parC	Fluoroquinolones
	16sRNA methylation, dihydrofolate reductase	tetracycline, trimethoprim
Limiting the access of antibiotics to the target sites	Upregulation of multidrug efflux pumps to expel antibiotics	
	RND family pumps	
	MATE family pumps	Aminoglycosides, tigecycline
	MFS family pumps	fluoroquinolones, imipenem,
	SMC family pumps	erythromycin, chloramphenicol

HOST-PATHOGEN REACTIONS

Tentatively, *A. baumannii* is perceived by the immune system at the early (within hours) phase of infection. The primary line of host-microorganism interactions entails innate immune pattern recognition receptors (PRRs) which senses preserved designs of microbes, called pathogen-associated molecular patterns (PAMPs). Damage-associated molecular patterns (DAMPs) are likewise discharged by host cells, like PAMPs that are additionally detected by PRRs. Toll-like receptors (TLRs) are the most explored group of PRRs, and, they include TLR2 and TLR4 which are important cell surface sensors of bacterial infections [38]. Those reactions, nonetheless, may not necessarily in every case be adequately viable to curb *A. baumannii* infection, specifically when exceptionally

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virulent *A. baumannii* strains are involved. Moreover, *A. baumannii* may evade the host-resistant systems to establish an infection successfully [39].

Furthermore, recent research suggests that downstream inflammasomes have a role in the *A. baumannii* infection, with macrophages and neutrophils playing a significant role as well as soluble antimicrobial factors [40]. Tumour necrotic factor and IL-1 supporter are released as a result of the PRR signaling cascades triggered by bacterial recognition, which heightens the inflammatory response. An important pro-inflammatory cytokine called interleukin 1 (IL-1) regulates the amount of inflammation the body experiences as a result of infection. For pro-IL-1 to develop into the secretory kind of "IL-1," the proteolytic activity of caspase-1, which is started by a multi-protein complex termed "inflammasome," is also anticipated. The inflammasome subgroups include AIM2 (absence in melanoma 2), NLRP3 (NLR family pyrin domain-containing 3), NLRC4 (NLR family CARD domain-containing protein 4), and others. [41].

The involvement of NLRP3 in various problems, including microbial infections, has been very much investigated. Viral, bacterial, or parasitic elements, extracellular ATP, receptive oxygen species (ROS), potassium (K^+) efflux, and lysosomal harm are notable to enact the NLRP3 inflammasome [41]. Moreover, the 'canonical inflammasome pathway' alludes to the arrangement of the NLRP3 inflammasome in light of PRR signaling and PAMP, for example, LPS or DAMP sensing.

Studies using host-microbe interaction models have been utilized to more readily comprehend the pathogenesis and virulence of *A. baumannii*, especially regarding its intimate interaction with the host during infection. It goes from *in vitro* to *in vivo* models rendering the ability to distinguish novel bacterial virulence factors, assess novel medications, and host immune reactions [14]. Animal models, specifically, have been a mainstay in the investigation of *A. baumannii* pathogenesis, particularly because of the wide exhibit of clinical symptoms expressed by the microorganism. While using these models, there are two key difficulties: the capacity to accurately and precisely mimic human sickness, and the microbes strains utilized in these interaction investigations [14]. Chen [39] expressed that most of the current information on the host's innate reaction to *A. baumannii* infection comes from mouse models of infection and also from *in vitro* examinations using human and murine primary cells or cell lines. Innate immune cells and proinflammatory cytokines and chemokines have been identified as basic in the host guard against *A. baumannii* infection. Furthermore, most early models required immunosuppressive drugs or mucin to upgrade the infection, which is probably going to confound the effect of the innate resistant reaction [39]. All the more critically, the importance of those exploratory findings to human infections still cannot seem to be determined. Therefore, critical endeavors are expected to explain the host's innate anti-*A. baumannii* mechanisms.

In-vivo models

Mammalian model: Murine models have been the most well-known choice for mammalian *in vivo* examinations. Greg Harris and others [42] used mouse models to study *Acinetobacter baumannii* infections [42]. These examinations were originally intended to assess the potency of antibiotics in the course of Acinetobacter infection but have since moved to examine bacterial pathogenesis, host response, and immunity, as well as novel therapeutic strategies that are alternatives [43, 44]. However, though these examinations would never completely mimic the human sickness infection process, they have produced a great deal of information to improve our understanding of bacterial pathogenesis and give a clearer image of how to move toward powerful infection control [14]. Besides, the extraordinary variety and accessibility of murine models combined with cost and different use cases set it as a staple infection model of choice. Furthermore, as *A. baumannii* can result in a seriously wide scope of infections, a reasonable determination of murine strains must be directed to best gain the nearest similarity to infections in people. A/J, BALB/c, C57BL/6, and Swiss Webster mice are probably the most predominant inbred and outbred strains that have been efficiently utilized [45].

Pneumonia model: Studies on lung infection using murine models have consistently improved, as pneumonia is the most well-known clinical sign of *A. baumannii* infections. Joly-Guillou and partners utilized this model for the first time in 1997 to test the viability of imipenem against acute *A. baumannii* pneumonia [46]. The reason for this model is to inject bacteria into the mouse to induce inflammatory reactions that are under acute pneumonia. Until now, two methodologies for eliciting this insusceptible immune reaction have been distinguished: intra-tracheal and intranasal introductions of microorganisms. The previous involves cannulating the trachea of sedated mice inoculated with bacterial suspension with a blunt-ended needle, while the last option includes bacterial suspension applied to the nostrils as the mouse inhales, breathing the suspension in [45, 46]. Moreover, the pneumonia model has likewise been utilized to test the viability of vaccines, with vaccination of immunocompetent mice before pneumonia infection resulting in a decrease in bacterial burden post-infection as compared to the non-vaccinated group [43].

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Sepsis model: The second most common clinical symptom of nosocomial *A. baumannii* infections is bacteremia, which is primarily brought on by bacterial LPS activating the human TLR4 receptor. In severe cases, this could be the result of bacteria from a previous pneumonic illness spreading throughout the body [14]. This aspect of sepsis has been demonstrated in mouse pneumonia models, where depletion of alveolar macrophages and neutrophils resulted in higher mortality and morbidity with extrapulmonary bacterial spread [47]. The mouse strains used in sepsis models up to this point are nearly identical to those used in pneumonia models, which primarily required the application of two primary techniques. The murine peritoneal sepsis model was the first and the most generally utilized, and it was broadly utilized in different microorganisms like *K. pneumoniae* before being taken on in *A. baumannii* antibiotic and virulence studies [24]. This model has been utilized broadly to determine minimum lethal doses (MLDs) part of which describe the different clinical strains mainly for pathogenesis and virulence studies, which, when contrasted with ATCC® reference strains, help to feature the development undertaken by the microbe over many years. Inducing system infection by delivering the microorganism retro-orbitally is an uncommon methodology that has the additional advantage of lowering complications and discomfort in the model, but it requires an exceptionally skilled operator [14].

Non-mammalian models: Although mammalian models are as yet the best ways of investigating host microorganism interactions, non-mammalian models have as of late gained prominence because of their different benefits over their mammalian partners [14]. Non-mammalian models are not constrained by moral or ethical limitations, and, are more affordable than mammalian models. These factors empower scientists to utilize huge quantities of microbes in a single study, making high-throughput screening for bacterial virulence elements, toxins, and bacterial pathogenicity conceivable. Such investigations can use a huge number of hosts as well as a different scope of bacterial strains, speeding up the portrayal of clinical strains as they arise [14].

Some of the models that have been used up to now include *Danio rerio* (zebra fish), *Caenorhabditis elegans* (nematode), *Galleria mellonella* (greater wax moth), and *Dictyostelium discoideum* (amoeba). The tiny soil-dwelling nematode *Caenorhabditis elegans* (*C. elegans*) measures around 1 mm in length when fully grown. As a bisexual, it reproduces quickly, in about 3 days, and can produce up to 400 progeny from a single adult. The study of the bacterial pathogenesis of *Listeria monocytogenes*, *Salmonella enterica*, *Burkholderia pseudomallei*, and *Legionella pneumophila* revealed that *C. elegans* is an attractive host for infection concentrates due to its all-encompassing portrayed genome, anatomical simplicity, and transparent body [48].

Dictyostelium discoideum, which has been utilized with *C. elegans*, is a one-celled amoeba that has likewise been proposed basically for its capacity to phagocytose microorganisms, a capacity that fits being utilized as a model for human macrophage-bacterial interactions [48]. One of the significant benefits is its capacity to develop at 37°C, allowing for more prominent relevance or pertinence to bacterial pathogenesis in human hosts, as well as the recognizable proof of mutant *A. baumannii* strains through co-culturing of one-celled amoeba with microscopic organisms. Since bacteria generally grow faster than a one-celled amoeba, they could form colonies first before being consumed by one-celled amoeba, which brought about noticeable plaques on the bacterial lawn, allowing *A. baumannii* to be identified [14].

In-vitro model: Various studies designated at clarifying bacterial virulence and pathogenesis have utilized *in vitro* models in addition to *in vivo* models to secure a preliminary insight into the intricate host-pathogen interactions. These studies have given the foundation for some *in vivo* trials to happen with complementing information to approve any findings, as they are easier and more practical. Since pathogens connect with a given host after fruitful passage, epithelial mucous layer cells have turned into the standard in most *in vitro* examinations [14]. This is valid for a great many illnesses and surfaces on the human body, and, assessing this interaction gives pivotal information about microbe virulence characteristics, immunomodulation, and antimicrobial activities as the infection propel [49].

In the majority of the *in vitro* experiments, epithelial cells from a particular piece of the body are co-infected with a bacterial strain well defined to the site of infection. This is the initial move toward determining the adherence and cytotoxicity properties of the microorganism. *In vitro* models are particularly significant for studying the main host immunological reaction to the presence of microbes, as co-infection and bacterial adherence to the host sets off an inflammatory reaction focused on the enlistment of immune cells required for bacterial leeway or clearance. However, the majority of the immune reaction/response to an unfamiliar microbe follows a fundamental example, a few explicit bacterial surface proteins are fit for clarifying a varied reaction that gives hints to the molecular mechanism behind bacterial pathogenesis, which can contrast based on infection site [50]. This variety can be illustrated by the need of the pathogen to adjust to a given climate by producing virulence patterned to its survival requests, as confirmed by biofilm and motility varieties seen in *A. baumannii* segregated from blood or sputum [50].

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In ongoing infection research using *in-vitro* models, a host cell line co-refined with immune cells has been utilized. It has been laid out using murine models that immune cells are basic during the early phases of infection, producing pro-inflammatory cytokines like IL-6, TNF-α, MIP-2, and MCP-1 in the lungs which upholds the clearance of *A. baumannii* infection [47]. *In-vitro* examinations employing simply immune cells, for example, those done by Qiu *et al*., [50], assist with elucidating the critical role performed by the immune cells, and these are involved in the innate immune system's foremost reaction to infection with phagocytosis detected within 10 minutes of co-incubation.

CLINICAL IMPACT OF THE ORGANISM

Acinetobacter baumannii, previously viewed as a low-virulence commensal bacterium, has turned into a successful pathogen [2]. It represents no danger to healthy individuals, yet it can cause severe infections in immunocompromised individuals and those in the intensive care units. It has developed from bench to bedside, producing, soft tissue and skin infections, wound infections, secondary meningitis, and urinary tract infections, among other extreme nosocomial infections [19]. Nonetheless, the main infections, with the most noteworthy death rates, are circulation system infections and ventilator-related pneumonia. Infection rates are higher in patients suffering from underlying diseases or people who have gone through major surgeries [4].

Intravascular catheters, open injuries, and mechanical ventilators are risk factors for infections by *A. baumannii*. Early identification of patients exposed to risk factors favors a positive therapeutic outcome. In healthcare-associated infections associated with imipenem-resistant *A. baumannii* strains, Lee and collaborators demonstrated the following as significant risk factors: previous intensive care unit (ICU) stay (OR, 21.54; 95% CI, 10.73 to 43.23) and previous exposure to third-generation cephalosporins (OR, 2.11; 95% CI, 1.13 to 3.95) or imipenem (OR, 9.18; 95% CI, 3.99 to 21.13), increased time at risk or days spent from admission to positive–culture date for *A. baumannii*-positive patients (OR, 1.02; 95% CI, 1.002 to 1.03), and age (OR, 1.03; 95% CI, 1.01 to 1.05) [52]. Lemos and collaborators described the male sex as a significant risk factor for MRAB-C bacteremia ($p < 0.001$; OR 3.39, 95% CI (1.76–6.54)) [52]. Other studies have introduced advanced age, renal failure, and prolonged hospital stay as important risk factors for the development of nosocomial *A. baumannii* infection [53].

As regards risk factors for mortality, inappropriate empirical antibiotic therapy, high APACHE II score, the severity of underlying disease, time of stay in the ICU, presence of fever and/or hypotension at the time blood sample for culture was obtained, and mechanical ventilation has been reported as significant. It must be noted that a high mortality rate has been associated with infections caused by carbapenem-resistant *A. baumannii* strains [54].

LABORATORY DIAGNOSIS OF *ACINETOBACTER BAUMANNII*

When dealing with a hospital-acquired infection, prompt and adequate treatment is critical. The microbe causing the infection should be recognized immediately to initiate appropriate treatment. Acinetobacter is Gram-negative and in the coccobacillus structure, yet during times of rapid development, it may be rod-shaped. It is hemolytic, oxidase negative, catalase positive, and indole negative. Kulah *et al*., [55] detailed that in light of its capacity to utilize numerous sources of nutrition, it tends to be cultivated on standard laboratory media and will even grow at 44°C. The genus will be distinguished using traditional laboratory techniques, but not the species [55].

There are robotized ways accessible today for quick and precise identification of an isolate at the species level. These strategies are phenotypic, relying on biochemistry and assimilation tests, which are typically performed manually, to distinguish the specie and genus of the microorganism quickly. To distinguish *A. baumannii* isolate, several analyzers that could be utilized are Vitek 2 (bioMérieux, Marcy l'Etoile, France) and Microscan WalkAway (Dade Behring, West Sacramento, CA). Notwithstanding, while these analyzers will distinguish the isolate as *A. baumannii*, they are detecting the *A. baumannii* complex. In any case, these analyzers have the additional advantage of automated susceptibility testing, which can assist the clinician in getting the best treatment choices [55].

One technique for distinguishing or identifying bacteria is molecular testing. Molecular testing can identify an isolate down to the genotype. Two of the molecular techniques utilized in laboratories today are 16s rRNA sequencing and pulsed-field gel electrophoresis (PFGE) [56]. Others are genomic fingerprinting techniques that have been projected and these include, ribotyping, PCR-based fingerprinting techniques like redundant extragenic palindromic succession-based PCR (rep-PCR), RNA spacer fingerprinting, enhanced ribosomal DNA limitation examination, and enhanced piece length polymorphism examination [10].

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Acinetobacter species can also be identified using brand-new techniques, such as grouping studies of the rpoB, gyrB, and 16S-23S ribosomal intergenic spacers [57].

ANTIMICROBIAL SUSCEPTIBILITY OF *ACINETOBACTER BAUMANNII*

Acinetobacter baumannii has the propensity to develop resistance to antibiotics therefore current treatment strategies remain limited. Beta-lactam antibiotics are the preferred drugs of choice for susceptible *A baumannii* infections. Carbapenems have become an increasingly critical therapeutic option for *Acinetobacter* infections because of increasing resistance to other antibiotics; however, there has been increasing resistance to carbapenems both in the United States and globally [58]. *Acinetobacter baumannii* is intrinsically resistant to many antibiotics, therefore relatively few antibiotics are active against it [59].

First-, second-, and third-generation cephalosporins, macrolides, and penicillins generally have little or no anti-*Acinetobacter* activity. Furthermore, their use may predispose to *Acinetobacter* colonization. However, some strains are sensitive to cefepime, ceftazidime, and sulbactam-containing beta-lactam/beta-lactamase–inhibitor drugs [60]. Antibiotics to which *A. baumannii* is susceptible to meropenem, colistin, polymyxin B, amikacin, rifampicin, minocycline, and tigecycline [61]. Monotherapy and combination therapy have been used successfully in the treatment of *A. baumannii* infections (e.g., amikacin, minocycline, or colistin ± rifampicin). Combination therapy is often suggested for therapy but there is no conclusive data to depict lower failure rates or lower rates for resistance development. However, combination therapy can be considered for empiric therapy when the local rates of antimicrobial resistance to certain antibiotics are high or when the isolate is resistant to several classes of antibiotics.

Acinetobacter baumannii has a diverse array of innate and acquired resistance determinants, which has attracted scientific attention. According to the Infectious Diseases Society of America (IDSA), *A. baumannii* is one of the "red alert" microorganisms that seriously jeopardize the effectiveness of our antibiotic arsenal [62]. Before the 1970s, several antibiotics, such as tetracyclines, aminoglycosides, and beta-lactams, may be used to treat Acinetobacter infections [16]. However, *A. baumannii* has developed resistance to many antibiotics [2].

Treatment of *A. baumannii* infections should be based on the results of thorough antibiotic susceptibility testing due to the diversity and range of resistance determinants in *A. baumannii*. The choice of an antibiotic for empirical treatment is difficult and should be based on institutional-level susceptibility data at the time. Carbapenems have so far been regarded as the medication for severe *A. baumannii* infections. However, even though this class of antibiotics is effective against the vast majority of *A. baumannii* strains worldwide, its clinical usefulness is steadily being threatened by the emergence of both enzymatic and membrane-based components of resistance. Liang and collaborators analyzed clinical isolates of *A. baumannii* in which 73.6% of such isolates were found to be resistant to quinolones (ciprofloxacin and levofloxacin), 71.3% to sulfonamides, and more than half (50–70%) to cephalosporins (cefazidime and cefepime), beta-lactam/beta-lactamase inhibitor combinations (tazobactam–piperacillin), and carbapenems (doripenem, imipenem, and meropenem). However, only 26.7% demonstrated resistance against the glycycline antibiotic tigecycline [63]. No resistance to colistin was observed in another study conducted by Chen and other collaborators [64].

Effective Antibiotic Therapies against *A. baumannii* according to Therapeutic Groups and Isolated Strains in Specific Clinical Scenarios.

		Effective Antibiotic Therapy
Isolated strains in specific clinical scenarios	Carbapenem- and sulbactam-resistant strains.	Doxycycline or minocycline, which in turn is more effective
	Carbapenem-resistant strains.	TMP-SMX
	MDR strains in the ICU.	Tigecycline.
Therapeutic groups	Synergistic therapeutic combinations with β-lactamase inhibitor sulbactam.	Sulbactam/cefepime,sulbactam/meropenem,sulbactam/amikacin, sulbactam/rifampin,sulbactam/ticarcillin–clavulanate, sulbactam/ampicillin, sulbactam/colistin [65], and sulbactam/cefoperazone [66].

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		Effective Antibiotic Therapy
	Synergistic therapeutic combinations with polymyxin E (colistin).	Colistin/carbapenem[67],colistin/minocycline,colistin/tigecycline, colistin/rifampin [68], colistin/sulbactam [65], colistin/daptomycin [69], colistin/fusidic acid [70], and colistin/teicoplanin [69].
	Last-line therapeutic scheme.	Polymyxin E (colistin) in combination with rifampin or polymyxin B with tigecycline
	Alternative against increasing antibiotic resistance.	Phage Bφ-C62 [71].

ADJUNCTS TO ANTIMICROBIAL THERAPY

Bacteriophage therapy

The increase in MDR bacteria has rekindled interest in the use of bacteriophage, a virus that infects and kills bacteria, as a therapeutic agent [20]. Multidrug-resistant *A. baumannii* infections have been treated with a variety of lytic *A. baumannii* bacteriophages, including B-C62 and vB Ab-M-G7 [20].

Endolysins

Endolysin encoded by bacteriophages has also been considered. Endolysin damages the bacterial host's cell walls and constitutes a unique class of antibacterials with an exceptional mode of action. When it is combined with colistin, endolysin from *A. baumannii* bacteriophage ABP-01 degrades the cell wall of *A. baumannii* strains and intensifies antibacterial action. However, despite this, the majority of Gram-negative bacteria are resistant to endolysins due to their protective exterior barrier.

Endolysins have therefore recently been modified with specific external membrane-destabilizing peptides to acquire the ability to infiltrate the exterior layers to combat this problem. These endolysins are referred to as "artilysins" [72]. A few engineered artilysins have been developed to combat MDR-AB, and these have proven to be very potent antimicrobial substances. The diversity of the phage population has been assessed using viromes, endolysins, and CRISPR spacers. These discoveries might help in the creation of a powerful endolysin to fight MDR-AB [72].

Antimicrobial peptides

American alligator plasma peptide and antimicrobial peptide dendrimer G3KL are two peptides that demonstrate antibacterial action against MDR-AB in vitro. However, there are several substantial disadvantages to using antimicrobial enzymes or peptides. These include short serum half-life and higher cost of production compared to other substances [20].

Human microbiome restoration

Research into bacterial interference in non-epidemic situations was trialed in 1967 in an attempt to halt epidemics in newborn nurseries of virulent species of *Staphylococcus aureus* through the deliberate introduction of interfering strains of low virulence *S. aureus* 502A [73]. Despite its effectiveness in more than 4,000 infants, following a fatal infection of a newborn, the “routine” use of bacterial interference programs in non-epidemic situations was halted [74]. This project was well ahead of its time but can provide useful evidence and support for potential areas of further research in the use of recolonization therapy with non-virulent microbes.

An example of microbiome restoration is faecal microbiota transplantation (FMT) which has become increasingly accepted as a safe and effective intervention for the management of *Clostridium difficile* infection [75] with some studies demonstrating efficacy with a 91% primary cure rate and 98% secondary cure rate [76]. The potential benefit of FMT as a decolonization strategy for MDR-GNB has been tested in several studies with a high level of heterogeneity [77].

PREVENTION AND CONTROL OF *A. BAUMANNII*

There are many reports of successful control and eradication of MDR *A. baumannii* using a combination of techniques [78]. However, the current management of *Acinetobacter baumannii* prevention, infection, and outbreaks is based on observational studies and pharmacodynamic modeling [61]. While the various guidelines contain broad areas of agreement, there are some inconsistencies between the guidelines, reflecting the limited evidence available in the published literature [79]. Management is based on source control, including antibiotic stewardship, hand hygiene, contact precautions, education, and effective environmental

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cleaning [61]. Several studies suggest the closure of hospital units may be necessary to control an outbreak [80]. This can come at a great cost: the cost of closure due to an outbreak of *A. baumannii* is estimated on average at 266,500 GBP (350,000 USD) [81], the largest cost being associated with lost bed days through extended patient stays or ward closures, and which can result in reduced capacity to perform elective surgical procedures due to bed closures [80].

CONCLUSION

Infections with *A. baumannii* have been displayed to convey a worse prognosis than infections with other Acinetobacter species. Furthermore, the evolving epidemiology of *A. baumannii* will warrant the execution of a revised strategy of infection control measures in both clinical and community settings. Due to the magnitude and costs associated with hospital-acquired infections, and, the increase in multidrug-resistant organisms, it will be worthwhile to evaluate the current approaches and look for alternatives or adjuncts to traditional antibiotic therapies. Therefore new approaches should be considered to control the spread of MDR *A. baumannii* such as the use of promising emerging solutions which include bacteriophages, AMP, or recolonization therapies in adjunct to advanced cleaning strategies.

CONFLICTS OF INTEREST

The authors have declared that there is no conflict of interest.

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