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Review Article

Acinetobacter baumannii Virulence Factors, Resistance Mechanisms, and New Insights on Infection Treatment

Riham A. EL-Hakeem[a], Sarra E Saleh[a*], Mohammad M Aboulwafa[a,b], Nadia A Hassouna[a]

[a]*Department of Microbiology and Immunology, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt*
[b]*Faculty of Pharmacy, King Salman International University, Sinai, Egypt*

ABSTRACT

Acinetobacter baumannii is an alarming pathogen that threatens human health around the world and most of the antibiotics have become unable to cope with it. It has been classified by the World Health Organization (WHO) as a member of the most dangerous ESKAPE organisms "*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*" which show high resistance rates toward antibacterial agents. *A. baumannii* causes life-threatening infections with limited treatment options that include pneumonia, bacteremia, meningitis, urinary tract infection, and wound infection, and numerous reports have documented *A. baumannii* infection after SARS-CoV-2 infections in multiple publications through the COVID-19 catastrophe. Many virulence factors such as efflux pumps, outer membrane proteins (OMPs), phospholipase, lipopolysaccharide, capsule, protein secretion systems, nutrient-acquisition systems, biofilm production, and quorum sensing account for the pathological and lethal effects of *A. baumannii*. The present review concentrates on highlighting the major mechanisms of antibiotic resistance declared in *A. baumannii*, the virulence factors of *A. baumannii*, and the novel therapeutic strategies. These strategies include novel antibiotics, drug repurposing, antimicrobial peptides (AMPs), nanoparticles, bacteriophage therapy, monoclonal antibodies of humans (Hu-mAbs), and gene amendment in an attempt to help the scientific research society.

Keywords: *A. baumannii; infections; resistance; novel therapeutic strategies; virulence factors; infection control.*

***Correspondence** | Sarra E Saleh; Department of Microbiology and Immunology, Faculty of Pharmacy, Ain Shams University, Cairo 11566, Egypt. Email: sarradeif@pharma.asu.edu.eg

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1. Introduction

Antimicrobial resistance of *A. baumannii* has arisen as a triggering and substantial disaster that increases health system expenditures throughout the world. In current years it has been linked to abundant mortality, infections, and increased expenditures because of both the long duration of treatment and hospitalization. During the previous decades several multicenter studies data have declared that both outpatient-acquired and hospital-acquired antimicrobial resistance are upgrading with the elevated number of immunodeficient older patients **[1, 2]**. *A. baumannii* was originally described as *Micrococcus calco-aceticus* and was first isolated in 1911 by the dutch microbiologist Beijerinck from soil using media enriched with calcium acetate **[3]**. To differentiate it from the genus *Achromobacter* motile organisms the genus *Acinetobacter* comes from the "akinetos", a Greek word **[4]**. By 1968 the genus

Acinetobacter was accepted after Baumann et al., a comprehensive study of organisms such as *Moraxella lwoffi, Micrococcus calco-aceticus*, *Mima polymorpha*, *Alcaligenes hemolysans*, *Bacterium nitrate,* and *Herellea vaginicola*, which could not be further sub-classified into variable species and were confirmed to belong to a single genus depending on the phenotypical characteristics **[5]**.

The genus *Acinetobacter* comprises strictly aerobic, Gram-negative, non-fermenting, non-motile, non-fastidious, oxidase-negative, and catalase-positive bacteria with a 39% to 47% percent DNA G + C content **[6]**. The use of DNA–DNA hybridization technique had a great role in the identity establishment of almost thirty-three various *Acinetobacter* genospecies **[7, 8]**. Among these genospecies, the ACB complex (*A. calco-aceticus, A. baumannii,* and *Acinetobacter* genomic species 13TU), show phenotypic characteristics that make them difficult to be distinguished and they represent the most clinically important members of the genus **[9]**. *A. baumannii* compromises the highest clinical importance of the ACB complex, while *A. calcoaceticus* is seldomly described as a cause of huge pathological disorders and has been considered an environmental pathogen **[10]**.

One of the most important nosocomial pathogens is *A. baumannii* which was classified by the WHO organization as a member of the most dangerous ESKAPE organisms **[11]**. Numerous reports have documented *A. baumannii* infection after *SARS-CoV-2* infections in multiple publications through the COVID-19 catastrophe **[12]**. During the 1970s, *A. baumannii* clinical isolates were sensitive to commonly used antimicrobials, such as gentamicin, ampicillin, nalidixic acid, and chloramphenicol, while, by the end of 1970s, it arises as a serious pathological agent of hospital-acquired infections, especially with the use of broad-spectrum antimicrobials in medical care units **[8]**. Nowadays, it acquires a high nonsusceptibility rate toward the majority of first-option antimicrobials, however, tigecycline & colistin has become the reserved antibiotics for multidrug-resistant (MDR) *A. baumannii* treatment; unfortunately, colistin-resistance has been detected in various areas worldwide **[13]**. The carbapenem resistance rate of *A. baumannii* has increased by two-fold approximately beside its resistance to various antibiotic classes such as macrolides, fluoroquinolones, and cephalosporins, which has been declared to reach 80% in certain countries and 56% in others from 2005 till 2018 which is considered a great disaster **[14]**.

Li-Kuang et al. revealed that the nonsusceptibility rates of *A. baumannii* clinical isolates to quinolones (levofloxacin & ciprofloxacin) and sulfonamides were 73.6% and 71.3%, respectively. It showed more than half (50-70%) resistance rates to beta-lactam/beta-lactamase inhibitor combinations (piperacillin-tazobactam), cephalosporins (cefepime and ceftazidime) and carbapenems (imipenem, meropenem, and doripenem). However, it showed a 26.7% nonsusceptibility rate toward the tigecycline and 0% of the isolates were nonsusceptible to colistin **[15]**. *A. baumannii* is considered a major cause of about 2% of nosocomial disorders in Europe and the United States in 2011 **[16]**. About 45% of *A. baumannii* are considered MDR microorganisms, which was 4x higher in comparison to other Gm-ve microorganisms, like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. The MDR incidence rate of *A. baumannii* compromised about 70% in the Middle East and Latin America **[17]**. The WHO has considered *A. baumannii* which showed carbapenem-resistant as a critical group of pathogens that implement a crucial threatening to humanity's biosafety, triggering the significant

demand for novel antimicrobial agents **[18]**.

2. *A. baumannii* pathological manifestations

The likelihood of patients being colonized and medical equipment being contaminated by *A. baumannii* is mainly because it is ubiquitous and is carried on the skin of health care workers and can survive on dry surfaces for up to a month **[19]**. There are multiple *Acinetobacter* species; all can lead to human diseases, but mainly *A. baumannii* accounts for nearly 80% of infections **[20]**. The majority of *A. baumannii* disorders target mainly human body organs that are rich in fluid content, like the respiratory system, abdomen peritoneal cavity, and urinary tract. The recurrence of *A. baumannii* infections in any hospital is considered an alarm of dangerous illness, with about a thirty percent mortality rate **[21]**. Some of these infections are listed below.

2.1 Pneumonia

The adherence and biofilm formation of *A. baumannii* to the hospital devices such as the endotracheal tube and the creation of a niche for the rapid dissemination of the microbial cells resulted in the increase of carbapenem-resistant *Acinetobacter* incidences in the intensive care units (ICUs) **[20]**. *A. baumannii* can also enter the mechanically ventilated patient's alveoli directly, allowing the establishment of lung tissue infection **[20]**. *A. baumannii* hospital-acquired pneumonia is the major nosocomial infection, which has a frequency of 3-5% in ICUs and has 30-75% crude death rates being reported, it is considered the second most abundant pathological agent causing hospital-acquired infections among all the Gm-ve bacteria **[21]**. As it can localize tracheal tube sites, it causes community-acquired *Acinetobacter* pneumonia and results in community-acquired trachea bronchitis and bronchiolitis in immunocompromised patients and other risk groups but it still seldomly results in septicemia or community-acquired pneumonia **[22]**.

2.2. Bacteremia

A. baumannii bacteremia is mainly caused by the respiratory tract and intravascular catheter, however, urinary tract infections and surgical wound burns are less encountered and endocarditis is an infrequent cause of *A. baumannii* bacteremia. *A. baumannii* bacteremia death rate range is [34.0% to 43.4%] at the ICU and is about 16.3% in non-ICU patients **[23]**. *A. baumannii* is seldom an etiological agent of post-endoscopic retrograde cholangiopancreatography (ERCP) bacteremia and as shown in Jabri *et al.* case study; this infection may lead to death. This case emphasizes the need for appropriate consideration and precautions of infrequent pathogens causing bacteremia or sepsis in post-ERCP patients **[24]**.

2.3. Skin wounds and soft tissues infection

A. baumannii compromises (2.1%) of soft tissue and skin infections in ICU patients. It was detected in Iraq or Afghanistan war victims as an abundant isolated microbial agent in about 32.5% of battle victims who had open fractured tibia. However, it can cause soft tissue and skin infections among the outside population **[25]**. Guerrero *et al*. comparative study concluded four unique features concerning *A. baumannii* necrotizing SSTI (skin and soft tissues infection): **a)** present in patients with underlying accompanied disorders (e.g., cirrhosis, trauma); **b)** it is mostly lead to bacteremia; **c)** the presence of coinfection with another microorganism and multiple drug resistance complicated treatment in 64% of infections; **d)** 84% of documented cases required surgical debridement and 30% led to substantial mortality **[26]**.

2.4. Urinary tract infection

A. baumannii urinary tract infections are generally due to the colonization of percutaneous nephrostomy tubes or urinary catheters by the

pathogen**.** However, it seldomly causes urinary tract infections (UTI), compromising (1.6%) of ICU patients. Complicated UTI infrequently occurs in outpatients by *A. baumannii* **[24, 25]**.

2.5. Meningitis

Nosocomial meningitis is rarely caused by *A. baumannii*, but it is significantly important in postoperative meningitis **[25]**. Head trauma, neurosurgical operation, cerebrospinal fluid leakage, foreign body implantation, and wound infection compromise the major risk factors **[25]**. *A. baumannii* accounts for about 10% and 4% of Gram-negative *A. baumannii* acute bacterial meningitis in adults and nosocomial meningitis, respectively, with mortality rates up to 70% **[25, 26]**. MDR *A. baumannii* is a major causative agent of nosocomial post-neurosurgical meningitis **[26]**.

2.6. Other manifestations

A few *A. baumannii* endocarditis cases have been reported, with the majority of these cases associated with prosthetic valves **[27]**. Several reports worldwide have documented an increase in the prevalence of lower respiratory tract infections (LRTI) caused by *Acinetobacter* spp. **[28]**. *A. baumannii* was concluded to be one of the most frequent pathogens causing LRTI in ICUs, resulting in about 26.2% of the cases **[28, 29]**. Lagana *et al.* documented two cases of infective and fatal endocarditis on cardiac prostheses sustained by *A. baumannii* **[29]**. Although infrequent, MDR *A. baumannii* has been demonstrated to cause peritonitis in patients with peritoneal dialysis, resulting in significant infection with a high mortality rate **[30]**. Ocular infections have also been observed in recent years and are commonly accompanied by long-term use of contact lenses or post-ocular operations. Chen *et al.* documented two cases of *A. baumannii* ocular infection, one resulting in endogenous endophthalmitis and the other endophthalmitis following corneal transplant **[31, 32]**.

3. Virulence factors of *Acinetobacter* and pathogenesis

A. baumannii has many virulence factors involved in its infection (**Fig. 1**) including:

3.1. Motility

A. baumannii has two types of motility, surface-associated and twitching motility that help it to survive and spread on surfaces although being famous as a non-motile micro-organism Studies showed that this crucial pathogen had these two types of motility resulting in an increase in its virulence **[33, 34]**.

3.2. Omps (Outer membrane proteins)

A. baumannii Omps including OmpA, OprD-like OMPs, CarO, AbuO, TolB, OprF, etc. are a major virulence factor, which affect their pathogenesis, antibiotic resistance, and adaptation in host cells. **[35, 36, and 37]**. Outer membrane protein (OmpA) is the major *A. baumannii* outer membrane protein that has crucial roles in ferocity, including apoptosis induction in affected cells through the production of apoptosis triggering inducers, epithelial cells hanging on through using host cell fibronectin and the formation of biofilm **[38]**. Pure OmpA enhances a T-helper cell 1 mediated immunity **[39]**, and upregulates iNOS (inducible nitric oxide synthase) via a TLR (Toll-like receptor)-2-enhanced pathway **[40]**.

Additionally, CarO (Carbapenem susceptibility porin) was found to regulate the influx of β-lactams “selectively imipenem (IMP)” into *A. baumannii* **[41]**. *A. baumannii* releases a variety of OMPs including CarO into the surrounding media, when exposed to a high concentration of monovalent cations and becomes more tolerant to IMP effect. This finding explains why we cannot depend on the in

vitro MICs values of several antimicrobial agents to alleviate *A. baumannii* infection, especially in UTIs where there is a high level of monovalent cations such as KCl and NaCl **[42]**. CarO protein immunological role in *A. baumannii* is studied inadequately, revealing that *A. baumannii* clinical isolates that have higher expression levels of CarO mRNA, negatively regulated IL-6, IL-8, and TNF-α in lung epithelial cells **[43]**. CarO has shown an inhibitory effect on NF-kβ signaling which helps them in adhesion and virulence in host cells **[44]**. However, this observation is debatable as they depend on the ATCC 19606 strain which has a lower expression level of CarO than that of clinical strains **[43]**.

OprD (outer membrane porin) is an orthologous protein to a porin that participates in imipenem and basic amino acids transportation in *Pseudomonas aeruginosa* **[45]**. Reduced carbapenem influx due to changes in the expression level of OprD induces Carbapenem resistance **[46]**. Zahn *et al.* renamed OprD to OccAB1, while solving its crystal structure, showed that " out of four carboxylate channels [OccAB1, 2, 3, and 4]" OccAB1 has the biggest channel size that results in higher rates of small-molecule shuttle, including sugars, antibiotics and amino acids **[47]**. This large pore size facilitates the translocation of both negative and positive substrates at lower energy consumption levels **[48]**. Several studies had showed SNP clusters in OprD in MDR and tigecycline-resistant *A. baumannii* **[49, 50, 51]**. Downregulation of OprD was observed in MDR and pan-drug-resistant *A. baumannii* clinical strains **[52, 53]**.

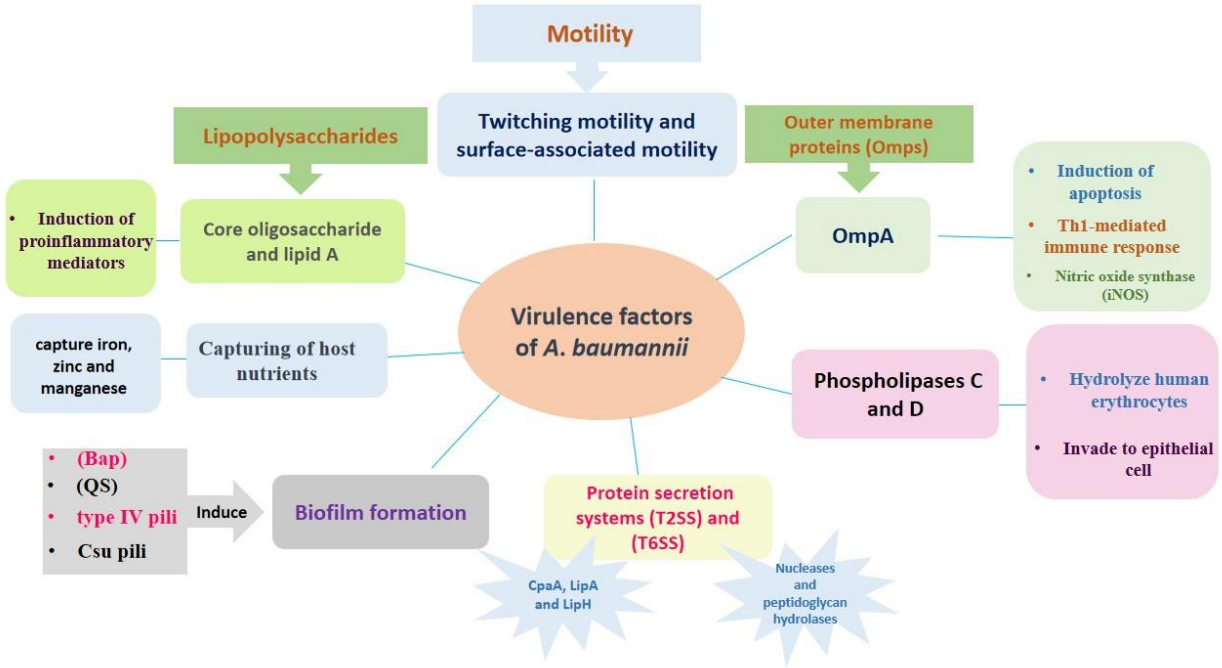

Fig. 1. Schematic representation of major *A. baumannii* virulence factors. Bap, biofilm-associated protein, Csu, chaperon/usher pilus system; QS, quorum sensing, T2SS, type II secretion system; T6SS, type VI secretion system; Omp, outer membrane protein; LipA, lipase enzyme A, LipH, Lipase enzyme H.

3.3. Lipopolysaccharides

A. baumannii lipopolysaccharides (LOS) that include only, lipid A and core oligosaccharide, are strong enhancers of circulating WBCs to produce proinflammatory reagents, which are cytotoxic to neutrophils and suppress their migration and their phagocytic ability **[54]**. The lipopolysaccharide virulence factor has become a crucial factor in the survival of the microorganism because of its vital role in the induction of proinflammatory mediators and colonization. It was declared that modification of lipopolysaccharides can result in declining antibiotic susceptibility **[55]**. Capsular polysaccharides that are located around the surface of the bacteria act as a defense hail against environmental strains and some antibiotics, so they have a definitive participation in the stays of the pathogen mainly in serum, which has a crucial role in preventing phagocytosis of the microorganism **[54, 56]**.

3.4. Biofilm formation

A. baumannii can use biofilm-associated proteins (Bap) in the development of biofilm structure as a result of stressful conditions. Biofilm formation assists bacterial cell colonization and its survival through the adherence to both living and nonliving surfaces leading to hospital device-linked diseases in medical facilities. It was documented that QS (quorum sensing) is concerned with biofilm production by auto-inducers such as signaling molecules **[57]**. As well as Csu pili and type IV pili are crucial for biofilm formation **[58]**. It was concluded that biofilm enhances the survival time of *A. baumannii* in dry areas **[59]**. Desiccation withstanding refers to the capability to be viable during dry circumstances and it is variable between the *A. baumannii* clinical isolates, as it can be up to a hundred days withstanding. This ability isn't yet fully defined and is multifactorial **[60, 61]**.

3.5. Other virulence factors include:

3.5.1. Phospholipases

Phospholipase C and phospholipase D are considered as another crucial virulence factor, mainly they act on the cell membrane phosphatidylcholine of eukaryotic which is found to be a target for phospholipases. These enzymes have a vital role in iron acquisition because of their ability to hemolysis the erythrocytes. Besides these phospholipases are included in epithelial cell invasion and support them to withstand serum **[62]**.

3.5.2. Protein secretion systems

Type II and Type VI protein secretion systems (T2SS & T6SS) give *A. baumannii* microorganisms the capability of interacting with the host and the environment. Type II protein secretion system uses a two-step pathway to form LipA, LipH, and CpaA effector proteins which are vital virulence enzymes, LipA was declared to possess serine hydrolase activity being capable of hydrolyzing 4-nitrophenyl myristate, also LipA allows the growth of *A. baumannii* in long-chain fatty acids supplemented minimal media as the sole carbon source, revealing its crucial role in nutrient acquisition **[63]**. LipA and LipH were confirmed as lipases through their ability to cleave *para*-nitro phenol palmitate. CpaA was previously shown to be a secreted zinc-dependent metalloendopeptidase that was capable of degrading fibrinogen and factor V, deregulating blood coagulation **[64]**.

As well as, T6SS can target other microorganisms through the injection of toxins like peptidoglycan hydrolases, nucleases, and cell membrane toxins and it has a crucial participation in several microbial pathogenesis **[12, 65]**. Additionally, host nutrient capturing can assist the *A. baumannii* persistence, the immune system alteration, and dissemination of infection **[12, 66]**. *A. baumannii* has variable mechanisms for

zinc (Zn), manganese (Mn) and iron (Fe)-capturing such as Zn-scavenging, the NRAMP (natural resistance-associated macrophage protein) family transporters and siderophores, respectively **[12, 66]**.

4. *A. baumannii* Antibiotic Resistance

Various strains of *A. baumannii* are settlers to variable areas all over the world **[67]**. MDR strains withstand antimicrobial agents by various resistance mechanisms **(Fig. 2**); each of them is mainly against certain types of antimicrobial agents.

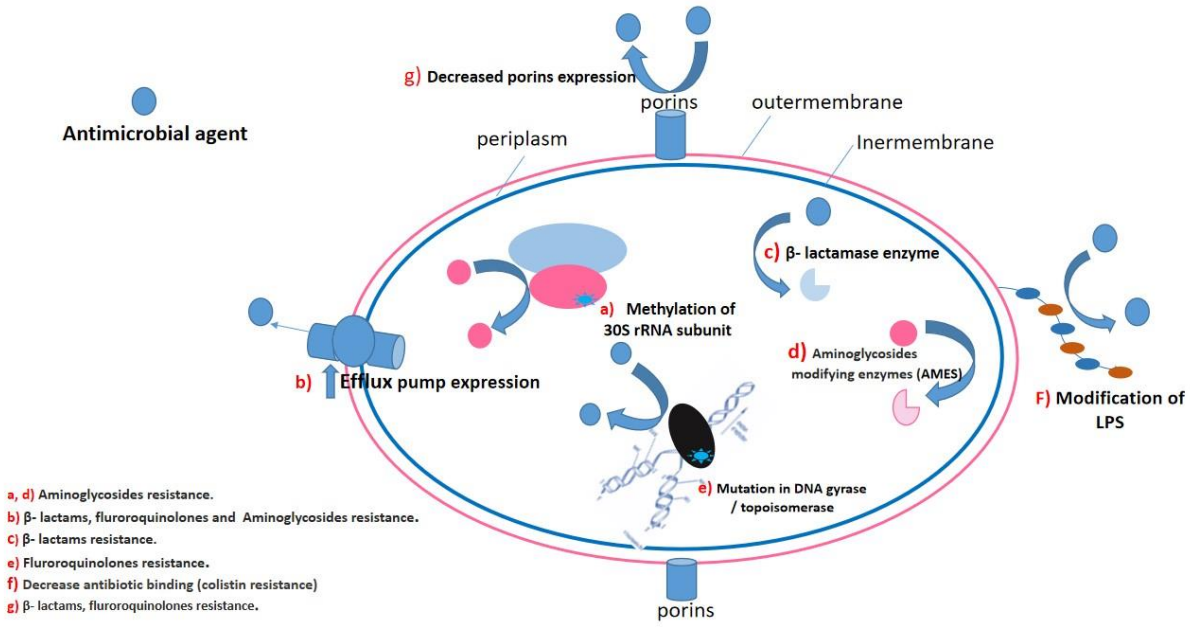

Fig. 2. Different mechanisms of resistance to quinolones, aminoglycosides, beta-lactams and colistin in *A. baumannii*. AME, aminoglycoside modifying enzyme; LPS, lipopolysaccharide.

4.1. Cephalosporins

Newly Ambler's class C β-lactamase enzyme showed higher nonsusceptibility toward cefotaxime and ceftazidime than cefepime. It was recovered from a clinical isolate that was found in a Cleveland OH, USA hospital **[68]**. The phylogenetic analysis of Ambler's class C β-lactamase and other *A. baumannii*, *A. pittii*, and *Oligella urethralis* class C β-lactamases, concluded that it was a non-redundant class of class C-β-lactamases. These enzymes were designed as ADC (Acinetobacter-derived cephalosporinases) and this enzyme was assigned as ADC-7, like the other 6 cephalosporinases that had been described previously **[68]**.

A. baumannii Amp C ADC-7 cannot be enhanced by Cefoxitin, in contrast with the majority of chromosomally related class C β – lactamases **[68]**. The insertion of the ISAba1 or ISAba125 sequence to the upstream of the ADC gene increase the ADC expression, resulting in greater promoter activity in comparison with the native promoter activity **[69, 70]**. Consequently, an increase in the minimum inhibitory concentration (MIC) is required for the various cephalosporins that are affected by these enzymes. Several documents revealed that there are *A. baumannii* strains that produce extended-spectrum class β-lactamase like ADC-33 provoked nonsusceptibility against cefepime and other cephalosporins **[71]**.

4.2. Carbapenems

Carbapenems are the first-line treatment of nonresistant *A. baumannii* isolates. Although, carbapenem resistance is increasing significantly all over the world and multiple resistance mechanisms are concluded to be involved **[12]**. Ambler's class B metallo-β-lactamases (non-OXA carbapenemases) has been detected in *A. baumannii*, while the New Delhi metallo-β-lactamase (NDM) group of enzymes as IMP, VIM, and SIM imipenemases (imipenemase, Verona and Seoul imipenemase) aren't common in *A. baumannii* **[72, 73]**. Additionally, the decreased expression of PBP-2 (penicillin-binding protein-2) can be considered a crucial resistance mechanism of carbapenems **[12, 74]**. The OXA51-like-β-lactamase (carbapenem-hydrolyzing Oxacillinase) and the *armA* 16S-ribosomal-methyltransferase gene overexpression are concluded to be major mechanisms that provoke non-susceptibility to carbapenems within various *A. baumannii* strains **[75, 76, 77]**. Also, the *A. baumannii* Class D β-lactams (OXA) is a main concern because it leads to the emergence of carbapenem resistance **[78, 79]**. The majority of these enzymes are carried on integron elements **[80]**. *A. baumannii* has an intrinsic carbapenem-hydrolyzing Oxacillinase as OXA-51-like and has other acquired carbapenemases, such as OXA-58-like, OXA-23, OXA-40-like and OXA-123-like **[81, 82]**. The OXA-23 was discovered to be accompanied by higher production and dissemination of carbapenem nonsusceptibility with clinical manifestations **[83]**.

4.3. Fluoroquinolones

A. baumannii fluoroquinolones resistance mechanism is mainly by the substitutions of the DNA gyrase and DNA topoisomerase IV quinolone resistance-determining regions (QRDRs) resulting in the reduction of fluoroquinolones binding ability to the enzyme-DNA complex **[84]**. As well as the efflux pumps overexpression alone can lead to moderate nonsusceptibility and enhance nonsusceptibility in strains with alterations in RDRQs **[85]**. Quinolone resistance determinants that are Plasmid-encoded are participating in fluoroquinolones resistance **[84]**.

4.4. Aminoglycosides

A. baumannii strains aminoglycoside resistance mechanisms include mainly; a) the aminoglycoside modifying enzymes production as AACs-enzymes (aminoglycoside acetyltransferases), specially *aac* (6)-Ih (involved in gentamicin and amikacin resistance) **[86, 87]**, APH enzymes (aminoglycoside phosphotransferases), as *aph* (3)-IA (involved in gentamicin resistance) **[86]** and ANT enzymes (aminoglycoside adenylyltransferase) as *ant* (2)-IA **[87]**. b) 16S ribosomal methyltransferase production, as ArmA ribosomal methyltransferase, initial one to be detected in an *A. baumannii* isolates **[88]**. ArmA ribosomal methyltransferase involves in the nonsusceptibility to amikacin, gentamicin, and tobramycin **[89, 90]**. **C)** As well as, decreased permeability and increasing efflux pump activity as multidrug and toxic compound extrusion (MATE) pump system and RND family AdeABC efflux pumps are other mechanisms of aminoglycosides resistance **[91]**.

4.5. Rifampicin

A. baumannii rifampicin resistance is mainly caused by the alterations of certain β-subunit amino acids of the bacterial RNA polymerase active site. rpo B mutations have also led to elevations in MICs of *A. baumannii* **[91]**. In addition, rifampicin enzymatic modification by the ADP ribosyl transferase (ARR-2) and efflux pump activation assist the resistance toward rifampin in *A. baumannii* strains **[92]**.

4.6. Tetracycline

The resistance against tetracyclines mainly tigecycline which has been assigned as one of the "last-resort" antibiotics for the XDR (extended drug resistant) *A. baumannii* treatment had emerged due to various plasmid-mediated *tet(X)* gene variants as Tet (X3, X4 and X5), which are mono-oxygenases that can inhibit all tetracyclines including tigecycline and the recently authorized omadacycline and eravacycline **[93]**. Tetracyclines resistance has been linked to different mechanisms, such as active efflux pumping of the antibiotics to the cell outside through two major efflux systems as the RND (resistance nodulation cell division) family-type pumps especially AdeABC and tetracycline major facilitator superfamily (MFS) efflux pumps as TetA and TetB **[94, 95]**. Generally, resistance to tetracycline antibiotics had been linked to three major mechanisms: a) ATP-dependent efflux pumps, b) tetracyclines enzyme inactivation, and c) RPPs (ribosomal protection proteins) **[96]**.

4.7. Colistin

A. baumannii resists colistin (Polymyxin-E) by modification of lipopolysaccharide (LPS) lipid A. The major detected modification method is the phosphoenol amine residue addition to the hepta-acylated structure of lipid A, leading to negative charge removal and reducing the polymyxin's binding ability to LPS **[97, 98]**. As well as the lack of the initial LPS makes *A. baumannii* develop colistin nonsusceptibility **[99]**. Biswas *et al*. concluded that, the polymyxin–rifampicin combination therapy is effective for the treatment of MDR Gram-negative bacteria with a hundred percent synergism toward MDR *A. baumannii* **[100]**.

5. Novel treatment options

Treatment varieties for *A. baumannii* diseases are limited because of the recurrent resistance rate of antimicrobial agents. Especially, the ACB complex which is accompanied by about eighty percent of infections and has provoked nonsusceptibility to all antibiotics that target gram-negative micro-organisms **[101]**. The disseminated prevalence of *A. baumannii* antimicrobial resistance, mainly toward last-resort antibiotics, is a crucial alarm. So, the researchers have to pay attention to novel treatment strategies development, some are summarized in **Fig. 3**.

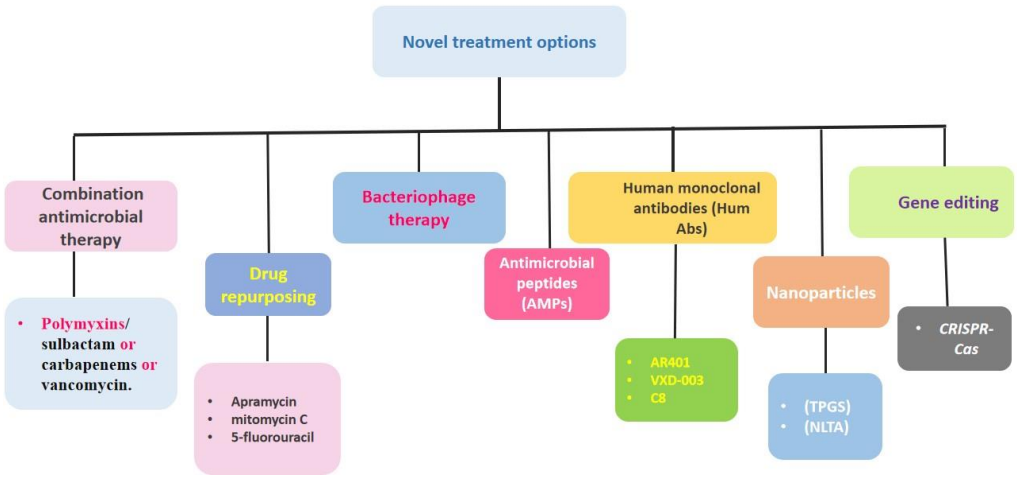

Fig. 3. Novel therapeutic treatment for *A. baumannii* infections; TPGS, tocopherol polyethylene glycol succinate, NLTA capped silver nanoparticles and copper nanoparticles capped with N-lauryltyramine.

5.1. Combination antimicrobial therapy

A combination antibiotics treatment strategy appears to have the most preferable outcomes for infections compared to monotherapy. Mostly, combinations are depending on polymyxins alongside other antimicrobials that act on the cell wall like carbapenems, vancomycin, and sulbactam. It is not preferable to use polymyxins alone toward infections by high-resistance strains, as this can enhance resistance against them, polymyxins-depending combinations are a suitable alternative to avoid treatment failure. Additionally, tigecycline-depending combinations seem to be efficient toward pan-drug-resistant (PDR) strains **[102]**.

5.2. Drug repurposing

Major advantages of drug repurposing, are rapidness, cost-effectiveness, and attractive proposition for the treatment of resistant infections. Three repurposed drugs have been suggested by several studies to be promising agents for the MDR *A. baumannii* infections treatment including, apramycin which is a monosubstituted deoxystreptamine, this distinctive structure that enables the apramycin molecule to intrinsically adapt to almost all resistance mechanisms found in MDR and XDR Gram-negative bacteria **[102]**. Additionally, apramycin was found to have lower toxicity than other disubstituted deoxystreptamine drug aminoglycoside classes **[103]**.**Mitomycin C** (MMC) is mainly used as an anticancer agent in gastric, bladder, and pancreatic cancer treatment **[104]**. Recently, Cruz-Muñiz *et al.* study revealed that MMC was able to kill stationary-phase cells and eradicate persister cells and biofilms of fatal *A. baumannii* infection, hence proposed MMC as a suitable candidate for repurposing as an antimicrobial agent **[105]**. Also, **5-fluorouracil (5-FU)** - an antimetabolite drug- is used as an anticancer agent in oesophageal, breast, colorectal, skin, and pancreatic cancers **[106]**. 5-FU has a wide antivirulence and antimicrobial effect on several bacterial pathogens, such as *Escherichia coli* and *Pseudomonas aeruginosa*, and some Gram-positive bacteria such as *Staphylococcus aureus* **[107, 108]**. However, no studies have revealed the antimicrobial activities of 5-FU against *A. baumannii*. Additionally, some researchers have declared various combinations as effective treatment alternatives for *A. baumannii* showing carbapenem-resistance, such as colistin\ mitotane, niclosamide\ colistin, and fusidic acid \ polymyxin b **[109]**.

5.3. Bacteriophage therapy

One of the most promising antibacterial approaches is the use of viruses to cure bacterial infections (Bacteriophage therapy), which cures and prevents infectious disorders by bacterial cell lysis. The major benefits of bacteriophage therapy are that the phage specifically assigns the pathological agents instead of the normal cells or the commensals **[110]**. The initial study concluded that the bacteriophage treatment is effective on *A. baumannii* was conducted in 2010 **[111]**. Consequently, the bacteriophage\ antimicrobial combination can be a successful option for the *A. baumannii* infections therapy, as well as the use of phage\ antibiotic combinations can help to prevent the phage resistance emergency. Some studies have introduced KARL-1 as a promising element combined mainly with other antimicrobial agents for the MDR *A. baumannii* therapy **[112]**. A recurrent study showed that a CPS depolymerase (capsular polysaccharide), which is extracted from the TSP (tail spike protein) of φAB6 phage has a major role in inhibiting biofilm development and microorganism attachment to the surface of hospital equipment, also has antimicrobial activity that could destroy microbial cells through membrane lysis **[113]**. However, this approach has several limitations because most clinical

infections are usually due to a variety of pathogenic bacteria, which limits the effect of specific bacteriophages to have a required therapeutic effect **[114]**. Bacteriophages can also transmit antibiotic resistance genes and toxins to bacteria in the lysogenic state as the bacteriophage genome integrates into the bacterial chromosomal DNA for replication or replicate in a free plasmid-like state **[115]**. The evaluation of phage therapy curative effects and quality is difficult as it has a more complex composition which includes both proteins and nucleic acids than other protein drugs whose purity and activity can be assessed based on specific antibody titers **[116]**. The clinical application of phage therapy lacks regulations and policies, so if there is an appropriate regulatory standard it can create opportunities to raise awareness of this promising treatment **[117]**. Additionally, there is no obvious standard for phage purification and isolation, making the isolated phage preparations efficacy variable. Also, there is no standardized procedure in clinical treatments with bacteriophages **[118]**.

5.4. Antimicrobial peptides (AMPs)

Another promising strategy against *A. baumannii* includes antimicrobial peptides (AMPs) that are a constituent of the nonspecific immunity of eukaryotic and prokaryotic organisms. They seek the attention of the research community because of their broad-spectrum activity and low resistance rates **[119]**. The cationic nature of AMPs allows them to target the cell membranes and disintegrate the lipid bilayer, leading to cytoplasmic leakage and microbial eradication **[120]**. They have variable amino acids structure with varying amino acids number "from five to > 100" and show a broad spectrum of activity, covering from viruses to parasites **[120]**. AMPs have other antimicrobial mechanisms including; membrane proteins delocalization **[121]**, and cytoplasmic membrane septum formation alteration **[122]**, they also inhibit the synthesis of the cell wall, proteins, DNA, and RNA **[123, 124]**, and have enzymatic activity **[125]**. Some can eradicate the biofilm-forming bacteria by direct biofilm formation inhibition or killing the microorganism inside the biofilm **[126]**. An updated mouse model experiment showed that the AMP candidates, dN4 and dC4 are efficient in the treatment of pneumonia produced by *A. baumannii* by inhibiting the biofilm formation in a dose-dependent manner and eliminating the established biofilm **[127]**. But also, the medical applications of antimicrobial peptides have major disadvantages such as high expenses, increased cell toxicity, harsh environmental conditions sensitivity as extreme pH, and instability in the circulatory system **[128, 129]**. However, amino acids in nature allow their structures to be modified easily to decrease their host cell toxicity and protease instability **[130]**.

5.5. Human monoclonal antibodies (Hu-mAbs)

Enhancing innate immunity is a promising strategy to eradicate *A. baumannii* virulent strains, as they can evade the innate immune system, resulting in sustained TLR4 ligation by their LPS which ultimately results in death by sepsis **[131, 132]**. Therefore, many researchers had paid great attention to monoclonal antibodies as a passive immunotherapeutic approach **[133]**. Human monoclonal antibodies (Hu-mAbs) are a promising strategy for *A. baumannii* infections treatment, as they are specific and do not affect the commensal microbiota. On the other hand, the opportunity for resistance decline as Hu-mAbs often affect the virulence proteins rather than the survival ones **[134]**. Nowadays, AR401, VXD-003, and C8 Hu-mAbs were analyzed for their therapeutic effect on *A. baumannii* infections **[134, 135]**, and C8 was found to upregulate opsonophagocytosis by tackling the capsular carbohydrate of bacterial cells. Several

studies on C8 Hu-mAbs have declared that C8 monotherapy or combination therapy has antimicrobial activity toward XDR *A. baumannii* infections **[135]**. Nielsen *et al*. also declared that the treatment with C8 had significantly decreased the blood bacterial density, sepsis biomarkers, and cytokine production as tumor necrosis factor α, IL-1β, interleukin [IL] 6, and IL-10 **[135]**. Despite their advantages, they have some limitations including; more time consumption and a high cost of production when compared to polyclonal antibodies **[136]**.

5.6. Nanoparticles

Nanoparticles have attracted much attention as an alternative treatment**.** Several studies declared the crucial effect of nanoparticles as antivirulence entities for *A. baumannii*. The TPGS/AgNPs (TPGS-capped AgNPs) hollow structure allows a conformation cavity to load the antimicrobial agents, also its small size allows them to penetrate the bacterial cell wall and cross into bacteria, increasing the antibiotic delivery inside the bacterial cells **[137, 138]**. Another two studies concluded the efflux inhibitory potential of nanoparticles in *A. baumannii* as copper nanoparticles capped with NLTA (N-lauryl tyramine) and TPGS (tocopherol polyethylene glycol succinate) capped silver nanoparticles **[139, 140]**. Additionally, silver nanoparticles have been declared to be capable of suppressing the transcription of various virulence genes and interfering with *A. baumannii* biofilm production **[139]**. This delivery system has some limitations including its entrapment in the mononuclear phagocytic system as in the spleen and liver **[141]**. The nanoparticles drug delivery system reduces the toxicity of the whole formulation, however, the toxicity of the nanoparticles itself is usually studied inadequately. Therefore, proper emphasis on the toxicity of the empty nanoparticles must be taken into consideration, especially in slow or non-degradable particles which can persist and accumulate on the drug delivery site, leading to chronic inflammatory reactions **[142]**.

5.7. Targeting OMPA as a potential virulent factor in *A. baumannii*

Mostly, there are two major strategies to develop a novel antimicrobial agent. One is by inhibiting the essential elements production which helps in the bacterial cell survival **[143, 144]**; the second is by inhibiting the antibiotic resistance genes or virulence factors to suppress pathogenicity or improve their sensitivity to antimicrobial agents **[145]**. Although, inhibiting a single essential component inevitably leads to the development of high-level drug-resistant strains **[146]**. As a result, the novel intervention strategies concentrate on the nonessential processes as a key to overcoming bacterial resistance **[147]**. There are various strategies to target OMPA including; a synthetic small polypeptide that specifically binds to and blocks OmpA as AOA-2 (a cyclic hexapeptide). AOA-2 blocks the OmpA "without bactericidal activity" decreasing the adhesion of *Pseudomonas aeruginosa*, *A. baumannii*, and *E. coli* to the biotic and abiotic surfaces, and significantly enhancing the sensitivity of *A. baumannii* **[148, 149]**. Additionally, other classic AMPs targeting OmpA have been gradually discovered as BMAP-28 (bovine myeloid antimicrobial peptide) **[150, 151]**. Monoclonal antibodies targeting AbOmpA used to be a considerable therapeutic method for the treatment of MDR and XDR *A. baumannii* infections **[133]**. Regulation of OMPA expression level is affected by the internal and external environment of the microorganism **[152]**. The study of Bravo Z. *et al.* revealed that biofilm formation and adhesion-related genes, *bfmR*, *OmpA*, and *csuAB* were down-regulated in starved cells, resulting in difficulties in biofilms formation and spreading of *A. baumannii* in blood **[153]**.

5.8. Gene editing

Gene editing as *clustered regularly interspaced short palindromic repeats* (*CRISPR*)/*CRISPR-associated* gene (*Cas*) systems is considered a promising novel strategy for several pathogens treatment. *CRISPR-Cas* acts by targeting and knocking out antibiotic-resistance genes and virulence factors. But, a limited number of studies have been conducted on *A. baumannii* treatment using a gene editing strategy so another research is required **[154]**.

Conclusions

The capability of *A. baumannii* has an infinite ability to acquire resistance mechanisms, enabling it to persist through the infection pathway and also to survive on healthcare facilities surfaces. However, the major crucial interest is the resistance emergence against the last resort of antimicrobial agents such as colistin and tigecycline which has led to an important challenge in the health care systems. Novel therapeutic options are a must to face the current multi or extended or pan-drug resistant pathogens, especially after the warning alarms of resistance toward "last-resort" antimicrobial agents. COVID-19 alarms the whole world to avoid the intractable nature of infections that can have serious and irreversible social and economic circumstances. The irrational use of antibiotics in hospitals can incredibly result in health hazards. The creation and construction of national and international protocols for antimicrobial stewardship programs would be a beneficial and promising opportunity to help physicians in making evidence-based treatment alternatives concerning antimicrobial treatment and implementation of better antibiotic use in hospitals.

Declarations

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Consent to publish

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Not available

Competing interests

The authors declare that they have no competing interests.

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Riham A. EL-Hakeem has collected the data for the manuscript under the supervision and guidance of authors; Sarra E Saleh, Mohammad M Aboulwafa, and Nadia A Hassouna, who have written the first draft of the manuscript. Sarra E Saleh and Mohammad M Aboulwafa have helped in writing and revising this manuscript. All authors have read and approved the final manuscript.

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