ERURJ 2024, 3, 1, 816-836
(Review)

Acinetobacter baumannii: An Overview of Virulence Factors, Resistance Mechanisms and Treatment Options of the Emerging Pathogen

Omar H. Badie[1]*, Ahmed F. Basyony[1], Dalia A. El-damasy[1], and Reham Samir[2]

[1] *Department of Microbiology and Immunology, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo 11829, Egypt*
[2] *Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt*

*Corresponding author: Omar H. Badie, E-mail: omar-hassan@eru.edu.eg , +201222674868

Received 18th July 2023, Revised 15th August 2023, Accepted 20th August 2023
DOI: 10.21608/erurj.2024.337760

ABSTRACT

In the current healthcare system, *Acinetobacter baumannii* is unquestionably one of the most aggressive bacteria causing nosocomial infections including pneumonia, bacteremia and wound infections. The frequent occurrence of *Acinetobacter baumannii* infections and outbreaks highlights the urgent requirement for using efficient antimicrobial agents to treat such cases due to the availability of few effective ones. This prompted the Centers for Disease Control and Prevention (CDC) to consider *Acinetobacter baumannii* as an urgent threat. Recent research on the virulence factors and resistance mechanisms of *Acinetobacter baumannii* is necessary to comprehend and combat this threat. Herein, we overviewed different virulence factors and resistance mechanisms involved in the pathogenesis of *Acinetobacter baumannii*. Virulence factors include outer membrane protein A (porins), biofilm formation, metal acquisition systems and lipopolysaccharide whereas antimicrobials resistance mechanisms involve β-lactamases, aminoglycosides-modifying enzymes, efflux systems, reduced membrane permeability and alteration of the target site of the antibiotics. Finally, a summary of potential and innovative therapies for infections caused by *Acinetobacter baumannii* was discussed.

Keywords: Acinetobacter baumannii, Infection, Virulence factors, Resistance mechanism

1. Introduction

High morbidity and mortality caused by *Acinetobacter baumannii* attracted the attention of the World Health Organization (WHO) to put this pathogen on the top of antimicrobial resistance research priority list (1).

The studies on *Acinetobacter* spp. started when it was first isolated from a soil sample and named *Micrococcus calcoaceticus* in 1911 (2). The genus *Acinetobacter* was officially documented only in 1971, by taxonomists based on common biochemical characters (2, 3). Although these bacteria show a twitching motility and coccobacillary morphology, they were named after the Greek word a-kinetos-bacter which means non-motile rod.

Molecular approaches have permitted identification of many available species within the *Acinetobacter* genus. This genus comprises strictly aerobic, non-fermentative, oxidase-negative, catalase-positive and non-pigmented Gram-negative bacteria (4-6). From the closely related species showing similar phenotypic and biochemical properties that are included in the *Acinetobacter calcoaceticus–Acinetobacter baumannii* complex (ACB complex), *A. baumannii* is considered as the commonest clinical species around the world (7). This opportunistic pathogen is one of the life-threatening nosocomial pathogens named ESKAPE, which include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. (8). *A. baumannii* causes serious infections, mainly ventilator-associated pneumonia, urinary tract, bloodstream, skin and soft tissue infections, particularly among patients in Intensive Care Units (ICUs) (9).

Unfortunately, a significant increase in the number of multi-drug resistant (MDR) *A. baumannii* isolates has been reported (10). In addition to innate resistance to several antibiotics, *A. baumannii* is flexibly acquiring or upregulating resistance genes, therefore limiting the effective therapeutic choices and rising mortality rates (10). Furthermore, *A. baumannii* has numerous potential virulence factors that permit its persistence in the environment, adherence to surfaces, invasion to host cells and the escape from the host immune system (11-14). *A. baumannii* has been considered as one of the most persistent pathogens causing nosocomial infections (1). As most clinical isolates of this Gram-negative bacteria are found to be multi-drug resistant, suitable alternative therapies are needed to control this infection (15).

2. Clinical Significance

A. baumannii is one of the most significant nosocomial pathogens, with known ability to cause infections like urinary tract infections, pneumonia, bacteremia, and wound infections (16). The most common clinical cases with high mortality rates include pneumonia and bacteremia (17). It results in a 26% mortality rate in medical facilities, rising to 43% in ICUs (18). The risk factors for acquiring MDR isolates involve recent exposure to antimicrobials, the application of urinary or venous catheters, severity of disease, duration of hospital accommodation, and recent surgical procedure (19-21). The risk of mortality from invasive *A. baumannii* infection has been also reported to be high, especially for isolates that are resistant to carbapenems (22).

2.1. Hospital-Acquired Pneumonia

One of the most common clinical cases associated with *A. baumannii* is hospital-acquired pneumonia (HAP), especially for patients on mechanical ventilator assistance (23). HAP is an infection of the pulmonary parenchyma in patients at least 48 h after admission to the hospital, or in 14 days after leaving the hospital. The clinical case of HAP principally involves the presence of "new lung infiltrate of an infectious source, leukocytosis, new-onset fever, purulent sputum, as well as deteriorated oxygenation" (24). On the other hand, ventilator-associated pneumonia (VAP) is an infection of pulmonary parenchyma appearing at least 48 h after endotracheal intubation, including also the same clinical situation of HAP. Despite the notable improvements in the understanding of the influencing causes and prevention, HAP and VAP remain to be frequent complications of hospitalized patients (24). Zhang and co-workers also reported in meta-analysis performed in China that the incidence of HAP was 12.8–20.4%, and that of VAP was 31.4–36.1% (25). The mortality rate of HAP has been reported to be 21–37.4% according to Behnia and co-workers (26), while the occurrence of HAP has been reported to extend hospital accommodation by 18–30 days (25). In large surveillance studies from the United States, 5 to 10% of cases of ICU-acquired pneumonia were caused by *A. baumannii* (27). The proportion of MDR *A. baumannii* among causative agents of HAP and VAP has been reported to be approximately 30–34% (28). The mortality rate of *A. baumannii* pneumonia was 37.2–48.1% (29). Upon screening of *A. baumannii* isolates obtained from patients with late-onset VAP hospitalized in some Egyptian

University hospitals, MDR-carbapenem resistant *A. baumannii* were frequently found with about 84% (30).

2.2. Bloodstream Infection

Bacteremia is a principal and widespread cause of the total mortality in patients with *A. baumannii* infection that ranges broadly from 29% to 63% (31-33). Together with the increasing exposure to antibiotics, multidrug resistance and carbapenem resistance, rates of bacteremia have been obviously escalating over years. Many previous studies have explored predictors of mortality in patients with *A. baumannii* bacteremia. Risk factors independently linked with mortality include selecting the suitable antimicrobial therapy, drug resistance, acuteness of illness, malignancy, and other comorbidities such as immunosuppression (34). In a study on bloodstream infections in patients with febrile neutropenic cancer in Egypt, MDR *A. baumannii* was responsible for about 13% of MDR Gram-negative bacteria causing bloodstream infections (35)

2.3. Wound Infection

A. baumannii wound infections have become an issue of interest with statements of rising incidences of outbreaks among victims of battle injuries and natural disasters (6). *A. baumannii* is commonly isolated from wounds of combat casualties from Iraq or Afghanistan (36). Highly resistant strains of *A. baumannii* were reported to be among of the most common pathogens causing severe and sometimes fatal wound infections (37). Moreover, *A. baumannii* may occasionally cause skin infections outside of the military population. The pathogen caused 15% of hospital-acquired skin infections in a previous study (38). It is a well-recognized pathogen in burn units and may be difficult to eradicate from such patients (39). While wound infection is regarded polymicrobial, the contribution of *A. baumannii* is progressively being linked to bad outcomes and may require specific treatment (37).

3. Transmission of Infection

A. baumannii can be transmitted through the closeness of patients or colonizers such as hospital surfaces, and even medical tools. Contamination of respiratory support equipment, suction appliances, and that used for intravascular access are actually potential modes of transmission of infection (40).

4. Virulence Factors

Numerous virulence factors help in the interaction of *A. baumannii* infection with the host effectively (13). The virulence potential of *A. baumannii* and the host reactions to infection generated by this bacterium are poorly understood (41). Virulence factors of *A. baumannii* were reported to include outer membrane proteins (porins), cell envelope factors, enzymes, biofilm production, motility, micronutrient acquisition systems and protein secretion systems (13). The discussed virulence factors are summarized in Table 1.

Table 1. Potential Virulence factors of *A. baumannii.*

Virulence factor	Role in interaction with host	References
Outer membrane protein A	Attachment process and host cell invasion	(42)
Biofilm formation	Attachment to epithelial cells and survival in hospitals	(43)
Metal acquisition systems	Acquiring patient nutrients leading to survival	(9, 44, 45)
Lipopolysaccharide	Resistance to human serum, survival in vivo and adhesion to host cells	(46-48)

According to reports, *A. baumannii* outer membrane protein A have a considerable impact on signal processing and pathogenesis (49). It is a significant surface-bound protein that aids in the attachment process, stimulating apoptosis at the beginning of infection, in addition to its role in epithelial cell invasion (42).

In order to survive in unfavourable environmental conditions and during host infection, bacteria often form complex structures known as biofilms that are attached to biotic or abiotic surfaces and implanted in extracellular polymeric materials in the form of matrix (50). Numerous host variables, including growth conditions, light, cell density and quorum sensing affect the formation of biofilms (51). The ability of *A. baumannii* to quickly attach to epithelial cells and a variety of medical devices, is essential for the pathogen's invasion of vulnerable hosts and survival in hospitals (43). Clinical strains of *A. baumannii* have the ability to create biofilm which is

especially prevalent on abiotic surfaces, in patients with sepsis, urinary tract catheters, or even shunt-associated meningitis (52).

The ability of *A. baumannii* to acquire patient nutrients, such as iron, manganese, and zinc, and adapt to the patient's metal-limited atmosphere is a key component in its endurance as a nosocomial pathogen (45). *A. baumannii* primarily uses five clusters of siderophores, which are iron-chelating molecules with high ability to capture iron. Additionally, the pathogen has direct iron receptors and transporters like FecA and FecI that enable the use of heme (53). Iron transporter alteration have been reported to lower virulence by reducing biofilm development and oxidative stress resistance (44).

Lipopolysaccharide (LPS), one of the virulence factors in Gram-negative pathogens, is involved in several stages of the illness process. The LPS from *A. baumannii* is crucial for resistance to typical human serum and provides a survival advantage in vivo. As an initial step in colonization, the antigenic O-polysaccharide of the LPS in conjunction with pili may encourage adhesion to host cells (46). *A. baumannii* pathogenicity is mostly determined by the existence of a capsule surrounding the bacterial surface, in addition to LPS. The capsule's repeating, tightly packed sugars operate as a barrier against a variety of environmental factors, including dryness, phagocytosis by host’s immune system, and certain antimicrobials (48). Despite variations in *A. baumannii* capsular sugars, the pathogen can always survive throughout infections and flourish in serum when enclosed in the capsule (54).

5. Resistance

Bacterial resistance is a normal outcome of how bacteria interact with their niche in the environment. Bacteria have accumulated a variety of defense mechanisms over time to secure their survival in a harsh environment. Consequently, it is thought that bacterial strains that are resistant to one or more antimicrobial substances have an intrinsic resistance, which is mediated by the resistance determinants (55). The development of the enzymes that can destroy the antimicrobial agent or stop its intracellular interaction to the target site is the general base of intrinsic resistance. This property of bacteria is demonstrated by their ability to continue exhibiting some level of antimicrobial compound resistance even in the absence of prior encounter (56). Bacteria have two genetic defense mechanisms against antibiotics: mutations, which typically alter the way the drug

works, and horizontal gene transfer acquisition of external genetic material (57). In terms of acquiring external material, mobile genetic elements allow bacteria to take up and transfer genes that are crucial to the spread of antibiotic resistance. Enzymatic (production of β-lactamases) and non-enzymatic processes including alteration of membrane permeability, activation of efflux pumps and alteration of the target site are the major mechanisms of the acquired antibiotic resistance. The wide cluster of antimicrobial resistance systems that have been depicted for *A. baumannii* is great and opponents those of other Gram-negative microbes (58, 59). The fast development of multi-and pandrug-resistant strains of *Acinetobacter* features its capacity to rapidly adapt to environmental pressing factors. The upregulation of innate resistance mechanisms combined with procurement of foreign determinants are special abilities that have brought *A. baumannii* incredible regard as a MDR pathogen (60). The discussed antimicrobial resistance mechanisms are presented in Figure 1.

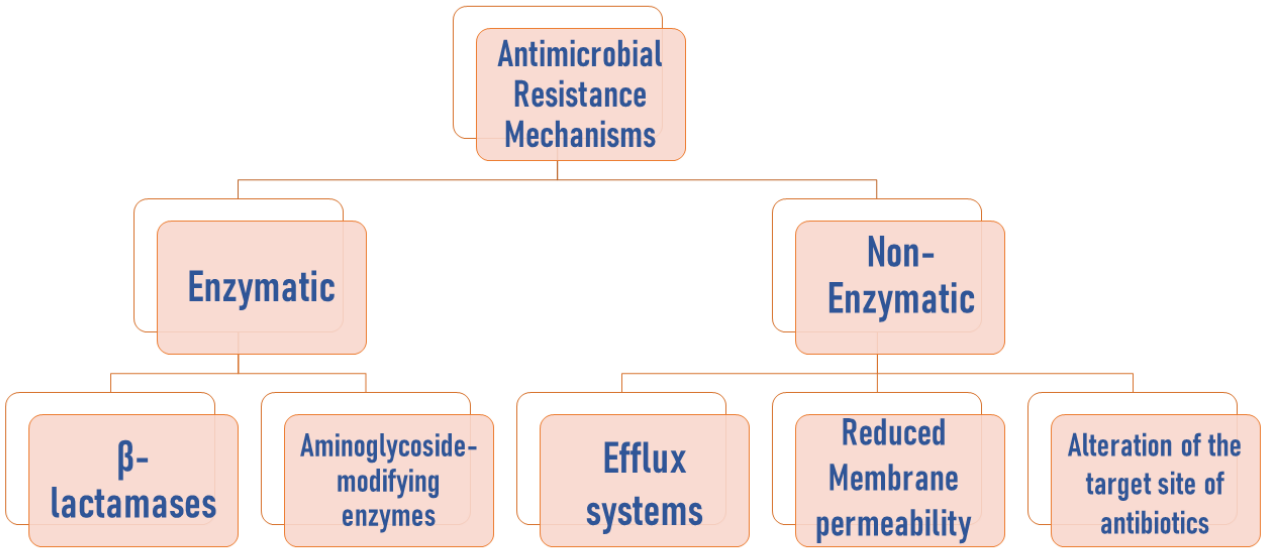

Figure 1. *Acinetobacter baumannii* antimicrobial resistance mechanisms

5.1. Enzymatic Mechanisms

The existence of transferable plasmids expressing a wide variety of enzymes implicated in the propagation of β-lactam resistance has promoted the prevalence of β-lactamase production in Gram-negative bacteria (55). Based on molecular and functional structure analysis, β-lactamases

were categorized (61). Using the amino acid sequences, Ambler divided the β-lactamases into four classes (A, B, C, and D). Serine is present in the active enzyme site for classes A, C, and D, whereas Zn-dependent metalloenzymes are present in class B (62). *A. baumannii* strains include all of the β-lactamases classified under the Ambler system.

The most common cause of β-lactam resistance is class A lactamases. These enzymes can hydrolyze penicillins and cephalosporins more effectively than carbapenems and are blocked by clavulanate (63). Over 2000 class A β-lactamases have been identified by phenotypic and biochemical investigations, with the majority of them being found in Gram-negative bacilli (64). Different molecular variants of the functional kinds of class A β-lactamases exhibit their capacity to hydrolyze cephalosporins and carbapenems (65). Numerous class A β-lactamases, including TEM, GES, CTX-M, SHV, SCO, PER, CARB, VEB, or KPC, were discovered in *A. baumannii*. Most of these (SHV-5, PER-1, PER-2, PER-7, TEM-92, CTX-M-15, VEB-1, GES-14, CARB -10, CTX-M-2) are Extended-spectrum β-lactamases (ESBL), while some (TEM-1, SCO-1) are narrow-spectrum β-lactamases.

Class B β-lactamases, often known as Metallo-β-lactamases (MBLs), have Zn or another heavy metal in the catalytic site as compared to class A enzymes, which have serine in the enzyme active site (66). Chelating substances like ethylenediaminetetraacetic acid (EDTA) can reduce the enzymatic activity of these forms of β-lactamases due to the chelation of the metal from the active enzyme site. *A. baumannii* has a variety of MBLs that have been identified (67). The bla-ampC gene that belongs to Class C β-lactamases was found in 65 of the 105 MDR *A. baumannii* strains in China (68). All 23 Taiwanese strains of the bacteria *A. baumannii* tested positive for ampC-type β-lactamases, according to the investigation (69).

In healthcare settings, carbapenem-resistant *A. baumannii* (CRAB) has emerged as a significant issue due to high prevalence of drug resistance. The most common mechanisms of resistance in CRAB are carbapenem hydrolyzing class D β-lactamases (CHDL), followed by class B MBLs (70). CHDL, also known as oxacillinases (OXA) for their capacity to hydrolyze oxacillin, contain serine in the active catalytic site. More than 400 OXA enzymes have been identified, the majority of which can hydrolyze carbapenems (61). One of the key mechanisms of resistance in *A. baumannii* is the existence of OXA-type β-lactamases, which hydrolyze carbapenems (71, 72). In *A. baumannii* strains, OXA enzymes such OXA-23, OXA-24/40, OXA-58, OXA-143, and OXA-235 are among the most common. OXA-23 was discovered in Scotland, spread over the

world, and is now present in large numbers in *A. baumannii* isolates (73, 74). OXA-type β-lactamase genes have been found on chromosomes or plasmids in *A. baumannii* strains (75). New Delhi Metallo β-lactamase-1 (NDM-1), a B β -lactamase pattern with a high occurrence, is receiving attention on a global scale. NDM-1 were classified as superbugs that were reportedly known to be impossible to treat. Using one of the detection techniques in a previous study performed in Egypt, the percentage of presence of NDM-1 gene was 44.44% of the MBLs producers (76).

One of the most crucial antibiotic groups for treating nosocomial infections brought on by *A. baumannii* strains is the aminoglycoside family (77). The primary mode of resistance in *A. baumannii* is the enzymatic alteration of aminoglycosides through the development of aminoglycoside-modifying enzymes that are divided into acetyltransferases, phosphotransferases, and nucleotidyl transferases depending on how they function (78). The primary aminoglycoside-modifying genes implicated in aminoglycoside resistance in *A. baumannii* are aac (3′)-I, aph (3′)-I, aac (6′)-Ib, ant (2″)-Ia, ant (3′)-I, aac(3)-Ia [aacC1], aac(3)-IIa [aacC2], aac(6′)-Ib [aacA4] (79).

5.2. Non-Enzymatic Mechanisms

When overexpressed, chromosomal genes encoding *A. baumannii* efflux systems can confer resistance to a number of antibiotics (80). Chromosome-encoded MDR efflux systems often contribute to intrinsic resistance by constitutive expression or acquired resistance through expression following mutation (81). Resistance Nodulation Division superfamily (RND), Multidrug and Toxic compound Extrusion family (MATE), Major Facilitator Superfamily (MFS), and Small Multidrug Resistance transporters (SMR) are four kinds of efflux pumps found in *A. baumannii* (71). The RND system, which includes the AdeABC pump and is the most prevalent one among the four efflux systems in *A. baumannii*, plays a crucial part in the organism's ability to withstand antibiotics, particularly aminoglycosides. The fusion protein AdeB, the outer membrane factor (AdeC), and the inner membrane of the pump (AdeA) make up the AdeABC pump (82). The adeRS operon, which encodes AdeABC, is expressed when the efflux pump is exposed to an excessive amount of hazardous substances or antibiotics, resulting in an MDR phenotype. This operon also contributes to the development of biofilm in *A. baumannii* (83). MATE is a different class of efflux pumps found in *A. baumannii*. AbeM, that belongs to MATE family was reported with other efflux pumps to play a role in the resistance to imipenem,

gentamicin, doxorubicin, norfloxacin, and ciprofloxacin (84). The MFS superfamily is crucial in the resistance of *A. baumannii* to many antibiotics including doxycycline, minocycline, chloramphenicol, tetracycline and fosfomycin (85-87). SMR, another efflux pump class reported in *A. baumannii*, which involves AbeS, with indicated participation in resistance to various antibiotics (88).

The Antimicrobial resistance might rise if the membrane permeability is reduced. By facilitating the transfer of molecules, the pores of the outer membrane play a crucial role in the virulence and resistance of different strains of *A. baumannii* (89). Reduced membrane porin density in *A. baumannii* is linked to increased carbapenem resistance (90).

One key mechanism of bacterial resistance is alteration of the target site of the antibiotics. This mechanism typically relies on point mutations that barely affect the homeostasis of bacterial cells. Mutation-mediated resistance mechanisms of *A. baumannii* to common antibiotics were reported. Spontaneous mutations in the gyrase and topoisomerase IV-encoding genes parC, gyrA, and gyrB occurred as resistance mechanisms to fluoroquinolones (91, 92). There are two known pathways for colistin resistance: First, mutations in the PmrAB two-component system modify the lipid A from LPS, and second, mutations in the lpxA, lpxC, and lpxD genes reduce the ability to produce LPS (93).

6. Treatment Options

Sensitive isolates of *A. baumannii* can be treated with conventional antibacterial agents, including the third and fourth generations of cephalosporin, carbapenems or fluoroquinolones (94). It was known that carbapenems were particularly effective at treating *A. baumannii* infections in vitro. Thus, carbapenems are one of the most important lines of defense for treating infections brought on by MDR *A. baumannii*. However, clinical strains of *A. baumannii* have become more resistant to carbapenems, especially in Europe, Latin America, Asia, and Australia (95).

Combined therapy is indicated once all conventional antibacterial agents become unsuccessful against *A. baumannii* (96). Combined therapy has shown exceptionally bactericidal activity against the MDR clinical isolates of *A. baumannii* (97, 98). Such synergic combinations include blends of two or three classes of the following antibacterials: sulbactam, tigecycline, aminoglycosides, polymyxins or β-lactams, such as broad-spectrum cephalosporins or carbapenems (99, 100).

Sulbactam, a common β-lactamase inhibitor, possesses an innate mechanism that makes it effective against *A. baumannii* isolates (101). Promising results of sulbactam against *A. baumannii* infections have been monitored both in vivo and in vitro (98). However, resistance to sulbactam has recently increased significantly so it is not recommended to use it empirically (102, 103).

Tigecycline, a synthetic derivative of minocycline, that acquires a particular mechanism of action with reported bacteriostatic activity against CRAB isolates (104). The treatment of *A. baumannii* infections, such as VAP, bacteremia, and skin infections using combination therapies including tigecycline, was previously reported (105, 106).

Clinicians have reconsidered the use of polymyxins, colistin in particular, for MDR *A. baumannii* infections as a result of the lack of adequate therapeutic choices (107). The effect of the bactericidal agent, colistin, depends mainly on the used concentration against *A. baumannii* (108). Colistin has demonstrated intravenous efficacy in the therapeutic outcomes of patients with meningitis or VAP, either in mono- or combination therapy (109, 110). However, the frequent use of colistin for the treatment of *A. baumannii* infections in patients with critical illness may result in rising resistance (111).

To develop better curative options for topical application, many institutions are working on small-molecule antibiotics that have a more narrow-spectrum with direct activity on *Acinetobacter* species (6).

7. Innovative Approaches for Treatment of *A. baumannii* Infections

Knowing that different *A. baumannii* strains has become resistant to many of the available antibiotics, the research has started to focus on the "post-antibiotic era," with special emphasis on the creation of innovative methods to stop the spread of MDR *A. baumannii*. The latest prevention approaches that include phage therapy, antimicrobial peptides, and the CRISPR Cas system will then be discussed.

Bacteriophages are viral parasites, that when genetically modified, can be used to make resistant strains more susceptible to antibiotics. Phage therapy has been revived as a result of the worrying rise in resistance rates to boost bacterial susceptibility by eradicating resistance and virulence markers (112). Additionally, in vitro and in vivo studies have demonstrated that phage

therapy has a promising likelihood of serving as an efficient and secure treatment for MDR *A. baumannii* strains (113-115).

Antimicrobial peptides (AMPs) might serve as a better option than antibiotics for preventing the spread of MDR *A. baumannii* strains. AMPs can be regarded as principal defense against infectious organisms. The capacity of AMPs to destroy cell membranes and cell walls, the inhibition of protein synthesis, nucleic acids, and the promotion of apoptosis and necrosis are the basic mechanisms of their antimicrobial effect. Due to these characteristics, AMPs have been proposed for preventing the spread of nosocomial infections (116). Several recent studies have reported the effect of AMPs on *A. baumannii* (117-120). Currently, the main goal of scientific research is to create technologies that will increase the effectiveness and specificity of AMPs in vivo, along with improving their safety profile and production costs (118, 121, 122).

Prokaryotes use the CRISPR-Cas system as an immune mechanism to battle off the invasion of foreign genetic material. A CRISPR array, a leader sequence, and Cas-related proteins are the typical components (123). Understanding how to disarm pathogens, develop effective therapeutics, and stop the horizontal gene transfer of antimicrobial resistance genes requires fundamental research into pathogen defense mechanisms and immunity, such as CRISPR-Cas systems. Recent studies involved understanding the CRISPR-Cas systems in *A. baumannii* (124, 125).

8. Conclusion

Because of its growing clinical value, there are plenty of studies about *A. baumannii*. It has a well-known capacity to endure in various healthcare settings and to develop antimicrobial resistance. The most problematic aspect of *A. baumannii* is its multidrug resistance, which renders new therapeutics useless against it. Antibiotic resistance mechanisms of *A. baumannii* include β-lactamases, enzymatic modification of aminoglycosides, overexpression of efflux pumps, reduced membrane porins, and alterations of target sites. To tackle the *A. baumannii* infection widespread in the meantime, we must understand how to maximize the efficacy of our present antimicrobial agents, possibly with combinational regimens concurrently with studying the different weapons of the threatening pathogen.

- **Conflict of Interest**

The authors declare no conflict of interest.

9. References

1. Monem S, Furmanek-Blaszk B, Łupkowska A, Kuczyńska-Wiśnik D, Stojowska-Swędrzyńska K, Laskowska E. Mechanisms protecting *Acinetobacter baumannii* against multiple stresses triggered by the host immune response, antibiotics, and outside host environment. International Journal of Molecular Sciences. 2020;21(15):5498.
2. Henriksen SD. *Moraxella, Acinetobacter,* and the Mimeae. Bacteriol Rev. 1973;37(4):522-61.
3. Elhosseiny NM, Attia ASJEm, infections. *Acinetobacter*: an emerging pathogen with a versatile secretome. 2018;7(1):1-15.
4. Gonzalez-Villoria AM, Valverde-Garduno V. Antibiotic-Resistant *Acinetobacter baumannii* Increasing Success Remains a Challenge as a Nosocomial Pathogen. Journal of Pathogens. 2016;2016:7318075.
5. Visca P, Seifert H, Towner KJ. *Acinetobacter* infection – an emerging threat to human health. IUBMB Life. 2011;63(12):1048-54.
6. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and Pathophysiological Overview of Acinetobacter Infections: a Century of Challenges. Clinical Microbiology Reviews. 2017;30(1):409-47.
7. Cerqueira GM, Peleg AY. Insights into *Acinetobacter baumannii* pathogenicity. IUBMB Life. 2011;63(12):1055-60.
8. Oliveira DMPD, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, et al. Antimicrobial Resistance in ESKAPE Pathogens. Clinical Microbiology Reviews. 2020;33(3):e00181-19.
9. Morris FC, Dexter C, Kostoulias X, Uddin MI, Peleg AY. The Mechanisms of Disease Caused by *Acinetobacter baumannii*. Frontiers in Microbiology. 2019;10.
10. Gallagher P, Baker S. Developing new therapeutic approaches for treating infections caused by multi-drug resistant *Acinetobacter baumannii*: *Acinetobacter baumannii* therapeutics. Journal of Infection. 2020;81(6):857-61.
11. García-Patiño MG, García-Contreras R, Licona-Limón P. The Immune Response against *Acinetobacter baumannii*, an Emerging Pathogen in Nosocomial Infections. Frontiers in Immunology. 2017;8.
12. Eze EC, Chenia HY, El Zowalaty ME. *Acinetobacter baumannii* biofilms: effects of physicochemical factors, virulence, antibiotic resistance determinants, gene regulation, and future antimicrobial treatments. Infect Drug Resist. 2018;11:2277-99.
13. Harding CM, Hennon SW, Feldman MF. Uncovering the mechanisms of *Acinetobacter baumannii* virulence. Nature Reviews Microbiology. 2018;16(2):91-102.
14. Parker SPaD. Innate Immune Responses to Acinetobacter baumannii in the Airway. Journal of Interferon & Cytokine Research. 2019;39(8):441-9.
15. Lood R, Winer BY, Pelzek AJ, Diez-Martinez R, Thandar M, Euler CW, et al. Novel Phage Lysin Capable of Killing the Multidrug-Resistant Gram-Negative Bacterium *Acinetobacter baumannii* in a Mouse Bacteremia Model. 2015;59(4):1983-91.
16. Dehbanipour R, Ghalavand Z. *Acinetobacter baumannii:* Pathogenesis, virulence factors, novel therapeutic options and mechanisms of resistance to antimicrobial agents with emphasis on tigecycline. Journal of Clinical Pharmacy and Therapeutics. 2022;47(11):1875-84.
17. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant *Acinetobacter baumannii:* in pursuit of an effective treatment. Clinical Microbiology and Infection. 2019;25(8):951-7.

18. Greene C, Vadlamudi G, Newton D, Foxman B, Xi C. The influence of biofilm formation and multidrug resistance on environmental survival of clinical and environmental isolates of *Acinetobacter baumannii*. American journal of infection control. 2016;44(5):e65-e71.
19. Cisneros JM, Rodríguez-Baño J, Fernández-Cuenca F, Ribera A, Vila J, Pascual A, et al. Risk-factors for the acquisition of imipenem-resistant *Acinetobacter baumannii* in Spain: a nationwide study. Clinical Microbiology and Infection. 2005;11(11):874-9.
20. Sheng W-H, Liao C-H, Lauderdale T-L, Ko W-C, Chen Y-S, Liu J-W, et al. A multicenter study of risk factors and outcome of hospitalized patients with infections due to carbapenem-resistant *Acinetobacter baumannii*. International Journal of Infectious Diseases. 2010;14(9):e764-e9.
21. Ng TM, Teng CB, Lye DC, Apisarnthanarak A. A multicenter case-case control study for risk factors and outcomes of extensively drug-resistant *Acinetobacter baumannii* bacteremia. Infect Control Hosp Epidemiol. 2014;35(1):49-55.
22. Lemos EV, de la Hoz FP, Einarson TR, McGhan WF, Quevedo E, Castañeda C, et al. Carbapenem resistance and mortality in patients with *Acinetobacter baumannii* infection: systematic review and meta-analysis. Clin Microbiol Infect. 2014;20(5):416-23.
23. Inchai J, Pothirat C, Bumroongkit C, Limsukon A, Khositsakulchai W, Liwsrisakun C. Prognostic factors associated with mortality of drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Journal of Intensive Care. 2015;3(1):9.
24. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61-e111.
25. Zhang Y, Yao Z, Zhan S, Yang Z, Wei D, Zhang J, et al. Disease burden of intensive care unit-acquired pneumonia in China: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2014;29:84-90.
26. Behnia M, Logan SC, Fallen L, Catalano P. Nosocomial and ventilator-associated pneumonia in a community hospital intensive care unit: a retrospective review and analysis. BMC research notes. 2014;7(1):1-9.
27. Weinstein RA, Gaynes R, Edwards JR, diseases NNISSJCi. Overview of nosocomial infections caused by gram-negative bacilli. 2005;41(6):848-54.
28. Costa RD, Baptista JP, Freitas R, Martins PJ. Hospital-acquired pneumonia in a multipurpose intensive care unit: one-year prospective study. Acta medica portuguesa. 2019;32(12):746-53.
29. Mohd Lim S, Zainal Abidin A, Liew SM, Roberts JA, Sime FB. The global prevalence of multidrug-resistance among *Acinetobacter baumannii* causing hospital-acquired and ventilator-associated pneumonia and its associated mortality: A systematic review and meta-analysis. Journal of Infection. 2019;79(6):593-600.
30. Tolba S, El Shatoury EH, Abo AlNasr NM. Prevalence of carbapenem resistant *Acinetobacter baumannii* (CRAB) in some Egyptian hospitals: evaluation of the use of blaOXA-51-like gene as species specific marker for CRAB. Egyptian Journal of Botany. 2019;59(3):723-33.
31. Gu Z, Han Y, Meng T, Zhao S, Zhao X, Gao C, et al. Risk Factors and Clinical Outcomes for Patients With *Acinetobacter baumannii* Bacteremia. Medicine (Baltimore). 2016;95(9):e2943.

32. Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant *Acinetobacter baumannii*. International Journal of Infectious Diseases. 2015;38:32-5.
33. Nutman A, Glick R, Temkin E, Hoshen M, Edgar R, Braun T, et al. A case-control study to identify predictors of 14-day mortality following carbapenem-resistant *Acinetobacter baumannii* bacteraemia. Clinical Microbiology and Infection. 2014;20(12):O1028-O34.
34. Lee Y-T, Kuo S-C, Yang S-P, Lin Y-T, Tseng F-C, Chen T-L, et al. Impact of appropriate antimicrobial therapy on mortality associated with *Acinetobacter baumannii* bacteremia: relation to severity of infection. Clinical infectious diseases. 2012;55(2):209-15.
35. Tohamy ST, Aboshanab KM, El-Mahallawy HA, El-Ansary MR, Afifi SS. Prevalence of multidrug-resistant Gram-negative pathogens isolated from febrile neutropenic cancer patients with bloodstream infections in Egypt and new synergistic antibiotic combinations. Infect Drug Resist. 2018;11:791-803.
36. Johnson EN, Burns TC, Hayda RA, Hospenthal DR, Murray CKJCID. Infectious complications of open type III tibial fractures among combat casualties. 2007;45(4):409-15.
37. Be NA, Allen JE, Brown TS, Gardner SN, McLoughlin KS, Forsberg JA, et al. Microbial profiling of combat wound infection through detection microarray and next-generation sequencing. Journal of clinical microbiology. 2014;52(7):2583-94.
38. Monnheimer M, Cooper P, Amegbletor HK, Pellio T, Groß U, Pfeifer Y, et al. High Prevalence of Carbapenemase-Producing *Acinetobacter baumannii* in Wound Infections, Ghana, 2017/2018. Microorganisms. 2021;9(3):537.
39. Trottier V, Segura PG, Namias N, King D, Pizano LR, Schulman CIJJobc, et al. Outcomes of *Acinetobacter baumannii* infection in critically ill burned patients. 2007;28(2):248-54.
40. Jung J, Park W. *Acinetobacter* species as model microorganisms in environmental microbiology: current state and perspectives. Applied Microbiology and Biotechnology. 2015;99(6):2533-48.
41. Bamunuarachchi NI, Khan F, Kim Y-M. Inhibition of virulence factors and biofilm formation of *Acinetobacter baumannii* by naturally-derived and synthetic drugs. Current Drug Targets. 2021;22(7):734-59.
42. Guo Y, Xun M, Han J. A bovine myeloid antimicrobial peptide (BMAP-28) and its analogs kill pan-drug-resistant *Acinetobacter baumannii* by interacting with outer membrane protein A (OmpA). Medicine. 2018;97(42).
43. Costa D, Johani K, Melo DS, Lopes L, Lopes Lima L, Tipple AFV, et al. Biofilm contamination of high-touched surfaces in intensive care units: epidemiology and potential impacts. Letters in applied microbiology. 2019;68(4):269-76.
44. Ajiboye TO, Skiebe E, Wilharm G. Contributions of ferric uptake regulator Fur to the sensitivity and oxidative response of *Acinetobacter baumannii* to antibiotics. Microbial Pathogenesis. 2018;119:35-41.
45. Tipton KA, Rather PN. An ompR-envZ two-component system ortholog regulates phase variation, osmotic tolerance, motility, and virulence in *Acinetobacter baumannii* strain AB5075. Journal of bacteriology. 2017;199(3):e00705-16.
46. Haseley SR, Pantophlet R, Brade L, Holst O, Brade H. Structural and serological characterisation of the O-antigenic polysaccharide of the lipopolysaccharide from *Acinetobacter junii* strain 65. European journal of biochemistry. 1997;245(2):477-81.

47. Khan K, Jalal K, Khan A, Al-Harrasi A, Uddin R. Comparative Metabolic Pathways Analysis and Subtractive Genomics Profiling to Prioritize Potential Drug Targets Against *Streptococcus pneumoniae*. Frontiers in Microbiology. 2022;12.
48. Singh JK, Adams FG, Brown MH. Diversity and function of capsular polysaccharide in *Acinetobacter baumannii*. Frontiers in Microbiology. 2019;9:3301.
49. Nie D, Hu Y, Chen Z, Li M, Hou Z, Luo X, et al. Outer membrane protein A (OmpA) as a potential therapeutic target for *Acinetobacter baumannii* infection. Journal of biomedical science. 2020;27(1):1-8.
50. Yang C-H, Su P-W, Moi S-H, Chuang L-Y. Biofilm formation in *Acinetobacter baumannii*: genotype-phenotype correlation. Molecules. 2019;24(10):1849.
51. Saipriya K, Swathi C, Ratnakar K, Sritharan V. Quorum-sensing system in *Acinetobacter baumannii*: a potential target for new drug development. Journal of applied microbiology. 2020;128(1):15-27.
52. Zeighami H, Valadkhani F, Shapouri R, Samadi E, Haghi F. Virulence characteristics of multidrug resistant biofilm forming *Acinetobacter baumannii* isolated from intensive care unit patients. BMC infectious diseases. 2019;19(1):1-9.
53. Morris FC, Dexter C, Kostoulias X, Uddin MI, Peleg AY. The mechanisms of disease caused by *Acinetobacter baumannii*. Frontiers in microbiology. 2019;10:1601.
54. Kenyon JJ, Hall RM. Variation in the complex carbohydrate biosynthesis loci of *Acinetobacter baumannii* genomes. PloS one. 2013;8(4):e62160.
55. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Microbiology spectrum. 2016;4(2):4.2. 15.
56. D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. Nature. 2011;477(7365):457-61.
57. Wright GD. Molecular mechanisms of antibiotic resistance. Chemical communications. 2011;47(14):4055-61.
58. Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global Challenge of Multidrug-Resistant *Acinetobacter baumannii*. Antimicrobial Agents and Chemotherapy. 2007;51(10):3471-84.
59. Poirel L, Nordmann P. Carbapenem resistance in *Acinetobacter baumannii:* mechanisms and epidemiology. Clinical Microbiology and Infection. 2006;12(9):826-36.
60. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: Emergence of a Successful Pathogen. Clinical Microbiology Reviews. 2008;21(3):538-82.
61. Bush K, Jacoby GA. Updated functional classification of β-lactamases. Antimicrobial agents and chemotherapy. 2010;54(3):969-76.
62. Ambler RP. The structure of β-lactamases. Philosophical Transactions of the Royal Society of London B, Biological Sciences. 1980;289(1036):321-31.
63. Jeon JH, Lee JH, Lee JJ, Park KS, Karim AM, Lee C-R, et al. Structural basis for carbapenem-hydrolyzing mechanisms of carbapenemases conferring antibiotic resistance. International journal of molecular sciences. 2015;16(5):9654-92.
64. Naas T, Dortet L, I Iorga B. Structural and functional aspects of class A carbapenemases. Current drug targets. 2016;17(9):1006-28.
65. Bush K. The ABCD's of β-lactamase nomenclature. Journal of Infection and Chemotherapy. 2013;19(4):549-59.
66. Palzkill T. Metallo-β-lactamase structure and function. Annals of the New York Academy of Sciences. 2013;1277(1):91-104.

67. Aoki N, Ishii Y, Tateda K, Saga T, Kimura S, Kikuchi Y, et al. Efficacy of calcium-EDTA as an inhibitor for metallo-β-lactamase in a mouse model of *Pseudomonas aeruginosa* pneumonia. Antimicrobial agents and chemotherapy. 2010;54(11):4582-8.
68. Lin M-F, Chang K-C, Lan C-Y, Chou J, Kuo J-W, Chang C-K, et al. Molecular epidemiology and antimicrobial resistance determinants of multidrug-resistant *Acinetobacter baumannii* in five proximal hospitals in Taiwan. Japanese journal of infectious diseases. 2011;64(3):222-7.
69. Sun X, Liu B, Chen Y, Huang H, Wang G, Li F, et al. Molecular characterization of Ambler class A to D β-lactamases, IS Aba1, and integrons reveals multidrug-resistant *Acinetobacter* spp. isolates in northeastern China. Journal of Chemotherapy. 2016;28(6):469-75.
70. Radwan M Sahar SMS, El-Damacy, M DAaHO. Microbiological Study on Nosocomial *Acinetobacter baumannii* Infection with Molecular Characterization of Metallo Beta- Lactamases. Journal of Medical Microbiology & Diagnosis. 2020; 09.
71. Lin M-F, Lan C-Y. Antimicrobial resistance in *Acinetobacter baumannii*: From bench to bedside. World Journal of Clinical Cases: WJCC. 2014;2(12):787.
72. Nowak P, Paluchowska P. *Acinetobacter baumannii*: biology and drug resistance—role of carbapenemases. Folia histochemica et cytobiologica. 2016;54(2):61-74.
73. Davandeh I, Erac B, Aydemir SŞ. Investigation of class-d beta-lactamases causing carbapenem resistance in clinical *Acinetobacter baumannii* isolates. Turkish Journal of Medical Sciences. 2017;47(5):1661-6.
74. McLeod DC, Lyon JA. Imipenem/cilastatin: the first carbapenem antibiotic. Drug intelligence & clinical pharmacy. 1985;19(12):894-9.
75. Evans BA, Amyes SG. OXA β-lactamases. Clinical microbiology reviews. 2014;27(2):241-63.
76. Shabayek SM, El-Damasy DA, Hassanin O, Radwan s. Testing of antibiotic combinations in NDM-1-producing nosocomial carbapenem resistant *Acinetobacter baumannii*. Azhar International Journal of Pharmaceutical and Medical Sciences. 2021;1(1):32-9.
77. Zhou Y, Yu H, Guo Q, Xu X, Ye X, Wu S, et al. Distribution of 16S rRNA methylases among different species of Gram-negative bacilli with high-level resistance to aminoglycosides. European journal of clinical microbiology & infectious diseases. 2010;29(11):1349-53.
78. Tada T, Miyoshi-Akiyama T, Kato Y, Ohmagari N, Takeshita N, Hung NV, et al. Emergence of 16S rRNA methylase-producing *Acinetobacter baumannii* and *Pseudomonas aeruginosa* isolates in hospitals in Vietnam. BMC infectious diseases. 2013;13(1):1-6.
79. Sheikhalizadeh V, Hasani A, Rezaee MA, Rahmati-Yamchi M, Hasani A, Ghotaslou R, et al. Comprehensive study to investigate the role of various aminoglycoside resistance mechanisms in clinical isolates of *Acinetobacter baumannii*. Journal of Infection and Chemotherapy. 2017;23(2):74-9.
80. Chen H, Cao J, Zhou C, Liu H, Zhang X, Zhou T. Biofilm formation restrained by subinhibitory concentrations of tigecyclin in *Acinetobacter baumannii* is associated with downregulation of efflux pumps. Chemotherapy. 2017;62(2):128-33.
81. Poole K. Efflux-mediated antimicrobial resistance. Journal of Antimicrobial Chemotherapy. 2005;56(1):20-51.
82. Coyne S, Courvalin P, Périchon B. Efflux-mediated antibiotic resistance in *Acinetobacter* spp. Antimicrobial agents and chemotherapy. 2011;55(3):947-53.

83. Yoon E-J, Nait Chabane Y, Goussard S, Snesrud E, Courvalin P, Dé E, et al. Contribution of resistance-nodulation-cell division efflux systems to antibiotic resistance and biofilm formation in *Acinetobacter baumannii*. MBio. 2015;6(2):e00309-15.
84. Su X-Z, Chen J, Mizushima T, Kuroda T, Tsuchiya T. AbeM, an H+-coupled *Acinetobacter baumannii* multidrug efflux pump belonging to the MATE family of transporters. Antimicrobial agents and chemotherapy. 2005;49(10):4362-4.
85. Roca I, Marti S, Espinal P, Martinez P, Gibert I, Vila J. CraA, a major facilitator superfamily efflux pump associated with chloramphenicol resistance in *Acinetobacter baumannii*. Antimicrobial agents and chemotherapy. 2009;53(9):4013-4.
86. Ribera A, Roca I, Ruiz J, Gibert I, Vila J. Partial characterization of a transposon containing the tet (A) determinant in a clinical isolate of *Acinetobacter baumannii*. Journal of Antimicrobial Chemotherapy. 2003;52(3):477-80.
87. Sharma A, Sharma R, Bhattacharyya T, Bhando T, Pathania R. Fosfomycin resistance in *Acinetobacter baumannii* is mediated by efflux through a major facilitator superfamily (MFS) transporter—AbaF. Journal of Antimicrobial Chemotherapy. 2016;72(1):68-74.
88. Lytvynenko I, Brill S, Oswald C, Pos KM. Molecular basis of polyspecificity of the small multidrug resistance efflux pump AbeS from *Acinetobacter baumannii*. Journal of Molecular Biology. 2016;428(3):644-57.
89. Lee C-R, Lee JH, Park M, Park KS, Bae IK, Kim YB, et al. Biology of *Acinetobacter baumannii*: pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Frontiers in cellular and infection microbiology. 2017;7:55.
90. Catel-Ferreira M, Coadou G, Molle V, Mugnier P, Nordmann P, Siroy A, et al. Structure–function relationships of CarO, the carbapenem resistance-associated outer membrane protein of *Acinetobacter baumannii*. Journal of antimicrobial chemotherapy. 2011;66(9):2053-6.
91. Park S, Lee KM, Yoo YS, Yoo JS, Yoo JI, Kim HS, et al. Alterations of gyrA, gyrB, and parC and activity of efflux pump in fluoroquinolone-resistant *Acinetobacter baumannii*. Osong public health and research perspectives. 2011;2(3):164-70.
92. Ardebili A, Lari AR, Beheshti M, Lari ER. Association between mutations in gyrA and parC genes of *Acinetobacter baumannii* clinical isolates and ciprofloxacin resistance. Iranian journal of basic medical sciences. 2015;18(6):623.
93. Adams MD, Nickel GC, Bajaksouzian S, Lavender H, Murthy AR, Jacobs MR, et al. Resistance to colistin in *Acinetobacter baumannii* associated with mutations in the PmrAB two-component system. Antimicrobial agents and chemotherapy. 2009;53(9):3628-34.
94. Garnacho-Montero J, Timsit J-F. Managing Acinetobacter baumannii infections. Current opinion in infectious diseases. 2019;32(1):69-76.
95. Hamidian M, Nigro SJ. Emergence, molecular mechanisms and global spread of carbapenem-resistant *Acinetobacter baumannii*. Microbial genomics. 2019;5(10).
96. Lenhard JR, Thamlikitkul V, Silveira FP, Garonzik SM, Tao X, Forrest A, et al. Polymyxin-resistant, carbapenem-resistant *Acinetobacter baumannii* is eradicated by a triple combination of agents that lack individual activity. Journal of Antimicrobial Chemotherapy. 2017;72(5):1415-20.
97. Wang Y, Li H, Xie X, Wu X, Li X, Zhao Z, et al. In vitro and in vivo assessment of the antibacterial activity of colistin alone and in combination with other antibiotics against *Acinetobacter baumannii* and *Escherichia coli*. Journal of Global Antimicrobial Resistance. 2020;20:351-9.

98. Rodriguez CH, Brune A, Nastro M, Vay C, Famiglietti A. In vitro synergistic activity of the sulbactam/avibactam combination against extensively drug-resistant Acinetobacter baumannii. Journal of Medical Microbiology. 2020;69(7):928-31.
99. Azimi L, Tahbaz SV, Alaghehbandan R, Alinejad F, Lari AR. Synergistic Effect of Tazobactam on Amikacin MIC in *Acinetobacter baumannii* Isolated from Burn Patients in Tehran, Iran. Current Pharmaceutical Biotechnology. 2020;21(10):997-1004.
100. Zusman O, Altunin S, Koppel F, Dishon Benattar Y, Gedik H, Paul M. Polymyxin monotherapy or in combination against carbapenem-resistant bacteria: systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2016;72(1):29-39.
101. Bassetti M, Labate L, Russo C, Vena A, Giacobbe DR. Therapeutic options for difficult-to-treat *Acinetobacter baumannii* infections: a 2020 perspective. Expert Opinion on Pharmacotherapy. 2021;22(2):167-77.
102. Yang Y, Fu Y, Lan P, Xu Q, Jiang Y, Chen Y, et al. Molecular Epidemiology and Mechanism of Sulbactam Resistance in Acinetobacter baumannii Isolates with Diverse Genetic Backgrounds in China. Antimicrobial Agents and Chemotherapy. 2018;62(3):e01947-17.
103. Garnacho-Montero J, Dimopoulos G, Poulakou G, Akova M, Cisneros JM, De Waele J, et al. Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU. Intensive Care Medicine. 2015;41(12):2057-75.
104. Qin Y, Zhang J, Wu L, Zhang D, Fu L, Xue X. Comparison of the treatment efficacy between tigecycline plus high-dose cefoperazone-sulbactam and tigecycline monotherapy against ventilator-associated pneumonia caused by extensively drug-resistant *Acinetobacter baumannii*. International Journal Of Clinical Pharmacology And Therapeutics. 2018;56(3):120.
105. Assimakopoulos SF, Karamouzos V, Lefkaditi A, Sklavou C, Kolonitsiou F, Christofidou M, et al. Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant *Acinetobacter baumannii*: a case series study. Le Infezioni in Medicina. 2019;27(1):11-6.
106. Jean S-S, Hsieh T-C, Hsu C-W, Lee W-S, Bai K-J, Lam C. Comparison of the clinical efficacy between tigecycline plus extended-infusion imipenem and sulbactam plus imipenem against ventilator-associated pneumonia with pneumonic extensively drug-resistant *Acinetobacter baumannii* bacteremia, and correlation of clinical efficacy with in vitro synergy tests. Journal of Microbiology, Immunology and Infection. 2016;49(6):924-33.
107. Bian X, Liu X, Feng M, Bergen PJ, Li J, Chen Y, et al. Enhanced bacterial killing with colistin/sulbactam combination against carbapenem-resistant *Acinetobacter baumannii*. International Journal of Antimicrobial Agents. 2021;57(2):106271.
108. Chamoun S, Welander J, Martis-Thiele M-M, Ntzouni M, Claesson C, Vikström E, et al. Colistin Dependence in Extensively Drug-Resistant *Acinetobacter baumannii* Strain Is Associated with IS Ajo2 and IS Aba13 Insertions and Multiple Cellular Responses. International journal of molecular sciences. 2021;22(2):576.
109. Makris D, Petinaki E, Tsolaki V, Manoulakas E, Mantzarlis K, Apostolopoulou O, et al. Colistin versus colistin combined with ampicillin-sulbactam for multiresistant *Acinetobacter baumannii* ventilator-associated pneumonia treatment: an open-label prospective study. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2018;22(2):67.
110. Chusri S, Sakarunchai I, Kositpantawong N, Panthuwong S, Santimaleeworagun W, Pattharachayakul S, et al. Outcomes of adjunctive therapy with intrathecal or intraventricular administration of colistin for post-neurosurgical meningitis and ventriculitis due to carbapenem-

resistant *Acinetobacter baumannii*. International journal of antimicrobial agents. 2018;51(4):646-50.
111. Liu J, Shu Y, Zhu F, Feng B, Zhang Z, Liu L, et al. Comparative efficacy and safety of combination therapy with high-dose sulbactam or colistin with additional antibacterial agents for multiple drug-resistant and extensively drug-resistant *Acinetobacter baumannii* infections: A systematic review and network meta-analysis. Journal of Global Antimicrobial Resistance. 2021;24:136-47.
112. Lin DM, Koskella B, Lin HC. Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. World journal of gastrointestinal pharmacology and therapeutics. 2017;8(3):162.
113. Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J, Lessor L, et al. Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant Acinetobacter baumannii Infection. Antimicrobial Agents and Chemotherapy. 2017;61(10):e00954-17.
114. Hua Y, Luo T, Yang Y, Dong D, Wang R, Wang Y, et al. Phage therapy as a promising new treatment for lung infection caused by carbapenem-resistant *Acinetobacter baumannii* in mice. Frontiers in microbiology. 2018:2659.
115. Jeon J, Park J-H, Yong D. Efficacy of bacteriophage treatment against carbapenem-resistant *Acinetobacter baumannii* in *Galleria mellonella* larvae and a mouse model of acute pneumonia. BMC microbiology. 2019;19(1):1-14.
116. Kumar P, Kizhakkedathu JN, Straus SK. Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility in vivo. Biomolecules. 2018;8(1):4.
117. Mohan NM, Zorgani A, Jalowicki G, Kerr A, Khaldi N, Martins M. Unlocking NuriPep 1653 from common pea protein: A potent antimicrobial peptide to tackle a pan-drug resistant *Acinetobacter baumannii*. Frontiers in microbiology. 2019;10:2086.
118. Jenei S, Tiricz H, Szolomájer J, Tímár E, Klement É, Al Bouni MA, et al. Potent chimeric antimicrobial derivatives of the Medicago truncatula NCR247 symbiotic peptide. Frontiers in microbiology. 2020:270.
119. Jaśkiewicz M, Neubauer D, Kazor K, Bartoszewska S, Kamysz W. Antimicrobial Activity of Selected Antimicrobial Peptides Against Planktonic Culture and Biofilm of *Acinetobacter baumannii*. Probiotics and Antimicrobial Proteins. 2019;11(1):317-24.
120. Hacioglu M, Oyardi O, Bozkurt-Guzel C, Savage PB. Antibiofilm activities of ceragenins and antimicrobial peptides against fungal-bacterial mono and multispecies biofilms. The Journal of Antibiotics. 2020;73(7):455-62.
121. Khan A, Xu M, Wang T, You C, Wang X, Ren H, et al. Catechol cross-linked antimicrobial peptide hydrogels prevent multidrug-resistant *Acinetobacter baumannii* infection in burn wounds. Bioscience Reports. 2019;39(6).
122. Taheri B, Mohammadi M, Momenzadeh N, Farshadzadeh Z, Roozbehani M, Dehghani P, et al. Substitution of lysine for isoleucine at the center of the nonpolar face of the antimicrobial peptide, piscidin-1, leads to an increase in the rapidity of bactericidal activity and a reduction in toxicity. Infection and Drug Resistance. 2019:1629-47.
123. Shabbir MAB, Shabbir MZ, Wu Q, Mahmood S, Sajid A, Maan MK, et al. CRISPR-cas system: biological function in microbes and its use to treat antimicrobial resistant pathogens. Annals of Clinical Microbiology and Antimicrobials. 2019;18(1):21.

124. Guo T, Sun X, Li M, Wang Y, Jiao H, Li G. The Involvement of the csy1 Gene in the Antimicrobial Resistance of *Acinetobacter baumannii*. Frontiers in Medicine. 2022;9.
125. Wang Y, Yang J, Sun X, Li M, Zhang P, Zhu Z, et al. CRISPR-Cas in *Acinetobacter baumannii* Contributes to Antibiotic Susceptibility by Targeting Endogenous AbaI. Microbiology Spectrum. 2022;10(4):e00829-22.