Impact of Therapeutics on Carbapenem-Resistant *Acinetobacter baumannii*

Journal- Research & Review: Journal of Microbiology and Virology.

Article Received- April 23, 2024

Article Accepted- June 09, 2024

Article Published-

Article Type- Research

ISSN- 2230-9853, Volume 14, Issue 1, Year 2024.

Raj Nandini[1], Deepanshi Kaura[2], Reema Gabrani[3]*

[1,2] Students, Department of Biotechnology, Jaypee Institute of Information Technology, A-10, Sector-62, Noida, Uttar Pradesh-201307

[3] Professor, Department of Biotechnology, Jaypee Institute of Information Technology, A-10, Sector-62, Noida, Uttar Pradesh-201307

*Email: *Corresponding author: reema.gabrani@mail.jiit.ac.in*

ABSTRACT

Acinetobacter baumannii, a formidable pathogen in healthcare settings, poses a significant threat due to its propensity to cause nosocomial infections. This bacterium exhibits several attributes that enable it to evade the human body's natural defenses. *A. baumannii*'s remarkable adaptability is highlighted by its ease in acquiring antibiotic resistance determinants, rendering it challenging to treat. Its ability to thrive in hospital environments underscores the urgent need for stringent infection control practices and enhanced sanitation measures. Its resistance to beta-lactam antibiotics and its unique ability to form biofilms - resilient communities of microorganisms adhering to surfaces, offers a protective shield against antibiotics and promote the exchange of genetic material.

This review delves into the intricacies of *A. baumannii*'s resistance to well-known antibiotics, like Carbapenems, biofilm formation, aminoglycoside-modifying enzymes, antibiotic-hydrolysing genes, overexpression of efflux pumps, and alteration of outer membrane porins. We examine the various factors that influence resistance phenotypes and genes within biofilms through mechanisms such as conjugation and transformation. In addition, we investigate both intrinsic and extrinsic factors affecting the biofilm formation process, including surface properties, growth conditions, and growth medium.

Device-related infections associated with *A. baumannii* colonization are a significant concern in healthcare. Research into novel antimicrobial agents and the development of rapid diagnostic tools are vital steps toward mitigating the impact of *A. baumannii* in clinical settings. The review outlines various strategies for preventing *A. baumannii* resistance, including the use of antibiotic combinations, monoclonal antibodies, quorum sensing inhibitors, efflux pump inhibitors, antimicrobial peptides, and phage therapy. Understanding the multifaceted attributes of *A. baumannii*, and its mechanisms of resistance is critical for developing effective interventions to combat this challenging pathogen in healthcare settings.

Keywords: Aminoglycoside-modifying enzymes; Antibiotic resistance; Antimicrobial peptides; Biofilm; Efflux pumps; Nosocomial infections

INTRODUCTION

Acinetobacter baumannii, classified as a gram-negative bacterium, has emerged as a significant opportunistic pathogen, with notable prevalence in healthcare environments [1]. Its capability to induce a range of infections, combined with a troubling propensity to develop antibiotic resistance, has elevated the pathogen to a considerable public health concern on a global scale. The emergence of carbapenem-resistant *A. baumannii* (CRAB) has exacerbated the complexities associated with treating infections instigated by this pathogen [2]. CRAB's resistance to carbapenem antibiotics, once the frontline defence against *Acinetobacter* infections, has led to increased morbidity, mortality, and prolonged hospitalization periods.

The escalation of *A. baumannii* as a pathogen associated with healthcare settings is underscored by its growing incidence, particularly among combat personnel returning from conflict zones

[3] ,prominently observed in Iraq, where it gained the nickname "Iraqibacter" [4]. The adaptability of Acinetobacter baumannii, coupled with its resistance mechanisms and the ineffectiveness of antibiotic therapy, has raised significant global concerns, as emphasized by international health authorities such as the World Health Organization (WHO) and the Center for Disease Control and Prevention [5]. Its ability to colonize various body sites, including the blood, urinary tract, lungs, and wounds, further complicates healthcare protocols, making it essential to understand its biology and resistance mechanisms comprehensively.

This comprehensive exploration delves into the multifaceted aspects of *A. baumannii*, focusing on its biology, antibiotic resistance mechanisms, and the diseases it causes, particularly in the context of carbapenem resistance. The report encompasses a brief about the diverse range of diseases it induces, and the current therapeutic options available, which are often limited and met with inefficacy. By uncovering the intricacies of this formidable pathogen, we aim to contribute valuable insights to the field, paving the way for innovative approaches to combat its infections and mitigate the challenges it poses in healthcare settings.

The intricate resistance mechanisms employed by CRAB, including the production of carbapenemases, alteration of outer membrane porins, aminoglycoside-modifying enzymes, and biofilm formation, are scrutinized [6]. Through a detailed examination of its biology and resistance mechanisms, this review aims to shed light on potential avenues for therapeutic advancements, ultimately improving patient outcomes and enhancing healthcare practices in the face of this formidable adversary.

In response to the challenges posed by CRAB, researchers have explored novel therapeutic avenues, investigating distinct approaches like antimicrobial peptides, monoclonal antibodies and more. These therapeutics provide valuable insights into potential advancements and highlight the importance of diverse strategies in the quest to combat CRAB infections.

As the global healthcare community grapples with the escalating threat of antibiotic-resistant pathogens, understanding the intricacies of *A. baumannii* and exploring innovative therapeutic options are imperative for improving patient outcomes and shaping the future of infectious disease management.

DISEASES CAUSED BY CRAB

CRAB poses a substantial threat within healthcare environments, contributing to a broad spectrum of infections [7]. Its high drug resistance rates, especially the emergence of carbapenem-resistant strains, have significantly impacted the management and treatment of these infections [8]. Figure 1 depicts a flowchart of different diseases caused by CRAB.

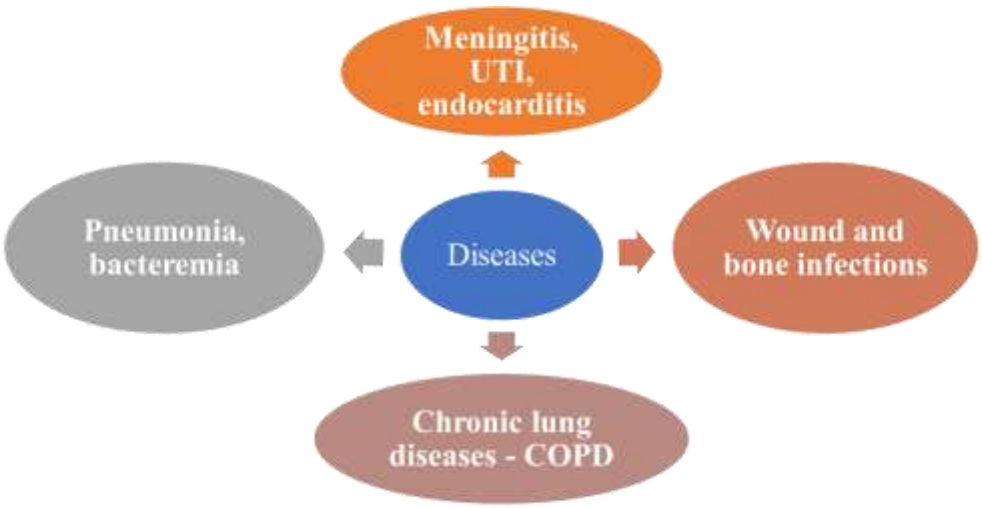

Fig. 1 Flowchart highlighting the diseases caused by CRAB.

2.1 Pneumonia and Blood Stream Infections

CRAB is known to cause severe pneumonia and bloodstream infections [9]. These infections can be life-threatening, particularly in immunocompromised patients or those with underlying health conditions. Patients requiring mechanical ventilation face a heightened risk, as *A. baumannii* can develop biofilms on the surface of the endotracheal tube. This phenomenon may contribute to the relatively elevated rates of colonization observed in the lower respiratory tract [3].

2.2 Infections Related to Medical Devices

CRAB is also commonly associated with infections related to medical devices. It can happen through - the hands of health care staff, contact with an infected person, venous catheters, urinary catheters, and airborne infection when an infected person coughs or sneezes.

Infections caused by *Acinetobacter baumannii* rarely manifest outside of healthcare settings. Nevertheless, individuals with compromised immune systems, chronic lung disease, or diabetes may exhibit increased susceptibility to such infections. People infected by this bacterium generally have prolonged hospital stays [3].

2.3 Battlefield Trauma and Other Wounds

CRAB is a significant concern in battlefield trauma and other types of wounds. This bacterium has been recognized as a frequent culprit in wound infections among military personnel wounded in combat, as well as in civilian trauma patients. It is extensively documented as a pathogen in burn units and presents challenges in their treatment.

2.4 Diseases due to Biofilm Formation

CRAB is acknowledged for its propensity to form biofilms, which are communities of bacteria enclosed within a protective matrix, adhering to surfaces. These biofilms can lead to the development of various diseases, such as meningitis, catheter-associated UTIs, surgical site and wound infections, endocarditis (infection of the lining and valves of the heart), bone infections, and bacteremia [3].

MECHANISMS OF RESISTANCE

The formidable challenge of carbapenem resistance in Acinetobacter baumannii within clinical settings requires a thorough grasp of the complex mechanisms employed by this pathogen. These resistance mechanisms can be broadly classified into three main groups: enzymes that render antibiotics inactive, diminished entry into the bacterial target site, and modification of the target or cellular functions through mutations. Furthermore, A. baumannii showcases a noteworthy ability to swiftly amass resistance determinants, enhancing its resilience in healthcare environments [10].

3.1 Enzymes Inactivating Antibiotics - Beta-lactamases

Acinetobacter baumannii employs a sophisticated arsenal of resistance mechanisms, prominently featuring the utilisation of beta-lactamases. These enzymes serve as a frontline defence, hydrolyzing antibiotics and imparting resistance against penicillins, cephalosporins, and carbapenems. The beta-lactam ring, a structural hallmark shared by these antibiotics, becomes a primary target for hydrolysis by these enzymes, rendering the antibiotics inactive and disrupting their ability to inhibit bacterial cell wall synthesis [10].

The resistance strategies employed by *A. baumannii* extend beyond beta-lactamase activity, encompassing increased efflux and decreased influx of antibiotics. Some strains of *A. baumannii* elevate the efflux of antibiotics, effectively pumping them out of the bacterial cell and reducing their intracellular concentration. Simultaneously, beta-lactamases contribute to reduced antibiotic influx by modifying or degrading these drugs before they reach their intended target sites within the bacterial cell [10].

Furthermore, beta-lactamases play a crucial role in protecting specific sites on the bacterial cell, preventing antibiotics from binding and exerting their inhibitory effects. The target molecules of these antibiotics, including penicillins, synthetic cephalosporins, and carbapenems, share the common beta-lactam ring. The cellular targets for these antibiotics are penicillin-binding proteins (PBPs), which play a fundamental role in bacterial cell wall synthesis [10].

In the synthesis process, PBPs catalyze the final step, transpeptidation, in peptidoglycan synthesis. Preventing transpeptidation disrupts the assembly of the bacteria's cell wall, resulting in the breakdown of the cell structure and eventual bacterial demise [10].

The consequences of beta-lactamase activity in *A. baumannii* are profound, contributing significantly to resistance against various beta-lactam antibiotics. When coupled with other resistance mechanisms, such as increased efflux and decreased influx, *A. baumannii* emerges as a formidable nosocomial pathogen, posing a serious challenge in clinical settings [10].

The classification of beta-lactamases in *A. baumannii* includes different classes based on their substrate specificity and structural characteristics. Class A hydrolyzes cephalosporins and penicillins, constrained by clavulanic acid. Class B or the metallo beta-lactamases catalyze the hydrolysis of almost all beta-lactams, inhibited by EDTA due to the presence of Zn at the active

site. Class C or the chromosomally-mediated AmpC contributes to resistance to third-generation cephalosporins. Class D or Oxicillinases are involved in carbapenem hydrolysis. Figure 2 shows how the beta-lactamases contribute to the antibiotic resistance.

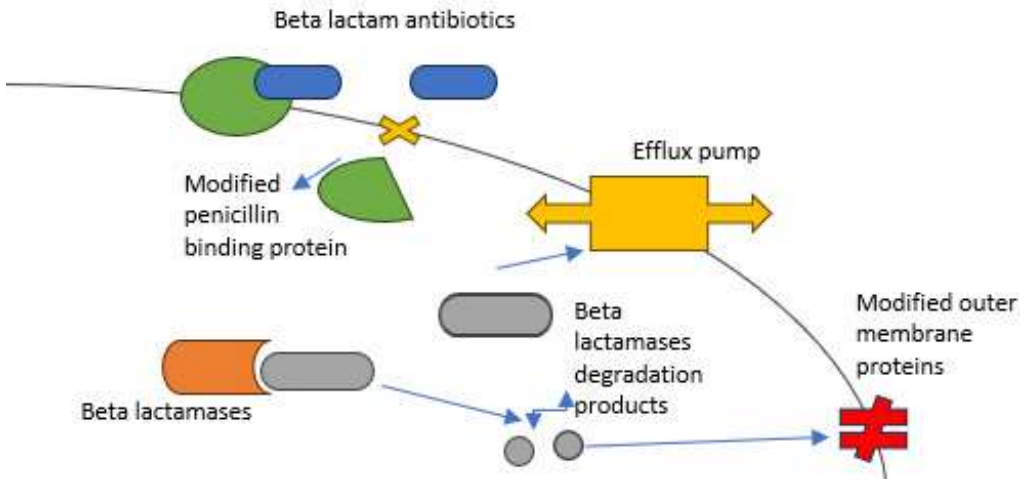

Fig 2: Resistance mechanism of beta-lactamases

3.2 Reduced Entry into the Target Site

3.2.1 Porin Channels and Outer Membrane Proteins

Porin channels, crucial protein conduits embedded in the outer bacterial membrane, play a pivotal role in facilitating the entry of nutrients and drugs into bacterial cells. In the context of *Acinetobacter baumannii*, certain strains exhibit a noteworthy reduction in both the size and number of porin channels. This diminution acts as a tangible impediment, particularly for carbapenems, forming a physical barrier that hinders the efficient entry of antibiotics. The altered porin channels, coupled with variations in outer membrane proteins, collectively contribute to a compromised permeability of the bacterial cell envelope. These structural modifications pose an additional layer of resistance, further impeding the effective penetration of antibiotics [10][11].

3.2.2 Efflux Pumps

Efflux pumps, intricate protein systems embedded in the bacterial cell membrane, serve as active defence mechanisms employed by *A. baumannii.* These specialized proteins actively expel drugs

from within the bacterial cell to the external environment. *A. baumannii* utilizes efflux pumps as a strategic manoeuvre to reduce intracellular concentrations of drugs. The action of efflux pumps represents a dynamic form of resistance, actively thwarting antibiotics from achieving effective concentrations at their intended targets [10][11].

3.2.3 Aminoglycoside-Modifying Enzymes (AMEs)

Aminoglycosides, a class of antibiotics including gentamicin, kanamycin, and amikacin, are widely utilized in treating severe bacterial infections. However, *A. baumannii* showcases a sophisticated defence mechanism against aminoglycosides through the presence of Aminoglycoside-Modifying Enzymes (AMEs). These enzymes, including acetyltransferases, nucleotidyltransferases, and phosphotransferases, play a pivotal role in chemically modifying aminoglycoside antibiotics [10].

AMEs introduce chemical groups, such as acetyl, phosphate, or adenylate, to specific sites on aminoglycoside molecules. This chemical modification alters the structure of the antibiotic, influencing its interaction with the bacterial ribosome. The modifications induced by AMEs result in a diminished binding affinity between the modified antibiotics and ribosomal RNA within bacterial cells. This reduced affinity disrupts the antibiotics' ability to effectively bind to the bacterial ribosome during protein synthesis [10].

While unmodified aminoglycosides, when bound to the ribosome, disrupt protein synthesis leading to bacterial cell death, the modified antibiotics with reduced binding affinity exhibit decreased effectiveness in inhibiting protein synthesis. This phenomenon significantly contributes to antibiotic resistance in *A. baumannii*, underscoring the challenges in clinical efficacy posed by the emergence of resistance mechanisms in this pathogen [10]. Figure 3 depicts the mechanism employed by the AMEs.

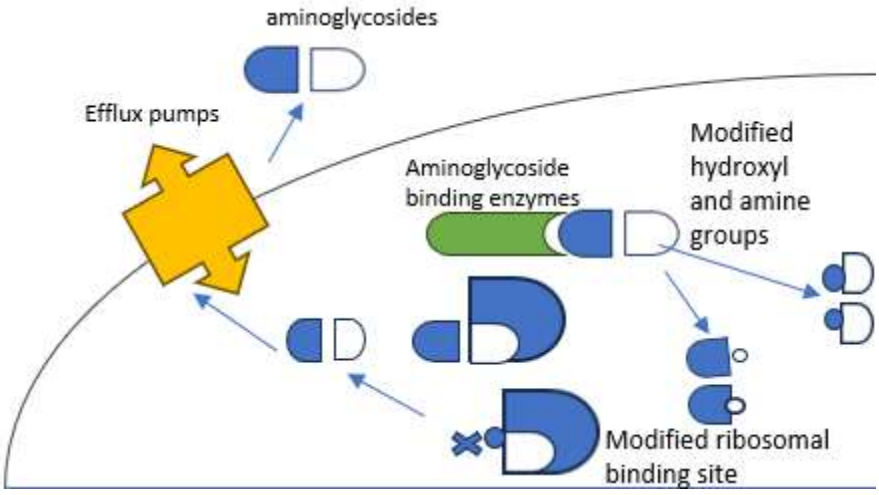

Fig 3: Resistance mechanism opted by aminoglycoside-binding enzymes

*3.3 Alteration of Target or Cellular Functions - **Point Mutations***

Genetic mutations in genes encoding target proteins or porin channels can reduce the affinity of antibiotics for their targets or up-regulate cellular functions involved in drug efflux. Mutations occurring in genes encoding target proteins or porin channels can have profound effects on antibiotic susceptibility. Point mutations may decrease the affinity of antibiotics for their target proteins or up-regulate cellular functions involved in drug efflux. These mutations can alter the structural and functional properties of cellular components, making them less susceptible to the inhibitory actions of antibiotics [10].

3.4 Biofilm Formation

Acinetobacter baumannii employs a sophisticated survival strategy through the formation of intricate biofilms, that are complex microbial communities encased in an extracellular matrix. Particularly renowned for its formidable biofilm-forming prowess, *A. baumannii* poses a substantial threat in healthcare environments, notably within hospitals. This resilient biofilm formation adds an extra layer of intricacy to the bacterium's already robust antibiotic resistance mechanisms [11].

The biofilm formation process begins with the initial attachment of *A. baumannii* to surfaces, often associated with medical devices. Following this, the release of extracellular polymeric substances, such as exopolysaccharides, occurs. This results in the formation of a matrix that acts as a strong physical obstacle, hindering the entry of antibiotics. As the biofilm matures, it attains a high level of resistance against environmental stresses and immune system defences, presenting a formidable challenge for traditional antibiotic treatments [11]. Figure 4 highlights the process of formation of biofilms in CRAB.

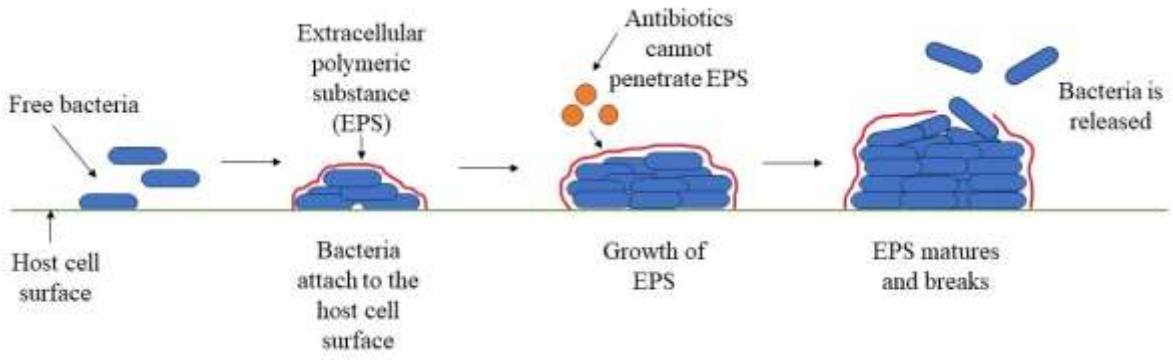

Fig 4: Biofilm Formation

Moreover, the metabolic slowdown exhibited by bacteria within mature biofilms contributes to reduced metabolic activity, further diminishing their susceptibility to antibiotics. This intricate interplay of biofilm formation stages underscores the formidable adaptability of *A. baumannii*, emphasizing the critical need for innovative approaches to combat its persistent presence in healthcare settings [11].

1. CURRENT THERAPY OPTIONS – ANTIBIOTIC THERAPY

Current treatment options for Carbapenem-resistant *Acinetobacter baumannii* infections primarily rely on antibiotic therapy; however, options beyond this approach are limited and are under research. A variety of antibiotics have been employed in the treatment of infections caused by CRAB, including colistin, tigecycline, polymyxin B, and sulbactam [12], given in mono and combination therapy. However, most cases are ridden with inefficacy. Ongoing research is focused on identifying novel antimicrobial agents and alternative treatment approaches, such as combination therapies and the use of bacteriophages [11].

2. EMERGING THERAPEUTICS FOR CRAB INFECTIONS

In response to the rise of CRAB infections, researchers have been exploring various alternative therapies to combat these multidrug-resistant bacteria. Here we discuss some up-and-coming therapeutic strategies for these infections. These novel therapeutic approaches hold promise in effectively treating CRAB infections and overcoming antimicrobial resistance. Table 1 summaries the discussed therapeutic methods.

Table 1: Emerging therapeutics to combat CRAB infections

Therapeutics	Mechanism
Antimicrobial Peptides	• Inhibits the growth and destroy the structure of biofilms by affecting the quorum sensing signalling pathway • Down-regulates genes in the beta-lactam resistance pathway and affects the expression of energy metabolism
Monoclonal Antibodies	• Targeting the capsular carbohydrate present on the bacterial surface, serves to enhance opsonophagocytosis
Efflux Pump Inhibitors	• Binding to the efflux pump and blocking its activity • Modulating the expression of efflux pump genes

Phage Therapy	• Bind to bacterial cell wall receptors and subsequently lyse the cell during the lytic phase
Combination Therapy	• Involves the use of multiple antibiotics (e.g. colistin - econazole, colistin - mAB C8) to enhance treatment efficacy

2.1 Antimicrobial Peptides

Antimicrobial peptides are receiving growing interest as a potential treatment for addressing infections caused by multidrug-resistant bacteria like CRAB. These peptides are natural molecules found in various organisms, playing a vital role in their innate immune system [13].

AMPs exert their antimicrobial activity through various mechanisms, including disrupting the bacterial cell membrane and reaching targets that conventional antibiotics may find challenging to access. They interfere with intracellular processes and modulate the host immune response by inhibiting the growth and destroying the structure of biofilms by affecting the quorum-sensing signalling pathway. They can also down-regulate genes in the beta-lactam resistance pathway and affect the expression of energy metabolism. Additionally, the broad-spectrum antimicrobial activity of AMPs makes them an attractive candidate for combating multidrug-resistant pathogens [13].

Several studies have investigated the effectiveness of antimicrobial peptides against CRAB infections [14]. These findings have sparked interest in further exploring the potential of AMPs as a therapeutic option for CRAB infections. Results from in vitro and in vivo studies have shown promising activity of AMPs against CRAB infections. In vitro studies have demonstrated that AMPs can effectively kill CRAB strains, with some peptides displaying even greater potency than conventional antibiotics [13]. They also can disrupt biofilm formation and down-regulating genes related to membrane proteins, drug resistance, and pilus formation.

5.2 Phage Therapy

Phage therapy, a promising alternative to antibiotic treatments, has gained attention in recent years for its potential in treating infections caused by carbapenem resistant *A. baumanii* and other multidrug-resistant bacteria. Clinical investigations have shown that phage therapy can be effective when appropriate phages are administered in sufficient quantities and targeted to the site of infection [15][16].

Phage therapy harnesses the power of bacteriophages and viruses with the ability to infect and lyse bacteria, providing a targeted strategy to specifically combat and eradicate CRAB.

In the lytic cycle, bacteriophages invade and eradicate specific bacteria by causing cell lysis. Phages show specificity towards different bacteria by binding to receptors on the bacterial cell walls. The introduction of DNA into the bacterial cell initiates viral replication, assembly, and eventual cell lysis. The newly formed bacteriophages are then released into the surroundings, ready to infect other bacteria [15].

In the lysogenic cycle, temperate phages integrate into the host genome or exist as plasmids, adjusting to coexist harmoniously with the bacteria [16]. They may remain dormant or replicate alongside the host bacterium without causing immediate cell lysis. Under specific conditions, lysogenic phages can transition to the lytic cycle, resulting in cell lysis and the release of progeny phages.

5.3 Monoclonal Antibodies

Monoclonal antibodies (mAbs) constitute a sophisticated strategy for combatting CRAB infections. These are engineered to target specific components on the surface of CRAB playing a pivotal role in enhancing immune recognition and facilitating opsonophagocytosis. Upon administration, mAbs exhibit high specificity in binding to unique bacterial surface structures, marking CRAB cells for efficient identification by immune cells such as macrophages and neutrophils. This dual function of enhanced immune recognition and opsonophagocytosis serves as a powerful mechanism to bolster the host's immune response against CRAB [17][18].

Monoclonal antibodies also serve as a valuable complement to traditional antibiotic treatments, amplifying the host's immune defence mechanisms, particularly in bloodstream and lung infections. By activating and fortifying the natural immune responses, particularly in cases where

the immune system faces challenges in controlling the infection independently, mAbs contribute to a comprehensive therapeutic approach. Moreover, the combined use of monoclonal antibodies with antibiotics presents a potential avenue for reducing the risk of antibiotic resistance development [18].

5.4 Efflux Pump Inhibitors

Efflux pump inhibitors (EPIs) emerge as a pivotal strategy in overcoming antibiotic resistance in *Acinetobacter baumannii*. These inhibitors act by directly interfering with the function of efflux pumps, critical components embedded in the bacterial cell membrane responsible for expelling antibiotics and other toxic substances. EPIs exert their inhibitory effects through two main mechanisms: firstly, by physically interacting with efflux pump proteins, impeding their normal functioning and preventing the active removal of antibiotics from the bacterial cell; secondly, by binding to specific sites on the efflux pump, hindering its ability to transport antibiotics out of the cell, thereby increasing the intracellular antibiotic concentration and enhancing their efficacy [19].

Moreover, EPIs exhibit a regulatory role in gene expression within *Acinetobacter baumannii*, influencing the expression of efflux pump genes. EPIs may down-regulate gene expression, thereby reducing the production of efflux pumps, or preventing overexpression in response to antibiotic exposure, maintaining a more susceptible phenotype [19].

By blocking efflux pumps, EPIs elevate the intracellular concentration of antibiotics, overcoming bacterial defence mechanisms and augmenting antibiotic efficacy. Notably, this strategy proves valuable in combating the notorious multi-drug resistance of *Acinetobacter baumannii*, sensitizing the bacterium to antibiotics that were previously expelled by efflux pumps [19].

5.5 Combination Therapy

Combination therapy, a strategic approach involving the concurrent administration of multiple antibiotics and treatment modalities like colistin-imipenem, imipenem-sulbactam and colistin-C8 mAB, respectively, aims to combat Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) [17]. This approach is rooted in the rationale that employing different antibiotics together can target CRAB through diverse mechanisms, potentially augmenting treatment efficacy. Despite

the potential benefits in certain cases, concerns persist regarding the associated risks of toxicity and the development of antibiotic resistance. While combination therapy offers a promising avenue to enhance treatment outcomes against CRAB, careful consideration and monitoring are essential to navigate the delicate balance between efficacy and potential adverse effects [20].

CONCLUSION

In conclusion, the comprehensive exploration into *Acinetobacter baumannii*, particularly its carbapenem-resistant strains, has shed light on the formidable challenges it poses in healthcare settings [21]. The rise of this strain presents a global public health risk, emphasizing the urgency to understand its biology, and resistance mechanisms, and develop effective therapeutic strategies [22].

The diseases caused by CRAB, such as bloodstream infections, UTIs, and wound infections, contribute to prolonged hospitalization periods and increased morbidity and mortality rates. The complexity of its resistance mechanisms, including the production of carbapenemases, alteration of outer membrane porins, and biofilm formation, has made the development of novel therapeutic approaches imperative [23].

Current therapy options, primarily relying on antibiotics like colistin, tigecycline, polymyxin B, and sulbactam, face challenges due to the increasing ineffectiveness of these drugs. The overuse and misuse of antibiotics, coupled with the bacterium's intrinsic ability to acquire and transfer resistance genes, contribute to the rising prevalence of carbapenem resistance [23].

The proposed therapies, including antimicrobial peptides, monoclonal antibodies, efflux pump inhibitors, phage therapy, and combination therapy, offer promising avenues for combating CRAB infections. The proposed therapies, with their diverse mechanisms of action, highlight the need for a multifaceted approach to effectively tackle the challenges posed by CRAB [24].

The future of combating CRAB infections lies in continued research, clinical trials, and the translation of promising candidates like antimicrobial peptides and monoclonal antibodies into viable therapeutic options. The importance of early intervention, understanding bacterial virulence factors, and the potential synergy with existing antibiotics underscore the complexity of addressing CRAB infections [24].

3. FUTURE PERSPECTIVES AND DIRECTIONS

The future lies in developing precision therapeutics that tailor interventions to the specific resistance profiles of *A. baumannii* strains. By honing in on strain-specific vulnerabilities, treatment efficacy can be heightened while minimizing collateral damage to the patient's microbiome. Exploring synergistic combination therapies is crucial in the face of *A. baumannii's* multidrug resistance. Investigating interactions between existing antibiotics, emerging antimicrobial agents, and immunotherapies could reveal potent and novel treatment regimens [25].

The development of immunomodulation strategies, including immunostimulants or immune checkpoint inhibitors, holds promise in enhancing the host's innate defences against *A. baumannii*. This approach aims to complement traditional antimicrobial strategies. Advancements in phage therapy research offer a promising avenue. Tailoring bacteriophages to target specific *A. baumannii* strains, understanding pharmacokinetics, and optimizing delivery methods could elevate phage therapy as a viable treatment option [26].

Innovative technologies for disrupting biofilms present great promise. Research should delve into nanotechnological approaches, antimicrobial coatings, and biofilm-targeted agents to enhance antibiotic penetration and improve treatment outcomes. Robust genomic surveillance programs are essential to monitor the evolution of *A. baumannii* strains. Real-time tracking of resistance patterns and the identification of emerging strains is critical for proactive antimicrobial stewardship. Investigating vaccine development against A. baumannii offers a preventive approach. Understanding key virulence factors and employing novel adjuvants may pave the way for effective vaccines, reducing the incidence of infections [26].

Global collaboration is paramount in addressing the widespread challenge of *A. baumannii*. International partnerships for data sharing, research coordination, and standardizing diagnostic and treatment protocols can accelerate progress in combating this pathogen. In embracing these prospects, the battle against *A. baumannii* can advance with a holistic and collaborative

approach, incorporating precision medicine, innovative therapies, and global cooperation to confront this formidable pathogen effectively.

4. REFERENCES

1. T.-H. Wang, Y.-S. Leu, N.-Y. Wang, C.-P. Liu, and T.-R. Yan, "Prevalence of different carbapenemase genes among carbapenem-resistant *Acinetobacter baumannii* blood isolates in Taiwan," *Antimicrobial Resistance & Infection Control*, vol. 7, no. 1, Oct. 2018, doi: https://doi.org/10.1186/s13756-018-0410-5.
2. Peechanika Chopjitt, Thidathip Wongsurawat, Piroon Jenjaroenpun, Parichart Boueroy, Rujirat Hatrongjit, and Anusak Kerdsin, "Complete Genome Sequences of Four Extensively Drug-Resistant *Acinetobacter baumannii* Isolates from Thailand," *Microbiology resource announcements*, vol. 9, no. 40, Oct. 2020, doi: https://doi.org/10.1128/mra.00949-20.
3. A. Howard, M. O'Donoghue, A. Feeney, and R. D. Sleator, "*Acinetobacter baumannii*," *Virulence*, vol. 3, no. 3, pp. 243–250, May 2012, doi: https://doi.org/10.4161/viru.19700.
4. S. Shahraki Zahedani and R. Javadi , "Evaluation of Antibiotic Resistance Patterns and Frequency of Carbapenemase-Producing *Acinetobacter baumannii* Isolates by the Carbacineto NP Test," *Medical Laboratory Journal*, vol. 12, no. 2, pp. 13–19, Mar. 2018, doi: https://doi.org/10.29252/mlj.12.2.13.
5. Y. Lv *et al.*, "Faucet aerators as a reservoir for Carbapenem-resistant *Acinetobacter baumannii*: a healthcare-associated infection outbreak in a neurosurgical intensive care unit," *Antimicrobial Resistance & Infection Control*, vol. 8, no. 1, Dec. 2019, doi: https://doi.org/10.1186/s13756-019-0635-y.
6. G. Sycz *et al.*, "Modern *Acinetobacter baumannii* clinical isolates replicate inside spacious vacuoles and egress from macrophages," *PLOS Pathogens*, vol. 17, no. 8, p. e1009802, Aug. 2021, doi: https://doi.org/10.1371/journal.ppat.1009802.
7. S. Cesur, S. Kınıklı, S. Cesur, M. Yücel, Ç. Ataman Hatipoğlu, and B. Dinç, "Determination of polymyxin B, minocycline, colistin and phosphomycin susceptibilities in *Acinetobacter baumannii* strains showing carbapenem resistant multidrug resistance phenotype," *Journal of Health Sciences and Medicine*, Dec. 2018, doi: https://doi.org/10.32322/jhsm.456990.
8. H. Jin, F. Qiu, H. Ji, and Q. Lu, "Analysis of drug resistance in 1,861 strains of *Acinetobacter baumannii*," *Biomedical Reports*, vol. 4, no. 4, pp. 463–466, Feb. 2016, doi: https://doi.org/10.3892/br.2016.598.

9. K. Abdullah, P. C. Iwen, and B. Abdalhamid, “Characterization of Carbapenem-Resistant *Acinetobacter baumannii* Isolates from Clinical Specimens,” *Microbiology Resource Announcements*, vol. 10, no. 29, Jul. 2021, doi: https://doi.org/10.1128/mra.00571-21.
10. Kyriakidis I, Vasileiou E, Pana ZD, Tragiannidis A. *Acinetobacter baumannii* Antibiotic Resistance Mechanisms. Pathogens. 2021 Mar 19;10(3):373. doi: 10.3390/pathogens10030373. PMID: 33808905; PMCID: PMC8003822. (resistance mechanisms)
11. Roy S, Chowdhury G, Mukhopadhyay AK, Dutta S, Basu S. Convergence of Biofilm Formation and Antibiotic Resistance in *Acinetobacter baumannii* Infection. Front Med (Lausanne). 2022 Mar 24;9:793615. doi: 10.3389/fmed.2022.793615. PMID: 35402433; PMCID: PMC8987773.
12. H. TÜNAY, T. DEMİRDAL, and N. DEMİRTÜRK, “HASTANE KAYNAKLI PAN DRUG RESİSTANT *ACİNETOBACTER BAUMANNİİ* ENFEKSİYONLARINDA RİSK FAKTÖRLERİNİN ARAŞTIRILMASI,” *Acta Medica Alanya*, Oct. 2019, doi: https://doi.org/10.30565/medalanya.543371.
13. Zhang QY, Yan ZB, Meng YM, Hong XY, Shao G, Ma JJ, Cheng XR, Liu J, Kang J, Fu CY. Antimicrobial peptides: mechanism of action, activity and clinical potential. Mil Med Res. 2021 Sep 9;8(1):48. doi: 10.1186/s40779-021-00343-2. PMID: 34496967; PMCID: PMC8425997.
14. Mandal Santi M. , Roy Anupam , Ghosh Ananta K. , Hazra Tapas K. , Basak Amit , Franco Octavio L.; Challenges and future prospects of antibiotic therapy: from peptides to phages utilization; Frontiers in Pharmacology; 5; 2014; https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2014.00105 ; DOI:10.3389/fphar.2014.00105
15. LaVergne S, Hamilton T, Biswas B, Kumaraswamy M, Schooley RT, Wooten D. Phage Therapy for a Multidrug-Resistant Acinetobacter baumannii Craniectomy Site Infection. Open Forum Infect Dis. 2018 Mar 23;5(4):ofy064. doi: 10.1093/ofid/ofy064. PMID: 29687015; PMCID: PMC5905571.
16. Tu Q, Pu M, Li Y, Wang Y, Li M, Song L, Li M, An X, Fan H, Tong Y. Acinetobacter Baumannii Phages: Past, Present and Future. Viruses. 2023 Mar 3;15(3):673. doi: 10.3390/v15030673. PMID: 36992382; PMCID: PMC10057898.

17. Nielsen TB, Pantapalangkoor P, Luna BM, Bruhn KW, Yan J, Dekitani K, Hsieh S, Yeshoua B, Pascual B, Vinogradov E, Hujer KM, Domitrovic TN, Bonomo RA, Russo TA, Lesczcyniecka M, Schneider T, Spellberg B. Monoclonal Antibody Protects Against Acinetobacter baumannii Infection by Enhancing Bacterial Clearance and Evading Sepsis. J Infect Dis. 2017 Aug 15;216(4):489-501. doi: 10.1093/infdis/jix315. PMID: 28931235; PMCID: PMC5853763.
18. Yeganeh, O., Shabani, M., Pakzad, P. *et al.* Evaluation the reactivity of a peptide-based monoclonal antibody derived from OmpA with drug resistant pulsotypes of *Acinetobacter baumannii* as a potential therapeutic approach. *Ann Clin Microbiol Antimicrob* **21**, 30 (2022). https://doi.org/10.1186/s12941-022-00523-51
19. Abdi SN, Ghotaslou R, Ganbarov K, Mobed A, Tanomand A, Yousefi M, Asgharzadeh M, Kafil HS. *Acinetobacter baumannii* Efflux Pumps and Antibiotic Resistance. Infect Drug Resist. 2020 Feb 12;13:423-434. doi: 10.2147/IDR.S228089. PMID: 32104014; PMCID: PMC7024869.
20. Viehman, J.A., Nguyen, M.H. & Doi, Y. Treatment Options for Carbapenem-Resistant and Extensively Drug-Resistant *Acinetobacter baumannii* Infections. *Drugs* **74**, 1315–1333 (2014). https://doi.org/10.1007/s40265-014-0267-8
21. Vahhabi A, Hasani A, Rezaee MA, et al. Carbapenem resistance in *Acinetobacter baumannii* clinical isolates from northwest Iran: high prevalence of OXA genes in sync. *Iran J Microbiol*. 2021;13(3):282-293. doi:10.18502/ijm.v13i3.6388
22. Li, S., Duan, X., Peng, Y. *et al.* Molecular characteristics of carbapenem-resistant *Acinetobacter* spp. from clinical infection samples and fecal survey samples in Southern China. *BMC Infect Dis* 19, 900 (2019). https://doi.org/10.1186/s12879-019-4423-3
23. Bartal C, Rolston KVI, Nesher L. Carbapenem-resistant Acinetobacter baumannii: Colonization, Infection and Current Treatment Options. *Infect Dis Ther*. 2022;11(2):683-694. doi:10.1007/s40121-022-00597-w
24. M. Nguyen, S.G. Joshi, Carbapenem resistance in Acinetobacter baumannii, and their importance in hospital-acquired infections: a scientific review, *Journal of Applied Microbiology*, Volume 131, Issue 6, 1 December 2021, Pages 2715–2738, https://doi.org/10.1111/jam.15130

25. McConnell MJ, Actis L, Pachón J. Acinetobacter baumannii: human infections, factors contributing to pathogenesis and animal models. FEMS Microbiol Rev. 2013 Mar;37(2):130-55. doi: 10.1111/j.1574-6976.2012.00344.x. Epub 2012 Jun 18. PMID: 22568581.
26. Wright MS, Haft DH, Harkins DM, Perez F, Hujer KM, Bajaksouzian S, Benard MF, Jacobs MR, Bonomo RA, Adams MD. New insights into dissemination and variation of the health care-associated pathogen Acinetobacter baumannii from genomic analysis. mBio. 2014 Jan 21;5(1):e00963-13. doi: 10.1128/mBio.00963-13. Erratum in: MBio. 2015;6(3):e00585. PMID: 24449752; PMCID: PMC3903280.