

Impact of Therapeutics on Carbapenem-resistant *Acinetobacter baumannii*

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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 promotes 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-hydrolyzing 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

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INTRODUCTION

Acinetobacter baumannii, a gram-negative bacterium, has emerged as a significant opportunistic pathogen with a notable prevalence in healthcare environments [1]. Its ability to induce a range of infections, combined with a troubling propensity to develop antibiotic resistance, has elevated the pathogen to a considerable global public health concern. The emergence of carbapenem-resistant *A. baumannii* (CRAB) has exacerbated the complexities associated with treating infections caused by this pathogen [2]. CRAB resistance to carbapenem antibiotics, once the frontline defense 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 carbapenem resistance. The report encompasses a brief overview of 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 into the field, paving the way for innovative approaches to combat 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, have been 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 for investigating distinct approaches, such as antimicrobial peptides and monoclonal antibodies. These therapeutics provide valuable insights into potential advancements and highlight the importance of diverse strategies for combating 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 to healthcare environments and contributes to a broad spectrum of infections [7]. Its high drug resistance rates, especially the emergence of carbapenem-resistant strains, have significantly affected the management and treatment of these infections [8]. Figure 1 shows a flowchart of the different diseases caused by CRAB infection.

Pneumonia and Blood Stream Infections

CRAB causes 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].

Infections Related to Medical Devices

CRAB is commonly associated with infections related to medical devices. It can occur through the hands of healthcare 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 an increased susceptibility to such infections. People infected by this bacterium generally have a prolonged hospital stays [3].

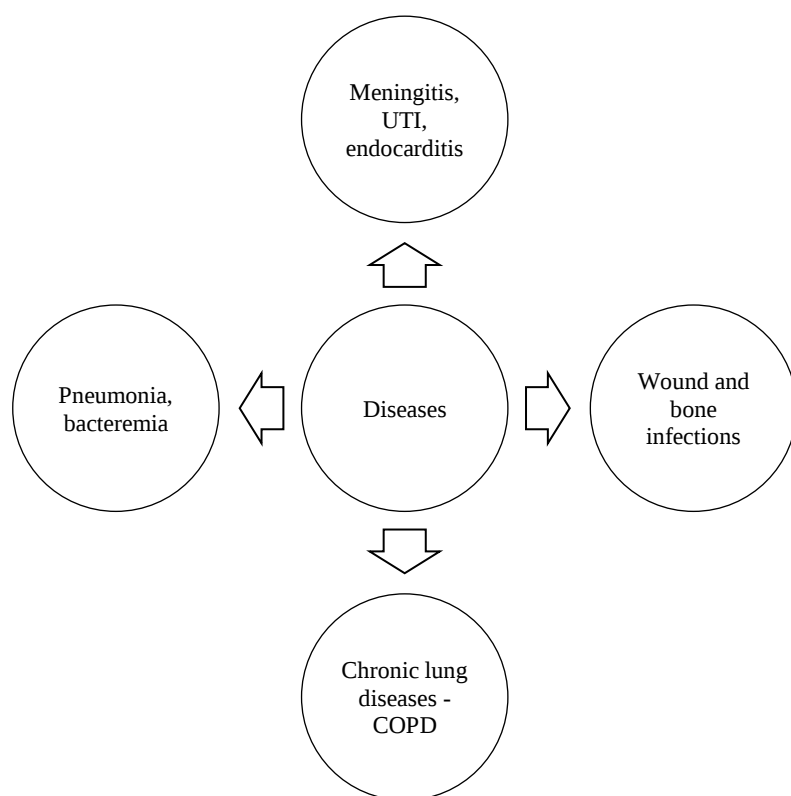


Figure 1. Flowchart highlighting the diseases caused by CRAB.

Battlefield Trauma and Other Wounds

CRAB is a significant concern in battlefield trauma and other wound types. 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 has been extensively documented as a pathogen in burn units and presents challenges in its treatment.

Diseases Due to Biofilm Formation

CRAB is acknowledged for its propensity to form biofilms, which are communities of bacteria enclosed within a protective matrix that adhere 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* in clinical settings requires a thorough understanding 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 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].

Enzymes Inactivating Antibiotics—Beta-Lactamases

Acinetobacter baumannii employs a sophisticated arsenal of resistance mechanisms, prominently featuring the utilization of β -lactamases. These enzymes serve as frontline defenses, hydrolyze antibiotics, and impart resistance against penicillin, 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].

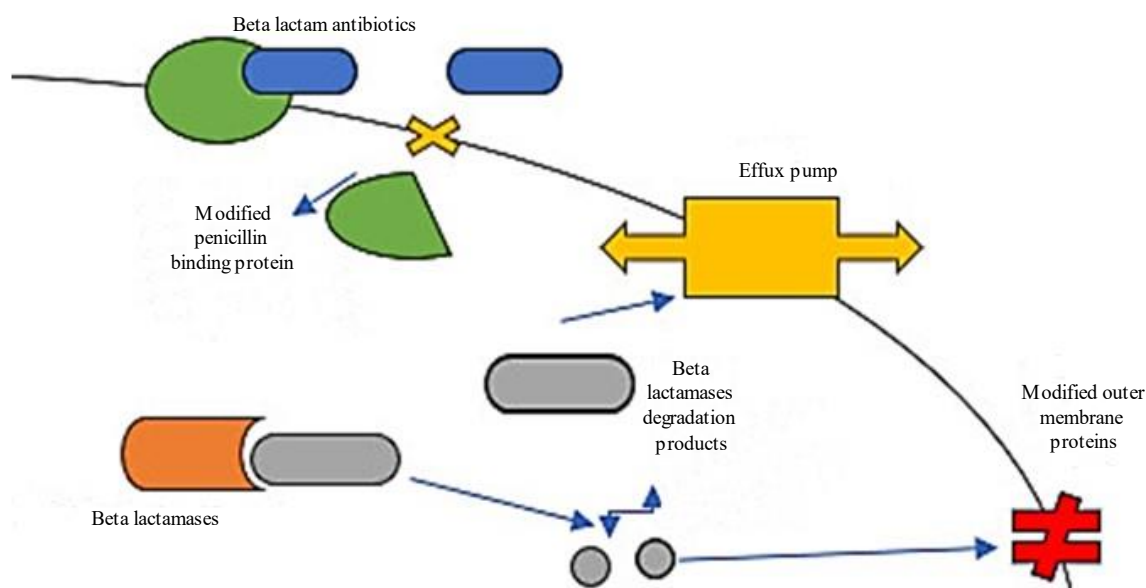


Figure 2. Resistance mechanism of beta-lactamases.

The resistance strategies employed by *A. baumannii* extend beyond β -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, β -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 penicillin, synthetic cephalosporins, and carbapenems, share a common β -lactam ring. The cellular targets of these antibiotics are penicillin-binding proteins (PBPs), which play fundamental roles in bacterial cell wall synthesis [10].

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

The consequences of β -lactamase activity in *A. baumannii* are profound and contribute significantly to resistance against various β -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 β -lactamases in *A. baumannii* includes different classes based on their substrate specificity and structural characteristics. Class A hydrolyzes cephalosporins and penicillin that are constrained by clavulanic acid. Class B metallo-beta-lactamases catalyze the hydrolysis of almost all beta-lactams, which is inhibited by EDTA due to the presence of Zn at the active site. Class C or chromosomally mediated AmpC contributes to the resistance to third-generation cephalosporins. Class D or Oxacillinases are involved in carbapenem hydrolysis. Figure 2 shows how β -lactamases contribute to antibiotic resistance.

Reduced Entry into the Target Site

Porin Channels and Outer Membrane Proteins

Porin channels, which are 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 noteworthy reductions in both the size and number of porin channels. This diminution acts as a tangible impediment, particularly for carbapenems, and forms a physical barrier that hinders the efficient entry of antibiotics. The altered porin channels, coupled with variations in outer membrane proteins, collectively contribute to the compromised permeability of the bacterial cell envelope. These structural modifications create an additional layer of resistance, further impeding the effective penetration of antibiotics [10, 11].

Efflux Pumps

Efflux pumps, which are intricate protein systems embedded in the bacterial cell membrane, serve as active defense mechanisms employed by *A. baumannii*. These specialized proteins actively expel drugs from within the bacterial cells to the external environment. *A. baumannii* utilizes efflux pumps as a strategic maneuver to reduce the intracellular concentrations of drugs. The action of efflux pumps represents a dynamic form of resistance that actively thwarts antibiotics from achieving effective concentrations of their intended targets [10, 11].

Aminoglycoside-Modifying Enzymes

Aminoglycosides, a class of antibiotics including gentamicin, kanamycin, and amikacin, are widely used to treat severe bacterial infections. However, *A. baumannii* shows a sophisticated defense mechanism against aminoglycosides in the presence of aminoglycoside-modifying enzymes (AMEs). These enzymes, including acetyltransferases, nucleotidyltransferases, and phosphotransferases, play pivotal roles in chemically modifying aminoglycoside antibiotics [10].

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

While unmodified aminoglycosides, when bound to the ribosome, disrupt protein synthesis, leading to bacterial cell death, 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 against this pathogen [10]. Figure 3 depicts the mechanism employed by AMEs.

Alteration of Target or Cellular Functions-Point Mutations

Mutations in genes encoding target proteins or porin channels can reduce the affinity of antibiotics for their targets or upregulate cellular functions involved in drug efflux. Mutations in the 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 upregulate the 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 action of antibiotics [10].

Biofilm Formation

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

Biofilm formation begins with the initial attachment of *A. baumannii* to surfaces, which is often associated with medical devices. Release of extracellular polymeric substances as exopolysaccharides.

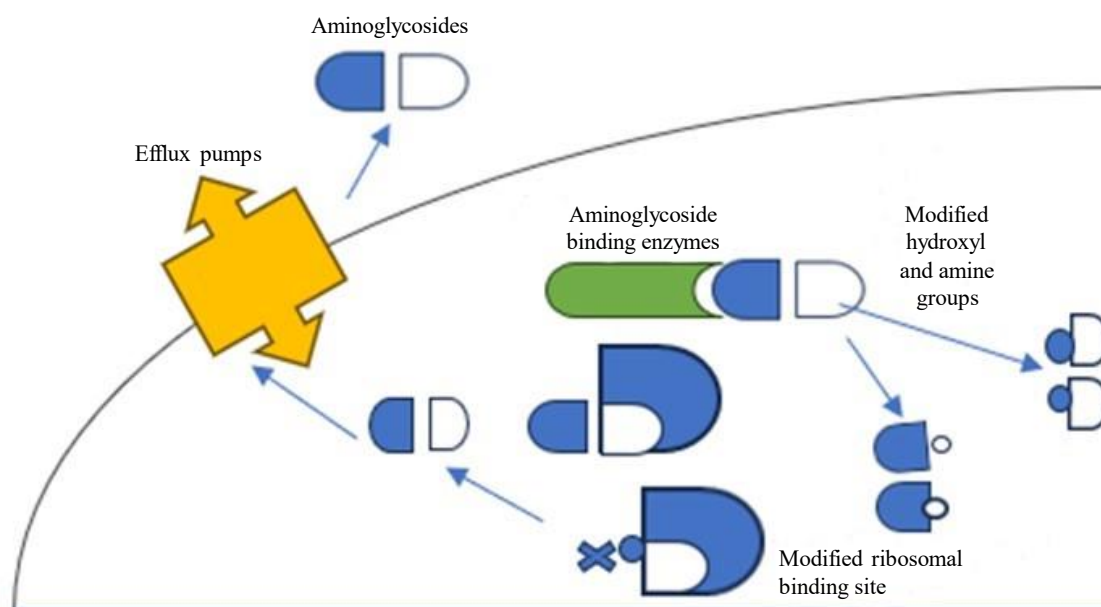


Figure 3. Resistance mechanism opted by aminoglycoside-binding enzymes.

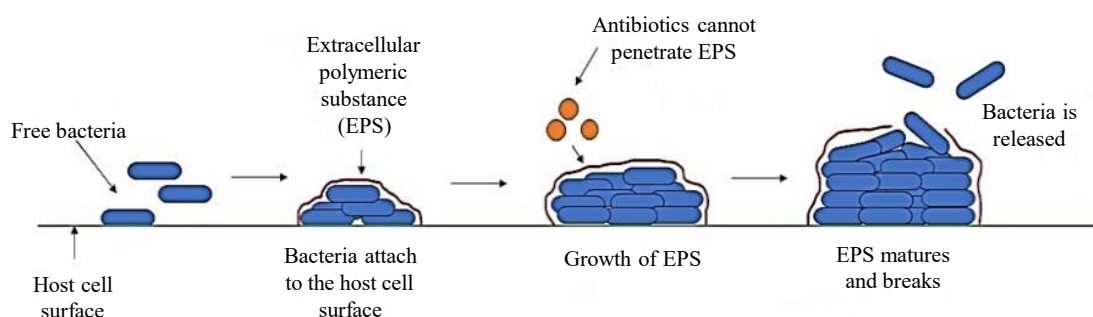


Figure 4. Biofilm formation.

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 defenses, presenting a formidable challenge for traditional antibiotic treatment [11]. Figure 4 highlights the process of biofilm formation in CRAB.

Moreover, the metabolic slowdown exhibited by bacteria within mature biofilms contributes to reduced metabolic activity, which further diminishes 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].

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 investigation. A variety of antibiotics, including colistin, tigecycline, polymyxin B, and sulbactam [12], have been used to treat infections therapy. However, most cases are ridden due to inefficacy. Ongoing research is focused on identifying novel antimicrobial agents and alternative treatment approaches such as combination therapies and bacteriophages [11].

EMERGING THERAPEUTICS FOR CRAB INFECTIONS

In response to the rise in CRAB infections, researchers have been exploring various alternative therapies to combat these multidrug-resistant bacteria. Here, we discuss some upcoming therapeutics

Table 1. Emerging therapeutics to combat CRAB infections.

Therapeutics	Mechanism
Antimicrobial peptides	• Inhibits the growth and destroys the structure of biofilms by affecting the quorum-sensing signaling 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

strategies for treating these infections. These novel therapeutic approaches are promising for effectively treating CRAB infections and overcoming antimicrobial resistance. Table 1 summarizes the therapeutic methods discussed.

Antimicrobial Peptides

Antimicrobial peptides are receiving growing interest as a potential treatment for infections caused by multidrug-resistant bacteria such as CRAB. These peptides are natural molecules found in various organisms that play a vital role in the innate immune system [13].

AMPs exert their antimicrobial activity through various mechanisms, including disruption of the bacterial cell membrane and reaching targets that conventional antibiotics may find challenging. They interfere with intracellular processes and modulate the host immune response by inhibiting growth and destroying the structure of biofilms by affecting the quorum-sensing signaling pathway. They can also downregulate genes in the beta-lactam resistance pathway and affect energy metabolism. Additionally, the broad-spectrum antimicrobial activity of AMPs makes them attractive candidates 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 exploring the potential of AMPs as therapeutic options 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 can also disrupt biofilm formation and downregulate the expression of genes related to membrane proteins, drug resistance, and pilus formation.

Phage Therapy

Phage therapy, a promising alternative to antibiotic treatment, has gained attention in recent years for its potential in treating infections caused by carbapenem-resistant *A. baumannii* 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 infection site [15, 16].

Phage therapy harnesses the ability of bacteriophages and viruses to infect and lyse bacteria, providing a targeted strategy to specifically combat and eradicate CRAB. During the lytic cycle, bacteriophages invade and eradicate specific bacteria by causing cell lysis. Phages show specificity towards different bacteria by binding to receptors on bacterial cell walls. The introduction of DNA into bacterial cells 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 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 release of progeny phages.

Monoclonal Antibodies

The use of monoclonal antibodies (mAbs) constitutes a sophisticated strategy for combating CRAB infections. These are engineered to target specific components on the surface of CRAB, thereby 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 immune response against CRAB [17, 18].

Monoclonal antibodies also serve as a valuable complement to traditional antibiotic treatments, amplifying the host's immune defense mechanisms, particularly in the bloodstream and lung infections. By activating and fortifying 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 and antibiotics presents a potential avenue for reducing the risk of antibiotic resistance development [18].

Efflux Pump Inhibitors

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

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

By blocking efflux pumps, EPIs elevate the intracellular concentration of antibiotics, overcome bacterial defense mechanisms, and augment antibiotic efficacy. Notably, this strategy proved valuable in combating the notorious multidrug resistance of *Acinetobacter baumannii*, sensitizing the bacterium to antibiotics that were previously expelled by efflux pumps [19].

Combination Therapy

Combination therapy, a strategic approach involving concurrent administration of multiple antibiotics and treatment modalities such as colistin-imipenem, imipenem-sulbactam, and colistin-C8 mAB, 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 the 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 for CRAB, careful consideration and monitoring are essential to navigate the delicate balance between efficacy and potential adverse effects [20].

FUTURE PERSPECTIVES AND DIRECTIONS

The future lies in developing precise therapeutics that tailor interventions to the specific resistance profiles of *A. baumannii* strains. By honing strain-specific vulnerabilities, treatment efficacy can be increased while minimizing collateral damage to a patient's microbiome. Exploring synergistic combination therapies is crucial for the resistance in *A. baumannii*'s multidrug resistance. Investigating the interactions among existing antibiotics, emerging antimicrobial agents, and immunotherapies could reveal potent and novel treatment regimens [21, 22].

The development of immunomodulatory strategies, including immunostimulants or immune checkpoint inhibitors, holds promise for enhancing the host's innate defense against *A. baumannii*. This approach aims to complement traditional antimicrobial strategies. Advancements in phage therapy research have offered promising avenues. Tailoring bacteriophages to target specific *A. baumannii* strains, understanding pharmacokinetics, and optimizing delivery methods could elevate phage therapy as a viable treatment option [23, 24].

Innovative technologies for biofilm disruption are promising. Research should focus on 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 the development of vaccines against *A. baumannii* is a preventive approach. Understanding key virulence factors and employing novel adjuvants may pave the way for effective vaccines and reduce the incidence of infections [25, 26].

Global collaboration is paramount for addressing the widespread challenges faced by *A. baumannii*. International partnerships for data sharing, research coordination, and standardizing diagnostic and treatment protocols can accelerate the 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 effectively confront this formidable pathogen.

CONCLUSION

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

Diseases caused by CRAB, such as bloodstream infections, UTIs, and wound infections, contribute to prolonged hospitalization 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.

Current therapeutic options, primarily relying on antibiotics such as colistin, tigecycline, polymyxin B, and sulbactam, face challenges owing to the increasing ineffectiveness of these drugs. The overuse and misuse of antibiotics, coupled with the intrinsic ability of bacteria to acquire and transfer resistance genes, contributes to the rising prevalence of carbapenem resistance.

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

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

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