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Carbapenem-Resistant Acinetobacter baumannii Biofilms in Hospital-Acquired Infections: Pathogenesis, Clinical Impact, and Therapeutic Challenges

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Abstract

Carbapenem-resistant Acinetobacter baumannii (CRAB) has emerged as one of the major challenges in modern healthcare settings, ranked by the World Health Organization (WHO) as a critical-priority pathogen requiring urgent development of new antimicrobials. The organism's ability to form robust biofilms on both biotic and abiotic surfaces represents a central pillar of its pathogenicity in hospital-acquired infections (HAIs), including ventilator-associated pneumonia (VAP), catheter-associated bloodstream infections (CABSI), wound infections, and urinary tract infections. This review summarizes recent findings on the molecular mechanisms underpinning biofilm formation in CRAB, encompassing the roles of surface adhesins, quorum sensing, extracellular polymeric substances, and horizontal gene transfer in carbapenem resistance. We further examine the clinical epidemiology of CRAB-associated HAIs, including attributable mortality, morbidity, and economic burden across global healthcare systems. The article critically evaluates current and emerging therapeutic strategies, including polymyxins, tigecycline, cefiderocol, sulbactam-durlobactam, novel bacteriophage-based therapies, anti-biofilm compounds, and photodynamic inactivation approaches. Significant therapeutic gaps persist, underscoring the need for multidisciplinary strategies that integrate robust infection prevention measures, antimicrobial stewardship, and translational research into next-generation anti-biofilm agents. Future directions in genomic surveillance and combination therapy optimization are discussed.

Keywords: A. baumannii, Drug resistance, Biofilm, Hospital-acquired infections, Antimicrobial resistance, Quorum sensing

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1 Introduction

Hospital-acquired infections (HAIs) play a role in excess morbidity, extended hospital stays, and significant healthcare costs, making them chronic and increasing danger to patient safety worldwide (Odoom & Donkor, 2025). Because of its unique ability to develop antimicrobial resistance, its resilience in a variety of settings, and its capacity to survive on clinical surfaces and medical devices through biofilm formation, *Acinetobacter baumannii* has become particularly well-known among the bacterial pathogens linked to HAIs during the past 20 years (Ibrahim et al., 2021). This organism was once an opportunistic nuisance, but the advent of carbapenem-resistant strains, or CRAB, has turned it into a clinical disaster, especially in burn units, intensive care units (ICUs), and among immunodeficient patients (Susanna et al., 2026).

The epidemiological trend of CRAB is concerning. Global surveillance networks have reported higher incidences in Europe, North America, Asia, and the Middle East, with carbapenem resistance rates in some Mediterranean and Middle Eastern intensive care units higher than 80% of all *A. baumannii* isolates (Pogue et al., 2022). The WHO's 2017 Global Priority Pathogens List placed carbapenem-resistant *A. baumannii* at the top of the critical priority tier, showing an agreement among scientists worldwide that this bacterium poses an existential threat to the efficacy of modern medical treatments (WHO, 2017). Surgery, organ transplantation, mechanical breathing, and central venous catheterization are all aspects of advanced medical care that also increase possibilities for CRAB colonization and infection.

The ability of CRAB to form biofilms—structured communities of bacteria embedded within a self-produced extracellular matrix (ECM) that stick to surfaces ranging from prosthetic joints and surgical wound beds to endotracheal tubes and urinary catheters—is essential to its success as a nosocomial pathogen (de Breij et al., 2018).Because biofilm-dwelling bacteria have antibiotic resistance that is 100–1000 times higher than that of their planktonic counterparts, even last-resort drugs like polymyxins and tigecycline are less effective against them (Gedefie et al., 2021). Also, the biofilm matrix protects bacteria from host immune responses, resulting in persistent and chronic infections that are very difficult to cure (Flemming et al., 2016).

The goal of this review is to provide a detailed, scientifically supported analysis of CRAB biofilms in relation to HAIs. It combines current microbiological, genetic, clinical, and therapeutic views to give a comprehensive understanding of this significant topic and to identify future research and clinical practice methods.

2.0 Taxonomy, Microbiology, And Environmental Persistence

2.1 Taxonomic Classification and Genomic Features

Acinetobacter baumannii is an aerobic, gram-negative, non-fermenting coccobacillus that is a member of the order Pseudomonadales and family Moraxellaceae (Antunes et al., 2022). For definitive identification, molecular techniques like 16S rRNA sequencing, MALDI-TOF mass spectrometry, or whole-genome sequencing (WGS) are required because the *Acinetobacter calcoaceticus – baumannii* (ACB) complex comprises multiple genomic species that are phenotypically indistinguishable by traditional biochemical testing (Wyres et al., 2020). The pan-genome of *A. baumannii* is remarkably vast, indicating a broad capability for genomic plasticity and horizontal gene transfer (HGT), despite its comparatively small genome of roughly 3.8–4.0 Mb (Azam & Khan, 2019).

Genomic islands (RIs) are large sections of foreign DNA obtained by horizontal gene transfer (HGT), and they often contain resistance determinant groups. Genes expressing resistance to beta-lactams, aminoglycosides, tetracyclines, chloramphenicol, and sulfonamides can be found in a single transferable element. According to Ramirez et al. (2020), these AbaR resistance islands were among the first to be discovered. This genomic architecture allows *A. baumannii* to rapidly develop multidrug resistance (MDR) phenotypes under the selection pressure of antibiotic usage in clinical settings.

2.2 Environmental Survival and Desiccation Tolerance

A. baumannii stands out from many other gram-negative infections due to its exceptional resistance to desiccation and ability to live on dry, lifeless hospital surfaces for weeks to months (Ye et al., 2020; Tipton et al., 2018). Changes in outer membrane protein (OMP) profiles, increased formation of outer membrane vesicles (OMVs), accumulation of suitable solutes such trehalose,

and activation of stress-response sigma factors are some of the mechanisms that underlie desiccation tolerance (Hess et al., 2020). Environmental decontamination is a crucial

component of infection control systems because these characteristics make cross-transmission easier through contaminated surfaces, healthcare workers' hands, and shared medical equipment.

Environmental persistence is further enhanced by biofilm development. Under circumstances that kill planktonic bacteria, such as exposure to popular hospital disinfectants such quaternary ammonium compounds and chlorhexidine at standard doses, biofilm-embedded CRAB on clinical surfaces can continue to be viable and virulent (Huang et al., 2019). This calls for improved disinfection procedures, such as the use of UV-C irradiation in high-risk clinical areas and hydrogen peroxide vapor systems.

3.0 Biofilm Formation: Molecular Mechanisms and Regulation

3.1 Stages of Biofilm Development

Like other gram-negative pathogens, *A. baumannii* develops biofilms through a multi-stage program consisting of five broadly defined phases: (1) initial reversible attachment, (2) irreversible adherence, (3) microcolony formation, (4) biofilm maturation, and (5) dispersal (Koo et al., 2017; Sauer et al., 2022). Each stage is controlled by several molecular processes, such as surface structures, regulatory systems, and environmental sensing mechanisms.

3.2 Initial Attachment and Adhesion Determinants

When planktonic bacteria come into touch with a biotic or abiotic surface, biofilm formation begins. To aid in initial adhesion, *A. baumannii* uses a variety of surface-associated features. The csu (Csu pilus assembly) operon encodes type I pili, which are essential for adhering to abiotic surfaces like polystyrene and medical-grade polyurethane (Huertas et al., 2020). The significance of this operon is highlighted by the dramatic reduction in biofilm formation caused by genetic disruption of csuC or csuE (Huertas et al., 2020). Environmental signal perception and biofilm start are linked by the BfmRS two-component regulatory system, which positively controls csu operon expression (Russo et al., 2016).

OmpA, an outer membrane protein, has a complex function in the pathogenesis and biofilm production of *A. baumannii*. In addition to mediating adhesion to human bronchial epithelial cells and supporting intracellular survival in macrophages, OmpA also takes role in surface attachment in the initial stages of biofilm formation (Eijkelkamp et al., 2015). On both abiotic substrates and

the surfaces of epithelial cells, OmpA-deficient mutants exhibit markedly decreased biofilm formation. Furthermore, infection of wound surfaces and implanted devices is facilitated by the surface-exposed protein Acinetobacter trimeric autotransporter (Ata), which facilitates adhesion to human extracellular matrix proteins such as collagen and fibronectin (Nie et al., 2020).

3.3 Extracellular Polymeric Substances and Matrix Architecture

Bacteria multiply and release extracellular polymeric substances (EPS), which make up the biofilm matrix, after initial attachment is achieved. Poly-β-(1,6)-N-acetylglucosamine (PNAG), also referred to as poly-N-acetyl glucosamine (PNAG) or polysaccharide intercellular adhesin (PIA), along with extracellular DNA (eDNA), proteins, and lipopolysaccharide (LPS) components, make up the majority of the EPS in *A. baumannii* (Ibberson & Whiteley, 2020). The biosynthesis and secretion machinery needed to produce PNAG is encoded by the pgaABCD gene. PNAG is a crucial structural element of *A. baumannii* biofilms since the deletion of pgaB, which codes for a periplasmic deacetylase necessary for PNAG processing, prevents biofilm formation (Ibberson & Whiteley, 2020).

Another important structural and functional element of the biofilm matrix is extracellular DNA (eDNA). In the biofilm community, eDNA serves as a horizontal gene transfer vehicle, improves food uptake, and provides structural scaffolding. It is mainly released through autolysis or active secretion through membrane vesicles (Flemming et al., 2016). *A. baumannii* biofilms are severely disrupted in vitro by DNase I treatment, confirming eDNA as a therapeutic target (Luo et al., 2015). Large cell-wall-anchored proteins called biofilm-associated surface proteins (Bap) also support intercellular adhesion and matrix integrity in later phases of biofilm development (Runci et al., 2019).

3.4 Quorum Sensing and Biofilm Regulation

Quorum sensing (QS), a bacterial cell-to-cell communication system, coordinates gene expression in a population-density-dependent way by producing and detecting diffusible signaling molecules called autoinducers (AIs). The primary QS system in *A. baumannii* is N- acyl-homoserine lactones (AHLs); the abaI/abaR system is the most thoroughly studied system (Bhargava et al., 2020). The AHL synthase AbaI produces N-(3-hydroxydodecanoyl)-L- homoserine lactone (3-OH-C12-HSL), and the corresponding receptor/transcriptional regulator is

AbaR. When AHL concentrations exceed a threshold, AbaR activates the expression of genes linked to biofilm formation, motility, and virulence factor synthesis.

In murine pneumonia models, loss of abaI function greatly hinders biofilm formation and decreases *A. baumannii's* ability to establish infection, indicating that QS is necessary for both biofilm architecture and full virulence in vivo (Bhargava et al., 2020; Gedefie et al., 2021). Crucially, QS also controls the expression of multiple antibiotic resistance genes in biofilms, establishing a regulatory connection between drug tolerance and the biofilm phenotype. Hence, halogenated furanones, ajoene, and synthetic peptides are examples of QS inhibitors (QSIs) that disrupt QS signaling and have gained attention as an anti-biofilm technique (Brackman & Coenye, 2015).

3.5 Antibiotic Resistance Within Biofilms

Antibiotic resistance in biofilm bacteria is caused by a variety of interrelated and cooperative mechanisms. Hydrophilic antibiotics like beta-lactams and aminoglycosides are prevented from penetrating deeper levels of the biofilm by the EPS matrix, which functions as a physical and chemical diffusion barrier (Hall & Mah, 2017). Positively charged antibiotics like aminoglycosides can be bound by anionic matrix components, especially alginate-like exopolysaccharides and eDNA, which lowers the antibiotics' effective concentration at the bacterial cell surface (Wilton et al., 2016).

Bacteria in the deeper layers of mature biofilms reach a metabolically quiescent condition marked by slower growth rates within the nutrition and oxygen-limited microenvironments. Slow- growing or dormant subpopulations are naturally less vulnerable because the majority of antibiotics' bactericidal activity depends on active bacterial metabolism, especially cell wall synthesis (beta-lactams), DNA replication (fluoroquinolones), and ribosomal function (aminoglycosides) (Balaban et al., 2019). Persisters, a tiny percentage of phenotypically antibiotic-tolerant cells that are genetically identical to susceptible cells but survive antibiotic exposure because of their metabolic dormancy, are the result of this physiological tolerance (Meylan et al., 2018).

The high cell density, close cell proximity, and amount of eDNA within biofilms significantly promote horizontal gene transfer. Within biofilm communities, conjugative plasmids containing carbapenem resistance genes, such as OXA-type carbapenemases (OXA-23, OXA-24/40, OXA-51, OXA-58), New Delhi Metallo-beta-lactamase (NDM), and Verona Integron-encoded Metallo-beta-lactamase (VIM), are effectively transferred between cells, hastening the spread of resistance determinants (Hamidian & Nigro, 2019; Tamma et al., 2022).

4.0 Carbapenem Resistance Mechanisms in *A. Baumannii*

4.1 OXA-Type Carbapenemases

The generation of OXA-type beta-lactamases (class D serine-based enzymes), which have modest but clinically relevant hydrolytic activity against carbapenems, is primarily responsible for *A. baumannii's* resistance to carbapenems (figure 1). When expressed at basal levels, the intrinsic OXA-51-like enzyme, which is found in almost all *A. baumannii* strains, only confers low-level carbapenem resistance; however, upregulation through insertion sequence (IS) elements, such as ISAba1, positioned upstream of the gene, dramatically amplifies expression and clinically relevant resistance (Mugnier et al., 2021). The most epidemiologically significant acquired carbapenemases in *A. baumannii* are OXA-23, OXA-24/40, and OXA-58. Strains that produce OXA-23 have spread around the world and are especially common in Europe, Asia, and South America (Tamma et al.,2022).

Although they are less common in *A. baumannii* than in Klebsiella pneumoniae or Pseudomonas aeruginosa, metallo-beta-lactamases (MBLs) including NDM-1, VIM-2, and IMP are being reported more often, especially in isolates from South Asia (Jeon et al., 2015). Since MBLs are not inhibited by currently known beta-lactamase inhibitors like avibactam, MBL-producing *A.*

baumannii isolates provide a serious treatment challenge because they are often co-resistant to all beta-lactams.

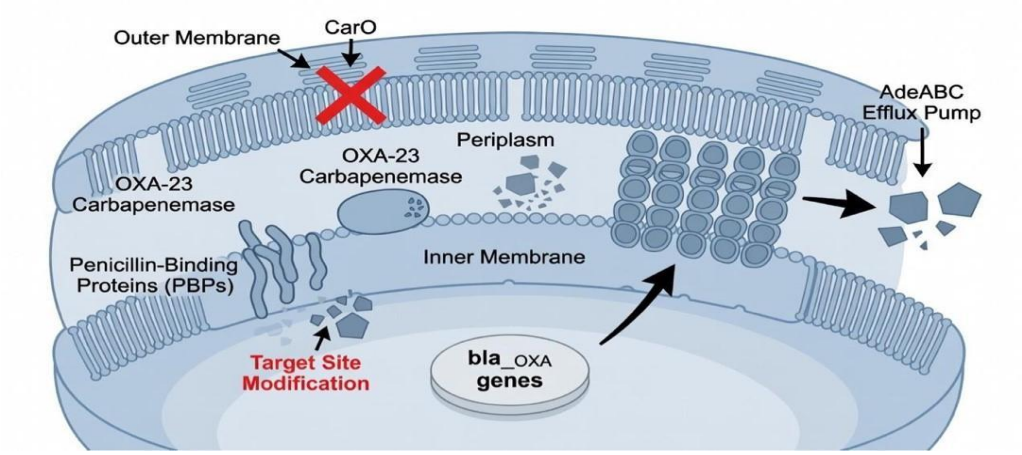

Figure 1: OXA-Mediated Carbapenem Resistance Mechanisms in *Acinetobacter baumannii* –the Non-Enzymatic Resistance Mechanisms

A. baumannii develops carbapenem resistance by a coordinated group of non-enzymatic processes in addition to producing carbapenemase (figure 2). Carbapenem influx across the outer membrane is decreased by loss or alteration of outer membrane porins, especially CarO and OprD-like channels (Abdi et al., 2020). The MDR phenotype is caused by the active removal of carbapenems and other antibiotics from the periplasm by the upregulation of multidrug efflux pumps, particularly the resistance-nodulation-division (RND) family pumps AdeABC, AdeFGH, and AdeIJK (Mmatli et al., 2022). Changes to the molecular targets of carbapenems, penicillin- binding proteins (PBPs), lower drug binding affinity and further diminish the effectiveness of antibiotics.

Because of the combined effect of many resistance mechanisms, particularly their co-expression within biofilm communities, which creates an almost impermeable defense, CRAB is naturally resistant to most antimicrobials. Whole-genome sequencing investigations have shown that clinical CRAB isolates frequently possess many overlap resistance processes together (Azam & Khan, 2019; Hamidian & Nigro, 2019). This shows the extraordinary selective pressure that antibiotics with broad spectrum in intensive care units impose.

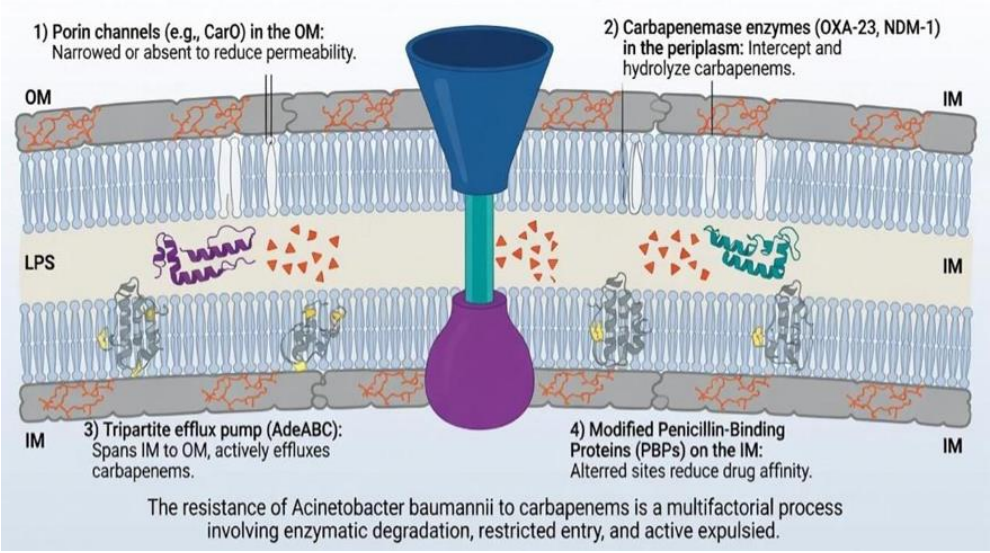

Figure 2: Mechanisms of Carbapenem Resistance in *Acinetobacter baumannii*

5.0 Clinical Epidemiology of Crab Hospital-Acquired Infections

5.1 Global Burden and Distribution

The highest incidence of CRAB-associated HAIs are found in settings with minimal resources and in intensive care units that use a lot of antibiotics. The global burden of these infections is significant and unevenly distributed. According to a comprehensive review by Cassini et al. (2016), *A. baumannii* is thought to be the cause of thousands of attributable deaths and 195,000 cases of HAI per year in EU member states. Carbapenem-resistant *A. baumannii* is classified as a "serious" antibiotic resistance problem in the United States by the Centers for Disease Control and Prevention (CDC), which reports approximately 8,500 healthcare-associated infections and an estimated 700 deaths each year (CDC, 2019).

CRAB carbapenem resistance rates are significantly higher in the Middle East and Southeast Asia. According to a multicenter study conducted in Asian intensive care units, 35–85% of *A. baumannii* isolates had carbapenem resistance, with India, Pakistan, and Thailand having the greatest rates (Lob et al., 2017). Tertiary care facilities in Egypt, Iran, and Lebanon have reported rates of more than 70–90% in the Middle East and North Africa (MENA) region (Pogue et al.,

2022). Spread of CRAB has been linked to military conflicts and mass casualty incidents. This was seen during the wars in Iraq and Afghanistan, when soldiers with traumatic wounds contracted CRAB infections from field and evacuation hospitals (Perez et al., 2020).

5.2 Clinical Syndromes Ventilator-Associated Pneumonia

The most prevalent and deadly clinical sign of CRAB in the intensive care unit is ventilator- associated pneumonia (VAP). Twenty to forty percent of late-onset VAP cases are caused by *A. baumannii*, the most common gram-negative cause of VAP in various high-burden settings (Poulakou et al., 2019). The pathophysiology of CRAB VAP include colonization of the upper respiratory tract, microaspiration of oropharyngeal secretions into the lower airways, where bacteria attach themselves to respiratory epithelium and endotracheal tube (ETT) surfaces and start the creation of biofilms. According to Papazian et al. (2020), the ETT biofilm is resistant to conventional antibiotic therapy and acts as a chronic source of reinfection.

CRAB VAP is associated with crude deaths rates of 40–70%, which is considerably greater than those caused by VAP caused by sensitive species (Poulakou et al., 2019). Additional mortality directly caused by CRAB VAP, compared to the primary disease, is estimated to be between 20 and 40 percent based on matched cohort analyses. Risk factors include prolonged artificial breathing (>5 days), immune suppression, burn injury, prior exposure to drugs (particularly carbapenems and cephalosporins), and admission to endemic intensive care units.

5.3 Catheter-Associated Bloodstream Infections

Catheter-associated infections of the blood stream (CABSI) are largely caused by CRAB, particularly in intensive care unit patients who have standard venous catheters (CVCs). Biofilm formation on the outside and inside surfaces of CVCs creates a substrate for chronic bacteremia. Replacing infected catheters is typically required for infection control, and crude death rates for CRAB CABSI range from 30 to 50% (Bassetti et al., 2018). In neonatal critical care units, *A. baumannii* has been identified as a major cause of advanced sepsis, a condition which is associated with high mortality and long-term brain damage in premature babies.

5.4 Wound and Burn Infections

CRAB is a significant pathogen in post-surgical site infections and burn wound infections, especially in patients who need extended hospital stays. Burns' damp, nutrient-rich environment

is perfect for *A. baumannii* colonization and biofilm production. Compared to patients with susceptible *A. baumannii* infections, burn patients with CRAB wound infections have considerably longer hospital stays, greater incidence of systemic sepsis, and worse mortality (Russotto et al., 2015). There is growing recognition of trauma-associated wound infections with CRAB, especially in patients with complex orthopedic wounds or penetrating injuries.

6.0 Clinical Impact: Morbidity, Mortality, And Economic Burden

6.1 Attributable Mortality

The severity of underlying illnesses in affected individuals makes it methodologically difficult to

quantify the attributable mortality of CRAB infections; yet, meta-analyses consistently show that carbapenem resistance imposes a high independent mortality risk. After controlling for covariates, a meta-analysis by Falagas et al. (2014) revealed that the odds ratio for mortality in CRAB versus carbapenem-susceptible *A. baumannii* infections was roughly 1.8– 2.5. According to published studies, the 30-day all-cause mortality rate for CRAB bacteremia varies from 40% to 70%, which is significantly greater than the 20 – 30% seen with susceptible bacteria. According to reports, endemic ICUs in high-burden settings have death rates of 50–75% for CRAB VAP (Poulakou et al., 2019).

Because biofilm-associated infections are linked to delayed diagnosis, treatment failure, and recurrent bacteremia from biofilm-coated implants or arterial lines, they have a very high death rate. A clinical characteristic of biofilm-associated infection, persistent CRAB bacteremia despite proper antibiotic therapy is linked to mortality that approaches 80% in certain series (Harding et al., 2018). Biofilm-mediated antibiotic tolerance and inherent carbapenem resistance combine to produce a clinical situation where traditional medical treatment often fails.

6.2 Economic and Healthcare System Impact

CRAB infections place a significant financial strain on healthcare systems. According to a cost- of-illness analysis conducted in the United States, each case of carbapenem-resistant *A. baumannii* infection resulted in excess healthcare costs of $30,000–$100,000 when compared to non-infected controls. These costs were mostly caused by the use of costly salvage antibiotics, extended ICU stays, and additional diagnostic testing (Peiffer-Smadja et al., 2021). The economic

cost per case in relation to per-capita GDP is disproportionately severe in lower-middle-income nations with limited healthcare resources.

In addition to direct expenses, CRAB infections cause indirect costs such as long-term impairment, lost productivity, and the financial ramifications of managing hospital outbreaks, such as ward closures, improved screening procedures, and personnel surcharges. Reduced hospital capacity, resource diversion from elective care, and harm to the institution's reputation are examples of system-level effects. According to modeling studies, the annual economic impact of all antibiotic-resistant illnesses in the US, of which CRAB is a significant component, exceeds $20 billion in direct healthcare expenditures and an additional $35 billion in societal expenses (CDC, 2019).

7.0 Therapeutic Challenges in Crab Biofilm Infections

7.1 Limitations of Current Antimicrobial Agents Polymyxins

Historically, the mainstay of last-resort treatment for CRAB infections has been polymyxins (colistin and polymyxin B). By competitively displacing divalent cations (Ca^{2+} and Mg^{2+}) from lipopolysaccharide, these cationic lipopeptide antibiotics cause membrane permeabilization

and cell death in gram-negative bacteria (Tsuji et al., 2019). Polymyxins, however, have limited effectiveness against biofilm-embedded CRAB for several reasons, including limited penetration through the EPS matrix, positively charged polymyxin molecules being sequestered by negatively charged matrix components like eDNA and exopolysaccharides, and the metabolically quiescent bacteria in biofilm interiors being less vulnerable to membrane-active agents.

Colistin monotherapy greatly reduces its clinical efficacy in biofilm infections and is linked to the quick evolution of resistance, especially by alteration of LPS lipid A via PmrAB and PhoPQ two- component systems (Tacconelli et al., 2019). Moreover, escalation techniques that could ordinarily overcome biofilm tolerance are limited by the nephrotoxic and neurotoxic side effects of polymyxins. Colistin monotherapy continues to have poor clinical results for bacteremia and CRAB VAP, with microbiological failure rates of 40–60% in certain groups.

7.2 Tigecycline and Sulbactam

Tigecycline, a broad-spectrum glycylcycline antibiotic, has been utilized in combination regimens for CRAB infections and maintains in vitro activity against numerous CRAB isolates

(Bassetti et al., 2020). The Food and Drug Administration (FDA) issued a black-box warning about increased all-cause mortality with tigecycline use for specific indications because the drug achieves suboptimal pharmacokinetic/pharmacodynamic (PK/PD) parameters in the bloodstream and lungs,

especially at standard dosing. To get around PK restrictions, high-dose tigecycline regimens (200 mg loading dose, 100 mg every 12 hours) have been suggested; however, there is still a lack of clinical data, and resistance develops due to upregulation of the RND efflux pump AdeABC.

In vitro and in animal models, sulbactam, a beta-lactamase inhibitor with intrinsic bactericidal action against *A. baumannii* through inhibition of the penicillin-binding proteins PBP1 and PBP3, has shown efficacy against certain CRAB strains (Penwell et al., 2015). Combinations of ampicillin and sulbactam have been used in clinical settings, especially for less severe CRAB infections where sulbactam MICs are still low. However, co-expression of sulbactam-hydrolyzing beta-lactamases and porin loss in many clinical CRAB isolates reduce the effectiveness of ampicillin-sulbactam.

7.3 Emerging and Novel Therapeutic Approaches - Cefiderocol

Cefiderocol is a new siderophore cephalosporin that circumvents traditional porin-mediated entry pathways by taking use of bacterial iron acquisition mechanisms to reach high-level accumulation inside bacterial cells (Ito et al., 2018). The FDA approved cefiderocol in 2019 for the treatment of gram-negative infections with few treatment choices after it showed strong in vitro activity against most CRAB isolates in global surveillance investigations, including strains carrying OXA and MBL carbapenemases. Cefiderocol and the best available treatment for carbapenem-resistant infections, such as *A. baumannii,* were compared in the CREDIBLE-CR trial. The results showed similar microbiological success but higher all-cause mortality in the cefiderocol arm, which was primarily due to selection bias toward the sickest patients (Bassetti et al., 2021).

Research on cefiderocol's effectiveness against biofilm-producing CRAB in vitro and in vivo is still ongoing. Because its siderophore moiety is actively transported even through the limited diffusion environment of the EPS, preliminary studies indicate that cefiderocol penetrates biofilm matrices more successfully than carbapenems or polymyxins. Long-term efficacy data are

required, nevertheless, as resistance development via siderophore receptor alterations during cefiderocol therapy has been documented.

7.4 *Sulbactam-Durlobactam*

Sulbactam (active against *A.baumannii* PBPs) and durlobactam, a novel diazabicyclooctane (DBO) beta-lactamase inhibitor that inhibits class A, C, and D beta-lactamases, including OXA-type carbapenemases, combine to form Sulbactam-durlobactam (SUL-DUR) (Penwell et al., 2015; McCreary et al., 2023). SUL-DUR is the first truly novel agent with specific mechanistic action against *A. baumannii's* primary resistance determinants, as demonstrated by the ATTACK trial, which showed that SUL-DUR achieved non-inferior clinical cure rates for CRAB VAP and bacteremia when compared to colistin-imipenem/cilastatin (McCreary et al., 2023). A major therapeutic advancement was made in 2023 with FDA approval. Determining the best dosage techniques and tracking the establishment of resistance in biofilm-associated illnesses will require ongoing practical experience. Table 1 below shows the limitations of current therapeutic options available and also emerging therapeutic approaches.

Table 1: Current Limitations and Emerging Therapeutic Approaches for CRAB Infections

Category	Agent / Combination	Mechanism of Action	Advantages	Limitations / Resistance	Clinical Notes
Current Therapy Limitations	Polymyxins (Colistin, Polymyxin B)	Disrupt bacterial membrane by displacing Ca^{2+} and Mg^{2+} from LPS → cell death	Last-resort drugs for CRAB	Poor biofilm penetration; sequestration by EPS; resistance via LPS modification (PmrAB, PhoPQ); nephro-toxicity & neurotoxicity	High failure rates (40-60%) in bacteremia & VAP
Current Therapy Limitations	Colistin Monotherapy	Same as above	Widely used	Rapid resistance development; poor efficacy in biofilms	Limited clinical success
Tigecycline	Tigecycline	Glycylcycline antibiotic inhibiting protein synthesis	Active against many CRAB isolates	Suboptimal PK/PD in blood & lungs;	High-dose regimens suggested but limited data
Sulbactam (± Ampicllin)	Sulbactam (± Ampicillin)	β-lactamase inhibitor; binds PBP1 & PBP3	Suboptimal PK/PD in blood & lungs;	Increased mortality warning_ Resistancorvig AdeBOC urhou puitp	High-dose regimens suggested but limited data
Emerging Therapies	Cefiderocol	Siderophore cephalosporin; uses iron transport system to enter bacteria	Strong activity vs A. baumannii	Resistance via β-lactamases & porin	FDA approved (2019); ongoing evaluation
Emerging	Cefiderocol	Sulbactam (targets PBPs)+ Durlobactam (DBO β-lactamase inhibitor blocking class A, C, D enzymes)	Strong activity vs CRAB; better biofilm penetration	Resistance via siderophore receptor mutations; higher	FDA approved (2023); non-inferior to colistin-based therapy
	Sulbactam–Durlobactam(SUL-DUR)	Sulbactam (targets PBPs) + Durlobactam (DBO β-lactamase inhibitor blocking class	Targets key optimal dosadonig still under study	FDA approved (2023); non-inferior to colistin-based therapy	FDA approved (2023); non-inferior to colistin-based therapy

7.5 Bacteriophage Therapy

In the age of antibiotic resistance, bacteriophages (phages), viruses that particularly attack and lyse bacteria, have garnered increased attention as anti-infective drugs (Singh et al., 2022). According to Gordillo Altamirano et al. (2021), phages have a number of potential benefits for CRAB biofilm infections, including the ability to multiply within biofilms, enter biofilm matrices, and create depolymerases that break down EPS components, making it easier to reach embedded bacteria. For usually incurable CRAB infections, such as prosthetic valve endocarditis and persistent wound infections, case reports and small case studies have shown positive results using compassionate-use phage therapy (Schooley et al., 2017).

The high specificity of phages (which necessitates the identification of lytic phages matched to the patient's infecting strain), the possibility of phage resistance developing quickly, regulatory obstacles, and the lack of extensive randomized controlled trial data are major obstacles to the clinical translation of phage therapy (Nandy et al., 2022; Masih & Singh, 2023). Phage cocktails that target several bacterial receptors may reduce the establishment of resistance, and phage-antibiotic synergy (PAS), the documented potentiation of antibiotic effectiveness by sublethal phage exposure, presents a potential combination approach (Gordillo Altamirano et al., 2021).

7.6 Anti-Biofilm Compounds and Novel Strategies

In order to potentially lessen the selective pressure for resistance while making bacteria more vulnerable to contemporaneous antibiotics, an increasing amount of research has concentrated on finding substances that particularly target biofilm formation rather than bacterial viability per se. In vitro and in animal models, quorum sensing inhibitors (QSIs) such halogenated furanones and synthetic brominated chemicals decrease AHL signaling and attenuate biofilm development in *A. baumannii* (Brackman & Coenye, 2015). By taking advantage of *A. baumannii's* iron acquisition

systems, gallium (Ga^{3+}) compounds displace iron (Fe^{3+}),

interfering with iron-dependent

metabolic processes and drastically lowering biofilm growth (Rangel et al., 2021).

When combined with antibiotics, dispersin B, a glycoside hydrolase that breaks down PNAG, has shown strong anti-biofilm efficacy against *A. baumannii*, lowering biofilm biomass by more than 90% in vitro (Thallinger et al., 2016). In vitro and ex vivo wound models have demonstrated the effectiveness of photodynamic inactivation (PDI), which uses photosensitizers activated by visible light to produce reactive oxygen species (ROS) that harm bacterial membranes and DNA

(Wen et al., 2017). Silver nanoparticles, zinc oxide nanoparticles, and antibiotic-loaded liposomes are examples of nanoparticle-based drug delivery systems that provide improved biofilm penetration and prolonged drug release, potentially bypassing traditional diffusion limits (Hameed et al., 2022).

Another frontier in anti-CRAB biofilm therapy is antimicrobial peptides (AMPs), which can be produced de novo or acquired from host innate immune systems. At low doses, AMPs such synthetic cationic peptides, defensins, and colistin analogues can break down bacterial membranes, enter biofilm matrix, and work in concert with traditional antibiotics. Crucially, because AMPs target basic structural characteristics of gram-negative membranes, resistance to them develops more slowly than resistance to other antibiotics (Kang et al., 2017).

Combination antibiotic therapy is commonly used and supported by in vitro and animal data due to the limits of any single agent against CRAB biofilm infections, while solid clinical trial evidence is still lacking. Numerous randomized trials and observational studies have assessed polymyxin-based combinations, such as colistin plus rifampicin, colistin plus tigecycline, and colistin plus carbapenems. For CRAB infections, a seminal randomized trial (AIDA trial) comparing colistin monotherapy with colistin + rifampicin indicated no mortality benefit from combination therapy, however the combination improved microbiological clearance (Paul et al., 2018).

More recently, preclinical research has been conducted on sulbactam-durlobactam combinations with cefiderocol, azithromycin (which possesses immunomodulatory and anti-biofilm effects at sub-MIC concentrations), and rifampicin. When combined with carbapenems, fosfomycin, an epoxide antibiotic that inhibits cell wall production, has shown anti-biofilm effectiveness against

A. baumannii and is a potentially useful repurposed drug (Vardakas et al., 2020). The best combination for biofilm-associated CRAB infections is yet unknown and will probably differ depending on the infection site, local resistance profiles, and PK/PD factors at the target site.

8.0 Infection Prevention and Control Strategies

8.1 Environmental and Contact Precautions

A multimodal strategy including strict hand hygiene, environmental decontamination, active surveillance, and standard and improved contact precautions is necessary for the effective control of CRAB transmission in healthcare settings. The foundation of CRAB containment is the use of gowns and gloves for all patient encounters, which have been demonstrated to lower transmission rates in endemic situations when strictly followed (Sands et al., 2021). Given the organism's persistence on surfaces, improved environmental cleaning procedures utilizing EPA-registered sporicidal chemicals, such as hydrogen peroxide vapor systems or diluted hypochlorite solutions, are crucial in rooms where CRAB patients have received treatment.

Early identification of colonized patients and the application of cohorting tactics are made possible by the use of active surveillance cultures (ASCs) to detect CRAB colonization upon admission, during hospitalization, and following outbreak episodes. Whole-genome sequencing in genomic epidemiology has revolutionized epidemic research by allowing accurate reconstruction of transmission chains and identification of environmental reservoirs with resolution not possible with traditional typing techniques (Ellington et al., 2017). Leading institutions are increasingly incorporating real-time genetic surveillance into their infection control procedures.

8.2 Antimicrobial Stewardship

Antimicrobial stewardship programs (ASPs) are essential for reducing the selective pressure that propels the establishment and persistence of CRAB. Core stewardship principles that are pertinent to CRAB prevention include limiting the use of broad-spectrum carbapenem, de- escalating treatment depending on

culture results, and using quick molecular diagnostics to provide early, focused therapy (Barlam et al., 2016). Numerous multicenter studies have shown that computer-assisted decision support systems and prospective audit-and-feedback programs reduce carbapenem usage and CRAB incidence. In critically sick patients at high risk for CRAB infection, stewardship must be weighed against the necessity of effective empirical therapy, since delayed suitable therapy is independently linked to higher death.

9.0 Future Directions in Research and Clinical Practice

9.1 Genomics and Precision Therapeutics

The therapeutic treatment of CRAB biofilm infections could be significantly improved by developments in genomic and metagenomic technology. Personalized antibiotic selection is made easier by the quick and thorough analysis of virulence factors, biofilm-related genes, and resistance determinants in clinical isolates made possible by whole-genome sequencing (Hamidian & Nigro, 2019). Clinical decision-making may be aided by the predictive modeling of biofilm formation potential and antibiotic susceptibility patterns made possible by machine learning algorithms applied to genomic and phenotypic data. Regulatory proteins, surface adhesins, and EPS biosynthesis enzymes that are selectively expressed in biofilm states are examples of potential biofilm-specific therapeutic targets that can be found by combining transcriptome and proteomic techniques.

9.2 Vaccine Development

Despite years of experimental study, there is presently no approved vaccine against *A. baumannii*. Vaccine candidates that have showed protective effectiveness in murine infection models include recombinant subunit vaccines that target OmpA, Ata, and Bap; outer membrane vesicle (OMV)- based vaccines; and whole-cell killed vaccines; however, their translation to clinical trials has been limited (García-Quintanilla et al., 2019). Because they are specifically produced in vivo during infection and may trigger antibodies that either prevent colonization or aid in the immune clearance of bacteria that dwell in biofilms, biofilm-associated antigens are interesting targets for vaccines. The creation of a safe and efficient CRAB vaccine would be a revolutionary advancement in the prevention of infections linked to healthcare, especially for vulnerable groups including burn victims, ICU patients, and immunocompromised people.

9.3 Regulatory and Global Policy Landscape

The CRAB crisis needs coordinated worldwide policy action. This includes creating international monitoring networks, increasing funds for antimicrobial research and development, and improving infection prevention capacity in low- and middle-income countries. The Pasteur Act, which was proposed in the United States, and the SECURE Act, which was proposed in Europe, have attempted to alter antimicrobial payment methods in order to promote pharmaceutical investment in antibiotics that target WHO major infections, such as CRAB (Renwick et al., 2018). The use of antibiotics in agriculture and the environment is closely associated with antimicrobial resistance in human healthcare, and global activities through the WHO, G7, and G20 have committed to the One Health framework. Following these policy objectives must be done to stop the development of CRAB-associated HAIs, particularly in improving hospital infection control systems worldwide.

10.0 Conclusion

Carbapenem-resistant *Acinetobacter baumannii* is one of the most difficult and urgent problems in modern infectious disease medicine. Due to its ability to form powerful biofilms on hospital surfaces and healthcare supplies, as well as an effective range of carbapenem resistance mechanisms, it is resistant to most antimicrobial treatments and a major cause of HAI-related death and morbidity globally. With a better understanding of the molecular pathophysiology of CRAB biofilm infections, potential helpful flaws in surface adhesion, quorum sensing, EPS generation, and iron absorption pathways have been revealed.

The continuous development of CRAB resistance needs ongoing monitoring and funding for next-generation medicines, even though recently approved drugs like cefiderocol and sulbactam- durlobactam represent important therapeutic improvements. Anti-biofilm technologies include phage treatment, dispersin enzymes, photodynamic inactivation, and nanoparticle-based delivery. These additional methods may increase the effectiveness of already existing antibiotics and reduce the selection pressure that leads to resistance. Translational combination of clinical science, pharmacology, and genetics will be necessary for specific therapy of CRAB biofilm infections.

At the end of the preventing CRAB in healthcare organizations requires a systems-level strategy that includes efficient infection control programs, careful antibiotic stewardship, rapid genomic analysis, and a constant dedication to drug discovery and global health justice. The amount of lives lost, the strain on healthcare institutions, and the ethics of modern medicine itself all show how high the stakes are.

Declaration: The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript.

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- Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable. – ~~**Yes**~~ / **Not Applicable**√

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