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ACINETOBACTER BAUMANNII AND THE RISE OF CARBAPENEM RESISTANCE: FROM PATHOGENESIS TO CLINICAL CONSEQUENCES

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ABSTRACT

Background: *Acinetobacter baumannii*, an opportunistic Gram-negative pathogen, represents a critical global health threat due to the escalating incidence of resistance to carbapenem antibiotics. This review explores the complex challenge of Carbapenem-Resistant *A. baumannii* (CRAB), beginning with its role as a predominant hospital-acquired pathogen. We detail the alarming worldwide epidemiology of CRAB, emphasizing its efficient dissemination driven by the ability to persist on hospital surfaces and medical devices. This environmental tenacity, combined with frequent patient transfers, facilitates rapid spread across healthcare networks, contributing significantly to endemicity.

The review investigates the organism's pathogenesis, highlighting key virulence factors such as biofilm formation and immune evasion that facilitate severe infections. A central focus is on the molecular basis of resistance, particularly the acquisition of diverse carbapenemase enzymes (e.g., OXA-types), efflux pump overexpression, and porin loss, which render carbapenems ineffective. The genetic plasticity of *A. baumannii*, often involving mobile genetic elements like plasmids, accelerates the horizontal transfer of these resistance genes, outpacing antibiotic development. The clinical consequences are severe, marked by limited treatment options and significantly high mortality rates in vulnerable patient populations, particularly those in intensive care units. These difficult-to-treat infections often necessitate last-resort polymyxins or novel combination therapies, further complicating patient management and increasing treatment costs. Understanding these intricate resistance and virulence strategies is essential for developing novel antimicrobial and infection control measures to mitigate this urgent public health crisis and improve patient outcomes.

Keywords: Gram Negative Bacilli, Carbapenem Resistant, Nosocomial Pathogen, Virulence Factor.

INTRODUCTION

History: The bacterial genus *Acinetobacter* was initially discovered in 1911 when Dutch microbiologist Beijerinck successfully isolated it from soil samples utilizing a minimal calcium acetate enriched medium.[1] Four decades and three years afterward, researchers Brisou and Prevot first characterized this microorganism as Micrococcus calcoaceticus. The taxonomic designation "*Acinetobacter*" stems from the Greek term "akinetos," signifying immobility, which serves to differentiate these organisms from their motile counterparts in the *Achromobacter* classification. During 1954, Brisou and Prevot additionally recognized *Acinetobacter anitratum* as a representative species belonging to the *Acinetobacter* classification.[2] Based on Bergey's Manual of Bacteriology from 1974, these microorganisms were categorized under the Neisseriaceae family, establishing *Acinetobacter calcoaceticus* as the primary species while recognizing *Acinetobacter anitratum* and *Acinetobacter lwoffi* as two distinct subspecies, differentiated by their glucose acidification capabilities.[3]

The *Acinetobacter* genus exhibits distinctive properties as Gram-negative, obligately aerobic, non-fermentative, non-motile, catalase-positive and oxidase-negative microorganisms possessing DNA G + C composition between 39-47% .During 1986, comprehensive DNA-DNA hybridization investigations performed by Bouvet and Grimont on *Acinetobacter* specimens resulted in the systematic organization of these bacteria into 26 designated species and 9 genomic categories.[4] Within this classification, four particular species - *Acinetobacter calcoaceticus, A. baumannii, Acinetobacter* genomic species 3, and *Acinetobacter* genomic species 13 TU demonstrated comparable phenotypic characteristics, frequently resulting in their grouped identification as the *Acinetobacter calcoaceticus* complex.[5]

Habitat: *Acinetobacter* organisms exist as independent saprophytic microorganisms that inhabit various ecological niches including terrestrial substrates, aquatic systems, wastewater, and maintain associations with human populations, nutritional sources, and animal hosts.[5] *A. baumannii* demonstrates remarkable capacity for survival on desiccated surfaces even when subjected to nutrient-depleted environments, thereby facilitating its endurance and dissemination across diverse natural ecosystems and healthcare facilities. Additionally, contaminated medical apparatus and instrumentation can function as persistent sources of infection, leading to extended nosocomial epidemic episodes. This bacterium can persist on dry surfaces for extended periods, even exceeding four months, facilitating its survival in the hospital environment.

Morphology: During their rapid growth phase, *Acinetobacter spp.* appears as short, plump rods, typically 1.0-1.5µm by 1.5-2.5µm in size, but they frequently become more coccoid during the stationary phase.[3] *Acinetobacter spp*. when grown on blood agar substrates, bacterial colonies display characteristic morphological features, presenting as colorless (white to cream-colored), smooth or mucoid appearances (when capsular structures are present) with a milky consistency and measuring 1-2mm in diameter following 18-24 hours of cultivation at 37°C. Conversely, when cultured on eosin methylene blue medium, colonies manifest a bluish to bluish-gray pigmentation. Growth on Herellea agar produces pale lavender-colored colonies, whereas cultivation on Leeds Acinetobacter medium results in pink colonies against a purple substrate.[3]

Significance of carbapenem resistance in *A. baumannii*: Carbapenems represent powerful antimicrobial compounds that demonstrate efficacy against both Gram-positive and Gram-negative bacterial pathogens. These medications are frequently utilized as final therapeutic options for severely ill patients. Presently, *A. baumannii* constitutes a widespread Gram-negative rod-shaped organism accountable for nosocomial infections, particularly within intensive care environments.[6]. The initial case of carbapenem-resistant *A. baumannii* was documented in 1991, and regrettably, the worldwide prevalence of this resistance pattern has been escalating.[6]

Epidemiology:

A. baumannii demonstrates extraordinary ability to obtain diverse resistance mechanisms.[7] Carbapenems, representing a group of β-lactam antimicrobials with potent efficacy against Gram-negative rod-shaped bacteria, were previously a favoured therapeutic choice for *Acinetobacter species* infections. Nevertheless, carbapenem sensitivity percentages differ across geographical regions. Based on data from the SENTRY Antimicrobial Surveillance Program (2013-2016), among *Acinetobacter species*, the most reduced susceptibility percentages to meropenem were documented in Latin America (13.7%), subsequently in the Europe (22.2%), US (54.9%) and Asia-Pacific area (21.0%).[8]

Seifert and associates,[9] gathering *Acinetobacter specimens* from 2016 through 2018, similarly recorded the minimal meropenem sensitivity rates 17.2% in Middle East Africa, followed by 19.6% in Latin America, 31.4% in Asia-South Pacific, 33.8% in Europe and 63.6% in North-America. The most recent findings from the WHO and the "European Centre for Disease Prevention and Control (ECDC)" demonstrate substantial variation in the proportions of carbapenem-resistant *Acinetobacter species* throughout Europe in 2020: among 38 nations and territories providing information, 3 documented occurrence percentages below 1%, while 35 recorded rates of 50% or greater.[10] The nations with the minimal rates included Ireland, the Netherlands, and Norway, whereas carbapenem resistance percentages reached or exceeded 50% in 21 countries, primarily concentrated in Southern and Eastern Europe.

Colistin resistance was uncommon throughout the 1990s, with the initial documented occurrence originating from the Czech Republic in 1999.[11] Information from the SENTRY Surveillance Program demonstrated a considerable reduction in colistin sensitivity percentages across all geographical areas between 2013–2016 when compared to 2005–2008. The most substantial decrease in colistin susceptibility within *Acinetobacter*-bloodstream infections (ABC) was noted in Europe (declining from 99.2% to 89.6%), subsequently in the Asia-Pacific area (from 99.1% to 93.7%) and North America (from 98.4% to 93.6%).[8]

Primary molecular characterization of *A. baumannii* specimens identified three lineages circulating throughout Europe, labelled as European clones I, II, and III.[12]

Additional investigation revealed that these lineages had disseminated worldwide with European clones I, II and III being reclassified as international clonal (IC) lineages I, II, and III [13]. Presently, nine international clones of A. baumannii, ICs 1–9 have been identified. Subsequently, two multilocus sequence typing (MLST) methodologies, Oxford and Pasteur, were established for characterizing A. baumannii specimens with each methodology

producing unique clonal complexes and sequence types.[14] The relationship between *A. baumannii* international clones as established by Oxford & Pasteur MLST methodologies are: A.baumannii IC1 (CC109OXF/CC1Past), IC2 (CC92OXF/CC2Past), IC3 (CC929OXF/CC124Past), IC4 (CC103OXF/CC15Past), IC5 (CC227OXF/CC79Past), IC6 (CC944OXF/CC78Past), IC7 (CC110OXF/ CC25Past), IC8 (CC447OXF/CC10Past), and IC9 (CC1078OXF/ CC464Past).[15] IC1 & IC2 frequently carry the acquired carbapenemase oxacillin-hydrolysing (OXA)-23 and represent the most effectively distributed clones globally.[16] Nevertheless, regional differences occur, with IC5 and IC7 being more common in Central and South America, while IC9 demonstrates greater predominance in Africa and the Middle East.

Achieving an accurate comprehension of *A. baumannii* clone distribution presents difficulties owing to the restricted availability of publicly accessible genomic sequence information from Africa, the Middle East, South America, and Russia.[16] A robust correlation has been documented between *A. baumannii* ICs 1–8 like sequences and blaOXA-51 indicating that blaOXA-51 sequencing could function as a simple test for identifying *A. baumannii* ICs.[17] In the US, it was calculated that 700 fatalities & 8500 cases were linked with carbapenem-resistant *Acinetobacter species* infections in 2017. These figures declined in 2018 (500 deaths and 6300 cases) and remained consistent in 2019 (500 deaths and 6000 cases) but rise in 2020 (700 deaths and 7500 cases). A 78% rise in healthcare facility-acquired carbapenem-resistant *Acinetobacter species* infections was identified between 2019 and 2020 in an initial assessment conducted by the Center for Disease Control and Prevention (CDC).[18]

Multilocus sequence typing (MLST) analysis demonstrated that all 21 CRAB specimens obtained between January and April 2020 were classified within the CC92/IC2 clonal lineage. Based on the Oxford MLST methodology, ST195 (n = 15) represented the most frequently detected ST, succeeded by ST369 (n=6). Additional US-conducted research examining 150 CRAB specimens from 120 patients throughout 4 healthcare facilities determined that the majority of specimens were categorized under CC2. Three CC2 sub-lineages were characterized within these specimens, with the majority of colistin-resistant specimens grouping within one of these lineages.

Pathogenesis and virulence of Carbapenem-Resistant A. baumannii:

Virulence factors involved in the pathogenesis of *Acinetobacter spp.* include: i. The presence of a polysaccharide capsule that modifies the bacterial surface to be more hydrophilic. ii. Fimbriae that facilitate the adhesion of the pathogen to human epithelial cells. iii. Enzymes that cause damage to tissue lipids. iv. Cell wall components lipid A and Lipopolysaccharide, which contribute to cellular toxicity. v. In vivo endotoxin production, leading to illness symptoms. vi. Slime production, which enhances virulence, particularly in mixed infections. vii. The requirement for iron for growth within the human body.

Porins: Porins operate as outer membrane proteins that modify cellular permeability characteristics. OmpA represents the most prevalent porin within the outer membrane and constitutes a thoroughly studied virulence factor demonstrating diverse biological functions in in vitro experimental systems . OmpA targets mitochondrial structures through binding to host cells, resulting in the discharge of cytochrome C and proapoptotic factors.[24],[40-41] It additionally facilitates the adherence and penetration of epithelial cells through fibronectin binding,[19] and interacts with factor H in serum, potentially allowing *A. baumannii* to escape complement-mediated destruction. Moreover, OmpA participates in the antimicrobial resistance mechanisms of *A. baumannii*. OmpA contributes to the expulsion of antibiotics across the outer membrane from the periplasmic compartment, working in conjunction with inner membrane efflux mechanisms.[19] By promoting biofilm formation and surface motility, OmpA improves the persistence & survival capabilities of Acinetobacter species. OmpA additionally controls the formation of outer membrane vesicles.

Another outer membrane protein, Omp 33-36, has been linked to the cytotoxicity of A. baumannii,[19] and also plays a role in antibiotic resistance. A research investigation documented that the *A. baumannii* isolate JC10/01, which demonstrated resistance to carbapenem antimicrobials, exhibited an absence of Omp33-36 and reduced MICs for meropenem & imipenem.

Additional outer membrane proteins, including Omp,[22] have been recognized as promising new and secure antigens for vaccine formulation. Carbapenemase-linked outer membrane proteins and OprD have similarly been demonstrated to correlate with virulence-associated elements, suggesting diminished pathogenicity in murine experimental models.

Capsular Polysaccharides and Lipopolysaccharide: This microorganism possesses a preserved gene cluster termed the K cluster, which potentially controls capsular polysaccharide synthesis.[20] Two-component systems, including BfmR and BfmS, are regulated by K-locus genes.[20] BfmS, a virulence factor, is crucial for biofilm formation,[29] while BfmR is associated with complement-mediated bactericidal activity and antibiotic resistance.[21]

Hyperproduction of capsular polysaccharides can occur in the presence of antibiotics; however, some mutants deficient in capsular polysaccharide exhibit reduced resistance to peptide antibiotics.[20] Lipopolysaccharide consists of a lipid A moiety, the core oligosaccharide, and the O antigen. It induces the release of TNF and IL-8 from macrophages LPS

performs an important function in pathogenicity and enhances the survival capabilities of Acinetobacter spp.[21-22]

Phospholipase: In phospholipid metabolism, phospholipase, a lipolytic enzyme, acts as a host invasion factor. Phospholipases are categorized into three distinct classes according to their cleavage locations: PLA, PLC, and PLD. PLA and PLC remove fatty acids from the glycerol structure and phospholipid-derived head groups, whereas PLD functions as a transphosphatidylase, separating the head groups. Phospholipid breakdown influences the integrity of the host cellular membrane, and separated head groups can disrupt cellular signalling processes, resulting in modifications to the host immune response.[35] PLC and PLD demonstrate considerable significance in Acinetobacter spp.[23] A. baumannii ATCC17978 contains two PLCs, identified as A1S0043 and A1S2055. A. baumannii ATCC 19606 harbours three PLD genes that contribute significantly to host cell penetration.[23]

Outer Membrane Vesicles: OMVs are released by the outer membrane of Gram-negative rod-shaped bacteria. These vesicles carry various virulence factors into the host cell and allow the pathogen to communicate with the host cell without direct contact.

Metal Acquisition System: Although iron is abundant in the environment, its ferric form is often inaccessible to bacteria under physiological conditions. This limited availability is due to iron's poor solubility at neutral pH and it's strong binding to host molecules like heme lactoferrin, and transferrin.[24] To overcome this, bacteria have evolved high-affinity iron chelators known as siderophores.[24] These siderophores, including catecholates and hydroxamates, exhibit a strong affinity for iron. A. baumannii produces a combination of siderophores, including a general iron siderophore and acinetobactin, which also functions as a virulence factor. Research indicates that the production of acinetobactin is significantly elevated in multidrug-resistant Acinetobacter strains.

A. baumannii also possesses the NfuA Fe-S scaffold protein, which plays a role in protecting against oxidative stress. Studies have shown that the haemolytic activity of Acinetobacter spp. increases under iron-limiting conditions. Thus, the efficient acquisition of iron is crucial for the virulence of A. baumannii.

Calprotectin, a host protein that chelates metals, restricts bacterial growth by sequestering essential metals like zinc and manganese. Acinetobacter employs the ZNuABIC zinc acquisition system, which is activated under zinc-limited conditions. A zinc metallochaperone, ZigA, has been identified in A.baumannii. ZigA tightly binds zinc, enabling bacterial growth even when zinc is scarce.

Protein Secretion System: A Type II secretion system (T2SS) has been recently identified in Acinetobacter species.[25] Structurally resembling the Type IV pili mechanism, T2SS facilitate protein movement from the periplasmic compartment through the outer cellular membrane. It consists of four subcomplexes: a pseudopilus, a cytoplasmic ATPase secretory complex, an inner membrane assembly platform, and an outer membrane complex.[26] The protein secretion through T2SS occurs via two phases: the target protein is initially transported to the periplasm by either the general secretory pathway or the twin-arginine transport (Tat) mechanism. Metallopeptidase (CpaA) and Lipases (LipA, LipH, LipN) have been recognized as substrates of T2SS.[26]

The Type V secretory system in *A. baumannii* comprises a trimeric membrane protein that promotes biofilm development. *A. baumannii* additionally contains a Type VI secretion system, which has been examined using bioinformatics approaches. Remarkably, plasmids harbouring the Type VI secretion system are suppressed in antibiotic-resistant cells. These observations indicate a possible molecular switching mechanism between antibiotic resistance & Type VI secretion.

Penicillin-Binding Protein 7/8 and β-lactamase PER-1: β-lactam antibiotic resistance can be facilitated through modifications in penicillin-binding proteins. Penicillin-binding protein 7, encoded by the pbpG gene, functions as a pathogenicity factor in *A. baumannii*,[27] The β-lactamase PER-1 has similarly been associated as a virulence determinant in *A. baumannii*, with its occurrence connected to enhanced cellular adherence.[28]

Others: CipA, a novel plasminogen-binding protein and inhibitor of complement proteins, contributes to serum resistance and thus acts as a virulence factor.[29] *A. baumannii* also possesses the translational elongation factor Tuf, which can facilitate the conversion of plasminogen into active plasmin, leading to proteolytic degradation and the inactivation of the C3b component. Surface antigen protein A1 (SurA1) is a major contributor to serum resistance and in vivo survival.[30]

Pili performs an essential function in the adherence and biofilm development by *Acinetobacter* .Genes responsible for Type IV pili synthesis are expressed in imipenem-resistant *Acinetobacter species*.[31] Additional proteins linked to pathogenicity have similarly been recognized, including OmpR/EnvZ, FhaBC, and AbeD,[32] which enhance virulence through facilitating host cellular destruction.

Carbapenem Resistance Mechanisms:

Modifications in penicillin-binding proteins: Decreased affinity of penicillin-binding proteins (PBPs) for carbapenems, frequently caused by reduced PBP expression, is linked with carbapenem resistance in *A. baumannii* isolates. Although mutations affecting the production levels or binding affinity of PBPs can result in β-lactam resistance, their contribution in A. baumannii is typically associated with only minimal carbapenem resistance.[33]

Absence of outer membrane porins: "Compromised membrane permeability caused by diminished expression or mutations in porin proteins represents another resistance mechanism. Porin channels and outer membrane proteins (OMPs) normally enable the penetration of antimicrobial compounds into the bacterial cell.[34] Various OMPs, including a 29-kDa protein (CarO or carbapenem-associated OMP), HMP-AB, and OmpW, participate in the transportation of β-lactams through the *A. baumannii* membrane and subsequently affect carbapenem sensitivity.[35] For example, reduced CarO expression has been demonstrated to diminish susceptibility to imipenem and meropenem.[36]

Enhanced expression of efflux pumps: Efflux pumps (EPs) can also substantially contribute to carbapenem resistance in *A. baumannii*.[35] In contrast to OMPs, efflux mechanisms actively eliminate various antimicrobial compounds by expelling them from the cell, resulting in multidrug resistance.[35,37] Although five efflux pump families exist, three are frequently identified in this pathogen: the multidrug and toxic compound extrusion (MATE) family, the major facilitator superfamily (MFS), and the resistance-nodulation-cell division (RND) family . AdeABC, AdeFGH, and AdeIJK are RND-type efflux pumps present in *Acinetobacter species* and contribute to decreased carbapenem susceptibility.[38] The RND family generally comprises a transporter protein in the inner membrane, a membrane fusion protein (MFP), and an OMP channel. The adeABC gene product, consisting of AdeA (MFP), AdeB (transporter protein), and AdeC (OMP), demonstrates the strongest correlation with carbapenem resistance. The adeABC expression is normally controlled by a response regulator (AdeR) and a sensor kinase (AdeS). Enhanced expression of the AdeABC efflux pump, especially when combined with carbapenem-hydrolysing oxacillinases (OXAs), leads to high-level carbapenem resistance.[35,38]

Production of carbapenem-hydrolysing β-lactamases (carbapenemases): Enzymatic neutralization or breakdown of carbapenems by carbapenemase enzymes represents the most crucial mechanism of carbapenem resistance in A. baumannii. These carbapenemase genes are frequently positioned on plasmids, enabling their transfer.[39]

According to their catalytic domain and substrate specificity, β-lactamase enzymes are organized into four primary molecular categories (Ambler classification): classes A, B, C & D. Carbapenemases are classified within classes A, B & D, whereas class C enzymes predominantly hydrolyze cephalosporins. Class B enzymes, alternatively termed metallo-β-lactamases (MBLs), necessitate a water molecule and a zinc ion for the hydrolysis of the β-lactam ring. Conversely, β-lactamases from classes A, C, and D are serine-based carbapenemases that employ a serine residue for their catalytic function.[40] Clinically significant carbapenemases identified in *A. baumannii* include *Klebsiella pneumoniae* carbapenemases (KPC) and Guiana extended-spectrum β-lactamase (GES) from class A; imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), Seoul imipenem's (SIM), and New Delhi Metallo-β-lactamase (NDM) from class B.[33]

CHDLs, alternatively designated as OXAs, hydrolyze isoxazolylpenicillins and constitute a common cause of carbapenem resistance in *A. baumannii.* The acquisition of these particular OXA-group β-lactamase genes, frequently carried on plasmids or other mobile genetic elements, results in the rapid distribution of multiple carbapenem resistance genes in this pathogen. These genes can be replicated independently and transferred between bacterial cells and species. Plasmids, consequently, perform a vital role in the rapid propagation of carbapenem resistance.[41]

Six principal groups exist within Class D β-lactamases (CHDLs): the intrinsic OXA-51-like enzymes and the acquired OXA-24/40-like, OXA-58-like, OXA-23-like, OXA-143-like & OXA-235-like β-lactamases.[33,40] CHDL genes are commonly linked with upstream insertion elements, which can result in overexpression of OXA-type carbapenemases and consequent carbapenem resistance.[34] Although diverse mechanisms can affect carbapenem susceptibility in *A. baumannii*, enzymatic mechanisms, especially the presence of MBLs and CHDLs and the acquisition of carbapenemase-encoding genes, represent the most powerful drivers of resistance.[42]

Resistance genetics in A. baumannii: Insertion sequences (ISs), representing the smallest mobile DNA segments, can induce carbapenem resistance through mutations and genomic rearrangements. These sequences frequently contain promoter regions that can result in the overexpression of downstream resistance determinants. ISAba1 represents a particularly crucial IS among the approximately 30 different variants identified in *A. baumannii* owing to its mobility and its capacity to enhance the expression of OXA-type carbapenemases. Although ISAba1 is exclusive to A. baumannii, the occurrence of other IS elements is similarly significant in diminishing susceptibility to other antibiotics in this species. Generally, ISs amplify resistance development and the dissemination of virulence determinants within *A. baumannii.*[43]

Unlike OXA-type carbapenemase genes, MBL genes are typically positioned within integrons. Integrons represent genetic elements capable of obtaining antibiotic resistance genes and facilitating their transcription and expression. Due to their limited mobility, integrons are commonly found integrated into plasmids or transposons, which function as vehicles for resistance distribution. Class 1 integrons constitute the most common type identified in A. baumannii strains worldwide.[33] A major clinical consequence of integrons is that the excessive use of a single antimicrobial agent can stimulate the overexpression of multiple resistance genes under the

regulation of a shared promoter. Typically, *A. baumannii* strains harbouring these integrons demonstrate substantially elevated levels of drug resistance compared to strains without them.

Resistance islands (RIs) constitute another category of mobile genetic elements that contribute to carbapenem resistance in *A. baumannii*. RIs are characterized as specific genomic regions that can accommodate multiple horizontally acquired antimicrobial resistance determinant.[33,44] The initially identified AbaR, AbaR1, was discovered in the multidrug-resistant AYE strain in 2006.[33] It harbours a cluster of 45 resistance genes, including blaOXA69, a member of the blaOXA51-like group, conferring resistance to chloramphenicol, aminocyclitols, tetracycline and aminoglycosides.[44] AbaR25, a variant of AbaR4, has been linked with CRAB isolates in Latvia. Investigations on these isolates revealed the presence of AbaR25 carrying blaOXA-23-like genes in *A. baumannii*[44] overall, research has established that multidrug-resistant *A. baumannii* strains can obtain their antimicrobial resistance characteristics through ISs, integrons, and RIs. This exceptional adaptability renders A. baumannii a challenging nosocomial pathogen and a significant threat to hospitalized patients.

Pathological conditions caused by CRAB and their clinical consequences: The majority of *A. baumannii* infections affect organ systems containing substantial fluid volumes, including the urogenital and pulmonary systems and the peritoneal space, and are frequently linked with implanted medical equipment. Differentiating between infection and colonization by *A. baumannii* can be challenging. Nevertheless, the recovery of A. baumannii from hospitalized patients is typically regarded as an indicator of critical illness with a corresponding mortality rate of roughly 30%.[45]

Healthcare-associated *Acinetobacter* pneumonia: Most *A. baumannii* isolates from hospitalized individuals are obtained from the respiratory system, making it difficult to distinguish upper respiratory colonization from actual pneumonia. The prevalence of this microorganism differs among various healthcare environments but represents the second most frequent causative agent among Gram negative bacteria.[46] Nosocomial pneumonia develops in ICUs with a frequency spanning from 3% to 75% and documented crude mortality rates of 30% to 75% .

Community-onset *Acinetobacter* pneumonia: Acinetobacter can easily colonize tracheostomy sites and trigger community-acquired bronchiolitis and tracheobronchitis in healthy paediatric patients and immunocompromised adults. However, it infrequently causes community-acquired pneumonia and sepsis in these populations. Nonetheless, community-acquired pneumonia caused by *A. baumannii* has been documented in tropical areas of Australia and Asia during wet seasons, especially in individuals with alcohol dependency or chronic obstructive pulmonary disease.[47]

Bacteraemia (bloodstream infection): A. baumannii bacteraemia most frequently stems from intravascular and respiratory tract catheters. Surgical wounds, burns and the urogenital system are lesser common sources and endocarditis represents a rare complication. The origin of septicaemia remains undetermined in approximately 21% to 70% of episodes.[48] A US investigation (1995-2002) revealed that *A. baumannii* was accountable for 1.3% of all nosocomial bloodstream infections (0.6 bloodstream infections per 10,000 admissions). Moreover, *A. baumannii* more commonly caused ICU-acquired bloodstream infections compared to infections acquired in general wards.[49] The overall mortality rate linked with A. baumannii bloodstream infections ranged from ICU (34-43.4%) and ICU outside (16.3%).[49]

Combat injuries and other wound infections: A. baumannii can cause dermal and soft tissue infections beyond the military population, representing 2.1% of ICU-acquired skin and soft tissue infections. Remarkably, *A. baumannii* was the most commonly isolated organism (32.5%) from combat casualties with open tibial fractures in Iraq and Afghanistan.

Urogenital tract infection: *A. baumannii* constitutes a rare causative agent of urogenital tract infections (UTIs), responsible for merely 1.6% of ICU-acquired UTIs in a single study. This microorganism is commonly associated with catheter-associated infections or colonization. It is unusual for *A. baumannii* to cause complex UTIs in ambulatory patients.

Meningitis: Nosocomial post-neurosurgical meningitis caused by multidrug-resistant *A. baumannii* represents an increasingly significant concern. In instances of acute bacterial meningitis among adult patients, *Acinetobacter* has accounted for roughly 10% of Gram-negative bacillary meningitis and 4% of all healthcare-associated meningitis cases. Mortality rates can reach as high as 70%, although the specific etiology is often difficult to establish.[50]

Additional clinical presentations: A limited number of documented cases of *A. baumannii* endocarditis exist with most involving artificial valves. *A. baumannii* can also cause ophthalmitis, peritonitis, keratitis or endocarditis associated with contact lens usage or following ocular surgery.

CONCLUSION

We have analysed the spectrum of infections caused by CRAB and their substantial clinical consequences. These include limited therapeutic options, leading to increased morbidity and mortality, as well as a significant economic burden on healthcare systems. By synthesizing current knowledge regarding CRAB's pathogenesis and its clinical impact, this review underscores the critical need for ongoing research and the development of innovative

therapeutic and preventative strategies to address this growing antimicrobial resistance crisis.

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