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Unraveling Acinetobacter's Journey to Antibiotic Resistance: A Comprehensive Review

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Abstract:
Acinetobacter baumannii has emerged as a major healthcare-associated pathogen due to its high level of antibiotic resistance, posing a worldwide health concern. The bacterium employs various mechanisms to acquire and disseminate resistance, including mobile genetic elements like insertion sequences, transposons, and plasmids. The resistance mechanisms employed by A. baumannii include antibiotic modification, reduced membrane permeability, active efflux pumps, and alterations in antibiotic targets. The production of β-lactamases, particularly Acinetobacter-derived cephalosporinases, contributes to resistance against carbapenems and cephalosporins. The worldwide spread of multidrug-resistant bacteria has increased drastically due to the limited alternatives to therapy available leading to the increased rates of death and morbidity. To address this challenge, researchers are exploring combination therapies and novel antimicrobial adjuvants to enhance drug efficacy.

Keywords*: Acinetobacter baumannii, antibiotic resistance, beta-lactamases, combination therapy*

Introduction:

Acinetobacter baumannii (A .baumannii) has developed as a significant hospital-acquired pathogen, especially in critical care units, causing serious infections with high fatality and morbidity rates[1]. Its capability to acquire multidrug resistance has led the World Health Organization to prioritize it for new antibiotic development [2]. These bacteria are implicated in various infections, including pneumonia, bacteremia, and urinary tract infections. The success of *A. baumannii* as an infective agent is attributed to its ability to develop drug resistance and tolerate harsh environments rapidly [3]. *A. baumannii's* virulence factors include outer membrane proteins, biofilm formation, and lipopolysaccharide, while its resistance mechanisms involve β-lactamases, efflux systems, and altered antibiotic target sites[4]. Quorum sensing acts as a part of biofilm formation, though its impact on other virulence factors remains unclear [5]. The emergence of strains resistant to many antibiotics and carbapenem poses a significant threat

to public health, particularly in hospital settings [6]. Understanding the resistance mechanisms and factors that lead to the virulence of *A. baumannii* is crucial for developing effective treatment strategies[3]. Current approaches include colistin-based combination therapy and stringent infection control measures [3]. However, the increasing spread of resistant strains necessitates the development of novel antibiotics and alternative treatments, such as antimicrobial peptides[3,6] .

Historical Background of Acinetobacter:

The genus *Acinetobacter*, discovered in 1911, comprises Gram-negative, non-fermenting coccobacilli, aerobic opportunistic pathogens producing various nosocomial infections[7]. Initially believed to be a single species, *A. calcoaceticus*, the genus has undergone significant taxonomic changes, with 19 genomospecies identified by 1996[8]. Phylogenetic analysis using 16S rDNA sequencing confirmed *Acinetobacter* as an organism belonging to gamma subclass proteobacteriae., revealing distinct species clusters and potential novel species[9] (Rainey et al., 1994). Historically, *Acinetobacter* species were classified under various genera, including Mima, Herellea, and *Moraxella*. The most clinically relevant biotypes are *A. calcoaceticus* var. *lwoffi*, and *A. calcoaceticus* var. *anitratus* which are associated with infections in immunocompromised patients, often linked to medical devices and equipment[10]. Among the *Acinetobacter* spp., the prevalent species is *A .baumannii* which produces significant nosocomial infection[11]. Initially sensitive to most antibiotics in the early 1970s, *Acinetobacter* rapidly developed resistance to various antimicrobials[12]. By the 2000s, high resistance rates to carbapenems were reported in Europe and the USA[12]. Previous research showed increasing resistance to widely used antibiotics, including ampicillin-sulbactam, cephalosporins, and aztreonam[11,13]. Imipenem remained effective against all strains in earlier studies[13], but recent reports indicate emerging resistance to reserved antibiotics like tigecycline and colistin [12]. The rapid development of antibiotic resistance in *Acinetobacter* species emphasizes the necessity of continuing observation and prudent antibiotic usage to reserve treatment options for these challenging pathogens.

Clinical significance of Acinetobacter species:

Acinetobacter infections have emerged as an important cause of hospital-acquired infections worldwide, especially in intensive care units[14]. These opportunistic bacteria primarily cause blood infections and ventilator-associated pneumonia. *A. baumannii* is the topmost clinically relevant species, often affecting immunocompromised patients. The ability of bacteria to endure on hospital surfaces, develop multidrug resistance, and cause serious infections in critically ill patients contributes to its clinical significance[14]. *Acinetobacter* species exhibit multidrug resistance, with high resistance rates to carbapenems and other antibiotics[15,16]. The fatality rate associated with multidrug-resistant infections produced by *Acinetobacter* is significant, ranging from 7.9% to 43% in some studies[17,18,19]. Colistin and tigecycline remain effective treatment options in many cases[16]. The evolving antibiotic resistance in *Acinetobacter* species poses a significant challenge for infection control and treatment strategies[19]

Mechanisms of antibiotic resistance

Gram-negative, non-fermentative *A. baumannii* bacteria are distinguished by their strong inherent resistance to antibiotics, mainly due to decreased outer membrane permeability coupled with secondary mechanisms like efflux pumps and inducible cephalosporinases[20]. *A. baumannii* is considered a prototype of multiresistant bacteria, capable of acquiring resistance through genetic elements and mutations affecting porin expression and efflux pumps[21,22]. The interplay between reduced permeability and active efflux systems contributes to resistance against unrelated antimicrobial agents[21]. Additionally, these pathogens can acquire resistance genes encoding β-lactamases and aminoglycoside-modifying enzymes[23]. The accumulation of numerous resistance methods, including mutations in topoisomerases and diminished expression of outer membrane proteins, may lead to the expansion of multiple resistant or even pan-resistant strains[23].

Beta lactamases:

Acinetobacter species, particularly *A. baumannii*, has increasing antimicrobial resistance, primarily due to β-lactamases[24]. These enzymes belong to Ambler classes A to D, with PER, IMP, AmpC, and OXA-23 being dominant. The beta-lactamases produced by *Acinetobacter* include Class A Beta-lactamases: These include TEM and SHV enzymes. Class B Metallo-beta-lactamases (MBLs): Examples are IMP (Imipenemase), VIM (Verona integron-encoded metallo-beta-lactamase), and NDM (New Delhi metallo-beta-lactamase. Class C Beta-lactamases: These are also known as cephalosporinases. Class D Beta-lactamases: OXA-type carbapenemases, such as OXA-58, OXA-23, and OXA-24, are particularly prevalent in A. baumannii and are a main contributor for carbapenem resistance The prevalence of strains producing multiple β-lactamases has increased over time,

correlating with higher resistance rates to various antibiotics[24]. Historically, TEM-type penicillinases were most common, with CARB-type and cephalosporinases emerging later[25]. Class D carbapenemases are frequent, while class A and B carbapenemases are also significant[26]. The spread of multidrug-resistant *Acinetobacter* strains harboring many genes for the production of β-lactamase has become a serious issue, often associated with mobile genetic elements like ISAba1 and integrons[27].

Target modification:

Mutations in genes encoding antibiotic targets, such as gyrA and parC, contribute to fluoroquinolone resistance[27]. Additionally, the acquisition of plasmid-associated resistance genes further enhances antibiotic resistance[27]. Resistance to Aminoglycoside in *A .baumannii* is primarily mediated by aminoglycoside-modifying enzymes (AMEs)[28]. These enzymes, including acetyltransferases, nucleotidyltransferases, and phosphotransferases, modify specific sites on the aminoglycoside molecule, rendering it ineffective[29]. The AME genes usually found in *A. baumannii* include aacC1, aacC2, aacA4, and aphA6, with varying prevalence rates[28]. The presence of these genes correlates with resilent resistance rates to aminoglycosides such as amikacin, gentamicin,, and tobramycin[28]. Additionally, aminoglycoside-modifying enzyme genes, such as aacC1, aacC2, and aacA4, contribute to resistance against multiple antibiotics in A. baumannii. The widespread occurrence of AMEs in *A .baumannii* highlights the need for new strategies to combat aminoglycoside resistance, such as developing enzyme inhibitors or new aminoglycosides resistant to modification[29].

Efflux pumps:

Multidrug resistance is greatly influenced by efflux pumps especially belonging to the resistance-nodulation-division (RND) superfamily. Overexpression of AdeABC, AdeIJK, and AdeFGH pumps, regulated by various mechanisms, provides resistance to an extensive range of antibiotics and biocides[30]. Additionally, non-RND efflux systems and acquired narrow-spectrum pumps contribute to resistance. Tet(A) and Tet(B) efflux pumps are specific for tetracyclines. Timely detection and recognition of multidrug-resistant *A .baumannii* strains are critical for controlling their spread in healthcare settings[31]. Efflux pumps and porin channel deletions also contribute to resistance against multiple antibiotic classes.

Decreased permeability:

Acinetobacter species exhibit high inherent resistance to many antibiotics, partly owing to decreased outer membrane permeability. The major porin in *A. baumannii*, OmpAAb, shows reduced permeability compared to other bacterial porins, contributing to antibiotic resistance[32]. In *A. calcoaceticus*, mutants resistant to various β-lactams demonstrated reduced outer membrane permeability and reduced production of a 46.5 kDa porin protein[33]. This decreased permeability, combined with altered penicillin-binding proteins, enhances resistance to β-lactams. In *A. baumannii,* reduced membrane permeability and constitutive expression of efflux pumpsinteract ot produce both intrinsic and acquired multidrug resistance[21]. The existence of multidrug efflux pumps such as AdeABC and AdeIJK, β-lactamases, and low permeability of OmpAAb are important factors contributing to the high levels of intrinsic antibiotic resistance seen in A. baumannii[32].

Biofilm formation:

Research have repeatedly shown a close relationship between biofilm production and antibiotic resistance in *Acinetobacter* isolates[34,35,36,37]. Biofilm-producing strains showed higher resistance to various antibiotics, including ampicillin-sulbactam, amikacin, ciprofloxacin, and ceftazidime[37]. Imipenem resistance is substantially linked to biofilm production [35]. The prevalence of biofilm-producing *Acinetobacter* isolates ranged from 60% to 68% across studies, with a high proportion of these isolates exhibiting MDR[36,37]. Colistin demonstrated the highest sensitivity among tested antibiotics [36]. The use of EDTA showed promise in reducing biofilm formation by 55-75% [35]. These findings highlight the therapeutic challenges posed by biofilm-producing, multidrug-resistant *Acinetobacter* species in clinical settings.

Genetic mechanisms:

Horizontal gene transfer (HGT) is a significant mechanism in the transfer of antibiotic resistance genes (ARGs) among bacteria, particularly in *Acinetobacter* species. Bacterial predation by *A. baylyi* significantly enhances cross-species HGT[38]. *A. baumannii* employs various HGT mechanisms, including transduction, natural transformation and outer membrane vesicle-mediated transfer, to acquire carbapenemase genes[39]. Experimental studies with *A. baylyi* demonstrate that ARGs can spread through HGT without antibiotic selection, but their long-term persistence

depends on fitness costs and genetic mobility[40]. Microfluidic techniques have revealed that both HGT and vertical gene transfer (VGT) contribute to ARG transmission in bacterial communities. The presence of antibiotics can influence HGT and VGT rates differently, depending on their inhibitory mechanisms and targets[41]**.** Understanding these complex dynamics is necessary for anticipating and combating the spread of resistance to antibiotics in microbial populations.

Role of plasmids and integrons:

Integrons and plasmids have crucial roles in dissemination of resistance to antibiotics among *Acinetobacter* species. Integrons are significantly correlated with multidrug resistance and epidemic behavior in *A. baumannii* [42]. Conjugative mega-plasmids facilitate the spread of resistance genes between *Acinetobacter* species and can mobilize smaller plasmids[43]. These mega-plasmids accumulate resistance genes to antibiotics through the incorporation of integrons and transposons in clinical strains[43]. Mobile genetic elements such as conjugative plasmids, integrons, transposons, and insertion sequences are key factors in acquiring and disseminating antibiotic resistance in *Acinetobacter* [44]. The prevalent integrons in *A. baumannii* is class 1, often carrys various antibiotic resistance gene cassettes[45]. Hybrid integrons and the diversity of gene cassettes presence highlight the complex method of resistance acquisition in species of *Acinetobacter*[45].

Evolution of Multidrug Resistance (MDR) in *Acinteobacter*:

The development of drug resistance in *Acinetobacter* species had been a growing concern from the year 1970s. Initially sensitive to most antibiotics, resistance to β-lactams and aminoglycosides emerged rapidly[46]. By the late 1990s, resistance rates to various antibiotics, including ciprofloxacin and imipenem, had increased significantly[47]. This trend continued into the 2000s, with studies in Iran showing increased rate of resistance to carbapenems, lipopeptides, and aminoglycosides[48]. The timeline of resistance development shows a progression from cephalosporin resistance in 1975 to widespread carbapenem resistance by 2000, particularly in Europe and the USA[12]. Colistin and tigecycline remained effective options, but emerging resistance to these last-resort antibiotics are reported[12].

Current prevalence and resistance patterns:

Global trends of resistance:

Global trends show a concerning increase in antibiotic resistance among *Acinetobacter* species, particularly *A. baumannii*. Accoring to Studies, in both non-OECD and -OECD countries reveal high resistance rates to routinely used antibiotics, with OECD nations experiencing a faster increase in recent years[49]. In Ethiopia, a five-year analysis demonstrated rising multidrug resistance and carbapenem non-susceptibility in *Acinetobacter* species[50]. Similarly, a study in India reported high resistance levels to various antibiotics, including ciprofloxacin, cefepime, and amikacin[51]. Multidrug-resistant *A. baumannii's* global proliferation is linked to transfer of a few clones between hospitals and regions, amplified by increased antibiotic use[52]. These trends pose a significant threat to infection control, with some infections becoming untreatable using existing antimicrobial agents, necessitating urgent action from healthcare systems and pharmaceutical companies[52].

Trends in India:

Acinetobacter species are the leading cause of hospital-acquired infections, particularly in India. Studies from various regions of India report isolation rates of 2.9-4.8% from clinical samples, with *A. baumannii* being the predominant species[53]. These bacteria exhibit high levels of antibiotic resistance, with multidrug-resistant strains accounting for 54.7% of isolates in one study[54]. Resistance rates to commonly used antibiotics vary across regions, with cephalosporins and fluoroquinolones showing particularly high resistance[15]. Carbapenems remain relatively effective, though resistance rates of 19-41.67% have been reported[15],[54]. Risk factors for *Acinetobacter* infections include advanced age, prolonged hospital stay, invasive procedures, and ICU admission [53,54].

Recent studies in India have reported high rates of resistance to antimicrobial among *Acinetobacter* species, particularly within hospital settings. In Gujarat, resistance rates to commonly used antibiotics ranged from 41.67% to 79.71% [15]. A 5-year surveillance at a trauma center revealed increasing resistance trends, with over 90% resistance to multiple antibiotics[51]. Metallo-β-lactamase production and Extended-spectrum β-lactamase and was identified in 14.4% and 31.5% of isolates, respectively[55] . Risk factors for *Acinetobacter* infections included elderly age, prolonged hospital stay, comorbidities, and invasive procedures[54]. Multidrug resistance was observed

in 54.7% of isolates, with 5.8% being pan-drug resistant[54] . Carbapenems and piperacillin/tazobactam showed lower resistance rates compared to other antibiotics, while colistin remained effective against pan-drug resistant strains[51,54] .

Resistance Profiles:

Acinetobacter baumannii exhibits varying resistance profiles across healthcare settings. *A. baumannii* isolates showed highest antimicrobial resistance, with susceptibility rates below 20% in Critical care units[56]. The environmental contamination is widespread (16.48%), in nursing facilities with concerning rates of resistance even in medical and rehabilitation settings[57]. *A. baumannii* is more frequently isolated from ICUs (52.92%) and respiratory departments (12.33%), primarily from sputum specimens (94.62%)[56]. In tertiary care hospitals, *A. baumannii* displays high resistance to multiple antibiotics, including imipenem (5.2%), meropenem (9.75%), and ceftazidime (74.1%)[58] . Resistance mechanisms may include antibiotic-modifying enzymes, extended-spectrum β-lactamases production, and target site modification[59]. The frequency and resistance patterns among the *A. baumannii* underscore its significance as a challenging nosocomial pathogen across various healthcare settings.

A .baumannii has developed as a major pathogen, developing resistance to last-resort antibiotics like colistin, carbapenems, and tigecycline[60]. Colistin resistance reported globally with the highest rates in Asia, is primarily due to lipopolysaccharide modifications or the PmrAB two-component system[61]. The resistance that evolved during a treatment of colistin and tigecycline during treatment often leads to persistent or recurrent infections[62]. Monotherapy of colistin is insufficient to avoid resistance, necessitating combination therapies as a potential solution[61]. Colistin/rifampicin and colistin/carbapenem combinations have shown promising results in vitro, in vivo, and clinically[61]. Early identification and recognition of multidrug-resistant *A. baumannii* are Critical for controlling its spread[63].

Molecular Characterisation of Resistant Strains:

Identification of key resistant genes

A .baumannii, a major source of hospital-acquired infections, rapidly develops antibiotic resistance. Multiple studies have identified key resistance genes in A. baumannii isolates. All the *A. baumannii* isolates that were examined were found to have blaOXA-51-like and ampC genes linked to β-lactam resistance[64,65]. Common resistance genes include blaTEM, strB, and tet(B)[65]. Whole genome sequencing revealed blaADC-25 as the most prevalent resistance gene across all sequence types, conferring β-lactam resistance[66]. Multiple clonal types have been identified, with some strains possessing up to 12 resistance determinants [65,67]. Notably, blaOXA-58-like and blaPER-like genes were initially identified in MDR *A. baumannii* isolates of USA[67]. Continuous monitoring of resistance profiles is crucial for effective infection control and treatment.

Molecular techniques play an important role in identifying and characterizing antibiotic resistance in *Acinetobacter* species, particularly *A. baumannii*. Whole genome sequencing and PCR-based methods, including PCR-RFLP and RT-qPCR, are commonly used for species identification and resistance gene detection [68,69]. Analysis of the 16S rRNA Sequences and rpoB genes has proven effective for accurate species-level identification[68]. Mass spectrometry, specifically targeted label-free proteomics using selected reaction monitoring, enables rapid quantitative detection of resistance-associated proteins, including β-lactamases and efflux pump components[69]. These molecular approaches have revealed that *A. baumannii* acquires resistance by various mechanisms, via horizontal gene transfer and mutations leading to gene disruption or altered expression[63]. Addressing these mechanisms is critical for devising effective treatments to tackle multidrug-resistant A. baumannii, a major problem in hospital settings[70].

Molecular studies on *Acinetobacter* species have revealed important trends in antimicrobial resistance and epidemiology. *A. baumannii* resistant to carbapenem strains have been identified in many nations, with OXA-58 and OXA-23 carbapenemases playing significant roles[71,72]. Molecular typing methods, such as pulsed-field gel electrophoresis, have shown shifts in clonal distribution over time[71]. *Acinetobacter* genomic species 3 has emerged as a predominant species in some settings. The spread of resistance genes is facilitated by insertion sequences like ISAba1 and inter-species plasmid transfer[72]. International clones I, II, and III have been determined as major causes of outbreaks[70]. Various molecular typing methods are now available for epidemiological studies, each with its advantages and limitations[73]. These findings underscore the importance of management of antimicrobial and infection control methods.

Environmental and healthcare-related factors contributing to resistance:

Hospital surroundings contribute significantly to fostering resistance to antibiotics of *A .baumannii*. Studies have detected MDR *A. baumannii* in various hospital environments, including water, surfaces, and air with intensive care units (ICUs) being particularly vulnerable[74,75]. Environmental contamination is a significant reservoir for outbreaks, necessitating thorough cleaning and disinfection to control spread[75,76]. Curtains and other dry fabrics have been identified as important dissemination sources[76]. *A. baumannii* from a hospital context often exhibit resistance to multiple drugs and possess various virulence factors, posing a serious public health threat[77]. Effective control measures include implementing rigorous infection control protocols, restricting carbapenem use, and regularly changing curtains[76]. Early detection and prompt intervention are crucial to preventing the dissemination of resistant *A. baumannii* in hospital settings[74].

Influence of environmental reservoirs:

Acinetobacter species, particularly *A. baumannii*, are important pathogens with environmental reservoirs that contribute to outbreaks and community-acquired infections. Environmental surveillance in hospital settings can predict and help control MRAB infections[78]. The genus *Acinetobacter* has undergone ecological differentiation, with some lineages evolving towards host association[79]. Extra-hospital reservoirs such as pets, slaughtered animals, human lice, and human carriage potentially contribute to community-acquired infections [80]. *Acinetobacter* species may be found in several natural settings, including surface water, wastewater, sewage, human skin, plants, animals, and food [81]. While some species play beneficial roles in soil improvement and detoxification, others, like *A. baumannii*, are significant pathogens. Understanding these environmental reservoirs is crucial for controlling *Acinetobacter* infections and predicting their emergence in both community and hospital environments.

Clinical management and treatment challenges:

Infections caused by Carbapenem-resistant *Acinetobacter baumannii* (CRAB) pose major therapeutic problems due to limited options and high mortality rates[82]. Current treatments include a combination of high-dose ampicillin-sulbactam and tigecycline or polymyxins[83]. Colistin with sulbactam has shown superior therapeutical efficacy compared to colistin monotherapy or colistin with tigecycline for extensively drug-resistant (XDR) and MDR *A. baumannii* infections[84]. Tigecycline has demonstrated considerable antimicrobial activity against MDR *Acinetobacter*, but clinical data supporting its use, especially for ventilator-associated pneumonia or bacteremia, remain limited[85]. However, polymyxins have dosing difficulties and significant side effects[83]. Newer options like eravacycline and cefiderocol show potential but lack sufficient data for use as sole agents[83,86]. Combination therapy proves to have been the most effective approach, with the involvement of infectious disease specialists recommended for optimal management[83] Novel therapeutics:

Bacteriophage therapy is now recognized as an effective approach to combat multidrug-resistant *A. baumannii*, a critical priority pathogen[87]. Various strategies have been explored including phage cocktails, single phage therapy, and combination therapy with antibiotics[88]. Enzymes like endolysins and depolymerases derived from phages have also shown potential in targeting A. baumannii[87]. In-vivo investigation of phage treatment has shown improvement in survival rates and bacterial clearance in mouse models[89]. The phage YMC13/01/C62 ABA BP (Bϕ-C62) has exhibited strong lytic activity against carbapenem-resistant strains in vitro and in vivo[89]. While bacteriophages offer a promising alternative to traditional antibiotics, further research is needed to address challenges in their clinical application, particularly for in vivo[90]. Future treatment options may include bacteriophages and antimicrobial peptides[88]. Overall, the development of novel medications is crucial to addressing the urgent need for effective CRAB treatments[86].

Conclusion:

Acinetobacter species, especially *A. baumannii*, have emerged as major nosocomial infectious agents, causing infections in intensive care units. These bacteria are difficult because of the intrinsic and acquired antimicrobial resistance, with some strains resistant to all currently available antibiotics except colistin. The virulence of *Acinetobacter* stems from its ability to evade host immunity and trigger sepsis through lipopolysaccharide-mediated mechanisms. Treatment options are limited, with imipenem, amikacin, ampicillin/sulbactam, colistin, and tigecycline showing some efficacy. However, the optimal therapy remains unclear, and combination treatments may be necessary. The ideal treatment for infections caused by MDR A. baumannii is not yet determined, highlighting the necessity of well-designed clinical studies to guide therapeutic decisions Additionally, knowledge of local susceptibility patterns is crucial for selecting appropriate empirical or targeted therapy. Given the high mortality rates linked with infections caused by multidrug-resistant *Acinetobacter*, prevention through aggressive

control measures is crucial. New therapeutic options are urgently needed to address this global threat.

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