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Acinetobacter: A War Zone in the Hospital

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Review Article

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ABSTRACT

Acinetobacter baumannii has emerged as a significant hospital pathogen because of the increasing number of infections and the global spread of strains with resistance to multiple antibiotic classes. An important contribution to the epidemiology of infections with *A. baumannii* has been the return of military personnel who have fought in Iraq or Afghanistan. In spite of its clinical relevance, until recently, there has been limited scientific data regarding the microbiological and pharmacological aspects of this organism. The availability of complete genome sequences, molecular tools for manipulating the bacterial genome, and animal models of infection facilitated the identification of factors that play a role in *A. baumannii* persistence and infection. This review summarizes the currently available data on the microbiology of *A. baumanni* and its clinical and pharmacotherapeutic implications on healthcare.

Keywords: Acinetobacter baumannii; pathogen transmission; drug resistance; nosocomial; microbiology; molecular diagnostics.

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1. INTRODUCTION

A. baumannii has emerged as one of the most troublesome pathogens for health care institutions globally. Its clinical significance, especially over the last 15 years, has been propelled by its remarkable ability to upregulate or acquire resistance determinants, making it one of the most sinister organisms threatening the current antibiotic era [1,2]. It has also attained notoriety by causing crippling infections in soldiers at war in Iraq, earning it the epithet "Iraqibacter" [3].

The genus was first described in 1911 and *A. baumannii* is just one of the many Acinetobacter species that can cause disease in humans, but it accounts for approximately 80% of all reported Acinetobacter infections [1,2]. Acting in synergy with its resistance profile is the uncanny ability of *A. baumannii* to survive for prolonged periods throughout a hospital environment, thus potentiating its ability for nosocomial spread [1,2,3].

Significant advances have been made in our understanding of this organism. In the present review, we describe these advances and also attempt to provide an appraisal of the relevant microbiological characteristics and clinical implications of *A. baumannii*.

2. EPIDEMIOLOGY

Since the early 1980s, hospital outbreaks of *A. baumannii* infections in Europe, mainly in England, France, Germany, Italy, Spain, and The Netherlands have been investigated using molecular epidemiological typing methods. Transmission of such strains has been observed between hospitals, most probably via transfer of colonized patients [2,4,5]. International transfer of colonized patients has led to the introduction and subsequent epidemic spread of multidrug-resistant *A. baumannii* strains from Southern into Northern European countries, such as Belgium and Germany [6,7]. Intercontinental spread of multidrug-resistant *A. baumannii* has also been described between Europe and other countries as a consequence of airline travel [6,7].

National surveillance studies in North America have demonstrated significant trends in the emergence of multidrug-resistant *Acinetobacter* strains [2,5]. Nosocomial *Acinetobacter* infections have some seasonal variation in the United States, with an unexplained upswing in late summer months [2,8]. Rates of nonsusceptibility to meropenem, imipenem, ceftazidime, piperacillin-tazobactam, ciprofloxacin, and gentamicin in Latin America are among the highest in the world [8,9].

Numerous outbreaks of pandrug-resistant *A. baumannii* have been documented in Asian and Middle Eastern hospitals and a variety of carbapenemases have been described to originate there [2,3,9-11]. Outbreaks of carbapenem-resistant *A. baumannii* have also occurred in French Polynesia [11]. Most recently, reduced susceptibility to tigecycline of multidrug-resistant *A. baumannii* strains has been described in Australia [2,12].

2.1 *A. baumannii* and War

An important contribution to the epidemiology of infections with *A. baumannii* has been the return of military personnel who have fought in Iraq or Afghanistan [2,3,13]. An increase in infections with *A. baumannii* was first observed in U.S. military personnel in March 2003, soon after combat operations commenced in Iraq. Most injured military personnel were first treated at field hospitals before being evacuated [1,2,13,14]. In a careful outbreak investigation, it was determined that neither preinjury skin colonization nor introduction of the organism from soil at the time of traumatic injury was the source of infection. Rather, multiple *A. baumannii* isolates were cultured from a range of inanimate surfaces in field hospitals and were genotypically linked to patient isolates [1,2,13,14]. The reservoir for these infections is not well known and may be different for each treatment facility, but the evidence strongly suggests the high numbers of wounded soldiers and the transfer of these soldiers from one treatment facility to another aids the transmission and the growing resistance of *A. baumannii* [1,2,13,14].

3. HISTORY

In 1911, Martinus Willem Beijerinck, a Dutch microbiologist, described an organism named *Micrococcus calcoaceticus* that was isolated from soil by enrichment [2]. The current genus designation, *Acinetobacter,* was proposed by Brisou and Prevot in 1954 to separate the nonmotile from the motile microorganisms within the genus *Achromobacter* [15]. In 1986, Bouvet and Grimont, delineated 12 DNA groups of *Acinetobacter* using DNA-DNA hybridization and proposed 4 new species 3. The genus

Acinetobacter, comprises *A. calcoaceticus*, *A. baumannii*, *Acinetobacter* genomic species 3, and *Acinetobacter* genomic species 13TU, these are very closely related and difficult to distinguish from each other by phenotypic properties. It has therefore been proposed to refer to these species as the *A. calcoaceticus* - *A. baumannii* complex [16]. This group of organisms comprises the vast majority of both community-acquired and nosocomial infections.

4. MICROBIOLOGY

A. baumannii is a gram-negative, strictly aerobic, nonfermenting, nonfastidious, nonmotile, catalase-positive, oxidase-negative coccobacillus with numerous virulence factors [2]. These virulence factors aid in the attachment and persistence on solid and dry surfaces, the ability to obtain essential nutrients, the innate ability to adhere and destroy epithelial cells, along with the ability to produce gelatinases and proteinases which damage host tissues [17]. With *Acinetobacter* being recovered from virtually all samples obtained from soil and surface water, these hardy organisms are considered ubiquitous [2,4]. They are also an integral member of the human skin flora, with upto 43% of nonhospitalized individuals being colonized [18].

A. baumannii has the ability to form biofilms, which play an important role in colonization. A biofilm is an aggregate of microorganisms in which cells adhere to each other and to a surface with a self-produced matrix of extracellular DNA, proteins, and polysaccharides [4,18,19]. Biofilms help the bacteria resist disinfection while allowing the cells to exchange resistance genes, facilitating the persistence of the pathogen [4,19].

Acinetobacter species grow well at 37℃ incubation temperature on media routinely used in clinical microbiology laboratories, such as sheep blood agar or tryptic soy agar. These organisms form smooth, mucoid, grayish white colonies resembling those of *Enterobacteriaceae*, with a colony diameter of 1.5 to 3 mm following overnight culture [2,4]. Unfortunately, there is no single metabolic test which can distinguish Acinetobacters from other similar nonfermenting gram-negative bacteria. A reliable method for identification of acinetobacters at the genus level is the transformation assay as described by Elliot Juni, based on a unique property of mutant *Acinetobacter* strain BD413 *trpE27*, a naturally transformable tryptophan auxotroph recently identified as *A. baylyi*, to be transformed by crude DNA of any *Acinetobacter* species to a wild-type phenotype [20].

Various molecular methods have been developed and validated for identification of Acinetobacters. These include amplified 16S rRNA gene restriction analysis (ARDRA), high-resolution fingerprint analysis by amplified fragment length polymorphism (AFLP), ribotyping, tRNA spacer fingerprinting, and sequencing of the *rpoB* (RNA polymerase-subunit) gene and its flanking spacers among others. ARDRA and AFLP analysis are currently the most widely validated and accepted reference techniques for species identification of Acinetobacters [2,21,22].

5. VIRULENCE FACTORS

Virulence mechanisms in *A. baumannii* include siderophore-mediated iron acquisition systems, biofilm formation, adherence and OMP function, and the *A. baumannii* LPS [2,19,23,24]. In order for *A. baumannii* to thrive in the iron-deficient environment of a human host, it secretes lowmolecular- mass ferric binding compounds, or siderophores [23]. The ability of *A. baumannii* to adhere to and form biofilms on inanimate objects and surfaces may explain its success in the hospital environment. Adherence of *A. baumannii* to human bronchial epithelial cells and erythrocytes has also been demonstrated, with similar pilus like structures appearing important for adherence [19,23,24]. After adherence to human cells, it appears that *A. baumannii* can induce apoptosis via an OMP (Omp38) [2,25]. This protein appears to localize to the mitochondria, leading to both caspase-dependent and -independent pathways of apoptosis. *A. baumannii* LPS has been identified as the major immunostimulatory factor which has also demonstrated potent endotoxic potential, stimulating the proinflammatory cytokines interleukin-8 and tumor necrosis factor alpha [26]. Humoral immune responses have also been described for *Acinetobacter* infection, with antibodies being targeted toward iron-repressable OMPs and the O polysaccharide component of LPS [2].

6. MECHANISMS OF ANTIBIOTIC RESISTANCE

The ability of *A. baumannii* to acquire antibiotic resistance mechanisms has allowed this organism to persist in hospital environments and

has facilitated the global emergence of MDR strains. β-lactam resistance in *A. baumannii* is due to its ability of enzymatic degradation by β -lactamases. *A. baumannii* strains possess chromosomally encoded Amp C cephalosporinases, also known as *Acinetobacter*-derived cephalosporinases (ADCs) [4,27,28]. The key determinant regulating overexpression of this enzyme in *A. baumannii* is the presence of an upstream IS element known as IS*Aba1* [29]. They encode a transposase and therefore are mobile. Second, they can contain promoter regions that lead to overexpression of downstream resistance determinants. Unlike the OXA-type enzymes, MBLs are most commonly found within integrons, which are specialized genetic structures that facilitate the acquisition and expression of resistance determinants. Other ESBLs identified in *A. baumannii* include TEM-92, TEM-116, SHV-12, CTX-M-2, CTX-M-43, TEM-1 and TEM-2 [30,31]. Of the β-lactamases, those with carbapenemase activity are most concerning and include the serine oxacillinases (Ambler class D OXA type) and the metallo-β-lactamases (MBLs).

Resistance has also been ascribed to nonenzymatic mechanisms, including changes in outer membrane proteins (OMPs), multidrug efflux pumps, and alterations in the affinity or expression of penicillin-binding proteins [2,4,24,31-33]. The presence of genes coding for aminoglycoside- modifying enzymes has been noted in multidrug-resistant *A. baumannii* strains [4,34,35]. This emerging resistance mechanism impairs aminoglycoside binding to its target site and confers high-level resistance to all clinically useful aminoglycosides. Modifications to DNA gyrase or topoisomerase IV through mutations in the *gyrA* and *parC* genes have been described for *A. baumannii* [36]. These mutations interfere with target site binding. Similar to aminoglycosides, many quinolones are also substrates for multidrug efflux pumps [2,36].

7. DEFINITIONS AND TRANSMISSION MULTI-DRUG RESISTANCE

Multidrug resistance is resistance to more than two of the following five drug classes: antipseudomonal cephalosporins (ceftazidime or cefepime), antipseudomonal carbapenems (imipenem or meropenem), ampicillin-sulbactam, fluoroquinolones (ciprofloxacin or levofloxacin), and aminoglycosides (gentamicin, tobramycin, or amikacin) [2,37]. Pan-drug resistance is often defined as resistance to all antimicrobials that undergo first-line susceptibility testing that have therapeutic potential against *A. baumannii*. *A. baumannii* has the ability to live on dry environmental surfaces in an ICU for up to 13 days—10 days more than other gram-negative bacteria. Studies have shown similar abilities by *A. baumannii* in humid conditions and on bed rails [4,37]. It is this ability to survive for long periods coupled with its ability to demonstrate a number of antimicrobial resistance genes that have made *A. baumannii* a successful hospital pathogen [37].

8. CLINICAL PICTURE

8.1 Hospital-Acquired Pneumonia

In most institutions, the majority of *A. baumannii* isolates are from the respiratory tracts of hospitalized patients. Between 5 and 10% of cases of ICU-acquired pneumonia are due to *A. baumannii* [8,38]. Typically, patients with *A. baumannii* infections have had prolonged ICU stays, although in outbreak situations, earlier acquisition of infection may occur [8,38].

8.2 Community-Acquired Pneumonia

Community-acquired pneumonia due to *A. baumannii* has been described for tropical regions of Australia and Asia [39]. The disease most typically occurs during the rainy season among people with a history of alcohol abuse [8]. It is characterized by a fulminant clinical course, secondary bloodstream infection, and mortality rate of 40 to 60% [40].

8.3 Bloodstream Infection

A. baumannii is a more common cause of ICU-acquired bloodstream infection than of non-ICU-ward infection (1.6% versus 0.9% of bloodstream infections). *A. baumannii* bloodstream infection had the third highest crude mortality rate in the ICU, exceeded only by *P. aeruginosa* and *Candida* sp. Infections [1,37].

8.4 Battlefield Trauma

A. baumannii may occasionally cause skin/soft tissue infections outside of the military population. It is a well-known pathogen in burn units and may be difficult to eradicate from such patients [1,2]. *A. baumannii* is commonly isolated from wounds of combat casualties from Iraq and Afghanistan [41-43]. It is the most commonly

isolated organism (32.5% of cases) in combat victims with open tibial fractures [41].

8.5 UTI

A. baumannii is an occasional cause of UTI, being responsible for just 1.6% of ICU-acquired UTIs. Typically, the organism is associated with catheter-associated infection or colonization [2,41].

8.6 Meningitis

Nosocomial, postneurosurgical *A. baumannii* meningitis is an important entity. Typical patients have undergone neurosurgery and have an external ventricular drain [44]. Mortality may be as high as 70%, although the cause of mortality may often difficult to discern [44].

8.7 Other Manifestations

A small number of case reports of *Acinetobacter* endocarditis exist [45-47]. Most cases have involved prosthetic valves. *Acinetobacter* may cause endophthalmitis or keratitis, sometimes related to contact lens use or following eye surgery [45-48].

9. INFECTION CONTROL PERSPECTIVE

Three factors lead to the persistence of *A. baumannii* in the hospital environment, namely resistance to major antimicrobial drugs, resistance to desiccation, and resistance to disinfectants. The overall mean survival time is 27 days, with a range of 21 to 33 days [1,2,4]. Prolonged survival of *A. baumannii* in a clinical setting, i.e., on patients' bed rails, has been found to be associated with an ongoing outbreak in an ICU and illustrates that dry vectors can be secondary reservoirs where *A. baumannii* can survive [2,8,37]. Recommendations for all health care facilities include improvement of hand hygiene, use of contact precautions until the patient tests culture-negative for the target organism, active surveillance cultures, education of hospital personnel, improved environmental cleaning, and better communication about patients with these infections to not just personnel within the facility but also between facilities. Lower rates of infection have been reported when the rooms and equipment were cleaned completely and more frequently [1,2,4,5,37]. Bleach solutions and other disinfectants should be used in rooms and on equipment often and thoroughly to effectively control transmission of *A. baumannii*. To control the spread of *A. baumannii* in the hospital, potential reservoirs of the organism and the modes of transmission need to be identified [1,2,4,5,37].

9.1 Hospital Outbreaks and Control Measures

Infection control interventions during an *A. baumannii* outbreak include, molecular epidemiologic investigations to determine if a clonal outbreak strain is present. Environmental cultures should be used to determine if a common environmental source is present. Enhanced environmental cleaning should be performed in order to eliminate the organism from the peripatient environment. Enhanced isolation procedures, aimed at optimizing contact isolation and improving hand hygiene, should be implemented. Antibiotic management processes should be used to ensure that "at-risk" antibiotics are not being used excessively. Three classes of antibiotics which have been implicated in the emergence of multi-drug resistance are broad-spectrum cephalosporins, carbapenems, and fluoroquinolones [1,2,4,5,37]. Monitoring adherence to such infection control interventions is also important [1,2,4,5,37].

10. LABORATORY DIAGNOSTIC TECHNIQUES

Acinetobacters have the ability to use various sources of nutrition and grow at 44℃; this enables them to be cultured on routine laboratory media [15]. While these standard laboratory techniques may identify the genus, species identification is not possible [3]. Hence, phenotypic typing systems based on biochemical profiles (biotyping), antibiotic susceptibility patterns, serological reactions (serotyping), phage typing, and protein profiles have now been replaced by a multitude of molecular typing systems, including, plasmid profiling; ribotyping; PFGE; randomly amplified polymorphic DNA analysis; repetitive extragenic palindromic sequence-based (REP) PCR; AFLP analysis, a high-resolution genomic fingerprinting method; integrase gene PCR; infrequent-restriction-site PCR; and more recently, MLST and multilocus PCR–ESI-MS [2,4,49-53]. Among these Pulsed-field gel electrophoresis (PFGE) and 16s rDNA (ribosomal DNA) sequencing are two commonly used molecular methods. PFGE is a type of gel electrophoresis used to separate large molecules of DNA up to 2000 kb. A second molecular

method employed is the rDNA sequencing [54]. In this method, selective primers for 16s rDNA are used to isolate and amplify the DNA from bacterial colonies. This rDNA is then sequenced and results compared with the *Acinetobacter* genotypes on public-domain sequence databases [54]. Apart from being invaluable in identifying causes of bacterial infection, these molecular methods immensely aid a healthcare facility in infection control measures by highlighting areas of weakness and identifying sources of infection [54]. Plasmid analysis is another technique commonly used for epidemiological typing of *A. baumannii* strains, it is also one of the methods used in the study of epidemiology of *Acinetobacter* species outside the *A. baumannii* group [4,55].

11. THERAPEUTIC STRATEGIES

A. baumannii is one of the "red alert" pathogens that greatly threaten the utility of our current antibacterial armamentarium [56]. Given the current therapeutic environment, optimizing the use of existing antimicrobials is critical. To achieve this goal, a thorough understanding of the pharmacokinetic and pharmacodynamic parameters that predict maximal drug efficacy yet minimize the evolution of drug resistance, as well as an evidence-based approach to therapeutic strategies for highly drug-resistant strains is required.

11.1 Existing Antimicrobial Agents

Therapy should be based on the results of adequately performed antimicrobial susceptibility testing. Carbapenems have been thought of as the agent of choice for serious *A. baumannii* infections. However, the clinical utility of this class of antimicrobial is increasingly being jeopardized by the emergence of both enzymatic and membrane-based mechanisms of resistance [1,2,4,57].

11.2 Sulbactam

Unlike clavulanic acid and tazobactam, it has clinically relevant intrinsic antimicrobial activity against *Acinetobacter* and *Bacteroides* spp., mediated by its binding to penicillin-binding protein 2 [58,59]. Despite the absence of randomized clinical trials, sulbactam has shown promising results against *A. baumannii* strains with various susceptibility profiles. The use of a sulbactam-containing regimen for milder infections may be an appropriate strategy in limiting excessive carbapenem use [56,58].

11.3 Polymyxins

They target the anionic LPS molecules in the outer cell membranes of gram-negative bacteria, leading to interactions between the inner and outer cell membranes, with associated lipid exchange, membrane disturbance, osmotic instability, and eventual cell death [60].

Overall, the efficacy of the drug has been highly encouraging in both adult and pediatric populations, with favorable or curative responses ranging from 57% to 80% [1,4,56,60-62]. Nebulized colistin is increasingly being used in an attempt to minimize systemic toxicity and improve drug deposition at the site of infection [1,4,56,60-62]. Rates of clinical cure appeared superior with supplemental nebulized colistin. Nosocomial meningitis is an increasingly important entity, with multidrug-resistant gram-negative pathogens being implicated as an etiology with greater frequency. To optimize therapy of these infections, intrathecal or intraventricular colistin has been utilized. Of concern, rates of resistance to the polymyxins have recently been reported to be as high as 3.2% for multi drug resistant *A. baumannii* [60-62].

11.4 Tigecycline

It is a semisynthetic derivative of minocycline, which inhibits the 30S ribosomal subunit, but its unique feature is its ability to evade the major determinants of tetracycline resistance, i.e., the efflux pumps and the determinants that provide ribosomal protection [2,56,63]. No difference was observed for all tigecycline combinations, including combinations with amikacin, meropenem, imipenem ciprofloxacin, levofloxacin, ampicillin-sulbactam, rifampin, carbapenem, and the next generation of cephalosporins with activity against MRSA, ceftobiprole and ceftaroline [2,56,63].

11.5 Combination Therapy

Combination therapy is an interesting concept where a combination of two or more agents known to be nonsusceptible is amalgamated to create an active and effective antimicrobial combination. This strategy aids in preventing the emergence of resistance and facilitate improved therapeutic efficacy [2,64]. The combination therapy showing best potential is with either sulbactam or polymyxins. Other combinations being evaluated with *in vitro* techniques and

animal models, include various combinations of quinolones, β-lactams, and/or amikacin [2,56,64-67]. Quinolone combination therapies have shown varied outcomes, with reduced efficacy being described when ciprofloxacin was used for ciprofloxacin-resistant *A. baumannii.* A lack of enhanced activity was also observed when levofloxacin was combined with imipenem or amikacin [2,56,67].

12. FUTURE THERAPEUTIC CONSIDERATIONS

Newer therapeutic options can be divided into those that inhibit a currently recognized mechanism of resistance or those that have a novel mechanism of action. Cationic antimicrobial peptides that are capable of inhibiting both aminoglycoside phosphor-transferases and acetyltransferases have been described [68]. The importance of multidrug efflux pumps in *A. baumannii* is recognized, with tigecycline identified as a substrate of the RND-type pump AdeABC [56,69]. Eukaryotic antimicrobial peptides are cationic peptides which act primarily by disturbing the cell membranes and share a similar structure and charge profile with the polymyxins, but the final steps in pathogen lethality have been shown to be different [70].

Bacterial conjugation is a novel antimicrobial strategy resulting in antibacterial gene transfer [71]. This approach uses attenuated *E. coli* as a vector for a conjugative plasmid carrying bactericidal genes that disrupt protein synthesis. Topical agents that may be effective for environmental cleaning of *A. baumannii*, including highly charged copper-based biocides [72]. Such agents have broad-spectrum activity, including activity against *Clostridium difficile* spores.

Other innovative therapeutic avenues against *A. baumannii* include the use of bacteriophage treatment, improvement in host response via passive or active immunization, and modification of bacterial virulence by inhibition of quorum sensing, other bacterial secretion systems, or LPS biosynthesis [56,72-79].

13. CONCLUSIONS

Despite dramatic strides being made in our comprehension of *A. baumannii,* many dark areas remain unexplored. Whole-genome sequencing has helped uncover significant facts about this organism's genetic complexity. The ability of *A. baumannii* to survive and regulate its expansive repertoire of drug resistance determinants is noteworthy. Nosocomial *A. baumannii* infections add to the morbidity of admitted patients, and healthcare facilities worldwide are faced with the challenges of pan-drug resistance. An in-depth knowledge of anti-microbial therapy for these infections is crucial. New modalities of therapy are definitely indicated and Healthcare workers and the Scientific community must work together to enhance our armamentarium against *A. baumannii.*

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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