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Epidemiology, Clinical Conditions, Pathogenesis and Mechanism of Resistant of *Acinetobacter baumannii*: A Narrative Review

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Abstract

The world is facing a growing threat from multidrug-resistant (MDR) gram negative "superbugs," such as *Acinetobacter baumannii*. This morbidity and mortality loss caused there of indirectly hampers the economic developments in countries. These multidrug-resistant A. baumannii worldwide represents a major public health problem. The development of antibiotics decreased the mortality among the human and animals leading to a better life expectancy. But the injudicious use of antimicrobials and selection pressure the microbes have developed resistance which became more prominent during last few decades. High antimicrobial resistance was observed against all β-lactam and non- β-lactam antibiotics by the MBL producers. In developing countries also, the misuse and underuse of antimicrobials due to lack of awareness of patients, medical workers and financial problems emerged the antimicrobial resistant strains. Due to rapid globalization of human population by travel and other factor these resistant strains spread easily between developed and developing countries making it a global problem.

Keywords: Acinetobacter baumannii; multidrug resistance; virulence factors; antibiotics; pathogenesis; hospital acquired

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Introduction

Over the last decades, *Acinetobacter baumannii* has globally emerged as a highly alarming nosocomial pathogen. Its clinical significance has been largely driven by a remarkable ability to acquire or upregulate various resistance determinants, making it one of the most successful multidrug-resistant (MDR) organisms threatening ongoing antibiotic therapy[1]. On top of such fascinating resistance acquisition, *A. baumannii* is endowed with various mechanisms of survival under a broad range of environments, potentiating capacity for hospital spread[2]. The attributable mortalities in patients with *A. baumannii* healthcare-associated infections, of which ventilator-associated pneumonia and bloodstream infections are the most common, can range from 5% in general hospital wards to 54.0% in the intensive care unit (ICU)3, with increasing reports of community-acquired *Acinetobacter baumannii* infections[4].

Acinetobacter is a gram negative coccobacillus[5] that during the past three decades has emerged from an organism of questionable pathogenicity to an infectious agent of importance to hospitals worldwide[6]. *Acinetobacter* was first described in 1911 by a Dutch microbiologist by the name of Martinus Willem Beigerinck as *Micrococcus calco-aceticus*[7]. Since then, it has had several names, becoming known

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Acinetobacter in the 1950s[5]. The genus *Acinetobacter* can presently be defined as gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive and oxidase-negative coccobacillary bacteria with a DNA G and C content of 39.0% to 47.0%[8]. Nonetheless, Gram-staining of *Acinetobacter* can be variable and the morphologic characteristics may change depending on the growth phase[8].

Different Species of Genus *Acinetobacter*

At least 33 species within the *Acinetobacter* genus have so far been identified, including 24 named species and 9 currently described as genomic species (gen. sp.) given that no phenotypic properties have been found to differentiate them from other species[9]. In 1986, twelve *Acinetobacter* genomic species within the *Acinetobacter* genus were identified by DNA-DNA hybridization[10]. Six of these DNA groups could be differentiated by phenotypic properties and were given the following formal species names: *Acinetobacter calcoaceticus* (*Acinetobacter* gen. sp. 1), *Acinetobacter baumannii* (*Acinetobacter* gen. sp. 2), *Acinetobacter haemolyticus* (*Acinetobacter* gen. sp. 4), *Acinetobacter junii* (*Acinetobacter* gen. sp. 5), *Acinetobacter johnsonii* (*Acinetobacter* gen. sp. 7) and *Acinetobacter lwoffii* (*Acinetobacter* gen. sp. 8). The study reported an uncertain genotypic and phenotypic differentiation of *Acinetobacter* gen. sp. 9 from *Acinetobacter lwoffii*.

In 2001 and 2003, Nemec[11] identified three novel species (*Acinetobacter schindleri*, *Acinetobacter ursingii* and *Acinetobacter parvus*). Concurrently seven novel species were identified (*Acinetobacter baylyi, Acinetobacter bouvetii, Acinetobacter towneri, Acinetobacter tandoii, Acinetobacter grimontii, Acinetobacter tjernbergiae* and *Acinetobacter gerneri*)11. However, *Acinetobacter grimontii* was later re-classified within the *Acinetobacter junii species*. One novel species was identified and named as *Acinetobacter septicus* in 2008 although it was soon after re-classified within the *Acinetobacter ursingii* species[12].

Three novel species (*Acinetobacter soli, Acinetobacter beijerinckii* and *Acinetobacter gyllenbergii*) were also identified in 2008 and 2009 by two different research groups[12]. Furthermore, *Acinetobacter gen. sp.* 10, *Acinetobacter gen. sp.* 11, *Acinetobacter gen. sp.* 3 and *Acinetobacter gen. sp.* 13TU have recently been named *Acinetobacter berezinae*, *Acinetobacter guillouiae, Acinetobacter pittii* and *Acinetobacter nosocomialis*, respectively, given that they can phenotypically be differentiated from other species within the genus *Acinetobacter*[13].

Natural Habitat of Acinetobacter species

Members of the genus *Acinetobacter* are considered ubiquitous organism. This holds true for the genus *Acinetobacter*, since *Acinetobacter* can be recovered after enrichment culture from virtually all samples obtained from soil or surface water[14]. The organism does not always act as an infecting pathogen, as it is widely distributed in nature and has tremendous colonizing potential[8]. The organism prefers moist environment, therefore, its colonization among damaged tissues is common[15]. *Acinetobacter* species are apparently the only group of gram negative bacteria that may be natural residents of human skin[16]. A study from Germany reported high carriage rates of *Acinetobacter spp.* On human skin and mucus membranes among in patients (75%) and control non-hospitalized persons (43.0%). The most frequently isolated species in that study were *Acinetobacter lwoffii* (47.0%) and *Acinetobacter johnsonii* (21.0%). Unpredictably, the clinically important *Acinetobacter baumannii* and *Acinetobacter nosocomialis* species (0.5% and 1.0%, respectively) were not found to be common human skin colonizers[16].

In patients hospitalized on a regular ward, the carriage rate of *Acinetobacter* species was even higher, at 75.0%16. *Acinetobacter* species fecal carriage and carrier rate is 25.0% among healthy individuals, with *Acinetobacter* johnsonii and *Acinetobacter* genomic species 11 predominating[17]. In contrast, *Acinetobacter baumannii*, the most important *nosocomial Acinetobacter* species, was found only rarely on human skin, 0.5% cases and 3.0% cases respectively[18].

Epidemiology

Histologically, Acinetobacter has been a pathogen of hot and humid climates, where it has been a major cause of infections, particularly in intensive care units (ICUs), and sometimes a cause of community-acquired pneumonia[19]. Over the past two decades, Acinetobacter infections have become an increasingly common nosocomial problem in temperate climates[20]. Its natural habitats are water and soil and it has been isolated from foods, arthropods and the environment[6]. In humans, *Acinetobacter* can colonize skin, wounds and the respiratory and the gastrointestinal tracts. Some strains of *Acinetobacter* can survive environmental desiccation for weeks, a characteristic that promotes transmission through fomite contamination in

hospitals[5].

An increase in the use of broad-spectrum antibiotics may contribute to the isolating of more antimicrobial resistant bacteria, but war and natural diseasters may also play a part. This is not only evidenced by the current war, but also by traumatic diseasters such as earthquakes, like the marmara earthquakein 1999. The GATA Hydarpasa Training Hospital, one of the major treatment facilities after this diseaster, recovered *Acinetobacter baumannii* from 31.2% of all the ICU patients. Before the earthquake, the bacteria were isolated from only approximately 7.3% of patients21. A*cinetobacter baumannii* does not have fastidious growth requirements and is able to grow at various temperatures and pH conditions[8].

Pathogenesis

Although *Acinetobacter* cause hospital-acquired infections, it is considered to be an organism of low virulence. There are characteristics that are possible virulence factors like hydrophobicity of the bacteria which is related to adherence, hydrophobicity is higher in strains isolated from infected catheters and tracheal devices[22], a polysaccharide capsule formed of L-rhamnose, D-glucose, D-glucoronic acid and D-manose, protect bacteria from phagocytosis[23]. Two types of fimbriae like thin, about 3nm, responsible for the ability to adhere to human epithelial cells and thick, about 5nm, responsible for twitching motility[24]. Enzymes such as butyrate esterase, caprylate esterase and leucine arylamidase that are involved in the hydrolysis of short chain fatty acids and damage of tissue lipids[25]. The potentiality toxic role of the lipopolysaccharide component of the cell wall[26].

Clinical Manifestation

The most frequent clinical manifestations of *Acinetobacter* infection are ventilator-associated pneumonia and bloodstream infections[27]. Vascular catheters and the respiratory tract have been the most frequent sources of *Acinetobacter bacteremias*[28] for which crude mortality rates parallel those attributed to other gram-negative bacilli (28 to 32%)[29]. *Acinetobacter* pneumonia occurs predominantly in ICU patients who require mechanical ventilation and tends to be characterized by a late onset. Affected patients spend more days in the ICU and on a ventilator before having positive cultures than do patients with pneumonia caused by other gram-negative bacilli or uninfected patients[8]. The clinical effects of ventilator-associated pneumonia have been variable. A recent study showed higher mortality among patients with multidrug-resistant *Acinetobacter* infections than among patients infected with susceptible *Acinetobacter* strains or uninfected patients. The severity of illness is more in multidrug-resistant *Acinetobacter* infections in patients who had hospitalized in ICU[30].In other studies, mortality among patients with pneumonia due to multidrug-resistant *Acinetobacter* was similar to that among patients with infection caused by other pathogens[4].

Mechanisms of Antibiotic Resistance

The prolonged administration or misuse of antimicrobials resulted in selection pressure which favors the evolution of resistant strains and subsequently their transmission causes spread of the resistant strains in the environment. The long-term use of a single antibiotic favored development of strains resistant to both same antibiotics along with other related antibiotics[31]. The spread of resistance traits occurs among different ecological groups and taxonomical groups by the presence of mobile genetic elements like bacteriophage, plasmids, naked DNA, transposons etc[32]. The main resistance mechanisms to multiple antibiotics in *Acinetobacter species* and other superbugs can be summarily outlined as follows production of hydrolysing enzymes for like β-lactam hydrolysis by different kinds of β-lactamases (Class A to D β-lactamases), changes in penicillin-binding proteins (PBPs) that prevent the action of β-lactams, alterations in the structure and number of porin proteins that result in decreased permeability to antibiotics through the outer membrane of the bacterial cell and the activity of efflux pumps that further decrease the concentration of antibiotics within the bacterial cell[33]. By Mutation of target sites, they resist the action of Fluoroquinolones and by modification of Aminoglycosides by bacterial enzymes they resist Aminoglycosides[34]. MDR, XTR and TDR TB microorganisms show resistance to antibiotics by spontaneous mutation in various genes[35]. Resistance to Macrolides and related antibiotics mostly occurs due to the r RNA modification responsible for their bindings with ribosomes[36].

Prevention and Control

Antimicrobial resistant bacteria are the emerging current threats. The followings are some control and preventive measures should be taken to minimize their

developments, spread and to promote development of new therapeutics. Most of the infections spread and occur from the contact of infected persons and lack of hygienic practices. Proper sanitation and hygiene maintenance in food and other things can reduce the spread of superbugs. Inappropriate use of antibiotics occurs due to unnecessary length of treatment, wrong prescription and its use without infections[37]. Both physicians and people education about it can check the development of resistant strains. Some policies and regulations should be practiced in both developing and developed countries to check the unnecessary drug promotions[38]. Antibiotics are used vividly in food animals like chicken, cattle, pigs, agricultural fields and fish farming methods. These uses establish a direct link for the appearance of resistance in humans[39]. Attempts should be taken to check the spread of antimicrobial resistances by restricting human to human transmission of resistant strains, decreasing the use of broad spectrum antimicrobial and developing new and novel antimicrobials[40]. Steps should be taken to prevent infections by inhibiting key gene products involved in the infection process[41].

Conclusion

Acinetobacter baumannii is one of the main pathogens of nosocomial infection and clinical opportunity infection, and it is also the most important strain causing outbreak of *Acinetobacter* in hospital environment. With the extensive application of broad-spectrum antibacterial drugs and the popularization of interventional procedures, *Acinetobacter baumannii* is resistant to a variety of antibiotics, and gradually develops into multi-drug resistance and even total drug resistance. Vivid research and application of Nanotechnology for identification of resistant bacteria and therapy for combating superbugs should be practiced.

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Conflict of Interest
The authors have no conflicts of interest to disclose.

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Authors' contributions
Uddin BMM, Rahman MA, Yeasmin MM, Mahjabin M conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Chowdhury SJ, Ahmed I contributed to the analysis of the data, interpretation of the results and critically reviewing the manuscript. Uddin BMM involved in the manuscript review and editing. All authors read and approved the final manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
None

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