Chapter

Virulence and Antibiotic Resistance of *Acinetobacter baumannii* among Urinary Tract Infections

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Abstract

Acinetobacter baumannii is one of the opportunistic bacteria firstly related with the hospital acquired infection influencing primarily to weakening the patient in the ICU. It is sometimes transferred to the patient by transient colonization of hands of the workers of healthcare, and persistence on eco-surfaces. Acinetobacter baumannii inhalation aerosolized through endo-tracheal suctioning of the ventilated patient is widespread among ventilator-related pneumonia (VAP). It is infections mainly associated with ventilator-related pneumonia (VAP), community Acquired Pneumonia (CAP), invasive bacterial infections (IBIs) and UTI (urinary tract infection). It is one of the prominent uropathogens problematic with antibiotic resistance especially carbapenem resistant Acinetobacter baumannii (CRAB). Their colonization of urinary tract and establishment of infection may attributed mainly to set of virulence factors like: Acinetobactin-assisted iron acquisition system, Bap (biofilm-related protein), phospholipase D, Ata (Acinetobacter trimeric autotransporter), chaperone-usher type pilus (Csu), OmpA (outer membrane protein A), and Plasminogen-binding protein (CipA). The common drugs used for treatment Acinetobacter baumannii infections involve polymyxins, glycylcyclines, tetracyclines, mono-bactams, fluoroquinolones, aminoglycosides, antipseudomonal carbapenems, antipseudomonal cephalosporins, and sulbactam. The rates of MDR isolation or also comprehensively the resistant Acinetobacter baumannii are significantly increased and so the combination of two or more (colistin, tigecycline, or colistin-rifampicin combination therapy) drugs is sometimes used to treat infections of MDR-AB. As a conclusion the Acinetobacter baumannii engagement in urinary tract infections attributed mainly to their adhesins, invasins and intrinsic antibiotic resistance.

Keywords: *A. baumannii*, CRAB, Ata, TAA, OmpA, CAP, VAP, colistin

1. Introduction

Acinetobacter baumannii is a polymorphic bacterium, rode shaped, gram negative, immobile, and aerobic. It is an opportunistic bacterium mainly related with the hospital acquired disease. It has highly incidence among immune-compromised

people, especially those who have suffered from prolonged hospital stay (more than 90 days) [1]. A. baumannii bacterium is one of the major states of the infections of hospitals that firstly affect the exhausted patients in the ICU, notwithstanding the prevalence to long-term care facilities and to regular wards is becoming larger. It is distinguished by its great determination in environments and has a specially ability for enhancing the resistance to every antibiotic [2].

Acinetobacter baumannii usually causes the hospital infections, mostly catheter-related bacteremia, and aspiration pneumonia, but also can cause infections of urinary tract and soft tissue. Community-acquired infections Acinetobacter species are progressively recorded. Transfer of Acinetobacter, and sub-sequent diseases are expedited by environmental persistence of the microbes, resistance to dehydration and avoiding host immunity [3–5].

The characteristics of virulence exhibited by species of Acinetobacter mainly arises from avoiding of quick removal by the innate immunological system, actively expediting a highly bacterial density which leads to the formation of receptor of lipopolysaccharide-Toll-like 4 (TLR4)-assisted sepsis. Polysaccharides of capsule are critical virulence agents that enable immune evasion, whereas LPSs lead to the septic shock [6]. The newly increase in casualties, greatly related with the infected combat soldiers reverting from the conflict districts, and a high increasing in casualties of multidrug resistant isolates (MDRs) have increased the emerging opportunistic bacterium profile, significantly [7]. MDR-*A. baumannii*, defined as a strain resistant to 3 or more groups of antimicrobial agents. They are involving the carbapenem, which has emerged as a main cause of healthcare-related infection [8, 9]. The infections of A. baumannii are difficult for treating and related with highly, and mortality, and staying for a long time at hospitals [10, 11].

2. Acinetobacter spp.

Bacteria of the genus Acinetobacter are ubiquitous, free living, saprophytic organisms that can be isolated from soil, water, sewage, and a wide variety of foods. They are common components of food spoilage flora. *Acinetobacter johnsonii* and *Acinetobacter lwoffi* are the species most often isolated from foods, but other species, like the opportunistic pathogen *Acinetobacter baumannii* also can be found in spoilage flora [12]. *Acinetobacter* genus is very variant, consisting of negative and positive oxidase, non-pigmented, and gram negative cocco-bacilli. In spite of there are more than fifty species of the varied Acinetobacter, most of them are non-pathogenic environmental microorganisms. The most common infections are by A. baumannii, followed by A. lwoffii, and A. calcoaceticus [13, 14]. Acinetobacter was found out by Beigerinck, Martinus Willem, a microbiologist from Netherlands in 1911. However, for long times, the bacterium Acinetobacter had a low-virulence, sensitive to the used common antibiotics, but from 1970, resistance of Acinetobacter led to increase and became one of the severe problems, particularly in the conditions of hospitals. Currently, the infections by A. baumannii are distinguished to be an important problem and difficult for the controlling and treating in critical care conditions [15–17]. A. baumannii lives equally in the humid, and dry environments, is resistant to the disinfectant, and extreme drying. It enables for forming the biofilm that expedites bacterial binding to the tissue, as well as different surfaces of the environment, and rapidly acquires mechanisms of the antibiotic resistance. These characteristics are believed to have led to the quick endemic prevalence of Acinetobacter baumannii in environments of hospitals and several intensive care units worldwide, especially in countries of Europe. Also, in 2015, the report of the European Antimicrobial Resistance Control Network

referred to that the association of strains of MRD-A. baumannii throughout Europe was stably increasing.

However, the highest levels of the drug resistance Acinetobacter baumannii were remarked in the states of Baltic particularly in Lithuania and in Southeastern and Southern Europe. In 2017, this bacterial species was involved in the general priority list of WHO for drug-resistant bacteria for a big need to the development of research, and the insistence for novel antimicrobial agents [18]. *Acinetobacter* spp. are normally dwell skin, mucous membranes or the pharynx, and human respiratory secretions as normal flora It accountable for a wide variety of local and systemic infections, including pneumonia, septicemia, wound infections and urinary tract infections. The main body areas populated by these microorganisms in hospitalized patients are the skin, oropharynx, and digestive tract [19–21]. Additionally it can survive in dry abiotic environment like medical devices, disposables mattresses, pillows and equipment for long periods. It can stay on glass for 20 days and their staying on another dry surface may be 4 moths [22].

3. Urinary tract infections

A. baumannii infections involve body systems that with high levels of fluids such as urinary and respiratory tract, peritoneal cavity, and are linked to indwelling devices [21]. The UTI (Urinary tract infection) has a main public health concern in sciences of medicine and represents one of the most commonly infectious diseases classified next to infections of the upper respiratory tract. They precipitate to nosocomial infections in several hospitals and account approx. 35% of all diseases obtained in the hospitals. Unhealthy lacks of proper genital washing and sexual intercourse have led to spread UTI. [23]. Genitourinary infections regards third important hospital infections proceed by respiratory and surgical wound infections A. baumannii responsible for 5-9% of UTIS [24–26].

A. baumannii compile 1-2% of all healthcare-related infections in the USA, Europe and Middle East [27]. A. baumannii Catheter associated UTIs (CAUTI) is most recently UTIs rerated to biofilm formation among uropathogens. A. baumannii was implicated as uropathogens and 20% of all isolates were isolated from patients with UTIs [28]. This organism is usually linked to catheter-associated infection or colonization. It is unusual for *A. baumannii* to cause complicated UTI in outpatients. Epidemiologically MDR-AB were widespread worldwide: Europe, North America, Argentina, Brazil, China, Taiwan, Hong Kong, Japan, and Korea [29–31]. Cross-transmission and diffusion from the hospital environment are more likely than endogenous sources to be the source of infecting or colonizing organisms in nosocomial infections [32]. *A. baumannii* very dangerous specially in individuals who have recently undergone major surgery, have malignant diseases or burns or immuno-suppressed patients such as the elderly, neonates with low birth weights, and patients with prolonged illnesses [33]. War-associated infections was clearly linked to *A. baumannii* when reported during the Korean War, the Vietnam War, and the wars in Iraq and Afghanistan [34, 35]. Biofilm formation were investigated among more than 75% of A. baumannii isolates and it can bind to the host epithelial cells via set of adhesins like Csu, OmpA and Bap [36–39].

4. Virulence factors

The interaction between cells of the host and pathogens is important in the pathogenesis of some bacteria leads to its internalization. Although proving the

infections, the bacteria must be colonizing the host. The binding of pathogens to cells of the host is enhanced by different molecules expression or structures by cells of bacteria. Adhesion depends on the interferences of proteins of the host cell surface or soluble proteins with receptors. The proteins act as a bridge between cells of the host and bacteria. Adherence of microbes to cells of the host as a first step of colonization is an important virulence agent [40, 41]. Few molecular agents are needed to the virulence of A. baumannii in human. They involve excessively phospholipase D, OmpA (outer membrane protein A), Csu (chaperone usher type pilus), Bap (biofilm associated protein), acinetobactin assisted Fe acquisition system, and Ata (Acinetobacter trimeric autotransporter), [42]. The role of each of them in virulence was listed below:

4.1 Bap (biofilm-associated protein)

In vitro, cells of A. baumannii easily form the biofilm, and the capability of nosocomial strains for forming the biofilm on the medical devices as in tissues of the host finds a critical agent in the virulence of bacteria. The cells that synthesize the biofilms are included in the polymeric conglomerate of polysaccharides and proteins. The biofilm resists immune defenses of the host, antibiotics and detergents, and antibiotic resistance to bacteria in these habitats can be increased to 1000 times [43, 44]. The biofilm finally grows by producing poly-beta (1-6) N-acetyl-glucosamine controlled by pgalocus. The extracellular matrix gives an adhesion among the cells of bacteria, allowing the synthesis of multilayer structures. Also, many surface proteins are included in the process, and show to expressively contribute to the binding of the bacterial cells to abiotic or biological surfaces. Directly, Bap (biofilm associated protein), a special cell surface protein, is included in the formation of the biofilm by Acinetobacter baumannii and plays a main role in the processes of infectious bacteria. It is involved in intercellular adhesion within the mature biofilm [45]. Bap (Acinetobacter baumannii biofilm-related protein) is necessary to form a mature biofilm on the medically-relevant surfaces, involving polystyrene, titanium, and polypropylene, and Bap acts as the surface structure included in A. baumannii adherence to normal human neonatal keratinocytes and normal human bronchial epithelial cells. The finding Bap increases hydrophobicity of surface of the cell of bacteria [46]. Bap is A giant protein plays a great role in the formation of biofilms and adhesion to cells of the host in A. baumannii. Most of the protein is synthesized by arrays of 80 to 110 modules featuring Ig-like (immunoglobulin-like) motifs. Bap types includes BLP1, and BLP2 which included in the formation of biofilms and assembled in dissimilar A. baumannii isolates. However, adhesion patterns and phenotypes of the biofilm of some clinical strains appear to be associated with the finding broadspectrum antibiotic resistances. Also, the arrangement of the development, and formation of the biofilms diverse like surfaces on which these bacteria persist and components of cells that contribute in the multi-step programmed process. The regulatory processes related with the synthesis of biofilms involve sensing density of the cells of bacteria, the finding various nutrients and concentrations of free cations found for the cells of bacteria. Extracellularlly, some of the signals maybe sensed by 2 component regulatory systems like Bfm RS. The transcriptional regulatory system activates expressions of usher-chaperone assembly systems accountable to produce pili, needed for the synthesis of the biofilms on the polystyrene surfaces, and cell attachment. Nevertheless, this system is not required for the formation of biofilms on abiotic surfaces when the cells are cultured in the industrial medium. Interestingly, system of Bfm RS controls the shape of the cell under certain cultural setting. Biofilm tolerance to host immune defenses, disinfectants, and antimicrobials [47, 48].

4.2 OmpA (Outer membrane protein A)

The main protein of outer membranes, (OmpA), is the most abundant surface protein. Also, it is necessary to bind A. baumannii to human alveolar epithelium, but it also plays a useful role in the enhancement of biofilms on plastics. Among the identified proteins of outer membrane in A. baumannii, AbOmpA acts as a porin, which is required for adhesion of eukaryotic cells, and participates to resistance of serum and the biofilm formation, partially. The OmpA group is proposed to have a variety of functions, involving adhesion to epithelial cells of the host, functions of biofilms, and complement resistance [49]. Additionally, overexpression of chromosomal efflux systems was received great attention. However, the over-production of these systems confers increased MDR to antibacterial factors and induces death of cells of the host through nuclear and mitochondrial targeting [50–52]. OmpA thought to participate to the antibacteral resistance of *A. baumannii* during a probable interaction between efflux pump systems and its OmpA-like domain [53].

4.3 Phospholipase D

PL (Phospholipase) is an essential enzyme, necessary for phosphatidylcholine metabolism and was studied in a variety spectrum of microbes. About, 3 phospholipase classes (PLC, PLD, and PLA) were identified by the cleavage site. PLA analyzes the fatty acid of the glycerol backbone. When PLC cleavage, the phosphorylated head groups are released from PLD and phospholipid cleaves off just the head group. The releasing the polar head group and the releasing the phosphorylated head group can affect the constancy of membranes of the host cells. Additionally, phospholipase can interfere with cellular signaling by generating 2nd messengers such as phosphatidic acid, which can modify the immune responses of the host [54]. It is assumed that many pathogens exploit certain enzymes for enhancement of membranes in the coordinated form, thus, these enzymes play an important role as virulent agents. An example is PLD (phospholipase D), an enzyme that hydrolyses structural phospholipids which results in PA (phosphatidic acid) production, a 2nd messenger that acts as an assistor in several cellular processes. Phospholipase as a virulence agent was implicated in many bacteria. In vivo, PLD of A. baumannii supports pathogenesis and invasion [55, 56]. The disrupting A. baumannii phospholipase D caused reducing capability of organisms to grow in the blood serum, decreased pathogenesis and decreasing epithelial cell invasion [57].

4.4 Csu (chaperone-usher type pilus)

The attachment of primary cell can be reasonably assisted by a pili -like structure encoded by the position of csu, which is widely spread among clinical strains. A. baumannii ability to form the biofilm largely depends on pilus, which assists formation and attachment of biofilms. In similar, csu E, is one of the members of the system of usher-chaperone. Genes clustered together in the form of opera csu, whose products form pili-like bundle structures in these bacteria. This gene has confirmed to be a meaningful agent in the formation of A. baumannii biofilm [58, 59].

4.5 Acinetobacter trimeric autotransporter (Ata)

The Ata (Acinetobacter Trimeric automatic transmission adhesive) pertains to the trimeric autotransporter adhesin super-family which is meaningful virulence agents in several gram negative pathogens. Also, the TAA (Trimeric

autotransporter), called as the Vc type secretion system, is declared by several A. baumannii isolates, an opportunistic bacteria, answerable for the infections in hospitals globally. The TAA, is a modular homotrimeric virulence agent, including conserved membrane anchoring domain, the signal peptide, and complex stalk. In vivo, mechanisms of the evolutionary underlying the development of this adhesin is not clear. The Ata is an useful multi-functional virulence agent in the bacterium Acinetobacter baumannii that assists the invasion and the adhesion, participates with pathogenicity, and incites apoptosis [60]. It was found that the Ata is acting as a multi-functional virulence agent of Acinetobacter baumannii by (1) mediating the invasion and adhesion in cells of epithelial and endothelial, (2) leading to the programmed cell death in a caspas-dependent manner, (3) leading to the secreting IL-6 and IL-8 as proinflammatory cytokines, and (4) in vivo, contributes to the virulence. These results forcefully propose that The Ata was uses as useful virulence factors for the bacterium Acinetobacter baumannii through the infections in models of insect and human [61].

4.6 System of Acinetobactin-assisted iron acquisition

The siderophore is highly converged iron chelators synthesized and applied using some bacteria to thrive under the iron-reducing which conditions typically encountered in hosts and the environment [62]. A. baumannii produces up to 3 siderophores namely, baumannoferrin, fimsbactin, and acinetobactin. The producing baumannoferrin, and acinetobactin is beggarly conserved among clinical strains, whereas the producting fimsbactin is lesser common. Fimsbactins are structurally linked to acinetobactin by the finding catecholate, and phenolate oxazoline metal binding motifs. Both are derived from nonribosomal peptide synthesis lines with similar catalytic domain, identities, and orientations [63]. The system of acetinopactin-assisted iron acquisition was the most distinctive system in Acinetobacter baumannii. Acinetobactins, catechol-hydroxamate siderophores, and non cyclic derivative of DHBA, that associated with N-hydroxyhistamine, and threonine. Acinetobactins are synthesized and used by 3 hypothetical systems encoded within the gene clusters of acinetobactin in Acinetobacter baumannii. Acinetobactins are manufactured from threonine, hydroxy histamine, and DHBA by the encoded proteins by genes in the gene cluster. The mixed kind siderophore, which constitutes of hydroxamite groups and catechols groups, shows a significant affinity of Fe. Acinetobacter baumannii that is produced acinetobactin is secreted system of the siderophore efflux the super-family of ABC [64].

4.7 CipA (plasminogen binding protein)

The CipA (Plasminogen-binding protein) is an external membrane protein, links to active forms of the plasmin, and plasminogen, to break down fibrinogen and encourage the spread of bacteria. Also, this CipA plasmin breaks down C3b. Nevertheless, there is no correlation among CipA plasmin levels, and complement resistance so far. Thus, the mechanism by which CipA gives the complement resistance still needs clarification. The CipA disrupts the system of alternative supplements and supports the penetration of layers of endothelium [65].

5. Antibiotic resistance and therapeutics options

A. baumannii remains difficult for treatment that has an important challenge to the clinician and cost to the systems of healthcare. Commonly, the used antibiotics

to treat infections of Acinetobacter baumannii involve polymyxins, glycylcyclines, tetracyclines, fluoroquinolones, aminoglycosides, mono-bactams, antipseudomonal carbapenems, antipseudomonal cephalosporins, and sulbactam [66]. Colistin was widely investigated as a mono-therapy or as a part of the combination treatment, but its application is limited because of the nephrotoxicity. Previously, infections of Acinetobacter baumannii to CNS (central nervous system) following neurosurgery were recorded and treated with relative success by tigecycline, colistin, intraventricular or/and intravenous or colistin-rifampicin combination thretment [67]. Application of Colistin exhibits an upward tendency because of the VAP overseas and emergence of the bacterial infections of MDR [68]. Nevertheless, none of tigecycline or polymyxins was excessively agreed for the medical uses in China. Actually, using combinations of beta-lactamase inhibitor (sulbactam/ampicillin and sulbactam/cefoperazone) or meropenem as the basis of the therapy program associated by levofloxacin or etilmicin is repeatedly used in therapies of the empiric antibiotics. Recently, broad spectrum antibiotics were greatly applied in the clinical practices, whereas the rate Acinetobacter baumannii resistance shows obvious increases [69, 70]. Significantly, the rates resistant Acinetobacter baumannii of or even comprehensively MDR isolation are increased in clinic. The studies were exhibited that the rate resistance of Acinetobacter baumannii to most the tested antibiotics is more than 50%. Thus, the combination of two or more antibiotics is sometimes used in treatment of the infections of MDR-AB [71, 72].

However, due to its widespread use, resistance of AB to carbapenem antibiotics quickly increased, in particular among isolates obtained from the ICU. In China, the incidence of resistance of carbapenem (CRAB) increased from the percentage 31% in 2005 to the percentage 66.7% in 2014. In USA, it increased from the percentage 20.6% in 2002 to the percentage 49.2% in 2008. Very few drugs are now available to treat CRAB (carbapenem resistant AB). It is hypersensitive to just a few drugs, like tigecycline and polymyxin, in vitro [73–75].

Currently, the best therapy for the infections of CRAB is illegible. In China, tigecycline based combination treatment, polymyxin based combination treatment, and sulbactam based combination treatment are devised to treat MDR Gram negative rode bacteria. Nevertheless, these devises are based on small scale retrospective researches, lacking comprehensive and systematic clinical study evidence, and no large scale clinical randomized controlled trials were achieved to assess their activity in the patient with MDR-A. baumannii. Polymyxin is not greatly applied in Mainland China because of the toxic side influences of it [76, 77]. Thus, currently, tigecycline treatment and sulbactam treatment are the major clinical therapies for CRAB. Nevertheless, several controversies surround tigecycline regimen to treat infections of A. baumannii bloodstream (BSI). The US Food and Drug Administration devised that tigecycline was autonomously related with highly risks of mortality and must just be applied in conditions where therapeutic preferences were limited. However, tigecycline exerts a suitable therapeutic influence depending to some researches, whereas many other researches recorded that tigecycline increases the mortality of patient [78, 79].

As a member of Gram negative bacteria, A. baumannii equipped with sets of resistance mechanisms including: i) structural bacterial shields (Presence of the porin channels and efflux mechanisms), ii) enzymatic inactivation of antibiotics (oxacillinase (OXA-type), metallo–beta-lactamases (MBLs), iii) alteration of the target or cellular functions due to mutations [80–82].

Due to extensive resistance to antibiotics, new strategies were proposed as alternative therapy. Antimicrobial peptides (AMPs) are one of the antimicrobial agents with high potential to produce new anti-*Acinetobacter* drugs. Melittin, Histatin-8,

Omega76, AM-CATH36, Hymenochirin, and Mastoparan were suitaple AMPs and have the highest anti-*A. baumannii* [83–85].

Pahge or bacteriophage therapy is another alternative therapy for MDRAP. Phages are specific to different bacteria, and they bind to receptors on bacterial cell walls to inject deoxyribonucleic acid into the cell and ultimately lyse the cell in the lytic phase. Lytic bacteriophage therapy may be an opportunity to combat the rapidly growing number of MDR bacteria [86]. Lytic phage, the YMC 13/03/R2096 ABA BP (phage BΦ-R2096), which specifically causes the lysis of CRAB strains [87].

6. Conclusion

As a conclusion the Acinetobacter baumannii engagement in urinary tract infections attributed mainly to their adhesins, invasins and intrinsic antibiotic resistance.

Conflict of interest

There is no 'conflict of interest' for this work.

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