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Article Review

General Characteristics of the Bacterium *Acinetobacter baumannii* in Iraq

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Abstract: *Acinetobacter baumannii* is a public causative agent of nosocomial infections and it has got a pathogen of augmented clinical importance because of its remarkable ability to cause outbreaks of infections and to gain resistance to nearly all presently used antibiotics including the carbapenems. *A. baumannii* possess a number of properties which permit them to be more effective as a pathogen. These properties may be virulence factors such as enzymes, toxins or toxin transfer system which straight affect the host cell and its ability to form biofilms or motility in different mechanics includes motility (twitching), swarming and swimming. These characteristics are impartial some of the identified factors which make *A. baumannii* acts as a pathogen.

Keywords: *Acinetobacter baumannii*, Pathogenicity, Biofilm, Adhesion, Efflux pumps

Introduction

Acinetobacter baumannii is an opportunistic pathogen of a Gram-negative, which has emerged in recent decades as a global cause of hospital-acquired infection with high morbidity and mortality (Wong et al., 2017). These bacteria cause many infections such as bacteremia, meningitis, wound infections, pneumonia and urinary tract infections (Gonzalez-Villoria & Valverde-Garduno, 2016). *A. baumannii* is spread in different environments. It may exist in water and soil and has the ability to live on dry and wet surfaces as it exists in a hospital environment (Tavakol et al., 2018). The main cause of infection is due to its resistance to various types of antibiotics (Wong et al., 2017).

These bacteria have multiple antibiotic resistance as they have the ability to develop multiple mechanisms against major antibiotic classes such as Cephalosporin, Aminoglycoside, Quinolone and Carbapenem (Nageeb et al., 2015). Carbapenem is the optimal and effective treatment for infections caused by these bacteria, but in recent years, the proportion of resistance to these antibiotics has increased and may be due to the production of carbapenemase enzymes such as Oxacillinase, as well as change the target sites of the proteins associated with penicillin-binding proteins, and pumps influx. The permeability of the outer membrane due to loss or reduction of the expression reduced expression in the outer membrane proteins (Pourhajibagher et al., 2016). *A. baumannii* is associated with its ability to produce many virulence factors such as biofilm membrane formation, capsule production, protease enzymes, lipase production, gelatinase adhesion and adhesion due to factors such as cilia that increase bacterial adhesion (Abdulla et al., 2015). The ability of bacteria to form a biofilm is one of the important virulence factors of *A. baumannii*, and the biofilm is a structure formed by the action of a group of bacterial microorganisms. As a matrix of polymeric materials produced as extracellular materials (Dekić et al., 2017), there are multiple genes involved in different stages of the formation of *A. baumannii* biomembrane including

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ompA encoding the OmpA protein (Outer membrane protein) and the bap gene. Bap (Biofilm associated protein) encodes surface protein (Ahmad et al., 2016). The resistance of bacteria to antibiotics and their ability to form a biofilm provide protection against disinfectants and desiccation, making it easier to stay in a hospital environment, which makes it difficult to treat and control (Ivanković et al., 2017).

Nomenclature and Taxonomy

Acinetobacter bacteria were described at the beginning of the twentieth century in 1911 by the Dutch scientist Beijerinck when he isolated it from the soil and water using calcium acetate-rich media and called it *Micrococcus calcoaceticus* (Sepahvand et al., 2016). In 1954, Brisou and Prevot suggested the current designation *Acinetobacter*, meaning in Greek non-motile, to distinguish it from the other motile bacteria within the genus *Achromobacter* (Gonzalez-Villoria & Valverde-Garduno, 2016). After that, in 1968, bacteria of the genus *Acinetobacter* became acceptable when Baumann published a comprehensive study on the genus *Acinetobacter* and difficulty of classified it at the gender level based on its phenotypic qualities, and also revealed some of the basic characteristics for this genus; obligate aerobic, negative for oxidase and catalase positive and non-pigment producing genus (Baumann et al., 1968). *Acinetobacter* includes two species: *A. calcoaceticus* and *A. lowffi* based on glucose oxidation and acid production (Nandi & Arjuna, 2017). Visca et al. (2011) reported that this genus was divided into 12 genospecies according to the DNA-hybridization technique, six of which were named as *A. calcoceticus*, *A. baumannii*, *A. haemolyticus*, *A. johnsonii*, *A. lowffii* and *A. radioresistensaeg*.

Ramette & Kronenberg (2018) referred to species related to the genus *Acinetobacter* such as *A. baumannii*, *A. pittii*, *A. nosocomialis*, *A. dijkshoorniae* and *A. seifertii* as difficult to distinguish them phenotypically. So, they are placed within a group called *Acinetobacter calcoaceticus- Acinetobacter baumanii* (ACB) Complex. Previously, *Acinetobacter* was classified within the family Neisseriaceae, but the recent classification categorized it in the family Moraxellaceae together with the genus *Psychrobacter* and *Moraxella* (Jung & Park, 2015).

Thus, the taxonomical classification is given as follows:

Kingdom Bacteria
Phylum Proteobacteria
Class Gammaproteobacteria
Order Pseudomonadales
Family Moraxellaceae
Acinetobacter baumannii Bouvet & Grimont, 1986

General Characteristics of *Acinetobacter*

Acinetobacter is characterized as coccobacilli aerobic, Gram-negative, non-fermenting lactose, oxidase positive and oxidase negative and catalase positive (Lin & Lan, 2014). Although such bacteria are non-motile, some gliding or twitching on semi solid media due to the presence of polar fimbriae (Yeom et al., 2013). In non-spore forming, flagellates are absent (Römling et al., 2013). This genus is widely spread in environments where represented resistant pathogens to drying and antibiotics, which help them to survive and spread in a hospital environment (Varda Brkić et al., 2015). They do not lose dye easily and can appear as positive bacilli for Gram stain (Asif et al., 2018). The members of *Acinetobacter* appear in the form of swollen bacilli in the log phase, ranging in length from 2.5-1.5 micrometer and a diameter of 1-1.5 micrometer and coccoid is shown during stationary phase (Jung & Park, 2015).

Acinetobacter colonies appear on the blood agar as a convex, white to cream, after incubation at 37° C for 18-24 hours, non-hemolytic, except *Acinetobacter haemolyticus*, which is hemolytic. On MacConkey agar, the colonies show in a light pink color indicating that lactose is not fermented (Asif et al., 2018). *Acinetobacter* is an important microorganism in the soil that contributes to the biodegradation of a number of environmental pollutants because of its ability to remove and destroy a wide range of pollutants such as phenol, crude oil, chlorinated biphenyl and biphenyl in addition to the removal of phosphates and heavy metals from the soil through the use of chemical compounds contaminated as essential materials for growth, which increases their importance in the field of environment and biotechnology, which belongs to their ability to produce lipase and proteases enzymes, and bioemulsifier (Abdel-El-Haleem, 2003; Gutnick & Bach, 2008).

General Characteristics of *Acinetobacter baumannii*

A. baumannii is one of the most important pathogens among *Acinetobacter* species. It is an important opportunistic pathogen that is responsible for a variety of nosocomial infections. This bacteria have the ability to survive in dry environments for a long time and spread through the water, air, and skin of the infected patients, as well as through the hands of hospital staff. The infections by these bacteria are due to poor hygiene and the use of contaminated medical devices such as catheters and respiratory devices (Raro et al., 2017).

Acinetobacter lives as normal flora on human skin, respiratory secretions, mucous membranes and pharynx (Gallego, 2016). These bacteria cause many diseases, including pneumonia, bacteremia, skin infections, soft tissue infection, meningitis, urinary tract infection, surgical site infections and nosocomial or ventilator associate pneumonia, especially in patients of wound and burns infections (Antunes et al. 2014; Zhao et al., 2015). *Acinetobacter* is considered as the second pathogen after *Pseudomonas aeruginosa*, which was isolated from the hospital environment (Talukdar et al., 2018). *Acinetobacter* species, particularly *A. baumannii* has become of a medical importance, because of its potential ability to survive for long periods in hospitals. It has the ability to resist dehydration and stay on dry surfaces for several months. These bacteria are present on door handles, tank surfaces as well as contamination of medical devices (Cheng et al., 2018). Almasaudi (2018) reported that *Acinetobacter*, especially *A. baumannii* became a red- alert human pathogen, primarily because of its exceptional ability to develop resistance to all currently available antibiotics. *A. baumannii* can grow at 44° C, which is distinct it from other species of the same genus (Asif et al., 2018). One of the main characteristics of *A. baumannii* is the ability of clinical isolates to develop multiple antibiotic resistance which occurs either by mutations or genetic elements such as plasmids, transposons or resistant islands. Their unique abilities to invade surfaces and remain in environments have made it very difficult to eliminate in clinical cases (Gallego, 2016). This species was first isolated in 1968 by scientist Baumann from soil, water and food samples such as meat and vegetables, as well as from clinical samples of human beings such as blood, husk and pleural fluid (Brook et al., 2004). Recently, the interest with *A. baumannii* has increased through the infections that recorded in the US military. It is reported that this bacterium has caused many infections among US military personnel who have served in Iraq and Afghanistan, so it is called Iraqi bacter (Lee et al., 2017).

Genetic Content of *A. baumannii*

The bacterial chromosome of *A. baumannii* is described as a single chromosome containing 3,976,747 base pairs, 3,454 bp of which are specialized for protein synthesis (Smith et al., 2007). *A. baumannii* includes many strains, the most famous of which is the AYE strain containing 86 Kpb as a resistance region called AbaR1, consisting of 45 resisrance genes. This area is found on the chromosome of bacteria and contain the necessary

genes that encoded for antibiotic resistance (Lean et al., 2015). Among these genes, 25 genes are encoded for many antibiotics resistant included tetracycline, chloramphenicol, cotrimoxazole and aminoglycosides and also encoded for resistance of heavy metals such as arsenic and mercury (Kholodii et al., 2004). There are 14 genes of resistance encoded of Class 1 integrons, which are responsible for the gene expression, recombination and integration (Fournier et al., 2006). The strain AYE.of *A. baumannii* also contains two plasmids, pACICU1 and pACICU2 28.2 and 64.3 base pairs, respectively. The pACICU1 plasmid contains no any antibiotic-resistance genes, while the pACICU2 plasmid carries two copies of the oxa58 gene encoded for carbapenem resistance. In addition, it carries ISAba125 gene and contains an area of about 20 kpb comprehensive genes involved in transport genes, indicating that this plasmid may be a conjugated plasmid (Imperi et al., 2011).

Epidemiology

A. baumannii is a healthcare-related pathogen. Many articles had been reported that many infections occurred in hospitals caused by mentioned bacteria, including septicemia, bacteremia, endocarditis, and meningitis (Vashist et al., 2011). *A. baumannii* causes seasonal infections that occur at the end of summer and the beginning of winter and studies have shown that they rise by 50% during the period from July to October and prefer wet habitats. Smoking and alcoholism make patients more susceptible to pneumonia. These bacteria have increased in times of war and natural disasters, such as the 1999 Marmara earthquake and Asia's tsunami in 2004 (Ahmad et al., 2016). The most vulnerable people to *A. baumannii* are those with cancerous tumors, undergoing surgery, the elderly, low-weight newborns and patients with the prolonged disease (Gallego, 2016). Numerous epidemiological studies have shown many infections occurred with strains of multi drug resistance in different regions of the world, including Europe, China, Japan, Korea and Brazil (Almasaudi, 2018). A study at the intensive care hospital in Riyadh showed that most isolated bacteria from older patients were *A. baumannii* (Kamolvit et al., 2015). The uncontrolled air movement inside and outside the hospital environment makes bacteria more able to cause infection, which helps spread easily in the environment through sneezing, coughing, talking and contact with hospital materials (Solomon et al., 2017). These bacteria have the ability to survive on dry surfaces under limited nutrient conditions, making it easier to survive in nature and medical environments (Almasaudi, 2018). The death rate for people infected with *A. baumannii* is about 8-23% and in the intensive care unit 10-43% (Stefan-Mikić, 2017). *A. baumannii*-acquired pneumonia has been reported in places where rain occurs in different parts of the world, as well as the people who drink alcohol and suffer from chronic diseases (Almasaudi, 2018).

Pathogenicity

A. baumannii is an opportunistic pathogen that grows in different environments. Patients with immunosuppression are more likely to develop these bacteria even during treatment. These bacteria enter the body through soft tissues and can colonize many sites such as the respiratory tract, the central nervous system, the eye and the blood stream infection (Howard et al., 2012). *A. baumannii* is widespread in nature, and recently the infections caused by these bacteria have become a serious problem due to high drug resistance (Wong et al., 2017). Mortality rates from meningitis caused by *A. baumannii* after neuro surgery are about 70% (Mihu & Martinez, 2011), 50% of bacteremia and about 23-75% of pneumonia and intensive care unit (ICU) mortality is 54% (Ghajavand et al., 2015). Numerous studies have shown infection in different parts of the world, including Brazil, Korea and Argentina, often associated with hospital-acquired infections (Almasaudi, 2018). The pathogenicity of these

bacteria is due to their resistance to many antibiotics, including Cephalosporins, Penicillins, Fluoroquinolones and Carbapenems (Cho et al., 2018).

Virulence Factors

Genotypic and phenotypic analysis in *A. baumannii* determine various virulence factors responsible for pathogenesis. Relatively few virulence factors have been identified for these bacteria compared to other Gram-negative pathogens (McConnell et al., 2013).

Biofilm

A biofilm is a group of bacterial cells attached to living or nonliving surfaces (Singh et al., 2016). The biofilm is constructed in three-dimensional structures where the cells are connected together and encapsulated in an extracellular polymeric substance (EPS) matrix which include exopolysaccharides, nucleic acid, proteins and macromolecules (Barraud et al., 2015).

The biofilm consists of four stages: the bacterial adhesion to the surface, the formation of small colonies, the maturation and the separation stage (Gupta et al., 2016). The biofilm contributes in bacterial resistance against antibiotics and pathogenicity (Farshadzahed et al., 2018). It participated with 80% of the microbial infections of bacteria, including cystic fibrosis, otitis media, blood stream infections and urinary tract infections (Pour et al., 2011; Singh et al., 2016). *A. baumannii* has the ability to form a biofilm on non-living surfaces such as glass, polystyrene and polypropylene (Reena et al., 2017). The biofilm is an important virulence factor in *A. baumannii* and protects it from stress environmental conditions, so these isolates that produce a strong biofilm remain alive for long periods in that environment (Dekić et al., 2017). Bacterial cells communicate with each other through the Quorum-sensing system, which helps the bacteria to coordinate gene expression. It produces special signals called auto inducers which control various physiological processes, including the production of virulence factors and the development of antibiotic resistance (Subhadra et al., 2016). The formation of bacterial biofilm process makes it able to tolerate harsh environmental factors such as nutrient deficiencies, low pH and provides the necessary protection for bacterial populations from host defenses, which prolongs the duration of bacterial infection of the host (Sharma et al., 2014).

Outer Membrane Proteins

OmpA is one of the main proteins in the outer membrane of *A. baumannii*, with a molecular weight of 38 kDa (Badmasti et al., 2015). It is encoded by a gene called ompA, which plays an important role in the formation of biofilm for bacterial strains of *A. baumannii*. OmpA contributes in the resistance of some antibiotics such as Chloramphenicol, Aztreonam and Nalidixic acid as it works in cooperation with efflux pumps in streaming antibiotic out the cellular membrane (Smani et al., 2014). OmpA has an important role in adhesion on the epithelial cells and induces apoptosis by targeting mitochondria (Sato et al., 2017). OmpA regulates biological processes of the outer membrane of bacteria and has an effect in immunological defense mechanisms as it binds to the complement factor H and this inhibits the alternative complement pathway (Kim et al., 2016). Protein is also called Omp38, which is also considered as an important virulence factor for both *A. baumannii* and *K. pneumoniae*, which cause worsening of the infection with pneumonia in the experimental mice (Sánchez-Encinales et al., 2017).

Biofilm-associated Proteins (Bap)

A. baumannii has a large superficial protein consisting of 8,620 amino acids (Reena et al., 2017). Bap gene founded in most bacterial isolates and encoded for the Biofilm associated

with the biofilm-associated protein, a protein that spreads on the cell surface and plays an important role in adhesion to the host cell and non-living surfaces and participate in the development of the biofilm (Alejandro et al., 2018). The biofilm associated protein has an important effect on the formation of the biofilm in the Gram negative and positive bacteria. The bap gene is an accessory genome components. In *E. faecalis,* it is found in pathogenic islands, and *S. aureus* is present in transposons (Ubedo et al., 2003; Ploneczka-Janeczko et al., 2014). The expression of Bap protein is influenced by the concentration of iron element in the cultural medium as the expression is quadrupled at a low iron concentration (Azizi et al., 2016), and the concentration of iron has an effect in the early stages of the biofilm formation process (Eijkelkamp et al., 2011).

Capsule

The capsule of *A. baumannii* consists of long chains of polysaccharide, linked to the bacterial cell wall. Is an important virulence factor found in many pathogens such as *Streptococcus pneumonia, Neisseria meningitides, Haemophilus influenza* and *Klebsiella pneumonia* (Bansal et al., 2014). The presence of the capsule enhances the virulence of bacteria that cause multiple diseases such as pneumonia, meningitis, cystic fibrosis, tooth decay and periodontitis. The capsule plays a potential role in the adhesion of bacterial cells and protects them from dehydration conditions and phagocytosis process (Bansal et al., 2014). It also protects the bacteria from killing by complement, acts as a barrier against antibiotics and it stimulates the immune system for antibodies production that can be used for rapid diagnosis. The capsule prevents the entry and penetration of dyes that used in staining bacteria, therefore, cannot be dyed and uses the Negative Staining method to show and distinguish the capsule (Kandi, 2015).

Protease

Proteases are enzymes that hydrolyzed large protein molecules and break them down into small proteins. The enzymes break down the long protein chain by hydrolysis of the peptide through breaking bonds that bind the amino acids together with the protein-forming peptide chain. There are of two types of protease enzyme, either intracellular or extracellular (Singh et al., 2016). The production of the enzyme depends on the components of the medium such as the source of carbon and nitrogen, pH, temperature and incubation time (Khusro, 2016). King et al. (2013) revealed that protease is often involved in controlling on cell communication with each other. *A. baumannii* produces a serine protease in the medium it grows, and when it excreted in the lungs of infected patients causes cystic fibrosis and destroys the epithelial cells of the lungs, in other hands, when released in large quantities, necrosis in the affected regions (Parker et al., 2012).

Lipase

Enzymes break down the ester bond in fatty substances and hydrolyze triglycerides to form monoglycerides, diglycerides and free fatty acids.

Most of the bacterial lipase enzymes are excreted outside the cell. Values of pH affect its activity and stability and the enzyme loses its activity in *A. baumannii* when the pH is reduced from 6.5 to 4 in the external medium (Gururaj et al., 2016).

Adhesion

The process of bacterial adhering to the surfaces, including the target cell surfaces, is an important step and a basis for settlement and stability, then the growth of bacteria and injury occurred. In the case of instability of bacteria and non-adherence to the target surface, they are displaced and disposed of (Payam et al., 2018). The adhesion of bacteria in the tooth surface

caused infection and formation of the biofilm, thereby causing decay. Exopolymeric polymers, pili and flagella are also responsible for bacterial adhesion, forming a bridge between the bacterial cell and the external surface (Ishii et al., 2004).

Pili are classified according to the form or according to the function they performed. On this basis different types of pili can be observed, including:

Type I Pili: This type has the ability to induce the agglutination of erythrocytes contained mannose sugar, as well as the agglutination of red blood cells of guinea pigs is attributed to this type of pili (Duncan et al., 2005).

Type IV pili, which are extracellular appendages consisting of under single units of a protein called the major pillin, which is collected in a narrow spiral fiber with a diameter of 6-9 nanometers and a length of more than 2-5 micrometer, one or more of which proteins is called minor pillin. Pili are founded in Gram-negative and positive bacteria and are related to twitching motility, horizontal gene transfer, host cell adhesion and biofilm formation (Piepenbrink et al., 2016).

Gelatinase

Gelatinase is an enzyme included in a variety of proteolytic enzymes that have the ability to hydrolyze gelatin into amino acids, peptides, polypeptides and other components such as pheromones, collagen and fibrinogen (Balan et al., 2012). It hydrolases collagen in fat tissue of wound infections, hydrolases gelatin into its secondary components and contributes to the initiation of the inflammatory response (Al-Warid & Al-Thahab, 2014).

Efflux Pumps (EP)

Efflux pumps are transporters founded in bacteria, their function is protecting the bacterial cells from the harmful effect of organic chemicals, as well as being responsible for resistance *A. baumannii* toward different classes of antibiotics, involving aminoglycosides, Qinolones, B-Lactams, Carbapenems, Chloramphenicol and Macrolides by decreasing drug accumulation (Chopra & Roberts, 2001). The efflux pumps caused a multi drug play a strategic role in pathogenicity of bacteria. There are five groups of efflux pumps, including ATP binding cassette (ABC) family, resistance nodulation division (RND) super family, the multidrug and toxic compounds extrusion (MATE), the major facilitator superfamily (MFS) and the small multidrug resistance (SMR) family transporters. The resistance of *A. baumannii* to antimicrobial agents is due to these categories of efflux pumps. There are other types of efflux pumps for drug proton anti porters (Vila et al., 2007).

The main efflux pumps that participated in multidrug resistance belongs to two groups: first group of proton motive force dependent exporters and the second group of RND family, in addition to MFS and SMR families. In *A. baumannii*, the resistance of efflux pumps to Tetracycline and Minocycline is related to MFS family, while their resistance to Aminoglycosides, β-Lactams, Chloramphenicol, Erythromycin, Tetracycline and Ethidium bromide is belonging to RND family of efflux pumps (Wieczorek et al., 2008). The ABC family releases the antimicrobial by utilizing the proton motive force as the driving force for efflux (Poole, 2002). A MATE family of efflux pumps is associated with the resistance to Norfloxacin, Ofloxacin, Ciprofloxacin and Gentamycin (Vila et al., 2007). The mechanism of EP system is regulated by the presence of tetracycline. In the absence of tetracycline, the repressor protein stops the transcription process for structural genes, while in the presence of antibiotic, the process begins when the complex of tetracycline Mg^{+2} binds with repressor protein, converting the configuration of this protein and allowing transcription of the structural genes of the efflux pumps system (Kedracka-Krok et al., 2005). There are many genes encoding for an efflux proteins, some of which AdeM is represented as a member of the MATE family of efflux pumps and acted to release aminoglycosides, fluoroquinolones and

AdeG as a member of an RND family that associated with resistance to different groups of antibiotics, while AdeFGH efflux pumps, increased the synthesis and transport of AHL signals, that enhanced process of biofilm formation (Lee et al., 2011; He et al., 2015).

Quorum Sensing AHL

Quorum sensing is a bacterial cell- cell communication process which involves the production, detection and response to extracellular signal molecules called auto inducers (AIs). Many processes including sporulation, bioluminescence, biofilim formation, antibiotics resistance, competence and virulence factors secretion are controlled by Quorum-sensing system (Rutherford & Bassler, 2012). Nearly in all Gram-negative bacteria, there are four common characteristics of Quorum-sensing systems. First, the auto inducers in such systems are acyl-homoserine lactons (AHLs) or other molecules that are synthesized from S-adenosyl methionine (SAM), and they are able to freely diffusion through the membrane of bacteria. Second, auto inducers which bind with specific receptors which reside either in the cytoplasm or in the inner membrane of bacteria. Third, dozens to hundreds of genes, that promote a different biological processes, are typically altered by the system of Quorum- sensing. Fourth, in a process named auto induction, auto inducer-driven activation of quorum- sensing enhanced increased synthesis of the auto inducer, which established a feed forward loop that is proposed to underpin synchronous of gene expression in the bacterial population (Papenfort & Bassler, 2016).

The genes which are controlled on system of quorum sensing of *A. baumannii* include Las l, Las R, RhlR and RhlI that performed some activities responsible for gene expression of virulence factors such as swarming motility and formation of biofilm for *A. baumannii* by production of N-3-hydroxydodecanoyl-L-HSL 3 hydroxyl- C12-HSL (Clemmer et al., 2011), while the disturbance of abal gene, that release the AHSL molecules, leads to reduction in biofilm formation with 30-40% relative to these of the isogenic parental strains (Niu et al., 2008).

A study by Bhargava et al. (2015) showed that catalase and super oxide dismutase (SOD), which participated in the elimination of reactive oxygen species (ROS) are positively controlled by the quorum sensing system in *A. baumannii*).

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