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Review Article

An Emergence of Multidrug Resistant Nosocomial Pathogen- *Acinetobacter Baumannii*

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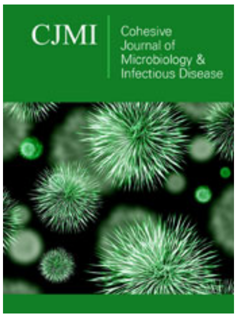
Abstract

Nosocomial infections have been recognized as one of the most critical problems in hospitalization, particularly in critical care units. As these infections prolong hospitalization, require extensive diagnostics and treatment, leads to high cost. The emergence of multidrug resistant pathogens has become a threat in critically ill, immuno-compromised patients due to the extensive use of antimicrobial. The most common types of nosocomial infections are pneumonia, urinary tract infections, meningitis, wound, soft tissue, surgical site infections and blood stream infections. These infections can be life threatening, capable of making of therapeutic options very difficult and limits the critical care settings. *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter spp are most common nosocomial pathogens. Among all nosocomial species Multidrug Resistance (MDR) *A. baumnaii* is most pathogenic microorganism. Here a review on *A. baumannii* in relation to nosocomial infection is carried out. This review includes risk factors, diagnosis modalities, pathogenesis, MDR properties, mechanism of MDR and treatment of *A. baumannii.*

ISSN: 2578-0190



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Submission: February 01, 2022
Published: April 21, 2022

Volume 5 - Issue 5

How to cite this article: Satani S and Ratna Trivedi*, An Emergence of Multidrug Resistant Nosocomial Pathogen- Acinetobacter Baumannii. Cohesive J Microbiol Infect Dis. 5(5). CJMI. 000623. 2022. DOI: 10.31031/CJMI.2022.05.000623

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Introduction

Acinetobacter baumannii is gram negative, coccobacillus which is ubiquitous in hospital environments. In 1911, Martinis Willem Bergerinck, a Dutch Microbiologist discovered a gram negative, oxidase negative, non-fermentative organism named Micrococcus calcoaceticus from soil on a calcium acetate mineral medium, later on known to be in genus Acinetobacter [1,2]. In 1968 Baumann et al. [3] published comprehensive study on different organisms comprising a single genus, and then the genus Acinetobacter was widely accepted [3]. In late 1970s, Acinetobacter began to be recognized as a nosocomial pathogen [4]. In 1986, Bouvet and Grimont used DNA-DNA hybridization methods to propose 4 new species of Acinetobacter, including *Acinetobacter baumannii*. According to Wong *Acinetobacter baumannii* has the ability to persist longer on dry surfaces under nutrient limiting conditions. They have observed that under such conditions the cell wall becomes thicker making it more persistence. This results into rapid transmission in hospitals and other natural environmental [5]. Certain outbreaks studies have revealed that few colonies of strains of *Acinetobacter baumannii* can remain viable for certain months to years on solid surfaces especially nosocomial surfaces [6]. *Acinetobacter baumannii* are known as "Iraqibacter" as it was found present in wound infections in soldiers returned from Iraq and Afghanistan. *A. baumannii* has gained attention in last few years because of its multidrug resistance properties which make its potential nosocomial pathogen [1]. Here a comprehensive review is prepared to summaries recent information and development related to *A. baumannii*. It has given special emphasized on infections, risk factors, pathogenesis, genetic aspects for virulence and mechanism of antibiotic resistance.

Prevalence of *A. Baumannii* in various diseases

As described earlier, *A. baumannii* infections has more prevalence in the patients who are hospitalized due to critical illness, who has serious underlying diseases, who were subjected to invasive and surgical procedures and who were treated with broad spectrum antibiotics for longer duration [7]. It is seen that most of *A. baumannii* infections involve fluid rich organ systems such as urinary tract, respiratory tract and peritoneal cavity. The most common infections are pneumonia, urinary tract infection, meningitis and trauma. *A. baumannii* can cause hospital acquired or community acquired pneumonia. In hospitalized acquired pneumonia *A. baumannii* can be easily isolated from upper respiratory tract but it becomes very difficult to differentiate between upper airway colonization from true pneumonia. Study has shown that A*. baumannii* is the second most common etiologic agent among all gram-negative bacteria [8]. Only in US surveillance studies have shown that 5 to 10 % of cases from ICUs have A. baumannii infection as patients have longer ICU stay [9]. Study has shown that hospital acquired pneumonia due to *A. baumannii* in ICU has a frequency of 3-5% with mortality rate of 30-75% [10-16]. Whereas community acquired pneumonia has higher prevalence in Australia and Asia especially in rainy season. Patients with alcohol abuse, smoking, diabetes and COPD are more prone to infection as compared to person with healthy habits. This is characterized by fulminant clinical condition and bloodstream infection. It has a mortality rate of 40% to 60% [10]. The major source of infection for community acquired pneumonia is throat carriage which can be spreaded up to 10% of community residents [11].

Bacteraemia is a condition where blood stream gets infection with bacteria. In majority of cases the origin of bacteraemia is not known. In US Surveillance studies carried out during 1995-2002, it was observed that out of total bacteraemia episodes, around 1.3% of all nosocomial bloodstream infections are because of A*. baumannii* and it was the 10th most common etiologic agent for bacteraemia. It was seen that in patients who are suffering from bacteraemia and hospitalized in ICU 34%-43% mortality rate whereas patients of outside ICU have only 16% mortality rate. It was also seen that, *A. baumannii* has initiated more ICU- acquired bloodstream infections as compared to non-ICU ward infections [11,12]. When *A. baumannii* gets associated with catheter of the patient then it will lead to urinary tract infection. However, the rate of infection is very less having rate of less than 2% of all ICU patients. In case of patients who are outside ICU, infection of *A. baumannii* is extremely rare [11,13]. Meningitis is a clinical condition where swelling is seen in protective membrane of brain and spinal cord. There are various causes for meningitis including injuries, cancer, certain drug and infection. Recent studies have shown that there is in increase in incidence of nosocomial meningitis due to *A. baumannii*. It contributes to 10% of total nosocomial infection caused by gram negative bacteria with high mortality rate of around 70% [14]. *A. baumannii* is also found present in the wound of military population. It was predominant in the wounds of militants returned from Afghanistan or Iraq. Around 32.5% cased were having *A. baumannii* infection with open tibial fractures. Not only in military population, but also in common population *A. baumannii* can be seen in wound or skin infection. However, the rate of infection is 2.1% only [7,15,16]. Few reports have also suggested that *A. baumannii* may cause endocarditis at some extent, especially in the conditions where prosthetic valves are involved. A single case report of bloody diarrhea was reported in an infant due to Acinetobacter haemolyticus strain. Some reports revealed that *Acinetobacter spp*. may cause keratitis, peritonitis, endopthalmitis related to eye or contact lens surgery [17]. Infection with Multidrug Resistance (MDR) is seen with the patients who were hospitalized for longer period of time especially in ICU. These patients were treated with third generation antibiotics for longer duration which make the microorganisms resistance against them. Studies have shown that the risk factors for MDR strains infection increases many folds in the patient who have undergone surgeries and exposed to infected patients. Treatment of such kind of infection is very difficult and leads to higher mortality rate.

Risk Factors for *A. Baumannii* Infections

Risk factors for the *A. baumannii* are varying depending on the type of infection. The below (Table 1) provides complete information about the risk factors associated with type of infection.

Table 1: Risk factors of infections caused by *A. baumannii.*

Type of Infection	Risk Factors
Hospital acquired	Mechanical ventilation
	Fecal colonization with A. baumannii
	ICU stay
	Indwelling devices
	Length of hospital stay
	Parenteral nutrition
	Previous infection
	Surgery
	Treatment with broad-spectrum antibiotics
	Wounds
Community acquired	Alcoholism
	Cigarette smoking
	Chronic lung disease
	Diabetes mellitus

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Multidrug resistant	Exposure to colonized or infected patients
	Invasive procedures
	Mechanical ventilation, particularly if prolonged
	Prolonged hospitalization (particularly in the ICU)
	Use of broad-spectrum antibiotics
	(eg, 3rd generation cephalosporin, carbapenems, fluoroquinolones)

Pathogenesis and virulence factors of *A. baumannii*

In recent years, several virulence factors responsible for the pathogenecity in *A. baumannii* have been identified using phenotypic and genomic approaches [18]. Major factors include porins, exopolysaccharide, lipopolysaccharides, phospholipase, outer membrane vesicles, protein secretion systems, penicillin binding proteins etc. Porins are made up of protein located on the surface of cell. They are known to play a variety of roles in maintaining cellular structural integrity, bacterial conjugation, antibiotic resistance and pore formation. In *A. baumannii*, Omp A is one the most abundant porins present in outer membrane. Omp A plays a major role in adherence and invasion. It also induced apoptosis by releasing cytochrome c and complement resistance [18,19]. Omp A also regulates biogenesis of outer membrane vesicles and facilitates surface motility and biofilm formation [20,21]. Other porins namely Omp33-36 are responsible for cytotoxicity action through water passage channel. One study it was also shown that Omp33-36 induces apoptosis in connective tissues and immune cells by modulating autophagy in human cells. Studies have shown that deletion of the Omp33-36 gene reduces adherence and invasion of human lung epithelial cells [22-25]. In addition to porins, capsular exopolysaccharides and lipoproteins can also contribute to pathogenecity. Study has shown that the K locus has a conserved gene cluster in the patients having *A. baumannii* which determine the production of capsular polysaccharides responsible for pathogenicity [26]. A study has revealed that antibiotics induce hyper-production of capsular polysaccharides, which increases resistance against host complement and increase its virulence [27]. In a study carried out by Liou et al. [28] has demonstrated that the presence of BFMS as virulence factor plays an important role in biofilm formation, adherence to eukaryotic cells, and resistance to human serum [28]. Lipo polysachharides, are biomolecules made up of lipid A moiety, an oligosaccharide core and O antigen. They are immuno-reactive molecules which plays vital role in virulence and induce production of TNF and IL-8 from macrophages [29]. Phospholipases are the enzymes responsible for phospholipids metabolism. These might be virulence factors in many bacteria. They are broadly classified into three classes such as A, C and D. Among the three, PL-C and PL-D act as virulence factors in *A. baumannii*. In a study carried out by Camarena, they have shown that inactivation of two genes associate with phopholiase namely A1S_0043 and A1S_2055 lead reduction in cytotoxicity [29]. Sthal in their study has revealed that the virulence in *A. baumannii* strain ATCC 19606 is mediated by concreted action of three PLDs [30]. In addition to LPS and porins, Outer Membrane Vesicles (OMVs) also play vital role on pathogenesis.

Table 2: Functions of virulence determinants possessed by *A. baumannii.*

Virulence Determinant	Function
Car O	Decrese Proinflammatory responses
Acel	Active efflux of Chlorhexidine
LPS	Adherence to host cells
T2SS	Export of Effector Proteins & Toxins
T6SS	Motility,Biofilm Formation and Horizontal gene transfer
Csu Pilus	Cell attachment, Biofilm Formation
BapAb	Biofilm Maturation
Omp	Apoptosis
PLD	Bacterial resistance in Human Serum
PLC	Toxicity to Epithelial cells
CpaA	Inactivation of factor XII
CPS	Antiphagocyic effect, Barrier against environmental stress
PNAG	Adhesion

These OMVs are composed of LPS, periplasmic proteins, phospholipids, DNA/RNA. These molecules are secreted by outer membranes of gram-negative bacteria having 20-200nm diameters. OMVs facilitate the pathogen to interact with the host cell without close contact. *A. baumannii* possess several OMVs belong to phospholipases and proteases, which are responsible for virulence [31,32]. Previous studies have revealed that the presence of outer membrane vesicles can act as an acellular vaccine in *A. baumannii* strains [33]. *A. baumannii* also known to have type II protein secretion system (T2SS) which is a multi-protein complex having similar

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structure as type IV pilli system [34]. T2SS is composed of pseudopilus, ATPase, inner-membrane assembly and outer-membrane dodameric complex. The whole assembly is responsible for export of effector proteins [34,35]. These proteins are responsible for virulence factor to invade into the host cells. T6SS is another protein system which was first identified in Pseudomonas aeuroginosa and Vibrio cholera. T6SS is composed of accessory factors and structural proteins and has a spike like structure to penetrate the target cell [35]. Type 5 secretory system of *A. baumannii* was found to mediate the biofilm formation and adherence to extracellular matrix which enhances the virulence efficiency [36]. Not only proteins but sometime siderosphores are also secreted from cells. Siderosphores are low molecular weight, iron chelating compound. It is mainly responsible for transportation of iron across the membranes. These siderosphores can modulate the host cellular pathways and add on virulence. Studies have confirmed that *A. baumannii* contains siderosphores as well as acinetobactin. Acinetobactin is a special class of siderosphore having catecholate and hydroxamate function groups, which can lead to impaired biosynthesis leading cell damage. In addition to all the above factors some other factors were also known to contribute to virulence characteristic. These factors as penicillin binding protein (PBP7/8), CipA, Sur A1, Tuf ect [36-51]. Below table summarize all major virulence determinant possessed by *A. baumannii* (Table 2).

Mechanism of antibiotic resistance

Antibiotic resistance properties of *A. baumannii* make it more fatal pathogen as compared to other common pathogens. These include various enzymes, structural modifications and genetic alterations. Among all the enzymes β-lactamase is a key enzyme which provides protection against penicillin's, cephamycin's, cephalosporins, and carbapenems. All these antibiotics are commonly known as β-lactum antibiotics as they contain β-lactum ring having four carbons. β-lactamase hydrolyse this structure and destroy all the antibiotics resulted into antibiotic resistance. Even it was observed that certain species of *A. baumannii* are able to resist carbapenems, a strong antibiotic used for MDR microorganisms. Beta metallo-beta lactamases and a class of D OXA of *A. baumannii* are known to destroy the drug and provide the resistance. *A. baumannii* was also known to alter the structure of porin and other proteins. Because of this modification antibiotics cannot enter into the cells and not able to destroy the pathogen. Study has shown that *A. baumannii* gain resistance against colistin though alteration of membrane permeability only. Efflux pump present in the pathogen is responsible for throwing out the antibiotics out of the cell. There are four type of efflux pumps in *A. baumannii* which are Major Facililator Superfamily (MFS), Resistance Nodulation Cell Division (RND), Small Multidrug Resistance (SMR) and Multidrug and Toxic Compound Extrusion (MATE). AdeABC gene was found responsible for this efflux activity. In addition to AdeABC gene, two other genes namely gyr A and par C were also found associate with antibiotic resistance. Gyr A is a unit of DNA gyrase and par C is a subunit of topoisomerase IV. Point mutation in these two genes alters the membrane binding efficiency which makes them resistance against quinolones. More details about resistance due to enzymes, gene and efflux are summarised in the Table 3; [1,39-75].

Table 3: Summary of various antibiotic resistance mechanisms in *A. baumannii.*

Enzyme Group	Description	Antibiotic Resistance/Action	References
Beta lactamase gene			
ADC	Chromosomally integrated cephalosporinase	Extended spectrum cephalosporins	[42]
OXA	A group of Carbapenem hydrolyzing oxicillinases	Carbapenem Resistance	[43]
IMP	Stronger Carbapenem hydrolyzing activity than OXA	Carbapenem Resistance	[44]
VM	Acquired Metallo-b-latamase	All b-lactams except monobactams	[45]
TEM	A broad-spectrum enzyme	Narrow spectrum cephalosporins, penicillins except temocilin	[42,45]
CTX-M	A broad-spectrum enzyme	Extended Spectrum B- lactamase	[46,47]
SHV	Plasmid mediated SHV-1 & atleast 23-variants	Extended spectrum cephalosporins, ampicillins	[48]
VEB-1	A broad-spectrum enzyme	Extended spectrum b-lactamase	[49]
PER-1 & 2	Plasmid or chromosomally encoded	Extended spectrum enzyme	[50,51]
AME Genes-Aminoglycoside modifying Enzymes			
aadB	Enzyme inactivation by adenylation	Kanamycin, Tobramycin and Gentamicin	[52-54]
aacC1	Enzyme inactivation by acetylation	Gentamicin, lividomicin, apramicin	[55]
aacC2	Enzyme inactivation by acetylation	A no. of aminoglycosides including those all above	[52]
aapH6	Enzyme inactivation by phosphorylation	Kanamycin, neomycin, gentamicin, paromomycin, amikacin and others	[55]

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aadA1	3'- hydroxyl position in streptomycin and 9'- hydroxyl in spectinomycin are modified	Streptomycin and spectinomycin	[52]
Genes Encoding-Efflux pumps			
Ade ABC	Chromosomally encoded, composed of Ade A, B, C Proteins	Aminoglycosides, quinolones, tetracyclin, and trimethoprim	[56]
Ade M	RND pumps	Flouroquinoles	[56]
Ade FGH	Resistance nodulation super family	Clindamycin resistance	[57]
Ade IJK	Resistance nodulation super family	Beta lactams, chloramphenicol, tetracycine, Resistance	[58]
Tet A & Tet B	Transposon mediated efflux pumps	Minocycline resistance	[58]
Cml A	Major facilitator super family	Chloramphenicol resistance	[59]
Cra A	Major facilitator super family	Chloramphenicol resistance	[60]
Amv A	Major facilitator super family	Erythromycin resistance	[61]
Aba F	Major facilitator super family	Fosomycin resitance	[62]
Abe M	Multidrug & Compound extrusion family	Norfloxacin, ciprofloxacin resistance	[63]
Abe S	Small multidrug resistance family	Norfloxacin, erythromycin, ciprofloxacin Resistance	[11]
Alteration of target sites			
gyr A	DNA Gyrase	Quinolones	[42,63,64,40]
par C	Point mutation at Ser 80	Quinolones	[40,42]
Arm A	16 S r RNA methylation	Aminoglycoside resistance	[65]
PBP2	Change in PBP	Imipenem	[66]
Tet M	Ribosomal Protection	Tetracycin resistance	[67]
DHFR	Dihydrofolate reductase	Trimethoprim resistance	[41]
Pmr C,Lpx A,Lpx C,Lpx D	Lipopolysaccharide	Colistin resistance	[68-70]
Permiability defects			
Car O	Porins	Carbapenem resistance	[71]
Omp 22-33	Porins	Induce apoptosis	[72]
Omp 33-36	Porins	Carbapenem resistance	[73]
Omp 37	Porins	Carbapenem resistance	[74]
Omp 43	Porins	Carbapenem resistance	[75]
Omp 44	Porins	Carbapenem resistance	[74]
Omp 47	Porins	Carbapenem resistance	[74]

Diagnostic modalities of *A. baumannii* infection

As mentioned earlier there are several sites of infection. Based on the site of infections various dianostic modalities are applied for detection of infection. In case of ventilator associated pneumonia chest radiography, sputum analysis, PCR, oxygen saturation, hemodynamic studies and acute phase reactants are determined. In cathater associated urinary tract infections, urine analysis and culture test are more preferred. In case of blood stream associated infection blood investigation, blood culture and ECG are preferred. In case of surgical site infections blood tests such as CRP, FBC, blood culture and swad culture are more preferred. Not limited to these tests, many other tests are also suggestive of *A. bauminnii* infection depending on the site of infection [10,13,17,18,76].

Treatment

After the discovery of antibiotics in the early 19thcentury, treatment of most of the infectious diseases was carried out using antibiotic. Excessive use of these antibiotics results into genesis of antibiotic resistance microorganisms which are not easily controlled by regular antibiotics. In case of Acinetobacter infections initially ampicillin, gentamicin and nalidixic acid, either as mono or combination were highly used, and it was effective also at that time. But after few years, strains of Acinetobacter became resistance against these antibiotics. Hence, infection disease society of America has considered this specie as red alert pathogen [11]. This high resistance capacity against broad spectrum antibiotic leads to discover the new molecules and re-evaluation of old molecules for efficacy. This is being achieved by applying knowledge of pharmacodynamic and pharmacokinetic [77]. Few such antibiotics are now developed which are still effective against *A. baumannii* infection. Carbapenems like imipenem and meropenem are effective to certain geological location where strains as still sensitive against these molecules. According to a study, latin America has 40% resistance, Europe & North America has 13%-15% resistance, Singapore has 50% re-

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sistance, India has 85 % resistance and Pakistan has 62%-100% resistance against these drugs. Hence these drugs are not suitable for these areas. For the other location they can be used. Sulbactam is a beta lactamase inhibitor which has intrinsic bactericidal activity against Acinetobacter, mediated by penicillin binding proteins. Like the carbapenems, susceptibility of these drugs on *A. baumannii* varies from various geographic locations. In Germany, France and Spain sulbactam is used either as a single agent or as combination with ampicillin or cefoperazone. Studies have shown that combination of sulbactam with penicillin is more effective against *A. baumannii* as compared to sulbactum alone [78,79]. Study have shown that meningitis, pneumonia, urinary tract infections caused by MDR *A. baumannii* can be treated with sulbactam with upto 67.5% healing rate [80]. Tigecycine, a derivative of minocycline is highly used for treating community acquired pneumonia, skin infections, bacterimia, UTIs by MDR *A. baumannii*. Jung has carried out a study where critical patient who was suffering from ventilator associated pneumonia caused by *A. baumannii* was treated with tigecycline. This drug was proven effective against MDR *A. baumnaii* [81,82]. In 2005 Sader has reported the very first case of tigecycline resistance. Studies have shown that strains from Isreal have 66% resistance, India has 57.6%, Greece has 74.2% and Saudi Arabia has 56% resistance [83-85]. Colistin, is another broad-spectrum antibiotic which distracts the cell membrane resulting in the loss of integrity causes cell death. It was highly used between 1960s-1970s, but due to neuro and nephrotoxicity it was discontinued [86]. Studies have shown that colistin has 11%-76% of nephrotoxicities [86]. 86 Colistin and/or polymixin E was last alternate for treating *A. baumannii* infections [87]. In addition to polymixin E other molecules like tigecycine, sulbactam and trimethoprin are also used in combination with colostin [88-91]. Resistance to colistin was first time reported in 1999, in the Czech Republic [88]. Daadmi has reported 1.8% resistance to colistin in Saudi Arebia, Maspi et al. [90] has reported 48.8% resistance in Iran [89,90] and Gupta et al. [91] have reported 53.1% resistance.

Conclusion

Acinetobacter spp. are among one of the most potential nosocomial microorganisms across the globe. It is known to acquire extended resistance to most antimicrobial agents rapidly. As they have potential to survive in hospital environments for a longer duration leading nosocomial outbreaks. In view of this, to control the spread of this organism, suitable safety programmed should be implemented by healthcare facilities. Research should also be focus on development of new antibiotics which have better efficacy and lower resistance. At present the best way to avoid spreading MDR *A. baumannii* infection is to maintain cleanliness of the hospital and use antibiotic as per prescription. Colistin can be used as a last alternate for treatment of *A. baumannii* infection. Selection of antibiotic for treatment should be selected wisely keeping the geographical location in mind.

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