American Journal of Medical and Biological Research, 2022, Vol. 10, No. 1, 1-8
Available online at http://pubs.sciepub.com/ajmbr/10/1/1
Published by Science and Education Publishing
DOI:10.12691/ajmbr-10-1-1

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

Satani S., Ratna Trivedi*

Department of Environment Science, Shree Ramakrishna Institute of Computer Education and Applied Science, M.T.B. College Campus, Athwalines, Surat – 395001, Gujarat, India
*Corresponding author: drratnatrivedi@gmail.com

Received February 12, 2022; Revised March 15, 2022; Accepted March 23, 2022

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 excessive 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 exceedingly 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.baumannii* is most pathogenic microorganism. Here a review on *A. Baumannii* in relation to nosocomial infection is conducted. This review includes risk factors, diagnosis modalities, pathogenesis, MDR properties, mechanism of MDR and treatment of *A. Baumannii*.

Keywords: *MDR, mechanism of resistance, nosocomial infection, risk factor*

Cite This Article: Satani S., and Ratna Trivedi, "An Emergence of Multidrug Resistant Nosocomial Pathogen - *Acinetobacter baumannii*." *American Journal of Medical and Biological Research*, vol. 10, no. 1 (2022): 1-8. doi: 10.12691/ajmbr-10-1-1.

1. Introduction

Acinetobacter baumannii is gram negative, coccobacillus which is ubiquitous in hospital environments. In 1911, Martinus Willem Beijerinck, 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*., 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 *et al.*, *Acinetobacter baumannii* can 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 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 summarise current 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.

2. 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 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%. [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 spread 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 conducted 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 particular 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, endophthalmitis related to eye or contact lens surgery. [17]

Infection with multidrug resistance (MDR) is seen with the patients who were hospitalized for longer period, 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 exceedingly difficult and leads to higher mortality rate.

3. Risk Factors for *A. baumannii* Infections

Risk factors for the *A. baumannii* are varying depending on the type of infection. The below table (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 stays 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
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 (e.g., 3rd-generation cephalosporin, carbapenems, fluoroquinolones)

4. Pathogenesis and Virulence Factors of *A. baumannii*

In recent years, several virulence factors responsible for the pathogenicity 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 significant 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 Omp 33-36 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 Omp 33-36 gene reduces adherence and invasion of human lung epithelial cells. [22-25] In addition to porins, capsular exopolysaccharides and lipoproteins can also contribute to pathogenicity. 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.*, 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] Lipopolysaccharides 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 function as virulence factors in *A. baumannii.* In a study conducted by Camarena *et al*. in 2010, they have shown that inactivation of two genes associate with phospholipase namely A1S_0043 and A1S_2055 lead reduction in cytotoxicity. [29] Sthal *et al*., 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. These OMVs are composed of LPS, periplasmic proteins, phospholipids, DNA/RNA. These molecules are secreted by outer membranes of gram-negative bacteria having 20-200 nm 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 function 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 structure as type IV pili system. [34] T2SS is composed of pseudo pilus, 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 aeruginosa* 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 siderophore are also secreted from cells. Siderophores are low molecular weight, iron chelating compound. It is 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, etc. [37,38] Below table summarize all major virulence determinant possessed by *A. baumannii*. (Table 2)

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

Virulence Determinant	Function
Car O	Decrease 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	Antiphagocytic effect, barrier against environmental stress
PNAG	Adhesion

5. 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, cephamycin, cephalosporins, and carbapenems. All these antibiotics are commonly known as β-lactam antibiotics as they contain β- lactam 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* can 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 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 facilitator 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. [1,39,40,41]

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 oxacillinases	Carbapenem Resistance	[43]
IMP	Stronger Carbapenem hydrolyzing activity than OXA	Carbapenem Resistance	[44]
VM	Acquired Metallo-b-lactamase	All b-lactams except monobactams	[45]
TEM	A broad-spectrum enzyme	Narrow spectrum cephalosporins, penicillin except temocillin	[45-42]
CTX-M	A broad-spectrum enzyme	Extended Spectrum B- lactamase	[46,47]
SHV	Plasmid mediated SHV-1 & at least 23-variants	Extended spectrum cephalosporins, ampicillins	[48]
VEB-1	A broad-spectrum enzyme	Extended spectrum b-lactamase	[4,49]
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	[52,53,54]
aacC1	Enzyme inactivation by acetylation	Gentamicin, lividomicin, apramycin	[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]
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, tetracycline and trimethoprim	[56]
Ade M	RND pumps	Fluoroquinolones	[56]
Ade FGH	Resistance nodulation super family	Clindamycin resistance	[57]
Ade IJK	Resistance nodulation super family	Beta lactams, chloramphenicol, tetracycline Resistance	[56]
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	Fosfomycin resistance	[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	[40,42,64]
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	Tetracycline resistance	[67]
DHFR	Dihydrofolate reductase	Trimethoprim resistance	[41]
Pmr C, Lpx A, Lpx C, Lpx D	Lipopolysaccharide	Colistin resistance	[68,69,70]
Permeability 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]

6. *A. baumannii* Infected Patient Management

As mentioned earlier there are several sites of infection. Based on the site of infections various diagnostic modalities are applied for detection of infection and patient managemenet. 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]

7. Treatment

After the discovery of antibiotics in the early 19th century, 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% resistance, 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 compare to sulbactam alone. [78,79] Study have shown that meningitis, pneumonia, urinary tract infections caused by MDR *A. baumannii* can be treated with sulbactam with up to 67.5% healing rate. [80] Tigecycline, a derivative of minocycline is universally used for treating community acquired pneumonia, skin infections, bacteraemia, UTIs by MDR *A. baumannii*. Jung *et al*., has conducted 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. baumannii*. [81,82] In 2005 Sader *et al*., has reported the very first case of tigecycline resistance. Studies have shown that strains from Israel have 66% resistance, India has 57.6%, Greece has 74.2% and Saudi Arabia has 56% resistance. [83,84,85] 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% nephrotoxicity. [86] Colistin and/or polymyxin E was last alternate for treating *A. baumannii* infections. [87] In addition to polymyxin E other molecules like tigecycline, sulbactam and trimethoprim is also used in combination with colistin. Resistance to colistin was first time reported in 1999, in the Czech Republic. [88] Daadmi *et al*., has reported 1.8% resistance to colistin in Saudi Arebia, Maspi *et al*., has reported 48.8% resistance in Iran [89,90] and Gupta *et al* have reported 53.1% resistance. [91]

8. 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. They have potential to survive in hospital environments for a longer duration and therefore can result in nosocomial outbreaks. In view of this, and to control the spread of this organism, suitable safety programmes/strategies should be implemented by healthcare facilities. Research should also be focused on the 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 and minimize antibiotic misuse/overuse. 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 and the local antibiotic susceptibility profiles.

References

[1] Alsan, M. & Klompas, M. Acinetobacter baumannii: An Emerging and Important Pathogen. *Journal of Clinical Outcomes and Managment.* 17, 363-369 (2010).

[2] Bonomo, R. A. *Pathogenesis of Acinetobacter spp* (Case Western Reserve University, 2010).

[3] Baumann, P., Doudoroff, M. & Stanier, R. Y. A Study of the Moraxellk Group II. Oxidative-negative Species (Genus *Acinetobacter*). *Journal of bacteriology* 95, 1520-1541 (1968).

[4] Fournier, P. E. *et al.* Comparative genomics of multidrug resistance in Acinetobacter baumannii. *PLoS genetics* 2, e7, (2006).

[5] Du, X. *et al.* Predictors of mortality in patients infected with carbapenem-resistant Acinetobacter baumannii: A systematic review and meta-analysis. *American journal of infection control* 47, 1140-1145, (2019).

[6] Yang, C. H., Su, P. W., Moi, S. H. & Chuang, L. Y. Biofilm Formation in Acinetobacter Baumannii: Genotype-Phenotype Correlation. *Molecules* 24, (2019).

[7] Trottier, V. *et al.* Outcomes of Acinetobacter baumannii infection in critically ill burned patients. *Journal of burn care & research: official publication of the American Burn Association* 28, 248-254, (2007).

[8] Howard, A., O'Donoghue, M., Feeney, A. & Sleator, R. D. Acinetobacter baumannii: an emerging opportunistic pathogen. *Virulence* 3, 243-250, (2012).

[9] Gaynes, R. & Edwards, J. R. Overview of Nosocomial Infections Caused by Gram-Negative *Bacilli*. *Healthcare Epidemiology* 41, 848-854 (2005).

[10] Doughari, H. J., Ndakidemi, P. A., Human, I. S. & Benade, S. The ecology, biology and pathogenesis of Acinetobacter spp.: an overview. *Microbes and environments* 26, 101-112, (2011).

[11] Peleg, A. Y., Seifert, H. & Paterson, D. L. Acinetobacter baumannii: Emergence of a Successful Pathogen. *Clinical microbiology reviews* 21, 538-582, (2008).

[12] Garnacho-Montero, J. *et al.* Optimum treatment strategies for carbapenem-resistant Acinetobacter baumannii bacteremia. *Expert review of anti-infective therapy* 13, 769-777, (2015).

[13] Wood, G. C., Hanes, S. D., Boucher, B. A., Croce, M. A. & Fabian, T. C. Tetracyclines for treating multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Intensive care medicine* 29, 2072-2076, doi:10.1007/s00134-003-1811-2 (2003).

[14] Basri, R. *et al.* Burden of Bacterial Meningitis: A Retrospective Review on Laboratory Parameters and Factors Associated With Death in Meningitis, Kelantan Malaysia. *Nagoya J. Med. Sci. 77. 59-68, 2015* 77, 59-68 (2015).

[15] Johnson, E. N., Burns, T. C., Hayda, R. A., Hospenthal, D. R. & Murray, C. K. Infectious complications of open type III tibial fractures among combat casualties. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 45, 409-415, (2007).

[16] Murray, C. K. *et al.* Bacteriology of war wounds at the time of injury. *Military medicine* 171, 826-829, (2006).

[17] Bergogne-Be´re´zin, E. & Towner, K. J. Acinetobacter spp. as Nosocomial Pathogens: Microbiological, Clinical, and Epidemiological Features. *Clinical Microbiology Reviews, Apr. 1996, p. 148-165* 9, 148-165 (1996).

[18] Antunes, L. C., Visca, P. & Towner, K. J. Acinetobacter baumannii: evolution of a global pathogen. *Pathogens and disease* 71, 292-301, (2014).

[19] Choi, C. H. *et al.* Outer membrane protein 38 of Acinetobacter baumannii localizes to the mitochondria and induces apoptosis of epithelial cells. *Cellular microbiology* 7, 1127-1138, (2005).

[20] Gaddy, J. A. *et al.* Role of acinetobactin-mediated iron acquisition functions in the interaction of Acinetobacter baumannii strain ATCC 19606T with human lung epithelial cells, Galleria mellonella caterpillars, and mice. *Infect Immun* 80, 1015-1024, (2012).

[21] Gaddy, J. A., Tomaras, A. P. & Actis, L. A. The Acinetobacter baumannii 19606 OmpA Protein Plays a Role in Biofilm Formation on Abiotic Surfaces and in the Interaction of This Pathogen with Eukaryotic Cells. *Infection and Immunity* 77, 3150-3160, (2009).

[22] Rumbo, C. *et al.* The Acinetobacter baumannii Omp33-36 porin is a virulence factor that induces apoptosis and modulates autophagy in human cells. *Infect Immun* 82, 4666-4680, (2014).

[23] Smani, Y., Dominguez-Herrera, J. & Pachon, J. Association of the outer membrane protein Omp33 with fitness and virulence of Acinetobacter baumannii. *The Journal of infectious diseases* 208, 1561-1570, doi:10.1093/infdis/jit386 (2013).

[24] Smani, Y., McConnell, M. J. & Pacho´n, J. Role of Fibronectin in the Adhesion of *Acinetobacter baumannii* to Host Cells. *PloS one* 7, e33073, (2012).

[25] Smani, Y. & Pachon, J. Loss of the OprD homologue protein in Acinetobacter baumannii: impact on carbapenem susceptibility. *Antimicrobial agents and chemotherapy* 57, 677, (2013).

[26] Kenyon, J. J. & Hall, R. M. Variation in the Complex Carbohydrate Biosynthesis Loci of *Acinetobacter baumannii* Genomes. *PloS one* 8, e62160, (2013).

[27] Geisinger, E. & Isberg, R. R. Antibiotic modulation of capsular exopolysaccharide and virulence in Acinetobacter baumannii. *PLoS pathogens* 11, e1004691, (2015).

[28] Liou, M. L. *et al.* The sensor kinase BfmS mediates virulence in Acinetobacter baumannii. *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi* 47, 275-281, (2014).

[29] Luke, N. R. *et al.* Identification and characterization of a glycosyltransferase involved in Acinetobacter baumannii lipopolysaccharide core biosynthesis. *Infect Immun* 78, 2017-2023, (2010).

[30] Stahl, J., Bergmann, H., Gottig, S., Ebersberger, I. & Averhoff, B. Acinetobacter baumannii Virulence Is Mediated by the Concerted Action of Three Phospholipases D. *PloS one* 10, e0138360, (2015).

[31] Kwon, S. O., Gho, Y. S., Lee, J. C. & Kim, S. I. Proteome analysis of outer membrane vesicles from a clinical Acinetobacter baumannii isolate. *FEMS microbiology letters* 297, 150-156, (2009).

[32] Jin, J. S. *et al.* Acinetobacter baumannii Secretes Cytotoxic Outer Membrane Protein A via Outer Membrane Vesicles. *PloS one* 6, e17022, (2011).

[33] Huang, W. *et al.* Immunization against multidrug-resistant Acinetobacter baumannii effectively protects mice in both pneumonia and sepsis models. *PloS one* 9, e100727, (2014).

[34] Korotkov, K. V., Sandkvist, M. & Hol, W. G. The type II secretion system: biogenesis, molecular architecture and mechanism. *Nature reviews. Microbiology* 10, 336-351, (2012).

[35] Repizo, G. D. *et al.* Differential Role of the T6SS in Acinetobacter baumannii Virulence. *PloS one* 10, e0138265, (2015).

[36] Bentancor, L. V., Camacho-Peiro, A., Bozkurt-Guzel, C., Pier, G. B. & Maira-Litran, T. Identification of Ata, a multifunctional trimeric autotransporter of Acinetobacter baumannii. *Journal of bacteriology* 194, 3950-3960, (2012).

[37] Koenigs, A., Zipfel, P. F. & Kraiczy, P. Translation Elongation Factor Tuf of Acinetobacter baumannii Is a Plasminogen-Binding Protein. *PloS one* 10, e0138398, (2015).

[38] Liu, C. *et al.* Distribution of virulence-associated genes and antimicrobial susceptibility in clinical Acinetobacter baumannii isolates. *Oncotarget* 9, 21663-21673 (2018).

[39] Ardebili, A., Lari, A. R., Beheshti, M. & Lari, E. R. Association between mutations in gyrA and parC genes of *Acinetobacter baumannii* clinical isolates and ciprofloxacin resistance. *Iranian Journal of Basic Medical Sciences* 18, 623-626 (2015).

[40] Drlica, K. & Zhao, X. DNA Gyrase, Topoisomerase IV, and the 4-Quinolones. *Microbiology and Molecular Biology Reviews* 61, 377-392 (1997).

[41] Mak, J. K., Kim, M. J., Pham, J., Tapsall, J. & White, P. A. Antibiotic resistance determinants in nosocomial strains of multidrug-resistant Acinetobacter baumannii. *The Journal of antimicrobial chemotherapy* 63, 47-54, (2009).

[42] Hujer, K. M. *et al.* Analysis of antibiotic resistance genes in multidrug-resistant Acinetobacter sp. isolates from military and civilian patients treated at the Walter Reed Army Medical Center. *Antimicrobial agents and chemotherapy* 50, 4114-4123, (2006).

[43] Koh, T. H., Sng, L. H., Wang, G. C., Hsu, L. Y. & Zhao, Y. IMP-4 and OXA beta-lactamases in Acinetobacter baumannii from Singapore. *The Journal of antimicrobial chemotherapy* 59, 627-632, (2007).

[44] Landman, D. *et al.* Citywide Clonal Outbreak of Multiresistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Brooklyn, NY. *ARCH INTERN MED* 162, 1515-1520 (2002).

[45] Docquier, J. D. *et al.* On functional and structural heterogeneity of VIM-type metallo-beta-lactamases. *The Journal of antimicrobial chemotherapy* 51, 257-266, (2003).

[46] Nagano, N., Nagano, Y., Cordevant, C., Shibata, N. & Arakawa, Y. Nosocomial transmission of CTX-M-2 beta-lactamase-producing Acinetobacter baumannii in a neurosurgery ward. *Journal of clinical microbiology* 42, 3978-3984, (2004).

[47] Potron, A., Munoz-Price, L. S., Nordmann, P., Cleary, T. & Poirel, L. Genetic features of CTX-M-15-producing Acinetobacter baumannii from Haiti. *Antimicrobial agents and chemotherapy* 55, 5946-5948, (2011).

[48] LS, T. & RA, B. SHV-type beta-lactamases. *Current Pharmaceutical Design* 5, 847-864 (1999).

[49] Naas, T. *et al.* VEB-1 Extended-Spectrum β-lactamase–producing *Acinetobacter baumannii*, France. *Emerging Infectious Diseases* 12, 1214-1222, (2006).

[50] Jeon, B. C. *et al.* Investigation of a nosocomial outbreak of imipenem-resistant Acinetobacter baumannii producing the OXA-23 beta-lactamase in korea. *Journal of clinical microbiology* 43, 2241-2245, (2005).

[51] Pasteran, F. *et al.* Emergence of PER-2 and VEB-1a in Acinetobacter baumannii Strains in the Americas. *Antimicrobial agents and chemotherapy* 50, 3222-3224, (2006).

[52] Shaw, K. J., Rather, P. N., Hare, R. S. & Miller, G. H. Molecular Genetics of Aminoglycoside Resistance Genes and Familial Relationships of the Aminoglycoside-Modifying Enzymes. *Microbiological Reviews* 57, 138-163 (1993).

[53] Nemec, A., Dolzani, L., Brisse, S., van den Broek, P. & Dijkshoorn, L. Diversity of aminoglycoside-resistance genes and their association with class 1 integrons among strains of pan-European Acinetobacter baumannii clones. *Journal of medical microbiology* 53, 1233-1240, (2004).

[54] Jones, L. A., McIver, C. J., Kim, M. J., Rawlinson, W. D. & White, P. A. The aadB gene cassette is associated with blaSHV genes in Klebsiella species producing extended-spectrum beta-lactamases. *Antimicrobial agents and chemotherapy* 49, 794-797, (2005).

[55] N.Rather, P. Origins of the aminoglycoside modifying enzymes. *Drug Resistance Updates* 1, 285-291 (1998).

[56] Marchand, I., Damier-Piolle, L., Courvalin, P. & Lambert, T. Expression of the RND-type efflux pump AdeABC in Acinetobacter baumannii is regulated by the AdeRS two-component system. *Antimicrobial agents and chemotherapy* 48, 3298-3304, (2004).

[57] Coyne, S., Rosenfeld, N., Lambert, T., Courvalin, P. & Perichon, B. Overexpression of resistance-nodulation-cell division pump AdeFGH confers multidrug resistance in Acinetobacter baumannii. *Antimicrobial agents and chemotherapy* 54, 4389-4393, (2010).

[58] Vilacoba, E. *et al.* Emergence and Spread of Plasmid-Borne tet(B)::ISCR2 in Minocycline-Resistant Acinetobacter baumannii Isolates. *Antimicrobial agents and chemotherapy* 57, 651-654 (2013).

[59] Coyne, S., Courvalin, P. & Perichon, B. Efflux-mediated antibiotic resistance in Acinetobacter spp. *Antimicrobial agents and chemotherapy* 55, 947-953, (2011).

[60] Roca, I. *et al.* CraA, a major facilitator superfamily efflux pump associated with chloramphenicol resistance in Acinetobacter baumannii. *Antimicrobial agents and chemotherapy* 53, 4013-4014, (2009).

[61] Rajamohan, G., Srinivasan, V. B. & Gebreyes, W. A. Molecular and functional characterization of a novel efflux pump, AmvA, mediating antimicrobial and disinfectant resistance in Acinetobacter baumannii. *The Journal of antimicrobial chemotherapy* 65, 1919-1925, (2010).

[62] Sharma, A., Sharma, R., Bhattacharyya, T., Bhando, T. & Pathania, R. Fosfomycin resistance in Acinetobacter baumannii is mediated by efflux through a major facilitator superfamily (MFS) transporter-AbaF. *The Journal of antimicrobial chemotherapy* 72, 68-74, (2017).

[63] Su, X. Z., Chen, J., Mizushima, T., Kuroda, T. & Tsuchiya, T. AbeM, an H+-coupled Acinetobacter baumannii multidrug efflux pump belonging to the MATE family of transporters. *Antimicrobial agents and chemotherapy* 49, 4362-4364, (2005).

[64] Barnard, F. M. & Maxwell, A. Interaction between DNA gyrase and quinolones: effects of alanine mutations at GyrA subunit residues Ser(83) and Asp(87). *Antimicrobial agents and chemotherapy* 45, 1994-2000, (2001).

[65] Yu, Y. S., Zhou, H., Yang, Q., Chen, Y. G. & Li, L. J. Widespread occurrence of aminoglycoside resistance due to ArmA methylase in imipenem-resistant Acinetobacter baumannii isolates in China. *The Journal of antimicrobial chemotherapy* 60, 454-455, doi:10.1093/jac/dkm208 (2007).

[66] Cayo, R. *et al.* Analysis of genes encoding penicillin-binding proteins in clinical isolates of Acinetobacter baumannii. *Antimicrobial agents and chemotherapy* 55, 5907-5913, (2011).

[67] Ribera, A., Ruiz, J. & Vila, J. Presence of the Tet M determinant in a clinical isolate of Acinetobacter baumannii. *Antimicrobial agents and chemotherapy* 47, 2310-2312, (2003).

[68] Adams, M. D. *et al.* Resistance to colistin in Acinetobacter baumannii associated with mutations in the PmrAB two-component system. *Antimicrobial agents and chemotherapy* 53, 3628-3634, (2009).

[69] Moffatt, J. H. *et al.* Colistin resistance in Acinetobacter baumannii is mediated by complete loss of lipopolysaccharide production. *Antimicrobial agents and chemotherapy* 54, 4971-4977, (2010).

[70] Arroyo, L. A. *et al.* The pmrCAB operon mediates polymyxin resistance in Acinetobacter baumannii ATCC 17978 and clinical isolates through phosphoethanolamine modification of lipid A. *Antimicrobial agents and chemotherapy* 55, 3743-3751, (2011).

[71] Mussi, M. A., Relling, V. M., Limansky, A. S. & Viale, A. M. CarO, an Acinetobacter baumannii outer membrane protein involved in carbapenem resistance, is essential for L-ornithine uptake. *FEBS letters* 581, 5573-5578, (2007).

[72] Bou, G. n., M., G. C., Dom, A. & Carmen Quereda. Characterization of a Nosocomial Outbreak Caused by a Multiresistant Acinetobacter baumannii Strain with a Carbapenem-Hydrolyzing Enzyme: High-Level Carbapenem Resistance in A. baumannii Is Not Due Solely to the Presence of β-Lactamases. *Journal of clinical microbiology* 38, 3299-3505 (2000).

[73] del Mar Tomas, M. *et al.* Cloning and functional analysis of the gene encoding the 33- to 36-kilodalton outer membrane protein associated with carbapenem resistance in Acinetobacter baumannii. *Antimicrobial agents and chemotherapy* 49, 5172-5175, (2005).

[74] Quale, J., Bratu, S., Landman, D. & Heddurshetti, R. Molecular Epidemiology and Mechanisms of Carbapenem Resistance in Acinetobacter baumannii Endemic in New York City. *Clinical Infectious Diseases* 37, 214-220 (2003).

[75] Dupont, M., Pagès, J.-M., Lafitte, D., Siroy, A. & Bollet, C. Identification of an OprD homologue in Acinetobacter baumannii. *Journal of Proteome Research* 4, 2386-2390 (2005).

[76] Vijayakumar, S., Biswas, I. & Veeraraghavan, B. Accurate identification of clinically important Acinetobacter spp.: an update. *Future Science OA* 5, 1-18 (2019).

[77] Khan, M. F. & Aziz, F. Antibiotic Resistance: Preparation for Post-Antibiotic Era. *EC Microbiology* 3, 409-411 (2016).

[78] Urban, C. *et al.* Effect of sulbactam on infections caused by imipenem-resistant Acinetobacter calcoaceticus biotype anitratus. 167, 448-452 (1993).

[79] Corbella, X. *et al.* Efficacy of sulbactam alone and in combination with ampicillin in nosocomial infections caused by multiresistant Acinetobacter baumannii. *Journal of Antimicrobiology and Chemotherapy* 42, 793-802 (1998).

[80] Dinc, G. *et al.* Antimicrobial efficacy of doripenem and its combinations with sulbactam, amikacin, colistin, tigecycline in experimental sepsis of carbapenem-resistant Acinetobacter baumannii. *New Microbiologica* 38, 67-73 (2015).

[81] Paudel, R. & Nepal, H. P. Tigecycline: pharmacological concerns and resistance. *International Journal of Basic & Clinical Pharmacology* 9, 1296, (2020).

[82] Cunha, B. A., Mcdermott, B. & Nausheen, S. Single Daily High-Dose Tigecycline Therapy of a Multidrug-Resistant (MDR) Klebsiella pneumoniae and Enterobacter aerogenes Nosocomial Urinary Tract Infection. *Journal of Chemotherapy* 19, 753-754 (2007).

[83] Navon-Venezia, S., Leavitt, A. & Carmeli, Y. High tigecycline resistance in multidrug-resistant Acinetobacter baumannii. *Journal of Antimicrobiology and Chemotherapy* 59, 772-724 (2007).

[84] Al-Agamy, M. H. *et al.* First Detection of GES-5 Carbapenemase-Producing Acinetobacter baumannii Isolate. *Microbial Drug Resistance* 23, 556-562 (2017).

[85] Tsioutis, C. *et al.* Clinical epidemiology, treatment and prognostic factors of extensively drug-resistant Acinetobacter baumannii ventilator-associated pneumonia in critically ill patients. *International Journal of Antimicrobial Agents* 48, 492-497 (2016).

[86] Koksal, I., Kaya, S., Gencalioglu, E. & Yilmaz, G. Evaluation of Risk Factors for Intravenous Colistin Use-related Nephrotoxicity. *Oman Medical Journal* 31, 318-321, (2016).

[87] Ozkan, G. *et al.* How does colistin-induced nephropathy develop and can it be treated? *Antimicrobial agents and chemotherapy* 57, 3463-3469 (2013).

[88] Hejnar, P., Kolár, M. & Hájek, V. Characteristics of Acinetobacter strains (phenotype classification, antibiotic susceptibility and production of beta-lactamases) isolated from haemocultures from patients at the Teaching Hospital in Olomouc. *Acta University Palacki Olomuc Faculty of Medicine* 142, 73-77 (1999).

[89] Baadani, A. M., Thawadi, S. I., El-Khizzi, N. A. & Omrani, A. S. Prevalence of colistin and tigecycline resistance in Acinetobacter baumannii clinical isolates from 2 hospitals in Riyadh Region over a 2-year period. *Suadi Medicine Journal* 34, 248-253 (2013).

[90] Maspi, H., Hosseini, H. M., Amin, M. & Fooladi, A. A. I. High prevalence of extensively drug-resistant and metallo beta-lactamase-producing clinical Acinetobacter baumannii in Iran. *Microbiology and Pathology* 98, 155-159 (2016).

[91] Gupta, M. *et al*. Colistin-resistant Acinetobacter baumannii ventilator-associated pneumonia in a tertiary care hospital: an evolving threat. *Journal of Hospital Infection* 94, 72-73 (2016).