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Review Article

Antimicrobial Resistance Mechanisms in *Acinetobacter baumannii* in Recent Decade

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Abstract

In the last decade, *Acenitobacter baumannii* has become the center of attention for microbiologists. Even amongst the ESKAPE pathogens, whose innate ability to develop resistance to various major antibiotic classes poses a threat to the nature of the modern treatment, *A.baumannii* is often one of the first species to develop resistance to new drugs. Because of its ability to adapt even to those inhospitable environments which would otherwise be fatal to other pathogens, *A.baumannii* has emerged as one of the most dangerous pathogens known to humankind and surely worthy of every bit of consideration it is getting. To coop up with the strains of the surrounding, *A.baumannii* exhibits a different variety of mechanisms of resistance that helps the bacteria in its survival. With the help of genetic studies and loads of experiments, we have finally learned a great deal about the mechanisms behind *Aceintobacter Baumannii* tremendous ability to develop immunity against antibiotics. However, against *A.baumannii* multiple drug regimens are used which aid each other in killing the bacteria one way or the other. The field of genetics has helped the most in identifying the various mechanisms of resistance and of course, this knowledge will help us to discover new ways of treatment that are more efficient and beneficial in our battle against the resistant strains. The optimal treatment for the MDR has yet to be established. New data is being collected every day and this clinical data is necessary for the guidance of clinicians towards the right path for choosing the best drug therapy. The discovery of therapies along with controlled trials is essential to face this problem.

Keywords: *Acinetobacter Baumannii*, Beta lactamases, Efflux pumps.

INTRODUCTION

For an organism to be successful in parasitism, the infectious agent must have a proper portal of entry, must reach the site of selection for its multiplication and survival, must find an appropriate host, and last but not least must survive in the environment a new host is found. *Acinetobacter Baumannii* is surely one of those organisms with various resistance mechanisms against many of the known antibiotics. Only a few antibiotics are known which are effective in the treatment of the disease caused by this pathogen. This bacterium has developed various mechanisms through which the antibiotics are rendered useless. Acinetobacter has the capacity to survive in dry and inhospitable environments. It can spread from close contact with an infected person or by exposure to environments contaminated with the pathogen. Major infections that these bacteria cause are ventilator-associated pneumonia, blood infections, urinary tract infections, skin infections, and endocarditis.

It becomes a source of infection because it forms various colonies on medical instruments, skin, and eatables too. It affects the immuno compromised people and has become an increasingly important pathogen as a hospital derived infection (nosocomial). Currently, there are more than 50 Acinetobacter species designated out of which only a few are opportunistic pathogens. The name 'Acinetobacter' is derived from a Latin word that means 'motionless'. However, A. baumannii and A. nosocomialis strains are capable of two independent forms of bacterial locomotion i.e.

surface-associated motility and twitching motility. They lack cilia or flagella with which most bacteria use for locomotion. This bacterium is strictly aerobic, non-fermentative, and catalase-positive and frequently occurs in pairs. The most common site for Acinetobacter infection is the respiratory system. The main reasons for this association are its transient colonization on pharyngeal colonization and also the high frequency of tracheotomy colonizations.

Structure

A. baumannii is a gram-negative cocco bacillus that belongs to the family Moraxellaceae. Because of the striking resemblance of this pathogen with other pathogens of this family, it is somewhat difficult to distinguish it from the other members of the family. All members of the family are soil-borne except A.baumannii which is found mostly in hospital environments (nosocomial). The most important test in distinguishing this genius from the other members is the oxidase test [1]. Unlike other members, A. baumannii is oxidase positive. This bacterium shows locomotion either with the help of pili or by secreting exopolysaccharide which creates a film of sugar behind the bacteria as it moves from one place to another.

A. baumannii has been reported to show its effectiveness in those patients who were immuno compromised in some way like if they are suffering from HIV infection. Studies showed a high mortality rate in patients suffering from both HIV and AB pneumonia [2]. Since the organism has such a variety of mechanisms of developing resistance, it has become the leading challenge for the health community. According to WHO, the multidrug resistant pathogens are all listed in a group called ESKAPE which comprises of Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, *Acinetobacter Baumannii*, Pseudomona aeruginosa, and Enterobacter cloacae. These organisms showed tremendous resistance under antibiotic pressure. Seeing the potential of A.baumannii, WHO decided to put this organism in the ESKAPE group [3]. In this review, we shall give an insight into different antimicrobial resistance mechanisms shown by A.baumannii and how the antibiotics are rendered useless. It is very fatal if the patient does not receive aggressive treatment. Different strains have different mortality rate, in particular, recent clinical isolates such as AB5075 display the potential for fatal infections and large-scale outbreaks.

Various Mechanisms of Resistance in Acenitobacter Baumannii

1. Modification of LOS

The survival of a species depends upon how well it interacts with the surrounding environment. If the environment is hostile, the pathogen will experience difficulty in its application spread and survival. A.baumannii responds well to the changes in the environment and quickly adapts for its survival. On its surface, the bacteria have glycoconjugates through which they interact with the environment. A. baumannii has endotoxin in its outer membrane namely LOS, which is similar to LPS found in other Gram-Negative organisms but it contains fewer sugar molecules. Lipid A holds the endotoxin in its place. Colistin is a historic antibiotic that was used against this bacterium [4]. Colistin combined with rifampicin was used to treat carbapenem-resistant species [5]. This endotoxin is capable of causing lethal shock in the host.

However, A.baumannii started developing resistance against this via making changes in lipid a structure which decreases the binding of colistin with the bacterium. Several genetic studies showed mutations in pmrAB operon in clinically isolated resistant bacterium [6]. These mutations lead to the addition of phospho-ethanolamine in lipid a does not let the drug bind. Another study suggested that instead of modifying the lipid a molecule, complete loss of lipid A can be the cause of resistance. Mutations in the genome of the bacterium were the reason for this loss [7]. Later with the help of genetic studies, we found out that mutation in the first three genes in the production of lipid A namely LpxA, LpxC, and LpxD led to the resistance [8]. Later it was discovered that when LpxC inhibitors were given, the host showed a little bit of immunity against the bacteria. The bacteria were unable to cause sepsis in the host and protected the host from infection which would otherwise be fatal.

Another mechanism suggested in lipid a modification suggested that there was the addition of galactosamine with phosphoethanolamine on lipid A structure. These changes were present only in the clinical isolates from patients who had the resistant strains of this bacterium [9]. These modifications not only allow the bacterium to develop resistance against colistin but also against other drug classes as well particularly carbapenam [10]. The virulence of the bacteria is directly proportional to the shedding of LPS. The more this bacterium sheds lipopolysaccharide, the more it becomes virulent. Mutant strains which were deficient of capsular polysaccharides showed less intrinsic resistance to different classes of antibiotic.

2. Efflux pumps

This is one of the key mechanisms of antibiotic resistance in pathogens. Drugs are actively taken up by the pathogen. These drugs prove to be fatal for the organisms by accumulating inside the body of the pathogen to toxic levels and ultimately destroying them from the inside. Some bacteria defend themselves against this type of drug by developing resistance through the mechanism of efflux pumps. These efflux pumps require energy to pump the antibiotics out of the organism which would otherwise cause their death. By constantly secreting antibiotics out of the system,

bacteria that show this mechanism of resistance require elevated levels of the drug that are required to kill them or put a stop to their growth. Show their therapeutic areas of the drugs which once were effective and now rendered useless [11, 12].

A.baumannii is one of those bacteria that demonstrate resistance using the mechanism of efflux pumps. Studies show that when patients suffering from A.baumannii were given carbapenems, the clinical isolates of the pathogen showed an increase in the number of efflux pumps [13]. AdeABC efflux system was the system discovered in A.baumannii by using cryo-electron microscopy [14]. It was discovered that the energy required to drive this pump into an acting state comes from the influx of protons. This influx coupled with the efflux of the drug molecules results in resistance against the antibiotics.

Resistance through the efflux system develops as an acquired characteristic in response to antibiotic pressure. Several mutations were discovered genes encoding the pumps in the outer wall of the bacterium but the most commonly reported was the mutation in the AdeR-AdeS regulators [15]. This is one of those mechanisms demonstrated by A.baumannii which made it unique in the world of multi-drug resistant bacteria [16]. The multidrug transporter in this pathogen is AdeB [17] which takes molecules from cytoplasm and secrete them outside with the help of AdeA and AdeC [18]. The AdeABC system of proteins comes under the family named RND transporters. These transporters consist of periplasmic fusion membrane proteins (MFPs) and outer membrane factors (OMFs). AdeC and AdeA serve as MFPs and OMPs. The proper working of RND transporters remains unclear. In a study, genes encoding the transporters were destroyed and then the culture was incorporated with a plasmid encoding the genes were introduced. The antibiotic susceptibility was higher in the culture as compared to the culture obtained from patients having the same resistant strains [19]. This means that there are other factors as well which determine the impact of efflux systems in the bacterial strains.

AdeABC is a tightly regular system. There is vast clinical data that points out that the mutations in the genes encoding this system are common in MDR strains of different bacteria20. AdeABC has a vast variety of substrates and provides resistance against many of the different classes including β-lactams, fluoroquinolones, tetracyclines-tigecycline, macrolides [21], etc. AdeFGH and AdeIJK systems are also there but they are not as important as AdeABC. AdeIJK Was reported to show some intrinsic resistance mechanisms similar to AdeABC and antifolates and fusidic acid as well.

3. AbaR Pathogenic islands

A very serious epidemiological and therapeutic problem that has become a global concern these days is a hospital-acquired infection caused by multidrug-resistant (MDR) strains of *Acinetobacter Baumannii*. These complications are being really fatal for hospitalized patients so extensive studies are needed to find the causes, effects, and remedies for this problem. Many international lineages have been seen to show association to resistance to several antibiotics, notably with European (EU) clones I and II [22, 23].

There are many mechanisms through which A.baumannii has shown to be demonstrating resistance to many antibiotics and several therapies. According to recent studies, bacteria were noticed to be possessing horizontal genes present in clusters providing it striking combating power against many antibiotics and heavy metals hence the emerging resistance causing nosocomial infections. These clusters were found to be integrated into specific regions of ATPase genes [24, 25].

Five open reading frames were observed to comprise the backbone structure of AbaR and these open reading frames integrated the transpositional modules that were orf1, tniA, tniB, orf2, and orf3. Along with this universal stress protein (uspA) and sulfate permease (sul) strains encoded by two other genes were also found to be part of the overall composition. Later on, the idea arose that AbaR emerged from the ancestral transposon suggested being related to Tn7. Because it was observed through bioinformatics analysis that three open reading frames which were encoded by a transposition module showed imitations to Tn7's transposition associated proteins [25, 26].

About nine genomic resistant islands (A. baumannii resistance islands [AbaRs]) have been observed. Out of these nine, eight were discovered in strains of EU clone I. These are AbaR1, AbaR3, AbaR5, AbaR6, AbaR7, AbaR8, AbaR9, and AbaR [10, 27-32]. In the exception of AbaR6 and AbaR7, all of these AbaRs have a common structure demonstrated by a 16, 3-kb backbone transposon transversed by a compound transposon. This transposon consisted of copies of Tn6018 attached to a variable resistance region [31]. AbaRs from two EU clones were identified and constituted a transposon related to Tn602131. These findings clearly suggested that resistance associated with genomic islands clearly involved two main clones of *Acinetobacter Baumannii*.

4. Biofilm

As mentioned earlier the survival of an always-on depends upon its interaction with the environment. One of the most important factors that play a role in the survival of A.baumannii is the

formation of biofilm [33]. A biofilm comprises a community of microorganisms that are attached to surfaces like polystyrene and glass as well as biotic surfaces such as epithelial cells and fungal filaments. The life of the microorganisms living in a biofilm depends upon the surface on which they are attached [34]. Biofilm not increases the survival rate of the organisms under harsh environments but also contributes to several mechanisms of transmissibility, resistance, etc [35]. So it won't be an overstatement that biofilm is the reason behind the success of the survival of many organisms. Among many other virulence factors, biofilm stands out as one of the most important ones. Bacteria can survive rapid changes in the environment.

There is a phenomenon called 'quorum sensing' which plays a vital role in the development of biofilm. This quorum sensing system plays its role by conducting signals with help of molecules called autoinducers. Autoinducers are signaling molecules that conduct the important process of communication between the residents in the biofilm [36]. It causes the expression of some genes which mediate the development of biofilm. QS Maintains the population density in the biofilm [25]. It acts on the signal trans-regulatory proteins [37] that increase the expression of some genes which are responsible for the maintenance of biofilm. The signaling factor used by QS is N-acyl-homoserine lactones or AHL genes [38].

The use of hydrophilic material in medical instruments in hospitals is another source to reduce the spread of the pathogen. The attachment of the biofilm is mediated by Cus E and CusS chaperones. These chaperones make changes in the structure of the pili in such a way that they make the tip hydrophobic [39] which helps the biofilm to attach to different surfaces for a longer duration of time. After observing under electron microscopy, it was revealed that the biofilm was containing exopolysaccharide and pili as part of the several layers of cellular aggregations found in biofilm [40]. The interaction with biotic surfaces does not require regulation from the Cus S and CusE [41].

5. Beta-lactamases

All penicillins are made up of 6-aminopenicillanic acid and contain a beta-lactam ring structure. This beta-lactam ring structure is vital for the antibacterial activity of antibiotics. Other major drug classes that comprise beta-lactam rings in their structure are cephalosporins, carbapenems, carbacephem, and monobactams. To kill bacteria, these antibiotics will halt the synthesis of cell walls in the bacterial organism. The first known beta-lactam antibiotic was discovered in 1928 by a Scottish scientist named Alexander Fleming [42].

The discovery of penicillin was a revolutionary step in the field of microbiology. This step is still a source of much fruitful advancement for microbiologists. However, as time passed, the bacteria also developed resistance against these types of antibiotics through various mechanisms like introducing modifications in the binding proteins [43], or like in some gram-negative rods changing the porin structures [44] in the outer cell wall or producing enzymes called beta-lactamases that would destroy the structure of antibiotics through the help of enzymatic hydrolysis of the beta-lactam ring [45]. Several mechanisms are reported for the resistance against beta-lactams by A. baumannii but the most prevalent one is the hydrolysis of the beta-lactam ring.

Carbapenems get inside the bacteria through special protein gateways called carbapenem associated outer membrane proteins [46]. After their entry, they cause acetylation of the penicillin-binding proteins [47]. Penicillin-binding proteins play their role by maintaining the integrity of cell wall composition. Their acetylation by carbapenems disrupts the integrity of the bacterial cell wall making them more and more susceptible to damage. Recent studies show that once inside, carbapenems bind to multiple penicillin-binding proteins [47, 48].

Carbapenemases are a type of beta-lactamases that possess the ability to break the antibiotics through the process of hydrolysis. There are various types of carbapenemases classes but the most significant are class A, B, C, and D. The class A and D beta-lactamases have serine at their active site whereas class B beta-lactamases are all metalloenzymes with zinc on their active site. All of the classes are found in *Acinetobacter Baumannii*. Out of these three, the most prevalent class found in A.baumannii is class D [49]. Class D carbapenemases are also called OXA beta-lactamases. The first beta-lactamase activity belonging to class D in A.baumannii was reported by Paton [50]. He discovered a novel beta-lactamase named AR-1 (Acinetobacter resistant to imipenem). Genetic studies later revealed that it belonged to class D. Class a beta-lactamases was found in Klebsiella pneumoniae [51].

Due to the persistence of *Acinetobacter Baumannii*, it is believed that there are special genes that are encoded in the genome of A.baumannii for the resistance against the carbapenems [52]. All the clinical isolates showed the presence of blaOXA-51 in their genome [53]. The most common mechanism is the horizontal acquisition of carbapenemases genes [54]. Hundreds of OXA-type enzymes have been identified and many of the variants actually possess carbapenemase activity. When these bacteria are exposed to antibiotic pressure, there is the insertion of ISAba1 which contributes to the overexpression of OXA carbapenemase genes. All the clinical isolates

showed this mutation. Those isolates which had ISAba1 right next to the OXA gene were carbapenem resistant [55].

6. Small RNAs

Small RNAs are post-transcriptional gene regulators in the gene expression of bacteria. They contribute to various important biological processes like maintaining the virulence of bacteria, their metabolism, functional integrity as well as antibiotic resistance. These are non-coding RNAs that are important for any organism. Their importance cannot be neglected as evidence suggests that the emergence of new hyper-virulent strains is probably coupled to small RNAs. Various mechanisms have been described how small RNAs perform their function. For example, studies suggest that sRNAs perform their role by base-pairing with target mRNAs, or by modulating protein activity [56]. Depending upon the need of the hour, they may increase or decrease the gene expression by altering the process of translation and making the protein structure more or less stable [56, 57]. These small RNA transcripts perform their functions by modulating gene expression at the post-transcriptional level.

At present, only limited work has been done to investigate the role of small regulatory RNA transcripts. Numerous RNA transcripts have been listed but the most commonly found transcripts in the multi-drug resistant strains of A.Baumannii is the sRNA AbsR [28]. Along with AbsR28, AbsR25 and AbsR11 were also found in MDR strains of Aceintobacter baumannii [58].

AbsR25 brings changes in the genome in such a way that there is an increase in the expression of efflux pumps [59]. Normally, the chaperone Hfq is required for the proper functioning of small RNAs. Hfq is the central component as these chaperones help the small RNAs to bind to their cognate mRNAs. These belong to the protein class LSm. In A.baumanniii, instead of Hfq chaperone, there is a protein present in which there is a large terminus that makes the protein join with glycine. Studies suggested that this affinity between the C-terminus and glycine is necessary for the RNA binding [60].

CONCLUSION

Finding an effective drug regime against any of the members of ESKAPE organism has proven to be very difficult for clinicians. Currently, Aceintobacter baumannii infections are being treated by giving various antibiotic drug classes out of which the most common being carbapenems (imipenem, doripenem, etc.) [61]. The clinical cure rate for imipenem against a susceptible strain of A.baumannii was 57 to 83 percent [62]. The other classes are cephalosporins, aminoglycosides, beta-lactams with beta-lactam inhibitors, etc. First and foremost it should be checked whether the strain is carbapenem-resistant or not so that we can change to a different regime as quickly as possible. If the strain is resistant to carbapenems, it poses great limitations to therapeutic options. The second drug of choice is using beta-lactam antibiotics. However, studies suggest that using beta-lactam alone is not a good option as the bacteria develop resistance by producing enzymes called beta-lactamases which destroy the beta-lactam ring structure through the process of hydrolysis. So it is always considered better to use a beta-lactamase inhibitor along with a beta-lactam antibiotic. Tigecycline has shown increased antimicrobial activity even against the multidrug-resistant strains of *Acinetobacter Baumannii* [63]. The combination of colistin with rifampin also yields good results.

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