

Article review

The Underlying Impact of Antimicrobial Agents Resistance of *Acinetobacter Baumannii*

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Introduction

Whenever the bacterium *Acinetobacter Baumannii* is mentioned the antimicrobial agents resistance come directly into the mind. This bacteria have been widely distributed worldwide since it have the ability to maintain their living in any surrounding niches including the harsh ones.(Lin, 2014).

Being resistant made it a problematic pathogen that makes therapists unable to treat their patients because some of *Acinetobacter Baumannii* strains are extensively multidrug resistant(XDR) (Moubareck and Halat, 2020)

A. Baumannii is characterized as Gram negative coccobacilli has the ability to produce catalase but lacking oxidase and fail to ferment glucose.(Kamali *et al.*, 2020) *A. Baumannii* can cause wide range of infections comprising various body systems, of which respiratory tract, urinary tract, skin, and blood.(Nwadike, Ojide and Kalu, 2014)

This pathogen can surprisingly develop its means of resistance to antibiotics either by acquisition of resistance genes or modifying present ones (Kröger *et al.*, 2017). *A. Baumannii* shows resistance to penicilins, cephalosporins, Aminoglycosides, carbapenems, fluoroquinolones, tetracyclines, and even polymyxins. (Lima, 2018).

Phenotypic features of resistance

Several mechanisms are expressed by *Acinetobacter baumannii* that enables it to show high resistance to various antibiotics. The most important features of resistance are the following:

The Beta-Lactamases: these are large number of enzymes that render the beta lactam antibiotics, which comprise multiple antibiotics with various modifications of beta lactam ring the target of those enzymes; inactive. The four types of Ambler classes that have been identified in this organism comprise class A, serine-dependent enzymes inhibited by clavulanate or tazobactam. They hydrolyze all penicillins and cephalosporins with the exception of cephamycins ; classB , These are zinc-dependent metallo- β -lactamases (MBLs), that strongly hydrolyze all β -lactams, including carbapenems, but not aztreonam; class C Also known as *Acinetobacter*-derived cephalosporinases (ADCs), chromosomally encoded AmpC cephalosporinases are intrinsic to all *A. baumannii* strains and class D or the oxacillinases (OXAs), are serine-dependent and commonly hydrolyze oxacillin much faster than benzylpenicillin, hence the name . In various bacteria, over 400 OXA-type enzymes are already known, of which many are carbapenemases.(Moubareck and Halat, 2020)

Multidrug resistance efflux pumps

This mechanism includes resistance to tigecycline and imipenem. There are four groups of efflux pump that identified in this organism, comprising the following:

Category abbreviation	The family (category full name)
RND	resistance-nodulation-division superfamily
MFS	major facilitator superfamily
MATE	multidrug and toxic compound extrusion
SMR	Small multidrug resistance family

Acinetobacter baumannii also shows the macrolides resistance by efflux pumps that provides resistance to erythromycin (Okada *et al.*, 2017)

Target site modification (modifying enzymes)

This mechanism is used to inactivate aminoglycosides. These comprises three main types of enzymes; acetyltransferases, phosphotransferases, adenyltransferases. this organism can produce combinations of these enzymes. Besides resistance to colistin arises due to modifications of this target site (lipopolysaccharide moiety) in clinical isolates (Doi, Murray and Peleg, 2015)

Defects in permeability

This mechanism includes the ability of organism to reduce production of porin proteins that play pivotal role in permeability, which lead to reduce the concentrations of antibiotic inside bacterial cells increasing its resistance. OMP reduction may lead to resistance to carbapenems including imipenem. (Lima, 2018)

Alteration of target site

This mechanism includes resistance to several groups of antibiotics since it comprises various target sites as shown in the table:

Target site to be modified	Antibiotics to be resisted
penicillin-binding proteins (PBPs)	Imipenem
DNA gyrase	Quinolones
Ribosomes	Tetracyclines
Dihydrofolate reductase enzyme	Trimethoprim

(Lin, 2014)

Genotypic Underlying Features of Resistance

Beta lactamases

A wide number of genes have been identified in this organism that enable it to resist different types of Betalactamases some of them express enzymes with narrow spectrum, others have an extended spectrum effect, for the Ambler class A there are, *bla*-TEM, *bla*-SHV, *bla*-GES, *bla*-CTX-M, *bla*-SCO, *bla*-PER, *bla*-VEB, *bla*-KPC, and *bla*-CARB.. For the class B betalactamases it could produce *bla*-IMP genes, *bla*-VIM, *bla*-SIM, *bla*-NDM also for class C there is *bla*-AmpC while for the group D there are huge number of genes including genes of nine different subgroups of *bla*-OXA genes with more than 50 different gene. (Lee *et al.*, 2017)

Efflux pump

Efflux pumps play an important role in evading the deleterious effect of some naturally produced molecules and those extracellular compounds like toxins and antibiotics. (Abdi *et al.*, 2020)

In *A. baumannii*, efflux pump confer resistance to tigecycline and imipenem. There are number of gene families that mentioned earlier. Which include the following important genes *adeABC*, *adeFGH*, *adeIJK*, *tetA*, *tetB*, *cmlA*, *craA*, *amvA*, *abaF*, *abeM*, *abeS* (Xiao *et al.*, 2016)

Efflux pumps are varied in their specify, some are specific that can deal only with a single substrate, while others are wide spectrum that can transport completely different compounds such as different types of antimicrobial agents which is highly correlated with multidrug resistant strains. (Abdi *et al.*, 2020)

Modifying enzymes

As shown previously there are diffent groups of enzymes that can modify aminoglycosides antibiotic leading to loss of their antimicrobial activity the following genes represent the most studied ones (*aacC1*, *aacC2*), (*aacA4*), (*aadB*), (*aadA1*), (*aphA1*). These genes may be harbored on transposable elements which increases their dissemination among bacteria (Lin, 2014)

Alteration of target sites

Each antimicrobial agent has its specific target site. Bacterial resistance mechanisms may go far as changing the composition of the antibiotic target site to reduce the affinity of binding or to protect the target site resulting in inhibition of the antibiotic action. To counteract imipenem, bacteria may alter gene *pbp2*, also to protect 16S rRNA it may alter it by methylation by the gene (*armA*), and to resist tetracycline the gene *tetM* is responsible of protecting ribosomes (Ibrahim, 2019). Similarly modification may occur in *gyrA/parC* genes to protect gyrase enzyme and topoisomerase type IV from the effect of fluoroquinolones antibiotics (Moubareck and Halat, 2020).

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