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REVIEWS

Acinetobacter baumannii as Nosocomial Pathogenic Bacteria

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1. INTRODUCTION AND NATURAL HABITAT

The *Acinetobacter* genus has emerged as a nosocomial infection with a wide range of mortality and morbidity in recent years. Although this microorganism which was isolated from clinical samples in the 1970s, still known as an opportunistic bacteria [1]. The bacterial taxonomy is as follow: Bacteria; Proteobacteria; Gammaproteobacteria; Pseudomonadales; Moraxellaceae, *Genus: Acinetobacter*. The distinguished variant species by Bouvet and Grimont are including as: *Acinetobacter baumannii*, *Acinetobacter calcoaceticus*, *Acinetobacter haemolyticus*, *Acinetobacter johnsonii*, *Acinetobacter jejuni* and *Acinetobacter lwoffii* [2–4]. The *Acinetobacter* genus consists of *A. calcoaceticus*, *Acinetobacter* genomic species 3 and *Acinetobacter* species TU13. These species are very similar but the phenotypic characterization is extremely difficult. Later on, it was also suggested that these species may be categorized in *Acinetobacter-calcoaceticus–Acinetobacter baumannii* complex [5]. The other types of this bacterium that are called *Acinetobacter parvus*, *Acinetobacter schindleri*, *Acinetobacter ursingii* were isolated from the human body; and seven other strains, including *Acinetobacter baylyi*, *Acinetobacter bouvetii*, *Acinetobacter grimontii*, *Acinetobacter tjernbergiae*, *Acinetobacter towneri*, *Acinetobacter tandoii*, *Acinetobacter gerneri* have originated from the mud [6–8]. Currently it has been stated that *Acinetobacter baumannii* and related species, *Acinetobacter nosocomialis* and *Acinetobacter pittii* (*Acinetobacter baumannii* complex) are regarded as a wide range of clinical infections. *Acinetobacter variabilis* was discovered recently by Krizova [7]. The genomic species 3 and TU13 were respectively replaced by *Acinetobacter nosocomialis* and *Acinetobacter pittii* [8, 9]. A number of the *Acinetobacter* genus, for example *A. johnsonii*, *A. lwoffii* and *A. radioresistens* are found on the skin normal flora especially in tropical inhabitants [10]. In contrast, *A. baumannii* is also isolated from hospitalized patients and environments however, can be colonized about 41 percent in intensive care unit patients [11, 12]. Another group that consists of antibiotic sensitive cluster (*A. johnsonii* and *A. calcoaceticus*) is obtained from environmental resources, soil and contaminated waters. According to several studies, the most members of the last two groups have carbapenem resistance genes [13].

2. EPIDEMIOLOGY AND DISEASES

Patients are the primary source of infection which can spread the bacteria through clinical environment, medical equipment and hospital staff. In addition, *Acinetobacter* incidence infections can be influenced by person to person contact and bacterial resistance to antibiotics and disinfectants [14, 15]. Since the 1980s, the prevalence of bacteria has been reported across the world, encompass Europe, especially the UK, Germany, Italy, Spain and United States by transmission of multi-drug resistant strains [16, 17]. Many studies in North America have indicated the emergence of multidrug resistant strains. *Acinetobacter* nosocomial infections are in relation with seasonal infectious diseases, particularly with summer. The highest rate of resistance to imipenem, meropenem, ceftazidime, ciprofloxacin, piperacillin–tazobactam and gentamicin has been observed in Latin America [18]. As a result of conducted studies in Asian countries, most of bacteria, isolated from acquired pneumonia (13.6%) and ventilator-associated pneumonia (36.5%), were belonged to *Acinetobacter* species. *Acinetobacter* has more dispersion in China compare to Thailand and Malaysia [19]. The frequency of carbapenem-resistant *Acinetobacter* strains in India was stated to be nearly 35 percent [20, 21]. According to statistics published by ECDC[1], the resistance rate of carbapenem in *Acinetobacter* strains has been reached up to 25%. The prevalence of *Acinetobacter* among nosocomial infections in Bosnia was 51.4%, in which 74.1% were belonged to respiratory infections [22]. Although the rate of multi-drug resistant strains of *Acinetobacter* is almost 30% in Italy [23]. In general, researches show that the community-acquired bacterial infections are often detected in tropical and subtropical regions such as Singapore, Hong Kong, and Taiwan predominantly

[1] European Centre for Disease Prevention and Control.

Table 1. Various genomic species of the genus *Acinetobacter*

Species name	Genomic species no.	Type or representative strain	Major habitat or source
A. baumannii	2	ATCC 19606^T	Human clinical specimens
A. baylyi		DSM 14961^T	Activated sludge, soil
A. beijerinckii		NIPH 838^T	Soil, water
A. bereziniae	10	ATCC 17924^T	Human specimens, soil
A. bouvetii		DSM 14964^T	Activated sludge
A. calcoaceticus	1	ATCC 23055^T	Soil, water
A. gerneri		DSM 14967^T	Activated sludge
A. grimontii		DSM 14968^T	Activated sludge
A. guillouiae	11	ATCC 11171^T	Human faeces, water, soil
A. gyllenhergii		NIPH 2150^T	Human specimens
A. haemolyticus	4	ATCC 17906^T	Human specimens
A. johnsonii	7	ATCC 17909^T	Human skin, water, soil
A. junii	5	ATCC 17908^T	Human specimens
A. lwoffii	8/9	ATCC 15309^T	Human skin
A. parvus		NIPH384^T	Humans and animals
A. radioresistens	12	IAM 13186^T	Human specimens, soil
A. schindleri		NIPH 1034^T	Human specimens
A. soli		KCTC 22184^T	Soil
A. tandoii		DSM 14970^T	Activated sludge, soil
A. tjernbergiae		DSM 14971^T	Activated sludge
A. towneri		DSM 14962^T	Activated sludge
A. ursingii		NIPH137^T	Human specimens
A. venetianus		ATCC 31012^T	Marine water
A. pittii[a]	3	ATCC 19004	Human clinical specimens
	6	ATCC 17979	Human specimens
A. nosocomialis[a]	13TU	ATCC 17903	Human clinical specimens
	13BJ, 14TU	ATCC 17905	Human specimens
	14BJ	CCUG 14816	Human specimens
	15 BJ	SEIP 23.78	Human specimens
	15TU	M 15la	Human specimens
	16	ATCC 17988	Human specimens
	17	SEIP Ac87.314	Human specimens, soil
	Between 1 and 3	10095	Human clinical specimens
	Close to 13TU	10090	Human clinical specimens

in rainy months with a prevalence of 88% among patients which admitted to care centers [24–27]. On the other hand a number of various infections are related to this microorganism such as:

Pneumonia

The ventilator-associated pneumonia (VAP) is the most related infection with *A. baumannii* especially in intensive care units. Falagas and Lee studies performed the high percentage of death in this type of pneumonia [28, 29]. Albeit it's notable that alcohol consumption and tropical zone are predisposing factors in VAP [18]. The first community-acquired pneumonia death was reported in Korea [30].

Bacteremia

A. baumannii bacteremia is respected as a third cause of mortality and morbidity in intensive care units [31].

Trauma and Burn Infections

A. baumannii is one of the main reasons of skin and soft tissue infections in burn wounds and trauma [32, 33]. Recognition between contamination and true infections

and also the MDR strains existence have created a prominent challenge for infections treatment process [34].

However *A. baumannii* is also reported from meningitis, osteomyelitis, ICU-urinary tract infections, dental plaques, chronic and aggressive periodontitis and polymicrobial bacterial infections [35–37].

3. PATHOGENICITY FACTORS

The precise mechanism which involved in *A. baumannii* incidence is not clear so the predominant virulence factors are listed as below:

Adhesion and Attachment

Attachment of bacteria to epithelial cells is considered as one of the initial steps for colonization and infection in the host tissue. Epidemiological studies imply that *Acinetobacter* species can be colonized and survive on human skin and mucous membranes for days or weeks. Lee et al. described the adherence of *A. baumannii* to human bronchial epithelial cells in invitro [38]. The main cause of this phenomenon is correlated with bacteria adhesion molecules such as: OmpA, Omp33–36, Bap and cellular fibronectin [39].

Motility

There is a debate over the existence of *A. baumannii* motility. Recent studies demonstrated that *A. baumannii* is able to twitching because of the type IV pili. There is a positive correlation between the conserved sequences of pili subunits. Although there is no any empirical evidence on the existence of type IV pili in the twitching motility in *A. baumannii*, but in a study by Eijkelkamp, it was stated that this gene has been found in bacteria and the full sequence has been accessed [40]. The pili are under the control of signal transduction systems which include chemosensor complex (regulator and two-component system) [41]. As reported by Clemmer, twitching motility of the bacteria depends on the *T* gene of pili. Disabling this gene will lead to a 54 percent reduction in movement in mutant strains. Furthermore, increasing the agar concentration may reduce the *A. baumannii* motility. Both free iron concentration and the cell population have an important role in *A. baumannii* motility [42]. It should be noted that ditching motility has been also observed in *Acinetobacter anitratus* [42, 43].

Outer Membrane Proteins (OMP)

Most of outer membrane proteins in Gram-negative bacteria are associated with antibiotic resistance, compatibility and pathogenicity in host cells. This factor plays a critical function in binding, bacterial invasion and prevents lysis by complement system activation. It has been associated with the apoptosis of epithelial cells through mitochondrial targeting [43]. This factor creates a resistance to the serum in *Acinetobacter* by binding to H factor [44]. *A. baumannii* can cause death of HEp-2 cells through cell death receptors or apoptosis of mitochondrial decay. The mechanism is related to apoptosis precursors [45].

Outer Membrane Vesicles (OMV)

OMVs are round-shaped nanovesicles that contain components of LPS, outer membrane proteins, lipids and nucleic acids [46]. Moreover, they involved in quorum sensing, virulence factors transferring, phagolysosome fusion inhibition, transferring genes and biofilm production [47]. Kwon studies show that these vesicles are produced during the growth phase [48]. The vesicles have antigenic properties, which can be used as vaccine targets. Previous studies suggested that vaccination with these particles leads to the rehabilitation of antibodies against multiple antigens of bacteria with bactericidal activity [49]. Jin et al. studies proved that the vesicles play an important role in transferring of outer membrane protein A to the host cells, which induce cytotoxicity after packaging the protein in the vesicles [46].

LPS

Bacterial LPS plays essential role in resistance to polymyxin antimicrobial peptides, complement activation, stimulate inflammation by stimulating TLR-2[2], TLR-2, TLR-4 and responses as well as synergistic interaction with exopolysaccharide capsule [50–52].

Capsule

There are many evidences for the existence of capsule in *A. baumannii* strains. For example, the strains which harbor the *waal* gene have ability to produce capsule formation [50]. Capsule has an important function in protecting bacteria against the host innate immune responses [53]. Russo et al. stated that K1 capsule of *A. baumannii* strains AB307-0294 is required to grow and survive in human serum in the peritoneal fluid. Likewise capsule is essential for survival in soft tissue infection in mice [53, 54]. The tyrosine kinase of the inner membrane, Wcz, is responsible for capsule accumulation and Wza causes the transferring of capsules from periplasmic space and outer membrane respectively. Also the role of *ptk* and *epsA* genes, in coding the related proteins have been identified [54].

Biofilm Formation

Acinetobacter has the ability in biofilm formation on biotic and abiotic surfaces [55]. Bacteria colonization, microcolony formation and exopolysaccharides secretion eventually lead to biofilm formation [56].

[2] Toll-like receptors.

Biofilm also can affect the drug resistance and escapes from the host immune system. This process is controlled by Quorum sensing and two-component regulatory systems [57]. Pili, outer membrane proteins, extracellular polysaccharide and Bap are the most important factors in biofilm formation [39]. The Bap factor may lead to progress and sustainable development of biofilm through the maturation of biofilm formation on biotic and abiotic surfaces [57]. Espinal study illustrated that *A. baumannii* can produce biofilm in desiccated condition and protects the bacteria against the variation in wet circumstances [58]. Recent studies have pointed that the formation of biofilm is at least three times higher in the solid-liquid phase. Extracellular polysaccharide compounds (PNAG[3]) is an essential factor for biofilm formation in *S. aureus*, *S. epidermidis* and *A. baumannii* which is encoded by *pgaABCD* locus cell-cell adhesions, protecting bacteria from innate immunity, biofilm stability in dynamic and stressful conditions have been affected by mentioned factor and considered as a vaccine candidate [59, 60].

Pili and Secretion Systems

Type I pili. Type I pili are respected as the most common structure of the outer surface protein in pathogenic bacteria. Eijkelkamp et al. identified four clusters of these genes in *A. baumannii*, which is called *csu*-cluster. Proteomics studies verify that CsuD, CsuC and type I pili are effective in adherence [50].

Type IV pili. Cell surface-binding, twitching and biofilm formation are influenced by type IV pili. The numbers of *Acinetobacter* strains have pili encoded genes. The *comP* gene encoding the pilus-like protein which is homologous to pilA of type IV secretion system in *Acinetobacter* strains [61, 62].

Type V secretion system. The Ata auto-transporter secretion system in *A. baumannii* ATCC 17978 has an important role in pathogenicity, biofilm formation, binding to extracellular matrix proteins and attachment. Investigators identified that Ata is related to 58% of clinical isolates, while global strains do not harbor this gene [50].

Type VI secretion system. The Type VI secretion system (T6SSs) is recognized to be involved in cell invasion and competition amongst pathogens. It has been proposed for type 1 pili regulation and bacterial interaction. A number of studies have been reported the performance of this system in *A. baumannii* strains. It should be stated that *A. nosocomialis* strain M2 is using T6SS for destroying *E. coli* strains [50]. The T6SS gene cluster is controlled by resistance plasmid. This plasmid can be extremely conserved in *A. baumannii* [63].

[3] Poly-N-acetylglucosamine.

Enzymes

Hydrolytic enzymes of *Acinetobacter* are consisting of phospholipases C and D [64]. These are lipolytic enzymes that catalyze the phospholipids releasing. These enzymes contribute to the pathogenesis of Gram-negative bacteria through the host cells lysis. Decomposition of the phospholipids in mucosal tissues will facilitate the bacterial invasion [65, 66].

Iron Uptake System: Pathogenic bacteria are using the iron acquisition systems for gaining the low level of free iron in the host. Binding to special receptors, transferring proteins and siderophores are the most prominent mechanisms for iron uptake [40]. Siderophores are high-affinity iron chelators which are produced by pathogenic bacteria and divided into three main categories based on iron chelating ligand, including catecholates, carboxylates and hydroxamates. Acinetobactin, a catechol- hydroxamate siderophore, is one of the iron acquisition systems that are broadly found in *A. baumannii*. Acinetobactin biosynthesis is encoded by *basA-J* genes and ABC super family. Acinetobactin complex is transmitted through protein receptors which are encoded by *bau A-F* genes [67]. The number of acinetobactin producing strains utilizing the 30 and 15% of the saturated iron concentration in transferrin and lactoferrin as a sole source of iron. Inactivation of *bauA* and *basD* genes affects the ability of strains to the growth in iron limited condition. These results clarify that *A. baumannii* is able to survive in difficult conditions of iron deficiency, as well as emphasizing on the role of acinetobactin in bacterial infection and pathogenicity [68]. Feo system is another mechanism for providing iron, which is having cytosolic protein (FeoA), inner membrane protease (FeoB) and FeoC as repressor components [61].

Blue-Light-Sensing Protein

The Blue-light-sensing protein A (BlsA) can influence the *A. baumannii* pathogenicity. The BlsA protein expression is increased in the absence of light, however in the presence of blue light, the bacteria cannot produce biofilm [69].

4. LABORATORY DIAGNOSIS

Acinetobacter species are identified by Gram-negative, aerobic, non-fermentative, non-motile, catalase positive, indole negative and oxidase negative characteristics with gray-white mucoidal colonies with a diameter of 1.5 to 3 mm. The species grow in standard microbiology media such as blood agar with 5% sheep blood and trypticase soy agar [70]. The bacteria morphology is changing from coccobacilli to bacilli form in stationary phase and during rapid growth respectively [71]. To increase the number of *Acinetobacter* isolates from the environmental and clinical specimens, swab samples can be located in an enrichment medium with low pH containing acetate [72]. Some

Table 2. Phenotypic characteristics of *Acinetobacter* species [85]

Name of test	*Acinetobacter* species				
	Acb complex	*A. iwoffii*	*A. haemolyticus*	*A. junii*	*A. radioresistens*
Gram staining	Gram-negative cocci or coccobacilli				
Catalase	+	+	+	+	+
Oxidase	–	–	–	–	–
Motility	–	–	–	–	–
Urease	V	V	–	–	–
Citrate	+	–	+	+	–
OF glucose	+	–	V	–	–
Nitrate reduction test	–	–	–	–	–
Hemolysis	–	–	+	–	–
Gelatin hydrolysis	–	–	+	–	–
Growth at 42°C	+	–	–	–	–
Chloramphenicol sensitivity	R	S	R	R	R
Arginine hydrolysis	+	–	+	+	+

V: variable, S: sensitive, R: resistant, *A. iwojfii*: *Acinetobacter iwoffii*, *Acb*: *Acinetobacter calcoaceticus–baumannii*, *A. haemolyticus*: *Acinetobacter hemolyticus*, *A. junii*: *Acinetobacter junii*, *A. radioresistens: Acinetobacter radioresistens*, OF: oxidation-fermentation.

strains have sliding motility due to polar fimbriae. A few strains have the ability to grow at 41 to 44°C, but some environmental species are not able to grow at temperatures above 30°C. On the other hand, some strains are capable to produce acid through oxidation of D-glucose, D-ribose, D-xylose and L-arabinose. Both analytic systems, Vitek-2 and Microscan Walk-Away, are used to identify the *A. baumannii* isolates, but not preferred for *Acinetobacter baumannii* complex [73, 74]. For conforming the phenotypic methods (Biotyping, Phenotyping, Serotyping), molecular methods such as (ARDRA)[4] [75], AFLP[5] [76], Ribotyping [77], tRNA spacer fingerprinting [78], Restriction analysis of the 16S–23S RNA Intergenic Spacer Sequences [79], Sequence analysis of the 16S–23S rRNA gene spacer region [80], Sequencing of the rpoB [81], MLST[6], PFGE[7], repetitive extragenic palindromic sequence, 16s rDNA (ribosomal DNA) have been recognized [82], while ARDRA and AFLP techniques are reliable and well-established for *Acinetobacter* species classification [83, 84].

5. *Acinetobacter* DRUG RESISTANCE AND TREATMENT

The treatment of *A. baumannii* multidrug-resistant strains is one of the main challenges of health care units. Drug resistance strains were emerged accordance to genetic mobile elements essentially plasmids, integrons and transposons. More than 30 types of IS elements (i.e., IS*Aba*1 and IS*Aba*125) have been found in *Acinetobacter* strains [86–88]. The bla_{OXA-23} gene in *A. baumannii* is transferred by Tn2006 and Tn2009 [89]. The bla_{OXA-58} gene is encoded by plasmid and provided by IS elements. It is noteworthy that bla_{PER-1}, bla_{PER-7} and bla_{VEB-1} have been transmitted by these sequences [90]. Moreover Resistance Islands such as AbaRI have been identified in *A. baumannii* which have resistance genes for 45 different antibiotics and also heavy metals [87, 91].

It should be mentioned that this microorganism has an innate resistance to numerous antibiotics predominantly aminoglycosides, quinolones and broad-spectrum of beta-lactams [92, 93].

Beta-Lactam

Resistance to this class of antibiotics is in effect of hydrolysis of antibiotics by beta-lactamase enzymes, changes in penicillin-binding proteins, modifying the structure and number of pore-forming proteins and activity of the efflux pumps [94].

Enzymatic Mechanisms

AmpC. AmpC enzyme encoded by both chromosomal and plasmid genes, belongs to class C beta-lactamase which is important in resistance to penicillins and extended-spectrum cephalosporins except cefepime and also carbapenems [95, 96].

Oxacilinase. *Acinetobacter* has class D of oxacilinase which has the innate ability to hydrolyze the clox-

[4] ARDRA:Amplified Ribosomal DNA Restriction Analysis.
[5] AFLP: Amplified Fragment Length Polymorphism.
[6] Multilocus Sequence Typing.
[7] Pulsed-Field Gel Electrophoresis.

acillin and oxacillin. Five phylogenic subtypes of class D beta-lactamase have been identified in *A. baumannii*. This oxacilinase is belonging to bla_{OXA51}-like β-lactamase with penicillin and carbapenem hydrolyzing activity [97]. The $bla_{OXA-51/69}$ and bla_{OXA-24} are identified as the first gene cluster from carbapenem resistant strain in Spain. This class is consisting of $bla_{OXA-25/26}$ and bla_{OXA-72}. The third cluster is bla_{OXA-58} which has been found in *Acinetobacter* in Australia and Romania. In general CHDLs[8] is originated from carbapenem resistance plasmids [97, 98].

Metallo-beta-lactamase. Carbapenems are recognized as one of the most effectual antimicrobial agents for treatment of *A. baumannii* multi-drug resistant strains, while nowadays resistance to these antibiotics has been increased. Alternatively, these strains were resistance to all classes of antibiotics except colistin and tigecycline, however resistant to these drugs has been also reported [99]. One of the most common mechanisms of resistance to carbapenems is producing oxacilinase which is related to bla_{OXA-23}, bla_{OXA-40} and bla_{OXA-58} [97, 98]. Class B (Metallo-β-lactamase) strains consisting of VIM, IMP, and SIM have been reported in *A. baumannii*, especially in the regions of Asia-Pacific and Latin America. These genes result in resistance to all carbapenems except aztreonam which is associated with class 1 integron [97, 100]. Recently, *New Delhi* metallo-beta-lactamase (NDM) has been found in clinical *A. baumannii*. At the present, NDM-1 and NDM-2 are acknowledged as one of the causes of CRAB (Carbapenem-resistant *Acinetobacter baumannii*) in Europe, China, Japan and Egypt [101, 102]. *Klebsiella pneumoniae* carbapenemase (*KPC*)-producing bacteria are related as *A. baumannii* carbapenem resistant strains, for instance type 2, 3 and 4 of bla_{KPC} genes were reported in Puerto Rico [103]. The novel narrow-spectrum beta-lactamase SCO-1, TEM-1, CARB-2, CARB-4, CARB-8, bla_{OXA-20}, bla_{OXA-21} and bla_{OXA-37} have been recognized in *A. baumannii*. The presence of *PER-1*-type *ESBLs* has been observed for the first time in European countries [97, 104]. The bla_{PER-7} gene that was isolated from patient in Paris, in comparison to type-1 has the more hydrolytic enzyme activity against aztreonam and cephalosporins [105–107]. The bla_{PER} and bla_{VEB} beta-lactamase genes have been found as a second class of beta-lactamases in Enterobacteriaceae and also in *A. baumannii* and associated with hospital outbreak strains. It should be noted that the bla_{CTX-M} variants, especially $bla_{CTX-M15}$ has a low prevalence in *A. baumannii* [107–109].

Non Enzymatic Mechanisms

Membrane permeability. Membrane permeability may cause one of the reasons of Gram-negative bacteria resistance mechanism, in which Limanesky and colleagues demonstrated that the lack of 29-kDa outer membrane protein has a considerable role in resistance to carbapenems [109]. Proteomics studies showed that special outer membrane proteins (HMP-AB) may cause resistance to beta-lactam antimicrobial agents [110, 111]. Resistance to beta-lactams can be occurring amongst the efflux systems, resistance-nodulation-cell division (*RND*) pumps and related components such as AdeABC [112, 113]. Roca and colleagues illustrated that AdeABC efflux system is involved in pumping out the monobactams and third-generation of cephalosporins [114]. On the other hand the lack of membrane pores as 33-kDa protein, 29-kDa protein (carO) and 49-kDa protein which are homologous to OprD have a pivotal function in antimicrobial resistance mechanisms [115].

Penicillin-binding proteins (PBPs). Exchanging the affinity or the protein expression can prompt antimicrobial resistance profiles. In some strains, resistant to carbapenems is correlated with an increasing in the expression level of these proteins with low affinity.

Aminoglycosides. Resistance to aminoglycosides in the *A. baumannii* is involved by aminoglycosides modifying enzymes which are present in bacterial chromosome, plasmids, integrons or Acinetobacter Resistance Island with the aim of altering the hydroxyl and amino groups like acetyl-transferase, nucleotidyl-transferase and phosphotransferase [116, 117]. The *armA* gene (aminoglycoside resistance methyltransferase) that may found in combination with the bla_{OXA-23}, is contributing to resistance to all types of aminoglycosides [118].

Quinolones. Resistance to quinolones is related to a point mutation in quinolone-resistance determining region (QRDR) in DNA gyrase and type-V topoisomerase. The mutation in g*yrase A* and *parC* genes can cause the rearrangement of Ser83 to Leu in gyrase A and Ser80 to Leu in *parC* in *A. baumannii* [119–121].

Polymyxin. The majority of *A. baumannii* strains are susceptible to polymyxin. This antibiotic alters bacterial outer membrane permeability and disrupts the cytoplasmic membrane. The colistin resistant strains are producing outer membrane proteins which comprise outer membrane proteins, chaperones, protein biosynthetic factors and metabolic enzymes [122]. Mutation and increasing expression of *pmrA/pmrB* genes have an effective role in resistance to colistin. Resistance can occur through the loss of the ability to produce the lipopolysaccharide components by mutation in *lpxA*, *B*, and *C* genes [123, 124].

Efflux system. Bacteria can extrude the antimicrobial agents out of the cell via pumps. These pumps are divided into five categories based on the similarity of amino acid sequences, an energy sources, number of components and type of substrates.

(1) ATP-Binding Cassette (ABC);

(2) Multidrug and Toxic Compound Extrusion (MATE);

[8] Carbapenem-Hydrolysing Class D Beta-Lactamases.

(3) Small Multidrug Resistance (SMR);

(4) Major Facilitator Superfamily (MFS);

(5) *Resistance-Nodulation-Division* (RND) [125].

The first known RND in *A. baumannii* is AdeABC, in which type B has been accepted as multidrug transporter protein, but type A and C are outer membrane and periplasmic proteins [126]. This system is under the control of Ade SR Two-component system that expresses this pump to reduce the susceptibility to antibiotics similar to gentamicin, kanamycin, tobramycin, netilmicin, amikacin, erythromycin, tetracycline, trimethoprim, chloramphenicol, ofloxacin, pefloxacin, norfloxacin and tigecycline [127, 128]. AdeABC efflux pump-encoding genes with class 1 integron have been seen in *Acinetobacter* strains [129]. With disabling adeIJK efflux pump through the allelic displacement, the resistance to AdeABC pump has been decreased [129, 130]. The third type of RND pump is AdeFGH that responsible for resistance to clindamycin, fluoroquinolone, chloramphenicol, trimethoprim, and also in reducing the susceptibility to tetracycline, tigecycline and sulfonamides [111]. The CraA efflux pump of MFS family is regarded in chloramphenicol resistance *A. baumannii* strains or intrinsic resistance to other antibiotics [131]. The AmvA family is another pump which is responsible for erythromycin excretion [132]. Tet efflux pump can be transported by mobile genetic elements (transposon, plasmid or resistance Islands). This type is consisting of two parts A and B which contributed in resistance to tetracycline and tetracycline/minocycline respectively [133]. The AbeM is the only member of the MATE family with significant role in pumping out the aminoglycoside, fluoroquinolone, chloramphenicol, trimethoprim and ethidium bromide [134]. Also SMR family (Abe S) is known in resistance to chloramphenicol, novobiocin and erythromycin [135].

Treatment

The following antimicrobial agents are used to treat *Acinetobacter* various infections:

Carbapenems. Carbapenems are still remaining choice as antimicrobial agents for *Acinetobacter* susceptible isolates. The imipenem is the most potent agent in comparison to meropenem, for treatment of multidrug-resistant strains [1]. Unfortunately, carbapenem-resistant *Acinetobacter* isolates are increasingly reported worldwide.

Beta-Lactamase inhibitors. Beta-Lactamase inhibitors (sulbactam) have intrinsic activity against many *Acinetobacter* strains. The presence of beta-lactam antibiotics (e.g., Ampicillin) in combination with the beta-lactamase inhibitor does not contribute activity or synergy [104, 136]. Monotherapy with sulbactam is not recommended for severe *Acinetobacter* infections. Levin et al. reported a cure rate of 67% using ampicillin-sulbactam to treat carbapenem-resistant *Acinetobacter* infections [137].

Tigecycline. Tigecycline, a relatively new glycylcycline agent has bacteriostatic activity against multidrug-resistant *Acinetobacter* species [3].

Aminoglycosides. Aminoglycoside agents (tobramycin and amikacin) are therapeutic options for multidrug-resistant *Acinetobacter* isolates. These agents are usually used in combination with other antimicrobial agents.

Polymyxin. Due to limited therapeutic options, clinicians have returned to the use of polymyxin B or polymyxin E (Colistin) for the most MDR strains [4].

Future Therapeutic Considerations. Using highly charged copper-based biocides, bacteriophage treatment, passive or active immunization, modification of bacterial virulence factors, by inhibition of quorum sensing and bacterial secretion systems are the novel therapeutic strategies against *Acinetobacter* infections [5].

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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