Review Article

Pathobiology of Multidrug Resistant *Acinetobacter baumannii*: An update

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ABSTRACT

Acinetobacter baumannii is an opportunistic nosocomial pathogen responsible for mortality and mobidity associated with hospital acquired infections worldwide. Antimicrobial resistance due to natural and acquired modes facilitates *A. baumannii* as one of the most significant nosocomial pathogens. Challenging most issue is the carbapenem resistance in *A. baumannii* in the healthcare settings worldwide, which is conferred by several mechanisms including: beta-lactamases, reduced permeability of the outer membrane, efflux pumps, and modification of penicillin-binding proteins. Among these, carbapenem-hydrolysing enzymes are the foremost mechanism that belongs to Ambler class D and B beta-lactamases. Several techniques are used to study the molecular epidemiology like WGS, PFGE, MLST, RFLP and RAPD. Among these, MLST is the gold standard, which are prevalently used to study the evolutionary genetics and clonal relatedness of *A. baumannii* clones. *A. baumannii* has been investigated in a number of outbreaks in clinical settings and spread of infections in hospital environments. To enhance our knowledge, in this review, we study the taxonomy, lab diagnosis, molecular techniques of identification, mechanisms of its antimicrobial resistance, molecular epidemiology and outbreaks, bacterial cell firness and use of animal models in multidrug resistant (MDR) *A. baumannii*.

Key words: *Acinetobacter baumannii*, Molecular Epidemiology, Antimicrobial Resistance, Virulence Factors, Outbreaks.

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INTRODUCTION

Acinetobacter baumannii is strictly aerobic, non-motile, glucose non-fermenting, non-fastidious, Gram-negative, oxidase-negative, catalase positive coccobacillus, most frequently linked with the hospital settings. *A. baumannii* is the genospecies that is associated most frequently with hospital outbreaks.[1] In India, *A. baumannii* is responsible for ~10% of total hospital-acquired infections.[2,3] The capability to survive in unfavorable environment and escalated antibiotic resistance renders *A. baumannii* as one of the principal nosocomial pathogens. *A. baumannii* can cause an array of hospital infections like; respiratory infections in particular bloodstream infections (BSI), ventilator-associated pneumonia (VAP), meningitis, soft tissue infections, endocarditis, and osteomyelitis, urinary tract infections, burn, skin, and surgical wound infections.[4]

Clinical significance of *A. baumannii* has drastically emerged in last four decades along with the progressively increased antimicrobial resistance.[4] *A. baumannii* has been described as the pathogen of formost significance in hospital settings by IDSA (Infectious Diseases Society of America).[5] Pan-drug or multidrug resistant (MDR) isolates are fetching a common problem in the hospital settings and an escalated intrinsic resistance to many groups of antimicrobials (*e.g.* glycopeptides, macrolides, lincosamides, and streptogramins).[6] While carbapenems are considered as antibiotic of only hope from a long time, the resistance rates of *A. baumannii* clinical strains to these antimicrobials are increasing worldwide.[5] Strains of carbapenem resistant *A. baumannii* (CRAB) frequently report the rise in resistance to other classes of antibiotics too, being susceptible to

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colistin and tigecycline only and presenting intermediate susceptibility to rifampicin only, even though resistance to colistin and tigecycline has also been investigated.[7,8] Resistance to carbapenem is developed by coexistence of several mechanisms in *A. baumannii* including reduced outer membrane permeability, increased expression of efflux pumps, synthesis of different class of beta-lactamases, and alteration of penicillin-binding proteins.[9] Carbapenem-hydrolyzing enzymes play a crucial role in conferring resistance to carbapenem in *A. baumannii*.[5,10-15] Literature associated with CRAB was accessed through PubMed. Various molecular epidemiology investigations in the different regions were observed in the present study.

Taxonomy

A. baumannii is a rising bacterial pathogen that causes a wide range of life threatening infections, particularly in hospitalized patients.[16,17,1] *Acinetobacter* history is not very recent. In 1911, a Dutch microbiologist, Martinus Willem Beijerinck observed an organism as *Micrococcus calcoaceticus* which was retrieved from soil. *Acinetobacter* has gone though a considerable taxonomic change over the past 4 decades. The genus *Acinetobacter* has gone through extensive changes in taxonomic nomenclature over the past few years. This bacterial strain had been designated previously as Bacterium anitratum, *Herellea vaginicola, Mima polymorpha, Achromobacter, Micrococcus calcoaceticus, Diplococcus,* B5W and *Cytophaga. Acinetobacter* spp. play a crucial role in the infection and colonization of patients admitted to hospitals. *Acinetobacter* genus comes under family *Moraxellaceae.* The recent advancements in molecular biology methods enabled the identification of at least 34 different species (Table 1), *A. baumannii* being the most clinically relevant spp.[18] Current taxonomy of *Acinetobacter* spp. Froms a complex called; Abc (*A. calcoaceticus–A. baumannii* complex), which is compsided of *A. calcoaceticus*, *A. baumannii, A. pittii* and *A. nosocomialis* also known as genomic species 1, 2, 3 and 13TU respectively). These are genetically more interconnected and hard to differentiate phenotypically.[18] Genomic species 3 and 13TU are well known and now they are recently been characterized as *A. pittii* and *A. nosocomialis*, respectively.[19] Infections caused by *Acinetobacter* spp. are reported more frequently in various healthcare settings all over the world. Amongst all, *A. baumannii* is more prevalent and become a frequent cause of nosocomial infections, particularly in the intensive care unit (ICU) patients.[20,21] However, they have been drawn in an array of infections like; UTI (urinary tract infection), bacteremia and secondary meningitis, but their leading role is as agents of predominantly ventilator-associated pneumonia and nosocomial pneumonia in ICU patients.

Laboratory Diagnosis

The morphology of *Acinetobacter* spp. ranges from coccoid to coccobacillary, based upon the bacterial phase growth. Most of the *Acinetobacter* spp. can grow on generally used microbiological media, showing smooth, dome shaped colonies of approx 2 mm diameter, with some species pigmentation like; yellow, grey or pale. The clinically important species grow at 37°C temperature whereas the environmental species may be grown at below 37°C. Commercially available selective media or the Leeds selective medium can be used[22] to improvise the isolation of *Acinetobacter* spp. from a mixed culture source. Hemolytic activity is rarely observed on 5% sheep blood agar, and hydrolysis of urea and gelatin, as well as acid formation from glucose are included in rare spp. The above mentioned tests allow genus level identification, but individual species identification of *Acinetobacter* genus is difficult in routine microbiology practice. But just phenotypically identifying an *Acinetobacter* spp. is not enough; a confirmatory test is also needed for validating the phenotypic tests. This is true even for the automated identification systems that are commercially available (VITEK, MicroScan WalkAway, Phoenix, API 20NE), nowadays utilized in clinical microbiology laboratories in routine dignosis. Therefore, identification of *Acinetobacter* species for

Table 1. Different species of Acinetobacter.

S. No.	Acinetobacter Species	S. No.	Acinetobacter Species
1	*A. baumannii*	18	*A. pittii* (3 TU)
2	*A. bereziniae*	19	*A. nosocomialis* (13 TU)
3	*A. baylyi*	20	*A. beijerinckii*
4	*A. nectaris*	21	*A. lwoffii*
5	*A. boissieri*	22	*A. parvus*
6	*A. grimontii*	23	*A. guillouiae*
7	*A. puyangensis*	24	*A. brisouii*
8	*A. bouvetii*	25	*A. kookii*
9	*A. gerneri*	26	*A. radioresistens*
10	*A. gyllenbergii*	27	*A. soli*
11	*A. schindleri*	28	*A. qingfengensis*
12	*A. calcoaceticus*	29	*A. rudis*
13	*A. harbinensis*	30	*A. tandoii*
14	*A. johnsonii*	31	*A. ursingii*
15	*A. indicus*	32	*A. towneri*
16	*A. tjernbergiae*	33	*A. haemolyticus*
17	*A. junii*	34	*A. venetianus*

routine, epidemiological and clinical studies is done only by chemotaxonomic systems. For accurate identification of *Acinetobacter* spp., extensive efforts are specified with the aim to better explain their ecology, pathogenicity and epidemiology,[1] especially for *A. baumannii*, *A. nosocomialis* and *A. pittii*.

Molecular Techniques of Identification

Molecular techniques used to identify *Acinetobacter* species ranges from DNA hybridization, ribotyping,[23] AFLP (amplified fragment length polymorphism),[24] ARDRA (amplified ribosomal DNA restriction analysis),[25] tRNA spacer fingerprinting[26] restriction analysis of the 16S-23S rRNA intergenic spacer sequences,[27] and 16S-23S rRNA spacer region gene sequence analysis.[29] AFLP and ARDRA analysis are widely used for identification of all species of *Acinetobacter* genus but ribotyping and *rpo*B sequencing methods are less laborious with more accurate result.[1] Recently, MALDI-TOF (Matrix-assisted laser desorption ionization time of flight) MS (mass spectrometry) has been used for the *Acinetobacter* identification upto speacies level.[30,31] To improve the accuracy, new efforts have been initiated[32,33] but current molecular techniques will still be mandatory for confirmation of species. PCR based identification has been used to identify the *A. baumannii* species utilizing gyrB[34] and OXA-51[35] genes.

Multilocus sequence typing (MLST) offers a prevailing tool for characterization of molecular epidemiology of clinical strains of significant bacterial pathogens and recommended as a latest way to learn the population biology of *A. baumannii*.[36] MLST scheme for *A. baumannii* was developed in 2005 by Bartual *et al.* which is based on comparison of DNA sequence of internal fragments of seven housekeeping genes.[37] MLST facilitates the possibility to transfer typing data from one laboratory to another and to compare the results via the internet. Therefore, MLST is increasingly used to study global epidemiologic as a promising authoritative tool for studies, as well as to study population biology of different bacterial species.

There are numerous studies available on MLST typing of *A. baumannii* from various parts in the Europe, few of which have revealed the existence of three different clusters, termed as pan-European clonal complexes I, II and III.[38-40] However, in another study isolates of *A. baumannii* of military personnel from repatriated British and US injured in Iraq revealed to be identical from clinical isolates from the UK.[41,42] A global spread of carbapenem-non-susceptible *A. baumannii* was studied from 139 centres covering 32 countries, almost half of them (17 countries) clustered with EUII control strains.[43] *A. baumannii* harbouring OXA-23 oxacilinase contributed to hospital-outbreaks all over the globe and recently had a tendency to replace OXA-58-producing strains in few countries.[1,44,45,43,46] In 2006, the first outbreak of *A. baumannii* in Germany carrying the carbapenemase OXA-23 was documented and nowadays it resulted for about 80% of MDR *A. baumannii*.[43,47] Few studies have recognized this species as a rising pathogen predominantly in hospitalized animals.[48,47] Christa *et al.* recently isolated carbapenem-non-susceptible *A. baumannii* strain from the urine of a hospitalized cat belonged to the international clone IC1/ST231.[49] Other human IC1/ST231 strains are also extremely linked to the animal strain indicating that a spread of such MDR strains between animals and humans.[50]

Antimicrobial Resistance

Nowadays, one of the major problems faced by clinicians, hospitals, and personnel dealing with public health care is multi-drug resistance acquired by *A. baumannii*. Along with other Gram-negative bacteria new mechanisms are acquired by *A. baumannii* via plasmids, transposons and integrons. *A. baumannii* is described by elevated intrinsic resistance to a lot of antimicrobials (macrolides, glycopeptides, streptogramins and lincosamides).[6] This bacterium has got the capability to acquire the resistance to other classes of antimicrobial agents utilized in the treatment. The procedure may be coupled with genetic modification causing membrane alterations (OMPs), overexpression of antibiotic modifying enzymes, overexpression of efflux pumps (EP), alteration of antimicrobial agents target sites, and acquirement of new resistance determinants (Figure 1).

Multiple antimicrobials like cephalosporins, penicillins, aminoglycosides, tetracyclines and quinolones have become ineffective in the treatment of *A. baumannii* due to increased accumulation of resistance determinants. As a result, carbapenems are left as one of the most important therapeutic alternatives due to their good activity and low toxicity in *A. baumannii* infections.[51] During early 1970s, *Acinetobacter* spp. caused nosocomial infections, which were successfully treated with

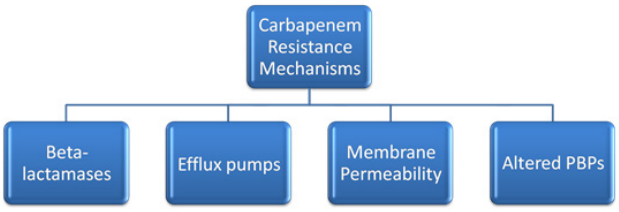

Figure 1. Different elements responsible for acquiring carbapenem antimicrobial resistance in *A. baumannii*.

minocycline, gentamicin, nalidixic acid, carbenicillin or ampicillin either as mono-therapy or in combinations, but consecutive surveys of *Acinetobacter* spp. have shown increased resistance in the clinical isolates.[52-54] Multiple mechanisms in *A. baumannii* have been reported to be implicated in resistance to β-lactams consist of (Figure 1).

a) Enzymatic mechanisms (β-lactamases)

b) Non-enzymatic mechanisms involving altered membrane permeability and expression of efflux pumps.

c) Sequence variation of PBPs (Penicillins binding proteins).

β-lactamase hydrolyzes and resulted in increased resistance to the cephalosporins, penicillins and carbapenems.[55,56] β-lactamases produced by *A. baumannii* are encoding genes present either chromosomally or in plasmids.

Enzymatic mechanisms (Carbapenemases)

Enzymes produced by bacterial community are liable for hydrolytic neutralization of different classes of β-lactam antibiotics like; cephalosporins, penicillins, carbapenems and monobactam, which are symbolized by β-lactamases. Such enzymes are classified into four molecular classes as per sequence homology: A, B, C and D (Figure 2). On the basis of involvement of divalent cations in activation of enzyme, carbapenemases are devided into metallo- β-lactamases (class B) and non-metallo-β-lactamases (class A, C and D).[11] Resistance to carbapenems can be conferred by overproduction of beta-lactamases AmpC beta-lactamases comes under Ambler class C classification, preferred ESBL (extended-spectrum beta-lactamases).[10] As per current information, the most considerable mechanism of carbapenem resistance in *A. baumannii* is coupled with carbapenemases, the most resourceful class of β-lactamases. Resistance to carbapenems is confered by β-lactamases by disrupting β-lactam ring amide bond. Metallo-enzymes utilize divalent cation (zinc) in addition to a water molecule for hydrolysis in order to cleave the β-lactam ring of carbapenems. CHDL (Carbapenem hydrolysing class-D beta-lactamases) are considered as the most prominent cause of *A. baumannii* carbapenem resistance. These enzymes are symbolized as oxacillinases (OXAs) because of their capacity to hydrolyse isoxazolyl-penicillin - oxacillin quite quicker than benzylpenicillin.[13,14] To date, six groups of OXAs have been identified among *A. baumannii*: OXA-23-like, OXA-51-like, OXA-40/24-like, OXA-48-like, OXA-58-like and OXA-143-like[15,5] (Figure 2).

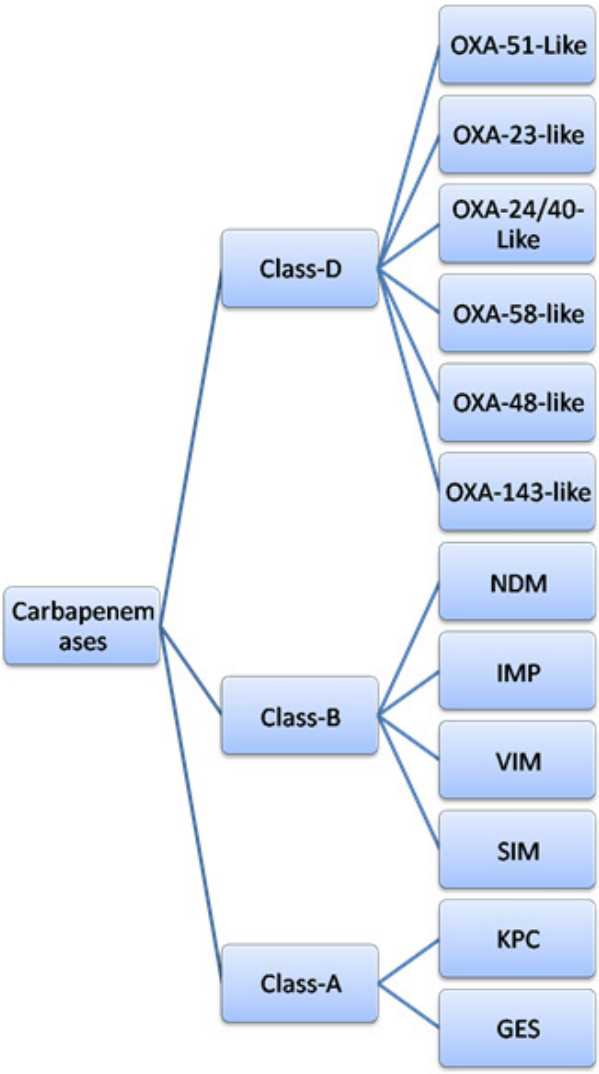

Figure 2. Different types and classes of carbapenemases found in multidrug resistant *A. baumannii*.

A mounting number of class A (GES and KPC), class B carbapenemases (NDM, IMP, SIM and VIM), and class D carbapenemases (oxacillinases) have been surfaced. Numerous class A carbapenemases have been crystallized (e.g. SME-1, KPC-2 and NmcA). Such enzymes hold a distinguishing type of active-site components, which are thought to be implicated in the carbapenems hydrolysis. Generally class-C β-lactamases are considered in carbapenemases class. Most of the enzymes in Class C β-lactamases class show weaker activity in hydrolysis of carbapenems.

OXA-23 enzyme showed 56% protein sequence similarity with OXA-51/69, primarily found on a plasmid of *A. baumannii* strain in Scotland and represented as the first oxacillinase harboring carbapenemase activity.[57] Then onwards, *bla* OXA-23 gene was identified throughout the world, both on plasmids or on the chromosome,

and it appeared to be exclusive of genus *Acinetobacter* with an exception of *Proteus mirabilis* isolate from France.[58] Another cluster of class D enzymes was assigned after the OXA-24/40 enzyme were predicted first time as separate enzymes but after re-sequencing they were confirmed identical, initially isolated from Spain from an isolate of carbapenem-resistant *A. baumannii*.[59]

The third group is OXA-58, sharing 59% protein sequence identity with OXA-51/69 and identified in *A. baumannii*,[60] and < 50% protein sequence identity with OXA-24/40 and OXA-23. The *bla* OXA-58 gene is typically plasmid-encoded, which is most likely associated with its extensive circulation all over the world. However, *bla* OXA-58 is mainly prevalent in Greece and Italy,[61-65] where several outbreaks in pediatric and intensive care units[66-68] have been caused by OXA-58 producing carbapenem resistant *A. baumannii*. The fourth group of acquired CHDLs was identified more recently as a novel OXA- 143 enzyme in the clinical isolate of *A. baumannii* in Brazil.[69] In general, the intensity of carbapenem hydrolysis by CHDLs is considerably stumpy. Therefore, as a substrate, imipenem is preferred over meropenem and hence raising a contest on exact input of CHDLs to carbapenem resistance.[70,71] Some studies have addressed this question by using either transformation experiments or knock- out mutants to learning changes in susceptibility to carbapenems in both ordinary and recombinant plasmids holding CHDLs in different hosts.

Non-enzymatic Mechanisms (Efflux Pumps)

Among various mechanisms associated with a multidrug resistance, increased expression of chromosomally encoded efflux pumps has been proposed as the first step in the development of a MDR phenotype.[72] Efflux pumps are bacterial cell membrane components that excrete metabolic end-products and toxic substances, including antimicrobials.[73] The majority of multidrug efflux pumps prevalent in Gram-negative bacteria are completely different in their structure in that they pass through both the inner cytoplasmic membrane and outer membranes by utilizing 3 protein components.[74] The resistance-nodulation-division (RND) efflux family, which is most frequently associated with antimicrobial resistance in GNB, is composed of a cytoplasmic membrane spanning transporter protein interacting with a periplasmic MFP (membrane fusion protein) and an OMP (outer membrane protein) to facilitate the drug transport across the outer membrane.[75,76] These efflux systems include the MexAB-OprM system (previously described as MexAB-OprK) of *P. aeruginosa*[77] and the AcrAB system of *E. coli*. Apart from MexAB-OprM system, 3 more RND efflux systems have been characterized: MexXY-OprM, MexEF-OprN and MexCD-OprJ.[78,72] Interestingly, OprN are the only mutants that come into sight to pump out imipenem.

To date, three RND efflux pump systems have been described in *A. baumannii*: AdeABC,[79] AdeFGH[80] Each efflux pump is tightly regulated, e.g. AdeRS two-component regulatory system regulates the AdeABC,[82] AdeL (LysR-type transcriptional regulator) does the same for AdeFGH[80] and TetR transcriptional regulator AdeN regulates AdeIJK.[83] Up-regulation of efflux pumps expression has led to rise in antimicrobial resistance in *A. baumannii*.[84] Along with RND family, MATE and MF superfamily have also been found contributing to antimicrobial resistance in *A. baumannii*.[79,82,85] Limited data exists about the prevalence of RND efflux pumps in *A. baumannii*. Nemec *et al.* reported that the adeB gene was present in 87% of 116 genetically diverse predominantly European *A. baumannii* isolates.[86] Recently, Yoon *et al.* studied the role of the Ade RND efflux pumps in fitness and pathogenesis of *A. baumannii*.[87] The majority of the *A. baumannii* isolates have displayed a close evolutionary relationship and suggested a serious nosocomial spread and nosocomial infections of CRAB in some studies.[88]

Molecular Epidemiology

Acinetobacter spp. are widely scattered in nature ubiquitously and can be isolated from humans, animals and even from fresh-water and soil samples too. A few *Acinetobacter* spp., primarily *A. johnsonii*, *A. radioresistens* and *A. lwoffii* represent the normal skin flora. In contrast, *A. baumannii* is typically isolated from hospitalized patients and hospital settings, but not outside hospitals.[1] However, current surveillances program using molecular techniques to correctly identify *A. baumannii* demonstrated the ability of this pathogen to reside outside hospitals.[89] Patients with *A. baumannii* infection showed different parts of body being colonized by it; e.g. respiratory tract, oral cavity, the skin, and the intestinal tract.[90] Primary reservoir of *Acinetobacter* infection is formed by the infected patient; such patients frequently spread a huge number of bacterial cells the environment surrounding them, which further contaminate medical devices and from there hospital staff circulate it throughout the hospital. Frequent outbreaks of *A. baumannii* resulted via colonization of patients, hospital-wide circulation by engaged medical staff, continued survival in the hospital settings and resistance to wide range of antimicrobials

and antiseptic agents. Patient-to-patient spread and airborne transmission have also been confirmed along with indirect contact.[91,92]

A. baumannii has been seen traced in severe nosocomial infections and hospital outbreaks worldwide. 11.9% urinary tract infections (UTI), 17.1% of bloodstream infections and 21.8% of pneumonia were reportedly caused by *Acinetobacter* spp. In the ICUs of European hospitals.[18] Recently outbreaks and infections have been more commonly reported in the nursing homes or long-term care facilities.[93] *A. baumannii* was found in almost all of the outbreaks, predominantly in the ICU site, with less reports of *A. pittii* and *A. nosocomialis*. Other *Acinetobacter* spp. associated with healthcare related infections are rare; such as *A. haemolyticus, A. bereziniae*, *A. johnsonii, A. guillouiae*, *A. junii*, *A. parvus*, *A. lwoffii*, *A. schindleri, A. radioresistens*, *A. ursingii* and *A. soli*. These are mainly limited to catheter-related bloodstream infections (CRBSI)[94-96] or point source infections.[97,98,25] They are normally more susceptible to antibiotics and are typically associated with insignificant virulence. Other *Acinetobacter* spp. have been observed infrequently for small-sized outbreaks, and are regularly found to be associated with infected infusion fluids. *A. baumannii* have also been reported for causing community-acquired infections, typically in patients residing sub-tropical areas with co-morbidities.[1]

A. baumannii dissemination has been repeatedly documented in one centre or in a nation-wide level. Three European clones I–III were found spreading successfully in European hospitals.[99] Surveillance program revealed their epidemiology and found out to be disseminated worldwide and predominantly in the diverse geographical areas; therefore they are re-classified as international clones (IC) I–III.[40] *A. baumannii* nurture quickly[100] and strains with same international clone may deviate greatly; consequently, IC I–III **is** incapable of delineating the epidemiological association. Multi-locus sequence typing (MLST) differentiated the epidemiological connection among *A. baumannii* isolates in a better way[37] followed by AFLP analysis,[24] whole-genome sequencing (WGS) analysis,[101-103] pulsed-field gel electrophoresis,[104] and other molecular techniques.[99]

Virulence Factors

Inspite of being pathogen of low virulence,[1] few studies showed an array of pathogenicity markers of *A. baumannii* like; adherence, and invasion of host cells, biofilm formation, iron acquisition and host cell death.[105] Therefore, *A. baumannii* has been steadily gaining significance in the hospital seetings as a human pathogen.[4] Till date, many virulence factors (VF) have been illustrated in *A. baumannii*. Genetic manipulations, genome sequencing, and applications of recent molecular analysis methods and animal models allow broadened knowledge of additional virulence determinants. Various virulence factors have been shown to add on the *A. baumannii* pathogenicity, like; capsular polysaccharides (CPS), lipopolysaccharide (LPS), outer membrane protein A of *A. baumannii* (AbOmpA), phospholipase D (PLD), outer membrane vesicles (OMV), and biofilm.[106,31,107,108]

The ompA (outer membrane protein) gene has been found mendatory for *A. baumannii* persistence in the mouse lung.[109] Surface capsular polysaccharides have been investigated in many isolates of *A. baumannii* infections where a fixed gene cluster was traced, called the K locus also involved in antimicrobial resistance.[110] Phospholipase C (PLC), and phospholipase D (PLD) have been identified as virulence factors in *A. baumannii*.[111-113] Outer membrane vescicles (OMVs) of *A. baumannii* with more virulence factors induces cytotoxicity and a stronger innate immune response.[114] Siderophores are low molecular weight compounds with high affinity for iron. Acinetobactin siderophore is a virulence factor of *A. baumannii*.[115] *A*cinetobactin is the mixed type siderophore with an oxazoline ring derived from threonine.[106] Recently, it has been investigated in a study that acinetobactin is more frequently in MDR virulent strains than avirulent ones of *A. baumannii*.[106]

Over the last two decades, several investigations have depicted factors confering escalated antibiotic resistance to *A. baumannii*. A quick adaptation of *A. baumannii* against antimicrobial agents using *in vivo* work has defined the associated genetic burden, including nosocomial healthcare environments.[116-119] Many investigations have also reported the significance of other virulence factors too.[120,115]

A. baumannii Outbreaks

A. baumannii has been reported as a common cause of outbreaks in hospitals and long term healthcare centers, where this pathogen is linked with extended stay in hospital and probably escalating mortality.[121,122] Usually, a single clone was found to cause outbreaks in each institution by utilizing above mentioned methods, but outbreaks with multiple clones may not be rare.[123] Presently, multidrug resistance is defined for a bacterium if it is found resistant to at least one antimicrobial agent in 3 or more antimicrobial categories (antipseudomonal penicillins, antipseudomonal carbapenems, aminoglycosides, antipseudomonal fluoroquinolones, ampicillin-sulbactam, trimethoprim-

sulphamethoxazole, extended-spectrum cephalosporins, tetracyclines and polymyxins).[124] Half of *A. baumannii* were MDR in the United States in 2010.[125] Outbreaks of MDR strains cause a greater threat compared to susceptible strains to healthcare organization, causing massive economical cost, mortality and morbidity.

A. baumannii outbreaks have been experienced in military medical facilities by treating personnel allocated in Iraq and Afghanistan.[126,127] It was assumed that earlier colonized soldiers were auto-inoculated or during traumatic injury, *Acinetobacter* spp. were introduced from soil or water but that was not supported by cultures samples collected from healthy soldiers, water samples, soil samples or samples from fresh wounds.[128,129]

The normal flora of animal has never been screened, though different *Acinetobacter* spp. have been documented from animals including *A. baumannii* as occasionally isolated species from infected sites of animals.[130,48] Recently, reports of outbreak of MDR Acb complex in animals have been reported in a veterinary hospital of Israel between 2010 and 2012. This study described a severe outbreak caused by a MDR member of the *Acinetobacter calcoaceticus-baumannii* complex in dogs and cats and are probable highly fatal and difficult to exterminate.[131]

A seasonal difference in the occurrence of *Acinetobacter* infections has also been observed in USA[132,133] due to greater humidity during the days of summer. Notably, *A. baumannii* has also been recovered from around 22% of body lice by sampling from homeless people.[134] This interesting finding could be a result from silent bacteremia in such people; however the clinical implication was not yet clear of this observation.

Widespread contamination of environment is frequently demonstrated, and infection outbreaks have been traced to equipment of respiratory care, humidifiers, patient care items and wound care procedures.[135] A recent outbreak reported by Wilks *et al.* of MDR *Acinetobacter baumannii-calcoaceticus* infection, found contamination on curtains, door handles, laryngoscope blades, patient lifting equipment, keyboards and mops.[136] Hospital equipment has been implicated, highlighting the requirement for particular attention to disinfection of commonly shared items and extra caution with wound care procedures and respiratory care.[135,137] One or more epidemic clones of *Acinetobacter* frequently coexist with endemic strains, make it difficult to identify and manage transmission.[138,139] There has been a disagreement concerning the mortality directly attributed to infections caused by *A. baumannii*. The information retrieved from studies added to the previously available knowledge on this matter and substantiated that *A. baumannii* infections are undeniably related with increased mortality.[20] Infections due to *A. baumannii* have been frequently considered by clinicians and researchers not to be associated with considerable mortality.[21] In reality, *A. baumannii* has been positioned in the record of low-virulence pathogens.[140] These viewpoints have created virtual widespread beliefs among the medical community that this bug is not a cause of significant mortality in hospitalized patients, and have given rise to disagreement on the matter of attributable mortality due to *A. baumannii*.[21,141] However, the reviewed statistics put forward that *A. baumannii* infection is coupled with substantial mortality.[142]

In many health care organizations, endemic, infection due to MDR *A. baumannii* reveals multifarious epidemiologic reports and multiple strains showing co-existence. Abbo *et al.* (2005) performed a study on 118 patients with MDR *A. baumannii* infection in Israel and reported 10 different clones by PFGE-typing, along with many small groups of patients with uncommon source acknowledged, in spite of extensive investigation and molecular testing.[143] Molecular- typing by PFGE or other techniques can be utilized to identify outbreaks of *Acinetobacter* infection and to supervise regional, international or inter-institutional transmission.[144,145] Nemec *et al.* (2004) in Western Europe, utilized ribotyping method and AFLP to reveal the genetic similarity of *Acinetobacter* isolates.[145]

Molecular epidemiology of *A. baumannii* has been investigated in Northeast Ohio by merging ESI-MS (electro-spray-ionization mass spectrometry) and rep-PCR, and the data showed changing sequence types over a period of 11 years.[146] PFGE has been used to exhibit inter-institutional burden of infection caused by carbapenem-resistant *Acinetobacter* at acute care hospitals in United Kingdom, New York, Iberian Peninsula and Argentina.[147,148,46,149] PFGE was used by Gales *et al.* to demonstrate the epidemic spread of *Acinetobacter* spp. clones between Argentina and Brazil.[150]

Bacterial Cell Fitness

A key feature to decide the success of resistant bacteria is the fitness cost of antibiotic resistance mechanisms.[151] Fitness of the bacteria is the capability to fine-tune metabolism to adapt itself according to environmental conditions with the intention to grow and survive. Efflux systems of bacteria pump out not only the antibiotics but also several other metabolites and add on to the pathogenicity of Gram-negative bacteria.[152] Over-expression of efflux pumps has various contrasting effect on bacterial cell fitness and their virulence potential.[153] *S. maltophilia*, SmeDEF overproduction

reduced the fitness and decrease virulence,[119] whereas Ade RND efflux pump overproduction and Omp33 (an outer membrane protein) found associated with *A. baumannii* fitness.[87,154] Calculation of the maximum growth rate in the batch culture, *in vitro* competition index (CI) deduced generation time, end point analysis, and growth kinetics have been obseverd as the best possible marker to compare bacterial fitness of different susceptibility patterns.[155,152]

Infection Models

Animal host/models are very crucial to study pathogenesis and virulence associated with infectious agents including several bacterial pathogens. Several studies have indicated the development of fitness and virulence assays for *A. baumannii* and other human pathogens utilizing variety of mammalian infection models, especially rodents. Invertebrate infection models are gaining popularity as a substitute bacuase of the difficulties faced in haldling vertebrates models like; handle large numbers of animals, specialized staff to maintain the animals and complex facilities.[156] Successful invertebrate models of pathogenesis include *Drosophila melanogaster* (fruit fly),[157] *Bombyx mori* (silkworm),[158] *Galleria mellonella* (wax moth),[159] *Caenorhabditis elegans* (nematode)[160] and *Dictyostelium discoideum* (amoeba).[161] For bacterial pathogenesis studies, *C. elegans* and *G. mellonella* models are considered as most useful and standard laboratory models. However, for *A. baumannii* pathogenesis, *C. elegans* has several advantages over *G. mellonella* like; simple life cycle and short generation time.[162] There are very less studies on *A. baumannii* pathogenesis utilizing *C. elegans* as a host model but Vallejo *et al.* 2015 recently optimized the *C. elegans* model to study the pathogenesis of *A. baumannii*.[163]

CONCLUSION

Herein, we reviewed the recent advancements in the molecular epidemiology of CRAB isolates. We noticed some general features, like; (1) *A. baumanii* corresponds to the leading pathogenic genospecies; (2) involvement of *A. baumanii* in most cases of nosocomial infections and outbreaks in healthcare settings; (3) progressive rise in carbapenem resistance rates; (4) global spread of predominant *blaOXA-23* gene; (5) RND-type efflux pump features as the dominant one in the carbapenem resistant isolates of *A. baumannii*; (6) Bacterial fitness of *A. bauamnnii* and (7) Animal models to study the pathogenesis and associated virulence factors of *A. baumannii*. Therefore, we assume that after obtaining our own results and Figures, we will lead to depict a casuistic report, which would be pertinent to prevent or control the spread of carbapenem resistant *A. baumannii* isolates.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

CRAB: Carbapenem Resistant *A. baumannii*; **CSAB:** Carbapenem Susceptible A. baumannii; **MDR:** Multidrug Resistance; **WGS:** Whole Genome Sequencing; **MLST:** Multi Locus Sequence Typing; **PFGE:** Pulse Field Gel Electrophoresis; **RFLP:** Restriction Fragment Length Polymorphism; **RAPD:** Randomly Amplified Polymorphic DNA.

SUMMARY

- This study describes the multiple factors associated with *Acinetobacter baumannii* causing nosocomial infections worldwide.
- As per WHO 2017 reports, *A. baumannii* has been enlisted as priority pathogens.
- Escalated multidrug resistance has become a serious threat in treating *A. baumannii* infections.
- Herein, we elaborated different mechanisms of resistance and molecular epidemiology of MDR *A. baumannii*.
- Pathogenetic potential, bacterial fitness and infection host models are also described for better understanding of *A. baumannii* pathobiology.

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