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*Review Article*

# Epidemiology, Molecular Characteristics and Genotypic Resistant Profiles of *Acinetobacter baumannii*: A Narrative Review

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**Abstract**

*Acinetobacter baumannii* is an important opportunistic pathogen and is often involved in various nosocomial infections, such as bacteremia, urinary tract infection, surgical site infection, and nosocomial and ventilator associated pneumonia, especially in patients admitted to ICU. Acinetobacter baumannii is notable for its remarkable innate and acquired resistance to multiple antimicrobial classes, including extended-spectrum cephalosporins and carbapenems. Resistance to carbapenems is the most concerning, as carbapenems have a potent activity against Acinetobacter spp and are often used as a last resort for the treatment of infections due to multidrug resistant Acinetobacter baumannii isolates. In developing countries also, the misuse and underuse of antimicrobials due to lack of awareness of patients, medical workers and financial problems emerged the antimicrobial resistant strains. Due to rapid globalization of human population by travel and other factor these resistant strains spread easily between developed and developing countries making it a global problem.

**Keywords:** *Acinetobacter baumannii*; multidrug resistant; Opportunistic pathogen
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## Introduction

Multidrug resistant Acinetobacter baumannii is a rapidly emerging opportunistic pathogen associated with a variety of nosocomial infection, including ventilator-associated pneumonia, bacteremia, surgical site infections, secondary meningitis and urinary tract infections[1]. Artificial ventilation and other invasive procedures, exposure to antibiotics, colonization pressure, environmental contamination in ICU and underlying illness facilitate the spread of these multidrug-resistant species in ICU[2].

Formerly, *Acinetobacter* species were susceptible to beta-lactam antibiotics, mainly ceftazidime and carbapenems. In recent times, the clinical isolates demonstrating resistance to cephalosporins and carbapenems are very high[3]. High level of resistance was recorded for ampicillin (86.3%), cefazolin (93.2%), gentamicin (61.5%), cefotaxime (65.8%), ceftriaxone (61.5%) and ciprofloxacin (69.2%)[4]. However, several studies have suggested that tigecycline and colistin may be effective in infections caused by carbapenem resistant strains of *Acinetobacter baumannii*[5-6]. Reduced Acinetobacter baumannii susceptibility to these drugs has recently been reported from several countries across the world[7-8]. The production of beta-lactamases, changes in permeability, increase in the efflux pump and modification of penicillin binding proteins (PBPs) have been described

regarding resistance to beta-lactam antibiotics[9]. Several mechanisms for acquiring colistin resistance have been described in *Acinetobacter baumannii*. Mutations in the genes encoding the two-component signaling protein pmrA and PmrB and mutation in lipopolysaccharide biosynthesis genes lpxA, lpxC and lpxD mediate colistin resistance[10-11]. Tigecycline non susceptibility in *Acinetobacter bauamnnii* isolates has been associated with over expression of a variety of efflux pumps such as AdeABC, AdeIJK, AdeFGH, AbeM and AdeDE[12].

**The genus Acinetobacter**

*Acinetobacter* was first described in 1911 by a Dutch microbiologist by the name of Martinus Willem Beigerinck as *Micrococcus calco-aceticus*. Since then, it has had several names, becoming known *Acinetobacter* in the 1950s[13]. The genus *Acinetobacter* can presently be defined as gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive and oxidase-negative coccobacillary bacteria with a DNA G and C content of 39% to 47%[1]. Nonetheless, gram-staining of *Acinetobacter* can be variable and the morphologic characteristics may change depending on the growth phase[14].

**Acinetobacter species**

At least 33 species within the Acinetobacter genus have so far been identified, including 24 named species and 9 currently described as genomic species (gen.sp.) given that no phenotypic properties have been found to differentiate them from other species[15]. In 1986, twelve *Acinetobacter* genomic species within the *Acinetobacter* genus were identified by DNA-DNA hybridization[16]. Six of these DNA groups could be differentiated by phenotypic properties and were given the following formal species names: *Acinetobacter calcoaceticus* (*Acinetobacter* gen. sp. 1), *Acinetobacter baumannii* (*Acinetobacter* gen. sp. 2), *Acinetobacter haemolyticus* (*Acinetobacter* gen. sp. 4), *Acinetobacter* junii (*Acinetobacter* gen. sp. 5), *Acinetobacter* johnsonii (*Acinetobacter* gen. sp. 7) and *Acinetobacter lwoffii* (*Acinetobacter* gen. sp. 8). The study reported an uncertain genotypic and phenotypic differentiation of *Acinetobacter* gen. sp. 9 from *Acinetobacter lwoffii*. In 2001 and 2003, Nemec identified three novel species names as *Acinetobacter schindleri*, *Acinetobacter* ursingii and *Acinetobacter* parvus[15]. Concurrently seven novel species were identified (*Acinetobacter baylyi*, *Acinetobacter bouvetii, Acinetobacter towneri*, *Acinetobacter tandoii*, *Acinetobacter grimontii*, *Acinetobacter tjernbergiae* and *Acinetobacter gerneri*)[17]. However, *Acinetobacter grimontii* was later re-classified within the *Acinetobacter* junii species. One novel species was identified and named as *Acinetobacter* septicus in 2008 although it was soon after re-classified within the *Acinetobacter ursingii* species[18]. Three novel species (*Acinetobacter soli*, *Acinetobacter beijerinckii* and *Acinetobacter gyllenbergii)* were also identified in 2008 and 2009 by two different research groups[19]. Furthermore, *Acinetobacter* gen. sp. 10, *Acinetobacter* gen. sp. 11, *Acinetobacter* gen. sp. 3 and *Acinetobacter* gen. sp. 13TU have recently been named *Acinetobacter berezinae*, *Acinetobacter guillouiae, Acinetobacter pittii* and *Acinetobacter nosocomialis*, respectively, given that they can phenotypically be differentiated from other species within the genus *Acinetobacter*[20].

**Natural Habitat**

Members of the genus *Acinatobacter* are considered ubiquitous organism. This holds true for the genus *Acinetobacter*, since *Acinetobacters* can be recovered after enrichment culture from virtually all samples obtained from soil or surface water[21]. The organism does not always act as an infecting pathogen, as it is widely distributed in nature and has tremendous colonizing potential[14].

The organism prefers moist environment, therefore, its colonization among damaged tissues is common[22]. *Acinetobacter* species are apparently the only group of gram-negative bacteria that may be natural residents of human skin[23]. A study from Germany reported high carriage rates of *Acinetobacter* spp. on human skin and mucus membrane among in patients (75%) and control non-hospitalized persons (43.0%). The most frequently isolated species in that study were *Acinetobacter lwoffii* (47.0%) and *Acinetobacter johnsonii* (21.0%). Unpredictably, the clinically important *Acinetobacter baumannii* and *Acinetobacter nosocomialis* species (0.5% and 1.0%, respectively) were not found to be common human skin colonizers[23].

In patients hospitalized on a regular ward, the carriage rate of *Acinetobacter* species was even higher, at 75.0%[23]. *Acinetobacter* species are fecal carriage and carrier rate is 25.0% among healthy individuals, with *Acinetobacter johnsonii* and *Acinetobacter genomic* species 11 predominating[24]. In contrast, *Acinetobacter baumannii*, the most important nosocomial *Acinetobacter* species, was

found only rarely on human skin, 0.5% and 3.0% respectively[25].

**Epidemiology**

The ecology of bacteria belonging to the genus *Acinetobacter* is diverse. These organisms have been recovered from soil, surface water, vegetables, animals, human body lice and humans[21]. Bacteria of this species have been isolated mainly from hospitalized patients, but also from hospital environment[26]. There are indications that skin and mucous membrane colonized by clinically relevant species is an important source of infections in hospitalized patients, thereby contributing to the development and persistence of outbreaks[14]. *Acinetobacter baumannii* has the capacity to survive on inanimate surfaces, such as ventilation equipment and bedding materials for upto five months[27].

The incidence of *Acinetobacter baumannii* infections varies widely: from less than 1% in different European hospitals to 32.0% among ventilated patients in a Taiwanese hospital[28]. *Acinetobacter baumannii*, *Acinetobacter pittii* and *Acinetobacter nosocomialis* are the species most frequently involved in these infections[29]. *Acinetobacter baumannii* strains have become endemic in multiple centres and outbreaks have been observed worldwide[1].

A systematic review of published nosocomial outbreaks in the intensive care units (ICU) setting from 2005 to 2010 has revealed that *Acinetobacter baumannii* was responsible for almost 25% of ICU infection outbreaks[30]. Three major lineages of genetically highly related *Acinetobacter baumannii* strains, designated European (EU) clone I, II and III are frequently implicated in outbreaks[31]. A recent striking manifestation is the occurrence of *Acinetobacter baumannii* infections in soldiers severely injured during the conflicts in Iraq and Afghanistan[32]. Although *Acinetobacter* is mainly associated with nosocomial infection, several cases of community-acquired pneumonia, mostly associated with underlying diseases, have been reported[33].

**Morphology and Identification**

Typical Organism: Members of the genus *Acinetobacter* are gram-negative *coccobacilli*, during periods of rapid growth (exponential phase), the organism typically appear bacillary or *coccobacillary* 1-1.5 by 1.5-2.5 microns in size. Notably they become more coccoid or diplococcal as the culture ages (stationary phase). The Acinetobacter are non-motile but occasionally an odd twitching motility can be demonstrated[34].

**Culture Characteristics:** *Acinetobacter* is easily isolated in standard cultures but is relatively nonreactive in many biochemical tests commonly used to differentiate among gram-negative bacilli. *Acinetobacter* are non-lactose fermenters but may produce a slight pinkish hue that could be mistaken for lactose fermentation. The Older cultures frequently capsulated, occasionally causing problems with destaining the crystal violet. *Acinetobacter* are strictly aerobic and are capable of growing at a wide range of temperatures. For the most part, the species are not fastidious and capably grow on the standard nutritional medium used in the laboratory. Occasionally, strains may be encountered that are fastidious, failing to grow in nutrient broth and forming smaller colonies in Blood agar. For clinical isolates, growth on MacConkey agar is variable and presenting as either colorless or light pink colonies. A. c*alcoaceticus-A. baumannii* complex colonies resembles those of *Enterobacteriaceae,* with a diameter of 1.5 to 3 mm after overnight culture, whereas most of the other *Acinetobacter* species produce smaller and more translucent colonies. Unlike the Enterobacteriaceae, some *Acinetobacter* species outside the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex may not grow on MacConkey agar[1]. The colonies are 1-2 mm in diameter (smaller than typical Enterobacteriaceae) and are typically doomed, smooth to slightly mucoid and opaque. Pigmentation is usually grayish-white, although some strain may appear pale yellow. Hemolytic activity on Blood agar is variable, although a diffusible brown pigment has been observed when glucose has been added to the medium[35].

**Growth characteristics:** Most clinical strains of Acinetobacter grow optimally at 37°C, while the environmental isolates prefer low temperatures. Utilization of carbohydrates varies considerably among the species. Nitrates are not reduced to nitrites. The ability to hydrolyze gelatin and urease is variable. Members of the genus Acinetobacter are gram negative, catalase positive and oxidase negative[1].

**Virulence Factors**

Despite the increasing clinical importance of Acinetobacter baumannii infections, relatively little is known about the factors that contribute to its pathogenesis. Of the studies addressing Acinetobacter baumannii that have been carried out over the preceding decades, the majority either describe the epidemiology, risk factors, and outcomes of infections caused by these bacteria or aimed to optimize antibiotic regimens for the treatment of

infections produced by MDR strains. While these studies provide important information regarding the epidemiology and clinical management of *Acinetobacter baumannii* infections, they do not address the underlying biological basis for the increasing success of this organism as a human pathogen[36]. Prevalence of Virulence Factors (VF) contributed to pathogenesis in bacteria[37]. Virulence factors help bacteria to colonize on the epithelium, evade and inhibit the host's immune response through biofilm formation and obtain nutrition from the host[38-39]. During the past decades, new virulence factors have been described in *Escherichia coli*. Pathogenicity associated islands (PAI) are blocks of virulence factor genes that provide a mechanism to coordinate horizontal transfer of virulence factor genes between lineages, and even between species, and have emerged as characteristic of diverse pathogenic bacteria, including *uropathogenic* E. coli strains[40]. Recognized or determine virulence factor in *uropathogenic* E. coli include diverse adhesins, as P fimbriae (pap genes), S and F1C fimbriae (sfa), Drantigen family (afa/dra), type 1 fimbriae (fimH) and curli fibers (csg), fibronectin receptor (fbn), toxins, as cytotoxic necrotizing factor (cnf), siderophores, as yersiniabactin (fyuA) and aerobactin (iutA); invasins as IbeA; polysaccharide coatings as group II and III capsules (kpsMT); serum resistance (traT) and colicin V production (cvaC)[40-45]. Identification of virulence factors in *Acinetobacter baumannii* is a kee to fighting this pathogen. Genes coding for some recognized virulence factors identified in uropathgenic E. coli strains were detected in *Acinetobacter baumannii*[46-49].

**Antibiotic Resistance Profiles**

The wide array of antimicrobial resistance mechanisms for *Acinetobacter baumannii* is impressive and rivals those of other non-fermentative gram-negative pathogens[50]. Definitions of multidrug-resistant *Acinetobacter* species vary, referring to a wide array of genotype and phenotypes. Two of the most common definitions of multidrug resistance are carbapenem resistance or resistance to 3 classes of antimicrobials[51]. *Acinetobacter baumannii* is considered the paradigm of multidrug-resistant bacteria as the organism has an ever-increasing list of resistance determinants that can rapidly nullify most of the therapeutic armamentarium. Both acquired and intrinsic resistance mechanisms can contribute this multi-resistance. The ability to acquire such resistance for multiple drugs may be due to either the acquisition of genetic elements carrying multiple resistant determinants or mutations affecting the expression of porins and/or efflux pumps, which can minimize the activity of unrelated antimicrobial agents[52]. The genetic surroundings of these resistance determinants provided more evidence for genetic promiscuity, with an array of broad-host-range mobile genetic elements identified, including three class I integrons, transposons and insertion sequence (IS) elements[2].

**Resistance to β-lactams:** The main resistance mechanisms to multiple antibiotics in Acinetobacter spp. can be summarily outlined as follows (i) production of hydrolysing enzymes for e. g, β-lactam hydrolysis by different kinds of β-lactamases (Class A to D β-lactamases), (ii) changes in penicillin-binding proteins (PBPs) that prevent the action of β-lactams, (iii) alterations in the structure and number of porin proteins that result in decreased permeability to antibiotics through the outer membrane of the bacterial cell and (iv) the activity of efflux pumps that further decrease the concentration of antibiotics within the bacterial cell[53]. Attempts have been done to sort β-lactamases since 1968. The classifications are derived from two major approaches; the first one is rooted on functional criteria and second one is based on molecular structure (amino acid sequence) of the enzyme. Some researcher cited the latest functional classification of β-lactamases founded on enzyme inhibition profile and antimicrobial substrate profile[54]. According to their classification scheme, β-lactamases are segregated into groups (1-4) and subgroups (a-f). Group 1 are cephalosporinases, not well inhibited by clavulanic acid, group 2 β-lactamases are penicillinase or both penicillinase and cephalosporinases, generally inhibited by β-lactamase inhibitors and group 3 are penicillinase, cephalosporinases and carbapenemase (metallo-β-lactamases), poorly inhibited by all classical β-lactamase inhibitors except EDTA and p-chloromercuribenzoate (pCMB) and group 4 are penicillinases, not inhibited by clavulanic acid. Depending on nucleotide and amino acid sequence of the enzymes, Ambler first recommended the Structural classification of β-lactamases. As only four amino acid sequences were known during that time, the author distinguished serine-based class A penicillinase from class B MBL[55]. Afterward a new class of serine based β-lactamases designated as class C that has only a few sequences homology to class A enzymes, was detected[56]. Subsequently the class D enzyme was described; the OXA β-lactamases bear little resemblance to either class A or class C[57]. The classification schemes of β-lactamases and its correlation with moleculer structure are shown in table 2.2.

**Table 1: Classification schemes for β-lactamases and itscorrelation with molecular structure54**

| Bush-Jacoby-Medeitors group | Bush group | Richmond-Skyes class | Mitsuhashi-Inouetype | Molecular class | Preferred substrate | Inhibited by: CA | EDT | Representative enzyme |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Ia, Ib, Id | CSase | C | Ceph | - | - | Ampc of gram (-ve) bacteria; MIR-1 |
| 2a | 2a | NI | Pcase V | A | Pen | + | - | Pcase from gram positive bacteria |
| 2b | 2b | III | Pcase I | A | Pen, ceph | + | - | TEM-1, TEM-2, SHV-1 |
| 2be | 2b | NI except KI | CXase | A | Pen,narrow-spectrum and extended spectrum ceph.monobac | + | - | TEM-3toTEM-26,SHV-2 toSHV-6,*K.Oxytoca* KI |
| 2br | | NI | NI | A | Pen | +/- | | TEM-30 toTEM-36, TRC-1 |
| 2c | 2c | II, V | Pcase IV | A | Pen, carben | + | - | PSE-1, PSE-3, PSE-4 |
| 2d | 2d | V | PcaseII, PCaseIII | D | Pen, cloxa | +/- | | OXA-1 to OXA-11, PSE-2 (OXA-10) |
| 2e | 2e | 1e | CXase | A | Ceph | + | - | Inducible Csase from *p.vulgaris* |
| 2f | | NI | NI | A | Pen, ceph, carbapenem | + | - | NMC-A from *Entrobactercloacae,* Sme-1 from *Serratia marcescens* |
| 3 | 3 | NI | NI | B | Most β-lactams, includingcarbap | - | + | LI from *Xanthomonas maltophilia,* CerA from *Bacteroids fragilis* |
| 4 | 4 | NI | NI | ND | Pen | - | ? | Penicillinase from *P.cepacia* |

Note: CA: clavulanic acid, Carbap: carbapenem, Carben: carbenicillin, Ceph: cephalosporin, CSase: cephalosporinase, CXase: cefuroxime-hydrolyzing ß-lactamase, Monobac: monobactam, ND: not determined, NI: not included, PCase: penicillinase, pen: penicillin.

The over-expression of intrinsic and/or the horizontal obtaining of acquired β-lactamase genes encoding enzymes from the four different moleculer classes A to D is the main mechanism of Acinetobacter resistance to β-lactams[58-59].

**A-class:** A wide range of class A β-lactamases including the narrow- spectrum (TEM-1, TEM-2, CARB-5 and SCO-1), extended-spectrum (TEM-92, TEM-16, SHV-2, SHV-5, SHV-12, CTX-M-2, CTX-M-3, CTX-M-43, PER-1, PER-2, PER-6, VEB-1, VEB-1a, VEB-3, GES-11 and GES-12) and carbapenem- hydrolyzing (GES-14, KPC-2, KPC-3, KPC-4 and KPC-10) variants have been identified mainly in *Acinetobacter baumannii* but also among *Acinetobacter* isolates from other species[60]. The molecular class A beta-lactamases of the KPC family are a group of potent carbapenemases identified initially in a *Klebsiella pneumoniae* isolate from the United States and later in other members of the *Enterobacteriaceae* family and in other geographical regions world wide[61]. *Pseudomonas aeruginosa* positive for the *bla*KPC gene has been recently identified in Colombia, Puerto Rico, and Trinidad and Tobago[62]. Up to date, eight different KPC variants (KPC-2 to -9) have being identified differing by 1 or 2 two amino acid substitutions. KPC-2 and -3 are the most common variants identified in *Enterobacteriaceae* and P. aeruginosa. KPC-6, -7, and -8 have been identified only in *Klebsiella pneumoniae*, while KPC-9 was detected in *Escherichia coli* and KPC-5 in P. aeruginosa. All the KPC variants except for KPC-7 and -9 have been detected in Puerto Rico[63]. The presence of the KPC gene in clinical isolates of *Acinetobacter* species in Puerto Rico is identified as a novel KPC variant, KPC-1064. The presence of this gene suggests the possibility of horizontal transmission, as

this carbapenemase has been associated with mobile genetic elements (transposons) which can be transferred from one bacterium to another[65]. Class A β-lactamase genes are generally considered to be less widespread among *Acinetobacter* than *Enterobacteriaceae* species[66]. However, assessment of the true prevalence of extended –spectrum class A β-lactamase in *Acinetobacter* might be underestimated since it has been hindered by difficulties with laboratory detection, especially in the presence of intrinsic AmpC enzyme[67].

**B-class:** Class B β-lactamases (metallo-β-lactamases, MBLs) confer high levels of carbapenem resistance as well as resistance to all other β-lactams except for aztreonam. MBLs are characterized from other classes of β-lactamases by being susceptible to EDTA inhibition due to the requirement of zinc ions (Zn+2) in the active site[68]. Several IMP (IMP-1, IMP-2, IMP-4, IMP-5, IMP-6, IMP-8, IMP-11) and VIM (VIM-1, VIM-2, VIM-4, VIM-11) variants have been detected among isolates from the *Acinetobacter baumannii-Acinetobacter calcoaceticus* complex[69]. SIM-1 was first described in *Acinetobacter baumannii* isolates from Korea[70]. The study reported a lower level of carbapenem resistance conferred by SIM-1 compared with that coferred by IMP and VIM variants[70]. NDM-1, the new Delhi metallo-β-lactamase, is a novel metallo-β-lactamse (MBL) conferring resistance to almost all β-lactam antibiotics, including carbapenems, recently identified in *Klebsiella pneumoniae* and *Escherichia coli* isolates from a Swedish patient who travelled to New Delhi, India[71]. Following the first description, sporadic cases of infected patients have been reported in India, the UK and the USA72-73. Kumarasamy et al[73] have recently reported the emergence and spread of 180 cases of patients infected with bacteria carrying the NDM-1 encoding gene from Pakistan, India and the UK. Interestingly, most patients from the UK had travelled to India or Pakistan within 1 year and had been hospitalized in these countries, suggesting that these organisms were acquired from a local source in Asia. Since August 2010, other cases have been reported worldwide, including in the USA, Canada, Europe, Japan, Africa, Oman and Australia[74].

The rapid spread and dissemination of these multidrug-resistant bacteria worldwide represents a major public health problem, thus the US Centers for Disease Control and Prevention (CDC) has recently planned to add NDM-1 producing MDR bacteria as agents of communicable diseases and hospitals must immediately report any suspect cases, particularly those for which the patient received medical treatment in India or Pakistan. The aim of this work was to develop a rapid real-time polymerase chain reaction (PCR) assay to detect the NDM-1 encoding gene in bacteria. Interestingly, resistance to carbapenems mediated by the coexistence of *bla*NDM-1, *bla*OXA-23 and *bla*IMP has been detected in pan-drug resistant *Acinetobacter baumannii* isolates from China. The *bla*NDM-1-positive strain was more resistant to antibiotics than the strains that were harbouring both OXA-23 and IMP. Fortunately, it was found that this *bla*NDM-1-positive *Acinetobacter baumannii* strain was susceptible to several fluoroquinolone antibiotics and to polymyxin *B75*.

NDM-2, a variant of NDM-1 with only one amino acid substitution, has recently been described in an *Acinetobacter baumannii* isolate recovered from a patient transferred to Germany from Egypt[76]. In *Acinetobacter baumannii*, six IMP variants belonging to three different phylogroups have been identified and reported namely IMP-1 in Italy, Japan and South Korea; IMP-2 in Italy and Japan; IMP-4 in Hongkong; IMP-5 in Portugal; IMP-6 in Brazil and IMP-11 in Japan[68]. In addition, IMP-4 has been identified in clinical isolates of *Acinetobacter* junii in Australia[77].

On the contrary, there are only few studies that have documented VIM type of MBL in *Acinetobacter*. Surprisingly, P. aeruginosa isolates collected from the same hospital showed the presence of VIM type of MBL and there was no cross transmission observed. VIM-2 producing *Acinetobacter* spp. have been isolated in the Far East and in Germany, while the VIM-1 determinant has been reported only in Greece[78-80]. VIM-4 is nothing but a point mutant of VIM-1 and that has been previously identified only in *Enterobacteriaceae* and *Pseudomonas* spp.[81].

C-class: Class C β-lactamases (AmpC cephalosporinases) are enzymes able, when over-expressed, to hydrolyze most penicillins, cephalothin, cefazolin, cefoxitin, ceftazidime and β- lactamase inhibitor/β-lactam combination, but generally not cefepime or carbapenem. So far, the chromosomal-encoded AmpC cephalosporinase genes have only been identified in a few *Acinetobacter* species (A.*baumannii*, A pittii and A. baylyi)[82].

Constitutive over-expression of AmpC β-lactamases in gram-negative organisms occurs either by deregulation of the AmpC chromosomal gene or by acquisition of a transferable AmpC gene on a plasmid or other transferable element. The transferable AmpC gene products are commonly called plasmid-mediated AmpC β-lactamases[83]. Several plasmid encoded AmpC beta-lactamases (MIR-1, CMY-1 to CMY-11. BIL-1, FOX-1 to FOX-5, LAT-1 to

LAT-4, ACT-1, MOX-1, MOX-2, ACC, DHA-1 and DHA-2) have been isolated from *Klebsiella pneumoniae*, K. oxytoca, Salmonella spp., Proteus mirabilis, *Escherichia coli*, Citrobacter freundi and Enterobacter aerogens. Plasmid mediated enzymes are grouped into six families based on similarities with enzymes of chromosomal origins[84]. Plasmid mediated genes that encode extended-spectrum β-lactamases (ESBLs) or AmpC enzyme, can spread to other organisms within hospital setting[85]. Multiple β-lactamases within one organism (e.g., multiple ESBLs or ESBL-AmpC combinations) can make phenotypic identification of the β-lactamases difficulty. Unfortunately, for these reasons, plasmid-mediated AmpC β-lactamase resistance goes undetected in most clinical laboratories[86].

**D-class:** The most common carbapenemases detected in *Acinetobacter* are CHDLs (carbapenem hydrolyzing oxacillinases) that are also referred as Classs -D oxacillinases. Among the nine clusters of carbapenem hydrolysing oxacillinases, four have been identified in *Acinetobacter baumannii*. These included members of OXA-23, -24, -51 and -58 families. In addition, recently a novel class D enzyme named OXA-143 has been reported from germany, OXA-58 oxacillinase was the first enzyme to be identified in an *Acinetobacter baumannii* isolate in France and subsequently this has been reported among *Acinetobacter baumannii* isolates in several countries[87].

Recently, a new OXA class D β-lactamase Oxa-97 has been reported in Tunisia which belongs to Oxa 58-like (subgroup) in Africa[88]. In one instance, a novel Oxa-143-CHDL in *Acinetobacter baumannii* which is not associated with insertion sequence (IS) elements[89]. Oxa-143 is a class D carbapenemase is similar to OXA-66/OXA-51-like enzyme that contributes to imipenem resistance, which was first reported from Taiwan. Off late, OXA-72 oxacillinase has been also reported in several carbapenem resistant *Acinetobacter baumannii* in Taiwan[90].

**Resistance to colistin:** The rapid development of carbapenem-resistant MDR *Acinetobacter baumannii* has led to the use of polymyxins (in particular polymyxin B and colistin or polymyxin E) as the drug of "last resort"[91]. Polymyxins are cyclic, positively charged peptide antibiotics capable of posing antimicrobial activities to a broad variety of gram-negative pathogens, including *Acinetobacter baumannii*, due to their interaction with the lipid A moiety of lipopolysaccharide (LPS). This leads to the disorganization and disruption of the outer membrane integrity, causing cytoplasmic leakage[92]. Unfortunately, the intensive use of the polymyxins in recent years has led to the emergence of polymyxin heteroresistant and resistant *Acinetobacter baumannii*, as high as 40.7% reported in Spain and 30.6% in Korea[93-94]. The basis of polymyxin resistance in *Acinetobacter baumannii* has only recently been investigated and several mechanisms have been proposed. Several genetic loci have been implicated in the resistance towards polymyxins in *Acinetobacter*, namely, the pmrCAB operon and the lpxA, lpxC, lpxD, and lpxB genes, that are involved in LPS biosynthesis[11,95-96]. Resistance can arise through mutations in the two component system PmrAB, in which the downstream target PmrC catalyzes the addition of phosphoethanolamine to the lipid A component of LPS[95]. This modification reduces the net negative charge of the outer membrane thus reducing the affinity of polymyxins for the target. Mutations or insertions in the genes encoding the lipid A biosynthesis machinery, namely, the lpxA, lpxC, or lpxD genes, also mediate polymyxin resistance by abolishing the production of LPS, thereby eliminating the target of polymyxins[11].

**Resistance to Tigecycline:** Tigecycline, a new class of glycylcyclines, is modified by addition of a 9-t-butyl-glycylamido side chain to minocycline[97]. The drug binds to bacterial ribosomes with high affinity and therefore evades the major resistance mechanisms of tetracycline, retaining activity against a broad range of both gram-positive and gram-negative bacteria, including multidrug-resistant *Acinetobacter baumannii*[98]. However, tigecycline resistance has emerged recently and been detected during treatment with this agent[99]. Tigecycline nonsusceptibility in *Acinetobacter baumannii* isolates has been associated with overexpression of a variety of efflux pumps. The major clinically relevant efflux pumps, such as AdeABC, AdeIJK, AdeFGH, AbeM, and AdeDE, have all been identified in *Acinetobacter baumannii*. These efflux pumps display broad substrate specificity, and tigecycline is one such substrate[100].

**Clinical Symptoms**

The most frequent clinical manifestations of Acinetobacter infection are ventilator-associated pneumonia and bloodstream infections[101]. Vascular catheters and the respiratory tract have been the most frequent sources of *Acinetobacter bacteremias* for which crude mortality rates parallel those attributed to other gram-negative bacilli (28 to 32%)102-103. *Acinetobacter pneumonia* occurs predominantly in ICU patients who require mechanical

ventilation and tends to be characterized by a late onset. Affected patients spend more days in the ICU and on a ventilator before having positive cultures than do patients with pneumonias caused by other gram-negative bacilli or uninfected patients[14]. The clinical effect of ventilator-associated pneumonias has been variable. A recent study showed higher mortality among patients with multidrug-resistant *Acinetobacter* infections than among patients infected with susceptible Acinetobacter strains or uninfected patients. The severity of illness is more in multidrug-resistant *Acinetobacter* infections in patients who had hospitalized in ICU[104]. In other studies, mortality among patients with pneumonia due to multidrug-resistant *Acinetobacter* was similar to that among patients with infection caused by other pathogens[105].

## Prevention and Control

Antimicrobial resistant bacteria are the emerging current threats. The followings are some control and preventive measures should be taken to minimize their developments, spread and to promote development of new therapeutics. Most of the infections spread and occur from the contact of infected persons and lack of hygienic practices. Proper sanitation and hygiene maintenance in food and other things can reduce the spread of superbugs. Inappropriate use of antibiotics occurs due to unnecessary length of treatment, wrong prescription and its use without infections[106]. Both physicians and people education about it can check the development of resistant strains. Some policies and regulations should be practiced in both developing and developed countries to check the unnecessary drug promotions[107]. Antibiotics are used vividly in food animals like chicken, cattle, pigs, agricultural fields and fish farming methods. These uses establish a direct link for the appearance of resistance in humans[108]. Attempts should be taken to check the spread of antimicrobial resistances by restricting human to human transmission of resistant strains, decreasing the use of broad spectrum antimicrobial and developing new and novel antimicrobials[109]. Steps should be taken to prevent infections by inhibiting key gene products involved in the infection process[110].

## Conclusion

*Acinetobacter baumannii* is one of the main pathogens of nosocomial infection and clinical opportunity infection, and it is also the most important strain causing outbreak of *Acinetobacter* in hospital environment. With the extensive application of broad-spectrum antibacterial drugs and the popularization of interventional procedures, *Acinetobacter baumannii* is resistant to a variety of antibiotics, and gradually develops into multi-drug resistance and even total drug resistance. Vivid research and application of Nanotechnology for identification of resistant bacteria and therapy for combating superbugs should be practiced.

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