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## REVIEW

# *Acinetobacter* spp. as nosocomial pathogens: Epidemiology and resistance features



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### KEYWORDS

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**Abstract** The genus *Acinetobacter* is a major cause of nosocomial infections; it is increasingly being associated with various epidemics and has become a widespread concern in a variety of hospitals worldwide. Multi-antibiotic resistant *Acinetobacter baumannii*, is now recognized to be of great clinical significance. Numerous reports relay to the spread of *A. baumannii* in the hospital settings which leads to enhanced nosocomial outbreaks associated with high death rates. However, many other *Acinetobacter* spp. also can cause nosocomial infections. This review focused on the role of *Acinetobacter* spp. as nosocomial pathogens in addition to their persistence, antimicrobial resistance patterns and epidemiology.

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## 1. Historical background of the genus *Acinetobacter*

The discovery of the genus *Acinetobacter* occurred in 1911, where Beijerinck identified a pathogen named *Micrococcus calcoaceticus* from soil on a calcium acetate-mineral medium (Dijkshoorn, 2008; Doughari et al., 2011). It has had several names, becoming known as *Acinetobacter* in the 1950s (Munoz-Price and Weinstein, 2008). *Acinetobacter* group were previously insufficiently defined for a very long time and confusedly classified into different genera e.g. *Achromobacter anitratus*, *Achromobacter mucosus*, *Alcaligenes haemolysans*, *Cytophaga*, *Diplococcus mucosus*, *Bacterium anitratum*, *Herellea vaginicola*, *Lingelshemia*, *Mimapolymorpha*, *M. calcoaceticus*, *Moraxella lwoffii* and *Neisseria winogradskyi* (Jung and Park, 2015). The genus *Acinetobacter* (from the Greek *akinetos*, i.e., nonmotile), was originally suggested in 1954 by Brisou and Prevot (1954) to distinguish the organisms based on their motility in the tribe “*Achromobacteraceae*” and was composed of non-pigmented Gram-negative saprophytic bacteria comprising both oxidase-negative and oxidase-positive species (Brisou and Prevot, 1954; Jung and Park, 2015). In 1957, Brisou identified a typical species named *Acinetobacter anitratum* (Brisou, 1957; Jung and Park, 2015). In 1974, Bergy’s Manual of Bacteriology placed these bacteria in the

family *Neisseriaceae* with only *Acinetobacter calcoaceticus* as a species and the two subspecies *A. anitratum* and *Acinetobacter lwoffii*, based on the observation that *Acinetobacter* has the potential to acidify glucose (Doughari et al., 2011; Balachandran et al., 2015). In the literature, the species *A. calcoaceticus* has been divided into two subspecies. *Anitratum* and *A. calcoaceticus* bv. *lwoffii*, based on similar characteristics (Peleg et al., 2008).

## 2. Morphological and physiological characteristics

*Acinetobacter* spp. are short, plump, typically 1.0–1.5 µm by 1.5–2.5 µm in size as measured during the rapid phase of their growth but often develop into more coccoid in the stationary phase, usually present in pairs or long chains of variable length (Jung and Park, 2015). *Acinetobacter* spp. are non-fastidious and can be easily grown on regular laboratory media. On blood agar plates, colonies display typical shapes and size, being colorless (white or cream colored), smooth, or mucoid (when capsule is present), milky, 1–2 mm in diameter (after 18–24 h incubation at 37 °C), whereas colonies display bluish to bluish gray color on eosin methylene blue agar. On Herellea agar, the colonies are pale lavender in color, while on Leeds *Acinetobacter* medium, the colonies are pink on a purple

background (Doughari et al., 2011). Characteristic of colonies on MacConkey agar are light lavender color indicating non-lactose fermenters. The genus *Acinetobacter* comprises species that are strictly aerobic, non-motile, catalase-positive, indole-negative, oxidase-negative, Gram-negative, and citrate positive (Kurcik-Trajkovska, 2009) with G + C content of 39–47% (Peleg et al., 2008). They are non-glucose-fermenting encapsulated cocco-bacilli rods which prevail in fluid media, particularly during the early stages of growth (Kurcik-Trajkovska, 2009). Many strains are unable to reduce nitrates to nitrites and the optimum temperature is 33–35 °C (Doughari et al., 2011). The cell wall of *Acinetobacter* is typical of that of Gram negative bacteria, however de-staining is difficult because it keeps the crystal violet and this can lead to erroneous detection as Gram-positive cocci.

### 3. Current taxonomy

The species' names have endured substantial taxonomic changes over the years due to the advanced understanding of molecular methods of the genetic make-up of this group of microorganisms. Recent classifications which seem to have gained wide acceptance among bacterial taxonomists have accepted this group of bacteria as gamma *Proteobacteria* categorized in the order *Pseudomonadales* and the family *Moraxellaceae*. Thus the taxonomical classification is given as; Domain: Bacteria, Phylum: Proteobacteria, Class: Gamma *Proteobacteria*, Order: Pseudomonadales, Family: Moraxellaceae, Genus: *Acinetobacter*. The species *A. baumannii*, *Acinetobacter haemolyticus* and *A. calcoaceticus* are of clinical significance (Jung and Park, 2015).

### 4. Natural habitats for *A. baumannii*

*Acinetobacter* is a heterogeneous group of organisms that are typically free living saprophytes, found almost everywhere, commonly distributed in the environment. However, different species of the genus are generally associated with various habitats e.g. soil, water, sewage, human, foods and animals (Kurcik-Trajkovska, 2009; Doughari et al., 2011; Jung and Park, 2015).

*Acinetobacter* spp. are generally considered a part of the normal flora of the skin (Towner, 2006), mucous membranes or the pharynx, and human respiratory secretions (Munoz-Price and Weinstein, 2008) and are accountable for a wide variety of local and systemic infections, including pneumonia, septicemia and wound infections (Beggs et al., 2006). The main body areas populated by these microorganisms in hospitalized patients are the skin, oropharynx, and digestive tract (Jung and Park, 2015). In a study conducted by Seifert et al. (1997), *Acinetobacter* spp. were isolated from various locations of the healthy individuals' body including the forehead, nose, ear, throat, trachea, conjunctiva, hand, vagina and perineum, inhabiting humid areas, such as axillae, the groin and toe webs (Seifert et al., 1997).

*Acinetobacter* spp. have frequently been isolated from animals including birds; fish and rainbow trout (Peleg et al., 2008; Kanafani and Kanj, 2014). They have also found that food is also known to inhabit *A. baumannii* species. It has been identified in a variety of food items, such as raw vegetables, fruits, milk and dairy products (Kanafani and Kanj, 2014).

*Acinetobacter* spp. can endure dry conditions for long periods thus *A. baumannii* is frequently isolated from reusable medical equipments such as ventilator tubing, arterial pressure monitoring devices, humidifiers, washbasins, plastic urinals and respirometers (Kanafani and Kanj, 2014). They have also been isolated from the skin of healthcare personnel, mattresses, pillows and in all types of ventilator equipment and moist situations (Beggs et al., 2006; Kanafani and Kanj, 2014).

### 5. Survival under harshest conditions and resistance to desiccation

*A. baumannii* has the ability to survive on dry surfaces under nutrient limiting conditions facilitates their persistence and transmission in natural and medical environment. Furthermore, colonized medical devices and equipment could serve as reservoirs in prolonged hospital outbreaks (Kanafani and Kanj, 2014). Majority of *A. baumannii* strains persist longer than *Escherichia coli* on dry surfaces; some of them can even remain viable for more than 4 months. Additionally, *A. baumannii* survived for more than 20 days on glass surfaces while placed at room temperature and persisted on both moist and dry surfaces. This characteristic enables the organism to survive in hospitals to spread infections. In fact, the soldiers' infections by *Acinetobacter* were not acquired from the environment but during their admission to medical facilities (Lee et al., 2011; Kanafani and Kanj, 2014). *Acinetobacter* spp. are more frequently found on inanimate objects and hands of staff in the ICU than *Staphylococcus aureus* and *Pseudomonas* spp. It is hard to determine the significance of recovery of *Acinetobacter* spp. from clinical materials, since they are frequently colonized instead of infected (Lee et al., 2011; Kanafani and Kanj, 2014).

### 6. Virulence factors of *Acinetobacter*

*Acinetobacter* is considered to be an organism of low virulence (Kurcik-Trajkovska, 2009; Kanafani and Kanj, 2014). The possible virulence factors are: cell surface hydrophobicity, outer membrane proteins (OMPs), toxic slime polysaccharides and verotoxins. *Acinetobacter* spp. has been demonstrated to exhibit cell surface hydrophobicity, an important determinant bacterial adhesion and which may also help it avoid being phagocytosed (Kurcik-Trajkovska, 2009; Doughari et al., 2011; Kanafani and Kanj, 2014). Several OMPs belonging to the OmpA family have been characterized in different *Acinetobacter* strains. Outer membrane proteins (OMPs), that are present in some Gram-negative bacteria, are known to have crucial roles in pathogenesis and adaptation in host cells as well as in antibiotic resistance (Doughari et al., 2011; Kanafani and Kanj, 2014). *A. baumannii* lipopolysaccharides (endotoxins) are potent stimulators of circulating white blood cells to release pro-inflammatory substances (Erridge et al., 2007; Kanafani and Kanj, 2014). They are toxic to neutrophils, and inhibit their migration as well as their phagocytosis (Kurcik-Trajkovska, 2009; Doughari et al., 2011; Kanafani and Kanj, 2014). *A. baumannii* produce many factors like extracellular enzymes, cytotoxins and secreted vascular permeability that play a significant role in the pathogenesis and cause harm to host tissues especially in respiratory tract infection (Tomaras et al., 2008; Kanafani and Kanj, 2014). Other

virulence conferring enzymes secreted by the bacteria include esterases, certain amino-peptidases, and acid phosphatases (Doughari et al., 2011; Kanafani and Kanj, 2014). Verotoxins can be classified into two antigenic groups, vtx-1 and vtx-2. The mechanism by which *A. haemolyticus* produces the toxin is not well understood. The toxins belong to a particular protein subfamily, the RNA *N*-glycosidases which directly target the cell ribosome machinery, inhibiting protein synthesis (Lambert et al., 1993; Kanafani and Kanj, 2014).

## 7. Infections with *A. baumannii*

Most infections with *A. baumannii* involve organ systems that contain high levels of fluids. Such systems include among others the urinary and respiratory tract, peritoneal cavity, and are linked to indwelling devices. The difference between the infection and colonization with *A. baumannii* is difficult to differentiate. It is believed that the retrieval of *A. baumannii* in the hospitalized patient is a sign of severe illness, with a related mortality of about 30% (Jung and Park, 2015).

### 7.1. Hospital-acquired *Acinetobacter pneumonia*

The majority of *A. baumannii* pathogens are isolated from the respiratory tracts of hospitalized patients and it is very difficult to differentiate between upper airway colonization from true pneumonia. The incidence of this microorganism varies from one site to another. However, it is the second most common etiologic agent among all the Gram-negative bacteria (Luna and Aruj, 2007). Nosocomial pneumonia occurs in intensive care units (ICUs) with a frequency of 3–5% and with crude death rates of 30–75% being reported (Doughari et al., 2011).

### 7.2. Community-acquired *Acinetobacter pneumonia*

*Acinetobacter* easily inhabit tracheostomy sites and result in community acquired bronchiolitis and tracheobronchitis in healthy children and in immuno-compromised adults but rarely cause community-acquired pneumonia and sepsis (Whitman et al., 2008). However, community-acquired pneumonia due to *A. baumannii* has been identified in tropical regions of Australia and Asia during the rainy season in people who have a history of alcohol abuse or have chronic obstructive pulmonary disease (Peleg et al., 2008; Whitman et al., 2008).

### 7.3. Bacteremia (blood stream infection)

Bacteremia by *A. baumannii* is most commonly caused by intravascular and respiratory tract catheter. The origin from surgical wounds, burns and the urinary tract is less encountered and is infrequent from endocarditis. The origin of the bacteremia is unknown in about 21–70% of the episodes (Cisneros and Rodriguez-Bano, 2002).

In United States study (1995–2002), *A. baumannii* uses 1.3% of all the nosocomial bloodstream infections (0.6 bloodstream infection/10,000 admissions). Moreover, *A. baumannii* initiated more ICU-acquired bloodstream infection when compared to non-ICU-ward infection (Cisneros and Rodriguez-Bano, 2002; Garnacho-Montero et al., 2015). The overall death rate from *A. baumannii* blood stream infections ranged

from 34.0% to 43.4% at the ICU and 16.3% outside the ICU (Peleg et al., 2008; Garnacho-Montero et al., 2015).

### 7.4. Trauma and other wound infection

*A. baumannii* can be the cause of skin/soft tissue infections outside of the military population; it led to 2.1% of ICU-acquired skin/soft tissue infections. Moreover, *A. baumannii* isolated from combat casualties in Iraq or Afghanistan was the most frequently isolated organism (32.5% of cases) from battle victims with open tibia fractures (Falagas et al., 2015).

### 7.5. Urinary tract infection

*A. baumannii* is an infrequent cause of UTI; according to one study, it is responsible for only 1.6% of ICU-acquired UTIs. This organism is usually linked to catheter-associated infection or colonization. It is unusual for *A. baumannii* to cause complicated UTI in outpatients (Peleg et al., 2008; Falagas et al., 2015).

### 7.6. Meningitis

Nosocomial post neurosurgical meningitis, caused by multidrug-resistant *A. baumannii*, is an increasingly important issue (Doughari et al., 2011; Basri et al., 2015). In a number of acute bacterial meningitis in adults, *Acinetobacter* was responsible for around 10% of Gram-negative bacillary and 4% of all nosocomial meningitides. Mortality may be as high as 70%, although its cause is often hard to discern (Peleg et al., 2008; Basri et al., 2015).

### 7.7. Other manifestations

A small number of reported cases of *A. baumannii* endocarditis exist. The majority of these cases involved prosthetic valves. *A. baumannii* may cause endocarditis, peritonitis, ophthalmitis or keratitis associated with contact lens use or following eye surgery (Bergogne-Berezin and Towner, 1996; Peleg et al., 2008).

## 8. Epidemiology of *A. baumannii*

*A. baumannii* is primarily a healthcare-associated pathogen and many reports indicated it as the cause of outbreaks and nosocomial infections including septicemia, bacteremia, ventilator-associated pneumonia, wound sepsis, endocarditis, meningitis, and urinary tract infections (Vashist et al., 2011). MDR *Acinetobacter* only poses a minimal threat to healthcare workers or patients' family members since it rarely causes any serious infection in healthy people. Outbreaks are frequently encountered in intensive-care and burn units which involve patients on mechanical ventilation [www.hopkinsmedicine.org/heic/ID/mdr](http://www.hopkinsmedicine.org/heic/ID/mdr) (Kanafani and Kanj, 2014).

### 8.1. Global epidemiology of *A. baumannii*

*A. baumannii* is commonly found in water and soil (Kanafani and Kanj, 2014) in addition to many health care environments, causing human colonizer in the hospital (Villegas and Hartstein, 2003). Several epidemiology studies have reported

the occurrence of MDR *A. baumannii* infections in different regions of the world including Europe, North America, Argentina, Brazil, China, Taiwan, Hong Kong, Japan, and Korea (Kanafani and Kanj, 2014) and often associated with nosocomial infections. Community acquired pneumonia have been reported in tropical regions of the world especially during warm and humid months (Doughari et al., 2011; Kanafani and Kanj, 2014). United Kingdom and US military detected an escalation in the number of highly resistant isolates of *Acinetobacter baumannii calcoaceticus* complex among military personnel who were wounded while deployed to Iraq and Afghanistan (Peleg et al., 2008).

### 8.2. Middle East epidemiology of *A. baumannii*

Several cases of MDR *A. baumannii* have been reported from hospitals in the United Arab Emirates, Bahrain, Saudi Arabia, Palestine and Lebanon (Mugnier et al., 2008; Mugnier et al., 2009). A retrospective study to evaluate the prevalence of multidrug resistant bacteria that causes infections in patients at the intensive care units (ICUs) of Riyadh Military Hospital, Saudi Arabia, showed that most common types of bacteria isolated from intensive care patients were *A. baumannii*, which represent 40.9% of the samples (Saeed et al., 2010). In another retrospective study in an adult ICU tertiary care Hospital in Riyadh, Saudi Arabia, showed that most frequently isolated organism was *A. baumannii* (Kamolvit et al., 2015).

### 8.3. Epidemiology of outbreaks

One important feature of *A. baumannii* is its tendency to cause outbreaks due to its resistant antimicrobial agents and its ability to overcome desiccation (Fournier et al., 2006). Specific resistant clones are the predominant cause of outbreaks and three European clones (designated as I, II and III) have disseminated in geographically distinct areas and in specific institutional outbreaks, the majority of *A. baumannii* isolates usually belong to a single clone (Karageorgopoulos and Falagas, 2008; Zowawi et al., 2015).

## 9. Modes of transmission

### 9.1. Environmental contamination

Environmental sites that are most likely to be colonized are those in the vicinity of affected patients, for example, fomites such as feather pillows, bed linen, surrounding curtains, along with bedrails, bedside tables, water used for nasogastric feeding or ventilator rinsing and gas taps behind the beds in addition to door handles, computer keyboards, sinks, and/or even cleaning equipment (Karageorgopoulos and Falagas, 2008). Contamination of hospital equipment from the hospital environment with *Acinetobacter* outbreaks has been often identified, ranging from suctioning equipment to pillows and mattresses and most reports refer to respiratory equipment used for mechanical ventilation, suctioning, devices related to intravascular access (Karageorgopoulos and Falagas, 2008; Jung and Park, 2015). Moreover, in a study done in Netherlands, both *A. baumannii* and genomic species 13 were shown to be the source of contamination of feather pillows that were

causing an outbreak (Weernink et al., 1995; Kanafani and Kanj, 2014). Also, wet mattresses have been identified to be the reservoir of infection and reported an *A. calcoaceticus* outbreak in a burn unit (Sherertz and Sullivan, 1985; Ebringer, 2015).

### 9.2. Air-borne transmission and aerial dissemination

Concerning the epidemiology of healthcare-associated infection, only little light has been shed on the importance of air-borne route of transmission although there is an increasing evidence that may be a mode of transmission of major Gram-negative bacteria pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. Weernink et al. (1995) investigated the airborne diffusion of *Acinetobacter* spp. from patient's pillows using settle plates; they found aerial dispersal of this microorganism from feather pillows, but not from synthetic pillows. Another proof of the airborne dissemination of *Acinetobacter* spp. was shown in a study in Hong Kong (Houang et al., 2001). Moreover, in a Danish study, Gerner-Smidt (1987) used both settle plates and a slit sampler to recover an outbreak of strain *A. calcoaceticus* subsp. *Anitratum* from the air in an ICU (Gerner-Smidt, 1987; Townsend et al., 2015).

### 9.3. Hand of stuff

The hands of healthcare personnel can be colonized with *A. baumannii* outbreak strains, thus facilitating spread to patients (Karageorgopoulos and Falagas, 2008). Health-care workers with damaged skin are at increased risk of developing hand colonization with *A. baumannii*. Epidemiological studies demonstrate that hand-carriage rates among nurses and physicians varied between 3% and 23% and was usually transient, except in the case of injured skin (Cisneros and Rodriguez-Bano, 2002; Townsend et al., 2015).

## 10. Colonized patient

The potential modes of *A. baumannii* transmission into a ward are displayed through a colonized patient being the most likely mode. After its diffusion to a ward, *A. baumannii* can be transmitted from the colonized patient to the surroundings and to other susceptible patients. Transfer of *Acinetobacter* to several patients is boosted by a combination of multiple-site patient colonization, widespread environmental contamination, persistence on dry surfaces and hands for long periods, and the ability to develop or gain resistance to nearly all classes of antimicrobial agents (Villegas and Hartstein, 2003). The presence of colonized patients leads to maintaining the persistence of multidrug-resistant *A. baumannii* species in the health care setting (Eliopoulos et al., 2008). Cross-transmission and diffusion from the hospital environment are more likely than endogenous sources to be the source of infecting or colonizing organisms in nosocomial infections (Luna and Aruj, 2007; Kanafani and Kanj, 2014). A strategy of weekly pharyngeal and rectal swab cultures in 73 patients newly admitted in an ICU identified 46 (96%) of 48 patients who became colonized with *A. baumannii* (Karageorgopoulos and Falagas, 2008).

## 11. Risk factors

It is generally agreed that *A. baumannii* is the most medically significant *Acinetobacter* spp. The clinical impact of the *Acinetobacter* was increasing morbidity or mortality and their infections are responsible for the increase in patient mortality that occurs in critically ill patients (Doughari et al., 2011). It is considered as a low virulence organism except when isolated in critically ill or immuno-compromised patients. These organisms are most often associated with nosocomially rather than community-acquired infections (Jain and Danziger, 2004; Islahi et al., 2015). The ability of *A. baumannii* to develop multidrug resistance and to persist in harsh environmental conditions makes infections by *Acinetobacter* very dangerous specially in individuals who have recently undergone major surgery, have malignant diseases or burns or immuno-suppressed patients such as the elderly, neonates with low birth weights, and patients with prolonged illnesses (Doughari et al., 2011; Kanafani and Kanj, 2014). Patients with mechanical ventilation, particularly of prolonged duration, longer hospital or ICU stay, greater degree of exposure to infected or colonized patients in the neighboring hospital environment have an increasing risk for the acquisition of multidrug-resistant outbreak strains (Kanafani and Kanj, 2014).

## 12. Multidrug resistant *A. baumannii*

For the past 30 years, strains of *A. baumannii* have acquired resistance to newly developed antimicrobial drugs; these strains are known as MDR *A. baumannii*. It became prevalent in many hospitals all over the world and has been recently recognized there as a leading nosocomial pathogen (Abbo et al., 2005; Kanafani and Kanj, 2014). Different terminology like multidrug resistant (MDR), extensive drug resistant (XDR), and pan-drug resistant (PDR) have been used with various definitions to describe the degree of antimicrobial resistance for *Acinetobacter* spp. MDR *Acinetobacter* spp. can refer to being resistant to a minimum of three classes of antimicrobial drugs e.g. all penicillins and cephalosporins fluoroquinolones, and aminoglycosides (Jung and Park, 2015). Another specific definition of multidrug resistance is whenever there is resistance to more than two of the following five drug classes: anti-pseudomonal cephalosporins (ceftazidime or cefepime), anti-pseudomonal carbapenems (imipenem or meropenem), ampicillin-sulbactam, fluoroquinolones (ciprofloxacin or levofloxacin), and aminoglycosides (gentamicin, tobramycin, or amikacin) (Peleg et al., 2008; Guide, 2010; Kanafani and Kanj, 2014).

MDR *Acinetobacter* strains which show additional resistant to carbapenems will be defined as XDR. Finally, PDR *Acinetobacter* spp. is a term given to the XDR *Acinetobacter* spp. that is also resistant to polymyxins and tigecycline. These categorizations help to define the extent of resistance and rational antimicrobial therapy in a clear way (Manchanda et al., 2010).

### 12.1. Genetics of resistance in *Acinetobacter*

*Acinetobacter* spp. are well suited for genetic exchange and belong to a unique class of Gram-negative bacteria labeled as “naturally transformable”. This remarkable capacity for

the acquisition of foreign genetic material, especially antibiotic resistance genes is possible (Gallagher et al., 2015). The major types of gene transfer among *A. baumannii* are:

#### 12.1.1. Transformation

In 1969, Juni and Janik (1969) discovered a hyper transformable *Acinetobacter* strain, i.e. a strain able to take up DNA from lysed bacterial cells and able to recombine this DNA into its genome, and designated this strain as “*A. calcoaceticus*”. Moreover, Juni and Janik (1969) showed that this strain could be transformed by DNA-extracts prepared from 265 bacterial strains belonging to eleven different genera, and that in fact these strains were close genetic relatives, all belonging to the genus *Acinetobacter* (Utnes et al., 2015).

#### 12.1.2. Conjugation

The first description of conjugation was reported in 1976 in an *A. calcoaceticus* strain. The vector used for conjugation was abroad-host-range plasmid RP4 and was able to mobilize chromosomal genes between different *A. calcoaceticus* mutants. Chromosomal transfer by conjugation has also been reported with the naturally occurring *Acinetobacter* plasmid pAV1 (Yang et al., 2015).

#### 12.1.3. Transduction

Several bacteriophages which are active against particular strains of *Acinetobacter* have been isolated. Although most of them are lytic phages, temperate phage P78 lysogenizes its host strain (Utnes et al., 2015). Nevertheless, this phage is specific for its host strain and cannot be used for genetic studies in *Acinetobacter* spp.

#### 12.1.4. Mobile genetic elements

Members of the genus *Acinetobacter* have a tendency to quickly develop resistance to the antimicrobial agents. They are intrinsically resistant to many antibiotics and have a great ability to acquire new resistance mechanisms. More than 25 years ago, Fournier et al. (2006) demonstrated that *A. baumannii* plasmids, transposons and integrons are generally major contributing factors in the acquisition and transfer of these mechanisms of resistance. The presence of class I and class II integrons in *A. baumannii* has been considerably linked to multiple antibiotic resistances and the nosocomial propagation of isolates has been illustrated in both environmental and clinical strains of *A. baumannii* worldwide (Fournier et al., 2006). A large number of *Acinetobacter* clinical isolates have integrons incorporated into their chromosome. The presence of these mobile elements in epidemic strains, possibly because most of the cassettes identified are associated with antibiotic resistance. Indeed, it has been implied that integrons contribute significantly to the diffusion of antibiotic resistance genes (Perez et al., 2007; Gheorghe et al., 2015). In *A. baumannii*, the (insertion sequences, IS) IS elements act as strong promoters of the production of  $\beta$ -lactamase and have a role to acquire other resistant phenotypes (Perez et al., 2007; Gheorghe et al., 2015). Fournier et al. (2006) described about 86 kb Resistance Island in the epidemical MDR *A. baumannii* strain AYE, which contained 45 of the 52 resistant genes. In the same position, in the susceptible *A. baumannii* strain SDF, there was a 20 kb genomic island that did not contain

any of the resistance genes. The complete genome of *A. baumannii* ATCC 17978 was sequenced and 28 putative alien islands have identified, 16 of them contained genes directly implicated in virulence (Smith et al., 2007; Gheorghe et al., 2015).

### 12.2. Mechanisms of antibiotic resistance

The mechanisms of antimicrobial resistance in *A. baumannii* are generally classified into five broad categories (Kamolvit et al., 2015).

#### 12.2.1. Antimicrobial-inactivating enzymes

Enzymatic degradation by  $\beta$ -lactamases is the most prevailing mechanism of  $\beta$ -lactam resistance in *A. baumannii*.  $\beta$ -lactamases are divided into 4 molecular groups: Ambler class A, Ambler class B (metallo enzymes), Class C  $\beta$ -lactamases, and Ambler class D (oxacillinases). These enzymes, at least partially, hydrolyze carbapenems along with other  $\beta$ -lactams (Jain and Danziger, 2004). Extended-spectrum  $\beta$ -lactamases (ESBLs) from the Ambler class A group have been described for *A. baumannii*. Many ESBLs were identified in *A. baumannii* including TEM-92 and 116 from Italy and Netherlands respectively, and SHV-12 from China and the Netherlands. In addition, CTX-M-2 and CTX-M-43 have been reported from Japan and Bolivia correspondingly. Further attention is being currently given to VEB-1, which circulated throughout hospitals in France (clonal dissemination) and was also recently encountered in Belgium and Argentina (VEB-1a), PER-1, from France, Turkey, Belgium, Romania, Korea, and United States and PER-2 from Argentina. Narrow-spectrum  $\beta$ -lactamases, such as TEM-1 and TEM-2, are also predominant in *A. baumannii* but their clinical importance is restricted due to the strength of other resistance factors (Jain and Danziger, 2004).

Ambler class B is an acquired resistance mechanism that is located on the chromosome or plasmids that hydrolyze all  $\beta$ -lactam antibiotics except aztreonam. There is a distinguishing metal ion in the active site, usually zinc, which aids in catalysis and differentiates it from class A and D carbapenemases (Perez et al., 2007). Two major metallo- $\beta$ -lactamases have been reported in *A. baumannii*: “Verona integron-encoded metallo- $\beta$ -lactamases” (VIM) and “Imipenem hydrolyzing  $\beta$ -lactamase” (IMP). IMP or VIM family has been described in various areas in the world, including Japan, Italy, Hong Kong, and Korea (Perez et al., 2007). Since MBLs are usually situated on mobile genetic elements easily transmitted among bacteria, they are considered to pose a significant threat (Urban et al., 2003).

*A. baumannii* characteristically produces an AmpC-type cephalosporinase recognized as *Acinetobacter*-derived cephalosporinases (ADCs) (Manchanda et al., 2010). These enzymes do not decrease the efficiency of expanded spectrum cephalosporins when expressed at a basal level. ADCs hydrolyze the antibiotic penicillins and extended spectrum cephalosporins.

The presence of an upstream insertion sequence (IS) element known as ISAbalor (*bla* genes code for class C cephalosporinases) is the main determinant regulating over expression of AmpC enzyme in *A. baumannii*. Cefepime and carbapenems seem to be resistant to the hydrolysis initiated

by these enzymes (Manchanda et al., 2010). It was found that about 28 *bla*<sub>ADC</sub> genes have been found and are listed in GenBank (Perez et al., 2007).

Class D (OXA) carbapenemases, another naturally occurring  $\beta$ -lactamase in *A. baumannii*, is the leading cause of carbapenem resistance in this microorganism (Manchanda et al., 2010). These were described in regions such as Scotland, Spain, France, Japan, Singapore, China, Brazil, Cuba, and Kuwait (Manchanda et al., 2010). Four groups of the Class D carbapenem-hydrolyzing enzymes CHDLs, including OXA-23-like, OXA-24-like, OXA-58-like, and OXA-51-like enzymes, have been identified in *A. baumannii*. Emergence and extensive diffusion of OXA-23, 24/40, and -58 carbapenemases among *Acinetobacter* spp. have been reported in Asia-Pacific countries.

OXA-23 was the first example of such an OXA carbapenemase in *A. baumannii*. It was detected in 1985, in a clinical isolate in Scotland before the introduction of carbapenems. Since then, the initially termed ARI-1 (*Acinetobacter* resistant to imipenem), which is a plasmid-encoded enzyme, has been reported in England, Brazil, Polynesia, Singapore, Korea, and China (Manchanda et al., 2010).

#### 12.2.2. Changes in OMPs

Understanding the involvement of porins or outer membrane proteins (OMPs) to antimicrobial resistance in *A. baumannii* has been a challenge. One report suggested that reduced expression or mutation in porins may be associated with carbapenem resistance. Carbapenem resistance in *Acinetobacter* spp. has been associated to the loss of proteins through porin channels from the outer membrane. It is possible that  $\beta$ -lactamases and outer-membrane changes work together to grant resistance to  $\beta$ -lactam agents (Manchanda et al., 2010). The loss of CarO, a 29-kDa protein, was recently proven to be related to imipenem and meropenem resistance, showing that this porin creates nonspecific channels. Another protein, Omp25, was identified in relation to CarO, but it lacked pore-forming ability. The *carO* gene disruption by distinct insertion elements leads to loss of the CarOporin in imipenem-resistant *A. baumannii*.

Detected clinical outbreaks of carbapenem-resistant *A. baumannii* due to porin loss, that included reduced expression of a number of OMPs such as 47, 44, and 37 kDa OMPs in *A. baumannii* strains endemic in New York City in addition to reduced expression of 22 kDa and 33 kDa OMPs in association with OXA-24 in Spain (Bonomo and Szabo, 2006). Heat-modifiable protein HMP-AB, a 33-36-kDa and 43 kDa proteins are also identified OMPs involved in  $\beta$ -lactam resistance (Jain and Danziger, 2004).

#### 12.2.3. Efflux pumps

Efflux pumps usually have 3 components, including the pump itself, present in the cytoplasmic membrane; an exit portal (porin channels that pass through the outer membrane) and a linker lipoprotein between the two. Resistance-nodulation-division (RND) type efflux pump has been illustrated in *A. baumannii* and is responsible for aminoglycoside, quinolones, tetracyclines, chloramphenicol, erythromycin, trimethoprim, and ethidium bromide resistance (Nowak et al., 2015). AbeM, which is another multidrug efflux pump from *A. baumannii*, has been newly identified and described as an element of the

multidrug and toxic complex; its spectrum of antibiotic substrates appears to be restricted to fluoroquinolones, among other toxic compounds (Perez et al., 2007). An expansive range of multidrug efflux systems is encoded by the genome of a multidrug-resistant *A. baumannii* strain. The (RND) family-type pump AdeABC is the most studied so far and it has a substrate profile that includes  $\beta$ -lactams (including carbapenems) and other antimicrobials. Similarly to other RND-type pumps, AdeABC has a three-component structure: AdeB creates the trans membrane component, AdeA forms the inner membrane fusion protein, and AdeC forms the OMP (Nowak et al., 2015). The over expression of the AdeABC efflux pump can also grant high-level resistance to carbapenems (in combination with carbapenem-hydrolyzing oxacillinases) (Perez et al., 2007). AdeABC is encoded on the chromosome and is normally regulated by a sensor kinase (AdeS) and a response regulator (AdeR) (Peleg et al., 2008). A mechanism that regulates the expression of this pump was illustrated as a two-step regulator (*adeR*) and sensor (*adeS*) system; in the *adeR* or *adeS* gene, a single point mutation leads to an amplified expression and thus to a higher efflux (Perez et al., 2007; Nowak et al., 2015).

#### 12.2.4. Changes in PBPs

Seven different PBPs (1a, 1c, 2, 3, 4, 4b and 5) in *A. baumannii* were found. The resistance of *A. baumannii* to carbapenems is related to decreased drug uptake because of porin deficiency, and diminished affinity for the drug due to modification of the PBP's by mutations which is described by a reduced expression of PBP-2, as shown in isolates from Seville, Spain (Perez et al., 2007).

#### 12.2.5. Resistance to antibiotics

**12.2.5.1. Resistance to aminoglycosides.** The presence of genes coding for aminoglycoside-modifying enzymes (AME) within class I integrons is very frequent in multidrug-resistant *A. baumannii* isolates. The main classes of enzymes comprising acetyltransferases, nucleotidyltransferases, and phosphotransferases have been described (Jung and Park, 2015). It was lately found that 16S rRNA methylation is mediated by a recently recognized group of 16S rRNAmethylases-mediated mechanism of high level of resistance to the parenterally administered aminoglycosides that are of current clinical use (Doi and Arakawa, 2007). The responsible genes are mostly harbored on transposons within transferable plasmids, enabling them to spread horizontally (Doi and Arakawa, 2007; Jung and Park, 2015). 16S rRNA methylases has been reported for *A. baumannii* (*armA*) strains from Japan, Korea, and the United States. A new type of AME has been lately discovered and found to play a main role in amikacin resistance among *Acinetobacter* spp. in Japan (Perez et al., 2007; Jung and Park, 2015). Other mechanisms of resistance include alterations in the target ribosomal protein, impaired transport of aminoglycosides to interior of the bacterial cell, and efflux pump-mediated removal of aminoglycosides from within the cell (Jung and Park, 2015).

**12.2.5.2. Resistance to quinolones.** Alteration in the structure of DNA gyrase or topoisomerase IV through mutations in the quinolones resistance-determining regions of the *gyrA* and

*parC* genes is the main cause for resistance of *A. baumannii* to quinolones. These changes decrease the affinity of the quinolones binding to the enzyme-DNA complex. Another mechanism of resistance to the quinolones is caused by efflux systems that reduce intracellular drug accumulation (Perez et al., 2007; Potron et al., 2015); comprising RND-type pump AdeABC and multi antimicrobial extrusion protein MATE pump AbeM. Until now, *qnr* genes and plasmid mediated quinolones resistance has not been reported for *A. baumannii* (Potron et al., 2015).

**12.2.5.3. Resistance to tetracyclines and glycylicyclines.** Two different types of resistance to tetracyclines have been well explained in *A. baumannii*. TetA and TetB are specific transposon-mediated efflux pumps; TetB controls the efflux of both tetracycline and minocycline, while TetA is only responsible for the efflux of tetracycline. The second mechanism is the ribosomal protection protein, which protects the ribosome from the effect of tetracycline. This protein is encoded by *tet(M)* gene; it helps in shielding the ribosome from tetracycline, doxycycline, and minocycline (Perez et al., 2007; Falagas et al., 2015). Apart from tetracycline-specific efflux pumps, this class of antimicrobials is also susceptible to efflux by the multidrug efflux systems, such as the AdeABC pump. Importantly, tigecycline, which is the first of a new class of modified tetracycline antimicrobials known as glycylicyclines, is also a substrate for this emerging efflux system. The function of the AdeABC efflux pump in diminished susceptibility to tigecycline was validated by insertional inactivation of the *adeB* gene, leading to a major drop in the MIC of tigecycline (4–0.5 g/ml). These data imply caution when tigecycline treatment for *A. baumannii* infection is considered in bloodstream and other sites where drug levels may be suboptimal (Falagas et al., 2015).

**12.2.5.4. Resistance to polymyxin.** Polymyxin B and polymyxin E (colistin, intravenous colistimethate sodium) are peptide antibiotics that were first isolated in 1947 and have been progressively used as a “last-resort” for the treatment of infections caused by MDR *A. baumannii*. Unfortunately, resistance to colistin in *A. baumannii* has been reported and conceived with great alarm (Perez et al., 2007). The mechanism of resistance remains unknown. Reduced binding to the Lipopolysaccharide (LPS) target site has been shown to cause resistance in *E. coli*, *Salmonella* spp., and *Ps. aeruginosa*. Furthermore, changes in OMPs causing lowered susceptibility to polymyxins have been reported for *Ps. aeruginosa*. More research is needed to adequately characterize to control infections caused by *A. baumannii*.

Determining the geographical dispersion of virulent or epidemic pathogens is accomplished by identifying and typing bacteria (Pogue et al., 2015). Molecular typing has a key role in studying the epidemiology of *A. baumannii* and in coping with its epidemic spread. The progress in molecular typing methods provided the clinical microbiology laboratory with powerful tools, leading to a better understanding of the epidemiology of bacterial infection (Pogue et al., 2015). Until now, many molecular techniques are being used at three different levels to control infections caused by *A. baumannii*.



### 13. Treatment

*A. baumannii* is considered by the Infectious Diseases Society of America as one of the “red alert” pathogens that significantly threaten the effectiveness of our current antibacterial armamentarium (Peleg et al., 2008). Unfortunately, as resistance has increased, a few antimicrobials can be reliably used for effective treatment of MDR *Acinetobacter* infections. Since few antimicrobials remain consistently effective in the treatment of nosocomial *Acinetobacter* infections, the search for new drugs and the reevaluation of older agents have become a priority (Jain and Danziger, 2004).

#### 13.1. Carbapenems

Carbapenems (imipenem and meropenem) resistance *Acinetobacter* is increasingly reported, making MDR *Acinetobacter* infections difficult to treat. However, carbapenems continue to be the treatment of choice in cases where isolates are still susceptible to this antimicrobial class (Manchanda et al., 2010).

#### 13.2. Sulbactam

Sulbactam, an inhibitor of  $\beta$ -lactamase, demonstrates *in vitro* bactericidal activity against *Acinetobacter* spp. (Luna and Aruj, 2007; Dinc et al. 2015) and it is suitable for mild infections. Several studies illustrate the use of several single agents in MDR *A. baumannii* infection therapy. The adequate performance (up to 67.5% healing rate) of sulbactam in treating various types of infections such as meningitis, pneumonia, peritonitis, surgical site and urinary tract infections, caused by MDR *A. baumannii* which also showed resistance to imipenem was further verified by prospective and retrospective set of patients (Dinc et al. 2015).

#### 13.3. Tigecycline

Tigecycline derivative of minocycline and has bacteriostatic activity against MDR *A. baumannii* (Dinc et al., 2015). High-level resistance to tigecycline has been reported for some multidrug-resistant *A. baumannii* isolates, with a concern that this organism can quickly escape this antimicrobial mediated efflux pumps. Over expression of a multi-drug efflux pump in *A. baumannii* isolates with reduced susceptibility to tigecycline has been described (Eliopoulos et al., 2008).

#### 13.4. Aminoglycosides

Tobramycin and amikacin are some of the aminoglycoside agents used as therapeutic options in cases of infection with multidrug-resistant *A. baumannii* isolates that retain susceptibility. These options are typically used in combination with another active antimicrobial agent. Many multidrug-resistant *A. baumannii* isolates maintain an intermediate susceptibility to amikacin or tobramycin to which resistance is highly correlated with aminoglycoside-modifying enzymes or efflux pump mechanisms (Yadav et al., 2015).

#### 13.5. Colistin

Colistin, a cationic polypeptide, is part of the polymyxin family (colistimethate or colistinsulfomethate or polymyxin E) and is a potent broad-spectrum antimicrobial agent. This agent was originally used in the 1960 s and 1970 s, but was not prescribed frequently because of concerns with nephrotoxicity and neurotoxicity (Vourli et al., 2015). Clinicians are going back to the use of polymyxin B or polymyxin E (colistin) for highly drug-resistant *A. baumannii* infections. Observational studies have shown a rate of 57–77% of cure or improvement among severely ill patients with multidrug-resistant *A. baumannii* infections treated with colistin. These infections included pneumonia, bacteremia, sepsis, intra-abdominal, and Central Nerves System infection (Vourli et al., 2015).

### 14. Conclusion

*Acinetobacter* has been known as a major cause of nosocomial infections worldwide and have shown a broad spectrum of resistance toward commonly used antimicrobial agents. In view of this, control measures need to be implemented to control the spread of this organism in the hospital environment. It is advisable that healthcare facilities should implement proper safety programs to limit the spread of these bacteria as well as other hazardous bacteria. Research should focus on identifying novel agents with lower resistance.

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