Acinetobacter baumannii: Infections and Drug Resistance

14

Jobina Rajkumari and Busi Siddhardha

Contents

J. Rajkumari · B. Siddhardha (✉)
Department of Microbiology, School of Life Sciences, Pondicherry University, Puducherry, India

B. Siddhardha et al. (eds.), *Model Organisms for Microbial Pathogenesis, Biofilm Formation and Antimicrobial Drug Discovery*,
https://doi.org/10.1007/978-981-15-1695-5_14

Abstract

Acinetobacter baumannii is currently considered a major clinical pathogen accountable for causing several nosocomial infections and hospital outbreaks all over the globe. *A. baumannii* is accountable for causing bloodstream infections, pneumonia, meningitis, wound infection, urinary tract infection, endocarditis, peritonitis, and keratitis especially in individuals with low immunity. The pathogen has been reported to exhibit resistance against broad classes of antibiotics including carbapenems, aminoglycoside, quinolones, tetracyclines, cephalosporins, and polymyxin. Various virulence mechanisms have been identified and proposed for the resistance of *A. baumannii* towards the different class of antibiotics including inactivation or alteration of antimicrobials, alteration in membrane proteins, efflux pumps system, changes in the drug target, and biofilm formation. Furthermore, the ability to acquire and express exogenous antibiotic resistance genes is another contributing factor in imparting drug resistance to the pathogen.

Keywords

A. baumannii · Carbapenems · Bacteremia · OmpA · Lipid A

14.1 Introduction

Acinetobacter baumannii is an opportunistic pathogen generally considered non-pathogenic to healthy individuals. However, in the past few decades, it has been extensively reported worldwide for its resistance to the conventional as well as recently developed antimicrobial drugs (Almasaudi 2018; Gokmen et al. 2016). There is an increasing prevalence of multidrug-resistant strains of *A. baumannii* especially in intensive care units (ICU) of the hospitals, causing infections in patients with invasive devices (ventilators and catheters) and low immunity (Singh et al. 2013). With its ability to develop antibiotic resistance and survive under dry conditions on inanimate objects for a long period, this gram-negative pathogen is responsible for causing numerous infections in the hospital environment (Inchai et al. 2015). *A. baumannii* is recognized as a major cause of life-threatening hospital-associated infections including pneumonia, meningitis, urinary tract infections, and severe bloodstream infection, especially in immune-compromised individuals (Santajit and Indrawattana 2016).

The indiscriminate administration of antibiotics along with various bacterial mechanisms has been attributed to the evolution of multiple drug-resistant strains of *A. baumannii* (Singh et al. 2013). This notorious pathogen also possesses a remarkable ability to rapidly acquire resistance foreign genetic material including a vast array of antibiotic resistance genes (Almasaudi 2018). Since the majority of the carbapenem-hydrolyzing enzymes are encoded in mobile genetic elements, it is proposed that the $bla_{\text{NDM-1}}$ gene in *A. baumannii* is apparently transmitted and

acquired from carbapenem-resistant Enterobacteriaceae (*Escherichia coli* and *Klebsiella* spp.) via horizontal gene transfer (Jain et al. 2019). Furthermore, the ability to survive in severe conditions of temperature, pH, and in the presence of commonly used antimicrobial agents facilitates *Acinetobacter* to easily disseminate in the hospital settings (Chopra et al. 2013).

The remarkable property of *A. baumannii* to develop resistance against many antibiotics is a huge concern in the healthcare setting as these infections are difficult to treat. They are linked to increased mortality and morbidity in cases of ventilator-associated pneumonia (Inchai et al. 2015). *A. baumannii* is also responsible for causing community-acquired infections in patients with a history of alcoholism, cancer, diabetes, and obstructive pulmonary disorders (Harding et al. 2018).

Carbapenems are the most commonly recognized drugs for the management of *A. baumannii* associated infections. Hence, the emergence of carbapenem-resistant strains of *A. baumannii* has become a major challenge globally. In *A. baumannii,* numerous mechanisms including the production of β-lactamases, loss of outer membrane protein (OMPs), and efflux pump were found to cause in carbapenem resistance (Shoja et al. 2017). Hence, understanding the resistance mechanisms of *A. baumannii* is vital for the development of alternative tools and novel antimicrobial agents to combat the ever-increasing problem of drug resistance (Santajit and Indrawattana 2016). In the past few decades, the incidence of *A. baumannii* infections and outbreaks has drastically increased globally (Necati Hakyemez et al. 2013). Thus, the management of *A. baumannii* infections is currently one of the biggest challenges in clinical practice. In this chapter, the clinical implications of *A. baumannii* and its associated mechanisms of antimicrobial resistance have been presented in detail.

14.2 Virulence Factors

Recent studies have led to the identification of numerous virulence factors of *A. baumannii.* Outer membrane protein A (OmpA), efflux pump, phospholipase, and capsular polysaccharides were found to contribute to the pathogenicity and also impart antimicrobial resistance to *A. baumannii.* In addition, the lipopolysaccharide (LPS) of *A. baumannii* was found to induce the production of inflammatory cytokines, i.e., interleukin-8 and tumor necrosis factor. Other potential virulence factors including biofilm formation, penicillin-binding proteins, and alteration in outer membrane vesicles (OMVs) have also been implicated for the pathogenicity of *A. baumannii* (Wong et al. 2017). Targeted studies have also led to the identification of few virulence determinants of *A. baumannii*, including phospholipase D, metal (zinc and iron) acquisition system. Additionally, in the serum-resistant strain of *A. baumannii,* it was observed that the genes involved in competence, iron acquisition, type IV pili biogenesis, and efflux pumps get upregulated during the growth of the pathogen in human serum (Subashchandrabose et al. 2016).

OmpA coupled with the membrane efflux systems collectively participates in the expulsion of antimicrobial compounds from the periplasmic space (Lee et al.

2017). OmpA is also involved in invasion of epithelial cell and apoptosis. Phospholipases C and D aid in epithelial cell invasion and also help in the survival of the bacterial pathogen in the human serum (Antunes et al. 2014). Metal acquisition plays a vital role in the *A. baumannii* virulence. *A. baumannii* produces iron siderophores and acinetobactin in an iron limiting environment. Similarly, in Zn-limiting conditions, the zinc acquisition system (ZnuABC) is generally upregulated (Lee et al. 2017). In addition, the quorum-sensing system and biofilm-forming ability also aid in the survival of the cells on inert surfaces thereby contributing to drug resistance (Antunes et al. 2014). The above-mentioned virulence determinants serve as an attractive target for the development of new preventive strategies and antibiotics.

14.3 Clinical Manifestations

A. baumannii is recognized to cause fatal nosocomial infections, most commonly in patients with chronic disease or has undergone surgeries. The colonization and subsequent infection of *A. baumannii* commonly takes place in organ with higher fluid content such as urinary tract, respiratory tract, peritoneal cavity, and indwelling medical devices (Almasaudi 2018). It reported to cause secondary meningitis and infections to eye, skin and soft tissue, burn wound, and urinary tract. However, the most common clinical manifestation with the highest mortality rates is recorded in cases of ventilator-associated pneumonia and bacteremia. The pathogen usually gains entry into the host system via intravascular catheters, open wounds, and medical in-dwellings (Antunes et al. 2014).

14.3.1 Bacteremia

Bacteremia is considered as the most significant infection caused by *A. baumannii* in health care settings which is also associated with marked antimicrobial resistance and high mortality (Chopra et al. 2013). *A. baumannii* associated bacteremia is generally nosocomial and occurs commonly in ICUs (Wong et al. 2017). *A. baumannii* bacteremia commonly originates from the respiratory tract and intravascular catheters (Cisneros and Rodriguez-Bano 2002). It accounts for 52% of cases in critical care, followed by 13% in surgery, 10% in general medical, and 17% in cases of cancer (Wareham et al. 2008).

14.3.2 Acinetobacter Pneumonia

Ventilator-associated pneumonia (VAP) is a major nosocomial infection among critically immune-compromised individuals. VAP accounts for 25% of all types of ICU-acquired infections and exerts a huge burden on morbidity and health care costs (Balkhy et al. 2014). In recent years, *A. baumannii* has been widely

documented and recognized as a major cause of VAP. The mortality rate in ICU patients with VAP ranged from 45.6% to 60.9% and VAP caused by extreme drug-resistant (XDR) *A. baumannii* has been found to be as high as 84.3%. Gokmen et al. (2016) reported three cases of VAP wherein the infection resulted due to the colonization of ICU-ventilator by carbapenem-resistant *A. baumannii* (CRA). All the isolated strains were carbapenem resistant and found to possess $bla_{\text{OXA-23}}$-like and $bla_{\text{OXA-51}}$-like gene (Gokmen et al. 2016).

A. baumannii can adhere and establish biofilms on the medical devices like the endotracheal tube and create a niche for the rapid dissemination of the bacterial cells, thus resulting in the increasing incidences of carbapenem-resistant *Acinetobacter* in the ICUs. *Acinetobacter* may also directly enter the alveoli of mechanically ventilated patients, thereby allowing the establishment of infection in lung tissue (Wong et al. 2017). In spite of the recent advancements in burns surgery and intensive care, VAP still remains the main cause of mortality in victims with major burn wounds. VAP is also accountable for significant morbidity and mortality in the intensive care pediatric ward (Rogers et al. 2014).

Community-acquired *A. baumannii* pneumonia (CAP-AB) is generally recorded during the rainy season especially in tropical parts of Australia and Asia. CAP-AB is particularly found in individuals with chronic obstructive pulmonary disease and cases of alcohol abuse (Almasaudi 2018). Oh et al. (2013) reported the first case of rapidly progressing and fatal CAP-AB in Korea wherein the patient died within 36 h of hospital admission (Oh et al. 2013).

14.3.3 Meningitis

Meningitis caused by multidrug-resistant *A. baumannii* usually arises post-neurosurgery or in the presence of a ventriculostomy (Wong et al. 2017). With mortality rate exceeding 15%, post-neurosurgical meningitis is a major clinical issue. The high-risk group for post-neurosurgical bacterial meningitis includes those with concomitant incision infection, cerebrospinal leakage, prolonged duration of surgery, a surgery that enters a sinus, prolonged external ventricular drainage, increased severity of illness, and need for repeat surgery (Kim et al. 2009).

14.3.4 Wound Infection

Patients with burn wounds are generally susceptible and associated with high risk for infection. *A. baumannii* infection represents a common cause of mortality in patients with burn wards. Shoja et al. (2017) reported a high population of carbapenem-resistant *A. baumannii* containing $bla_{\text{OXA-23}}$-like and $bla_{\text{OXA-24}}$-like genes among patients with burn wound (Shoja et al. 2017).

14.3.5 Urinary Tract Infection

Urinary tract infections are generally linked to the colonization of urinary catheters or percutaneous nephrostomy tubes by the pathogen (Wong et al. 2017). The cases of *A. baumannii* related UTI infections are rare with an estimated 1.6% being ICU-acquired UTIs. It is also unlikely for *A. baumannii* to cause severe UTI in outpatients (Almasaudi 2018).

14.3.6 Other Manifestations

A few reported cases of *A. baumannii* endocarditis exist, with the majority of these cases associated with prosthetic valves (Almasaudi 2018). Numerous reports from across the globe including India have documented the increasing prevalence of *Acinetobacter* spp. in lower respiratory tract infections (LRTI). In the recent study of Jain et al. (2019), *A. baumannii* was found to be among the most common pathogen responsible for LRTI in ICUs, accountable for almost 26.2% of the cases (Jain et al. 2019). Lagana et al. (2015) reported two cases of lethal and infective endocarditis on cardiac prostheses sustained by *A. baumannii* (Lagana et al. 2015).

Although not very frequent, MDR *A. baumannii* has been observed to cause peritonitis in peritoneal dialysis patients, thereby resulting in serious infection with a high possibility of mortality (Zhang et al. 2014). Ocular infections, particularly endophthalmitis and keratitis caused by *A. baumannii* have also been observed in recent years and mainly associated with prolonged use of contact lens or post-eye surgery. Chen et al. (2008) documented two cases of ocular infection caused by *A. baumannii*, one resulting in endogenous endophthalmitis and the other endophthalmitis following corneal transplant (Chen et al. 2008).

14.4 Mechanisms of Resistance

Antimicrobial resistance characteristics exhibited by the *A. baumannii* is contributed by multiple factors. The mechanisms of antimicrobial resistance in the clinical isolates of *A. baumannii* may be broadly divided into 4 categories: (1) inactivation or alteration of antimicrobials, (2) reduced entry and intracellular accumulation of antimicrobials, (3) alteration of the drug target, and (4) biofilm formation.

14.4.1 Inactivation or Alteration of Antimicrobials

A wide array of beta-lactamases produced by *Acinetobacter* species hydrolyze numerous class of drugs including β-lactams and cephalosporins, thereby conferring antibiotic resistance to *A. baumannii* (Manchanda et al. 2010). All the four classes of β-lactamases have been identified in *A. baumannii*. Some of the class A β-lactamases identified in *A. baumannii* includes CTX-M, GES, SCO, PER, KPC,

SHV, VEB, TEM, and CARB. Class β-lactamases are also known as metallo-β-lactamases (MBLs) and requires heavy metal like zinc or iron for catalysis (Lee et al. 2017). MBLs are known to impart resistance to carbapenems and to other β-lactams (Manchanda et al. 2010). Class C β-lactamases also known as AmpC cephalosporins are widely prevalent in *A. baumannii*. It is encoded by the *bla* gene and imparts broad-spectrum resistance to narrow and extended-spectrum cephalosporins, along with penicillin (Asif et al. 2018). Class D β-lactamases are also termed as oxacillinases (OXAs) due to their ability to hydrolyze isoxazolyl penicillin, oxacillin much faster than benzylpenicillin. The presence of class D β-lactamases and/or MBLs in *A. baumannii* is attributed to their high resistance towards carbapenems (Lee et al. 2017).

14.4.2 Reduced Entry and Intracellular Accumulation of Antimicrobials

The susceptibility towards a particular drug is determined by the balance in the uptake and elimination of antibiotics by the bacterial cell. Therefore, hampering the entry of antibiotic through the bacterial cell membrane is one of the strategies used by bacteria to develop antibiotic resistance (Santajit and Indrawattana 2016). The decrease in outer membrane permeability either due to alteration in porin channels and/or upregulation of multidrug efflux pumps significantly reduces the accessibility of the drugs towards the bacterial targets.

Porin channels along with other OMPs are known to facilitate the entry of antimicrobial agents inside the bacterial cells (Maragakis and Perl 2008). In *A. baumannii*, the presence of lesser porin channels with smaller size restricts the entry of the drug molecules to the intracellular bacterial targets (Singh et al. 2013). Many studies have also attributed carbapenem resistance to the reduction in the expression of OMPs (Asif et al. 2018). The loss of *A. baumannii* Omp29 which generates OXA-51-like or OXA-23-like carbapenemases is associated with high resistance towards imipenem. OmpA contributes to the resistance towards chloramphenicol, aztreonam, and nalidixic acid (Lee et al. 2017).

Acinetobacter species possess numerous efflux pumps system which actively removes a broad range of antimicrobial agents thereby preventing them from reaching the target site (Maragakis and Perl 2008). The most commonly expelled antimicrobials by the efflux pump system include tetracyclines, macrolides, and quinolones. The expulsion of the drug from the cell takes place at a high rate; hence, the drug concentrations are not sufficient enough to elicit an antibacterial effect (Santajit and Indrawattana 2016). The efflux system of *A. baumannii* is often associated with pathogenesis, virulence, and biofilm maturation. Furthermore, the overexpression of these efflux pumps plays a vital role in imparting antibiotic resistance (Ardehali et al. 2019).

The multidrug efflux systems may be categorized into (1) the ATP binding cassette (ABC), (2) major facilitator superfamily (MFS), (3) resistance nodulation division (RND), (4) multidrug and toxic compound extrusion (MATE), (5) SMR family,

Table 14.1 Efflux pumps of *Acinetobacter baumannii* belonging to different family and antimicrobial substrate

Efflux pump	Family	Antibiotics
Tet(A)	MFS	Tetracycline
Tet(B)	MFS	Minocycline, tetracycline
AbaF	MFS	Fosfomycin
AmvA	MFS	Erythromycin
MdfA	MFS	Ciprofloxacin, chloramphenicol
CmlA, CraA	MFS	Chloramphenicol
AdeABC	RND	β-lactams, chloramphenicol, fluoroquinolones, tetracycline, macrolide, aminoglycosides
AbeM	MATE	Aminoglycosides, chloramphenicol, fluoroquinolones, ethidium bromide, trimethoprim
AbeS	SMR	Chloramphenicol, erythromycin, nalidixic acid

and (6) the drug/metabolite transporter (DMT) superfamily. However, in the case of *A. baumannii,* the antimicrobial resistance is generally associated with MFS and RND family (Lee et al. 2011). Efflux pumps of *A. baumannii* belonging to different family and antimicrobial l substrate are summarized in Table 14.1.

Tet(A) and Tet(B) efflux systems belonging to the MFS confer resistance to tetracycline by exchanging a proton for a tetracycline-cation complex. In a recent study, Sharma et al. (2017) suggested that the AbaF efflux system mediates fosfomycin resistance to *A. baumannii* (Sharma et al. 2017). The MdfA efflux pumps mediate resistance to ciprofloxacin and chloramphenicol, while CmlA and CraA confer resistance to chloramphenicol (Vila et al. 2007). AmvA confers resistance to antibiotics (erythromycin), detergents (benzalkonium chloride), dyes (acriflavine), and disinfectants (methyl viologen) (Lee et al. 2017). Studies have also found that *A. baumannii* can actively pump disinfectant, chlorhexidine out of the cell using the *Acinetobacter* chlorhexidine transporter protein, AceI, thereby protecting the bacteria from external stress (Harding et al. 2018).

The RND-type efflux pump has been documented to impart resistance to aminoglycoside, chloramphenicol and macrolides (erythromycin), quinolones, tetracyclines, trimethoprim, and ethidium bromide (Almasaudi 2018). The AdeABC efflux pump in *A. baumannii* is also known to expel antimicrobial using proton motive force, thereby reducing the susceptibility of the pathogen towards β-lactams, fluoroquinolones, tetracycline, macrolides, chloramphenicol, and aminoglycosides (Asif et al. 2018). The overexpression of AdeABC also provides significant resistance to carbapenems, tigecycline, netilmicin, and gentamicin (Xu et al. 2019).

AbeM, a multidrug efflux pump of *A. baumannii* belonging to the MATE family, also utilizes the proton motive force to extrude aminoglycosides, chloramphenicol, fluoroquinolones, ethidium bromide, and trimethoprim out of the bacterial cell (Coyne et al. 2011). AbeS-efflux pump of the SMR family imparts resistance against chloramphenicol, erythromycin, and nalidixic acid (Lee et al. 2017).

14.4.3 Alteration of the Drug Target or Cellular Functions

The alteration in bacterial targets or functions as a result of point mutations decreases the affinity of antimicrobial drugs. In some cases, it may also up-regulate cellular functions such as efflux pumps or change the membrane proteins (Maragakis and Perl 2008). For example, mutations in the subunit of DNA gyrase, *gyrA* and topoisomerase IV, *parC* impart resistance against quinolones (Singh et al. 2013).

14.4.4 Biofilm Formation

Biofilms are complex microbial community predominantly attached to either a living or an inert surface. They are often encased by thick polysaccharide matrix constituting of self-produced polysaccharides, proteins, lipids, and extracellular DNA, which protects the biofilm structure from desiccation, immune system clearance, antibiotics, and other external stress (Maragakis and Perl 2008). Hence, it is difficult to eliminate biofilm encased bacterial pathogen using conventional antibiotics. The exceptionally high degree of antibiotic resistance of *Acinetobacter* and its ability to survive in the hospital setting may be attributed to its biofilm-forming ability (Babapour et al. 2016). A relationship between the biofilm-forming ability and drug resistance in the *A. baumannii* isolates due to the presence of extended-spectrum β-lactamase (ESBL) $bla_{\text{PER-1}}$ gene has been documented earlier (Badave and Kulkarni 2015).

Greene et al. (2016) provided evidence on the positive correlation between antibiotic resistance and tolerance to desiccation. It was observed that the high biofilm-forming MDR strains of *A. baumannii* were 50% less likely to die of desiccation as compared to the low biofilm-forming non-MDR strains (Greene et al. 2016). *Acinetobacter* is frequently isolated from indwelling devices, including cerebrospinal shunts, endotracheal tubes, vascular, and urinary catheters. Such colonization eventually leads to medical devices associated with infections like fever, pneumonia, bacteremia, and meningitis (Babapour et al. 2016). *A. baumannii* has also been reported to adhere to laryngeal, bronchial, and alveolar epithelial cells of the host (Doi et al. 2015).

Studies have shown the presence of high frequency of exogenous DNA in the genome of *A. baumannii* indicating the inherent ability of the pathogen to acquire resistance genes via horizontal gene transfer (Lee et al. 2017).

14.5 Resistance to Available Antimicrobial Drugs

The antimicrobial resistance of *A. baumannii* has progressively increased since the 1970s and in recent decades, it has acquired resistance to the majority of the commonly used antibiotics, thus leaving few choices of antimicrobial agents. Hence, the most serious concern in the management of *Acinetobacter* associated infection is its

Table 14.2 Mechanisms of resistance in *A. baumannii* towards different antibiotics

Class of antibiotic	Mechanisms of resistance
Carbapenems	Metallo-β-lactamases and class D OXA-type enzymes, altered outer membrane protein (OMPs) and porins channels, efflux pump-mediated expulsion
Aminoglycoside	Aminoglycoside modifying enzymes, alterations in the target ribosomal protein, altered OMPs and porins channels, efflux pump-mediated expulsion
Quinolones	Alteration in DNA gyrase and topoisomerase IV reduced expression of OMPs, efflux pump-mediated expulsion
Tetracyclines	Transposon-mediated efflux pumps, AdeABC efflux pump
Cephalosporins	AmpC β-lactamases, extended-spectrum β-lactamase (ESBL)
Polymyxin	Loss of lipopolysaccharides (LPS) production, alteration of cell membrane LPS

acquired MDR (Antunes et al. 2014). Table 14.2 represents the antibiotic resistance mechanisms observed in *A. baumannii* towards different classes of antibiotics.

14.5.1 Resistance to Carbapenems

A. baumannii also possesses AmpC-lactamase (bla_{ADC}) and OXA-51 serine-type oxacillinase ($bla_{OXA\text{-}51}$), which are known to naturally impart resistance to β-lactam antibiotics (Pagano et al. 2016). The carbapenemases includes the class D OXA-type enzymes and MBLs which contributes to the carbapenem resistance in *A. baumannii* (Lolans et al. 2006). Carbapenem resistance in *A. baumannii* involves either intrinsic or acquired $bla_{OXA\text{-}23}$, $bla_{OXA\text{-}24/40}$, and $bla_{OXA\text{-}58}$-like gene clusters (Singh et al. 2013). The second major mechanism is related to altered porins channels and penicillin-binding proteins. The smaller size and lower number of OMPs in *A. baumannii* causes a significant reduction in the permeability of the cell membrane to antimicrobial agents (Hsu et al. 2017). Finally, the upregulation of the RND-type efflux system (AdeABC, AdeFGH, and AdeIJK) also plays a considerable part in imparting resistance towards carbapenems (Hsu et al. 2017; Singh et al. 2013).

14.5.2 Resistance to Aminoglycoside

The major mechanism responsible for imparting resistance to *A. baumannii* towards aminoglycoside is the alteration in the amino or hydroxyl group of the drug by aminoglycoside modifying enzymes such as acetylases, adenylases, methyltransferases, and phosphotransferases (Asif et al. 2018). Other mechanisms include modification of the target ribosomal protein, efflux pump-mediated expulsion, and impaired transport of aminoglycosides like gentamicin, tobramycin, or amikacin into the bacterial cell (Almasaudi 2018).

14.5.3 Resistance to Quinolones

The most common mechanism involved in quinolones resistance is the mutations in the *gyrA* and *parC* genes which codes for DNA gyrase and topoisomerase IV. The resulting phenotypic alteration decreases the binding affinity of the quinolones to the enzyme-DNA complex. The reduction in intracellular drug accumulation due to the efflux systems and reduced expression of OMPs involved in drug influx also imparts resistance to quinolones (Doi et al. 2015). Plasmid-encoded genes found in *A. baumannii* such as *qnrA*, *qnrB,* and *qnrS* have also been identified to protect the DNA by preventing the interaction of quinolones to DNA gyrase and topoisomerase (Asif et al. 2018).

14.5.4 Resistance to Tetracyclines

A. baumannii exhibits two different resistance mechanisms towards tetracyclines. The first mechanism is regulated by transposon-mediated efflux pumps, TetA and TetB. TetA is responsible for the expulsion of tetracycline, while TetB ejects both tetracycline and minocycline out of the bacterial cell. The second mechanism is mediated by ribosomal protection protein encoded by *Tet(M)* gene. It protects the ribosome from the effect of doxycycline, tetracycline, and minocycline. The AdeABC efflux pump also aids in providing resistance to *A. baumannii* towards tigecycline (Almasaudi 2018).

14.5.5 Resistance to Cephalosporins

A majority of *A. baumannii* clinical isolates naturally produce AmpC β-lactamase which provides resistance against cephalosporins (ceftazidime or cefepime). Rezaee et al. (2013) studied the prevalence of various cephalosporin resistance mechanisms in the clinical isolates of *A. baumannii*. Out of the total 70 isolates screened, 98.5% of the cephalosporin-resistant isolates possess insertions upstream of the *ampC* gene, of which 69% and 8% were identified to be controlled by *ISAba1* and *ISAba125*, respectively (Rezaee et al. 2013). *A. baumannii* also produces extended-spectrum β-lactamase (ESBL) which also contributes to cephalosporin resistance (Doi et al. 2015).

14.5.6 Resistance to Polymyxin

The development of colistin (polymyxin E) resistance strains of *A. baumannii* is a matter of great concern (Almasaudi 2018). Till date, two primary mechanisms for colistin resistance have been recognized in *A. baumannii.* The first mechanism involves mutations in lipid A biosynthesis genes (*lpxA*, *lpxC*, and *lpxD*) which causes complete loss of lipopolysaccharides (LPS), an initial target of colistin (Cai

et al. 2012). The second mechanism involves a mutation in *pmrA* and *pmrB* which controls the expression of genes involved in lipid A synthesis (Asif et al. 2018).

14.6 Global Incidence of Drug Resistant *Acinetobacter baumannii*

The increasing prevalence of antibiotic resistant *Acinetobacter* spp. in different geographical regions of the globe has been revealed in numerous reports. The association of OXA-58-like and OXA-24-like enzymes to the carbapenem resistance in *A. baumannii* was documented in 2008 in the Czech Republic. A few years later in 2011, an MDR strain of *A. baumannii* possessing the genes for NDM-1 and OXA-23 was identified again in the Czech Republic (Senkyrikova et al. 2013). Mesli et al. (2013) documented the first description of autochthonous *Acinetobacter* spp. in western Algeria with the ability to produce oxacillinases bla_{OXA-23}-like, bla_{NDM-1}-like, and bla_{OXA-24}-like metallo-β-lactamases (Mesli et al. 2013). In another report, Khorsi et al. (2015) highlighted the high prevalence of imipenem resistance in *A. baumannii* isolated from Algiers hospitals. The antibiotic resistance was found to be mediated predominantly by bla_{OXA-23}-like, bla_{OXA-24}-like, and bla_{NDM-1}-like genes (Khorsi et al. 2015).

Carvalho et al. (2009) reported the transmission of OXA-23 producing MDR clones of *A. baumannii* in hospitals throughout Rio de Janeiro, Brazil. A total of 110 imipenem-resistant *A. baumannii* isolates were identified in samples collected from eight hospitals between January 2006 and September 2007. All the isolated strains were MDR with 87.3% producing the carbapenemase OXA-23 (Carvalho et al. 2009). Al-Agamy et al. (2014) reported the high frequency of β-lactamase encoding genes in 40 carbapenem-resistant *A. baumannii* isolates obtained from two hospitals in Egypt. The carbapenem resistance was mediated by β-lactamase encoding genes, bla_{OXA-23}, bla_{OXA-24}, and bla_{OXA-58}, $bla_{GES,}$ and *ISAba1–OXA* (Al-Agamy et al. 2014). Agodi et al. (2014) documented the emergence and dissemination of colistin- and carbapenem-resistant strains of *A. baumannii* in two hospitals in Sicily. The MDR strains were found to possess intrinsic bla_{OXA-51}-like carbapenemase gene and bla_{OXA-82}, which was flanked upstream by *ISAba1* (Agodi et al. 2014). Almaghrabi et al. (2018) reported the high frequency (69%) of MDR strains of *A. baumannii* in Aseer Region of Saudi Arabia. The isolates exhibited remarkable resistance to carbapenems and the drug resistance property was attributed to the presence of class D OXA-type enzymes (OXA-23 and OXA-24/40) (Almaghrabi et al. 2018).

The ever-increasing resistance of *A. baumannii* towards majority of the currently available antibiotics is a matter of great concern. This MDR pathogen is frequently associated with numerous hospital-associated infections resulting in high morbidity and mortality. Hence, the emergence and dissemination of these MDR strains of *A. baumannii* emphasize the urgent requirement to enforce infection control measures and develop effective treatment strategies to manage the further emergence and dissemination of these resistant *Acinetobacter* species.

References

Agodi A, Voulgari E, Barchitta M, Quattrocchi A, Bellocchi P, Poulou A, Tsakris A (2014) Spread of carbapenem- and colistin-resistant *Acinetobacter baumannii* ST2 clonal strain causing outbreaks in two Sicilian hospitals. J Hosp Infect 86(4):260–266

Al-Agamy MH, Khalaf NG, Tawfick MM, Shibl AM, El Kholy A (2014) Molecular characterization of carbapenem-insensitive *Acinetobacter baumannii* in Egypt. Int J Infect Dis 22:49–54

Almaghrabi MK, Joseph MRP, Assiry MM, Hamid ME (2018) Multidrug-resistant *Acinetobacter baumannii*: an emerging health threat in Aseer Region, Kingdom of Saudi Arabia. Can J Infect Dis Med Microbiol 2018:1

Almasaudi SB (2018) Acinetobacter spp. as nosocomial pathogens: epidemiology and resistance features. Saudi J Biol Sci 25(3):586–596

Antunes LC, Visca P, Towner KJ (2014) *Acinetobacter baumannii*: evolution of a global pathogen. Pathog Dis 71(3):292–301

Ardehali SH, Azimi T, Fallah F, Owrang M, Aghamohammadi N, Azimi L (2019) Role of efflux pumps in reduced susceptibility to tigecycline in *Acinetobacter baumannii*. New Microbes New Infect 30:100547

Asif M, Alvi IA, Rehman SU (2018) Insight into *Acinetobacter baumannii*: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. Infect Drug Resist 11:1249–1260

Babapour E, Haddadi A, Mirnejad R, Angaji SA, Amirmozafari N (2016) Biofilm formation in clinical isolates of nosocomial *Acinetobacter baumannii* and its relationship with multidrug resistance. Asian Pac J Trop Biomed 6(6):528–533

Badave GK, Kulkarni D (2015) Biofilm producing multidrug resistant *Acinetobacter baumannii*: an emerging challenge. J Clin Diagn Res 9(1):DC08–DC10

Balkhy HH, El-Saed A, Maghraby R, Al-Dorzi HM, Khan R, Rishu AH, Arabi YM (2014) Drug-resistant ventilator associated pneumonia in a tertiary care hospital in Saudi Arabia. Ann Thorac Med 9(2):104–111

Cai Y, Chai D, Wang R, Liang B, Bai N (2012) Colistin resistance of *Acinetobacter baumannii*: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 67(7): 1607–1615

Carvalho KR, Carvalho-Assef AP, Peirano G, Santos LC, Pereira MJ, Asensi MD (2009) Dissemination of multidrug-resistant *Acinetobacter baumannii* genotypes carrying bla(OXA-23) collected from hospitals in Rio de Janeiro, Brazil. Int J Antimicrob Agents 34(1):25–28

Chen KJ, Hou CH, Sun MH, Lai CC, Sun CC, Hsiao CH (2008) Endophthalmitis caused by *Acinetobacter baumannii*: report of two cases. J Clin Microbiol 46(3):1148–1150

Chopra T, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, Kaye KS (2013) Epidemiology of bloodstream infections caused by *Acinetobacter baumannii* and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes. Antimicrob Agents Chemother 57(12):6270–6275

Cisneros JM, Rodriguez-Bano J (2002) Nosocomial bacteremia due to *Acinetobacter baumannii*: epidemiology, clinical features and treatment. Clin Microbiol Infect 8(11):687–693

Coyne S, Courvalin P, Perichon B (2011) Efflux-mediated antibiotic resistance in Acinetobacter spp. Antimicrob Agents Chemother 55(3):947–953

Doi Y, Murray GL, Peleg AY (2015) *Acinetobacter baumannii*: evolution of antimicrobial resistance-treatment options. Semin Respir Crit Care Med 36(1):85–98

Gokmen TG, Akcimen B, Kayar B, Marzi M, Koksal F (2016) The outbreak of Acinetobacter baumannii producing OXA-23 and OXA-51 type carbapenemases in a state hospital. J Exp Clin Med 33(3):157–161

Greene C, Vadlamudi G, Newton D, Foxman B, Xi C (2016) The influence of biofilm formation and multidrug resistance on environmental survival of clinical and environmental isolates of *Acinetobacter baumannii*. Am J Infect Control 44(5):e65–e71

Harding CM, Hennon SW, Feldman MF (2018) Uncovering the mechanisms of *Acinetobacter baumannii* virulence. Nat Rev Microbiol 16(2):91–102

Hsu LY, Apisarnthanarak A, Khan E, Suwantarat N, Ghafur A, Tambyah PA (2017) Carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. Clin Microbiol Rev 30(1):1–22

Inchai J, Pothirat C, Bumroongkit C, Limsukon A, Khositsakulchai W, Liwsrisakun C (2015) Prognostic factors associated with mortality of drug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. J Intensive Care 3:9

Jain M, Sharma A, Sen MK, Rani V, Gaind R, Suri JC (2019) Phenotypic and molecular characterization of *Acinetobacter baumannii* isolates causing lower respiratory infections among ICU patients. Microb Pathog 128:75–81

Khorsi K, Messai Y, Hamidi M, Ammari H, Bakour R (2015) High prevalence of multidrug-resistance in *Acinetobacter baumannii* and dissemination of carbapenemase-encoding genes blaOXA-23-like, blaOXA-24-like and blaNDM-1 in Algiers hospitals. Asian Pac J Trop Med 8(6):438–446

Kim BN, Peleg AY, Lodise TP, Lipman J, Li J, Nation R, Paterson DL (2009) Management of meningitis due to antibiotic-resistant Acinetobacter species. Lancet Infect Dis 9(4):245–255

Lagana P, Melcarne L, Delia S (2015) *Acinetobacter baumannii* and endocarditis, rare complication but important clinical relevance. Int J Cardiol 187:678–679

Lee K, Yong D, Jeong SH, Chong Y (2011) Multidrug-resistant Acinetobacter spp: increasingly problematic nosocomial pathogens. Yonsei Med J 52(6):879–891

Lee CR, Lee JH, Park M, Park KS, Bae IK, Kim YB, Lee SH (2017) Biology of *Acinetobacter baumannii*: pathogenesis, antibiotic resistance mechanisms, and prospective treatment options. Front Cell Infect Microbiol 7:55

Lolans K, Rice TW, Munoz-Price LS, Quinn JP (2006) Multicity outbreak of carbapenem-resistant *Acinetobacter baumannii* isolates producing the carbapenemase OXA-40. Antimicrob Agents Chemother 50(9):2941–2945

Manchanda V, Sanchaita S, Singh N (2010) Multidrug resistant acinetobacter. J Global Infect Dis 2(3):291–304

Maragakis LL, Perl TM (2008) *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis 46(8):1254–1263

Mesli E, Berrazeg M, Drissi M, Bekkhoucha SN, Rolain JM (2013) Prevalence of carbapenemase-encoding genes including New Delhi metallo-beta-lactamase in Acinetobacter species Algeria. Int J Infect Dis 17(9):e739–e743

Necati Hakyemez I, Kucukbayrak A, Tas T, Burcu Yikilgan A, Akkaya A, Yasayacak A, Akdeniz H (2013) Nosocomial *Acinetobacter baumannii* infections and changing antibiotic resistance. Pak J Med Sci 29(5):1245–1248

Oh YJ, Song SH, Baik SH, Lee HH, Han IM, Oh DH (2013) A case of fulminant community-acquired *Acinetobacter baumannii* pneumonia in Korea. Korean J Intern Med 28(4):486–490

Pagano M, Martins AF, Barth AL (2016) Mobile genetic elements related to carbapenem resistance in *Acinetobacter baumannii*. Braz J Microbiol 47(4):785–792

Rezaee MA, Pajand O, Nahaei MR, Mahdian R, Aghazadeh M, Ghojazadeh M, Hojabri Z (2013) Prevalence of Ambler class A beta-lactamases and ampC expression in cephalosporin-resistant isolates of *Acinetobacter baumannii*. Diagn Microbiol Infect Dis 76(3):330–334

Rogers AD, Deal C, Argent AC, Hudson DA, Rode H (2014) Ventilator associated pneumonia in major paediatric burns. Burns 40(6):1141–1148

Santajit S, Indrawattana N (2016) Mechanisms of antimicrobial resistance in ESKAPE pathogens. Biomed Res Int 2016:2475067

Senkyrikova M, Husickova V, Chroma M, Sauer P, Bardon J, Kolar M (2013) *Acinetobacter baumannii* producing OXA-23 detected in the Czech Republic. SpringerPlus 2(1):296

Sharma A, Sharma R, Bhattacharyya T, Bhando T, Pathania R (2017) Fosfomycin resistance in *Acinetobacter baumannii* is mediated by efflux through a major facilitator superfamily (MFS) transporter-AbaF. J Antimicrob Chemother 72(1):68–74

Shoja S, Moosavian M, Rostami S, Farahani A, Peymani A, Ahmadi K, Ebrahimifard N (2017) Dissemination of carbapenem-resistant *Acinetobacter baumannii* in patients with burn injuries. J Chin Med Assoc 80(4):245–252

Singh H, Thangaraj P, Chakrabarti A (2013) *Acinetobacter baumannii*: a brief account of mechanisms of multidrug resistance and current and future therapeutic management. J Clin Diagn Res 7(11):2602–2605

Subashchandrabose S, Smith S, DeOrnellas V, Crepin S, Kole M, Zahdeh C, Mobley HL (2016) *Acinetobacter baumannii* genes required for bacterial survival during bloodstream infection. mSphere 1(1):e00013

Vila J, Marti S, Sanchez-Cespedes J (2007) Porins, efflux pumps and multidrug resistance in *Acinetobacter baumannii*. J Antimicrob Chemother 59(6):1210–1215

Wareham DW, Bean DC, Khanna P, Hennessy EM, Krahe D, Ely A, Millar M (2008) Bloodstream infection due to Acinetobacter spp: epidemiology, risk factors and impact of multi-drug resistance. Eur J Clin Microbiol Infect Dis 27(7):607–612

Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B (2017) Clinical and pathophysiological overview of Acinetobacter infections: a century of challenges. Clin Microbiol Rev 30(1):409–447

Xu C, Bilya SR, Xu W (2019) adeABC efflux gene in *Acinetobacter baumannii*. New Microbes New Infect 30:100549

Zhang W, Wu YG, Qi XM, Dai H, Lu W, Zhao M (2014) Peritoneal dialysis-related peritonitis with *Acinetobacter baumannii*: a review of seven cases. Perit Dial Int 34(3):317–321