**Chapter**

***Acinetobacter baumannii*: An Old Foe**

*Acinetobacter baumannii* is a major human pathogen that causes a wide range of clinical infections including a growing number of healthcare associated infections mainly ventilator associated pneumonia (VAP) that are driven by strains with certain virulence factors and resistance to most of the available antibiotics. It is a leading cause of VAP and involve in several severe infections associated with catheter-related bloodstream and urinary tract infections, cerebrospinal shunt-related meningitis, and wound infections. This chapter comprehensively covers the epidemiology, pathophysiology, clinical manifestations and its growing and changing trends over habitats and antibiotics.

**Historical perspective of the Genus *Acinetobacter***

The history of genus *Acinetobacter* dates back to 1911 when *Micrococcus calcoaceticus* was isolated from soil by a Dutch microbiologist, Beijerinck. [1]  Over the following decades, similar organisms were described and assigned to at least 15 different genera and species, including *Diplococcus mucosus*, [2] *Micrococcus calcoaceticus,*[1] *Alcaligenes haemolysans*, [3] *Mima polymorpha*, [4] *Moraxella lwoffi*, [5] *Herellea vaginicola*, [6] *Bacterium anitratum*, [7] *Moraxella lwoffi* var. *glucidolytica*, [8] *Neisseria winogradskyi*, [9] *Achromobacter anitratus*, [10] and *Achromobacter mucosus*. [11]

The current genus designation, *Acinetobacter* (derived from the Greek ακινɛτοσ [akinetos], meaning nonmotile) was initially proposed by Brisou and Prévot in 1954 to separate the nonmotile from the motile organisms within the genus *Achromobacter*. [12] Baumann *et al*. published a comprehensive survey and concluded that the different species listed above belonged to a single genus, for which the name *Acinetobacter* was proposed, and that further subclassification into different species based on phenotypic characteristics was not possible. [13] These findings resulted in the official acknowledgement of the genus *Acinetobacter* by the Sub- committee on the Taxonomy of *Moraxella* and Allied Bacteria in 1971. [14]

In the 1974 edition of *Bergey’s Manual of Systematic Bacteriology*, [15] the genus *Acinetobacter* was listed, with the description of a single species, *Acinetobacter calcoaceticus* (the type strain for both the genus and the species is *A. calcoaceticus* ATCC 23055). [1] In the “Approved List of Bacterial Names,” in contrast, two different species, *A. calcoaceticus* and *A. lwoffii*, were included, based on the observation that some acinetobacters were able to acidify glucose whereas others were not. [16] In the literature, based on the same properties, the species *A. calcoaceticus* was subdivided into two subspecies or biovars, *A. calcoaceticus* bv. *anitratus* (formerly called *Herellea vaginicola*) and *A. calcoaceticus* bv. *lwoffii* (formerly called *Mima polymorpha*). These designations, however, were never officially approved by taxonomists.

**Current Taxonomy**

The genus *Acinetobacter*, as currently defined, comprises Gram negative, strictly aerobic, non-fastidious, non-fermenting, non-motile, catalase positive, oxidase negative coccobacilli with a DNA G+C content of 39% to 47%. [17] Based on more recent taxonomic data, it was proposed that members of the genus *Acinetobacter* should be classified in the new family *Moraxellaceae* within the order *Gammaproteobacteria*, which includes the genera *Moraxella*, *Acinetobacter*, *Psychrobacter*, and related organisms. [18]

A major breakthrough was achieved in the long and complicated history of the *Acinetobacter* genus in 1986 by Bouvet and Grimont, who distinguished 12 DNA groups or genospecies based on DNA-DNA hybridization, some of which were given formal species names, including *A. baumannii*, *A. calcoaceticus*, *A. haemolyticus*, *A. johnsonii*, *A. junii*, *A. lwoffii* and *A. radioresistens*. [19] Likewise, *Acinetobacter* has undergone significant modification in nomenclature over the last decades increasing the actual number of validly described (genomic or groups) species to more than 50 species associated with a specific ecologic niche that shapes their genomic contents. [19, 20, 21]

The most clinically relevant members of the *Acinetobacter* genus phylogenetically cluster into the *Acinetobacter calcoaceticus-baumannii* (Acb) complex.[22] The Acb complex consists of five pathogenic species, *A. baumannii*, *A. nosocomialis*, *A. pittii*, *A. seifertii* and *A. dijkshoorniae*, as well as one non-pathogenic species, *A. calcoaceticus*.[23] These are very closely related and difficult to distinguish from each other by phenotypic properties. [24] The designation Acb complex may be misleading and not appropriate if used in a clinical context as it also consist of environmental non pathogenic species, i.e., *A. calcoaceticus* that has frequently been recovered from soil and water and never been implicated in serious clinical disease so far.

*A. baumannii* is the most resistant of these genospecies and has substantial clinical relevance being the most frequently isolated species from human clinical specimens. [19, 25] It’s capability to resist harsh environmental factors enables it to establish and spread rapidly in the hospital environment resulting in outbreaks. [26] A review of clinical *Acinetobacter* isolates suggests that *A. lwoffii* and *A. ursingii* may be emerging as possible pathogens. [25]

**Species Identification**

Both DNA-DNA hybridization and the 28 numbers of phenotypic identification tests of Bouvet and Grimont are laborious and far from being suitable for routine microbiology laboratories. Unfortunately, it is difficult to distinguish *A. baumannii* from other members of the Acb complex by simple phenotypic tests that are commonly used in routine diagnostic laboratories. [27]

Species identification with semiautomated commercial identification systems that are currently used in diagnostic microbiology, such as the API 20NE, Vitek 2, Phoenix, and MicroScan WalkAway systems, remains problematic. [27] This can be explained in part by their limited database content but also because the substrates used for bacterial species identification have not been tailored specifically to identify acinetobacters.

Therefore, this has hindered appropriate species identification. The need for species identification of acinetobacters in routine clinical laboratories has been questioned by some researchers. [24] Molecular methods that have been developed and validated for identification of acinetobacters include:

* Amplified 16S rRNA gene restriction analysis (ARDRA) [28]
* High-resolution fingerprint analysis by amplified fragment length polymorphism (AFLP) [29]
* Ribotyping [30]
* tRNA spacer fingerprinting [31]
* Restriction analysis of the 16S-23S rRNA intergenic spacer sequences [32]
* Sequence analysis of the 16S-23S rRNA gene spacer region [33]
* Sequencing of the *rpoB* (RNA polymerase β-subunit) gene and its flanking spacers [34]
* Matrix-associated laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry identification of species-specific outer membrane components [35, 36]

ARDRA and AFLP analysis are currently the most widely accepted and validated reference methods for species identification of acinetobacters, with a large library of profiles available for both reference and clinical strains, while tRNA fingerprinting, though generally also suitable for species identification, does not discriminate between *A.* *baumannii* and *A. nosocomialis*. Both ribotyping and sequence analysis of the 16S-23S rRNA gene spacer region were found to discriminate between species of the *A.* *calcoaceticus-A. baumannii* complex but have not been applied to other *Acinetobacter* species, and sequencing of the rpoB gene, although very promising, awaits further validation. MALDI-TOF mass spectrometry allows for species identification in less than 1 hour, but it requires expensive equipment and needs further evaluation. All these methods have contributed to a better understanding of the epidemiology and clinical significance of *Acinetobacter* species during recent years, but they are too laborious to be applied in day-to-day diagnostic microbiology, and their use for the time being is also confined mainly to reference laboratories.

More recent developments include the identification of *A. baumannii* by detection of the *bla*OXA-51-like carbapenemase gene intrinsic to this species [37] and a simple PCR-based method described by Higgins *et al*. [38] that exploits differences in their respective *gyrB* genes to rapidly differentiate between *A. baumannii* and *Acinetobacter* genomic species 13TU.

**Natural habitat**

Members of the genus *Acinetobacter* are considered ubiquitous organisms. 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. [39] *A. calcoaceticus* and *A. johnsonii* are prevalent in water and soil, and *A. baylyi* is frequently isolated from sewerage. [25] These earlier findings have contributed to the common misconception that *A. baumannii* is also ubiquitous in nature. [40] In fact, not all species of the genus *Acinetobacter* have their natural habitat in the environment. However, a systematic study to investigate the natural occurrence of the various *Acinetobacter* species in the environment has never been per- formed. [27]

Most *Acinetobacter* species that have been recovered from human clinical specimens have at least some significance as human pathogens. *A. baumannii,* *A. pittii* and *A. nosocomialis* are associated with health care infections, and they are closely related and phenotypically indistinguishable from each other. [25]

*Acinetobacter* spp. are part of the human skin flora. In an epidemiological survey performed to investigate the colonization of human skin and mucous membranes with *Acinetobacter* species, up to 43% of non-hospitalized individuals were found to be colonized with these organisms. [41] The most frequently isolated species were *A. lwoffii* (58%), *A. johnsonii* (20%), *A. junii* (10%), and *Acineto- bacter* genomic species 3 (6%). [42] *A. lwoffii* and *A. radioresistans* colonize human skin and cause infection in immunocompromised hosts. [25]

Dijkshoorn *et al*. studied fecal carriage of *Acinetobacter* spp.and found a carrier rate of 25% among healthy individuals, with *A. johnsonii* and *Acinetobacter* genomic species 11 predominating. [43]

In contrast, *A. baumannii*, the most important nosocomial *Acinetobacter* species, was found only rarely 0.5% [50] and 3% [49] on human skin. It was found only 0.8% in human feces. [43]

It is largely believed that two attributes such as drug resistance and environmental persistence have enabled *A. baumannii* to thrive in the nosocomial environment. [44] Commonest reservoirs of *A. baumannii* in a hospital setting include ventilators and their accessories, bed mattresses, intravenous devices, catheters, suction apparatus, central lines, sinks and taps. [45] The intensive care units (ICUs) are the most frequently affected areas [46] as the patients are usually need more invasive procedures for longer periods of time, and frequently receive high antibiotic selective pressure. *A. baumannii* has the ability to live on dry environmental surfaces in an ICU for up to 13 days, i.e. 10 days more than other Gram negative bacteria. [47]

In conclusion, *A. baumannii* does not appear to be a typical environmental organism. Existing data are not sufficient to determine if the occurrence of severe community-acquired *A. baumannii* infections that have been observed in tropical climates [48, 49] may be associated with an environmental source. Thus, the natural habitats of A. baumannii still remain to be defined.

**Morphological and biochemical characteristics of *A. baumannii***

*A. baumannii* may be identified presumptively as Gram-negative, catalase-positive, oxidase-negative, nonmotile, nonfermenting coccobacilli. They are short, plump, Gram-negative rods that are difficult to destain and may therefore be misidentified as either Gram-negative or Gram-positive cocci (hence the former designation *Mimae*). [27] They grow well on solid media that are routinely used in clinical microbiology laboratories, such as sheep blood agar or tryptic soy agar, at a 37°C incubation temperature. On sheep blood agar, these organisms form smooth, sometimes mucoid, grayish white colonies and non-haemolytic; with a colony diameter of 1.5 to 3 mm after overnight culture.[17] *A. baumannii* displays smooth pink (nonlactose fermenters) to red colonies on MacConkey’s agar and bluish to bluish grey coloured colonies on Simmon’s citrate agar. It is capable of producing acid from glucose, galactose, mannose, lactose, rhamnose and xylose; but not from mannitol and sucrose. It does not reduce nitrate and unable to produce indole. [50] Unfortunately, it is difficult to distinguish *A. baumannii* from other members of the Acb complex by simple phenotypic tests that are commonly used in routine diagnostic laboratories. [27]

To facilitate the isolation of acinetobacters from mixed bacterial populations, Leeds *Acinetobacter* medium was proposed. [51]

On eosin methylene blue agar (EMB), colonies are bluish to bluish grey. They are pale lavender in color on Herellea agar (HA), while on Leeds *Acinetobacter* Medium (LAM) the bacteria are pink on a purple background.

**Clinical manifestations of *A. baumannii* infections**

*A. baumannii* is mainly reported to be the most important nosocomial pathogens at the ICUs and health care settings housing very ill patients. [46, 47, 52, 53]It has become a major concern nowadays because of its increasing involvement in several severe infections associated with catheter-related bloodstream and urinary tract infections, ventilator-associated pneumonia (VAP), cerebrospinal shunt-related meningitis, and wound infections. [54] The incidence of this microorganism varies from one geographical region to another.

**Ventilator associated pneumonia**

*A. baumannii* is one of the most prevalent VAP causing pathogens. [55]In large surveillance studies from the United State, between 5% and 10% cases of ICU-acquired pneumonia were due to *A. baumannii*. [56] Nosocomial VAP has been reported to occur in patients in ICUs with a frequency of 3% to 5%, especially in patients on mechanical ventilators and crude mortality rate of 30% to 75%. [56] However, it is very difficult to distinguish upper airway colonization from true pneumonia in many circumstances.

**Bloodstream Infection**

*Acinetobacter* species account for 1% to 2% of all bloodstream infections and are typically associated with intravascular devices, with 63% of those infections caused by *A. baumannii,* followed by *A. nosocomialis* (20%) and *A. pittii* (8%) in one series of 295 bloodstream isolates. The mortality rate of those with *A. baumannii* bacteremia (36.8%) was significantly higher than those with *A. nosocomialis* (16.4%) and *A. pittii* (13%). [58] Presence of central venous catheter or dissemination of A. baumannii due to extensive pneumonia results in the bloodstream infections. The other predisposing factors that cause bacteremia are intravenous lines, mechanical ventilation, operations, renal transplants, chest tubes, urinary catheterization, trauma and long hospitalization. [59] It is very common in elderly immunocompromised individuals. The overall mortality rate from ICU-acquired bacteremia (34% to 43.4%) was higher in comparison to non-ICU wards (16.3%). [60]

**Trauma and other wound infections**

A. baumannii has been identified with trauma related or post surgical osteomyelitis, skin and soft tissue infections. [61, 62] About 2.1% of ICU acquired skin and soft tissue infections are reported to be caused by *A. baumannii*. [56] It is a well known pathogen in burn units and may be difficult to eradicate from such patients. [63]

**Urinary tract infections (UTI)**

*A. baumannii* is an occasional cause of UTI, being responsible for just 1.6% of ICU-acquired UTIs in one study. [56] Typically, the organism is associated with catheter-associated infection or colonization. It is not usual for this organism to cause uncomplicated UTI in healthy outpatients. [27]

**Meningitis**

Nosocomial postneurosurgical A. baumannii meningitis is an increasingly important entity. *A. baumannii* is reported to be the most isolated microorganism in critically ill neurosurgical patients with nosocomial meningitis. [64] Typical patients have undergone neurosurgery and have an external ventricular drain. [65]

**Other manifestations**

Menon *et al* has documented a case of endocarditis that was caused by *A. baumannii* complex. [66] A. baumannii may cause endophthalmitis or keratitis, sometimes related to contact lens use or following eye surgery. [67] Note that precise species identification remains an issue in these reports.

***A. baumannii* in community acquired pneumonia**

There are reports of *A. baumannii* being acquired through the community. Community acquired pneumonia due to *A. baumannii* has been described for tropical regions of Australia and Asia. [68, 69, 70, 49] It is characterized by a fulminant clinical course, secondary bloodstream infection, and mortality rate of 40 to 60%. [49] The source of infection may be throat carriage, which occurs in up to 10% of community residents with excessive alcohol consumption. [48]

In conclusion, *A. baumannii* causes a range of nosocomial infections across multiple anatomical sites. Most commonly, *A. baumannii* infections manifest as VAP. Less frequently, *A. baumannii* causes infections in the skin and soft tissues and at surgical sites as well as catheter-associated UTI. Common to each of these scenarios is a breach in an anatomical barrier that enables the entry of *A. baumannii* directly to the site of infection. Community-acquired infections caused by *A. baumannii* have also been reported. To date though, community-acquired infections have only presented in patients with underlying co-morbidities such as alcoholism, diabetes mellitus or other illnesses such as cancer and obstructive pulmonary disorders.

**Global epidemiology of *A. baumannii***

Various geographical areas have been reported for the outbreak of Acb, mainly *Acinetobacter baumannii* [71] in which India has also been the forefront of such studies. Infections caused by *A. baumannii* account for ~2% of all healthcare associated infections in the United States [72] and Europe [73]; however, these rates are twice as high in Asia and the Middle East [73]. Although infection rates are lower compared with other Gram-negative pathogens, globally, ~45% of all isolates are MDR, with rates as high as 70% in Latin America and the Middle East. [74]

 These daunting MDR rates are nearly four times higher than those observed for other Gram-negative pathogens, such as MDR *P. aeruginosa* and *K. pneumoniae*, for which global surveillance statistics are also available. [74] Pan drug resistant *A. baumannii* isolates have been reported from Asia and the Middle East. [75]

In a review comparing hospitals of 10 Asian countries, 1.2-87% of all *Acinetobacter* isolates from patients with VAP were MDR strains, and these MDR strains were most prevalent in India and Thailand. [52, 76] This results in high rates of morbidity and mortality in the healthcare system due to its wider resistance to the most potent antimicrobial drugs The clinical manifestations of bacteremia by *A. baumannii* are not specific.

**Pathogenesis and virulence mechanisms**

Over the past few decades, number of scientific studies focus on the pathogenesis of *Acinetobacter* species overwhelmingly using *A. baumannii* as the model organism. The genetic relatedness between members of the Acb complex and their phenotypical similarities might indicate that they share common virulence factors, rendering studies in *A. baumannii* potentially applicable to other pathogenic *Acinetobacter* species. Indeed, some clinically relevant and recently described virulence attributes of pathogenic *Acinetobacter* species were first described in *A. nosocomialis* and subsequently characterized in *A. baumannii*.[23]

The pathogenicity of *A. baumannii* relates to its ability to adhere to surfaces utilizing pili, to create biofilm on surfaces and human cells, to survive in iron-limited environments within the host (Table 1), and to acquire foreign genetic material to enhance survival and develop large repertoires of antibiotic resistance mechanisms.

**Table 1: Virulence factors of A. baumannii (adapted from Shadan *et al*., 2023) [77]**

|  |  |  |
| --- | --- | --- |
| **Virulence factors** | **Role in pathogenesis** | **References** |
| Autotransporter (Ata) | Support adherence and biofilm development | Thibau *et al*. (2019) |
| AbeD | Host cells killing | Srinivasan *et al*. (2015) |
| AdeRS | Regulator of virulence | Montaña *et al*. (2015) |
| BaeSR | Virulence regulator | Lin *et al*. (2014) |
| BfmRS | Virulence regulator/Csu pili expression | Kim *et al*. (2009) |
| Biofilm associate proteins | Adherence and biofiolm development | Brossard and Campagnari (2011) |
| BAP like proteins (BAP) | Enhancement of adherence | De Gregorio *et al*. (2015) |
| Capsular polysaccharides | Enhance bacterial survivality in tissues and biofilm formation | S[hashkov *et al*. (2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10038080/#B196)) |
| CipA | Enhance serum resistance and promote tissue invasion | Koenigs *et al*. (2016) |
| CheAY | Virulence regulator/Csu pili expression | Chen *et al*. (2017) |
| FhaBC | Promote the adherence in tissue and host cells killing | Pérez *et al*. (2017) |
| GacS | Promote neutrophil influx | Bhuiyan *et al*. (2016) |
| GigABCD | Support in vivo survivality and host cells killing | Gebhardt *et al*. (2015) |
| Iron acquisition system | Support in vivo survivality and host cells killing | Megeed *et al*. (2016) |
| Lipopolysaccharides (LPS) | Evasion of host immune system and tissue infection | Lees-Miller *et al*. (2013) |
| Manganese acquisition system (MumC/MumT) | Support in vivo survival | Juttukonda *et al*. (2016) |
| Outer membrane vesicles (OMVs) | carry virulence factors and antibiotic resistance gene | Li *et al*. (2016) |
| β-lactamase PER-1 | Support in vivo survival and serum resistance | Russo *et al*. (2009) |
| Penicillin binding protein7/8 | Support adherence and in vivo survival | Lee *et al*. (2008) |
| Pili | Promote adherence and biofilm formation | Tomaras *et al*. (2008) |
| Phospholipase (PLC/PLD) | Support in vivo survival and serum resistance | Fiester *et al*. (2016) |
| PmrAB | Antimicrobial resistance and LPS modification | Beceiro *et al*. (2011) |
| Porins (OmpA/OMP 33-36, Omp22) | Promote tissue adherence and invasion | Huang *et al*. (2016) |
| RecA | Support in vivo survival | Aranda *et al*. (2011) |
| SurA1 | Support in vivo survival and serum resistance | Liu *et al*. (2016) |
| Type I secretion system | Enhance biofilm formation | Harding *et al*. (2017b) |
| Type II secretion system | Support in vivo survival | Harding *et al*. (2016) |
| Type V secretion system | Promote adherence and biofilm formation | Bentancor *et al*. (2012b) |
| Type VI secretion system | Killing of competitor bacteria and support host colonization | Ruiz *et al*. (2015) |
| Tuf | Enhance serum resistance | Koenigs *et al*. (2015) |
| UspA | Support in vivo survivality and host cells killing | Gebhardt *et al*. (2015) |
| Zinc acquisition system (ZnuABC, ZigA, ZrlA) | Enhance in vivo survival and persistence | Lonergan *et al*. (2019) |

Thus, several *in vitro* and *in vivo* studies involving animal models have produced important information regarding the *A. baumannii* pathogenesis. Studies on the various acquisition systems like metal, nutrient and protein secretion systems have broadened the understanding of *A. baumanni* virulence. These qualities have led *Acinetobacter* spp. the ability to colonize and persist in nearly any body site if given the opportunity. Although many common features emerge, there is a clear absence of any discernable toxin or molecular determinant that can account for the virulence potential of a particular *A. baumannii* strain. [23] More extensive studies are still required on diverse secretion systems in *A. baumannii* to identify the genes linked to pathogenesis. Experimental approaches like whole genome sequencing, transposon (Tn) screening, and Tn-sequencing will provide a deep understanding of pathogenicity and might be useful for the development of novel antibiotics.

**Therapeutic strategies for *A. baumannii* infection**

*A. baumannii* is one of the six “superbugs” identified by the Infectious Diseases Society of America (IDSA) as “**ESKAPE**” group (**E**: *Enterococcus faecium*, **S**: *Staphylococcus aureus* or recently *Stenotrophomonas maltophila*, **K**: *Klebsiella pneumoniae* or recently **C**: *Clostridioides difficile*, **A**: *A. baumannii*, **P**: *Pseudomonas aeruginosa*, **E**: *Enterobacter* spp., or recently Enterobacterales). [78] In light of this, the CDC in the US published a classification of the most concerning AMR threats, where they categorized carbapenem-resistant *P. aeruginosa* and *A. baumannii*, *C. difficile*, MDR *Neisseria gonorrhoeae* and Enterobacterales showing resistance to both carbapenem and cephalosporin antibiotics as “urgent threats”. [79] Furthermore, *A. baumannii* figures in the list of “critical priority” pathogens by the WHO in 2024, to serve as a guide and to prioritize antimicrobial research and development (R&D) to various Gram-negative bacteria (including non-fermenters and members of the Enterobacterales), posing as particular threats due to their pathogenic potential and transmissibility (e.g., in nosocomial environments or nursing homes). [80]

Given the range and diversity of resistance determinants in *A. baumannii*, therapy should be based on the results of adequately performed antimicrobial susceptibility testing. Antibiotic selection for empirical therapy is challenging and must rely on recent institutional-level susceptibility data. So far, carbapenems have been thought of as the agents of choice for serious *A. baumannii* infections. However, although these drugs are still active against the vast majority of *A. baumannii* strains worldwide, the clinical utility of this class of antimicrobial is increasingly being jeopardized by the emergence of both enzymatic and membrane-based mechanisms of resistance.

The use of sulbactam (β-lactamase inhibitor) has shown clinically relevant intrinsic antimicrobial activity against certain organisms, specifically *Acinetobacter* spp. [81–86], that is mediated by its binding to penicillin-binding protein 2.

Urban *et al*. performed a small study assessing the clinical efficacy of sulbactam during an outbreak of *A. baumannii* resistant to carbapenems, aminoglycosides, and other β-lactams. [27] Of the 10 patients who received ampicillin-sulbactam for more than three days; 9 clinically responded. These results were supported by a further noncomparative study from Spain, which showed that 29/41 (95%) patients with non-life-threatening *A. baumannii* infections were cured or clinically improved with ampicillin-sulbactam or sulbactam alone. [81] All isolates were multidrug resistant but were susceptible to imipenem, sulbactam, and polymyxins. As pointed out in that study, the use of a sulbactam-containing regimen for milder infections may be an appropriate strategy in limiting excessive carbapenem use. An equivalent efficacy of sulbactam to that of imipenem has also been shown for treatment of *A. baumannii* bloodstream infection. [87-89] These data indicate that when *A. baumannii* is susceptible to sulbactam, this agent is probably as efficacious as any other. Unfortunately, *in vitro* susceptibilities of *A. baumannii* strains to sulbactam vary widely, depending on the geographic region. [89]

Till recently, polymyxins (colistin or Polymyxin E and Polymyxin B) are considered as the last resort. However, the potential limitations to the polymyxins therapy include nephrotoxicity and its poor penetration in lungs. [27] Many *in vitro* and animal studies support the role of combination therapy; particularly colistin in combination with a carbapenem and/or rifampin which appears most promising. [90-97]

A concerning void of new therapeutic options exists for *A. baumannii* infections. Of the recently licensed antimicrobials, tigecycline, a 9-*t*-butylglycylamido semisynthetic derivative of minocycline, has provided some hope, but clinical data are still limited. [27] As with other tetracycline derivatives, tigecycline inhibits the 30S ribosomal subunit, but its unique feature is its ability to evade the major determinants of tetracycline resistance, i.e., the *tet*(A) to *tet*(E) and *tet*(K) efflux pumps and the *tet*(M) and *tet*(O) determinants that provide ribosomal protection. [98, 99] However, its utility for treating *A. baumannii* causing pneumonia or other tissue-based infections warrants further evaluation. [27] Further clinical data on tigecycline’s efficacy in pneumonia are still awaited.

Other agents on the licensing horizon with activity against *A. baumannii* include doripenem which has a slight advantage over meropenem.[100] Clinical data for doripenem against *A. baumannii* are still awaited.

**Mechanisms of antibiotic resistance in *A. baumannii***

Several health-related agendas about antimicrobial resistance (AMR) have been featured and discussed in the Regional, National and International Health Regulations level such as the United Nation (UN) Sustainable Development Goals, etc. where India has been considered nowadays as “the AMR capital of the world”.[101] The World Health Organisation (WHO) released a global action plan for the containment of AMR, known as WHO global strategy, in 2001 which included the framework of multiple interventions that will help in slowing the emergence and reducing the spread of AMR microorganisms.[78]

Before 1970s, *A. baumannii* was susceptible to most of the antibiotics (Fig. 1).

**Fig. 1: Evolution of antibiotic resistance in A. baumannii (adapted from Gonzalez-Villoria and Valverde-Garduno, 2016).** [102]



The major alarm is the treatment of infections which are rapidly acquiring resistant to antibiotics. This includes extended spectrum β-lactamases to β-lactam and β-lactamase inhibitor, cephalosporins, and carbapenems. Furthermore, it has been linked to the loss or reduced expression of porins or overexpression of multidrug efflux pumps and mutations that change targets or cellular functions. [103] *A. baumannii* possesses a vast resistance island comprising of 45 resistance genes in its genome. [104] Comparative analysis of genome showed clusters of drug-resistant genes known as *A. baumannii* Resistant Islands (AbaRs), concentrated at certain specific region such as comM in the genome. [105] Many antibiotic resistance genes like aacC1, tetA (A), aphA1b and aadA1 have been reported to be present in these AbaR regions. [106] These massive regions are assumed to emerge from the mobile elements or integration of plasmids into its genome.

Thus, several intrinsic and acquired AMR mechanisms (Fig.2) are used by *A. baumannii* to show the potential of this organism to respond swiftly to changes in selective environmental pressure.

**Fig. 2: Mechanisms of antibiotic resistance in A. baumannii (adapted from Shin and Park, 2017).** [107]



The mechanisms of antibiotic resistance in *A*. *baumannii* are generally classified into following broad categories:

1. **Antibiotic-inactivating enzymes:** Enzymatic degradation by β-lactamases is the most prevailing mechanism of β-lactam resistance in *A*. *baumannii*. β-lactamases are enzymes that catalyze the hydrolysis of beta-lactam antibiotics and can be divided into four classes based on sequence motifs and differences in hydrolytic mechanism. [108, 109] The 4 molecular groups β-lactamases are: Ambler class A, Ambler class B (metallo enzymes), Class C β-lactamases, and Ambler class D (oxacillinases).

**Table 2: Mechanisms of *A. baumannii* resistance to beta-lactams (adapted from Kyriakidis *et al*., 2021).** [110]

|  |  |  |  |
| --- | --- | --- | --- |
| **Mechanism of Resistance** | **Element Name** | **Resistance** | **Element Symbol (Gene)** |
| **Class A beta lactamases** | class A broad-spectrum beta-lactamase TEM-1 | **Extended spectrum** | *blaTEM-1* |
| class A extended-spectrum beta-lactamase SHV-5 | *blaSHV-5* |
| class A extended-spectrum beta-lactamase SHV-12 | *blaSHV-12* |
| carbapenem-hydrolyzing class A beta-lactamase GES-5 | *blaGES-5* |
| class A extended-spectrum beta-lactamase GES-11 | *blaGES-11* |
| class A beta-lactamase GES-12 | *blaGES-12* |
| inhibitor-resistant class A extended-spectrum beta-lactamase PER-1 | *blaPER-1* |
| class A extended-spectrum beta-lactamase PER-7 | *blaPER-7* |
| class A extended-spectrum beta-lactamase VEB-1 | *blaVEB-1* |
| class A extended-spectrum beta-lactamase CTX-M-15 | *blaCTX-M-15* |
| class A extended-spectrum beta-lactamase CTX-M-55 | *blaCTX-M-55* |
| class A extended-spectrum beta-lactamase CTX-M-115 | *blaCTX-M-115* |
| carbapenem-hydrolyzing class A beta-lactamase KPC-2 | *blaKPC-2* |
| **Class B metallo-beta-lactamases** | subclass B1 metallo-beta-lactamase NDM-1 | **All (except monobactams)** | *blaNDM-1* |
| subclass B1 metallo-beta-lactamase IMP-1 | *blaIMP-1* |
| subclass B1 metallo-beta-lactamase IMP-4 | *blaIMP-4* |
| subclass B1 metallo-beta-lactamase IMP-14 | *blaIMP-14* |
| subclass B1 metallo-beta-lactamase IMP-16 | *blaIMP-16* |
| **Class C beta-lactamases** | class C extended-spectrum beta-lactamase ADC-11 | **Extended spectrum** | *blaADC-11* |
| class C beta-lactamase ADC-25 | *blaADC-25* |
| class C extended-spectrum beta-lactamase ADC-26 | *blaADC-26* |
| class C extended-spectrum beta-lactamase ADC-30 | *blaADC-30* |
| cefepime-hydrolyzing class C extended-spectrum beta-lactamase ADC-33 | *blaADC-33* |
| class C extended-spectrum beta-lactamase ADC-52 | *blaADC-52* |
| cefepime-hydrolyzing class C extended-spectrum beta-lactamase ADC-56 | *blaADC-56* |
| class C extended-spectrum beta-lactamase ADC-73 | *blaADC-73* |
| class C extended-spectrum beta-lactamase ADC-74 | *blaADC-74* |
| class C extended-spectrum beta-lactamase ADC-76 | *blaADC-76* |
| class C extended-spectrum beta-lactamase ADC-79 | *blaADC-79* |
| class C extended-spectrum beta-lactamase ADC-80 | *blaADC-80* |
| class C extended-spectrum beta-lactamase ADC-82 | *blaADC-82* |
| class C beta-lactamase ADC-152 | *blaADC-152* |
| class C beta-lactamase ADC-156 | *blaADC-156* |
| class C beta-lactamase ADC-162 | *blaADC-162* |
| class C beta-lactamase ADC-176 | *blaADC-176* |
| class C beta-lactamase ADC-182 | *blaADC-182* |
| class C beta-lactamase ADC-212 | *blaADC-212* |
| class C beta-lactamase ADC-222 | *blaADC-222* |
| Class D beta-lactamases (oxacillinases) | carbapenem-hydrolyzing class D beta-lactamase OXA-23 | **Carbapenems** | *blaOXA-23* |
| OXA-23 family carbapenem-hydrolyzing class D beta-lactamase OXA-239 | *blaOXA-239* |
| carbapenem-hydrolyzing class D beta-lactamase OXA-24 | **Carbapenems** | *blaOXA-24* |
| OXA-24 family carbapenem-hydrolyzing class D beta-lactamase OXA-72 | *blaOXA-72* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-51 | **Carbapenems** | *blaOXA-51* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-64 | *blaOXA-64* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-65 | *blaOXA-65* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-66 | *blaOXA-66* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-68 | *blaOXA-68* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-69 | *blaOXA-69* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-71 | *blaOXA-71* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-82 | *blaOXA-82* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-90 | *blaOXA-90* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-91 | *blaOXA-91* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-94 | *blaOXA-94* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-95 | *blaOXA-95* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-98 | *blaOXA-98* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-100 | *blaOXA-100* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-104 | *blaOXA-104* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-120 | *blaOXA-120* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-223 | *blaOXA-223* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-259 | *blaOXA-259* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-371 | *blaOXA-371* |
| OXA-51 family carbapenem-hydrolyzing class D beta-lactamase OXA-402 | *blaOXA-402* |
| carbapenem-hydrolyzing class D beta-lactamase OXA-58 | **Carbapenems** | *blaOXA-58* |
| OXA-58 family carbapenem-hydrolyzing class D beta-lactamase OXA-96 | *blaOXA-96* |
| OXA-134 family carbapenem-hydrolyzing class D beta-lactamase OXA-235 | **Carbapenems** | *blaOXA-235* |
| OXA-134 family carbapenem-hydrolyzing class D beta-lactamase OXA-237 | *blaOXA-237* |
| carbapenem-hydrolyzing class D beta-lactamase OXA-143 | **Carbapenems** | *blaOXA-143* |
| OXA-143 family carbapenem-hydrolyzing class D beta-lactamase OXA-253 | *blaOXA-253* |
| **Efflux pumps** | multidrug efflux RND transporter AdeABC outer membrane channel subunit AdeC | **Cephalosporins, Carbapenems** | *adeC* |
| *Acinetobacter baumannii* efflux resistant AdeR | *adeR\_A91V* |
| *Acinetobacter baumannii* efflux resistant AdeR | *adeR\_P56S* |
| *Acinetobacter baumannii* efflux resistant AdeR | *adeR\_P116L* |
| *Acinetobacter baumannii* efflux resistant AdeS | *adeS\_G336S, adeS\_N125K* |
| *Acinetobacter baumannii* efflux resistant AdeS | *adeS\_H189Y* |
| **Penicillin-binding proteins** | *Acinetobacter baumannii*carbapenem resistant FtsI | **Carbapenems** | *ftsI\_A515V* |

**Class A β-lactamases**:

Class A beta-lactamases mediate resistance to penicillin, cephalosporins, monobactams and carbapenems. These lactamases may have narrow spectrum, or they can acquire extended spectrum antibiotic activity through point mutations. Narrow spectrum lactamases are active, mostly against penicillins, and can be inhibited by clavulanic acid, [111] while ESBLs can hydrolyze extended spectrum cephalosporins, like ceftazidime, ceftriaxone, cefotaxime, as well as aztreonam. [112] ESBLs from the Ambler class A group have been described for *A*. *baumannii*, but assessment of their true prevalence is hindered by difficulties with laboratory detection, especially in the presence of AmpC. [27] Periodic surveillance of ESBL producing strains and detection of the respective genes such as *blaTEM-92*, *blaSHV*, *blaGES-11*, *blaGES-14*, *blaPER-1*, *blaPER-7*, and *blaVEB-1* can be of use in the clinical setting. [113-117] blaPER-1 is either plasmid or chromosomally encoded and also has an upstream IS element (IS*Pa12*) that may enhance its expression. [118] Other notable members of this class are the extended spectrum cefotaximases (CTX-M) and the *Klebsiella pneumoniae* carbapenemases (KPC). [117, 119, 120]

**Class B β-lactamases**:

Class B or metallo-beta-lactamases (MBLs) are encoded by mobile DNA (plasmids, integrons) and catalyze the hydrolysis of virtually all beta-lactamases (including carbapenems), but not monobactams, conferring multidrug-resistance. These enzymes require either zinc or another heavy metal for the catalysis and are further classified in three subclasses (B1, B2, and B3) based on sequence diversity and differences in the structure of their active sites. Moreover, four types of MBLs have been described in *A. baumannii*, namely IMP, VIM, NDM, and SIM. [121] Phenotypic methods are not sensitive enough and thus do not detect all MBL producing strains. [122] With the help of PCR, *blaVIM-1* was detected in 14.3% of *A. baumannii* isolates characterized as MBL negative by E-test, highlighting the importance of introducing molecular methods into every-day practice in order to detect these hidden MBLs. [123]

**Class C β-lactamases**:

Class C beta-lactamases are chromosomally encoded cephalosporinases (acinetobacter-derived cephalosporinase, ADC), inherent to all *A. baumannii*. Overexpression of these lactamases can be induced by the insertion of ISAba1 and ISAba125 sequences upstream of the encoding gene *blaADC* (formerly known as *blaAmpC*), which appear to be stronger promoters than the intrinsic promoter. [124, 125]

**Class D β-lactamases**:

Class D beta-lactamases, also called oxicillinases (OXA) or carbapenem-hydrolyzing class D β-lactamases (CHDLs), can inactivate all beta-lactams (mainly OXA-10 family) and comprise the main mechanism of carbapenem resistance. These enzymes are serine-dependent just like Class A and C beta-lactamases. [126] In addition, class D beta-lactamases usually cannot be inhibited by clavulanic acid, sulbactam, and tazobactam. [127] There are several *blaOXA* genes, including *blaOXA-51*, *blaOXA-23*, *blaOXA-24*, *blaOXA-58*, *blaOXA-143,* and *blaOXA-235*. The genes encoding these enzymes can be found on both the chromosome as well as the plasmids. Moreover, Wong *et al*. have recently confirmed that carbapenem resistance in clinical isolates of *A. baumannii* is mediated by over-expression of either OXA-23 or OXA-51 through insertion of ISAba1 in their promoter region. [128]

ii. **Outer Membrane Proteins:**

Antibiotic resistance due to beta-lactamases can be significantly enhanced when they collaborate with outer membrane proteins (OMPs). The low permeability outer membrane protein A (OmpA, 40 kDa) is the main non-specific porin in *A. baumannii* and has mainly a structural role. [129, 130]

1. **Efflux Pumps:**

Overexpression of AdeABC efflux pump is associated with *A. baumannii* carbapenem and cephalosporin resistance. [131-133] The AdeABC is a three-component efflux pump, member of the resistance–nodulation–division (RND) family. AdeB component expels antibiotics out of the cell, while AdeA is a membrane fusion protein and AdeC an outer membrane protein. [134]

1. **Penicillin-Binding Proteins:**

Penicillin-binding proteins (PBPs) are enzymes that catalyze the polymerization of peptidoglycan and are responsible for its insertion into the cell wall. [135] Beta-lactams bind to PBPs because they mimic their substrate. Inhibition of PBPs by beta-lactams then leads to an imbalance in cell wall metabolism and as a result to cell death. [136] Gehrlein *et al*. attributed imipenem resistance in a clone of *A. baumannii* strain No. 4852/88 to complex PBP alterations. [137]

1. **Resistance to Aminoglycosides:**

Aminoglycosides are protein synthesis inhibitors that exert their action after crossing bacterial cell wall and by disturbing peptide elongation at the 30S ribosomal subunit. Genes conferring resistance can be transported by means of integrons, gene cassettes, transposons, and conjugated elements. Beyond the molecular level, and at cellular level, aminoglycoside resistance genes can be transferred by means of mobilizable or conjugative plasmids, natural transformation, or transduction. [138] Table 3 describes resistance mechanisms that are unique for this antibiotic group.

**Table 3: Mechanisms of *A. baumannii* resistance to aminoglycosides (adapted from Kyriakidis *et al*., 2021).** [110]

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Element Name and Symbol** | **Resistance** | **Gene** |
| **Aminoglycoside acetyltransferases** | Aminoglycoside 2’-N-acetyltransferase AAC(2’)-Ib | GEN, TOB, DIB, NET | *aac(2′)-Ib* |
| Aminoglycoside 3-N-acetyltransferase | GEN | *aac(3)* |
| AAC(3)-I family aminoglycoside 3-N-acetyltransferase | GEN | *aac(3)-I* |
| Aminoglycoside N-acetyltransferase AAC(3)-Ia | AST, GEN, SIS | *aac(3)-Ia* |
| Aminoglycoside N-acetyltransferase AAC(3)-IId | GEN | *aac(3)-IId* |
| Aminoglycoside N-acetyltransferase AAC(3)-IIe | GEN | *aac(3)-IIe* |
| Aminoglycoside N-acetyltransferase AAC(3)-Iva | APR, GEN, TOB | *aac(3)-IVa* |
| Aminoglycoside 6’-N-acetyltransferase | all | *aac(6’)* |
| Aminoglycoside N-acetyltransferase AAC(6’)-31 | all | *aac(6’)-31* |
| Aminoglycoside 6’-N-acetyltransferase AAC(6’)-33 | all | *aac(6’)-33* |
| AAC(6’)-Ia family aminoglycoside 6’-N-acetyltransferase | AMI, KAN, TOB, putatively against all | *aac(6’)* |
| AAC(6’)-Ia family aminoglycoside 6’-N-acetyltransferase AacA16 | all | *aacA16* |
| Aminoglycoside 6’-N-acetyltransferase AacA34 | all | *aacA34* |
| AAC(6’)-Ia family aminoglycoside 6’-N-acetyltransferase AacA43 | KAN, TOB | *aacA43* |
| Aminoglycoside N-acetyltransferase AAC(6’)-Ian | AMI, KAN, TOB, putatively against all | *aac(6’)-Ian or aacA57-2* |
| AAC(6’)-Ib family aminoglycoside 6’-N-acetyltransferase | AMI, DIB, GEN, ISE, KAN, NET, SIS, TOB | *aac(6’)-Ib* |
| Aminoglycoside N-acetyltransferase AAC(6’)-Ib’ | GEN | *aac(6’)-Ib’* |
| AAC(6’)-Ighjkrstuvwx family aminoglycoside N-acetyltransferase | AMI, KAN, TOB | *aac(6’)-I* |
| Aminoglycoside N-acetyltransferase AAC(6’)-Ib3 | AMI, KAN, TOB | *aac(6’)-Ib3* |
| Aminoglycoside N-acetyltransferase AAC(6’)-Ib4 | GEN | *aac(6’)-Ib4* |
| aminoglycoside N-acetyltransferase AAC(6’)-Ih | AMI, KAN, TOB | *aac(6’)-Ih* |
| Aminoglycoside N-acetyltransferase AAC(6’)-Il | AMI, KAN, TOB | *aac(6’)-Il* |
| AAC(6’)-II family aminoglycoside 6’-N-acetyltransferase AacA35 | GEN, KAN, TOB | *aacA35* |
| Aminoglycoside N-acetyltransferase AAC(6’)-IIc | GEN, KAN, TOB | *aac(6’)-IIc* |
| Fluoroquinolone-acetylating aminoglycoside 6’-N-acetyltransferase AAC(6’)-Ib-cr | AMI, KAN, TOB, QUI | *aac(6’)-Ib-cr* |
| Fluoroquinolone-acetylating aminoglycoside 6’-N-acetyltransferase AAC(6’)-Ib-cr5 | AMI, KAN, TOB, QUI | *aac(6’)-Ib-cr5* |
| **Aminoglycoside adenyltransferases** | Aminoglycoside nucleotidyltransferase ANT(2’’)-Ia | *DIB, GEN, KAN, SIS, TOB* | *ant(2’’)-Ia* |
| ANT(3’’)-I family aminoglycoside nucleotidyltransferase | *STR, SPE* | *ant(3’’)* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA | *STR, SPE* | *ant(3’’)-Ia* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA1 | *STR* | *aadA1* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA2 | *STR* | *aadA2* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA5 | *STR* | *aadA5* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA11 | *STR* | *aadA11* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA13 | *STR* | *aadA13* |
| ANT(3’’)-Ia family aminoglycoside nucleotidyltransferase AadA16 | *STR* | *aadA16* |
| ANT(3’’)-II family aminoglycoside nucleotidyltransferase | *STR, SPE* | *ant(3’’)-II* |
| Aminoglycoside nucleotidyltransferase ANT(3’’)-IIa | *STR, SPE* | *ant(3’’)-IIa* |
| Aminoglycoside nucleotidyltransferase ANT(3’’)-IIc | *STR, SPE* | *ant(3’’)-IIc* |
| **Aminoglycoside phosphotransferases** | APH(3’) family aminoglycoside O-phosphotransferase | *all* | *aph(3’)* |
| Aminoglycoside O-phosphotransferase APH(3’)-Ia | *GEN, KAN, NEO, PAR, LIV, RIB* | *aph(3’)-Ia* |
| APH(3’)-II family aminoglycoside O-phosphotransferase | *KAN* | *aph(3’)-II* |
| Aminoglycoside O-phosphotransferase APH(3’)-IIa | *KAN* | *aph(3’)-IIa* |
| APH(3’)-VI family aminoglycoside O-phosphotransferase | *AMI, KAN* | *aph(3’)-VI* |
| Aminoglycoside O-phosphotransferase APH(3’)-VIa | *AMI, KAN* | *aph(3’)-VIa* |
| Aminoglycoside O-phosphotransferase APH(3’)-VIb | *AMI, KAN* | *aph(3’)-VIb* |
| Aminoglycoside O-phosphotransferase APH(3’’)-Ib | *STR* | *aph(3’’)-Ib* |
| Aminoglycoside O-phosphotransferase APH(4)-Ia | *HYG* | *aph(4)-Ia* |
| Aminoglycoside O-phosphotransferase APH(6)-Id | *STR* | *aph(6)-Id* |
| **Target mutation: 16S rRNA methylase genes** | ArmA family 16S rRNA (guanine(1405)-N(7))-methyltransferase | *GEN* | *armA* |
| 16S rRNA (guanine(1405)-N(7))-methyltransferase RmtB1 | *all* | *rmtB and rmtB1* |
| RmtE family 16S rRNA (guanine(1405)-N(7))-methyltransferase | *all* | *rmtE* |
| Efflux pump overactivity | Multidrug efflux MFS transporter AmvA | *Putatively against all* | *amvA* |
| Multidrug efflux RND transporter AdeABC outer membrane channel subunit AdeC |  | *adeC* |
| Multidrug efflux RND transporter periplasmic adaptor subunit AdeD |  | *adeD* |
| Multidrug efflux RND transporter permease subunit AdeE |  | *adeE* |
| Efflux system DNA-binding response regulator transcription factor AdeR |  | *adeR* |
| Two-component sensor histidine kinase AdeS two-component sensor histidine kinase |  | *adeS* |

AMI = amikacin; APR = apramycin; AST = astromicin; DIB = dibekacin; DNA = deoxyribonucleic acid; GEN = gentamicin; HYG = hygromycin; ISE = isepamicin; KAN = kanamycin; LIV = lividomycin; MFS = major facilitator superfamily; NEO = neomycin; NET = netilmicin; PAR = paromomycin; QUI = quinolone; RIB = ribostamycin; RNA = ribonucleic acid; RND = resistance/nodulation/cell division family; SIS = sisomicin; SMR = small multidrug resistance family; SPE = spectinomycin; STR = streptomycin; TOB = tobramycin.

1. **Resistance to Tetracyclines**

Tetracycline antibiotics bind to the 30S ribosomal subunit and thereby inhibit protein synthesis by deterring the start of translation. [139] Resistance to tetracycline antibiotics is attributed to three main mechanisms: [140]

* efflux dependent on ATP,
* inactivation of tetracyclines by enzymes,
* ribosomal protection proteins (RPPs)

Two types of efflux pumps that require energy are responsible for tetracycline resistance in *A. baumannii*. The resistance/nodulation/cell division (RND) family-type pumps are constitutive non-specific pumps originating from *adeA, adeB*, and *adeC* genes, which encode periplasmic adaptor subunits, permease subunits, and outer membrane pump elements, respectively. [131] RND pumps, and predominantly AdeABC, can effectively eliminate tetracyclines, while correspondingly, they mediate a substantial elevation of minimum inhibitory concentrations (MICs) for tigecyline, minocycline, and tetracycline. [141] The second category refers to tetracycline major facilitator superfamily (MFS) efflux pumps: TetA and TetB. [142] TetA seems to lead efflux of tigecycline into the periplasm, and subsequently, RND pumps drive to elimination through the outer membrane. [143]

1. **Resistance to Fluoroquinolones**

Quinolones are bactericidal with a broad spectrum that are characterized by a bicyclic core formation bearing resemblance to 4-quinolone. Quinolone antibiotics are mostly fluoroquinolones displaying efficacy against both Gram-negative and Gram-positive pathogens. [144] Regarding their mechanism of action, quinolone antibiotics interrupt DNA replication by averting bacterial DNA from loosening and being cloned. Quinolones exert their action by inhibiting the ligase activity of the type II topoisomerases, DNA gyrase, and topoisomerase IV, which normally induce supercoiling in collaboration with DNA nucleases. Disrupting ligase activity, bacteria remain with double-stranded DNA breaks and thus are led to cell death. Notably, quinolones primarily affect gyrase activity, while toxicity against topoisomerase IV is secondary.

Quinolone resistance occurs via three different mechanisms: [144, 145]

* Target mutations in gyrase and topoisomerase IV, which weaken the respective quinolone–enzyme interactions;
* Plasmid-borne resistance mediated by Qnr proteins, the AMEs AAC(6′)-Ib-cr and AAC(6′)-Ib-cr5, and by plasmid-encoded efflux pumps;
* Chromosome-derived resistance resulted by either low expression of porins or overexpression of chromosome-encoded efflux pumps.

A recent review reported resistance of *A. baumannii* to fluoroquinolones between 50% and 73% of cases, while the respective resistance in developing countries during the last years displayed a marked increase reaching 75% to 97.7%. [146]

Gap still exists in understanding which antibiotic resistance determinants are involved in the current antibiotic resistance, the underlying processes linking antibiotic resistance determinants to its expression and how to address it. Thus, a better understanding of such gaps is the necessity to curb the dearth of this epidemic disease throughout the world. It is important to note that special attention should be paid to reduce susceptibility to carbapenems that may be related to true carbapenemases, not only for producers of Class B (mainly VIM or IMP) or Class A (KPC), but also for those expressing Class D (OXA) that is increasingly identified. Furthermore, timely investigation of outbreaks are needed to be continuously adapted to the current situation, and thus requires the combination of traditional epidemiologic surveillance with molecular techniques to help identify potential routes of transmission and implement control measures.

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