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Review

Mobile Genetic Elements Contributing to Carbapenem Resistance in *Acinetobacter baumannii*: Current Insights

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Azzahrah Khairunnisa Mardhiyah[1], Yulia Rosa Saharman[2*], Fithriyah Sjatha[2]

[1]Master's Programme in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Department of Microbiology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Abstract.
Acinetobacter baumannii has become a major cause of hospital-acquired infections with the rapid development of resistance to multiple antibiotics, including critical carbapenems. This resistance challenge limits treatment options and increases morbidity and mortality. The genetic plasticity of *A. baumannii* facilitates the mobilization of resistance genes via mobile genetic elements (MGE). Addressing this crisis requires a deeper understanding of the mechanisms by which MGE propagates carbapenem resistance. This paper provides a solution by systematically reviewing recent research on the role of MGE in disseminating resistance genes. Following PRISMA guidelines, a comprehensive literature review was conducted across various databases. The review revealed that resistance mechanisms primarily involve carbapenem-hydrolyzing enzymes and MGE, such as integrons, transposons, insertion sequences, and plasmids. Notably, genes like $bla_{\text{OXA-23}}$ and bla_{NDM} are frequently mobilized by these elements, facilitating horizontal gene transfer and persistence. Understanding the mechanisms of MGE-mediated gene transfer is crucial for developing strategies to control the spread of antibiotic resistance in *A. baumannii*.

Corresponding Author :
Yulia Rosa Saharman
Department of Microbiology, Faculty of Medicine, Universitas Indonesia, Jakarta,
Email: yulia.rosa18@gmail.com

1. Introduction

Acinetobacter baumannii, a Gram-negative bacterium, has emerged as a significant cause of hospital-acquired infections, including bloodstream infections, ventilator-associated pneumonia, urinary tract infections, and wound infections [1]. Its persistence in hospital environments and rapid development of resistance to multiple antibiotics present a formidable challenge for healthcare professionals [2].

A pressing concern in managing *A. baumannii* infections is its increasing resistance to carbapenems, a last-resort class of antibiotics. Carbapenem-resistant *A. baumannii* (CRAB) severely limits therapeutic options, leading to higher morbidity and mortality rates. This resistance crisis underscores the urgency for new therapeutic strategies and effective infection control measures [3]. *A. baumannii* belongs to the group of pathogens known as ESKAPE, which includes *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Enterobacter* species. These pathogens are notorious for evading antimicrobial agents and are responsible for a substantial proportion of nosocomial infections globally [4-5]. In the United States, infections caused by ESKAPE pathogens result in over 2 million cases annually, leading to approximately 23,000 deaths [6]. Reflecting the severity of this issue, both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) classified *A. baumannii* as a critical priority pathogen in 2017, highlighting the urgent need for new antibiotics to treat CRAB [7]-8].

The mechanisms of carbapenem resistance in *A. baumannii* are complex and multifaceted. Primary mechanisms include the development of carbapenem-hydrolyzing enzymes, such as OXA β-Lactamase and metallo beta-lactamase (e.g., NDM). These enzymes degrade carbapenems, rendering them ineffective [9]. *A. baumannii* exhibits remarkable genetic plasticity, which facilitates the rapid acquisition and spreading of resistance factors via mobile genetic elements (MGE) [10]. MGE, such as integrons, transposons, insertion sequences, and plasmids, play crucial roles in horizontal gene transfer, particularly in spreading carbapenem resistance [11].

Recent studies have established strong associations between IS elements and the mobilization of carbapenem resistance genes, including $bla_{\text{OXA-23}}$, $bla_{\text{OXA-51}}$, $bla_{\text{OXA-58}}$, and bla_{NDM} [11-12]. Notably, $bla_{\text{OXA-23}}$, the most widespread carbapenemase gene in *A. baumannii*, is often associated with transposons like Tn*2006*, Tn*2008*, and Tn*2009* [11], [13]. Additionally, the role of conjugative plasmids in spreading resistance determinants has been highlighted. A study by Tang (2022) identified 30 plasmids as conjugative plasmids carrying bla_{NDM} genes [14]. Moreover, the emergence of resistance islands (RIs) in *A. baumannii*, which harbor clusters of horizontally acquired resistance genes, has significantly contributed to the multidrug-resistant (MDR) phenotype of this pathogen [15]. For instance, AbaR4-type islands, commonly found in international clone 2 (IC2), utilize Tn*6022* as a backbone and frequently carry the $bla_{\text{OXA-23}}$ gene [16]. These MGE further facilitate the mobilization of other antimicrobial resistance (AMR) genes.

The role of MGE in the spread of carbapenem resistance continues to evolve, with new research identifying additional mechanisms of resistance and novel MGE variants involved in their propagation. Despite progress, significant gaps remain in fully understanding the molecular dynamics of MGE-mediated resistance in *A. baumannii*. Addressing these gaps is crucial for developing targeted interventions to control the spread of CRAB. This paper aims to explore the latest research on MGE in *A. baumannii*, focusing on their mechanisms and the impact of these genetic elements in the propagation of carbapenem resistance, while identifying the research gaps that need further investigation. By reviewing recent developments, this study will shed light on the evolving threat posed by CRAB and the global health implications it presents.

2. Experimental Section

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) standards. We executed a systematic literature search of the PubMed, Science Direct, and Google Scholar databases using keywords including but not limited to *A. baumannii,* mechanism of action of carbapenem, mechanism of carbapenem resistance, Mobile Genetic Elements (MGE), and Antimicrobial Resistance Genes (ARG). The literature search encompassed all research published between 2019 and 2024. We analyzed recent research studies to understand the latest findings on MGE associated with Carbapenem Resistance in *Acinetobacter baumannii*. Keywords were used to search all databases, and a total of 721 articles were found, and 139 duplicate articles were removed. Articles with screening potential were identified from abstract to full-text publication. 512 prospective articles were rejected because they did not match the inclusion requirements. As a result, 69 papers matched the inclusion criteria and were prepared for review. Figure 1 depicts the workflow for the article selection process.

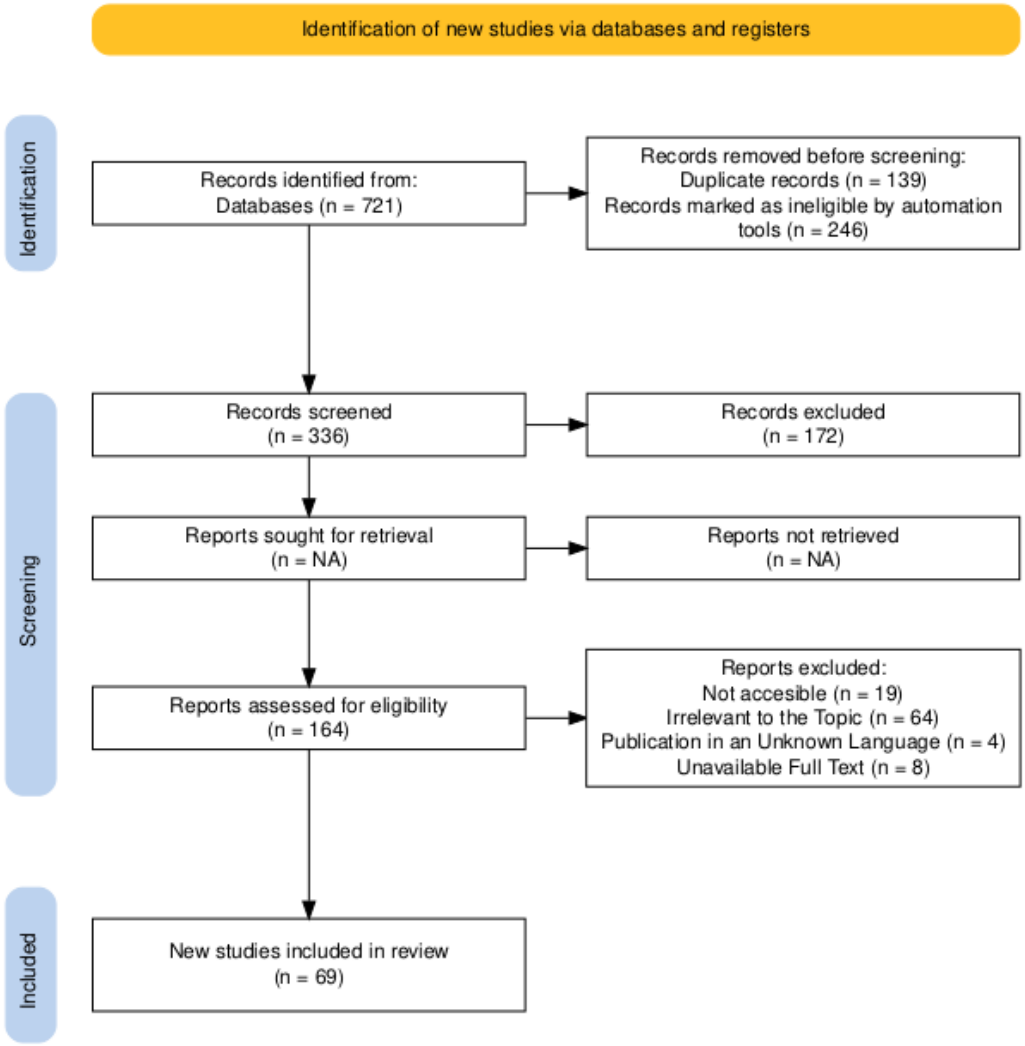

Figure 1. Schematic of research [17]

3. Results and Discussion

3.1 *Acinetobacter baumannii*

Acinetobacter baumannii is a prominent member of the genus *Acinetobacter* within the family Moraxellaceae. The genus Acinetobacter encompasses a diverse group of species characterized as gram-negative coccobacilli. These organisms are non-motile, non-fastidious, non-fermentative, catalase-positive, and oxidase-negative, with a DNA guanine-cytosine (GC) content ranging from 39% to 47% [18-19]. While the genus includes over 50 species, predominantly non-pathogenic and environmental in nature, *A. baumannii* stands out as the most virulent, followed by *A. calcoaceticus* and *A. lwoffii* [20].

A. baumannii exhibits several virulence factors that significantly contribute to its pathogenicity. These factors include lipopolysaccharides and capsular polysaccharides, outer membrane proteins/porins, enzymes, quorum sensing mechanisms, biofilm formation, motility, and protein secretion systems. The combination of these factors facilitates the bacterium's ability to infect and cause disease in humans, particularly in healthcare settings [19]. *A. baumannii* is notable for its ability to survive in a wide range of environmental conditions. It can thrive at temperatures between 20°C and 45°C and in pH levels ranging from 5.5 to 6. This adaptability allows *A. baumannii* to persist in various habitats, including soil, water, and food. Its resilience and survival capabilities on surfaces for extended periods are particularly problematic in hospital environments, where it can colonize and contaminate medical devices [19-20].

A. baumannii primarily affects immunocompromised individuals and is frequently isolated from medical equipment. It is a low-grade pathogen but can cause severe infections due to its opportunistic nature. Common infections associated with *A. baumannii* include respiratory tract infections, such as ventilator-associated pneumonia, wound infections, particularly in surgical or burn wounds, urinary tract infections, and bacteremia. The bacterium's ability to form biofilms on medical devices further complicates treatment and eradication efforts [19-20].

3.2 Carbapenem

Carbapenems are a class of beta-lactam antibiotics renowned for their broad spectrum of action against a wide range of Gram-positive and Gram-negative aerobic and anaerobic bacteria [21]. They are typically used to treat critical infections that do not respond to conventional antibiotic therapies. Carbapenems are highly valued for their extensive antimicrobial spectrum, safety, and tolerability profiles, making them a crucial component in combating severe infections caused by multidrug-resistant (MDR) pathogens [1], [22].

Carbapenems possess a unique chemical structure characterized by a penicillin-like five-membered ring. Unlike other beta-lactams, the sulfur atom at C-1 in the five-membered ring is substituted by a carbon atom, and a double bond is formed between C-2 and C-3. Additionally, the side chain of carbapenems is positioned in the trans configuration rather than the cis position found in other beta-lactams. This distinct structural configuration makes carbapenems resistant to most beta-lactamases, which are enzymes produced by bacteria to inactivate beta-lactam antibiotics [9]. The bactericidal activity of carbapenems involves penetrating the bacterial cell wall and interacting with penicillin-binding proteins (PBPs). This interaction inhibits the PBPs, which are essential for cell wall synthesis, leading to the inactivation of autolytic enzymes within the bacterial cell. As a result, the bacterial cell is unable to maintain its structural integrity and ultimately undergoes lysis and death [3], [9].

Carbapenems, including imipenem, meropenem, ertapenem, and doripenem, are approved for clinical use and are frequently prescribed to treat severe infections caused by MDR organisms [3]. They are incredibly effective against a wide range of infections, such as *Staphylococcus, Enterococcus, Streptococcus, Listeria, Enterobacteriaceae*, and various species of *Acinetobacter, Pseudomonas*, and *Bacteroides*. Importantly, carbapenems are effective against cephalosporin-resistant bacteria that

produce extended-spectrum beta-lactamases (ESBLs) [9], [21]. Among the pathogens targeted by carbapenems, *A. baumannii* is particularly notable. This nosocomial pathogen is known for its high level of resistance to multiple antibiotics, complicating treatment efforts [3].

3.3 Carbapenem Mechanism of resistance in *A. baumannii*

Carbapenem resistance in bacteria is a growing concern in clinical settings, driven by several mechanisms. One primary mechanism is the production of carbapenemase enzymes, which hydrolyze the carbapenem antibiotics, rendering them ineffective [23]. These enzymes can be chromosomally encoded or plasmid-mediated, facilitating their transfer between bacteria and leading to the rapid spread of resistance [21]. Carbapenemases belong to the β-lactamase family and are classified into Ambler classes A, B, and D.

In *A. baumannii,* the most common mechanisms involve the production of class B and class D carbapenemases [23]. Class B β-lactamases, or metallo-β-lactamases (MBLs), require zinc ions for their catalytic activity. Notable among these is the New Delhi Metallo-β-lactamase (NDM), with two variants reported in *A. baumannii*: NDM-1 and NDM-2, both found on bacterial plasmids. Class D β-lactamases, known as oxacillinases (OXA), primarily act on the antibiotic oxacillin and are encoded by bla_{OXA} genes [24]. Common oxacillinase variants in *A. baumannii* include OXA-51, which is naturally present on the *A. baumannii* chromosome, and OXA-58, OXA-23, and OXA-24, which can be acquired externally through plasmid or transposon-mediated gene transfer [9], [24].

Another mechanism involves alterations in the outer membrane porins of Gram-negative bacteria, which reduce the permeability of the antibiotic into the bacterial cell. Efflux pumps also contribute to resistance by actively expelling the antibiotic from the bacterial cell before it can exert its effect [23]. Additionally, modifications in the target penicillin-binding proteins (PBPs) can reduce the binding affinity of carbapenems, thereby diminishing their bactericidal activity [9], [21]. The combination of these mechanisms can occur within a single bacterial strain, further complicating treatment efforts and contributing to the persistence of resistant infections in healthcare environments.

3.4 MGE

Bacteria employ two primary genetic strategies to adapt to antibiotic challenges. The first mechanism involves spontaneous mutations that occur during DNA replication, leading to genetic variations that may confer resistance [25]. The second mechanism, horizontal gene transfer (HGT), involves the acquisition of foreign DNA from other bacteria, including resistance genes, through processes such as transformation, transduction, and conjugation [11], [25].

A. baumannii is particularly known for its high genome plasticity, enabling it to acquire and spread genes, especially those associated with antimicrobial resistance, which are commonly linked to mobile genetic elements (MGE) [12], [15]. MGE are genetic materials that can move within a genome or be transferred between species. In the realm of prokaryotic evolution, MGE plays a crucial role. They often confer fitness benefits to their hosts, such as enhanced bacterial survival, diversification of species, and expansion into new ecological niches. This advantage arises from the transfer of adaptive functions, including antibiotic resistance. However, when these resistance genes are acquired by human pathogens, they become a significant public health challenge [12], [26]. *A. baumannii* harbors various types of MGE, including plasmids, transposons (Tn), integrons, insertion sequences (IS), and resistance islands (Figure 2).

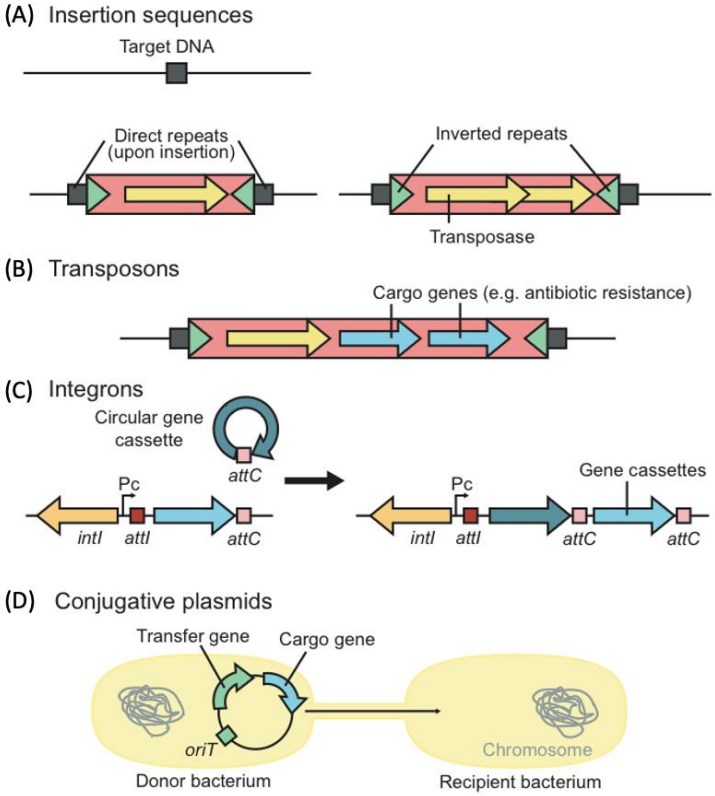

Figure 2. Overview of mobile genetic elements that contribute to Acinetobacter antibiotic resistance [11].

3.5 Plasmid

Plasmids are extrachromosomal DNA molecules that replicate independently of the host's chromosomal DNA and typically do not encode genes essential for the host's survival. However, they often carry genes that confer advantages under specific environmental situations, such as antibiotic resistance genes. *A. baumannii* may harbor numerous big plasmids ranging in size from 1.3 Kb to 400 Kb, although most are under 20 Kb [27]. Notably, high molecular weight plasmids are clinically significant because they typically include a diverse set of antibiotic-resistant genes as well as MGE-like transposons and integrons [28].

Structurally, plasmids are typically double-stranded circular DNA molecules, though some bacterial strains harbor linear forms [29]. They exist in various conformations, including open circular, covalently closed circular, or concatenated, the latter being a result of replication errors. Importantly, plasmids are capable of facilitating horizontal gene transfer (HGT) among bacteria via conjugation. Through this process, they can transfer not only their own genetic material but also MGE such as transposons, thus enabling rapid dissemination of antibiotic resistance genes [30].

Although plasmids do not carry essential genes for basic cellular functions like growth or multiplication, they carry accessory genes that provide particular advantages to the host cell, such as resistance to antibiotics or mechanisms for DNA repair [29]. A study by Camargo (2020) found that only 35% of *A. baumannii* plasmids directly encode resistance genes, highlighting the complexity of plasmid function beyond direct resistance [31]. Plasmids also act as vectors for other MGE, such as insertion sequences (IS) and transposons, which play a pivotal role in gene flux, enabling rapid genetic evolution within bacterial populations [11].

The categorization of *A. baumannii* plasmids based on their replication initiation protein domains provides insight into the diversity of plasmid types and their roles in resistance. For example, Lam (2022) identified that plasmids carrying resistance genes fall into distinct types, such as RP-T1, R3-T1, R3-T2, and R3-T3, with RP-T1 plasmids commonly harboring carbapenemase genes, including blaNDM and *bla*$_{\text{OXA-23}}$ [24], [32]. In laboratory settings, these RP-T1 plasmids have been shown to conjugate, mobilizing smaller resistance plasmids and enhancing gene transfer capabilities [33].

The clinical importance of these plasmids is further underscored by findings from Blackwell and Brovedan who demonstrated that RP-T1 plasmids, which are typically larger than 20 Kb, frequently contain multiple resistance determinants, including *bla*$_{\text{NDM}}$, *bla*$_{\text{OXA-23}}$, *sul1, sul2, mph(E), aph(3')-VI*, and *msr(E)* [27], [33]. Similarly, Vijayakumar (2022) and Sanchez (2024) identified large conjugative plasmids in clinical isolates from India, which carried crucial resistance genes such as *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{GES}}$ [15], [28]. The frequent association of these plasmids with integrons and IS elements, particularly IS*Aba1*, highlights their role as platforms for the assembly and dissemination of resistance genes.

Among these MGE, IS*Aba1* has garnered significant attention for its role in carbapenem resistance [34]. Insertion sequences like IS*Aba1*, often found upstream of bla$_{\text{OXA}}$ genes, enhance the expression of these beta-lactamase genes, leading to higher levels of carbapenem resistance [35]. This illustrates the dual role of plasmids in not only carrying resistance genes but also modulating their expression through MGE.

While not all plasmids directly contribute to antibiotic resistance, their ability to integrate MGE like IS elements highlights their essential role as facilitators of horizontal gene transfer. As Camargo (2020) noted, the presence of plasmids that do not directly encode resistance genes does not diminish their importance; they act as reservoirs and platforms for genetic evolution [31]. The ongoing ability of *A. baumannii* to adapt to antibiotic pressure through plasmid-mediated resistance, particularly via MGE, underscores the necessity for continued research and surveillance of these genetic elements.

In conclusion, plasmids in *A. baumannii* not only act as vectors for antibiotic resistance genes but also support the assembly and dissemination of such genes through MGE like IS elements and transposons. Their contribution to resistance is both direct by harboring resistance genes and indirect by facilitating gene transfer and expression. Understanding this complex interplay is crucial for addressing the rise of multidrug-resistant *A. baumannii* and for developing targeted strategies to limit the spread of resistance.

3.6 Insertion sequences

Insertion sequences (IS) are the simplest and most common genetic elements in bacteria, ranging from 0.7 to 2.5 Kb. These small transposable elements typically include a single open reading frame, although some may have two, encoding proteins involved in their own mobilization [29]. IS elements are flanked by inverted repeats (IR) and can generate direct repeats (DR) upon integration into the host genome [35]. They significantly contribute to antibiotic resistance and genomic variability by acting as vectors for gene transfer, either as part of composite transposons or by modulating gene expression through insertion or by providing internal promoters [36].

IS elements frequently drive gene expression via strong promoters, which plays a pivotal role in increasing resistance, particularly through the modulation of efflux pumps. Notably, IS elements are often concentrated in conjugative plasmids compared to chromosomal DNA, highlighting their importance in horizontal gene transfer (HGT) [37], [38]. The proliferation of IS elements within bacterial genomes enhances genetic heterogeneity, facilitating adaptability to different environments and potentially leading to increased virulence in various species [39]. These elements also serve as anchors for homologous recombination processes, promoting internal genomic rearrangements and the integration of exogenous DNA, which are critical for the evolution and adaptability of pathogens like *A. baumannii* [35], [38].

In *A. baumannii*, IS elements are directly linked to carbapenem resistance by facilitating the expression of OXA-type β-lactamases. The presence of IS elements such as IS*Aba2*, IS*Aba3*, and IS*Aba4* upstream of genes like *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-58}}$ can significantly enhance gene expression, leading to increased production of these carbapenem-hydrolyzing enzymes [35]. Among these, IS*Aba1* plays a particularly critical role. IS*Aba1* contains a strong promoter capable of driving the overexpression of downstream *bla*$_{\text{OXA}}$ genes, such as *bla*$_{\text{OXA-23}}$ and *bla*$_{\text{OXA-51}}$, which are directly involved in carbapenem resistance[21], [35]. A study by Hashemizadeh (2022) demonstrated that 94.2% of *A. baumannii* isolates harboring IS*Aba1* were associated with these resistance genes, further supporting its significant role in carbapenem resistance [35]. Vijayakumar (2020) similarly confirmed the association between IS*Aba1* and enhanced expression of *bla*$_{\text{OXA}}$ genes, reinforcing the importance of IS elements in the development of carbapenem resistance [38].

Other studies have revealed additional IS elements promoting resistance in *A. baumannii*. For instance, *bla*$_{\text{NDM}}$ was found to be associated with IS*Aba125*, which facilitated resistance to β-lactam antibiotics by promoting its expression [40], [41]. Further research has identified IS*Aba15*, IS*Aba16*, and IS*Aba19* upstream of *bla*$_{\text{OXA-66}}$, *bla*$_{\text{OXA-132}}$, and *bla*$_{\text{OXA-79}}$, respectively, highlighting the broader role of IS elements in the regulation of resistance genes across different strains [30]. Moreover, Salloum (2018) identified insertion sequences IS*Aba17* and IS*Aba13* upstream of the *bla*$_{\text{OXA-94}}$ gene, showing the diversity of IS elements involved in resistance mechanisms [42].

These findings demonstrate that the insertion of IS elements, particularly IS*Aba1*, is crucial in driving the overexpression of carbapenem resistance genes in *A. baumannii*. The widespread distribution and activity of IS elements across different resistance genes contribute significantly to the bacterium's ability to adapt and persist in antibiotic-rich environments, underscoring their critical role in the evolution of multi-drug resistance (MDR) in *A. baumannii*.

3.7 Transposons

Transposons are pivotal genetic elements that have a major role in the quick worldwide spread of resistance genes. These elements, traditionally larger than insertion sequences (ISs) and bound by inverted repeats, include a transposase gene and internal "passenger" genes, such as those encoding antibiotic resistance [13]. Transposons range in size between 3 to 40 kb and may contain multiple genes [43]. They are classified into two primary types: composite transposons and complex transposons. Composite transposons are characterized by resistance genes situated in a central region, flanked by IS elements at each end [35]. Complex transposons, on the other hand, exhibit a more intricate genetic structure compared to IS elements or composite transposons. Tn*3*, which was generated from the resistance plasmid R1, is an example of a complex transposon [30], [43].

Structurally, transposons share similarities with IS elements, but they differ by carrying additional genes, often including antibiotic resistance determinants [11]. The mobility of these elements is facilitated by transposase enzymes, which recognize the terminal repeats and enable either site-specific or random insertion into the genome [11], [13]. In *A. baumannii*, transposons have been shown to carry key resistance genes, including *bla*$_{\text{OXA-23}}$. Several transposons associated with *bla*$_{\text{OXA-23}}$ include Tn*2006*, Tn*2007*, Tn*2008*, Tn*2008B*, and Tn*2009*.

Among these, Tn*2006* is the most commonly reported transposon carrying *bla*$_{\text{OXA-23}}$ and is characterized by two inversely oriented copies of IS*Aba1* flanking the gene, significantly enhancing its expression and contributing to high levels of carbapenem resistance [30]. Tn*2008*, which closely resembles Tn*2006*, carries only a single copy of IS*Aba1*, while Tn*2007* harbors *bla*$_{\text{OXA-23}}$ flanked by a single copy of IS*Aba4* upstream[44]. Notably, Tn*2009* also carries *bla*$_{\text{OXA-23}}$ flanked by IS*Aba1*, though the arrangement of the IS*Aba1* copies is not inverted as in Tn*2006* [44]. Additionally, Tn*2008* and Tn*2008B* share a common structural feature, the "*bla*$_{\text{OXA-23}}$ -ΔATPase" region, which has been implicated in resistance mechanisms [21], [44]. These transposons, except Tn*2007*, are mobilized via

conjugative plasmids, which enhances their potential for horizontal gene transfer (HGT) across bacterial populations [35]. The global prevalence of these transposons has been widely documented. For instance, Hashemizadeh (2022) reported the presence of Tn*2009* in 39.2% of carbapenem-resistant *A. baumannii* isolates, followed by Tn*2008* (33.3%), Tn*2006* (24%), and Tn*2007* (1.2%) [35]. This data indicates the dominant role of transposons, particularly Tn*2009* and Tn*2008*, in the global spread of $bla_{\text{OXA-23}}$ and carbapenem resistance in *A. baumannii*.

Transposons also play a significant role in the dissemination of other resistance genes, such as bla_{NDM}. Typically, this gene is found in Tn*125-like* composite transposons [45]. However, other studies have identified this gene in novel transposons. Hamed (2022) introduced a new composite transposon, Tn*7382*, comprising two direct copies of IS*Aba14* flanking the *aphA6* and $bla_{\text{NDM-1}}$ genes, which encode for amikacin and carbapenem resistance, respectively [46]. Mann (2022) characterized Tn*6924* as a novel Tn*7* family transposon carrying bla_{NDM}, bounded by 29-bp inverted repeats with additional TnsB binding sites at each end, similar to Tn*7* [47]. Additionally, Brito (2022) reported the discovery of another novel transposon, Tn*6925*, which harbors the *aacC2* gene along with bla_{TEM}, further highlighting the diversity of transposons involved in antibiotic resistance mechanisms [48]. The identification of novel transposons carrying bla_{NDM} further underscores the ongoing evolution of resistance mechanisms, driven by the mobility of these elements.

3.8 Integrons

Integrons are mobile genetic elements (MGE) found in the chromosomes of many bacterial species, including *A. baumannii*. These elements play a critical role in the evolution and adaptation of bacteria by capturing, storing, and rearranging gene cassettes, which often encode antibiotic-resistance genes (ARGs) [49]. Integrons are made up of a gene that encodes the enzyme integrase, a particular integration site (attI), and a strong promoter gene [50]. These components enable the acquisition or excision of mobile gene cassettes, including efflux pump genes and drug resistance determinants, through a site-specific recombination process mediated by integrase [51]. Under antibiotic selective pressure, various gene cassettes in integrons can rearrange. Six types of integrons have been discovered according to the nucleotide arrangement of the integrase gene, with classes 1, 2, and 3 playing a major role in the transmission of antibiotic resistance genes (ARG) [52].

Class 1 and 2 integrons are frequently observed in *A. baumannii* and play a crucial role in antibiotic resistance, encoding genes for metallo-β-lactamases, β-lactamases, streptomycin, oxacillinases, aminoglycosides, chloramphenicol, and trimethoprim resistance [18]. Despite integrons being immobile, their association with mobile DNA elements such as transposons and plasmids facilitates the spread of antibiotic resistance. The integron system enables bacteria to receive gene cassettes and appropriately express them, resulting in functional proteins [49]. MGE, like transposons, plasmids, insertion sequences, and resistance islands, serve as information repositories for integrons shared by bacteria. This exchange is important for the distribution and dissemination of resistance genes [50].

Studies have shown that integrons are found in around 17% of bacterial chromosomes, with Class 1 integrons being highly prevalent in *A. baumannii*, followed by Class 2 integrons [21], [53]. A study conducted in Iran by Halaji detected Class 1 integrons in 63.9% of isolates, Class 2 integrons in 78.2%, and both classes in 49.6%, with no detection of Class 3 integrons [54]. Similarly, Azizi (2021) discovered Class 1 and Class 2 integrons in 70.77% and 26.15% of isolates, respectively, without finding Class 3 integrons.

Moreover, gene cassettes associated with integrons in *A. baumannii* commonly include $bla_{\text{OXA-23}}$, $bla_{\text{OXA-51}}$, and aminoglycoside resistance genes such as *aadA1*. Metallo-β-lactamases like $bla_{\text{VIM-25}}$ and $bla_{\text{IMP-1}}$ have also been frequently found in Class 1 integrons, while Class 2 integrons often carry cassettes such as $bla_{\text{IMP-4}}$, $bla_{\text{VIM-2}}$, and *dfrA2* [21]. The widespread dissemination of these gene cassettes within integrons underscores their role in *A. baumannii*'s ability to evade treatment through multi-drug

resistance. Interestingly, in addition to these common gene cassettes, unusual resistance elements like the extended-spectrum beta-lactamase gene *bla*$_{\text{CARB-2}}$ have been identified in some *A. baumannii* strains. For example, in the ACN21 strain, *bla*$_{\text{CARB-2}}$ was found upstream of *intI1*, illustrating how integrons can serve as repositories for even rare resistance genes [55]. This unusual finding highlights the versatility of integrons in acquiring and disseminating ARGs, even those not typically associated with *A. baumannii*, further complicating the treatment of infections caused by these resistant strains.

The evidence presented suggests that integrons, especially Class 1 and 2, are central to the accumulation and spread of resistance genes in *A. baumannii*. Their ability to capture and express gene cassettes, coupled with their association with MGE like plasmids and transposons, amplifies their role in resistance dissemination.

3.9 Resistance Islands

Resistance islands (RI) refer to specific genomic regions within bacterial chromosomes that harbor clusters of antibiotic-resistant genes [56]. These regions often include composite transposons and integrons, which are MGE capable of capturing and integrating various resistance genes. RI are believed to originate from plasmid conjugation, followed by chromosomal insertion, and have developed through repeated insertions and rearrangements of insertion sequences [12]. RI can be found at multiple locations within the bacterial chromosome and plays a significant role in the development and spread of multidrug resistance in bacteria [57]. *Acinetobacter baumannii* resistance islands (AbaR) contribute significantly to the multidrug resistance phenotype observed in this bacterium. The initial AbaR, named AbaR1, was identified in 2006 within the epidemic strain AYE and spans 86 kilobases [58]. In subsequent analyses of over 3,000 *A. baumannii* genomes, AbaR was discovered in about 65% of them [16], [59].

AbaR exhibits a variety of complex genetic configurations, incorporating different but related backbones as well as various MGE and antimicrobial resistance genes. In *A. baumannii*, different backbones are usually found in different epidemic clones [60]. For instance, international clone (IC) 1 is associated with resistance islands such as AbaR1, AbaR3, AbaR5, AbaR6, AbaR7, AbaR8, AbaR9, and AbaR10, while IC2 predominantly harbors AbaR4 [61]. These distinct genetic backbones highlight the adaptability of *A. baumannii* in evolving resistance strategies across different epidemic lineages. Furthermore, Bi et al. (2020) discovered that the AbaR3-type resistance island observed in IC2 is related to the Tn6019 backbone and is consistently associated with Tn*6018* or its elements, which include multiple antimicrobial resistance regions (MARRs). In contrast, AbaR4-type islands, which are mostly seen in IC2, employ Tn*6022* as a backbone element and occasionally carry the *bla*$_{\text{OXA-23}}$ gene [16]. Nonetheless, a study conducted by Douraghi (2020) revealed that all isolates from lineage 2 of IC1 harbor the *bla*$_{\text{OXA-23}}$ gene within AbaR4, integrated into the chromosomal comM gene [62]. This demonstrates the diverse and adaptable nature of AbaR in different epidemic clones of *A. baumannii.*

The variability in AbaR structures across epidemic clones further reflects their adaptability in diverse environments, driven by antibiotic selective pressure. The ability of AbaR elements to mobilize ARGs within different genetic backbones demonstrates their critical role in conferring resistance phenotypes. The accumulation of MGE, such as transposons, integrons, and insertion sequences (IS elements), within AbaR islands accelerates the dissemination of multidrug resistance (MDR) genes across clinical settings. This rapid spread of resistance genes presents significant challenges for infection control and treatment, emphasizing the critical role of MGE in propagating carbapenem resistance and complicating the clinical management of *A. baumannii* infections. Some of the MGE associated to Carbapenem Resistance in *A. baumannii* based on the results of the literature study are presented in Table 1.

Table 1. MGE associated with Carbapenem Resistance in *Acinetobacter baumannii*

Mobile genetic element		Resistance genes associated	Reference
Transposon	Tn*2006*	*bla*$_{\text{OXA-23}}$	[30], [63]
	Tn*2007*	*bla*$_{\text{OXA-23}}$	[35]
	Tn*2008a*	*bla*$_{\text{OXA-23}}$	[63]
	Tn*2008b*	*bla*$_{\text{OXA-23}}$	[64]
	Tn*2009*	*bla*$_{\text{OXA-23}}$	[65]
	Tn*6924*	*bla*$_{\text{NDM}}$	[47]
	Tn*6252*	*bla*$_{\text{OXA-235}}$	[63]
	Tn*6925*	*bla*$_{\text{TEM}}$	[48]
	Tn*125*	*bla*$_{\text{NDM-1}}$	[45]
Integron	*IntI*1	*bla*$_{\text{GES-11}}$	[35], [55], [66]
		bla$_{\text{GES-14}}$	
		bla$_{\text{VIM}}$	
		bla$_{\text{IMP}}$	
		bla$_{\text{CARB-2}}$	
		aac(3)-Ia	
	*IntI*2	*bla*$_{\text{IMP-4}}$	[21]
		bla$_{\text{VIM-2}}$	
		bla$_{\text{VEB}}$	
		bla$_{\text{CARB-4}}$	
		dfrA1	
		sat2	
		aadA1	
		orfX	
Insertion sequences	IS*Aba1*	*bla*$_{\text{OXA-23}}$ *bla*$_{\text{OXA-51}}$	[35]
		bla$_{\text{OXA-58}}$	
	IS*Aba2*	*bla*$_{\text{OXA-23,}}$ *bla*$_{\text{OXA-24}}$	[35]
		bla$_{\text{OXA-58}}$	
	IS*Aba3*	*bla*$_{\text{OXA-23,}}$ *bla*$_{\text{OXA-58}}$	[55]
		bla$_{\text{OXA-420}}$	
	IS*Aba4*	*bla*$_{\text{OXA-23,}}$ *bla*$_{\text{OXA-24}}$	[35]
		bla$_{\text{OXA-51,}}$ *bla*$_{\text{OXA-58}}$	
	IS*Aba10*	*bla*$_{\text{OXA-23}}$	[67]
	IS*Aba13*	*bla*$_{\text{OXA-94}}$	[42]
	IS*Aba15*	*bla*$_{\text{OXA-51}}$	[68]
	IS*Aba17*	*bla*$_{\text{OXA-94}}$	[42]
	IS*Aba19*	*bla*$_{\text{OXA-51}}$	[68]
	IS*Aba24*	*bla*$_{\text{ADC-25}}$	[69]
	IS*Aba125*	*bla*$_{\text{OXA-23,}}$ *bla*$_{\text{NDM-1}}$	[35], [40], [69]
	IS*18*	*bla*$_{\text{OXA-23}}$ *bla*$_{\text{OXA-51}}$	[13], [35]
		bla$_{\text{OXA-58}}$	

4. Conclusion

The resistance of *A. baumannii* to carbapenems is driven by a complex interplay of mechanisms, including the production of carbapenem-hydrolyzing enzymes such as OXA β-lactamases and metallo-β-lactamases like NDM. These enzymes effectively degrade carbapenems, rendering them ineffective. However, the genetic plasticity of *A. baumannii*, facilitated by mobile genetic elements (MGE), plays a crucial role in the dissemination and persistence of these resistance traits. Integrons, plasmids, insertion sequences, and transposons are integral to the horizontal transfer of resistance genes, such as $bla_{\text{OXA-23}}$ and bla_{NDM}, across bacterial populations.

Plasmids, often carrying a diverse array of resistance genes and other MGE, contribute significantly to the spread of antibiotic resistance. In particular, large conjugative plasmids can harbor multiple resistance genes and facilitate their transfer among bacteria. Insertion sequences, such as ISAba1, enhance the expression of resistance genes, further promoting resistance. Similarly, transposons, both composite and complex, contribute to the mobilization and global spread of resistance genes. Integrons, by capturing and rearranging gene cassettes encoding resistance determinants, add another layer of complexity to resistance patterns. Resistance islands, such as AbaR, illustrate the accumulation and dissemination of resistance genes within bacterial chromosomes, often integrating various MGEs and resistance determinants. The diversity and adaptability of these resistance islands reflect the dynamic nature of *A. baumannii* resistance mechanisms across different epidemic clones. Addressing the spread of MGEs and their associated resistance genes is therefore crucial for developing effective therapeutic strategies and managing infections caused by *A. baumannii*.

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