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Review

Mobile genetic elements related to carbapenem resistance in *Acinetobacter baumannii*

Mariana Pagano[a,c], *Andreza Francisco Martins*[b,c,*], *Afonso Luis Barth*[a,c]

[a] *Universidade Federal do Rio Grande do Sul (UFRGS), Faculdade de Farmácia, Programa de Pós-Graduação em Ciências Farmacêuticas, Porto Alegre, Brazil*

[b] *Universidade Federal do Rio Grande do Sul (UFRGS), Instituto de Ciências Básicas da Saúde, Porto Alegre, Brazil*

[c] *Hospital de Clínicas de Porto Alegre(HCPA), Porto Alegre, Brazil*

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ABSTRACT

Acinetobacter baumannii is widely recognized as an important pathogen associated with nosocomial infections. The treatment of these infections is often difficult due to the acquisition of resistance genes. *A. baumannii* presents a high genetic plasticity which allows the accumulation of these resistance determinants leading to multidrug resistance. It is highlighted the importance of the horizontal transfer of resistance genes, through mobile genetic elements and its relationship with increased incidence of multidrug resistant *A. baumannii* in hospitals. Considering that resistance to carbapenems is very important from the clinical and epidemiological point of view, the aim of this article is to present an overview of the current knowledge about genetic elements related to carbapenem resistance in *A. baumannii* such as integrons, transposons, resistance islands and insertion sequences.

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Introduction

The *Acinetobacter baumannii-calcoaceticus* (Abc) complex has emerged as an important nosocomial pathogen. Among the members of this complex, *A. baumannii*, *A. pittii*, and *A. nosocomialis* are the three most common *Acinetobacter* species isolated in clinical settings.[1] *A. baumannii* has been extensively studied due to its association with infections of high mortality rates. *A. pittii* and *A. nosocomialis* are increasingly identified as causative agents of nosocomial infections.[2]

A. baumannii is considered an important nosocomial pathogen, causing a wide range of infections, including ventilator-associated pneumonia, bloodstream infections, urinary tract infections and meningitis. This species is naturally highly resistant to a number of antimicrobials commonly used in the clinical practice, such as first and second generation cephalosporins, aminopenicillins, and chloramphenicol.

* *Corresponding author at*: Av. Sarmento Leite, 500/Prédio 12101, Bairro Farroupilha, Porto Alegre CEP 90050-170, Brazil.
E-mail: andrezafm20@gmail.com (A.F. Martins).

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A. baumannii contains an intrinsic AmpC β-lactamase (bla_{ADC}) and OXA-51 serine-type oxacilinase (bla_{OXA-51}), which contribute to the natural resistance to β-lactams.[3] Moreover, this organism presents a great capacity to acquire new resistance mechanisms, including those responsible for carbapenem resistance.[4]

Carbapenem resistance in *A. baumannii* involves mainly the carbapenem-hydrolysing class D β-lactamases (CHDLs – Ambler class D) and less frequently, the metallo-β-lactamases (MBLs – Ambler class B). Carbapenem resistance may also be caused by other mechanisms such as, production of other carbapenemases, porin modification or loss, or by modification of the penicillin-binding proteins.[1,5]

Several acquired class D OXA-type β-lactamases have been identified as a source of carbapenem resistance in *A. baumannii*. Five main groups of CHDLs have been described in *A. baumannii*, corresponding to OXA-23-like, OXA-24/40-like, OXA-58-like, OXA-143-like and OXA-235-like enzymes.[6] OXA-23-like enzymes are the most widespread in *A. baumannii* worldwide and have been identified in all continents.[6]

In Brazil, OXA-23-like-producing *A. baumannii* is disseminated in many states and it is responsible for high endemic levels of multidrug-resistance.[7,8] The $bla_{OXA-143}$ gene has thus far been detected only in *A. baumannii* isolates from Brazil and is the second most frequent CHDL encoding gene.[9–11]

The $bla_{OXA-143}$ gene is frequently found in the Southeast region of Brazil, especially in the state of São Paulo. It is important to note that two new variants of this gene were recently described. The variants $bla_{OXA-235}$ and $bla_{OXA-231}$ were described in Minas Gerais and Paraná states, respectively.[12,13] This data demonstrates the detection of these new variants of $bla_{OXA-143}$ in Brazil is a cause of great concern and shows the potential of these new CHDLs to spread to other Brazilian regions.

Although $bla_{OXA-24/40-like}$ gene is disseminated in *A. baumannii* in Europe, in Brazil, this gene is still rare, with only a very few reports of a bla_{OXA-72} ($bla_{OXA-24/40-like}$ variant) in São Paulo,[9] Recife,[14] Porto Alegre and Curitiba.

Despite MBLs are less commonly identified in *A. baumannii* than the OXA-type carbapenemases, their hydrolytic activities to carbapenems are significantly more potent. Four MBLs have been identified in *A. baumannii*: IMP, VIM, SIM and, more recently, NDM.[15] It is important to note that MBL genes, such as NDM and IMP-1, have been described in *Acinetobacter* non-*baumannii* species, which demonstrates the capacity of these resistance genes to spread among different *Acinetobacter* species.[16,17]

Most of Ambler class A ESBLs possess activity against penicillins and broad-spectrum cephalosporins. However, specific GES variants have been shown to possess the ability to compromise the efficacy of carbapenems. Among *A. baumannii*, the variants GES-11 and GES-14 possess specific residues enlarging their hydrolysis spectrum (Table 1).[18,19]

The elevated genetic plasticity presented by *A. baumannii* has allowed the accumulation of many resistance determinants, which contributed to the high incidence of *A. baumannii* multirresistant to antibiotics. In this review, we present and discuss the characteristics of the different mobile genetic elements involved in the transfer of resistance determinants in *A. baumannii*.

AbaR-type genomic resistance islands

Genomic islands containing resistance markers are referred to as resistance islands. Resistance islands have been described mainly in Proteobacteria, including *Shigella flexneri*, *Salmonella enterica*, *Vibrio cholerae*, *Staphylococcus aureus*, and more recently, in *A. baumannii*.[20,21] *A. baumannii* isolates harbor large clusters of horizontally transferred genes conferring resistance to multiple antibiotics and heavy metals, which are integrated at a specific site in a particular ATPase gene.[22]

Fournier et al. described for the first time the *A. baumannii* Resistant Island (AbaR). AbaR is defined as a region which has transposed into a specific position in the chromosome, creating a 5 bp duplication site (ACCGC).[21] The backbone of AbaR is comprised of five open reading frames (ORFs) – *orf1*, *tniA*, *tniB*, *orf2*, *orf3* – which constitute the transposition module, and two other genes encoding to the universal stress protein (*uspA*) and a sulfate permease (*sul*).[21–23]

Several AbaR have already been described containing a variety of resistance genes, including the $bla_{OXA-23-like}$, which confers resistance to carbapenems.[24] These resistance islands have been described in *A. baumannii* epidemic strains belonging to the important global clones, European Clone I (EC I) and European Clone II (EC II), known for their increased capacity to spread worldwide.[22]

Several other genomic resistance islands have been fully characterized in *A. baumannii*. The majority were found in strains of EC I, such as, AbaR1, AbaR3, AbaR5, AbaR6, AbaR7, AbaR8, AbaR9, and AbaR10. These AbaRs share a structure represented by a 16.3 kb backbone transposon (Tn*6019*) interrupted by a large compound transposon that contains a variable-resistance region bounded by directly oriented copies of Tn*6018*. Exceptions are AbaR6 and AbaR7, each with a large deleted region.[25] Much less is known about AbaRs in EC II. The resistance islands harbored by this clone are integrated at the same site of the ATPase gene as is known for AbaRs in EC I.[25]

AbaR1 is the largest resistance island described to date. This island contains 86 kb and was originally described in the epidemic *A. baumannii* strain AYE belonging to ECI. This strain was responsible for outbreaks in France during 2004.[21] *A. baumannii* AYE strain revealed the presence of a large gene cluster, containing many resistance determinants, inserted into the chromosome.[21]

Of the 45 resistance genes described in AbaR1 resistance island, 25 were associated with resistance to several classes of antibiotics. These include genes that had not been previously described in *Acinetobacter* species such as *strA*, *strB*, *aphA1*, and *aac69* (encoding resistance to aminoglycosides); putative tetracycline-resistance genes *tetA* (tetracycline efflux pump) and *tetR* (repressor protein); *dfrX* (resistance to cotrimoxazole); and the chloramphenicol-resistance gene *cmlA* (chloramphenicol efflux pump). Moreover, Fournier et al. (2006) described the presence of genes in AbaR1 that encode VEB-1 and OXA-10 β-lactamases, the aminoglycoside acetyltransferase gene *aac3*, and the aminoglycoside adenyltransferases *aadA1*/DA1/B; the cotrimoxazole resistance-associated *dfrI*; *cmlA5* and one copy of the chloramphenicol acetyl-transferase *cat*; the rifampin ADP-ribosyltransferase gene *arr-2*; and five

Table 1 – Characterization of the main mobile genetic elements associated with resistance in *Acinetobacter baumannii*.

Mobile genetic element	Resistance genes associated	Resistance profile	Geographic region	Reference
ISAba1	bla_{OXA-23} bla_{OXA-51} bla_{OXA-58} bla_{AmpC}	β-Lactams including carbapenems	Worldwide disseminated	Villalón et al., 2013 Mugnier et al., 2010 Mugnier et al., 2009
ISAba2	bla_{OXA-58} bla_{AmpC}	Carbapenems Cephalosporins	France Italy Spain	Villalón et al., 2013 Fernández Cuenca et al., 2012 Marqué et al., 2005
ISAba3	bla_{OXA-58}	Carbapenems	China Italy Taiwan Lebanon	Villalón et al., 2013 Donnarumma et al., 2010 Zarrilli et al., 2008 Fu et al., 2014
ISAba4	bla_{OXA-23}	Carbapenems	France Belgium	Bogaerts et al., 2008 Corvec et al., 2007
ISAba10	bla_{OXA-23}	Carbapenems	Korea	Lee et al., 2011
ISAba125	bla_{NDM-1} bla_{NDM-2} bla_{AmpC} *aphA6*	Carbapenems Cephalosporins Aminoglycosides	India Switzerland Greece Australia	Bonnin et al., 2012a Kaase et al., 2011 Mishra et al., 2013 Hamidian et al., 2012
IS18	bla_{OXA-58}	Carbapenems	Lebanon Turkey	Villalón et al., 2013 Zarrilli et al., 2008 Marqué et al., 2005
Tn2006	bla_{OXA-23}	Carbapenems	Spain Tahiti France Turkey Vietnam Romania Lybia Australia	Mugnier et al., 2010 Corvec et al., 2007
Tn2007	bla_{OXA-23}	Carbapenems	France Algeria	Corvec et al., 2007
Tn2008	bla_{OXA-23}	Carbapenems	United Arab Emirates Bahrain	Mugnier et al., 2010
Int1	bla_{GES-11} bla_{GES-14} *dfrA1* *sat2* *aadA1* *orfX* *ybfA* *ybfB*	β-Lactams including carbapenems Aminoglycosides	Europe (widespread) Korea Iran Brazil	Bonnin et al., 2011 Nemec et al., 2004 Lee et al., 2005 Japoni-Nejad et al., 2013 Mendes et al., 2007
Int2	*dfrA1* *sat2* *aadA1* *orfX* *ybfA* *ybfB* *ybgA*	Aminoglycosides	Argentina Chile Brazil	Pagano et al., 2012 Ramirez et al., 2012 Fonseca et al., 2011

copies of the sulfonamide-resistance gene *sulI* encoding dihydropteroate synthetase, a component of class 1 integrons.[21,26]

AbaR2 was described in the epidemic, multidrug-resistant *A. baumannii* strain named ACICU.[27] This strain belongs to ECII and carries the plasmid-mediated bla_{OXA-58}. *A. baumannii* AYE and ACICU belong to different clonal groups (European clones I and II, respectively), however, the presence of related resistance islands in both lineages suggests that AbaR1 and AbaR2 derived from an island acquired by a common *A. baumannii* ancestor before their divergence into two different clonal lineages.[21,27]

The genomic resistance island variant AbaR3 appears to be an ancestral of several AbaR variants which have arisen from AbaR3 by loss of segments of different lengths that include one or more of the antibiotic resistance genes.[28] AbaR3 contains eight genes associated with antibiotic resistance. Unique sequences in AbaR3 include a bla_{TEM} gene that is associated with a Tn*3* transposon and a small cluster of genes, including two that encode to a DNA topoisomerase and a single-strand binding protein that are similar to proteins from a broad-host-range plasmid.[29] In addition, it is noteworthy that the presence of genes for a plasmid-derived

DNA topoisomerase may contribute to the resistance island mobility.

Transposable elements

Transposable elements have the ability to move within the bacterial genome, being able to translocate themselves from one site of the genome to other sites. These transpositions are considered one of the major causes of bacterial DNA rearrangements, which in turn can cause changes in gene expression.[30] In *A. baumannii*, transposable elements, such as transposons and insertion sequences have been responsible for the expression and spread of antimicrobial resistance mechanisms.[1]

Insertion sequences

Bacterial insertion sequences (IS) are the least complex type of transposable elements; they rarely exceed 2 kb in size and may be as small as 0.5 kb. These elements possess an important role in the spread of resistance genes since the presence of two copies of the same IS flanking a resistance gene form a complex structure called composite transposon. Composite transposons are able to mobilize a variety of resistance genes, contributing to antimicrobial resistance dissemination.[31]

Besides their transposition role, some IS have been shown to activate or to increase the expression of neighbor genes. This capacity may be due to the presence of promoter regions in the insertion sequence or by the formation of new promoters after the insertion event.[31]

Some IS elements have an important role in *A. baumannii* antimicrobial resistance. IS*Aba1*, IS*Aba2*, IS*Aba3*, IS*Aba4* and IS18 are commonly associated with the expression of carbapenemases genes in *A. baumannii* (Table 1).[32] Villalón et al. (2013) investigated the presence of these IS elements in 59 multidrug-resistant *A. baumannii* isolates and observed a prevalence of 93.2%, 25.4%, 20.3% and 5.1% for IS*Aba1*, IS*Aba2*, IS*Aba3* and IS*18*, respectively. IS*Aba4* was not detected in any of the isolates in this study.[32]

It is important to note that IS elements such as IS*Aba1* can contribute to the spread of carbapenemase genes among different *Acinetobacter* species. Poirel et al. (2008) hypothesized that $bla_{\text{OXA-23}}$ was likely mobilized by the IS*Aba1* insertion sequence from *A. radioresistens* to *A. baumannii*.[33] The authors demonstrated that *A. radioresistens* is the progenitor of the $bla_{\text{OXA-23-like}}$ gene, which was mobilized to *A. baumannii* through IS*Aba1* insertions sequence provided by *A. baumannii*. This hypothesis is based on the identification of genes encoding both OXA-23-like and ATPase-like enzymes on the *A. radioresistens* chromosome without the presence of IS*Aba1* elements, that is involved in the mobilization of $bla_{\text{OXA-23}}$ gene.[33]

The IS*Aba1* element belongs to the IS4 family and has 11-bp inverted repeats sequences flanked by 9-bp direct repeats of the target sequence. Although this element is considered exclusive to *A. baumannii*, Segal et al. (2005) identified IS*Aba1* in *Acinetobacter lwoffii* isolates, demonstrating the high mobility of these elements and indicating that transposition events of the IS*Aba1* occur frequently.[34]

IS*Aba1* has been found upstream the $bla_{\text{OXA-23-like}}$, $bla_{\text{OXA-51-like}}$, $bla_{\text{OXA-58-like}}$ and bla_{AmpC} genes in *A. baumannii*. This IS acts as a promoter sequence which increases the expression of resistance genes. In fact, it was demonstrated that it is necessary the presence of IS*Aba1* upstream $bla_{\text{OXA-23}}$ and $bla_{\text{OXA-51}}$ for these genes to confer resistance to carbapenems.[35] Although several authors have demonstrated the relationship between IS*Aba1* upstream $bla_{\text{OXA-51}}$ and carbapenem resistance, this may not be enough to confer resistance, as *A. baumannii* isolates susceptible to carbapenems with the association IS*Aba1*/$bla_{\text{OXA-51}}$ have already been described.[36]

The IS*Aba2*, IS*Aba3* and IS*Aba4* elements have also been identified upstream $bla_{\text{OXA-58-like}}$ and $bla_{\text{OXA-23-like}}$ genes in *A. baumannii* isolates.[37] Giannouli et al. (2009) analyzed the insertion sequences of 24 *A. baumannii* isolates with $bla_{\text{OXA-58}}$ gene and identified the presence IS*Aba2*, IS18 or IS*Aba1* located at the 5′ end, while at 3′ end all isolates presented the IS*Aba3* element. Of note, the IS elements at 5′ end of $bla_{\text{OXA-58}}$ were evidenced in strains of distinct PFGE profiles and ST groups in the same geographical area. It suggests that these elements might have been acquired through horizontal gene transfer and confirms their dissemination capacity among *A. baumannii* isolates.[38]

Corvec et al. (2007) described the first *A. baumannii* isolate harboring an IS*Aba4* element upstream $bla_{\text{OXA-23}}$ gene, in France. Subsequently, it was shown that an isolate from Belgium containing the association of IS*Aba4* and the $bla_{\text{OXA-23}}$ presented the same PFGE profile as the isolate from France. These findings demonstrate the propensity of resistant strains to spread, highlighting the importance of epidemiological surveys to estimate the true prevalence of isolates harboring IS*Aba4*/$bla_{\text{OXA-23}}$.[39,40]

Lee et al. (2011) identified a novel 1203 bp insertion sequence, named IS*Aba10*. This element was found to be inserted into the IS*Aba1* element upstream $bla_{\text{OXA-23}}$ gene in an *A. baumannii* presenting high minimum inhibitory concentrations (MICs) to carbapenems (≥32 μg/mL). In addition, isolates without the insertion of this element showed MICs between 8 and 16 μg/mL. The authors suggested that this sequence may increase 2–5-fold the $bla_{\text{OXA-23}}$ gene expression. Based on these results, they suggested that the IS*Aba10* element may play an important role in carbapenem resistance by providing an additional promoter sequence to the $bla_{\text{OXA-23}}$ gene.[41]

IS elements have also been associated to metallo-β-lactamases such as bla_{NDM}, which have been increasingly reported in *Acinetobacter baumannii* and in other *Acinetobacter* species such as *A. johnsonnii*, *A. pittii*, *A. junii* and *A. lwoffii*.[16,42–44] The bla_{NDM} can be located either on the plasmid or chromosome in *Acinetobacter* species.[44] However, it was evidenced that the spread of the bla_{NDM} gene was not associated with clonal dissemination, but horizontal spread of the genetic structure.[42]

Several studies reported that bla_{NDM} gene is located between two copies of the IS*Aba125* element, forming a composite transposon named Tn*125*. IS*Aba125* element provides the -35 sequence of the hybrid promoter responsible for the expression of the bla_{NDM} gene.[45] Curiously, this IS element has been originally identified from an *A. baumannii* isolate

without any association with the bla_{NDM} gene. By contrast, this IS has been identified in *Enterobacteriaceae* and *P. aeruginosa* as a remnant of the Tn*125* and has never been identified alone in these species. This observation suggests that *A. baumannii* is a likely reservoir of IS*Aba125*. Findings like these highlight that even though *A. baumannii* is usually recognized as a final acceptor for resistance genes, it may acquire several resistance determinants and then transfer them to *Enterobacteriaceae* and *Pseudomonas* spp.

Recently, a study demonstrated that Tn*125* has been disrupted by IS*26* in *A. baumannii* NDM-producing isolates from India. This new rearrangement has resulted in bla_{NDM-1} being within an IS*26* composite transposon, which might potentially mobilize bla_{NDM-1} and contribute to the spread of the carbapenemase gene.[46]

Robledo et al. (2010) described the first report of bla_{KPC} gene in *A. baumannii* isolates from Puerto Rico. In that study, four variants of bla_{KPC} were identified: KPC-2, -3, and -4 and a novel variant, KPC-10. The integration of these genes in the *A. baumannii* chromosome was related to a transposition event mediated by the transposase of IS*Ecp1*.[31,47] This element is likely to be responsible for mobilizing numerous bla_{CTX-M} genes and several other resistance genes such as *qnr*B19, *rmt*C, bla_{ACC-1} and bla_{CMY-2}[g7,16,21].[48] In addition, it was responsible for the mobilization of $bla_{CTX-M-5}$ from a narrow range plasmid to the chromosome of *A. baumannii*, event similar to what Martinez et al. observed with bla_{KPC} gene.[47]

As described above, ISs can cause insertion mutations, genome rearrangements and enhance the spread of resistance and virulence determinants within pathogenic species. Besides being involved in the expression and spread of carbapenemases, IS elements such as IS*Aba1*, IS*Aba10* and IS*Aba825* are involved on the disruption of *car*O gene, which codes for an important outer membrane channel. The absence of this outer membrane protein has been correlated with reduced susceptibility to carbapenems.[41,49,50]

Transposons

Transposons sequences may vary in size from 3 to 40 kb, in some cases containing dozens of genes. These elements are into two main classes: composite transposons or complex transposons. Composite transposons have resistance genes in its central region; furthermore, these elements are flanked by an insertion sequence (IS) at each end. Complex transposons have a more complicated genetic structure than IS elements or composite transposons. The classic complex transposon is Tn*3*, which is derived from resistance plasmid R1.[51]

In *A. baumannii*, transposons have been characterized as genetic structures harboring important resistant genes, such as bla_{OXA-23}. Three transposons have been related to bla_{OXA-23}: Tn*2006*, Tn*2007* and Tn*2008*. In Tn*2006*, the bla_{OXA-23} gene is flanked by two copies of the insertion sequence IS*Aba1*, which is located in opposite directions. Tn*2008* is similar to Tn*2006* but lacks the second copy of IS*Aba1*. Finally, in Tn*2007* the bla_{OXA-23} gene is associated with one copy of IS*Aba4* located upstream to this gene.[52] Several studies have demonstrated that Tn*2006* is currently the most common determinant of carbapenem resistance, with a great ability to spread among *A. baumannii* isolates.[53]

Integrons

These elements are natural cloning and expression systems that incorporate ORFs by site-specific recombination and convert them to functional genes due to the presence of a promoter sequence (Rowe-Magnus et al., 2001). It is now well established that these mobile elements constitute the major vectors of antibiotic multiresistance in Gram-negative and, to a lesser extent, in Gram-positive bacteria.[54]

Five different classes of mobile integrons have been defined to date, based on the sequence of the encoded integrases.[54,55] It is known that three (classes 1, 2 and 3) of these classes have an important role in the dissemination of antimicrobial resistance genes.[55,56] These classes are well described in the literature and are associated to multiresistant phenotypes.[54,55]

Several studies have demonstrated a high prevalence of class 1 integrons in *A. baumannii* isolates in Europe, Asia and United States.[57] Due to its greater spread capacity, class 1 integrons are the main experimental model of integrons. This class is usually associated to functional or non functional transposons derived from Tn*402* which may be inserted into larger transposons as Tn*21*. Class 1 integrons have been associated to a variety of insertion sequences, including IS*26*, IS*1999*, IS*2000* e IS*6100*.[58]

Most acquired MBL genes in *A. baumannii* have been found within class 1 integrons, often containing an array of resistance gene cassettes.[1,6] Mendes et al. (2007) described seven bla_{IMP-1} harboring *Acinetobacter* spp. isolates recovered from Brazilian inpatients. All isolates possessed a class 1 integron, named In86, carrying the same cassette array: bla_{IMP}, *aac(6′)-31*, and *aadA1*, which was plasmid-located in five of the isolates (Mendes et al., 2007). This gene cassette contained a aminoglycoside resistance gene – *aac(6′)-31* – that might be capable of conferring resistance to all clinically available aminoglycosides. This gene was able to disseminate among unrelated *A. baumannii* clinical isolates from a Brazilian hospital (Mendes et al., 2007). Recently, Cayô et al., reported a new structure of class 1 integron, In990, harboring the *bla*IMP-10 in *A. baumannii* isolates from Brazil. The cassette arrangement of In990 was very similar to that of In86 described by Mendes et al.[59,60]

Class 2 integrons are included in the Tn*7* family of transposons, and consist of an integrase gene followed by gene cassettes. Tn*7* are identified as a sophisticated mobile genetic element containing a transposition module formed by five transposition genes, *tns*A, *tns*B, *tns*C, *tns*D, and *tns*E, rather than the one or two seen in many other transposable elements.[56] Class 3 integrons are less prevalent than class 2 and are also located in transposons.[54]

Despite reports of a higher prevalence of class 1 integrons in *A. baumannii*, studies conducted in Latin American countries such as Chile, Argentina and Brazil demonstrated a greater distribution of class 2 integrons among isolates of *A. baumannii* in these regions.[36,61] Fonseca et al. (2011) demonstrated that all class 2 integrons obtained from Brazilian isolates

were inserted into Tn7 transposon, besides having the gene cassette containing the arrangement of genes *dfrA1* (trimethoprim resistance), *sat2* (streptothricin resistance) and *aadA1* (spectinomycin and streptomycin resistance).[62]

Martins et al. (2015) investigated the association of class 2 integrons and gene cassettes with clonal lineages of *A. baumannii*. They reported the association of class 1 and 2 integrons with CC109/1 (International Clone I) and CC113/79 *A. baumannii* strains, respectively. The authors hypothesized that class 2 integron, predominant in Latin America, may be accounted for the high prevalence of the CC113/79 type. In the same study, a similar prevalence was observed for *A. nosocomialis*.[63]

Class 1 and 2 integrons have been described in *A. baumannii* isolates related to nosocomial infection outbreaks. In a study published by Turton et al. (2005), it was observed that all *A. baumannii* isolates associated with outbreaks contained class 1 integrons, in contrast, none sporadic isolate presented this class of integron.[64]

More than 130 different gene cassettes containing resistance genes have been identified in integrons. Distinct genes are evidenced in gene cassettes, promoting resistance to a variety of antimicrobial classes. Together, these gene cassettes provide resistance to most classes of antibiotics including β-lactams, all aminoglycosides, chloramphenicol, trimethoprim, streptothricin, rifampin, erythromycin, fosfomycin, lincomycin, quinolones, and antiseptics of the quaternary ammonium-compound family.[65] Besides these genes, several ORFs with unknown function have been identified in gene cassettes.[66]

In *A. baumannii*, gene cassettes have been described containing several genes, such as *aacA4* responsible for resistance to amikacin, netilmicin and tobramycin, the *catB8* gene is an acetyltransferase which encodes resistance to chloramphenicol, *aadA1* is responsible for resistance to streptomycin and spectinomycin, *aac3* responsible for resistance to gentamicin and bla_{OXA-10} encodes resistance to β-lactams, except carbapenems and extended-spectrum cephalosporins.[21]

Final remarks

This review highlighted the role of resistance determinants in the capacity of spread in *A. baumannii*. This species shows a considerable ability to acquire foreign DNA such as drug resistance genes, which provide a genetic diversity and overcomes the antibiotic selection pressure. It is important to note that the main carbapenem-resistance mechanism involved in *A. baumannii* (production of oxacillinases) presents a low hydrolytic power when it is not associated with an insertion sequence. Moreover, the capacity of OXA genes to spread is directly related to their association with a composite transposon (Tn*2006*). These features highlight the importance of investigating the genetic context of these genes in order to define their real clinical significance.

The continuous description of gene cassettes in integrons, mainly those leading to resistance to β-lactams and aminoglycosides, has been of great concern. Furthermore, the number of resistance genes inserted in the same plasmid, even in the same integron, seems to be increasing. This integration of resistance determinants in the same plasmid may facilitate the persistence in the environment for long periods because of the physical association of integrons with other elements, allowing their continued selection.[57]

In this context, the knowledge about the genetic structure of resistance determinants is very important in order to understand the capacity of resistance genes to spread in *A. baumannii*.

Conflicts of interest

The authors declare no conflicts of interest.

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