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REVIEW

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Mobile genetic elements in *Acinetobacter* antibiotic-resistance acquisition and dissemination

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Abstract

Pathogenic *Acinetobacter* species, most notably *Acinetobacter baumannii*, are a significant cause of healthcare-associated infections worldwide. *Acinetobacter* infections are of particular concern to global health due to the high rates of multidrug resistance and extensive drug resistance. Widespread genome sequencing and analysis has determined that bacterial antibiotic resistance is often acquired and disseminated through the movement of mobile genetic elements, including insertion sequences (IS), transposons, integrons, and conjugative plasmids. In *Acinetobacter* specifically, resistance to carbapenems and cephalosporins is highly correlated with IS, as many IS*Aba* elements encode strong outwardly facing promoters that are required for sufficient expression of β-lactamases to confer clinical resistance. Here, we review the role of mobile genetic elements in antibiotic resistance in *Acinetobacter* species through the framework of the mechanism of resistance acquisition and with a focus on experimentally validated mechanisms.

KEYWORDS
Acinetobacter, antibiotic resistance, insertion sequence, mobile genetic element, transposon

INTRODUCTION

Pathogenic *Acinetobacter* are a significant cause of opportunistic infections and represent a critical threat due to increasing antimicrobial resistance.[1] Antimicrobial-resistant infections cause a significant global health burden and were estimated to contribute to 4.95 million deaths worldwide in 2019.[2] The World Health Organization predicts a global rate of 10 million deaths per year due to drug-resistant bacterial infection by 2050 if no action is taken, emphasizing the critical importance of understanding multidrug-resistant (MDR) pathogens.[3] *Acinetobacter* spp. demonstrate this threat through growing levels of MDR incidence, including resistance to many last-resort antibiotics, such as colistin.[4,5]

Within *Acinetobacter* spp., *Acinetobacter baumannii* presents the highest concern as a healthcare-associated pathogen.[6] Carbapenem-resistant isolates of *A. baumannii* have increased in number worldwide,[7] and the United States Center for Disease Control and Prevention labeled carbapenem-resistant *A. baumannii* as a threat level "urgent" due to the difficulty in treatment.[8] *A. baumannii* can also cause community-acquired infections, which are less likely to be MDR but often have severe clinical outcomes.[9,10] Antibiotic resistance in *A. baumannii* is due to intrinsic and acquired antibiotic-resistance genes and is promoted in part by genomic plasticity and adaptation, including mobile genetic elements.[11,12]

The global increase of MDR *A. baumannii* has been linked to the expansion of multiple clones, often referred to as "global clones."[13] Most MDR strains have historically belonged to global clones I and II (GC1 and GC2) that were identified in the 1970s.[14,15] The emergence of antimicrobial resistance in GC1 corresponded with the acquisition of the AbaR resistance island, further modified in later sublineages.[16–18] More recently, researchers have identified infections by what were once uncommon global clones, such as III, VI, and VII, indicating the

broad increase in clonal invasiveness.[19,20] There are currently nine defined global clones for *A. baumannii* that are often found to cocirculate in hospital settings,[21] but GC1 and GC2 remain the most common globally.[1,22–24] The GC type of community-acquired strains is often not reported. One study found that a community-acquired strain does not fall within either GC1 or GC2 lineages, but is most closely related to a GC2 isolate,[25] and another one found in community-acquired pneumonia caused by a strain with multi-locus sequence type ST77 (Pasteur), which does not belong to a GC.[26] This is consistent with findings that community and nosocomial strains are distinct, with nosocomial strains typically having increased drug resistance.[27,28] Subtypes of the global clones and their antibiotic resistances can be determined by multiple factors beyond the presence of the AbaR. Notably, *Acinetobacter* insertion sequences (IS) elements can activate and mobilize carbapenem-hydrolyzing β-lactamases, which represent the greatest public health threat in *A. baumannii* infections.[7,22,29] Many potential roles for mobile genetic elements in *Acinetobacter* antibiotic resistance have been identified by genomic sequencing and analyses that are too numerous to comprehensively discuss in this review. Here, we review the role of mobile genetic elements in antibiotic resistance in *Acinetobacter* organized by the mechanism of resistance acquisition with an emphasis on experimentally validated mechanisms.

IS elements are the simplest and smallest mobile genetic elements at roughly 1 kb, consisting of terminal inverted repeats usually flanking one or two open reading frames encoding a transposase enzyme (Figure 1A). The transposase is responsible for the excision and integration of the element into the genome and does so by recognizing and binding the terminal inverted repeats as reviewed previously.[30,31] Transposition can be replicative using a "cut and paste" mechanism. IS element transposition can be site-specific or random and typically creates short (2–14 base pair) flanking direct repeats from the genomic insertion site, also known as transposition site duplication. IS elements are often named including the first three letters of the species in which they were discovered, thus *A. baumannii* IS elements are designated IS*Aba*. In *A. baumannii* laboratory strains, such as AB5075 and 17978, IS elements are one source of genetic differences between closely related strains passaged in different laboratories or distributed by culture collections.[32,33] IS elements can contribute to genomic variability as well as create significant phenotypic changes for the bacterial host, both favorable and unfavorable.

Transposons have a similar structure to IS elements but carry additional cargo genes, which can include antibiotic-resistance genes (Figure 1B). Composite transposons are comprised of complete IS elements that act as terminal repeats, flanking the cargo genes of the transposon (Figure 1C).[34] Transposons mobilize similarly to IS elements, using transposase enzymes that recognize the terminal repeats of the element and insert site-specifically or randomly. Specific transposon families and their role in antibiotic resistance have been reviewed in depth previously.[31]

Integrons and site-specific recombinases are genetic elements capable of acquiring resistance cassettes independently of one another (Figure 1D).[35] A gene cassette is a small nonautonomous mobile element typically associated with integrons and often encodes for

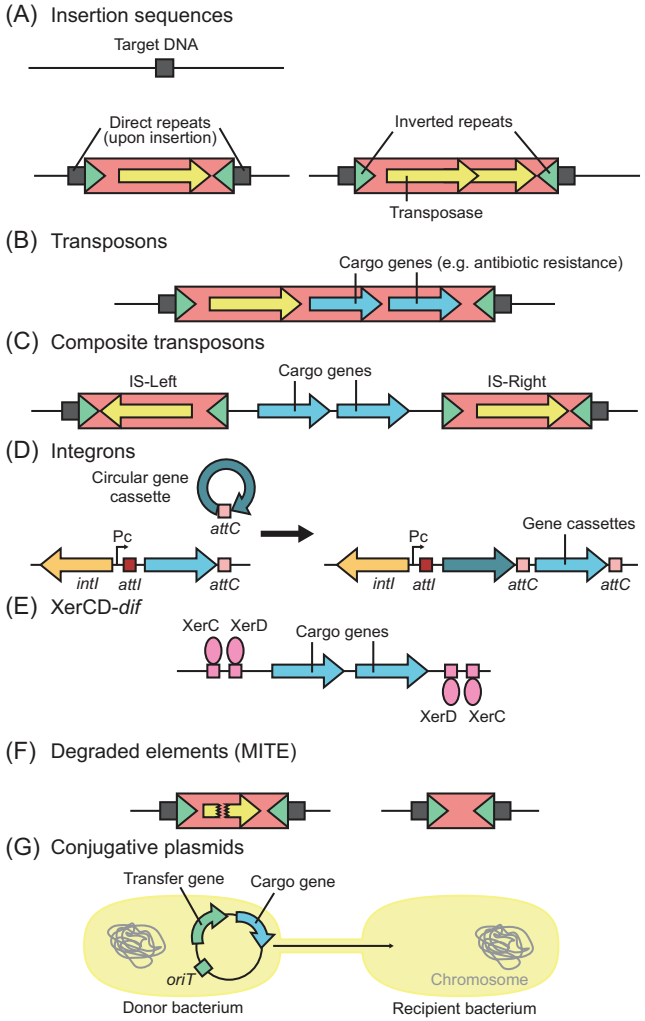

FIGURE 1 Overview of mobile genetic elements that contribute to *Acinetobacter* antibiotic resistance. (A) Insertion sequences (IS) are comprised of transposase genes flanked by inverted repeats; insertion into target DNA generates direct repeats (also known as transposition site duplications). (B) Transposons are similar to IS but can also carry cargo genes, including antibiotic-resistance genes. (C) Composite transposons are generated when cargo genes are flanked by IS elements, which can be in multiple orientations. (D) Integrons encode the *intI* integrase gene and incorporate gene cassettes at *att* sites. (E) XerCD-*dif* sites can include cargo genes flanked by XerC and XerD sites separated by small spacer sequences. In *Acinetobacter*, XerCD-*dif* sites are often encoded on plasmids flanking antibiotic-resistance genes. (F) Degraded elements, such as miniature inverted-repeat transposable elements (MITE), retain inverted repeats but do not encode their own transposase enzymes. (G) Conjugative plasmids can carry cargo genes and mobile genetic elements and can be transferred between bacteria by the origin of transfer (*oriT*).

antibiotic resistance.[36] Gene cassettes consist of one open reading frame without a promoter sequence and one recombination site called *attC* that is recognized by the IntI recombinase. The recombination site is critical for integration into an integron structure. Integrons are ubiquitous in bacterial genomes and exist as chromosomal integrons that are not typically involved in antibiotic resistance and mobile

integrons that are associated with antibiotic resistance.[35] All integrons contain a conserved "platform" comprised of the *intI* encoding a tyrosine recombinase, an *attI* recombination site, and a Pc promoter.[37] The tyrosine recombinase is responsible for the integration of new genes at the *attI* recombination site near the Pc promoter, which drives the expression of the cargo genes. By themselves, the stable platforms are nonmobile. Integrons only become mobile by association with transposons as a compounded element. In this case, the cargo genes are often associated with antibiotic resistance and are a cause of MDR in multiple organisms.[38–40] There are five classes of integrons which have been reviewed in depth.[35,41,42] Class 1 integrons are the most clinically relevant and can also be associated with IS*91*-like "common regions" to form IS*CR* which are capable of mobilization via transposition.[43] Additionally, XerCD-*dif* is a site-specific tyrosine recombinase system important for maintaining monomers of bacterial circular DNA (Figure 1E)[44] that has been posited to contribute to the dissemination of antibiotic resistance in *Acinetobacter*.[45]

Miniature inverted-repeat transposable elements (MITEs) are nonautonomous elements that are thought to be degraded from ancestral IS elements or transposons. MITEs retain inverted repeat structures but do not encode the cognate transposase enzyme (Figure 1F).[46] However, MITEs can be mobilized by transposases of other mobile genetic elements present in the genome. Complex MITE-containing genetic structures can be difficult to identify *de novo* because they often do not contain open reading frames. Despite the difficulty in identification, degraded elements have been found to contribute to the growing problem of antibiotic resistance in *Acinetobacter*.[47,48]

Conjugative plasmids are examples of extrachromosomal mobile genetic elements that can be transferred between bacteria and can also contain other nested elements (Figure 1G).[34] Conjugative plasmids are a major contributor to antibiotic-resistance dissemination and can be transmitted vertically—from parent cell to progeny—or horizontally by conjugation.[34] Conjugative plasmids often carry cargo genes that encode antibiotic resistance directly or within other elements, such as IS elements or transposons.[49] Conjugative plasmids encode replication initiation sites, an origin of transfer (*oriT*), and typically encode the transfer genes required for mobilization from the donor cell to a recipient cell (Figure 1G).[50] Conjugative plasmids can be broad-host-range and replicate in a variety of bacterial hosts or narrow-host-range which are limited to closely related taxa. The transfer of conjugative plasmids is a growing concern in terms of antibiotic resistance. Due to the potential broad-host-range for transfer, antibiotic-resistance genes can be exchanged across bacterial taxa, including pathogenic bacteria. This poses a great public health risk as treatment options for MDR and extensive drug resistance (XDR) pathogens are declining.

Compounded elements or "nesting doll" elements where one feature is embedded into another[51] complicate categorizing elements into one type.[52,53] Simple examples include IS elements, transposons, or integrons present on conjugative plasmids that allow horizontal gene transfer of multiple elements simultaneously.[54–56] Other well-described elements include the presence of IS within large transposon structures, for example, in the Tn*7* transposon family; however, Tn*7* transposons are separate entities than composite transposons.[57]

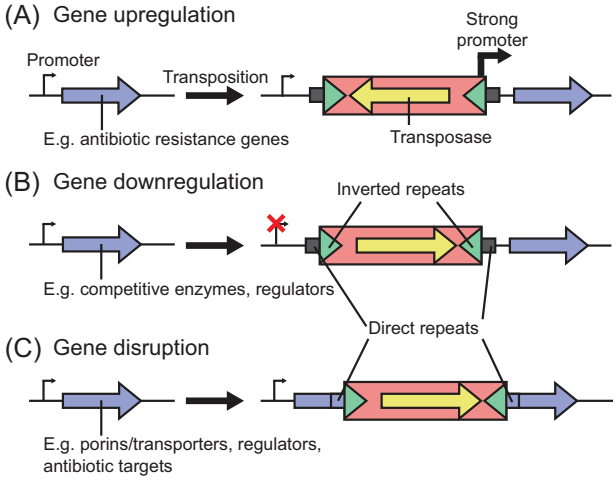

FIGURE 2 Mechanisms of antibiotic resistance by insertion sequence transposition. (A) Many IS*Aba* elements encode strong outward promoters and promote antibiotic resistance by increasing the expression of genes, such as intrinsic antibiotic-resistance genes. (B) IS elements can confer antibiotic resistance by downregulating competitive enzymes or regulators. (C) IS elements can confer antibiotic resistance by disrupting genes that encode porins, transporters, regulators, or antibiotic targets.
Abbreviation: IS, insertion sequences.

Compounded elements are often capable of mobilization and, therefore, contribute to antibiotic-resistance dissemination.

Bacteriophage are an additional type of mobile genetic element that likely contribute to antibiotic-resistance dissemination by horizontal gene transfer in *Acinetobacter*; however, we do not discuss their role in detail in this review. While mobile genetic elements differ in their characteristics, the mechanisms by which they contribute to antibiotic-resistance acquisition and dissemination often overlap. Here, we review work identifying mobile genetic elements in the acquisition and dissemination of antibiotic resistance organized by the mechanism of resistance acquisition.

MOBILE GENETIC ELEMENTS CAN CONFER ANTIBIOTIC RESISTANCE BY ALTERING GENE EXPRESSION

Transposition of IS elements or transposons can promote antibiotic resistance by changing bacterial gene expression, such as by providing strong promoter sequences to downstream genes, disrupting promoters to decrease expression, or inactivating genes (Figure 2). Because these effects do not require the element to encode for an antibiotic-resistance gene, simple elements, such as IS, can promote antibiotic resistance (summarized in Table 1).

IS elements can provide strong promoter sequences to express antibiotic-resistance genes

IS elements are significant contributors to carbapenem-resistant *Acinetobacter* by providing strong promoters to otherwise silent

TABLE 1 Regulation of gene expression by mobile genetic elements that confer antibiotic resistance

Species	Genetic element	Regulation mechanism	Antibiotic resistance	Reference
Acinetobacter baumannii	IS*Aba1*	Promoter sequence increased the expression of bla_{OXA-23}	Carbapenem	79, 95, 168
		Promoter sequence increased the expression of bla_{OXA-51}-like and likely bla_{OXA-23}-like	Carbapenem	66
		Promoter sequence increased the expression of $bla_{OXA-69/OXA-51}$	Carbapenem	66
		Promoter sequence increased the transcription of *sul2*	Sulfonamide	79, 86
		Promoter sequence increased the expression of *ampC*	Cephalosporin	60–63
		Promoter sequence increased the expression of *eptA*	Colistin	5
		Increased expression of bla_{OXA-51}	Carbapenem	4, 67, 68
		Promoter sequence increased the expression of bla_{OXA-66} of the bla_{OXA-51} family	Carbapenem	65
		Truncation and activation of *adeS*, which activates *adeABC* encoding an efflux pump	Tigecycline	87
		Promoter sequence increased the expression of *adeIJK*	Erythromycin Tetracycline Azithromycin	88
	IS*Aba1*, IS*Aba2*, IS*Aba3*-like, IS*18*	Promoter sequence for bla_{OXA-58}	Carbapenem	84
	IS*Aba3*/IS*Aba825*	Composite IS*Aba3*/IS*Aba825* promoter sequence increased the expression of bla_{OXA-58}	Carbapenem	85
	IS*Aba10*	Putative promoter sequence of bla_{OXA-23}	Carbapenem	95
	IS*Aba11*	Insertion decreased the transcription of *ispB*, restoring antibiotic resistance to Δ*mlaF* strain	Meropenem Imipenem Gentamicin	91
	IS*Aba13*	Insertion upstream decreased the transcription of *adeN*	Erythromycin Tetracycline Azithromycin	88
	IS*Aba125*	Promoter sequence increased the expression of *ampC*	Cephalosporin	64
		Promoter sequence increased the expression of bla_{NDM-1}	Carbapenem	74, 75
	IS*Aba4*	Increased expression of bla_{OXA-23}	Carbapenem	81, 82
Acinetobacter bereziniae	IS*18*	Promoter sequence for $bla_{OXA-257}$	Carbapenem	83
	IS*Aba1*, IS*Aba2*, IS*Aba3*-like, IS*18*	Promoter sequence for bla_{OXA-58}	Carbapenem	84
Acinetobacter nosocomialis	IS*Aba1*	Increased expression of bla_{OXA-51}	Carbapenem	4, 67, 68
Acinetobacter radioresistens	IS*Acra1*	Promoter sequence increased the expression of bla_{OXA-23}	Carbapenem	77

bla genes encoding β-lactamase enzymes. *A. baumannii* intrinsically encodes two classes of β-lactamases that do not confer clinical resistance at basal expression levels: (1) the chromosomally encoded *ampC* (also known as bla_{ADC}) encodes a cephalosporin-hydrolyzing β-lactamase[58] and (2) bla_{OXA-51} encodes a carbapenem-hydrolyzing class D β-lactamase OXA-51 family.[59] However, insertion of an IS element upstream of *ampC* or bla_{OXA-51} can provide a strong outward promoter and confer clinical resistance to cephalosporins or carbapenems, respectively. For example, IS*Aba1* has been identified to promote *ampC* expression and clinical cephalosporin resistance within composite transposons (IS elements are depicted in Figure 3).[60–63] IS*Aba125* inserted upstream of *ampC* also provides a strong promoter and confers cephalosporin resistance to the GC1 *A. baumannii* ACICU in a 9-kb genomic island that appears to be acquired from the GC2 lineage by

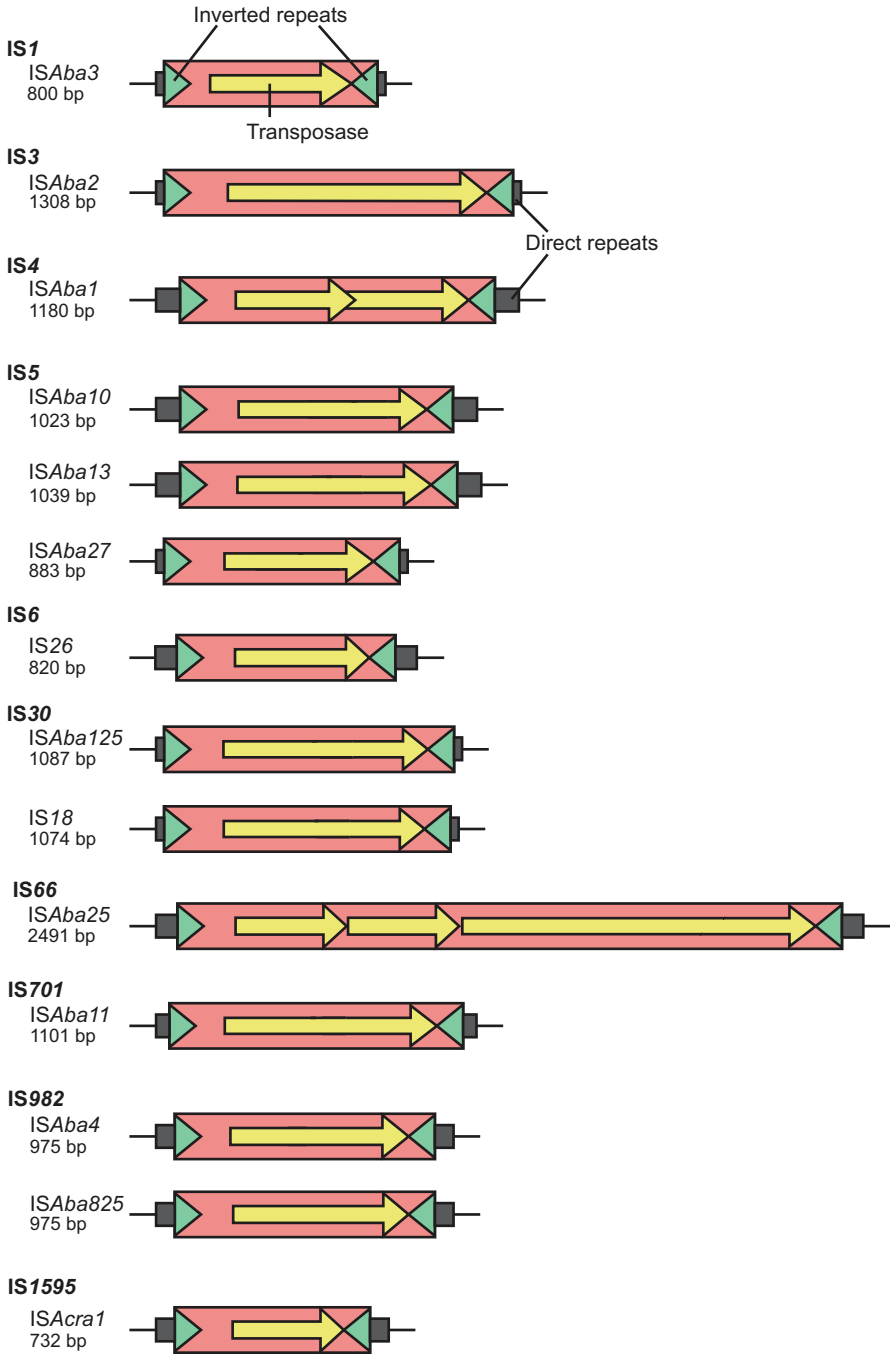

FIGURE 3 Families and sizes of *Acinetobacter* IS elements. Each IS element mentioned is grouped by IS family: IS*1* family, IS*Aba3*; IS*3* family, IS*Aba2*; IS*4* family, IS*Aba1*; IS*5* family, IS*Aba10*, IS*Aba13*, IS*Aba27*; IS*6* family, IS*26*; IS*30* family, IS*Aba125*, IS*18*; IS*66* family, IS*Aba25*; IS*701* family, IS*Aba11*; IS*982* family, IS*Aba4*, IS*Aba825*; IS*1595* family, IS*Acra1*. Variation in the number of transposase genes, IS length, and direct repeat length is depicted.

homologous recombination.[64] The dual role of IS elements as providing strong promoters and forming composite transposons is common in *Acinetobacter* genetic structures and is discussed in more detail below.

IS*Aba1* is similarly associated with promoting the expression of the intrinsic $bla_{\text{OXA-51}}$. One study isolated *A. baumannii* from a patient pre- and postantibiotic treatment, including imipenem; the pretreatment isolate was carbapenem sensitive, while the posttreatment isolate was carbapenem resistant.[65] Genetic analysis determined that the transposition of IS*Aba1* to upstream of the native $bla_{\text{OXA-66}}$ ($bla_{\text{OXA-51}}$ family) promoted expression of the carbapenemase, conferring clinical resistance.[65] Similarly, a reference library of *A. baumannii* clinical outbreak clones provided evidence that while most isolates had genes encoding the β-lactamase OXA-69/OXA-51, only isolates with IS*Aba1* upstream of $bla_{\text{OXA-69/OXA-51}}$ produced enough enzyme to be carbapenem resistant.[66] Other studies of clinical isolate collections from

Taiwan, Spain, and China have similarly shown that IS*Aba1* insertion upstream of bla_{OXA-51} was associated with significantly increased expression and carbapenem resistance.[4,67,68] Together, these findings demonstrate that IS-mediated enhancement of intrinsic β-lactamase genes is an important mechanism by which *A. baumannii* acquires clinical resistance to carbapenems and cephalosporins.

Carbapenem resistance conferred by the production of the New Delhi metallo-β-lactamase 1 (NDM-1) is also thought to require IS-mediated activation of bla_{NDM-1}. bla_{NDM-1} is not intrinsic to all *A. baumannii* strains, but is thought to have originated in *A. baumannii* as a chimera.[69] bla_{NDM-1} was identified in 2008 and is now globally disseminated in *Acinetobacter* and *Enterobacteriaceae*.[56,70,71] bla_{NDM-1} is thus far universally encoded downstream of an intact or truncated IS*Aba125*,[72,73] which provides a -35 promoter region to promote bla_{NDM-1} expression.[74,75] bla_{NDM-1} is often encoded within a composite transposon Tn*125*, which includes IS*Aba125* and is further discussed below.

Similarly, the carbapenem-hydrolyzing class D β-lactamase (CHDL) OXA-23 is thought to have originated in *Acinetobacter radioresistens* and is a significant contributor to carbapenem resistance in *A. baumannii* only when activated by adjacent IS elements.[76] Indeed, one study found that transposition of the native IS element IS*Acra1* to upstream of bla_{OXA-23} provides carbapenem resistance in *A. radioresistens* clinical isolates.[77] *A. radioresistens* is not typically found to cause infection; the fourth identified case of infection was documented in 2019.[78] Therefore, these data show that typically nonpathogenic bacteria can contribute to antibiotic resistance and dissemination through mobile genetic elements. IS*Aba1* is often found upstream of bla_{OXA-23}, providing a strong promoter and conferring carbapenem resistance in many clinical isolates. This was first demonstrated in *A. baumannii* strain RAM isolated from Cape Town, South Africa, where IS*Aba1* was shown to provide an extended -10 promoter sequence similar to sequences recognized by stress-responsive σ^S of *Escherichia coli* RNA polymerase.[79] However, the implications of this similarity are unclear as *A. baumannii* does not encode an σ^S homolog. Numerous studies since have identified a relationship between IS*Aba1* insertion upstream of bla_{OXA-23} and carbapenem resistance, and IS insertion is often part of a composite transposon structure as previously reviewed[80] and discussed below. IS*Aba4* has also been reported to activate bla_{OXA-23} expression in isolates from Algeria and France[81] and was similarly found adjacent to bla_{OXA-23} in an isolate from Egypt.[82] Together, these studies suggest that IS-mediated enhancement of expression is required for bla_{OXA-23} to confer carbapenem resistance.

IS elements are also associated with promoting the expression of acquired β-lactamases. In a carbapenem-resistant *Acinetobacter bereziniae* clinical bronchial secretion isolate, IS element IS*18* provided a strong promoter sequence to a novel β-lactamase gene, $bla_{OXA-257}$.[83] *A. bereziniae* is pathogenic but rarely antibiotic resistant, suggesting that the IS element was key to conferring carbapenem resistance. Similarly, in a survey of carbapenem-resistant *A. baumannii* isolates containing the acquired β-lactamase OXA-58, bla_{OXA-58} was typically located downstream of promoters introduced by IS elements, such as IS*Aba1*, IS*Aba2*, an IS*Aba3*-like element, and IS*18*.[84]

When kanamycin-tagged IS*Aba825* was experimentally introduced to *A. baumannii*, one group found that IS*Aba825* transposed and truncated a pre-existing IS*Aba3* sequence.[85] Upon further examination, the two IS elements generated a composite promoter sequence where the −10 region was within IS*Aba3* and −35 within IS*Aba825* upstream of a bla_{OXA-58} gene, conferring carbapenem resistance to the strain.[85] These studies are consistent with the model that the presence of *bla* genes is often not sufficient to confer clinical carbapenem or cephalosporin resistance and that a strong promoter provided by an IS element or other transposable element is often required for clinical resistance.

While IS element transposition is strongly associated with clinical β-lactam resistance, IS element provision of strong promoters has also been found to increase resistance to other classes of antibiotics. In addition to increasing bla_{OXA-23} expression in *A. baumannii* strain RAM, IS*Aba1* was also inserted upstream of the sulfonamide resistance gene *sul2* and has been shown to increase transcription.[79,86] In another example, an IS*Aba1* insertion truncated and activated the expression of *adeS*, part of a two-component system that activates the production of the AdeABC efflux pump and conferred tigecycline resistance.[87] An independent study found an IS*Aba1*-encoded promoter driving transcription of *adeIJK*, increasing ABUW5075 resistance to erythromycin and tetracycline when supplemented with host-derived fatty acids *in vitro*.[88] Similarly, IS*Aba1* transposition upstream of the novel gene *eptA* in *A. baumannii* increased its expression and resulted in resistance to the polymyxin colistin.[5] *eptA* encodes a phosphoethanolamine transferase and is a homolog to *pmrC* which is also known to be associated with polymyxin resistance when overexpressed.[5,89] This poses a threat as colistin is currently a last resort treatment for MDR *A. baumannii*.[90] Together, these studies show that IS element transposition can provide strong promoter sequences to diverse antibiotic-resistance genes, therefore, promoting MDR.

Downregulation of gene expression by IS element insertion can promote antibiotic resistance

IS elements have also been shown to confer antibiotic resistance by downregulation of gene expression (Figure 2B). For example, we previously isolated a suppressor mutant during a mouse model of *A. baumannii* lung infection in which antibiotic resistance was restored to an *mlaF* mutant strain.[91] This suppressor mutation was identified as an IS*Aba11* transposition to the 5′ untranslated region of *ispB*, an essential isoprenoid biosynthesis gene.[91] This suppressor mutation reduced the expression of *ispB* and restored resistance to multiple antibiotics, including meropenem, imipenem, and gentamicin.[91] The exact mechanism of restoring antibiotic resistance in this strain is unknown and may be related to competition for a shared metabolite used by IspB and undecaprenyl pyrophosphate synthase (UppS), which is required for cell envelope biogenesis. An *in vitro* study selective for erythromycin-resistant ABUW5075 in the presence of host fatty acids identified an IS*Aba13* transposition upstream of the transcriptional regulator *adeN*, resulting in a 13.4-fold decrease in transcription.[88] In this study, the

TABLE 2 Genetic disruptions that confer antibiotic resistance in *Acinetobacter*

Species	Genetic element	Gene(s) disrupted	Antibiotic resistance	Reference
Acinetobacter baumannii	IS*Aba1*	Hypothetical genes	Mecillinam or imipenem (in Δ*bfmRS* strain)	102
		adeS	Tigecycline	99
		adeN	Tigecycline	99
	IS*Aba10*	*carO*	Carbapenem	95
	IS*Aba11*	*lpxA*, *lpxC*	Colistin	100
		cspC, *ACX60_RS05385* (predicted NUDIX hydrolase), *mnmA*, *prmB*, *ctpA*, *tusE*, hypothetical genes	Mecillinam or imipenem (in Δ*bfmRS* strain)	102
		adeN	Ciprofloxacin	97
	IS*Aba27*	*carO*	Carbapenem	96
		adeN	Tigecycline	99
	IS*Aba125*	*carO*	Carbapenem	94
		lpxA	Polymixin B	101
		adeN	Tigecycline	99
	IS*Aba825*	*carO*	Carbapenem	94

presence of host fatty acids promoted the development of mutations cross-resistant to tetracycline and azithromycin. These examples show the variety of mechanisms by which mobile genetic elements can promote resistance phenotypes through disruption or downregulation of a gene. Additionally, these studies highlight the idea that mobile genetic element-mediated mutations selected in the host environment may confer enhanced resistance to antibiotics.

IS element disruption of bacterial genes to confer antibiotic resistance

IS are also found to confer antibiotic resistance by disrupting genes (Figure 2C). A recent analysis of nine pathogens found that mobile genetic element-mediated gene disruption is an important contributor to antibiotic resistance in clinical isolates.[92] One common mechanism of IS element transposition conferring antibiotic resistance is by disrupting membrane or secretory proteins required for antibiotics to enter the cell. Disruptions in porins have been shown to cause broad resistance to antimicrobials due to their nonspecific and passive diffusion properties.[93] Multiple analyses of *A. baumannii* carbapenem-resistant clinical isolates revealed insertions disrupting the outer membrane protein gene *carO* by IS*Aba825*, IS*Aba125*, IS*Aba10*, and IS*Aba27* (Table 2).[94–96]

Disruption of transcriptional regulators or antibiotic targets is another mechanism by which the transposition of IS can promote antibiotic resistance. In experimental evolution selecting for ciprofloxacin resistance in *A. baumannii* 17978, strains were isolated in which IS*701*-family IS*Aba11* transposition disrupted *adeN*.[97] AdeN is a repressor of the genes that encode the efflux pump AdeIJK that promote resistance to multiple antimicrobials.[98] Disruption of the Ade efflux pump system can be found in clinical isolates as well. One study found four independent isolates with IS element disruptions in *adeN* or *adeS*, which conferred tigecycline resistance.[99] Two of the isolates, IS*Aba1* inserted in *adeS* at two different sites, indicated independent transposition events.[99] In other isolates, *adeN* was disrupted by IS*Aba1*, IS*Aba125*, and IS*Aba27* conferring tigecycline resistance.[99] Disruption of *adeN* was associated with a 35-fold and 45-fold increase in *adeB* expression, while disruption of *adeS* was associated with a two-fold and six-fold increase in *adeJ* expression.[99] As an example of disruption of an antibiotic target, an experimental selection for resistance to the last-resort, polymyxin antibiotic (colistin) identified IS*Aba11* inactivation of lipid A biosynthesis genes *lpxA* and *lpxC*, which led to a loss of the colistin target lipooligosaccharide in *A. baumannii* 19606.[100] Similarly, when an *A. baumannii* clinical isolate was selected for resistance to polymyxin B *in vitro*, IS*Aba125* was found to disrupt *lpxA* in the resulting polymyxin B-resistant isolate.[101]

Finally, disruption of other processes can promote antibiotic resistance by unknown mechanisms. For example, a suppressor screen for mutations that restore antibiotic resistance to a Δ*bfmRS* mutant in *A. baumannii* 17978 identified numerous IS element disruptions, including IS*Aba11* insertions in the cold shock protein gene *cspC*, a predicted NUDIX hydrolase gene, the tRNA gene *mnmA*, *prmB* ribosomal protein, *ctpA* peptidase, two independent insertions in the *tusE* sulfite reductase gene, and multiple IS*Aba11* and IS*Aba1* insertions in hypothetical genes.[102] These studies show that IS-mediated gene-disruption can promote antibiotic resistance in both clinical and experimental settings.

MOBILE GENETIC ELEMENTS CARRYING GENES THAT CONFER ANTIBIOTIC RESISTANCE

Many mobile genetic elements contain genes that directly encode for antibiotic resistance, including carbapenems, tetracyclines, macrolides, and aminoglycosides (summarized in Table 3). Resistance genes may

TABLE 3 Selected transposons and integrons that carry antibiotic resistance genes

Species	Genetic element	Resistance gene	Abx resistance	Reference
Acinetobacter NFM2 (prawn isolate)	Tn*402*-like class 1 integron-MITE structure	*sul*	Sulfonamide	154
Acinetobacter spp.	*IN86* with MITE sequences	bla_{IMP-1} *acc(6')-31* *addA1*	Aminoglycoside	155
Acinetobacter baumannii	Tn*2006* (IS*Aba1* flanks)	bla_{OXA-23}	Carbapenem	81
	Tn*2007* (IS*Aba4* flank)	bla_{OXA-23}	Carbapenem	81
	Tn*2008* (IS*Aba1* flank)	bla_{OXA-23}	Carbapenem	104
	Tn*2008B* (IS*Aba1* flank)	bla_{OXA-23}	Carbapenem	105
	Tn*2009* (IS*Aba1* flanks)	bla_{OXA-23}	Carbapenem	106
	Tn*6924*	bla_{NDM} *aph46*	Carbapenem Amikacin	103
	Tn*6020*	*aphA1*	Tobramycin	126, 127
	Tn*6080*	IS*Aba1*-bla_{OXA-51}	Carbapenem	115, 116
	Tn*6168*	*ampC*	Cephalosporins	60
	Tn*6250* (IS*Aba1* flanks)	*strA* *srtB* *sul2*	Streptomycin Sulphonamide	125
	Tn*6252* (IS*Aba1* flanks)	$bla_{OXA-236}$	Carbapenem	125
	Tn*125* (IS*Aba125* flanks)	bla_{NDM-1}	Carbapenem	118–121
	Tn*aphA6* (IS*Aba125* flanks)	*aphA6*	Aminoglycoside	122, 123
	IS*CR1*	bla_{NDM-1}	Carbapenem	138
	IS*CR2*	*sul2*	Sulfonamide	137
	IS*CR27*	bla_{NDM-1}	Carbapenem	43
	intI1 *intI2* *intI3*	*aac(3)-Ia* *dfrA15* *aac(6')-Ib* *dfrA17* *dfrA7* *aadA5*	Multiple	169
	Tn*402*-like class 1 integron-MITE structure	*sul* bla_{IMP-5}	Sulfonamide Carbapenem	47
	XerCD-*dif*, IS*Aba825*, Tn*aphA6*	bla_{OXA-58} *aphA6*	Carbapenem Aminoglycoside	151
	XerCD-*dif*	bla_{OXA-24}	Carbapenem	144–146
	XerCD-*dif*	bla_{OXA-72}	Carbapenem	124, 150
	XerCD-*dif*	*Tet39* *msrE* *mphE*	Tetracycline Macrolide	152
	Class 1 integron bound by IS*26*	*aadB* *aadA2*	Tobramycin Streoptomycin/ Spectinomycin	136
	p1AB5075 integron-like structure	*aadB*	Tobramycin	139
Acinetobacter bereziniae	Class 1 integron-MITE structure	*aacA7* bla_{VIM-2} *accC1*	Aminoglycoside Carbapenem	48
Acinetobacter pittii	Class 1 integron	bla_{IMP-1}	Imipenem	135
	XerCD-*dif*	bla_{OXA-72}	Carbapenem	135, 148, 149
	XerCD-*dif*	$bla_{OXA-207}$	Carbapenem	147

(Continues)

TABLE 3 (Continued)

Species	Genetic element	Resistance gene	Abx resistance	Reference
Acinetobacter johnsonii	Class 1 integron-MITE structure containing an IS*CR1* region	bla_{PER-1}	Carbapenem	48
	Tn*6681* containing degraded IS*Aba1* elements and intact IS*Aba14* elements in pFM-M19 plasmid	bla_{OXA-23}	Carbapenem	109

be located on the bacterial chromosome or on a plasmid and can be trapped by transposons or other elements and subsequently mobilized into new genomic sites or recipient bacteria.

Antibiotic-resistance genes as transposon cargo

Antibiotic-resistance genes often serve as cargo genes for transposons. Antibiotic exposure may positively select for transposons that carry resistance genes, contributing to the maintenance of the transposon in the genome. The growing rate of *A. baumannii* carbapenem resistance is thought to be mostly caused by the spread of two European clones that carry *bla* genes.[15] However, one study isolated a new clone carrying a novel transposon, Tn*6924*, that contained the cargo genes bla_{NDM}, a metallo-β-lactamase conferring carbapenem resistance, and multiple copies of *aph46*, an amikacin resistance gene.[103] As discussed in the following sections, most transposons found to carry antibiotic-resistance genes in *Acinetobacter* are composite transposons generated by IS*Aba* elements. These composite transposons are thought to contribute to the intermolecular spread of antibiotic-resistance genes, including mobilization between the genome and conjugative plasmids.

Composite transposons and IS aid in the mobilization of antibiotic-resistance genes

As discussed above, IS activation of β-lactamase gene expression is a major contributor to carbapenem resistance in *Acinetobacter*. These *bla* genes are sometimes carried in composite transposons comprised of flanking IS elements that can also activate the expression of the *bla* gene. Bla_{OXA-23} is an important carbapenem-resistance determinant that is typically carried in one of five transposon structures: Tn*2006*, Tn*2007*, Tn*2008*, Tn*2008B*, and Tn*2009* (reviewed by Nigro and Hall, 2016).[80,81,104–106] Of these, Tn*2006* and Tn*2009* are composite transposons and only Tn*2006* has been experimentally confirmed to be capable of transposition.[107] However, while Tn*2008* and Tn*2008B* only have a single copy of IS*Aba1*, their IS*Aba1*-bla_{OXA-23} units have been observed in multiple locations in the genome with a characteristic 9-basepair direct repeat, suggesting that they are capable of transposing and, therefore, leading to their designation as transposons.[105,108] Similarly, Tn*2007* has a single copy of IS*Aba4* associated with bla_{OXA-23} and flanked by direct repeats, suggesting that it transposed at some point.[81] Recently, *A. johnsonii* M19 was found to carry the bla_{OXA-23} gene in the composite transposon Tn*6681* which contained degraded IS*Aba1* elements and intact IS*Aba14* elements in the conjugative plasmid pFM-M19, which could be conjugated to *E. coli*.[109] However, the role of IS element promoters in conferring carbapenem resistance and the ability of the Tn*6681* transposon to mobilize have not been explored.

The prevalence of each transposon structure appears to vary by location. In two independent collections of isolates in China, only Tn*2008* was identified as carrying bla_{OXA-23}.[110,111] However, another study in China showed that the majority of bla_{OXA-23} was found within Tn*2006*,[112] suggesting that there can be significant variability within a geographic region. In a concerning finding, sequencing of *A. baumannii* isolates from Egypt identified the presence of bla_{OXA-23} in these composite transposon structures, one of which was inserted in the prophage phiOXA-A35 in 6/54 strains.[82] PhiOXA-A35 is identical to a prophage in *A. baumannii* ABUW-5075[113] that was originally isolated in the United States,[114] demonstrating that the prophage has been found in multiple geographic areas. Mitomycin C was used to induce phage, and purified phage particles were isolated carrying bla_{OXA-23} as determined by PCR,[82] suggesting the potential for phage-mediated spread of bla_{OXA-23}.

Similar transposon structures have been identified carrying other antibiotic-resistance genes. The IS*Aba1*-bla_{OXA-51} complex has also been found on plasmids in *Acinetobacter* spp., suggesting that it is capable of transposition and thus has been named Tn*6080*.[115,116] Cephalosporin-resistant *A. baumannii* isolates from Australia and the United States contained the composite transposon Tn*6168* which has flanking IS*Aba1*, one of which activates a copy of the β-lactamase gene *ampC*.[60] IS*Aba1* has been shown to promote *ampC* transcription as discussed above.[61–63,117] bla_{NDM-1} has been found flanked by IS*Aba125* to generate Tn*125* in a number of isolates.[118–121] Krahn *et al.* also demonstrated the transfer of Tn*125* to a susceptible strain, but it was likely due to phage transduction rather than transposon-mediated mobilization.[120] Another study found bla_{OXA-58} flanked by an IS*Aba3*-like element, suggesting that it may have been mobilized within a composite transposon structure.[84] Tn*aphA6* has IS*Aba125* flanks and carries the *aphA6* gene that confers resistance to aminoglycosides;[122,123] a circular form of Tn*aphA6* has been identified, suggesting that it could contribute to interbacterial aminoglycoside resistance spread.[124] A clinical isolate, LAC-4, was studied due to its status of MDR and two novel composite transposons, Tn*6250* and Tn*6252*, encoding genes for streptomycin and sulphonamide resistance and carbapenem resistance, respectively.[125] LAC-4 also encoded an additional genomic island 3 (GI3) flanked by novel IS element IS*Aba25* that contained an RND-type efflux pump system AdeIJK hypothesized to contribute to

broad antibiotic resistance.[125] Many other genomics studies have identified similar structures, which are too numerous to comprehensively cover here.

In one notable example, transposition and amplification led to the within-patient evolution of tobramycin resistance. Serial samples collected from the same patient identified multiple instances of amplification of Tn*6020*, which encodes *aphA1* flanked by direct repeat copies of IS*26*.[126,127] One isolate had a 15.2-kb region and led to ~6X amplification; however, in another isolate, the duplication relied on the replicative transposition of Tn*6020*, which then allowed amplification of ~65X.[127] Subsequent long-read sequencing analysis determined that the amplification likely occurred via a circular translocatable unit.[128] Similar mechanisms could be selected for *in vitro* in other *A. baumannii* strains[127] and have been observed for a plasmid-based replicon in which $bla_{\text{OXA-58}}$ flanked by IS*Aba2*, IS*Aba3*, and IS*26* was amplified and conferred carbapenem resistance.[129,130] Tandem duplication of antibiotic-resistance genes flanked by IS elements has been observed in other organisms leading to antibiotic heteroresistance, in which a subpopulation of bacteria are antibiotic resistant and can lead to treatment failure (as previously reviewed).[131] Therefore, the mechanism of transposition and gene amplification has potentially broad clinical implications. A study in *Acinetobacter baylyi* found that IS*1236*-mediated gene amplification events were inconsistent with homologous recombination, suggesting that these amplifications may utilize illegitimate recombination, perhaps from transposase-mediated DNA cleavage.[132] While this *A. baylyi* study investigated a different IS element, it provides insight into potential genetic mechanisms by which tandem duplication and amplification may lead to clinical antibiotic resistance in pathogenic *Acinetobacter*. Together, these examples suggest that composite transposons generated from IS element flanks are important mediators of antibiotic-resistance gene mobilization in *Acinetobacter*.

Class 1 integrons can promote antibiotic resistance by the acquisition of antibiotic-resistance genes

Integrons are site-specific recombination systems that can incorporate arrays of foreign genes into a bacterial genome, including antibiotic-resistance cassettes. *Acinetobacter* species often carry integrons associated with antibiotic resistance.[133] An early 2002 survey of integrons in clonally divergent Italian *A. baumannii* isolates identified identical class 1 integron structures encoding resistance to multiple antibiotics suggesting transfer of class 1 integrons between strains.[134] In another example, in a large collection of *Acinetobacter nosocomialis* and *Acinetobacter pittii* isolates from Taiwan, two *A. pittii* isolates had plasmids encoding class 1 integrons carrying the imipenemase-encoding $bla_{\text{IMP-1}}$.[135] Similarly, an IS*26*-bound class 1 integron resistance island carrying *aadB* (tobramycin resistance) and *aadA2* (streptomycin/spectinomycin resistance) was recently identified in a new genomic locus and named AbGRI4.[136] Many *A. baumannii* integrons are encoded in association with IS*91*-like "common regions" (IS*CR*) that form transposable units.[43] For example, *A. baumannii* strains carry IS*CR2* with *sul2* that confers sulfonamide resistance.[137] Some *A. baumannii* strains carry the IS*CR3* family member IS*CR27*, which may have mobilized the $bla_{\text{NDM-1}}$ progenitor to *A. baumannii*,[69] while IS*CR1* may have contributed to the subsequent mobilization of carbapenem resistance by $bla_{\text{NDM-1}}$.[138] These examples show that class 1 integrons can be important platforms for assimilation of antibiotic-resistance genes and contribute to antibiotic-resistance dissemination by transposition when they are part of IS*CR* families.

A 2020 study showed that duplication of a plasmid-encoded composite class 1 integron controls virulence switching in *A. baumannii* AB5075.[139] Prior to this study, *A. baumannii* AB5075 and many other recent clinical isolates were known to have a biphasic virulent/opaque (VIR-O) or avirulent/transparent (AV-T) colony phenotype in which VIR-O colonies are also more resistant to hospital disinfectant and host stresses.[140–142] Anderson *et al.* showed that a third class, a low-switching opaque variant, is controlled by the copy number of antibiotic resistance carrying composite integron on the plasmid p1AB5075, likely due to expression levels of a small RNA encoded within the *aadB* tobramycin-resistance gene.[139] Duplication of the composite integron also increases resistance to antibiotics, such as tobramycin,[143] suggesting that there may be a tradeoff between antibiotic resistance and the virulent/opaque phenotype.

XerCD-dif sites in *Acinetobacter* plasmids are associated with antibiotic-resistance acquisition

The site-specific recombination system XerCD-*dif* (also known as p*dif* sites when encoded in plasmids) is thought to similarly integrate arrays of foreign genes. XerCD-*dif* systems are present in most microorganisms with circular chromosomes and plasmids, and they resolve dimers generated through homologous recombination.[44] *dif* sites are typically encoded near the terminus of the chromosome and include short sequences recognized by XerC and XerD, separated by a 6–11 bp spacer.[44] In *Acinetobacter*, XerCD-*dif* sites often flank antibiotic-resistance genes on plasmids and are, therefore, associated with antibiotic-resistance acquisition (reviewed in Balalovski and Grainge 2020).[45] $bla_{\text{OXA-24}}$ was the first resistance determinant found in XerCD-*dif* sites in multiple plasmids.[144–146] Similarly, a $bla_{\text{OXA-24}}$ variant, $bla_{\text{OXA-207}}$, that has reduced catalytic efficiency but increased oxacillinase activity, was found flanked by XerCD-*dif* in a carbapenem-resistant *A. pittii* isolate in Spain.[147] $bla_{\text{OXA-72}}$ is also commonly found flanked by XerC and XerD sites in *A. pitti*[135,148,149] and *A. baumannii*.[124,150] In one study, multiple nonself-transferrable plasmids carrying XerCD-*dif* were found in *A. baumannii* AB242, one of which carried IS*Aba825*-$bla_{\text{OXA-58}}$ and a Tn*aphA6* transposon; these plasmids could be electroporated into *A. nosocomialis* where they were observed to carry out intramolecular rearrangements at the XerCD sites.[151] XerCD-*dif* sites flanking *tet39* tetracycline-resistance gene and *msrE* and *mphE* macrolide-resistance genes have also been identified, suggesting a role for XerCD-*dif* system in integrating these resistance determinants.[152] *A. baumannii* XerCD have been shown to be functional proteins,[153] emphasizing their likely role in integrating

new antibiotic-resistance genes. However, the exact mechanisms by which XerCD-*dif* sites integrate antibiotic-resistance genes and contribute to their dissemination in *Acinetobacter* remain to be fully elucidated.

MITEs appear to contribute to the mobilization of class 1 integrons carrying antibiotic-resistance genes

Multiple integron structures have been found flanked by MITEs in *Acinetobacter* spp. For example, the *Acinetobacter* strain NFM2 (related to *Acinetobacter johnsonii*) was isolated from an ocean prawn in Australia and found to encode an MDR cassette within a Tn*402*-like class 1 integron flanked by 439-bp MITEs.[154] *A. johnsonii* isolated from hospital sewage in China was found to contain the identical class 1 integron-MITE structure in the same genomic location, but also incorporating an IS*CR1* region and carrying a different antibiotic-resistance gene, specifically a β-lactamase gene bla_{PER-1}.[48] Interestingly, *A. baumannii* strain 65FFC was found to encode an IMP-5 β-lactamase within an identical class 1 integron-MITE structure, but in a different genomic context.[47] Similarly, *A. bereziniae* strain 118FFC has a class 1 integron with *aacA7*-bla_{VIM-2}-*aacC1* but in the genomic context of disrupting an IS*26 tnpA* gene.[48] Portions of the MITE sequences were also found in *Acinetobacter* clinical isolates from soft tissue and bloodstream infections that carried a class 1 integron, In*86*, carrying bla_{IMP-1}, *aac(6′)-31*, and *aadA1*.[155] *Acinetobacter* class 1 integron-MITE has not been experimentally demonstrated to be capable of transposition, but a similar structure in *Enterobacter cloacae* has been demonstrated to transpose.[156] Together, these findings suggest that the Tn*402*-like class 1 integron-MITE structure can incorporate different antibiotic-resistance cassettes and transpose within the *Acinetobacter* genus.

CONJUGATIVE MOBILE GENETIC ELEMENTS AND THE INTERBACTERIAL SPREAD OF ANTIBIOTIC-RESISTANCE GENES

Conjugative mobile genetic elements are a major mechanism by which antibiotic-resistance genes are spread horizontally between strains and species. There are many examples of antibiotic resistance spread by conjugative mobile genetic elements that have been previously reviewed,[157,158] and, therefore, we will only briefly cover a few recent examples here (summarized in Table 3).

Conjugative plasmids aid in the dissemination of antibiotic-resistance genes

Conjugative plasmids are thought to be a large contributor to the interbacterial spread of antimicrobial resistance genes in *Acinetobacter*. For example, XDR *A. baumannii* were shown to be capable of transferring kanamycin resistance to susceptible environmental *Acinetobacter* strains on the GR6 conjugative plasmid.[159] Interestingly, a 2020 survey of *A. baumannii* plasmids found that only 35% of plasmids carried antibiotic resistance and that gene flux between plasmids was primarily associated with IS elements and transposons.[160] Nested elements, such as plasmids carrying IS elements and transposons, may, therefore, be significant contributors to the intermolecular spread of antibiotic-resistance genes. For example, the carbapenem-resistant isolate *A. baumannii* A85 carries a bla_{OXA-23} gene on a conjugative plasmid within the AbaR4 transposon, which is a composite structure of the Tn*2006* structure (which has flanking IS*Aba1* elements) inserted in Tn*6022*; this conjugative plasmid was shown experimentally to be capable of transferring carbapenem resistance to susceptible strains.[161] Similarly, Tn*2006* has been observed to be colocalized with Tn*aphA6* in a large conjugative plasmid in *A. baumannii* isolate D46.[162] More recently, the transposon Tn*6681* was found encoded on the pFM-M19 plasmid, which was demonstrated to be capable of conjugation and conferring carbapenem resistance to *E. coli* demonstrating intergenus transfer.[109] In a study of Bolivian *A. baumannii* hospital isolates, each was found to contain antibiotic-resistance genes on plasmids, both with and without additional mobile genetic elements.[163] The spread of antibiotic-resistance genes between isolates and species suggests that new modes of surveillance may be required to track these plasmid-based outbreaks.

Conjugative plasmids and fitness tradeoffs

In addition to carrying antibiotic-resistance genes, conjugative plasmids have been shown to encode strategies to balance antibiotic resistance and interbacterial competition. Weber *et al.* found that some MDR isolates of *A. baumannii* contain a conjugative plasmid that encodes negative regulators of the type VI secretion system (T6SS) as well as antibiotic-resistance genes.[164] Within this population, some bacteria undergo spontaneous loss of the large conjugative plasmid which then allows for the T6SS-mediated killing of competing bacteria but the loss of antibiotic resistance.[164] Others maintain the plasmid that confers resistance and represses the T6SS, therefore, creating a tradeoff between bacterial warfare and antibiotic resistance.[164] Another study showed that these conjugative plasmids must suppress their own T6SS in order to allow for successful conjugation to other cells due to requiring close cell–cell proximity.[165] These studies demonstrate the multifaceted effects of conjugative plasmids and the tradeoff between bacterial competition and antibiotic resistance.

To protect against spontaneous plasmid loss, some strains have integrated plasmid DNA into their chromosomes to preserve resistance genes. In isolates of *Acinetobacter calcoaceticus* subspecies *anitratus*, the plasmid RP4 codes for resistance to multiple antibiotics.[166] However, the RP4 plasmid cannot be maintained stably in the host, making integration of RP4 plasmid DNA into the host genome necessary to introduce a stable antibiotic-resistance gene.[166] Therefore, while conjugative plasmids may encode many resistance genes and systems used to defend the host cell, competition and spontaneous plasmid loss pose fitness tradeoffs and challenges for bacteria.

Conjugative transposons facilitate the dissemination of antibiotic resistance

In addition to large conjugative plasmids, some families of transposons are capable of conjugation independent of plasmids. In some cases, these transposons are capable of conjugation but require other host factors to do so. Nonautonomous conjugative transposons rely on a bacterial protein RecA or RecO to form the circular intermediate required for receiving a transfer.[52] One study found that *Acinetobacter baylyi* required RecA to receive exogenous circular DNA in the form of transposon Tn*1*,[167] indicating that host bacterial factors may be required to confer antibiotic resistance offered by some transposons. These studies demonstrate the potential of conjugative transposons to contribute to the ongoing health crisis of antibiotic-resistance dissemination.

CONCLUSIONS

Over the past few decades, rates of infection by MDR *Acinetobacter* have continued to increase. Infections by antibiotic-resistant bacteria pose a grave threat to human health due to the lack of available treatment options. Therefore, it is critical to understand not only the molecular mechanisms of antibiotic resistance but also how bacteria use natural genetic plasticity to acquire and disseminate resistance. The genomic characterization of *Acinetobacter* clinical isolates has led to important discoveries linking antibiotic resistance to mobile genetic elements. Mobile genetic elements can promote high levels of genetic diversity, bacterial fitness, and antibiotic resistance to environmental strains and human pathogens alike. While mobile genetic elements commonly confer antibiotic resistance by encoding resistance genes, they can also alter the expression of native bacterial genes to promote antibiotic resistance. In *Acinetobacter* specifically, IS elements play a major role in promoting carbapenem resistance by providing strong promoters to β-lactamase genes.

Additional work to characterize the molecular features of IS element transposition, integron function, and the mechanisms of XerCD-*dif* sites in *Acinetobacter* plasmids may shed light on how these elements contribute to the evolution of antibiotic resistance in *Acinetobacter*. The use of techniques, such as long-read sequencing, will also aid in the identification of tandem duplications of mobile elements. Long term, understanding the molecular mechanisms of how mobile genetic elements promote antibiotic resistance in *Acinetobacter* may lead to the development of improved surveillance and treatment. IS element transposition has been shown to lead to antibiotic-resistance evolution within patients receiving treatment;[65,127] therefore, a better understanding of these mechanisms may also lead to the development of therapeutics to prevent resistance development during the course of antibiotic treatment. For example, understanding the genetic and biochemical mechanisms leading to gene amplification and antibiotic heteroresistance may help identify pathways to target this important clinical problem. In summary, mobile genetic elements contribute to antibiotic-resistance acquisition and dissemination by multiple mechanisms in *Acinetobacter* species. A better understanding of the molecular features controlling mobile genetic element-mediated antibiotic resistance in *Acinetobacter* may lead to improved surveillance and treatment of this important public health threat.

AUTHOR CONTRIBUTIONS

H.R.N. and L.D.P. conceptualized the review. All authors drafted and edited the manuscript. J.R.P. generated tables. H.R.N. and L.D.P. generated the figures.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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