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Review

Class 1 Integrons, Gene Cassettes, Mobility, and Epidemiology

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Abstract Integrons are genetic elements that, although unable to move themselves, contain gene cassettes that can be mobilized to other integrons or to secondary sites in the bacterial genome. The majority of approximately 60 known gene cassettes encode resistance to antibiotics. Recently, a number of gene cassettes encoding extended-spectrum β-lactamases or carbapenemases have been described. Up to at least five cassettes may be present in an integron, which leads to multiresistance. Frequently, more than one integron is observed within the same bacterial cell. Integrons are widespread in their species distribution. Although integrons are normally reported from *Enterobacteriaceae* and other gram-negative bacteria, an integron has been described in *Corynebacterium glutamicum*, a gram-positive species. The gene cassette in this integron showed even higher expression when compared to the expression in *Escherichia coli*. Integrons have been reported from all continents and are found frequently. The widespread occurrence of integrons is thought to be due to their association with transposon plasmids, conjugative plasmids, or both. Integrons form an important source for the spread of antibiotic resistance, at least in gram-negative bacteria but also potentially in gram-positive bacteria. The aim of this review is to describe the versatility of integrons, especially their mobility and their ability to collect resistance genes.

Introduction

The present-day definition of integrons was formulated by Hall and Collis [1]. Integrons are elements that contain the genetic determinants of the components of a site-specific recombination system that recognizes and captures mobile gene cassettes. An integron includes the gene for an integrase (*int*) and for an adjacent recombination site (*attI*). Gene cassettes are not necessarily part of the integron, but when integrated, they become part of the integron. Expression of the integron relies on the promotor in the integron (P_{ANT}); thus, the promotor is part of the integron. Three classes of antibiotic-resistance-encoding integrons have been described. Each class has its own integrase. The majority of integrons described belong to class 1 and are associated with *sulI* (Figure 1). Class 2 integrons are embedded in Tn*7*-family transposons [1, 2]. Only one example of a class 3 integron is known [3, 4].

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Gene Cassettes

Gene cassettes consist of one coding sequence. At the 3′ end of this sequence, a so-called 59-base element is located. Gene cassettes may also contain a variable number of non-translated nucleotides. Most gene cassettes lack a promotor in front of the coding sequence (see the section "Expression" for details). The structure and function of the 59-base element, which has a variable length (Table 1), will be discussed in the section "Gene Cassette Mobility".

Currently, at least 59 gene cassettes are known (Table 1). Most of these gene cassettes encode proteins involved in resistance to antibiotics. At least two cassettes are involved in resistance against quarternary ammonium compounds, which are frequently used as

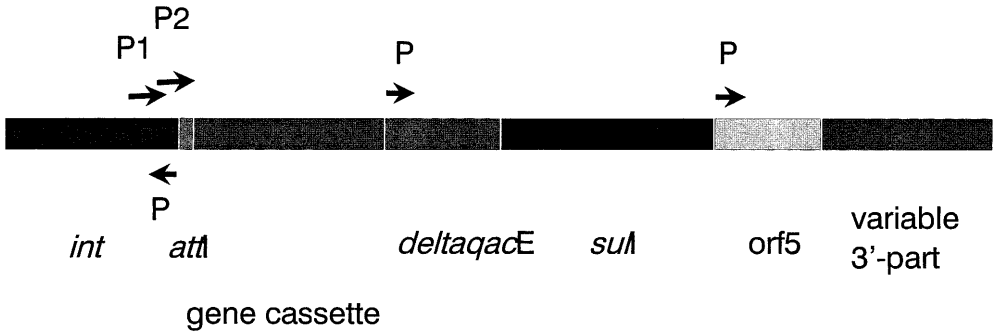

Figure 1 Schematic representation of a class 1 integron. See text for details

disinfectants and antiseptics. The function of the products encoded by at least six open reading frames (ORFs) located on gene cassettes is unknown.

Gene cassettes encoding resistance against antibiotics cover a wide range of antibiotics and antibiotic classes. Resistance to β-lactam antibiotics is caused not only by classical β-lactamases but also by extended-spectrum β-lactamases encoded by, amongst others, *oxa*-type genes. A carbapenemase encoded on a gene cassette also has been described. These β-lactamases have a zinc atom at their active center instead of a serine, as in most β-lactamases. Another group of important resistance genes present in integrons encodes resistance to aminoglycosides. At least 15 different gene cassettes have been described previously. Resistance to trimethoprim is encoded by at least eight different gene cassettes. Resistance to chloramphenicol is encoded either by one of seven gene cassettes encoding a chloramphenicol acetyltransferase or by one of the three known efflux pumps. Resistance to rifampin and erythromycin encoded on gene cassettes has also been described. Remarkably, most gene cassettes encode resistance against antibiotics that have been in use for a relatively long time. However, gene cassettes encoding resistance against newer antibiotics, like bla_{IMP}, bla_{VEB-1}, *oxa15*, *oxa19*, *oxa20* and *oxa21*, have also been described [5–10].

Integron Structure

Class 1 integrons include the gene for an integrase (*int*) and an adjacent recombination site (*attI*). Gene cassettes are not necessarily part of the integron, but when integrated, they become part of the integron. Expression of the integron relies on the promotor in the integron (P_{ANT}) and thus the promotor is part of the 5′-conserved segment of the integron. In fact, the P_{ANT} of class 1 integrons potentially contains two promotors, P1 and P2 (see the section "Expression"). The 3′ side of class 1 integrons is less defined. Most class 1 integrons have the so-called 3′-conserved segment [9, 11]. This segment includes a *ΔqacE* and a *sulI* gene and ORF5 (Figure 1). In addition, other sequences may be conserved between some integrons, but not all [12]. Duplications of the *sulI* gene in the 3′-conserved segment have been described for integrons In6 and In7 [13, 14].

The gene cassettes are integrated between the 5′- and 3′-conserved segments. The number of gene cassettes can vary between 0 for In0 [15] and at least five [16, 17]. Numerous different combinations of gene cassettes have been reported [9, 11, 13, 18–26]. Multiple copies of gene cassettes in an integron have also been described, such as the two copies of *oxa2* in In1 [27]. The reported sequences show minor differences, making it unlikely that duplication was involved.

Gene Cassette Mobility

The mobility of cassettes is mediated by the *intI1* gene, encoded IntI1. The IntI1 protein belongs to the family of integrases.The IntI1 protein possesses the three characteristic amino acids for this family of proteins, and mutation of these amino acids leads to reduced catalytic activity [28, 29].The integrase excises the gene cassettes as covalently closed supercoiled circular molecules [30]. Most likely, these circular cassettes can also be integrated. In fact, deletions, duplications and rearrangements of gene cassettes in integrons have been observed [31]. The formation of cointegrates between plasmids may also contribute to gene cassette exchange [32]. In this process, but also in integrase-mediated gene cassette exchange, the *upv1* gene from plasmid R46, which encodes a resolvase, may play a role [33, 34]. In fact, the *res* site recognized by the resolvase during cointegrate resolution lies partly within the outer boundary of the 5′CS, and the *upv1* gene is located nearby. Cointegrate formation by the integrase has been observed between integron-bearing plasmids [32]. Besides the integrase, the *attI* and 59-base elements are involved in gene cassette movement.

The 59-base elements (also known as *attC*) are not highly conserved and vary considerably in length (Table 1) [35–37]. They contain imperfect inverted repeats with two 7 bp core regions. The consensus for the LH (or left-hand) end is RYYYAAC and for the RH (or right-hand) end GTTRRRY [31, 35]. The

Table 1 Characteristics of class 1 integron gene cassettes

Gene[a]	Protein	Length of CDS[b]	Length of 59-base element	Gene cassette[c] length	Accession no.	Reference no.
Resistance to β-lactam antibiotics						
blaP1	PSE-1/CARB-2[d]	915	111	1044	Z18955	80
blaP2	–	915	111	1044	D13210	–
blaP3	CARB-4	867	>92	>1023	U14749	81
bla_{IMP}	IMP-1	741	127	880	D50438	5, 17
bla_{ESP}	ESP	741	–	880	D78375	82
bla_{VEB-1}	VEB-1	897	133	1059	AF010416	8
oxa1	OXA-1	831	90	1004	J02967	62
oxa2a	OXA-2	828	70	876	M95287	22, 27, 35, 83–86
oxa2b	OXA-2B	828	70	876	M95287	22, 27, 35, 83–86
oxa3	OXA-3	828	>56	>861	L07945	87
oxa5	OXA-5	804	106	915	X58272	88
oxa7	OXA-7	801	65	874	X75562	89
oxa9	OXA-9	840	69	840	M55547	90, 91
oxa10	OXA-10(PSE-2)	801	111	920	U37105	92
oxa15	OXA-15	–	–	–	U63835	6
oxa19	OXA-19	–	–	–	AF043381	10
oxa20	OXA-20	798	117	953	AF024602	9
oxa21	OXA-21	828	–	–	Y10693	7
Resistance to aminoglycosides						
aadA1a	AAD(3″)	792	60	856	X12870	93
aadA1b	AAD(3″)	792	60	856	M95287	22, 27, 35, 83–85
aadA2	AAD(3″)	780	60	856	X68227	52, 94
aadB	AAD(2″)	534	60	591	L06418	13, 14, 37, 84, 95
aac(6′)-Ia[e]	AAC(6′)-Ia	558	–	>778	M18967	95
aac(6′)-Ib	AAC(6′)-Ib	555	70	637	M55547	77, 90, 91, 96
aac(6′)-Id	AAC(6′)-Id	450	72	526	X12618	97
aac(6′)-Il	AAC(6′)-Il	521	109	720	–	98
aac(6′)-Iq	AAC(6′)-Iq	551	108	712	AF047556	99
aacA7	AAC(6′)-I	459	112	591	U13880	25
aac(6′)-IIa	AAC(6′)-IIa	555	60	628	M29695	100
aac(6′)-IIb	AAC(6′)-IIb	543	97	653	L06163	–
aac(3)-Ia	AAC(3)-Ia	465	109	577	X15852	77, 101
aac(3)-Ib	AAC(3)-Ib	465	>34	>498	L06157	102
aac(3)-VIa	AAC(3)VIa	901	–	–	–	103
Resistance to trimethoprim						
dfrA5	DHFRV	474	87	568	X12868	93
dfrA7	DHFRVII	474	134	617	X58425	2, 64, 104
dfrA12	DHFRXII	498	90	584	Z21672	63, 105
dfrA14	DHFRIb	483	>43	>523	S76821	106
–	DHFRXV	474	84	593	Z83311	20
dfrB1	DHFRIIa	237	57	485	U36276	–
dfrB2	DHFRIIb	237	57	384	J01773	107
dfrB3	DHFRIIc	237	57	408	X72585	2
Resistance to chloramphenicol						
catB2	CATB2	633	72	739	M80188	26
catB3	CATB3	633	60	739	U13880	25
catB5	CATB5	633	>25	>677	X82455	–
catB6	CATB6	633	77	730	AJ223604	17
cmlA	CmlA	1260	70	1549	U12338	16, 13, 24, 31, 35, 101
cmlA2	CmlA2	1434	68	–	–	108
cmlB	CmlB	–	–	–	–	109
Resistance to quarternary compounds (disinfectants and antiseptics)						
qacE	QacE	333	141	587	X72585	2
qacF	QacF	–	–	–	–	108
qacG	QacG	333	94	532	AJ223604	17
Resistance to rifampin						
arr-2	ARR-2	453	114	663	AF078527	109
Resistance to erythromycin						
ereA	EreA	–	–	–	–	Fluit, personal observation

Table 1 Continued

Gene[a]	Protein	Length of CDS[b]	Length of 59-base element	Gene cassette[c] length	Accession no.	Reference no.
Unidentified ORFs						
orfA	–	435	69	501	J01773/X12869	93, 107
orfC	–	378	60	507	X17477	110
orfD	–	291	60	320	M95287	84
orfE	–	246	60	262	U12338	16, 13, 24, 31, 35, 101
orfF	–	291	60	320	–	–
orfN	–	615	77	689	AJ223604	17

[a] Gene names may differ from the name given in the original publication
[b] The initiation codon is not always known; in these cases, generally the first initiation codon is assumed functional
[c] Gene cassette sizes are not always accurate [36]
[d] The genes for PSE-4 and CARB-3 differ in one nucleotide from the *blaP1* sequence
[e] The *aac(6′)-Ia* gene cassette contains an ORF (orfG) as well, followed by a 59-base element [36]
CDS, coding sequence; –, no data available; ORFs, open reading frames

recombination occurs close to one end of the 59-base element between the G and T residue of the consensus sequence GTTRRRY [30, 35, 38]. Due to the integration of a circular gene cassette, part of the 59-base element ends up at the 5′ side of the coding sequence of the gene cassette to which it belongs [30, 35]. In principle, integration can take place at the boundary of any two gene cassettes using two 59-base elements or between the 59- base element of the circular gene cassette and the *attI1* site [31, 32, 35, 39, 40], but the interaction between the 59-base element and the *attI1* site is preferred [30]. The *attI1* site, located at the 3′end of the 5′CS, is less complex than the 59-base element but has its 7 base core region GTTRRRY at the recombination cross-over point [39].

The IntI1 protein has been demonstrated to bind to both the *attI1*-site and the 59-base element. Binding to the first site is considerably stronger than to the second site. The *attI1* site contains two IntI1 binding sites. The first is a 14 bp sequence located 24–37 bp to the left of the cross-over site. The second site, which is a much weaker binding site, is an imperfect repeat of the first and is located 41–55 bp to the left of the cross-over-point. Mutational analysis showed that a single base pair change accounts for the difference in binding strength [28]. Recently, similar results were reported by Gravel et al. [41], although differences exist. It was shown that up to four integrase molecules appear to be able to bind to the *attI1* site. GTTA or GTTG sequences (also found as part of the core region) play an important role in this process, but it is not clear whether all four sites are necessary for recombination. The importance of a strong binding site for in vivo recombination has been demonstrated earlier by Recchia et al. [39], although Hansson et al. [42] found slightly different sites required for in vivo recombination. On the 59-base element, binding occurs putatively to the core regions at the LH and RH regions. In addition, two more putative binding sites have been identified. One is to the right of the LH core region and the other to the left of the RH core region [38].

Besides the recombination described above, recombination between one specific site and a secondary site has been demonstrated. This reaction can be mediated by either the Tn*21* integrase or the integron integrase IntI1 when the integration sites conform to the consensus sequence GWTMW or GNT, respectively [39, 43–47]. Recombination to a secondary site is infrequent but is more frequent when the consensus sequence is present as an inverted repeat separated by a few base pairs [47]. Potentially, this may lead to the integration of gene cassettes at locations outside the integron. However, the lack of a second specific site at this location will prevent excision.

The stability of gene cassette order and integrons is not clear. Martinez-Freijo et al. [48] reported three predominant types of integron in *Enterobacteriaceae* from ten different European hospitals. Sequencing revealed that the four integrons of the first type contained only the strong promotor, whereas eight of nine type 2 integrons used the weak and active P2 combination. The eight integrons of the third type likewise used the weak or the weak promotor and active P2 combination. Induction of changes with antibiotics did not succeed. These data suggest that, at least in European hospitals, integrons are rather stable structures.

Collis and Hall [31, 49] easily achieved the exchange of gene cassettes. These data suggest that, at least under certain circumstances, the order of the gene cassettes may change under antibiotic pressure.

Expression

The gene cassettes in an integron are expressed from a common promotor region located in the 5′CS of the

integron. The promotor region contains two potential promotors called P1 and P2. Four different P1 and two different P2 promotors have been described [22, 25] (Table 2). Levesque et al. [50] and Collis and Hall [49] also assessed the strength of these promotors relative to the derepressed *Escherichia coli tac* promotor. The strong version of the P1 promotor is six times more effective than the *tac* promotor, but the *tac* promotor is more efficient than the weak and hybrid promotors. The P2 promotor, with a spacing of only 14 nucleotides, is probably inactive because this spacing is unfavourable to expression, the optimum spacing being approximately 17 nucleotides. The weak and active second promotor initiates transcription three times more efficiently than the *tac* promotor. Therefore, the P2 promotor with this spacing is believed to be active, although its relative strength is unknown. The hybrid 1 and strong P1 promotors have only been found in combination with the inactive form of P2. Both the weak and the strong promotors have been described in association with the active form of P2.

The results are in agreement with data from Collis and Hall [49]. They also demonstrated that the position of the gene cassette in the integron determined the level of resistance observed. The highest level of resistance for a gene cassette was obtained when the gene cassette was located directly behind the 5′CS. Northern blots showed multiple transcripts originating from P1. Only longer transcripts contained sequences from the more distal gene cassettes. Apparently, premature termination of transcription occurs within the gene cassettes, and the 59-base elements may act as transcriptional terminators.

The start codons of many gene cassettes have not been determined, but the first in-frame start codon is generally assumed to function as such [51]. This codon often is located close to the 5′end of the gene cassette, and the supposed ribosome binding sites are weak at best. However, in the *aadA2* gene cassette, for example, the second start codon is used. This codon also has a suitable ribosome binding site upstream [52].

Besides the common arrangement where the gene cassettes are transcribed from a common promotor region, some gene cassettes appear to carry their own promotor sequences. The first gene cassette with its own promotor described was the chloramphenicol resistance determinant *cmlA* [16, 24]. The regulatory region includes a nine amino acid leader peptide, a potential ribosomal stall sequence, and two alternative stem-loop structures that may open up or close off the ribosome binding site and start coding preceding the coding sequence. In addition to the promotor sequence, potential translation attenuation signals were found [16]. The *qacE* and *qacG* gene cassettes carry their own promotor sequences as well [11, 17, 53].

Table 2 The integron promotors P1 and P2 –35 and –10 sequences, the separation of these sequences, and the relative strength of the promotors

Promotor	–35 region	–10 region	Spacing (nucleotides)	Strength
P1	TTGACA	TAAACT	17	strong
	TGGACA	TAAGCT	17	weak
	TGGACA	TAAACT	17	hybrid 1
	TTGACA	TAAGCT	17	hybrid 2
P2	TTGTTA	TACAGT	14	inactive
	TTGTTA	TACAGT	17	unknown

Integron Epidemiology

Only a few studies have made systematic surveys of integron distribution. One of the first studies was by Sallen et al. [54], who systematically screened 49 isolates from one location in France and showed integrons in 59% of the isolates belonging to six different species of *Enterobacteriaceae*. Some of these isolates carried multiple integrons. A Chilean study [55] investigated *Acinetobacter baumannii* isolates in which 17 integron-carrying isolates were found. Remarkably, the majority of the isolates carried the Tn*7* type integron, and 14 isolates carried both types of integron. Class 1 integrons are also prevalent among German blood isolates. Schmitz et al. [56] tested 278 consecutive blood isolates belonging to 11 different gram-negative species. Thirteen percent of these, belonging to six species, were shown to carry an integron.

Jones et al. [57] described a similar result for the Netherlands. Of 135 strains belonging to seven species of *Enterobacteriaceae*, more than half carried an integron. In addition to the high prevalence of integrons, many of the isolates carried multiple integrons (unpublished observation). This situation can be more or less extended to the rest of Western and Central Europe [58]. Screening of 163 strains of 13 species of gram-negative bacteria from nine countries showed that 42% of the strains carried an integron. The latter study also showed that integron-carrying strains tend to show resistance to a larger number of different antibiotics than strains without an integron. However, integron-related gene cassettes are not limited to gram-negative bacteria. A survey by Kazama et al. [59] demonstrated the presence of *qacEΔ1* in both staphylococcal and enterococcal isolates. Besides being found in isolates from humans, integrons are also found in gram-negative isolates from primates [60].

All these data suggest that integrons are common worldwide, especially in *Enterobacteriaceae*, and that they contribute to resistance.

Although integrons themselves are not mobile, they are sometimes found as part of transposons. Class 1 inte-

grons are found in Tn*21* and Tn*21*-related transposons [26, 61–64]. These transposons generally are located on plasmids. The location of transposons on potentially mobile plasmids further enhances the spread of gene cassettes. However, integrons are also found in many different locations. This finding strongly suggests that integrons are moved around, although they lack obvious enzymatic machinery to do so. Sequence data showed the presence of imperfect 25 base pair repeats flanked by 5 bp direct repeats at the boundaries of the integron in Tn*21* [65, 66]. These 25 base pair repeats were also detected at the 3′ end of integrons from various locations [2, 13]. Kholodii et al. [67, 68] observed strong homology of these and other sequences with sequences involved in the transposition of Tn*5053* from a *Xanthomonas* isolate from a mercury mine. The transposition genes of this transposon are closely related to the putative transposition genes from Tn*21* and Tn*5090* of plasmid R571, both of which carry an integron [2, 67]. In fact, Radström et al. [2] propose that integrons are transposons or at least transposon derivatives. Evidence for this suggestion was actually provided by Brown et al. [69], who showed that integrons In0, In2 and In5 are defective transposons. Kholodii et al. [67] suggested that the transposition of Tn*5053* may therefore provide a paradigm for the diverse locations where integrons are found.

Integron Evolution

The origin of gene cassettes is unknown. As noted, gene cassettes generally lack a promotor and contain a 59-base element, but how this combination arose is unknown. A likely explanation for the absence of a promotor would be that the cassettes arose via reverse transcription from mRNA [70]. This explanation requires the existence of a yet-unknown reverse transcriptase, but bacterial reverse transcriptases have been described [71].

The origin of the antibiotic resistance genes is also subject to speculation. Some resistance gene families, like the dihydrofolate reductase B family, are found only in combination with a 59-base element, suggesting a pool of antibiotic resistance genes different from the pool of resistance genes that are not linked to gene cassettes. However, the ability of gene cassettes to integrate at secondary sites complicates the tracing of the origin of the resistance genes.

The 59-base elements do not appear to be unique for gene cassettes in integrons: closely related elements were described in *Vibrio cholerae* by the groups of Roy (personal communication), Mazel et al. [72] and Recchia and Hall [70]. These 123–126 bp sequences, known as *Vibrio cholerae* repetitive DNA sequences (VCRs), are present in up to 100 copies in a part of the genome that appears to consist of arrays of single genes. It is not clear whether these VCRs are functional in the integration of the genes, but the potential integrase gene for these gene cassettes has been described [72]. Interestingly, a class 1 integron has been reported for *Vibrio cholerae* [73].

Since the 59-base elements cluster into different families, it has been speculated that these elements were attached to the reverse transcribed mRNA at some later point, but other possibilities certainly cannot be excluded. Originally, the 59-base elements may have originated from transcription terminators, which have inverted repeats, from inverted repeat sequences like REP and ERIC, which are scattered throughout the genomes of many bacterial species, or from tRNAs, whose genes often contain integrase recognition sites such as *attB* of lambdoid phages [70].

Not only the origin of gene cassettes is unknown but also how the conserved segments evolved. The *ΔqacE* and *sulI* genes may be remnants of gene cassettes. The evolution of the 5-conserved segment containing the integrase gene, the gene cassettes promotor(s) and the *att* site is less clear. The development of different promotor sequences that give rise to different levels of expression is especially intriguing [50].

Class 1 integrons were long believed to exist only in gram-negative bacteria, but recently the presence of a class 1 integron in *Corynebacterium glutamicum* was described. This integron differed in only two nucleotides from In6. One substitution was in the only gene cassette of this integron, *aadA2a*, the other in the -10 region of the promotor. This mution enhanced expression five times in both *Corynebacterium glutamicum* and *Escherichia coli* when compared to the original sequence [74]. This indicates that class 1 integrons also can be functional in gram-positive bacteria and that single point-mutations in the promotor region may increase the expression of the gene cassettes, potentially leading to higher levels of resistance. Bissonnette and Roy [15] proposed an evolutionary tree from the ancestral integron to the plethora of integrons observed today, but the value of this evolutionary tree can be questioned because of the potential for mobility of gene cassettes. Sundstrom [75] proposed a complete network for the exchange of gene cassettes extending into eukaryotes.

Although the origin of integrons and gene cassettes is still unclear, evidence has been provided that integrons continue to evolve. Remarkably, most integrons carry gene cassettes encoding resistance to the older antibiotics. However, gene cassettes encoding resistance against newer antibiotics, like bla_{IMP}, $bla_{\mathrm{VEB\text{-}1}}$, *oxa15* and *oxa21*, have also been described [5–8]. Apparently, new resistance genes against new generations of antimicrobial agents can still be recruited to the gene cassette pool or arise by mutation.

Concluding Remarks

Integrons are widespread versatile genetic elements, although they are not independently mobile. Their ability to integrate gene cassettes and especially gene cassettes encoding resistance to antimicrobial agents makes them prime pools for the further dissemination of antibiotic resistance. Since many integrons possess more than one antibiotic resistance-conferring gene cassette and are often located on genetic elements that carry other resistance determinants, selection for one antimicrobial resistance determinant selects for many. The association of these integrons with plasmids that confer the extended-spectrum β-lactamase phenotype on *Enterobacteriaceae* is an example [76, 77]. This makes these integrons even more dangerous to infected patients. Luckily, gene cassettes encoding resistance to the newest generations of antibiotics are still rare. The latest generation of antimicrobial agents may provide a line of defense against these bacteria, but can susceptibility to the older antibiotics be restored? Experiments by Chiew et al. [78] suggest it cannot be restored. Perhaps integrons offer one advantage: they make very convenient vectors in genetic engineering [79].

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