Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: Mechanisms and epidemiology

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Multidrug resistance is quite common among non-fermenting Gram-negative rods, in particular among clinically relevant species including *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* These bacterial species, which are mainly nosocomial pathogens, possess a diversity of resistance mechanisms that may lead to multidrug or even pandrug resistance. Extended-spectrum β-lactamases (ESBLs) conferring resistance to broad-spectrum cephalosporins, carbapenemases conferring resistance to carbapenems, and 16S rRNA methylases conferring resistance to all clinically relevant aminoglycosides are the most important causes of concern. Concomitant resistance to fluoroquinolones, polymyxins (colistin) and tigecycline may lead to pandrug resistance. The most important mechanisms of resistance in *P. aeruginosa* and *A. baumannii* and their most recent dissemination worldwide are detailed here.

1. Introduction

The emergence and spread of bacteria resistant to multiple antibiotics and at the origin of severe infections is currently of great concern. This is particularly true for nosocomial pathogens isolated in hospitals, where these superbugs may compromise advanced medicine, including surgery, transplantation, efficient treatment of immunocompromised and haematological patients, etc. Among the increasingly reported and commonly identified multidrug-resistant or even pandrug-resistant bacteria, the lactose-non-fermenting Gram-negative pathogens *Acinetobacter baumannii* and *Pseudomonas aeruginosa* occupy an important place. These bacterial species are quick to become multidrug-resistant owing to their additional intrinsic resistance mechanisms. They are responsible for hospital-acquired infections (bloodstream, urinary tract, pulmonary and device-related infections) and are frequently isolated from immunocompromised patients hospitalised in the intensive care unit. Resistance to multiple antibiotic classes, and notably to the β-lactam cephalosporins and carbapenems, is on the

rise worldwide. In this review, the emerging antibiotic resistance mechanisms in *A. baumannii* and *P. aeruginosa* are highlighted, with a special focus on the most prescribed antimicrobial agents, i.e. β-lactams, aminoglycosides and fluoroquinolones.

2. Resistance to β-lactams

2.1. Class A β-lactamases

2.1.1. Extended-spectrum β-lactamases (ESBLs)

The class A ESBLs confer resistance to expanded-spectrum cephalosporins and are inhibited in vitro by clavulanic acid and tazobactam [1]. They have been extensively identified in members of the Enterobacteriaceae family but are also reported from non-fermenters.

2.1.1.1. Acinetobacter baumannii. The most common ESBLs described in *A. baumannii* are the PER-, GES- and VEB-type β-lactamases. The first ESBL identified in *A. baumannii* was PER-1, being later widely detected in Turkey [2]. PER-1-producing *A. baumannii* are also considered to be widespread in South Korea [3], Hungary [4], Romania [5], Russia [6], Belgium [7] and the USA [8]. They have also been identified in Bulgaria, India, China, Iran and Kuwait [9–13] (Table 1). In *A. baumannii*, the *bla*PER-1 gene is part of a composite transposon named Tn*1213*, bracketed by two different insertion sequences (IS*Pa12* and IS*Pa13*) sharing similar

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Table 1
Ambler class A extended-spectrum β-lactamases (ESBLs) known in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

β-Lactamase	Host	Genetic support[a]	Country of isolation	Reference(s)
PER-1	*Acinetobacter baumannii*	C, P	Turkey	[2]
		C, P	South Korea	[3]
		?	Hungary	[4]
		C	Romania	[5]
		C	Russia	[6]
		C	Belgium	[7]
		?	USA	[8]
		?	Bulgaria	[9]
		C	India	[10]
		?	China	[11]
		?	Iran	[12]
		P	Kuwait	[13]
	Pseudomonas aeruginosa	C	France	[42]
		C, P	Turkey	[2]
		?	Belgium	[43]
		C	Italy	[44]
		C	Spain	[45]
		C	Poland	[46]
		P	Hungary	[47]
		C	Serbia	[47]
		?	Tunisia	[48]
		?	Japan	[49]
		?	China	[50]
		C	Greece	[51]
		?	Iran	[52]
PER-2	*Acinetobacter baumannii*	?	Argentina	[15]
	Pseudomonas aeruginosa	?	Bolivia	[38]
PER-3	*Acinetobacter baumannii*	C	Egypt	[16]
PER-7	*Acinetobacter baumannii*	C	France	[17]
		P	United Arab Emirates	[18]
PER-8	*Acinetobacter baumannii*	?	Nepal	Accession no. **AB985401**
VEB-1	*Acinetobacter baumannii*	C	France	[19–21]
		C	Belgium	[7]
		?	Argentina	[15]
		?	Iran	[12]
	Pseudomonas aeruginosa	C	France	[53]
		C, P	Thailand	[54]
		C, P	Kuwait	[55]
		C	India	[56]
		?	Bulgaria	[57]
		?	UK	[58]
		?	Denmark	[59]
		?	Iran	[12]
VEB-2	*Pseudomonas aeruginosa*	C	Thailand	[54]
VEB-3	*Acinetobacter baumannii*	?	Taiwan	[23]
	Pseudomonas aeruginosa	?	China	[60]
VEB-7	*Acinetobacter baumannii*	?	USA	Accession no. FJ825622
GES-1	*Pseudomonas aeruginosa*	C	France	[61]
		C	Brazil	[62]
		?	Argentina	[63]
GES-8 (IBC-2)	*Pseudomonas aeruginosa*	C	Greece	[64]
GES-9	*Pseudomonas aeruginosa*	C	France	[66]
GES-11	*Acinetobacter baumannii*	P	France	[25]
		P	Belgium	[26]
		?	Sweden	[27]
		P	Kuwait	[28]
		?	Turkey	[29]
		P	Tunisia	[30]
GES-12	*Acinetobacter baumannii*	P	Belgium	[26]
GES-13	*Pseudomonas aeruginosa*	C	Greece	[65]
GES-22	*Acinetobacter baumannii*	P	Turkey	[32]
SHV-2a	*Pseudomonas aeruginosa*	C	France	[67]
		C	Tunisia	[68]
SHV-5	*Acinetobacter baumannii*	C	France (from USA)	[33]
	Pseudomonas aeruginosa	C	Greece	[71]
SHV-12	*Acinetobacter baumannii*	P	The Netherlands	[35]
	Pseudomonas aeruginosa	C	Thailand	[69]
		C	Japan	[70]
TEM-4	*Pseudomonas aeruginosa*	C	France	[72]
TEM-21	*Pseudomonas aeruginosa*	C	France	[73]

Table 1 (*Continued*)

β-Lactamase	Host	Genetic support[a]	Country of isolation	Reference(s)
TEM-24	*Pseudomonas aeruginosa*	P	France	[74]
TEM-42	*Pseudomonas aeruginosa*	P	France	[75]
TEM-92	*Acinetobacter baumannii*	?	Italy	[34]
TEM-116	*Acinetobacter baumannii*	P	The Netherlands	[35]
CTX-M-1	*Pseudomonas aeruginosa*	?	The Netherlands	[76]
CTX-M-2	*Acinetobacter baumannii*	P	Japan	[36]
		?	USA	[37]
	Pseudomonas aeruginosa	C	Brazil	[77,78]
		?	Bolivia	[38]
CTX-M-3	*Pseudomonas aeruginosa*	?	China	[50]
CTX-M-14	*Pseudomonas aeruginosa*	?	China	[50]
CTX-M-15	*Acinetobacter baumannii*	P	India	[39]
		C	Haiti	[40]
	Pseudomonas aeruginosa	?	China	[50]
CTX-M-43	*Acinetobacter baumannii*	?	Bolivia	[38]
	Pseudomonas aeruginosa	?	Bolivia	[38]
RTG-4	*Acinetobacter baumannii*	P	France	[41]
BEL-1	*Pseudomonas aeruginosa*	C	Belgium	[79,80]
BEL-2	*Pseudomonas aeruginosa*	C	Belgium	[81]
BEL-3	*Pseudomonas aeruginosa*	?	Spain	[82]
PME-1	*Pseudomonas aeruginosa*	P	USA	[83]

[a] C, chromosome; P, plasmid; ?, unknown.

inverted repeat sequences [14]. Recently, the *bla*$_{PER-1}$ gene was identified in a composite transposon made of two copies of IS*Pa12* in an *A. baumannii* isolate from Kuwait [13]. PER-2, which is quite distantly related to PER-1 (86% amino acid identity), has so far been found exclusively in South America [15]. Recently, the *bla*$_{PER-3}$ gene, initially identified from *Aeromonas punctata* and *Aeromonas caviae*, has been identified in a single *A. baumannii* isolate in Egypt [16]. In addition, PER-7 (four amino acid substitutions compared with PER-1) has been identified in a single *A. baumannii* clinical isolate in France [17] and in the United Arab Emirates (UAE) [18]. The *bla*$_{PER-7}$ gene was associated with the insertion sequence (IS) element IS*CR1* that was also involved it its expression [17]. PER variants identified in *A. baumannii* are summarised Table 1.

Another important ESBL in *A. baumannii* is the Vietnamese extended-spectrum β-lactamase (VEB). VEB-1 is distantly related to other ESBLs, sharing only 38% amino acid identity with the closest ESBL, namely PER-1 [19]. VEB-1-producing *A. baumannii* were first identified in France, where a single clone was originally identified as the source of a hospital outbreak [20]. Genotyping analysis showed that this VEB-1-producing *A. baumannii* belonged to one of the two major clonal complexes of *A. baumannii*, termed worldwide clone 1 [20]. Further studies showed a nationwide dissemination of VEB-1 in France [21] and its neighbouring country Belgium [7]. In most cases, the *bla*$_{VEB-1}$ gene is identified as a gene cassette in class 1 integrons varying in size and structure [19]. However, in several *A. baumannii* isolates from Argentina, the *bla*$_{VEB-1}$ gene was associated with an IS*CR2* element, which was likely at the origin of the mobilisation of this ESBL gene [22]. VEB-1-producing *A. baumannii* have also been identified in Iran [12]. The *bla*$_{VEB-3}$ variant was reported in a single *A. baumannii* isolate from Taiwan [23] (Table 1).

Since 2010, GES-type ESBLs are increasingly reported from *A. baumannii*. Actually, GES-1 was firstly reported in 2000, being identified from a single *K. pneumoniae* isolate [24]. GES-11, differing from GES-1 by two amino acid substitutions and consequently possessing increased activity towards aztreonam, was first identified in 2009 from an *A. baumannii* isolate from France [25]. GES-11 was then detected in the same species in Belgium, Sweden, Kuwait, Turkey and Tunisia [26–30] and in the Middle East, which might act as a reservoir for multidrug-resistant bacteria [28]. Another

GES variant, namely GES-12, differs from GES-11 by a single Thr237Ala substitution. It has been identified from several isolates in Belgium [26] and possesses increased hydrolytic activity towards ceftazidime [31]. More recently, GES-22, differing from GES-11 by one amino acid substitution, was reported from two *A. baumannii* isolates from Turkey [32]. It was reported that GES-22 possessed a hydrolytic profile similar to that of GES-11 and that the *bla*$_{GES-22}$ gene was located on a class 1 integron inserted into a 75-kb plasmid [32].

On the other hand, the TEM- and SHV-type ESBLs, being widespread among Enterobacteriaceae, have been scarcely identified in *A. baumannii*. The corresponding *bla*$_{SHV}$ and *bla*$_{TEM}$ genes have been identified either on the chromosome (*bla*$_{SHV-5}$) or on plasmids (*bla*$_{SHV-12}$, *bla*$_{TEM-92}$, *bla*$_{TEM-116}$) [33–35]. Likewise, the genes encoding the CTX-M-type ESBLs, known to be extremely widespread among Enterobacteriaceae, have been rarely identified in *A. baumannii*. CTX-M-2-producing isolates have been identified in Japan and the USA [36,37], and a CTX-M-43-producing isolate has been found in Bolivia [38]. More recently, CTX-M-15-producing *A. baumannii* have been identified in India and Haiti [39,40]. The *bla*$_{CTX-M-15}$ gene was found to be associated with IS*Ecp1* in a transposon that integrated into the chromosome of *A. baumannii* [40]. A novel ESBL, named RTG-4, which is the first carbenicillinase to possess ESBL properties, was identified from an *A. baumannii* isolate from France in 2009 [41]. This is an atypical ESBL since it significantly hydrolyses cefepime and cefpirome, but hydrolyses ceftazidime only weakly [41].

Although widespread among Enterobacteriaceae, the rare identification of these ESBLs in *A. baumannii* may be due to limited horizontal gene transfer occurring between these different bacterial genders as a consequence of narrow-spectrum plasmid replication properties.

2.1.1.2. Pseudomonas aeruginosa. The PER-1 β-lactamase was the first ESBL identified in *P. aeruginosa* [42]. It was identified in a *P. aeruginosa* isolate from a Turkish patient hospitalised in the Paris area of France in 1991 [42]. National surveys from Turkey then showed that PER-1-producing *P. aeruginosa* isolates are widespread in Turkey [2]. PER-1 has been reported in European countries with no geographical border with Turkey, such as Belgium [43], Italy

[44], Spain [45], Poland [46], Hungary and Serbia [47] and Tunisia [48] as well as in Asian countries [49,50]. In addition, it was identified in Greece and Iran [51,52] (Table 1). Epidemiological surveys have shown that a predominant *P. aeruginosa* sequence type (ST) and single-locus variants, corresponding to international clonal complex CC11, is associated with wide dissemination of PER-1-producing *P. aeruginosa* isolates in Turkey, Belgium and Italy as well as in several Eastern European countries [46,47,51]. The PER-2 β-lactamase, which shares 86% amino acid identity with PER-1 and therefore represents another lineage of the PER-type enzymes, was identified only from a *P. aeruginosa* strain isolated in Bolivia [38] (Table 1).

Another ESBL from *P. aeruginosa* is VEB-1, which was identified from *P. aeruginosa* isolates recovered from patients hospitalised in France but transferred from Thailand [53]. Nosocomial spread of VEB-1-producing *P. aeruginosa* isolates was identified in Thailand [54]. Later, other VEB-like producing isolates were reported from Kuwait and India [55,56], but also in Iran, Bulgaria, the UK and Denmark, highlighting the worldwide dissemination of these VEB-producing strains [12,57–59] (Table 1). Isolates producing VEB-2 or VEB-3 were identified in Thailand and China, with these ESBLs differing from VEB-1 by only a single or two amino acid substitutions, respectively [54,60].

Other ESBLs are the GES enzymes, which have been detected in *P. aeruginosa* (Table 2). The bla_{GES-1} gene was identified from *P. aeruginosa* isolates from France and South America [61–63]. The structurally related ESBLs IBC-2 (differing from GES-1 by a single amino acid residue and then renamed GES-8) and GES-13 were isolated from two *P. aeruginosa* isolates in Greece [64,65]. Another variant, named GES-9, possessing a broad-spectrum hydrolysis profile extended to aztreonam, was identified in a single *P. aeruginosa* isolate from France [66].

The SHV-type ESBLs have been identified in very rare isolates of *P. aeruginosa*, being SHV-2a in France and Tunisia [67,68] and SHV-12 in Thailand [69] and Japan [70] (Table 1). A nosocomial outbreak of SHV-5-producing *P. aeruginosa* was also described in Greece [71]. TEM-type ESBLs have also been rarely reported from *P. aeruginosa*, being TEM-4 [72], TEM-21 [73], TEM-24 [74] and TEM-42 [75]. CTX-M-type ESBLs, with in some cases evidence of their horizontal transfer from Enterobacteriaceae to *P. aeruginosa*, are very rarely identified in *P. aeruginosa*. A single CTX-M-1-producing *P. aeruginosa* isolate has been reported from The Netherlands in 2006 [76], and CTX-M-2- or CTX-M-43-positive *P. aeruginosa* have been identified in South America [38,77,78]. Recently, CTX-M-3, CTX-M-14 and CTX-M-15 were identified from several *P. aeruginosa* isolates from China [50] (Table 1).

In 2005, another ESBL that had weak amino acid identity with other class A ESBLs but had similar biochemical properties was reported; the gene encoding BEL-1 was located in a class 1 integron inserted into the chromosome of a *P. aeruginosa* isolate recovered in a single hospital in Belgium [79]. Later, another study reported the dissemination of BEL-1-producing *P. aeruginosa* isolates in several hospitals located in different geographical areas in Belgium [80]. BEL-2 and BEL-3, each differing from BEL-1 by a single amino acid substitution, were identified in 2010 in a strain recovered in Belgium and Spain, respectively [81,82] (Table 1). Compared with BEL-1, BEL-2 possesses enhanced hydrolytic properties against expanded-spectrum cephalosporins [81].

The ESBL PME-1 is the latest identified ESBL from a clinical *P. aeruginosa* isolate and was recovered in Pennsylvania, USA, in 2008 [83]. This enzyme shares 43% amino acid identity with the closest ESBL CTX-M-9. PME-1 confers a high level of resistance to penicillins, ceftazidime and aztreonam and to a lesser extent cefotaxime, but spares cefepime and the carbapenems. The bla_{PME-1} gene was found to be located on an ca. 9-kb plasmid, flanked on both extremities by two copies of IS*CR24* [83].

2.1.2. Carbapenemases

2.1.2.1. Acinetobacter baumannii.
Although almost all class A ESBLs do not possess any significant carbapenemase activity, specific GES variants have been shown to possess the ability to compromise the efficacy of carbapenems (Table 2). These are GES enzymes possessing specific residues enlarging their hydrolysis spectrum, and some of them such as GES-5 have been identified in Enterobacteriaceae [84]. The GES-14 variant is one of these GES-type carbapenemases and has been identified in *A. baumannii* in France in 2011 [85], the bla_{GES-14} gene being part of a class 1 integron located on a self-transferable plasmid [85].

Another class A carbapenemase that is commonly identified among Enterobacteriaceae is KPC, with KPC-type enzymes possessing intrinsic high carbapenemase and ESBL activity [86]. These enzymes all confer resistance to all β-lactams, and the corresponding genes are located on mobile genetic elements, enhancing their spread [87]. Despite wide dissemination among enterobacterial species, only a few KPC-type β-lactamases have been identified in *A. baumannii*, being a series of isolates recovered in Puerto Rico [88]. In that study, ten *A. baumannii* isolates producing KPC-type enzymes were detected, corresponding to KPC-3 (7 isolates) and KPC-2, KPC-4 and KPC-10 in single isolates, respectively [88].

2.1.2.2. Pseudomonas aeruginosa.
As highlighted earlier, several GES-type ESBLs exhibit some carbapenemase properties. Actually, the first GES-type carbapenemase was identified from a *P. aeruginosa* isolate, being GES-2, differing from GES-1 by a single amino acid substitution [89]. This isolate was recovered from a patient hospitalised in South Africa and was actually part of an outbreak that occurred in the same hospital [90]. The GES-5 variant possessing significant carbapenemase activity has also been reported from *P. aeruginosa* isolates in China [91], South Africa [92], Brazil [93] and Turkey [94]. These bla_{GES}-type genes are part of class 1 integron structures [92]. Recently, a novel GES variant, GES-18, was identified from a *P. aeruginosa* isolate from Belgium. GES-18 differed from GES-5 by one amino acid substitution and also hydrolysed carbapenems [95].

Although rarely identified, KPC-producing *P. aeruginosa* isolates have been reported, first in Colombia in 2006 [96] and then in Puerto Rico [97,98], Trinidad and Tobago [99], the USA [100] and China [101]. They are increasingly identified in the Americas and the Caribbean region [102–104]. No clear evidence of horizontal transfer of the bla_{KPC} gene from Enterobacteriaceae to non-fermenters has been observed.

2.2. Class B β-lactamases

These β-lactamases, also named metallo-β-lactamases (MBLs), hydrolyse carbapenems and other β-lactams (except monobactams) very efficiently and they are not inhibited by the clinically available β-lactamase inhibitors such as clavulanic acid or tazobactam. However, their activity is inhibited by metal ion chelators [105,106].

2.2.1. Acinetobacter baumannii

Carbapenem resistance in this species is most often (if not always) linked to the production of carbapenemases. MBL enzymes are not the most commonly identified carbapenemases in *A. baumannii*; when identified, they are either IMP-like, VIM-like, SIM-1 or NDM-like enzymes [107]. Nine IMP variants have been identified in *A. baumannii*, namely IMP-1 in Italy [108], Japan [109], South Korea [110], India [111], Taiwan [112] and Kuwait [113], IMP-2 in Japan and Italy [109,114], IMP-4 in Hong-Kong [115], Australia and Singapore [116,117], IMP-5 in Portugal [118], IMP-6 in Brazil [119], IMP-8 in China [120], IMP-11 in Japan (accession no. **AB074436**),

Table 2
Ambler class A carbapenemases known in Acinetobacter baumannii and Pseudomonas aeruginosa.

β-Lactamase	Host	Genetic support[a]	Country of isolation	Reference(s)
GES-2	*Pseudomonas aeruginosa*	P	South Africa	[89,90]
GES-5	*Pseudomonas*	?	China	[91]
	aeruginosa	?	South Africa	[92]
		C	Brazil	[93]
		?	Turkey	[94]
GES-14	*Acinetobacter baumannii*	P	France	[85]
GES-18	*Pseudomonas aeruginosa*	C	Belgium	[95]
KPC-2	*Acinetobacter baumannii*	?	Puerto Rico	[88]
	Pseudomonas	C, P	Columbia	[96,102]
	aeruginosa	?	Puerto Rico	[97]
		?	Trinidad and Tobago	[99]
		P	USA	[100]
		C	China	[101]
		?	Argentina	[103]
		?	Brazil	[104]
KPC-3	*Acinetobacter baumannii*	?	Puerto Rico	[88]
KPC-4	*Acinetobacter baumannii*	?	Puerto Rico	[88]
KPC-5	*Pseudomonas aeruginosa*	?	Puerto Rico	[98]
KPC-10	*Acinetobacter baumannii*	?	Puerto Rico	[88]

[a] C, chromosome; P, plasmid;?, unknown.

IMP-14 in Thailand [121] and IMP-19 in Japan [122] (Table 3). Noteworthy, VIM-type enzymes that have been widely identified in Enterobacteriaceae have rarely been identified in *A. baumannii*. There are few reports of VIM-1-producers in Greece [123], VIM-2 in South Korea [110] and Kuwait [113], VIM-4 in Italy [124], VIM-6 in India (accession no. **EF645347**) and VIM-11 in Taiwan [23] (Table 3).

The SIM-1 carbapenemase has been reported only in the *A. baumannii* species so far, and only in South Korea, where this resistance trait appears to be widespread [125]. Analysis of the genetic support of the MBL-encoding genes identified in *A. baumannii* shows similar structures, with the bla_{IMP}, bla_{VIM} and bla_{SIM} genes being all embedded in class 1 integron structures [107].

NDM-1 is one of the most recently identified MBLs [126]. Whilst most studies indicate wide dissemination of the bla_{NDM-1}-like genes in Enterobacteriaceae, many studies reported on the acquisition of bla_{NDM-1}-like genes in *A. baumannii*. Indeed, NDM-1 was first reported in India from Enterobacteriaceae and then in *A. baumannii* [126,127]. Other reports are from different European countries and from China, Japan, Kenya, Brazil, Algeria and Syria [128–137]. An outbreak of NDM-1-producing *A. baumannii*, belonging to ST85, was recently reported in France [138], underscoring the growing concern related to the spread of these isolates in Europe. Identification of several ST85 isolates possessing the bla_{NDM-1} gene and originating from North Africa, with no obvious link to the Indian subcontinent, strongly suggests that the source of NDM-producing *A. baumannii* strains could be North Africa [139]. Another variant, NDM-2, was identified in *A. baumannii* strains recovered in Egypt [140], Israel [141] and the UAE [142]. Interestingly, it was evidenced that these NDM-2-producing isolates were clonally related, suggesting that the Middle East as well as the Balkan region and the Indian and China regions might act as reservoirs of NDM-2-producing *Acinetobacter* [143]. In these isolates, the bla_{NDM} gene was surrounded by two copies of IS*Aba125*, thus forming a 10 099-bp composite transposon named Tn*125* [144]. As opposed to what is observed in Enterobacteriaceae, the IS*Aba125* element located upstream of bla_{NDM} and that plays a role in its expression, is not truncated [144]. Our extensive studies showed that *A. baumannii* was likely the first target of bla_{NDM-1} gene acquisition before its transfer to Enterobacteriaceae and *P. aeruginosa* [144]. This represents a new paradigm in antibiotic resistance since it highlights that *Acinetobacter* spp. may be a source of an important resistance trait for Enterobacteriaceae.

2.2.2. Pseudomonas aeruginosa

Carbapenem resistance in *P. aeruginosa* is mostly related to porin (OprD) deficiency and more rarely to carbapenemases. Carbapenemases in *P. aeruginosa* are mainly MBLs of the IMP, VIM, SPM and GIM types. IMP-1 was first reported in Enterobacteriaceae and *P. aeruginosa* in Japan and is now globally distributed, suggesting horizontal transfer of bla_{IMP-1} between unrelated Gram-negative species [145]. IMP-like enzymes may be divided into several subgroups and the percentage amino acid identity within these groups actually ranges from 90% to 99% [106]. These variants possess very similar hydrolytic activities. Among the 51 known IMP variants, 32 have been reported from *P. aeruginosa* and have been identified throughout the world (Table 3).

Although VIM enzymes share <40% amino acid identity with the IMP-type enzymes, they share the same hydrolytic spectrum [186]. VIM-1 was the first MBL identified in *P. aeruginosa* [187] and has been reported in several European countries (Table 3). However, VIM-2 is now the most widespread MBL in *P. aeruginosa* as a source of multiple outbreaks [106]. Twenty-three of the forty-six VIM variants have been identified in *P. aeruginosa* (Table 3).

β-Lactamase SPM is quite different from VIM and IMP and, accordingly, represents a new subfamily of MBLs. SPM-1 was first isolated in Brazil in 1997 from a *P. aeruginosa* clinical isolate [207], which was highly resistant to all anti-Gram-negative antibiotics except colistin. Dissemination of multidrug-resistant *P. aeruginosa* producing SPM-1 was demonstrated in distinct regions of this country, however they have not disseminated in other countries [208], with the only exception of a single isolate identified in Switzerland from a patient who had previously been hospitalised in Brazil [209]. The bla_{SPM-1} gene is either chromosomal or plasmid-encoded. In addition, it is associated with the IS element IS*CR4* at the origin of its acquisition and expression and is likely transposed through a rolling-circle replication mechanism [210].

In 2002, a new type of acquired MBL, named GIM-1, was identified in clonally related *P. aeruginosa* isolates from Germany [211,212]. This enzyme also produced by enterobacterial species has only been identified in Germany.

NDM-1-producing *P. aeruginosa* isolates were first reported in 2011, with two strains recovered from Serbia [213]. In 2012, a single NDM-1-producing *P. aeruginosa* belonging to ST235 was isolated in France from a patient previously hospitalised in Serbia [214,215]. More recently, NDM-1-positive *P. aeruginosa* isolates were recovered in India (four isolates), Italy (a single isolate belonging to

Table 3
Ambler class B metallo-β-lactamases known in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

β-Lactamase	Host	Genetic environment or support[a]	Country of isolation	Reference(s)
IMP-1	*Acinetobacter baumannii*	?	Italy	[108]
		I	Japan	[109]
		?	South Korea	[110]
		?	India	[111]
		?	Taiwan	[112]
		?	Kuwait	[113]
	Pseudomonas aeruginosa	I	Japan	[146]
		I	South Korea	[110]
		?	Brazil	[147]
		?	China	[148]
		I	Turkey	[149]
		?	Singapore	[150]
		I	Thailand	[151]
IMP-2	*Acinetobacter baumannii*	I	Japan	[109]
		I	Italy	[114]
	Pseudomonas aeruginosa	I	Japan	[109]
IMP-4	*Acinetobacter baumannii*	I	Hong Kong	[115]
		?	Australia	[116]
		I	Singapore	[117]
	Pseudomonas aeruginosa	?	Malaysia	[152]
		I	Australia	[153]
IMP-5	*Acinetobacter baumannii*	I	Portugal	[118]
	Pseudomonas aeruginosa	I	Portugal	[154]
IMP-6	*Acinetobacter baumannii*	?	Brazil	[119]
	Pseudomonas aeruginosa	I	South Korea	[155]
		?	China	[156]
IMP-7	*Pseudomonas aeruginosa*	I	Canada	[157]
		?	Malaysia	[158]
		?	Slovakia	[159]
		I	Japan	[160]
		?	Singapore	[150]
		I	Czech Republic	[161]
		?	Denmark	[162]
IMP-8	*Acinetobacter baumannii*	I	China	[120]
IMP-9	*Pseudomonas aeruginosa*	I	China	[163]
IMP-10	*Pseudomonas aeruginosa*	I	Japan	[164]
IMP-11	*Acinetobacter baumannii*	?	Japan	Accession no. **AB074436**
	Pseudomonas aeruginosa	?	Japan	Accession no. **AB074437**
IMP-13	*Pseudomonas aeruginosa*	I	Austria	[165]
		I	Italy	[166]
		I	France	[167]
		I	Belgium	[168]
IMP-14	*Acinetobacter baumannii*	I	Thailand	[121]
	Pseudomonas aeruginosa	I	Thailand	[169]
IMP-15	*Pseudomonas aeruginosa*	I	Mexico	[170]
		I	Spain	[171]
		?	Germany	[172]
IMP-16	*Pseudomonas aeruginosa*	I	Brazil	[173]
IMP-18	*Pseudomonas aeruginosa*	?	USA	[174]
		I	Mexico	[175]
		I	Puerto Rico	[97]
IMP-19	*Acinetobacter baumannii*	?	Japan	[122]
	Pseudomonas aeruginosa	?	Japan	Accession no. **AB184876**
		I	Italy	[176]
IMP-20	*Pseudomonas aeruginosa*	I	Japan	Accession no. **AB196988**
IMP-21	*Pseudomonas aeruginosa*		Japan	Accession no. **AB204557**
IMP-22	*Pseudomonas aeruginosa*	I	Austria	[165]
		I	Italy	[177]
IMP-25	*Pseudomonas aeruginosa*	I	China	Accession no. **EU352796**
IMP-26	*Pseudomonas aeruginosa*	I	Malaysia	[178]
		?	Singapore	[179]
IMP-29	*Pseudomonas aeruginosa*	I	France	[180]
IMP-30	*Pseudomonas aeruginosa*	?	Russia	[181]
IMP-31	*Pseudomonas aeruginosa*	?	Germany	Accession no. **KF148593**
IMP-33	*Pseudomonas aeruginosa*	I	Italy	[182]
IMP-35	*Pseudomonas aeruginosa*	I	Germany	[183]
IMP-37	*Pseudomonas aeruginosa*	?	France	Accession no. **JX131372**
IMP-40	*Pseudomonas aeruginosa*	?	Japan	Accession no. **AB753457**

6

Table 3 (*Continued*)

β-Lactamase	Host	Genetic environment or support[a]	Country of isolation	Reference(s)
IMP-41	*Pseudomonas aeruginosa*	?	Japan	Accession no. **AB753458**
IMP-43	*Pseudomonas aeruginosa*	I	Japan	[184]
IMP-44	*Pseudomonas aeruginosa*	I	Japan	[184]
IMP-45	*Pseudomonas aeruginosa*	I	China	[185]
IMP-48	*Pseudomonas aeruginosa*	?	USA	Accession no. **KM087857**
VIM-1	*Acinetobacter baumannii*	I	Greece	[123]
	Pseudomonas aeruginosa	I	Italy	[187]
		I	France	[188]
		I	Greece	[189]
		?	Germany	[172]
		I	Italy	[176]
VIM-2	*Acinetobacter baumannii*	I	South Korea	[110]
	Pseudomonas aeruginosa	?	Kuwait	[113]
		I	Tunisia	[190]
		?	Thailand	[169]
		I	Austria	[165]
		I	Mexico	[170]
		?	India	[191]
		?	Kenya	[192]
		I	Hungary	[193]
		I	Malaysia	[194]
		I	South Korea	[106]
		I	Japan	[106]
		I	France	[106]
		I	Greece	[106]
		I	Italy	[106]
		I	Portugal	[106]
		?	Spain	[106]
		I	Croatia	[106]
		I	Poland	[106]
		I	Chile	[106]
		I	Venezuela	[106]
		?	Argentina	[106]
		I	USA	[106]
		?	Belgium	[172]
		?	Germany	[172]
		?	Turkey	[172]
VIM-3	*Pseudomonas aeruginosa*	?	Taiwan	[195]
VIM-4	*Acinetobacter baumannii*	?	Italy	[124]
	Pseudomonas aeruginosa	I	Greece	[106]
		?	Sweden	[106]
		I	Poland	[106]
		I	Hungary	[193,196]
		?	France	[172]
VIM-5	*Pseudomonas aeruginosa*	?	India	[191]
		I	Turkey	[106]
VIM-6	*Acinetobacter baumannii*	?	India	Accession no. **EF645347**
	Pseudomonas aeruginosa	I	India	[191]
		I	Indonesia	[197]
		I	South Korea	[197]
		I	Philippines	[197]
VIM-7	*Pseudomonas aeruginosa*	I	USA	[198]
VIM-8	*Pseudomonas aeruginosa*	?	Columbia	[199]
VIM-9	*Pseudomonas aeruginosa*	?	UK	Accession no. **AY524988**
VIM-10	*Pseudomonas aeruginosa*	?	UK	[58]
VIM-11	*Acinetobacter baumannii*	I	Taiwan	[23]
	Pseudomonas aeruginosa	I	India	[191]
		?	Argentina	[200]
		?	Italy	Accession no. **AY635904**
		I	Malaysia	[194]
VIM-13	*Pseudomonas aeruginosa*	I	Spain	[201]
VIM-14	*Pseudomonas aeruginosa*	?	Spain	Accession no. **EF055455**
		I	Italy	[202]
VIM-15	*Pseudomonas aeruginosa*	I	Bulgaria	[203]
VIM-16	*Pseudomonas aeruginosa*	I	Germany	[203]
VIM-17	*Pseudomonas aeruginosa*	I	Greece	[204]
VIM-18	*Pseudomonas aeruginosa*	I	India	[191]
VIM-20	*Pseudomonas aeruginosa*	?	Spain	[205]
VIM-28	*Pseudomonas aeruginosa*	I	Egypt	[206]
VIM-30	*Pseudomonas aeruginosa*	I	France	Accession no. **JN129451**
VIM-36	*Pseudomonas aeruginosa*	?	Belgium	[172]

Table 3 (*Continued*)

β-Lactamase	Host	Genetic environment or support[a]	Country of isolation	Reference(s)
VIM-37	*Pseudomonas aeruginosa*	?	Poland	[172]
VIM-38	*Pseudomonas aeruginosa*	I	Turkey	[94]
SIM-1	*Acinetobacter baumannii*	I	South Korea	[125]
NDM-1	*Acinetobacter*	C	Czech Republic	[128]
	baumannii	C	Germany	[129,131]
		C	Belgium	[130]
		C	Slovenia	[131]
		C	France	[131]
		C	Switzerland	[131]
		?	India	[127]
		P	China	[132]
		?	Japan	[133]
		?	Kenya	[134]
		P	Brazil	[135]
		?	Algeria	[136]
		?	Syria	[137]
	Pseudomonas	C	Serbia	[213]
	aeruginosa	C	France	[214,215]
		P	India	[216]
		C	Italy	[217]
		?	Egypt	[218]
		?	Slovakia	[219]
NDM-2	*Acinetobacter*	C	Egypt	[140]
	baumannii	C	Israel	[141]
		?	United Arab Emirates	[142]
SPM-1	*Pseudomonas*	IS*CR4*	Brazil	[207]
	aeruginosa	IS*CR4*	Switzerland	[209]
GIM-1	*Pseudomonas aeruginosa*	I	Germany	[211,212]
FIM-1	*Pseudomonas aeruginosa*	C	Italy	[221]

[a] I, integron present; C, chromosome; P, plasmid; ?, unknown.

ST235), Egypt and Slovakia [216–219]. Interestingly, the emergence of multidrug-resistant VIM-2-producing *P. aeruginosa* in Russia is also linked to a ST235-like dominant clone [220]. Association of ST235-like strains with MBL genes has been reported in several European countries [220], such as in Italy with VIM-1-producers, in Greece, Sweden, Hungary and Belgium with VIM-4-producers, in Spain with VIM-13-producers, and in France with IMP-29-producers [220]. This clone might therefore possess some specific traits enhancing its clonal dissemination.

Recently, a novel MBL named FIM-1, exhibiting its highest similarity (40% amino acid identity) with NDM-type enzymes, was reported in a *P. aeruginosa* isolate from Italy [221]. The *bla*FIM-1 gene was chromosomally located and was associated with IS*CR19*-like elements that were likely involved in its capture and mobilisation [221]; its origin remains unknown.

2.3. Class C β-lactamases

2.3.1. Acinetobacter baumannii

Acinetobacter baumannii naturally produces a gene encoding an AmpC-type cephalosporinase. This gene is usually expressed at a basal and low level, therefore the amount of AmpC produced does not have a significant impact on the activity of expanded-spectrum cephalosporins [222]. The presence of a specific IS element IS*Aba1* (belonging to the IS*4* family) upstream of this naturally occurring *ampC* gene provides promoter sequences enhancing its expression, resulting in resistance to broad-spectrum cephalosporins (but sparing carbapenems) [223]. By studying a series of *A. baumannii* strains, a variety of AmpC variants may be identified and these variants have been named ADC-type (*Acinetobacter*-derived cephalosporinase) enzymes [224]. Some ADC variants, such as ADC-33 and ADC-56, possess a slight extended activity towards expanded-spectrum cephalosporins, which allows the classification of these enzymes as extended-spectrum AmpC (ESAC) [225,226]. Indeed, they do hydrolyse ceftazidime more efficiently,

and in addition they hydrolyse fourth-generation cephalosporins such as cefepime, whereas wild-type AmpC enzymes do not. The true clinical significance of these enzymes remains unknown. No acquired AmpC-type-encoding gene has been identified so far in *A. baumannii*.

2.3.2. Pseudomonas aeruginosa

A chromosomal gene encoding an AmpC-type cephalosporinase is also intrinsic to *P. aeruginosa*. This *ampC* gene is associated with a LysR-type regulatory gene with which some β-lactam molecules may interact, leading to overexpression of this *ampC* gene [227]. Some β-lactams such as carbapenems are inducers of *ampC* gene expression, although they are not substrates of these cephalosporinases. Selection of mutants overproducing the *ampC* gene is frequently observed in *P. aeruginosa*, leading to acquired resistance to ticarcillin, piperacillin and broad-spectrum cephalosporins (ceftazidime) [227]. In addition, insertion of the IS*1669* element into the LysR regulatory gene (also known as the *ampR* gene) of *ampC* may lead to the overexpression of this enzyme [228]. Apart from these mechanisms leading to increased resistance to expanded-spectrum cephalosporins, very peculiar AmpC-type enzymes of *P. aeruginosa* have been identified possessing a broadened hydrolytic activity towards imipenem [229]. They correspond to naturally occurring, chromosomally encoded AmpC-type β-lactamases possessing an alanine residue at position 105 conferring an additional weak carbapenemase activity [229,230]. The true clinical significance of these enzymes as a source of carbapenem resistance remains to be clarified.

2.4. Class D β-lactamases

Class D β-lactamases, also known as oxacillinases, are β-lactamases grouped in a heterogeneous class of enzymes either with respect to their structural or biochemical properties [231]. These enzymes all hydrolyse amoxicillin and cefalotin and their

Table 4
Ambler class D β-lactamases known in Acinetobacter baumannii and Pseudomonas aeruginosa.

Host	Enzyme subfamily	Additional OXA members	Phenotype	Reference(s)
Acinetobacter baumannii	OXA-23 (ARI-1)	OXA-27, OXA-49	CHDL	[107,236,237]
	OXA-40	OXA-25, OXA-26, OXA-72	CHDL	[232,238–245]
	OXA-58	OXA-96, OXA-97	CHDL	[117,246–248]
	OXA-143		CHDL	[249]
	OXA-235	OXA-236, OXA-237	CHDL	[250]
Pseudomonas aeruginosa	OXA-2	OXA-15, OXA-32, OXA-34, OXA-36, OXA-141, OXA-161	ES-OXA	[231,252–254]
	OXA-10	OXA-11, OXA-13, OXA-14, OXA-16, OXA-17, OXA-19, OXA-28, OXA-129, OXA-142, OXA-145, OXA-147, OXA-183	ES-OXA	[231,255–262]
	OXA-1	OXA-31	ES-OXA	[263]
	OXA-56	OXA-128	ES-OXA	[261]
	OXA-18		ES-OXA	[264]
	OXA-45		ES-OXA	[265]
	OXA-40		CHDL	[267]
	OXA-198		CHDL	[268]

CHDL, carbapenem-hydrolysing class D β-lactamase; ES-OXA, extended-spectrum oxacillinase.

activities are usually not significantly inhibited by clavulanic acid [232]. Some class D β-lactamases hydrolyse expanded-spectrum cephalosporins and a few have been identified in *P. aeruginosa*, but none in *A. baumannii*. Most of these broad-spectrum class D β-lactamases, also called ES-OXA, are point-mutant derivatives of narrow-spectrum β-lactamases [231]. In contrast, carbapenemase activity is also an intrinsic property of many class D β-lactamases, therefore terming them carbapenem-hydrolysing class D β-lactamases (CHDLs) [231].

2.4.1. Acinetobacter baumannii

Acinetobacter baumannii possesses naturally occurring class D β-lactamases, known as OXA-51-like enzymes [233]. These enzymes exhibit weak carbapenemase activity and are classified as CHDLs. Noticeably, the corresponding genes are not (or only weakly) expressed in most isolates. However, once overexpressed they may subsequently be involved in reduced susceptibility to carbapenems [234]. Overexpression of these genes encoding OXA-51-like enzymes is often driven by the insertion of an IS*Aba1* element upstream of the bla_{OXA-51}-like gene, providing strong promoter sequences.

In addition to these naturally occurring class D β-lactamases, several acquired class D β-lactamases have been identified as a source of carbapenem resistance in *A. baumannii* [107]. These CHDLs confer only reduced susceptibility to carbapenems, but they spare broad-spectrum cephalosporins. Therefore, the high resistance to carbapenems often observed in many *A. baumannii* strains results from the association between a CHDL and other resistance mechanisms, including porin loss and overexpression of efflux systems [107]. Five main groups of acquired CHDLs have been described in *A. baumannii*, corresponding to OXA-23-, OXA-40-, OXA-58-, OXA-143 and OXA-235-like enzymes. The first and most common subgroup of CHDLs is made of OXA-23, OXA-27 and OXA-49 (Table 4) [107]. The bla_{OXA-23}-like genes are chromosome- or plasmid-encoded and they are part of transposons, namely Tn*2006* and Tn*2007* [235]. OXA-23-like enzymes are the most widespread CHDLs in *A. baumannii* worldwide and they have been identified on all continents [107,236]. OXA-23-producing *A. baumannii* are the most common sources of nosocomial outbreaks with carbapenem-resistant *A. baumannii* [231,237]. A second group of acquired CHDLs in *A. baumannii* comprises OXA-25, OXA-26, OXA-40 (formerly known as OXA-24) and OXA-72 (Table 4). OXA-25 has been identified in carbapenem-resistant *A. baumannii* isolates recovered from Spain, and OXA-26 in Belgium [238]. The OXA-40 CHDL was originally identified in a carbapenem-resistant *A. baumannii* isolate in France recovered from a Portuguese patient [239], and then extensively identified in Portugal and Spain, as in other parts of

the world [231,240,241]. The bla_{OXA-40}-like genes may be either chromosome- or plasmid-located. OXA-72 has also been identified in different parts of the world (Brazil, Lithuania, Croatia), but predominantly in Asia (China, South Korea, Taiwan, Japan) [231,242–245]. A third group of CHDLs corresponds to OXA-58 and its structurally related enzymes (OXA-96 and OXA-97), first identified from a carbapenem-resistant *A. baumannii* isolate recovered in France [246] in the context of a nosocomial outbreak in a burn unit [247]. This bla_{OXA-58} gene has now been reported worldwide [231], being always plasmid-borne and associated with IS elements at the origin of its expression [107]. OXA-96 and OXA-97 are point-mutant variants of OXA-58 sharing the same hydrolytic properties and identified in Singapore and Tunisia, respectively [117,248].

The OXA-143 CHDL was identified in 2009 from a clinical *A. baumannii* isolate that had been recovered in Brazil [249]. It shares 88% amino acid identity with OXA-40, 63% with OXA-23 and 52% with OXA-58. Its substrate profile was similar to those of other CHDLs and its corresponding gene was not integron- or transposon-encoded [249].

Ultimately, a novel subclass of CHDLs has recently been reported from isolates recovered in the USA and Mexico. This subgroup includes OXA-235, OXA-236 and OXA-237 [250], and the corresponding genes have been identified either on chromosomes or plasmids, and bracketed by two copies of IS*Aba1* [250].

2.4.2. Pseudomonas aeruginosa

Pseudomonas aeruginosa produces a naturally occurring class D β-lactamase, OXA-50, that does not contribute to the overall β-lactam resistance pattern of *P. aeruginosa*, except for latamoxef [251]. Most of the class D β-lactamases able to hydrolyse expanded-spectrum cephalosporins have been identified in *P. aeruginosa*. There are two main types of expanded-spectrum class D β-lactamases (ES-OXAs). Some are point-mutant derivatives of narrow-spectrum class D β-lactamases, with amino acid substitutions enlarging their spectrum of hydrolysis towards expanded-spectrum cephalosporins. These ES-OXAs mainly derive from the narrow-spectrum β-lactamases OXA-10 (OXA-11, -13, -14, -16, -17, -19, -28, -129, -142, -145, -147 and -183), OXA-2 (OXA-15, -32, -34, -36, -141 and -161) and OXA-1 (OXA-31) (Table 4) [231,252–263]. Other ES-OXAs share only weak amino acid identity with these latter enzymes. OXA-18, which is inhibited by clavulanic acid, was the first identified ES-OXA in a *P. aeruginosa* isolate in Paris from a patient previously hospitalised in Sicily [264]. This enzyme shares <50% amino acid identity with the other class D β-lactamases. OXA-45 is another ES-OXA, identified from a multidrug-resistant Texan *P. aeruginosa* isolate co-expressing

the class B β-lactamase VIM-7 [265]. OXA-45 shares the highest identity with OXA-18 (66%) and, as for OXA-18, its activity is well inhibited by clavulanic acid. Interestingly, the bla_{OXA-45} gene, located on a 24-kb plasmid, was not found as a form of a gene cassette but associated with two copies of an ISCR5-like element [266].

Only two acquired class D β-lactamases compromising the efficacy of carbapenems have been reported from *P. aeruginosa*. One is OXA-40, known to be widespread in *A. baumannii*, which was reported in a *P. aeruginosa* isolate in Spain in 2006 [267]. The other is OXA-198 characterised in a *P. aeruginosa* isolate from Belgium [268], sharing <30% amino acid identity with other CHDLs reported in Gram-negative organisms. The $bla_{OXA-198}$ gene was harboured by a class 1 integron carried by a non-typeable ca. 46-kb plasmid [268].

3. Broad resistance to aminoglycosides

Aminoglycosides are used in the treatment of a broad range of life-threatening infections. The activity of aminoglycosides depends on binding to a highly conserved motif of 16S rRNA. Mechanisms of aminoglycosides resistance include decreased outer membrane permeability, active efflux and amino acid substitutions in ribosomal proteins, whereas the most common resistance mechanism is enzymatic leading to modification of the drug. Methylation of 16S ribosomal RNA has recently been demonstrated to be another mechanism of resistance encountered in Gram-negative organisms, corresponding to a modification of the antibiotic target [269]. Methylases actually interfere in the binding of these antibiotics to their site of action. These 16S rRNA methylases confer a high level of resistance to clinically useful aminoglycosides such as amikacin, gentamicin and tobramycin [269,270]. The corresponding genes are associated with transposon structures, which are themselves located on transferable plasmids, enhancing their horizontal spread. Isolates producing 16S rRNA methylases are multidrug-resistant, in particular to broad-spectrum β-lactams through the production of ESBLs or MBLs. This multidrug resistance pattern makes treatment of these infections particularly challenging. Ten 16S rRNA methylases have been identified among Gram-negative isolates, namely ArmA, RmtA, RmtB, RmtC, RmtD, RmtD2, RmtE, RmtF, RmtG and NpmA [270–273]. The origin of these genes is likely *Streptomyces* [271] and their prevalence remains unknown depending on the geographical location (possibly more frequent in Asia).

3.1. Acinetobacter baumannii

The ArmA enzyme has been reported in many *A. baumannii* worldwide, conferring high-level resistance to all aminoglycosides. Such isolates have been identified in China [274], South Korea [275,276], Vietnam [277], Japan [278], North America [279], Norway [280], Italy [281], Bulgaria [282], Iran [283] and Algeria [136]. The *armA* gene was always found to be located on a functional composite transposon Tn1548 [279]. Despite being quite widespread among *A. baumannii* strains, the *armA* gene possesses a GC content of 30%, which significantly differs from that of the *A. baumannii* core genome estimated at ca. 39%. This highlights the fact that this gene was acquired horizontally from a source that still remains unknown [279]. Noteworthy, the ArmA-encoding gene is often identified among OXA-23-producing *A. baumannii* strains, however both resistance genes are not physically linked on a single plasmid [280–282].

Apart from numerous reports of ArmA-producing *A. baumannii* isolates, the 16S rRNA methylase RmtB has recently been identified in nine *A. baumannii* isolates from Vietnam [277].

3.2. Pseudomonas aeruginosa

The first 16S rRNA methylase recovered in *P. aeruginosa* was identified in 2003. It was a clinical isolate from Japan producing RmtA [284,285]. Other RmtA-producing *P. aeruginosa* were then identified in South Korea in 2009 [286]. The *rmtA* gene is located on mobile genetic elements such as transposon Tn5041 [285].

In 2007, the RmtD methylase was firstly reported from a pandrug-resistant *P. aeruginosa* clinical isolate co-producing the MBL SPM-1 in Brazil [287]. RmtD shares 40% amino acid identity with RmtA, and the genetic structures surrounding both corresponding genes shared similar features [287]. Subsequently, another study underscored that co-production of the MBL SPM-1 and the 16S rRNA methylase RmtD was common among imipenem-resistant *P. aeruginosa* isolates recovered in hospitals in São Paulo, Brazil [288]. In these isolates, both the bla_{SPM-1} and *rmtD* genes were found to be chromosomally located. The ArmA enzyme was also identified in *P. aeruginosa* co-producing the MBL IMP-1 in South Korea [289].

4. Broad resistance to fluoroquinolones

In Gram-negative organisms, acquisition of resistance to quinolones may be related to chromosomal mutations in genes encoding the topoisomerases or to mutations in the efflux pump regulation systems. In addition, plasmid-mediated quinolone resistance genes (coding for the Qnr proteins) have been identified in Enterobacteriaceae. These acquired Qnr proteins have not been identified in non-fermenters. In *P. aeruginosa* and *A. baumannii*, a single mutation in the *gyrA* gene encoding DNA gyrase is sufficient to confer clinically high-level resistance levels to fluoroquinolones. This is due to the fact that these species intrinsically possess a decreased susceptibility to these antibiotics owing to low permeability or constitutive expression of efflux pumps.

4.1. Acinetobacter baumannii

Overexpression of efflux pumps is a source of acquired resistance to fluoroquinolones in this species. Involvement of the *adeABC* operon encoding the AdeA, AdeB and AdeC proteins forming a resistance–nodulation–cell division (RND) efflux system has been demonstrated [290]. In this case, not only fluoroquinolones but also aminoglycosides, tetracyclines, chloramphenicol and trimethoprim are substrates of this efflux system. Therefore, co-selection of this kind of mechanism with non-quinolone antibiotic molecules is possible. Similarly, overexpression of the *adeIJK* operon encoding another RND efflux system of *A. baumannii* has also been shown to interfere with different antibiotics, including the fluoroquinolones [291]. Finally, overproduction of the AbeM efflux system [belonging to the multi-antimicrobial extrusion protein (MATE) family] also contributes to acquired resistance to fluoroquinolones [292].

4.2. Pseudomonas aeruginosa

As shown in *A. baumannii*, acquired resistance to fluoroquinolones, apart from being related to mutations in topoisomerase-encoding genes, is mainly related to efflux systems. Their downregulation or upregulation (depending on whether the regulator is positive or negative) contribute significantly to reduced activity of fluoroquinolones. In *P. aeruginosa*, involvement of the MexAB–OprM RND-type system, which expression is constitutive, has been demonstrated, and its wide effect has been highlighted, conferring reduced susceptibility also to chloramphenicol, tetracyclines and β-lactams [293]. Likewise, the *mexCD–oprJ* operon confers extrusion ability with regard to quinolones, penicillins and tetracyclines. Nevertheless, this impact is seen only when the

negative regulatory protein NfxB is altered, indicating that constitutive expression of this efflux system does not contribute to this resistance trait [294]. Another efflux system is MexEF–OprN, which is also not involved in reduced susceptibility unless overexpression is observed [295].

5. Resistance to tigecycline

Tigecycline, a semisynthetic derivative of minocycline, has a peculiar mechanism of action and overcomes the widely distributed *tet* gene-encoded resistance mechanism known to confer resistance to tetracycline. Tigecycline shows good activity towards Gram-negative pathogens that may produce a large array of resistance mechanisms, including ESBLs and carbapenemases [296]. The activity of tigecycline against *A. baumannii* is overall good, and successful results have been reported clinically [296]. Resistance has been noted on several occasions and might be due to upregulation of the AdeABC multidrug efflux pump [297]. Another *A. baumannii*-specific efflux system, named AdeIJK, has also been shown to interfere with the efficacy of tigecycline, acting synergistically with AdeABC [291]. Despite the fact that tigecycline has been shown to also be a substrate of the AdeFGH efflux pump [298], only AdeABC and AdeIJK efflux pumps appear to be involved in its resistance in clinical isolates [298–300]. Noteworthy, tigecycline resistance levels in *A. baumannii* isolates may increase during therapy with tigecycline in the case of brief exposure to the drug, compromising its efficiency [301]. It was recently reported that a mutation in the *trm* gene, encoding a methyltransferase, was associated with decreased susceptibility to tigecycline in an *A. baumannii* strain [302]. This Trm enzyme could therefore play a role in resistance to tigecycline, however further studies are needed to clarify the possible role of this methyltransferase in the decreased susceptibility to tigecycline [302].

6. Resistance to colistin

During the past decade, we have witnessed a renewal of clinical interest in polymyxins (colistin) owing to two concomitant facts: (i) the emergence of carbapenem-, cephalosporin- and aminoglycoside-resistant Gram-negative isolates; and (ii) the paucity of novel marketed antibiotic molecules. Actually, polymyxins remain most often active against these multidrug-resistant isolates [303]. Emergence of colistin resistance in relation to increased usage is worrisome since polymyxins are the last remaining therapeutic option in many cases. Acquisition of resistance is mostly related to modifications of the lipopolysaccharide (LPS) biosynthesis pathway.

6.1. Acinetobacter baumannii

Two mechanisms of resistance to colistin have been described in *A. baumannii*: (i) alterations of the lipid A component of LPS resulting from mutations in the PmrAB two-component system [304,305]; and (ii) complete loss of LPS production resulting from mutations in the *lpxA*, *lpxC* and *lpxD* genes encoding the enzymes that catalyse the first steps in LPS biosynthesis [306]. Resistance to colistin in *A. baumannii* clinical isolates is rarely reported, however evaluation of colistin susceptibility is difficult and often inaccurate, considering that many laboratories do not use the gold standard technique for testing, which is microdilution [307]. The first report of colistin-resistant *A. baumannii* was from South Korea in 2005 [303]. High colistin resistance rates were then reported in other Korean hospitals in 2007 [308], and an outbreak of pandrug-resistant (including colistin) *A. baumannii* strains was reported in Spain in 2009 [309]. More recently, colistin-resistant *A. baumannii*

were recovered in Iran and the USA [310,311]. Noteworthy, development of heteroresistance to colistin in an in vitro model might compromise the use of colistin as a therapeutic option [312].

6.2. Pseudomonas aeruginosa

The emergence of colistin-resistant *P. aeruginosa* isolates has also been reported worldwide [313–315]. As observed in *A. baumannii*, resistance to polymyxins is associated with modifications of the lipid A component of LPS. Several two-component regulatory systems, such as PmrAB, PhoPQ, ParRS, CprRS and ColRS, are involved in resistance to polymyxins in *P. aeruginosa* [316–318]. A recent study identified nine genes with amino acid alterations and altered expression levels in colistin-resistant *P. aeruginosa* isolates compared with an isogenic colistin-susceptible isolate [319]. Thus, resistance to colistin is basically mediated by a complicated regulatory network involving a large array of chromosomal genes, which is currently under investigation worldwide, with some side experiments aiming to evaluate the fitness cost of such resistance.

7. Concluding remarks

Increasing rates of bacterial resistance among non-fermenters are threatening the effectiveness of antibiotics used as last-resort therapeutic options. In *A. baumannii* and *P. aeruginosa*, acquisition of resistance traits to these molecules is becoming more and more frequent, leading to multidrug and pandrug resistance. The last years have shown that: (i) most of the broad-spectrum resistance patterns identified in Enterobacteriaceae may be also identified in *P. aeruginosa* and *A. baumannii*; (ii) accumulation of unrelated resistance mechanisms (e.g. to β-lactams and aminoglycosides) is observed daily worldwide; and (iii) *A. baumannii*, although being a weak pathogen compared with *P. aeruginosa*, may play a significant role in spreading broad-spectrum resistance genes to other Gram-negative organisms. International travel and transfer of hospitalised patients further enhances this spread. In parallel, antibiotic selective pressure is also on the rise, in particular for these last-resort antibiotics that have been used only scarcely until recently. Since very few novel and effective antibiotics for the treatment of infections due to multidrug-resistant Gram-negatives isolates are going to be launched in a near future, there is an urgent need to implement strategies that may slow the development of acquired resistance. Use of rapid diagnostic techniques for detection of resistance traits, development of selective media for early recognition of colonised patients, and improvement of antibiotic stewardship may contribute to this containment strategy against antibiotic resistance.

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