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MINIREVIEW

Aminoglycoside Resistance in *Pseudomonas aeruginosa*

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Aminoglycosides (35) are a vital component of antipseudomonal chemotherapy implicated in the treatment of a variety of infections (9, 45), particularly pulmonary infections in cystic fibrosis (CF) patients (22). These agents are bactericidal and exhibit synergy with other antimicrobials, most notably β-lactams, with which they are often administered for the treatment of *Pseudomonas aeruginosa* infections; and problems with toxicity (aminoglycosides are oto- and nephrotoxic) appear to be ameliorated by increasing the dosing intervals (157a) and, in lung infections at least, through the use of aerosolized agents (e.g., tobramycin) (22). Resistance to aminoglycosides has, however, been known for some time, with reports from the 1960s highlighting the general insusceptibilities of *P. aeruginosa* clinical isolates to, e.g., kanamycin (50, 51). Today, resistance to aminoglycosides with antipseudomonal activities, including gentamicin and tobramycin, but also amikacin, is also all too common and is present in virtually all areas of the world, but particularly in Europe and Latin America (Table 1). Such resistance is seen in respiratory isolates (96), particularly isolates from CF patients (57, 85, 115, 140), as well as bloodstream (86), urinary (12), wound (65), burn (36, 166), eye (2, 20), and aural (27, 128) isolates (Table 1). Resistance typically results from drug inactivation by plasmid- or chromosome-encoded enzymes harbored by resistant strains, although enzyme-independent resistance resultant from defects in uptake and accumulation (dubbed impermeability resistance) is also commonplace, particularly in isolates from CF patients (99–101, 114, 121, 131) and intensive care units (ICUs) (10, 48, 54).

MODIFYING ENZYMES

Inactivation of aminoglycosides, such as streptomycin, kanamycin, neomycin, and gentamicin, by resistant *P. aeruginosa* isolates has been known since the 1960s and 1970s (17, 29, 76, 157). Traditionally, aminoglycoside inactivation in resistant strains involves their modification by enzymes that phosphorylate (aminoglycoside phosphoryltransferase [APH]), acetylate (aminoglycoside acetyltransferase [AAC]), or adenylate (aminoglycoside nucleotidyltransferase [ANT]; also referred to as aminoglycoside adenytransferase) these antimicrobials (see references 6, 152, and 170 for reviews on these modifying enzymes); and such enzymes are common determinants of aminoglycoside resistance in *P. aeruginosa* (32, 37, 74, 98–101, 114, 121, 131, 146) (Table 2). Increasingly, too, individual aminoglycoside-resistant *P. aeruginosa* isolates carry multiple (i.e., two to five) modifying enzymes and exhibit broad-spectrum aminoglycoside resistance as a result (74, 98–101, 127, 131, 146).

AACs. *P. aeruginosa* resistance to aminoglycosides (i.e., gentamicin) owing to enzymatic N-acetylation has been known for some time (17, 135). Acetylation of aminoglycosides can occur at the 1, 3, 6′, and 2′ amino groups and involves virtually all medically useful compounds (e.g., gentamicin, tobramycin, netilmicin, and amikacin). Enzymes that modify the 3 position (3-*N*-aminoglycoside acetyltransferases [AAC(3)]) (11) and the 6′ position (6′-*N*-aminoglycoside acetyltransferases [AAC(6′)]) (52, 172) were discovered early in *P. aeruginosa* and remain the most common acetyltransferases and, with ANT(2″) (see below), the most common enzymes providing for aminoglycoside resistance in this organism (19, 32, 37, 74, 99–101, 114, 127, 146, 150) (Table 2). The AAC (3)-I family, of which three variants (Ia [154, 169], Ib [142], and Ic [125]) have been described in *P. aeruginosa*, is a common determinant of gentamicin resistance in this organism (3, 31, 32, 114, 142, 143, 150). AAC(3)-II (33, 74, 106, 127) and AAC(3)-III (163) are less commonly described AAC(3) enzymes that determine gentamicin resistance as well as tobramycin and netilmicin resistance [AAC(3)-II] or tobramycin and kanamycin resistance [AAC(3)-III] in *P. aeruginosa*.

The AAC(6′) family of enzymes provide resistance to tobramycin, netilmicin, kanamycin, and either amikacin (I subfamily) or gentamicin (II subfamily). AAC(6′)-II is not only the most common AAC(6′) but also the most common AAC in *P. aeruginosa* (32, 37, 99–101, 114, 127, 145) and is thus a significant determinant of gentamicin and tobramycin resistance in this organism. While AAC(6′)-I [also referred to as AAC(6′)-Ia] is less common, it is significant for amikacin resistance in *P. aeruginosa* (38, 74, 75, 106, 131), although a variant of this enzyme that fails to provide for amikacin resistance, AAC(6′)-Ib, has been reported in clinical isolates resistant to tobramycin (43). A variant of the latter enzyme, AAC(6′)-Ib′, that differs from AAC(6′)-Ib by a single amino acid and that has the same activity as AAC(6′)-II has been described in a few CF patient isolates resistant to tobramycin (89). A fused *aac(3)-I-aac(6′)-Ib* gene encoding an enzyme active against gentamicin, tobramycin, and kanamycin has also been described (34). Novel AAC(6′) enzymes similar in sequence to AAC(6′)-I but significantly shorter and dubbed AAC(6′)-29a and AAC(6′)-29b that provide resistance to all typical AAC(6′)-I substrates except netilmicin have been described (118). AAC(6′)-29b displays weak acetyltransferase activity, and aminoglycoside resis-

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TABLE 1. Summary of recent studies documenting the incidence of aminoglycoside resistance in clinical isolates of *P. aeruginosa*

Location, study[a]	Year(s)	% of isolates resistant to[b]:			Reference
		AMI	GEN	TOB	
Europe (all), SENTRY	1997-1998	5.1	18.3	17.8	139
North America (urinary), SENTRY	1998	6.7	13.3	8.8	95
Asia-Pacific (all), SENTRY	1997-1999	4.2		10.1	40
Canada (all), SENTRY	1997-1999	2.2		5.8	40
Europe (all), SENTRY	1997-1999	21.1		31.6	40
Latin America (all), SENTRY	1997-1999	30.5		35.8	40
United States (all), SENTRY	1997-1999	3.4		7.8	40
Asia-West Pacific (urinary), SENTRY	1998-1999	8.5	24.5	17.9	158
United Kingdom (all)	1999	5.6 (36)[c]	11.1 (43)[c]		57
Belgium and Luxembourg (nosocomial)	1999	10.5	23.5	19.5	161
Asia-Pacific (all), SENTRY	1997-2000	4.8	15.8	10.4	66
Europe (all), SENTRY	1997-2000	13.7	28.3	24.2	66
Latin America (all), SENTRY	1997-2000	26.8	38.2	34.5	66
North America (all), SENTRY	1997-2000	4.6	15.8	7.8	66
Europe (ICU), MYSTIC	1997-2000		38.9		44
Europe (blood), MYSTIC	1997-2001		26.8		160
Iran (burn)	1998-1999	53.3	90.7		36
United States (nosocomial)	1998-2001	4.7/3.7[d]	14.7/16.7[d]		67
Europe (urinary), ESGNI[e]	2000	19.4 (4)[f]	46 (23.8)[f]	35.3 (14.3)[f]	12
Latin America (urinary), SENTRY	2000	51.5	57.6	54.5	41
Latin America (skin and soft tissue), SENTRY	2000	36.2	46.6	43.1	134
Latin America (blood), SENTRY	2000	26.7			133
North America (skin and soft tissue), SENTRY	2000	2	10.5	6.6	122
North America (respiratory), SENTRY	2000	6.3	19.2	9.8	59
France (blood)	2000		27		26
United Kingdom (CF patients)	2000		47	10.1	115
Taiwan (all), TSAR	2000	10	30	25	83
North America and Europe (blood)	2000-2001	19/5.1/15.1/2.7/9.6/7.6[g]	48.4/20.1/33.9/24.7/21.4/21.3[g]		167
Latin America (all), SENTRY	2001	34.6	50.4		4
United States (all), MYSTIC	2001		17.8	9.1	124
United States and Europe (skin and soft tissue), TSN	2001	3.6/7.4/1.7/20.4/0.6[h]	15.5/29.3/8.7/44.9/20.8[h]		65
United States (blood) TSN—USA	2002		22.8		69
North America (all), MYSTIC	2002		8.4	6.9	108

[a] The geographical region included in the indicated studies and the sites of infection of the isolates examined (in parentheses) are highlighted. MYSTIC, Meropenem Yearly Susceptibility Test Information Collection; SENTRY, SENTRY Antimicrobial Surveillance Program; TSAR, Taiwan Surveillance of Antimicrobial Resistance; ESGNI, European Study Group on Nosocomial Infections; TSN, The Surveillance Network.

[b] Resistance rates were taken directly from the indicated studies or were calculated accordingly when the studies indicated rates of susceptibility. AMI, amikacin; GEN, gentamicin; TOB, tobramycin.

[c] Rates in parentheses are for isolates from CF patients only.

[d] Rates are for non-ICU isolates/ICU isolates.

[e] The data shown are for a 1-day study.

[f] Rates in parentheses are for isolates from European Union countries only.

[g] Rates are for France/Germany/Italy/Spain/Canada/the United States.

[h] Rates are for the United States/France/Germany/Italy/Spain.

tance appears to result from very tight binding (i.e., sequestering) of aminoglycosides by this enzyme (90).

APHs. Inactivation of aminoglycosides such as kanamycin (28, 135, 159), neomycin (77, 78), and streptomycin (77, 79, 80, 135) by resistant strains of *P. aeruginosa* as a result of phosphorylation has been known for >30 years. Inactivation is carried out by phosphotransferases [APH(3′)] that modify the 3′-OH of these antimicrobials, and these phosphotransferases are commonly encountered in *P. aeruginosa* (74, 99, 127). Several APH(3′) enzymes have been described in *P. aeruginosa*, with APH(3′)-I and -II being predominant in clinical isolates resistant to kanamycin (and neomycin) (99, 123, 131, 146, 177). Indeed, a chromosomal *aphA*-encoded APH(3′)-II-type enzyme, APH(3′)-IIb (53), is likely responsible for the general

TABLE 2. Mechanisms of aminoglycoside resistance in clinical isolates of *P. aeruginosa*[a]

Aminoglycoside resistance mechanism	Resistance to[b]:	Incidence (%)[c]	
		Miller et al. (98)[d]	Miller et al. (99)
AAC(6′)-I	T, N, A	1.1–18.8 (6.2)	1.25
AAC(6′)-II	**G, T, N**	**2.1–70.3 (32.5)**	**18.39**
AAC(3)-I	G	0.6–31.9 (8.3)	2.05
AAC(3)-II	G, T, N	1.1–55.3 (4.5)[e]	2.20
AAC(3)-III	G, T	0.1–7.1 (3.2)	0.10
AAC(3)-VI	G, T, N	0.2–6.3 (2.6)	0.15
AAC(3)-?	G, N	0.7–11.7 (4.5)	0.60
ANT(2′′)-I	**G, T**	**1.7–45.2 (16.9)**	**11.87**
ANT(4′)-II	T, A, I		0.05
APH(3′)-VI	A, I		0.20
Impermeability	**G, T, N, A, I**	**4.3–23.7 (14.0)**	**26.15**

[a] Mechanisms of aminoglycoside resistance in clinical strains and their incidence in the indicated studies are shown. The most prevalent mechanisms are indicated in boldface type.

[b] Only the major antipseudomonal aminoglycosides are indicated. T, tobramycin; N, netilmicin; A, amikacin; G, gentamicin; I, isepamicin.

[c] The incidence of the indicated resistance mechanisms in aminoglycoside-resistant clinical strains of *P. aeruginosa* when they occur singly. The data do not include instances in which the indicated mechanisms occur in combination with other aminoglycoside resistance mechanisms.

[d] The indicated publication summarizes data from several studies, and the numbers presented reflect the range of incidences for each mechanism seen in these individual studies. The numbers in parentheses are the averages for all the studies.

[e] The average incidence reported excludes the 55.3% incidence reported for a single small study in Chile.

insensitivity of *P. aeruginosa* to, e.g., kanamycin (112) that was noted in the 1960s, when this drug was first being used clinically (50, 51). Interestingly, a gene, *hpaA*, encoding an AraC-type positive regulator of *aph(3′)-IIb* and genes involved in the metabolism of 4-hydroxyphenylacetic acid (4-HPA) occur immediately upstream of the *aph(3′)-IIb* gene and form an operon with the *aph(3′)-IIb* gene (178). HpaA activation of these genes is stimulated by 4-HPA, suggesting that the phosphotransferase may, in fact, play an intended role in metabolism and only fortuitously provides resistance to aminoglycosides. APH(3′) enzymes that provide resistance to other aminoglycosides have also been described in *P. aeruginosa* and include APH(3′)-VI (amikacin and isepamicin) (74, 82, 99, 156) and APH(2″) (gentamicin and tobramycin) (74).

ANTs. The adenylation of aminoglycosides such as streptomycin (80) and gentamicin (5, 31) by resistant strains of *P. aeruginosa* has been known for >20 years. The most prevalent nucleotidyltransferase is the ANT(2″)-I enzyme, which, with AAC(6′) [and, to some extent, AAC(3)], represents the most common determinant of enzyme-dependent aminoglycoside resistance in *P. aeruginosa* (19, 32, 37, 99–101, 114, 146, 150). The ANT(2″)-I enzyme inactivates gentamicin and tobramycin but not netilmicin or amikacin and is thus found in gentamicin-resistant (19, 31, 114, 123) and tobramycin-resistant (89) clinical isolates. Other adenyltransferases associated with aminoglycoside resistance in *P. aeruginosa* include ANT(3″) (streptomycin resistance) (146) and ANT(4′)-II (amikacin, tobramycin, and isepamicin resistance) (63, 132, 147). Two variants of ANT(4′)-II, ANT(4′)-IIa (63, 147) and ANT(4′)-IIb (132), have been reported and are encoded by genes present in the chromosome and/or on plasmids of amikacin-resistant clinical isolates.

Aminoglycoside-modifying enzymes and mobile genetic elements. R factors encoding aminoglycoside-modifying enzymes and other resistance determinants have been known for some time in *P. aeruginosa* (38, 135), as have transposons that carry genes for aminoglycoside resistance and resistance to other compunds (e.g., sulfonamides and chloramphenicol) (130). Indeed, aminoglycoside-modifying enzymes are often encoded by mobile elements that harbor additional resistance determinants (106). *aac(3)* genes are often associated with transposons (33) and/or integrons (142, 143, 154, 169) in *P. aeruginosa*, including integrons carrying genes for extended-spectrum β-lactamases (34, 119) or metallo-β-lactamases (118, 125, 165), as well as other aminoglycoside-modifying enzymes (118). One reported multidrug-resistant isolate, for example, harbored an integron carrying *aac (3)-Ic*, in addition to genes for the VIM-2 metallo-β-lactamase and the CmlA chloramphenicol efflux pump (125). The presence of these determinants on integrons with multiple resistance genes may explain the multidrug resistance of many aminoglycoside-resistant *P. aeruginosa* isolates. *aac(6′)* genes are also often associated with integrons (105, 107, 116, 117) or transposons (43, 145) and may be associated with genes for narrow-spectrum β-lactamases (18), extended-spectrum β-lactamases (105, 107, 116, 117), or metallo-β-lactamases (155, 165) as well as with, again, genes encoding other aminoglycoside-modifying enzymes (18, 118). One *aac(6′)-I*-carrying isolate harbored this determinant on a plasmid-borne integron that also contained genes for chloramphenicol (chloramphenicol acetyltransferase), β-lactam (OXA β-lactamase), and gentamicin [ANT(2″)] resistance (18). A recent report (144) of plasmid-encoded amikacin resistance in clinical strains of *P. aeruginosa* may also reflect mobilization of an *aac(6′)* gene on, e.g., a transposon or integron. In one report, too, the *aph(3′)-VIa* gene of the highly amikacin-resistant strain being studied was present on a transposon (82). As with other aminoglycoside-modifying enzymes, genes for ANT enzymes can be integron associated, particularly the *aadA*-encoded ANT(3″) (9) enzyme that inactivates streptomycin and spectinomycin and that is commonplace on class 1 integrons (72, 73, 109, 143, 151, 162); but they can also be encoded by *aadB*, i.e., ANT(2″)-I (18) and, possibly, ANT(4′)-IIb (132). In some instances, too, these occur with other resistance genes, including those encoding β-lactamases (18, 151, 162). The *veb-1* metallo-β-lactamase gene that is typically integron associated can occur together, for example, with genes for both ANT(2″) and ANT(3′) in *P. aeruginosa* (47).

IMPERMEABILITY

Aminoglycoside resistance independent of inactivating enzymes has been known for some time in *P. aeruginosa* (13, 81, 157). Characterized by resistance to all aminoglycosides and often associated with reduced aminoglycoside accumulation (13, 91, 157), such resistance was attributed to reduced uptake owing to reduced permeability and, as such, was typically referred to as impermeability resistance. Numerous studies (74, 99–101, 114, 121, 150) have highlighted the significance of impermeability resistance in aminoglycoside-resistant clinical isolates, particularly in isolates from CF patients (in which it is

often the most common aminoglycoside resistance mechanism [62, 89, 137, 148]), including isolates originally identified as resistant to amikacin (62, 91, 131), gentamicin (13, 114), and tobramycin (89). In some instances, too, impermeability resistance occurs together with inactivating enzymes in promoting multiple aminoglycoside resistance in *P. aeruginosa* (89, 98–101, 127). Reports of an aminoglycoside-resistant variant that was isolated during treatment of experimental endocarditis in rabbits and that lacked enzymes and obvious outer membrane (OM) changes but that showed reduced levels of tobramycin uptake were also suggestive of impermeability resistance (113). Despite earlier conclusions that enzyme-independent resistance associated with reduced accumulation represented impermeability and reduced uptake, more recent studies (153, 164, 168) of such panaminoglycoside-resistant strains indicate that resistance is likely due to efflux (see below).

ADAPTIVE RESISTANCE

The ability to "train" *P. aeruginosa* to grow in the presence of elevated levels of aminoglycosides has been known for some time (61). Characterized by resistance not only to the selecting antimicrobial but to all aminoglycosides and loss of resistance in the absence of drug (46, 61), this reversible panaminoglycoside resistance came to be known as adaptive resistance (71). Shown to occur in vitro (7, 23, 46, 49, 70) and in vivo (8, 24, 171), resistance typically develops within a few hours of first exposure and disappears several hours after removal of the antibiotic. Intriguingly, resistance appears to result from reduced levels of aminoglycoside accumulation (23, 70), reminiscent of impermeability resistance. Indeed, a recent publication confirms the involvement of an aminoglycoside-inducible drug efflux system in the reduced accumulation that characterizes adaptive aminoglycoside resistance (60). Interestingly, adaptively aminoglycoside-resistant *P. aeruginosa* strains also show enhanced expression of genes associated with anaerobic respiration (68). Given the defect in aminoglycoside accumulation seen in anaerobically grown bacteria (138) and the reduced transport capability of *P. aeruginosa* grown with nitrate instead of oxygen as the terminal electron acceptor, it is also possible that reduced uptake also contributes to adaptive aminoglycoside resistance (i.e., aminoglycosides induce anaerobic respiration at the expense of aerobic respiration, and this comprises aminoglycoside uptake [68]).

EFFLUX

Recent studies have clarified the involvement of an efflux system of the resistance-nodulation-division (RND) family (for a review, see reference 120) MexXY (102) (also referred to as AmrAB [168]) in the reduced level of aminoglycoside accumulation that characterizes both impermeability resistance (153, 164, 168) and adaptive aminoglycoside resistance (60) in *P. aeruginosa*. The RND family of pumps is one of five families of drug efflux systems described to date in bacteria (120) and typically consists of three components that include an inner membrane drug-proton antiporter (the RND component), an OM channel-forming protein (the OM factor [OMF]), and a periplasmic link protein (the membrane fusion protein) that joins the other two components (120). MexX and MexY are the periplasmic and inner membrane proteins, respectively, and are encoded by the *mexXY* operon, while the apparent OMF for this system is OprM (1, 102), the product of the third gene of an operon encoding another three-component RND-type pump, MexAB-OprM (1, 93). Still, the demonstration that mutants lacking one of the OM proteins, OpmG, OpmH, or OpmI, were aminoglycoside hypersusceptible suggests that one or more of these may also function with MexXY, perhaps as the intended OMF for this efflux system (64).

MexXY actually accommodates a range of antimicrobials, including macrolides, tetracyclines, glycylcyclines, lincomycin, chloramphenicol, novobiocin, fluoroquinolones, and β-lactams (94, 102, 111), although it is implicated only in resistance to aminoglycosides, erythromycin, tetracyclines, and glycylcyclines in wild-type cells (1, 25), probably because only these agents induce *mexXY* expression (93). Similar three-component RND-type aminoglycoside efflux systems have been described in *Burkholderia pseudomallei* (AmrAB-OprA [103] and BpeAB-OprB [21]) and *Escherichia coli* (AcrAD-TolC [58, 129]). A very modest contribution of MexAB-OprM and a multidrug transporter of the small multidrug resistance family, $EmrE_{P.A.}$, to aminoglycoside resistance has also been noted (84). Interestingly, an in vitro-isolated mutant that was selected on gentamicin and ofloxacin and that showed increased levels of MexXY expression relative to that of the wild type has been reported (94), although it is unclear if MexXY is also responsible for the fluoroquinolone resistance. Certainly, there are as yet no reports of MexXY-mediated fluoroquinolone resistance in clinical strains (and no indication that strains with impermeability resistance are correspondingly fluoroquinolone resistant). Intriguingly, the well-known divalent cation antagonism of aminoglycosides in *P. aeruginosa* is also dependent on the presence of this efflux system (92).

Expression of *mexXY* is under the control of MexZ (also referred to as AmrR [168]) a repressor of the TetR and AcrR family encoded by a gene located immediately upstream of *mexXY* (1, 168). In vitro-constructed knockout mutations in *mexZ* have been shown to increase the level of *mexXY* expression but did not provide for aminoglycoside resistance (168), and in one study (153) MexXY-expressing aminoglycoside-resistant clinical isolates lacked mutations in *mexZ*, suggesting that aminoglycoside resistance attributable to MexXY may require additional components and other means of upregulating *mexXY*. In addition, while a recent report highlighting the presence of *mexZ* mutations in aminoglycoside-resistant clinical isolates expressing *mexXY* indicates that *mexZ* mutations may play a role in *mexXY* expression in clinical strains (164), it is by no means clear that such mutations were sufficient for aminoglycoside resistance. While the most significant observation regarding the regulation of *mexXY* is its inducibility by several substrate antimicrobials, it is unclear if this is mediated by the MexZ repressor (e.g., drugs target MexZ directly, obviating repressor activity, thereby permitting *mexXY* expression, as has been seen for other drug-inducible efflux systems [141]). Alternatively, *mexXY* expression may be responding to, e.g., the interaction of drugs with their ribosome targets; and, indeed, preliminary studies indicate that for some of these, this may well be the case (K. Boisson, M. L. Sobel, K. Poole, and P. Plesiat, unpublished data).

OUTER MEMBRANE

Several early studies documented an apparent role for the OM protein OprH in aminoglycoside resistance-expression of the protein in certain mutants and in cells grown under Mg^{2+}-limiting conditions correlated with resistance (110) and delayed uptake (55) of, e.g., the aminoglycoside streptomycin. Moreover, loss of this protein in specific mutant constructs subsequently restored susceptibility to these agents (176), further highlighting its contribution to resistance. More recent studies have, however, demonstrated that OprH is actually encoded by the first gene of a three-gene operon that includes *phoP* (which encodes a response regulator) and *phoQ* (which encodes a sensor kinase) (88) and that the low Mg^{2+} concentration-dependent and mutational resistance to aminoglycosides previously attributed to OprH is, in fact, related to PhoP-PhoQ activity (87). Apparently, then, previous *oprH* knockout mutations compromised resistance to aminoglycosides because of polar effects on expression of the downstream *phoPQ* genes (87). PhoP and PhoQ are implicated in resistance to polycationic antimicrobials (e.g., polymyxins) (88) and cationic antimicrobial peptides (87), in part because of their role in promoting an aminoarabinose modification of the lipid A portion of lipopolysaccharide (LPS) (97, 104). While the details of PhoPQ involvement in aminoglycoside resistance remain to be fully elucidated and its involvement in resistance to polycations and aminoglycosides appears to differ, it is possible that PhoPQ-dependent aminoglycoside resistance in *P. aeruginosa* involves a similar modification of LPS (97). Certainly, changes to the LPS component of the OM have long been implicated in resistance to aminoglycosides (15, 39, 149, 175), including resistance in clinical isolates (56). This is, perhaps, not surprising, given that LPS appears to be a necessary target for aminoglycoside binding in the process of its uptake across the OM of *P. aeruginosa* (126, 136).

OTHERS

In addition to the mechanisms already described, there are infrequent reports of ribosomal changes (80) and defects in electron transport that adversely affect aminoglycoside uptake (14, 16), contributing to aminoglycoside resistance in *P. aeruginosa*. Recently, too, clinical isolates of *P. aeruginosa* showing high-level panaminoglycoside resistance (in contrast to impermeability resistance, which is typically low- to moderate-level panaminoglycoside resistance) were shown to carry a gene, *rmtA*, that encodes a 16S rRNA methylase (174). Such an enzyme has been reported previously in aminoglycoside-producing actinomycetes; and although it is rarely seen in clinical pathogens, high-level aminoglycoside resistance owing to a 16S rRNA methylase has been reported in both *Serratia marcescens* (30) and *Klebsiella pneumoniae* (42). Significantly, the *rmtA* gene of *P. aeruginosa* appears to be associated with mobile genetic elements (173), which has important implications vis-à-vis the dissemination of this determinant among pathogenic *Pseudomonas* strains and, possibly, other gram-negative bacteria. Finally, the well-known resistance of biofilm-grown *P. aeruginosa* isolates to multiple antimicrobials, including aminoglycosides, is slowly being elucidated, with the demonstrated anaerobic growth of such organisms (56a) likely responsible, to some extent at least, for resistance to agents like aminoglycosides, given the apparent negative impact of anaerobic metabolism on aminoglycoside uptake (see above). A locus involved in the synthesis of periplasmic glucans, *ndvB*, has also recently been implicated in *P. aeruginosa* biofilm resistance to several agents, particularly tobramycin (90a). These glucans, which are specifically expressed in biofilm organisms, bind to tobramycin in vitro; and it has been suggested that similar binding in the periplasm of biofilm cells would restrict this agent's passage into the cytoplasm, where its targets lie.

CONCLUSIONS

While aminoglycosides remain useful agents for the treatment of severe *P. aeruginosa* infections, resistance continues to be an issue, particularly in Latin America and parts of Europe. As with any antimicrobial there are geographical variations in resistance rates that likely reflect differences in aminoglycoside prescription patterns and/or the quality of infection control practices, although geographical differences in the occurrence of individual aminoglycoside resistance determinants might also play a role. While the specificity of aminoglycoside-modifying enzymes, historically the major determinants of resistance to these agents, has in the past tended to compromise the use of only selected aminoglycosides, leaving others still effective, the increasing prevalence of strains harboring multiple aminoglycoside-modifying enzymes coupled with panaminoglycoside-exporting efflux systems threatens to compromise the use of this class of agents as a whole. The recent discovery, too, of a genetic determinant (*rmtA*) responsible for high-level panaminoglycoside resistance in *P. aeruginosa* is of great concern, given its probable mobility. Still, as with any agent, the prudent use of aminoglycosides and the use of effective infection control practices can go a long way to limiting the development and spread of aminoglycoside resistance, ensuring that these agents continue to find a place in the treatment of *P. aeruginosa* infections.

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