

# [Pseudomonas aeruginosa: resistance to the max](https://assignbuster.com/pseudomonas-aeruginosa-resistance-to-the-max/)

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## Introduction

*Pseudomonas aeruginosa* is a common nosocomial pathogen ( [Hidron et al., 2008](#B65) ; [Jones et al., 2009](#B83) ; [Zhanel et al., 2010](#B231) ) that causes infections with a high mortality rate ( [Mutlu and Wunderink, 2006](#B138) ; [Kerr and Snelling, 2009](#B88) ; [Mahar et al., 2010](#B117) ; [Lambert et al., 2011](#B97) ). This latter is, in part, attributable to the organism’s intrinsically high resistance to many antimicrobials ( [Poole, 2002](#B166) ) and the development of increased, particularly multidrug resistance in healthcare settings ( [Rossolini and Mantengoli, 2005](#B182) ; [Ferrara, 2006](#B43) ; [Giamarellos-Bourboulis et al., 2006](#B48) ; [Paterson, 2006](#B151) ; [Kerr and Snelling, 2009](#B88) ; [Shorr, 2009](#B195) ; [Hirsch and Tam, 2010](#B67) ; [Kallen et al., 2010](#B86) ; [Keen III, et al., 2010](#B87) ), both of which complicate anti-pseudomonal chemotherapy. Indeed, numerous studies point to a link between multidrug resistance and increased morbidity/mortality, as well as increased length of hospital stay and increased hospital costs ( [Slama, 2008](#B196) ; [Kerr and Snelling, 2009](#B88) ; [Mauldin et al., 2010](#B125) ; [Tumbarello et al., 2011](#B210) ). While acquisition of resistance genes [e. g., those encoding β-lactamases ( [Gupta, 2008](#B54) ; [Zhao and Hu, 2010](#B235) ) and aminoglycoside-modifying enzymes ( [Poole, 2005](#B169) ; [Ramirez and Tolmasky, 2010](#B176) )] via horizontal gene transfer can and do drive antimicrobial/multidrug resistance development in *P. aeruginosa* ( [Strateva and Yordanov, 2009](#B202) ), more commonly mutations of chromosomal genes (target site, efflux mutations) explain resistance in this organism ( [Lister et al., 2009](#B105) ; [Strateva and Yordanov, 2009](#B202) ). This review provides an overview of antimicrobial resistance in *P. aeruginosa* that is acquired, either via mutation of endogenous genes or via acquisition of exogenous resistance genes.

## Resistance to β-Lactams

β-Lactams, including penicillins (e. g., ticarcillin, piperacillin), cephalosporins (e. g., ceftazidime, cefepime), carbapenems (e. g., imipenem, meropenem), and monobactams (e. g., aztreonam) are commonly used in the treatment of *P. aeruginosa* infections ( [Paul et al., 2010](#B153) ). Resistance to these agents is increasing ( [Jones et al., 2009](#B83) ; [Zilberberg et al., 2010](#B237) ) and mediated by a variety of mechanisms, most commonly antibiotic cleavage by β-lactamase enzymes, antibiotic expulsion by chromosomally encoded efflux mechanisms and reduced drug uptake owing to loss of outer membrane porin proteins ( [Poole, 2004b](#B168) ; [Pfeifer et al., 2010](#B155) ).

### β-Lactamases

β-Lactamases, hydrolytic enzymes that disrupt the amide bond of the classical four-membered β-lactam ring thus rendering the antimicrobial ineffective, are a major determinant of resistance in Gram-negative bacteria, including *P. aeruginosa* . Four molecular classes of these enzymes have been described (A–D) and include metal dependent (Zn 2+ -requiring; class B) and metal-independent (active site serine; classes A, C, and D) β-lactamases (reviewed in [Helfand and Bonomo, 2003](#B63) ), all of which have been reported in *P. aeruginosa* ( [Zhao and Hu, 2010](#B235) ).

#### Endogenous β-lactamases

*Pseudomonas aeruginosa* typically carries chromosomal genes for two β-lactamases, a class C cephalosporinase, AmpC ( [Lodge et al., 1990](#B111) ), and a class D oxacillinase, PoxB ( [Girlich et al., 2004](#B52) ; [Kong et al., 2005](#B94) ). AmpC is a well-characterized β-lactamase ( [Jacoby, 2009](#B76) ) commonly linked to β-lactam resistance in clinical isolates ( [Arora and Bal, 2005](#B4) ; [Bratu et al., 2007](#B14) ; [Reinhardt et al., 2007](#B177) ; [Tam et al., 2007](#B206) , [2010](#B205) ; [Drissi et al., 2008](#B32) ; [Vettoretti et al., 2009](#B213) ; [Upadhyay et al., 2010](#B211) ; [Xavier et al., 2010](#B228) ) while PoxB activity was only detected in lab mutants lacking AmpC and its clinical significance is uncertain. AmpC, which is a common chromosomally encoded enzyme in many Gram-negative bacteria ( [Poole, 2004b](#B168) ; [Jacoby, 2009](#B76) ), is inducible by a number of β-lactam antibiotics (e. g., benzyl penicillin and narrow-spectrum cephalosporins) and thus contributes to intrinsic (i. e., natural, non-mutational) resistance to these ( [Livermore, 1991](#B107) ). It is not, however, inducible by monobactams (aztreonam; [Sakurai et al., 1990](#B186) ), the anti-pseudomonal penicillin piperacillin ( [Livermore, 1995](#B109) ), and many of the newer cephalosporins (e. g., cefotaxime, ceftriaxone, ceftazidime; [Livermore and Yang, 1987](#B110) ; [Livermore, 1995](#B109) ; [Poole, 2004b](#B168) ) that are, nonetheless, good substrates for the enzyme and as such resistance is dependent upon mutational derepression of *ampC* . Indeed, mutational derepression of *ampC* is the most common mechanism of resistance to β-lactams in *P. aeruginosa* ( [Arora and Bal, 2005](#B4) ; [Tam et al., 2007](#B206) ; [Drissi et al., 2008](#B32) ; [Xavier et al., 2010](#B228) ), including expanded-spectrum cephalosporins (e. g., ceftazidime; [Juan et al., 2005](#B84) ; [Picao et al., 2009a](#B156) ; [Queenan et al., 2010](#B175) ) and penicillins (e. g., ticarcillin; [Cavallo et al., 2007](#B22) ; [Dubois et al., 2008](#B35) ). Interestingly, while carbapenems (e. g., imipenem) are excellent inducers of *ampC* , their rapid bactericidal activity and stability to hydrolysis renders them effective against AmpC + *P. aeruginosa* ( [Jones, 1998](#B82) ) although derepressed AmpC appears to contribute to carbapenem resistance in conjunction with other mechanisms of resistance (e. g., loss of porin protein D; see below). Recently, the production of AmpC variants with improved activity against oxyiminocephalosporins (e. g., ceftazidime), cefepime, and carbapenems (including imipenem), first described in the Enterobacteriacae and referred to as extended-spectrum AmpC (ESAC; [Nordmann and Mammeri, 2007](#B141) ), have been reported in clinical isolates of *P. aeruginosa* ( [Rodriguez-Martinez et al., 2009a](#B180) , [b](#B181) ). These, too, appear to contribute to carbapenem resistance in conjunction with loss of OprD ( [Rodriguez-Martinez et al., 2009b](#B181) ).

#### Acquired β-lactamases

While the original β-lactamases were plasmid-encoded restricted-spectrum class A enzymes that only hydrolyzed penicillins and older, narrow-spectrum cephalosporins, more recently described acquired β-lactamases in *P. aeruginosa* include the extended-spectrum β-lactamase (ESBL) enzymes (classes A and D) able to hydrolyze a wider range of β-lactams, including the broad-spectrum cephalosporins and monobactams, and the carbapenemases (classes A, B, and D) that hydrolyze most β-lactams, including the carbapenems, but not aztreonam ( [Zhao and Hu, 2010](#B235) ). ESBLs and carbapenemases are typically encoded by plasmid- or transposon-bone genes, often on integrons ( [Poirel and Nordmann, 2002](#B164) ; [Castanheira et al., 2004](#B21) ; [Walsh et al., 2005](#B219) ; [Naas et al., 2006](#B139) ; [Bogaerts et al., 2007](#B10) ; [Gupta, 2008](#B54) ; [Li et al., 2008](#B101) ; [Castanheira et al., 2009](#B20) ; [Zhao et al., 2009](#B234) ; [Kotsakis et al., 2010](#B95) ; [Poirel et al., 2010b](#B160) ), genetic elements capable of capturing, and subsequently mobilizing resistance genes ( [Cambray et al., 2010](#B17) ), although some β-lactamase genes are associated with novel mobile insertion sequences termed IS *CR* elements ( [Poirel et al., 2004](#B163) ; [Picao et al., 2009a](#B156) , [b](#B157) ; [Kotsakis et al., 2010](#B95) ).

*Extended-spectrum β-lactamases.* More commonly reported in the Enterobacteriaceae, though present also in *P. aeruginosa* , ESBLs typically hydrolyze and, so, provide resistance to broad-spectrum cephalosporins (e. g., the third generation oxyiminocephalosporins cefotaxime and ceftazidime) and aztreonam, in addition to penicillins and narrow-spectrum cephalosporins (reviewed in [Paterson and Bonomo, 2005](#B152) ; [Bush, 2008](#B16) ). Classical ESBLS have evolved from restricted-spectrum class A TEM and SHV β-lactamases although a variety of non-TEM, non-SHV class A ESBLS have been described (e. g., CTX-M, PER, VEB, GES, BEL; [Poole, 2004b](#B168) ; [Paterson and Bonomo, 2005](#B152) ) and class D ESBLs derived from narrow-spectrum OXA β-lactamases are also well-known ( [Paterson and Bonomo, 2005](#B152) ; [Poirel et al., 2010b](#B160) ).

Class A ESBLs are typically identified in *P. aeruginosa* isolates showing resistance to ceftazidime (e. g., [De Champs et al., 2002](#B26) ; [Girlich et al., 2002](#B51) ; [Strateva et al., 2007](#B201) ; [Hocquet et al., 2010](#B70) ]. VEB-type ESBLs were the predominant ESBL reported in *P. aeruginosa* in a number of studies where ESBLs were commonly seen ( [Jiang et al., 2006](#B79) ; [Strateva et al., 2007](#B201) ; [Woodford et al., 2008](#B226) ; [Shahcheraghi et al., 2009](#B191) ) although PER-type ESBLs were also well-represented ( [Celenza et al., 2006](#B23) ; [Endimiani et al., 2006](#B38) ; [Shahcheraghi et al., 2009](#B191) ; [Glupczynski et al., 2010](#B53) ). While BEL-1 ( [Poirel et al., 2005](#B158) ; [Bogaerts et al., 2007](#B10) ) and CTX-M ( [al Naiemi et al., 2006](#B3) ; [Picao et al., 2009b](#B157) ) ESBLs are not frequently observed in *P. aeruginosa* , they were the predominant ESBLs reported in ESBL + *P. aeruginosa* in a Belgium study ( [Glupczynski et al., 2010](#B53) ) and a Bolivian study ( [Celenza et al., 2006](#B23) ), respectively. Recently, a second BEL ESBL, BEL-2 with enhanced activity against expanded-spectrum cephalosporins was recovered in Belgium ( [Poirel et al., 2010a](#B159) ). Similarly, a high prevalence of an SHV ESBL was reported in one study ( [Shahcheraghi et al., 2009](#B191) ) although this β-lactamase is seldom reported in *P. aeruginosa* ( [Mansour et al., 2009](#B120) ; [Hocquet et al., 2010](#B70) ). TEM-( [Dubois et al., 2005](#B36) ; [Shahcheraghi et al., 2009](#B191) ) and GES-( [Labuschagne et al., 2008](#B96) ; [Picao et al., 2009a](#B156) ; [Viedma et al., 2009](#B214) ; [Kotsakis et al., 2010](#B95) ) type ESBLs have also been described in *P. aeruginosa* .

Class D OXA enzymes (so named because of their preference for oxacillin and cloxacillin over benzylpenicillin, though not all class D enzymes show this property), are mostly narrow-spectrum β-lactamases that confer resistance to amino- and carboxypenicillins and narrow-spectrum cephalosporins ( [Poirel et al., 2010b](#B160) ) although several OXA-type enzymes are ESBLs (reviewed in [Poirel et al., 2010b](#B160) ). Occurring predominantly in *P. aeruginosa* these confer resistance to cefotaxime ( [Danel et al., 1999](#B24) ; [Aubert et al., 2001](#B5) ; [Fournier et al., 2010](#B45) ) or ceftazidime ( [Toleman et al., 2003](#B207) ; [Juan et al., 2009](#B85) ; [Fournier et al., 2010](#B45) ; [Hocquet et al., 2010](#B70) ), with some OXA β-lactamases also linked to resistance and/or reduced susceptibility to cefepime ( [Aubert et al., 2001](#B5) ; [Toleman et al., 2003](#B207) ; [Juan et al., 2009](#B85) ; [Fournier et al., 2010](#B45) ; [Liu et al., 2010](#B106) ) and/or aztreonam ( [Toleman et al., 2003](#B207) ; [Juan et al., 2009](#B85) ; [Fournier et al., 2010](#B45) ).

*Carbapenemases.* Carbapenems (e. g., meropenem, imipenem) are an important class of anti-pseudomonal β-lactam owing to their stability to most β-lactamases (see [El Gamal and Oh, 2010](#B37) for a recent review of carbapenems) and are of particular use in treating infections associated with ESBL- and AmpC-producers. β-lactamases capable of hydrolyzing carbapenems are known (reviewed in [Queenan and Bush, 2007](#B174) ; [Walsh, 2010](#B218) ) and include class A and class D carbapenemases (the latter also referred to as carbapenem-hydrolyzing class D β-lactamases, CHDLs; [Poirel et al., 2010b](#B160) ) and class B metallo-β-lactamases (MBLs; reviewed in [Walsh et al., 2005](#B219) ), though there are no hitherto reports of CHDLs in *P. aeruginosa* .

Class A β-lactamases with activity against carbapenems are uncommon and can be divided into five groups (GES, IMI, KPC, NMC-A, and SME; reviewed in [Walther-Rasmussen and Hoiby, 2007](#B220) ) of which only GES and KPC enzymes have been described to date in *P. aeruginosa* ( [Zhao and Hu, 2010](#B235) ). KPC enzymes show activity against most β-lactams including oxyiminocephalosporins, monobactams, and carbapenems and while they occur as yet rarely in *P. aeruginosa* (only KPC-2 and KPC-5 have been reported in this organism) the number of reports of KPC-producing *P. aeruginosa* is increasing ( [Villegas et al., 2007](#B215) ; [Akpaka et al., 2009](#B2) ; [Wolter et al., 2009a](#B223) ; [Poirel et al., 2010c](#B161) ). Interestingly, KPC-2 is more active against carbapenems than is KPC-5 while the latter shows better activity against ceftazidime ( [Wolter et al., 2009b](#B224) ). Of note, too, the presence of KPC enzymes in carbapenem-resistant isolates is often coupled with loss of the OprD outer membrane porin ( [Villegas et al., 2007](#B215) ; [Wolter et al., 2009a](#B223) ) that is the primary route of entry of these agents into *P. aeruginosa* ( [Trias and Nikaido, 1990](#B209) ). While all GES enzymes are ESBLs three of these also show reasonable activity against carbapenems (GES-2, -4, and -5), with GES-2 and -5 having been reported in *P. aeruginosa* ( [Walther-Rasmussen and Hoiby, 2007](#B220) ; [Viedma et al., 2009](#B214) ; [Wang et al., 2010](#B221) ).

Class B MBLs are by far the major determinants of β-lactamase-mediated resistance to carbapenems and the major cause of high-level resistance to these agents. Acquired MBLs include the VIM and IMP enzymes, of which there are numerous variants of the original VIM-1 and IMP-1 MBLs, as well as the SPM-1, GIM-1, NDM-1, AIM-1, and SIM-1 enzymes ( [Gupta, 2008](#B54) ; [Walsh, 2010](#B218) ). The VIM and IMP enzymes are by far the most common MBLs found in carbapenem-resistant bacteria ( [Walsh et al., 2005](#B219) ), including carbapenem-resistant *P. aeruginosa* ( [Gupta, 2008](#B54) ). The predominance of VIM vs. IMP in *P. aeruginosa* appears to be geographical, with IMP-type MBLs predominating in Asia where it was first discovered and VIM-type enzymes predominating in Europe though both enzymes are now disseminated globally, with VIM-2 in particular well established on five continents ( [Gupta, 2008](#B54) ; [Walsh, 2010](#B218) ; [Zhao and Hu, 2010](#B235) ). There are single reports, only, of the GIM-1 (found in five isolates from Germany; [Castanheira et al., 2004](#B21) ) and the AIM-1 ( [Gupta, 2008](#B54) ) MBLs in *P. aeruginosa* . SPM-1 is the predominant MBL in Brazil ( [Sader et al., 2005](#B184) ; [Picao et al., 2009a](#B156) ) and while previously found only in Brazilian clinical isolates it has now been reported in Europe ( [Salabi et al., 2010](#B187) ).

### Efflux

Five families of efflux systems that export and provide resistance to antimicrobials in bacteria have been described ( [Li and Nikaido, 2009](#B102) ) although members of the Resistance Nodulation Division (RND) family appear to be the most significant contributors to antimicrobial resistance in *P. aeruginosa* ( [Poole, 2004a](#B167) , [2007](#B170) ). There are 12 RND-type efflux systems present in *P. aeruginosa* of which three, MexAB-OprM, MexCD-OprJ, and MexXY-OprM have been shown to accommodate and provide resistance to β-lactams ( [Poole, 2004b](#B168) ). MexAB-OprM accommodates the broadest range of β-lactams (amongst these pumps) and is most frequently linked to β-lactam resistance in clinical isolates ( [Drissi et al., 2008](#B32) ; [Tomas et al., 2010](#B208) ). The MexXY-OprM efflux system has also been linked to β-lactam resistance in clinical isolates of *P. aeruginosa* (as one of several contributors; [Maniati et al., 2007](#B119) ; [Vettoretti et al., 2009](#B213) ). While MexAB-OprM, MexCD-OprJ, and MexXY-OprM have all been shown to accommodate carbapenems (except imipenem; [Okamoto et al., 2002](#B143) ) MexAB-OprM is by far the better exporter of these agents and the pump has been shown to contribute to reduced susceptibility to meropenem in clinical isolates ( [Pai et al., 2001](#B149) ; [Pournaras et al., 2005](#B172) ). Still, efflux appears to be a minor contributor to carbapenem resistance in this organism, typically operating in conjunction with other mechanisms ( [Quale et al., 2006](#B173) ; [Dotsch et al., 2009](#B30) ; [Hammami et al., 2009](#B60) ; [Wang et al., 2010](#B221) ). MexAB-OprM has also been implicated in resistance to the penicillin ticarcillin ( [Boutoille et al., 2004](#B13) ; [Cavallo et al., 2007](#B22) ; [Hocquet et al., 2007](#B71) ) and its expression linked statistically to aztreonam resistance ( [Quale et al., 2006](#B173) ). MexXY production, too, has been noted in ticarcillin-resistant *P. aeruginosa* ( [Hocquet et al., 2007](#B71) ) although a contribution to resistance was not proven and this efflux system is more commonly associated with resistance to the fourth generation cephalosporin cefepime in clinical isolates ( [Hocquet et al., 2006](#B69) ; [Pena et al., 2009](#B154) ). Indeed, cefepime commonly selects for MexXY-derepressed mutants *in vitro* ( [Queenan et al., 2010](#B175) ). MexXY-OprM was also responsible for reduced susceptibility to ceftobiprole in a clinical study of this the novel broad-spectrum cephalosporin ( [Baum et al., 2009](#B8) ) and mutants expressing *mexXY* are readily selected by this β-lactam *in vitro* ( [Queenan et al., 2010](#B175) ). Although MexCD-OprJ accommodates cefepime ( [Masuda et al., 2000](#B122) ) it has rarely been linked to resistance to this agent in clinical isolates ( [Jeannot et al., 2008](#B78) ).

### Permeability

By far the most common mechanism of resistance to the carbapenems (including imipenem) in *P. aeruginosa* is loss or alteration of the outer membrane porin protein OprD ( [Rodriguez-Martinez et al., 2009b](#B181) ; [Wang et al., 2010](#B221) ), the major portal for entry for carbapenems ( [Trias and Nikaido, 1990](#B209) ). While not providing the high-level resistance seen in MBL-producers, loss of OprD function is the major determinant of non-MBL-mediated resistance to these agents ( [Gutierrez et al., 2007](#B56) ; [Rodriguez-Martinez et al., 2009b](#B181) ; [Tomas et al., 2010](#B208) ; [Wang et al., 2010](#B221) ), often seen operating in conjunction with other mechanisms [e. g., derepressed *ampC* ( [Gutierrez et al., 2007](#B56) ; [Rodriguez-Martinez et al., 2009b](#B181) ; [Tomas et al., 2010](#B208) ; [Wang et al., 2010](#B221) ) or MexAB-OprM ( [Gutierrez et al., 2007](#B56) ; [Tomas et al., 2010](#B208) ; [Wang et al., 2010](#B221) )]. Indeed, carbapenem resistance resulting from loss of OprD requires the presence of AmpC (inducible or stably derepressed; [Livermore, 1992](#B108) ).

## Resistance to Fluoroquinolones

Fluoroquinolones (FQs), particularly ciprofloxacin, are commonly used in the treatment of *P. aeruginosa* infections. Resistance to these agents, particularly high-level resistance, is predominantly mediated by mutations in the DNA gyrase and topoismerase IV enzymes that are the targets of the FQs, though efflux is a significant contributing actor ( [Jacoby, 2005](#B75) ; [Drlica et al., 2009](#B33) ) often in combination with target site mutations ( [Higgins et al., 2003](#B66) ; [Henrichfreise et al., 2007](#B64) ; [Rejiba et al., 2008](#B178) ; [Tam et al., 2010](#B205) ).

### Target Site Mutations

The FQ class of antimicrobial acts on bacterial topoisomerases [topoisomerase II (a. k. a. gyrase) and topoisoemrase IV] that are responsible for the introduction and/or removal of supercoils in, as well as catenation/decatenation of DNA and, thus, play an essential role in DNA replication, transcription, recombination, and repair ( [Drlica and Zhao, 1997](#B34) ). In Gram-negative bacteria, gyrase is the preferred target of FQs, and resistance mutations thus tend to occur in this enzyme first with additional mutations in topoisomerase IV seen in some highly resistant isolates ( [Jacoby, 2005](#B75) ). DNA gyrase (GyrA and GyrB) and topoisomerase (ParC and ParE) are each comprised of two subunits, with FQ resistance mutations typically occurring in the so-called “ quinolone resistance determining region” (QRDR) of GyrA and/or ParC ( [Jacoby, 2005](#B75) ; [Drlica et al., 2009](#B33) ). Such mutations are common in FQ-resistant *P. aeruginosa* ( [Higgins et al., 2003](#B66) ; [Lee et al., 2005](#B99) ; [Muramatsu et al., 2005](#B137) ; [Henrichfreise et al., 2007](#B64) ; [Rejiba et al., 2008](#B178) ) with highly resistant isolates carrying multiple mutations in *gyrA* and/or *parC* ( [Nakano et al., 1997](#B140) ; [Higgins et al., 2003](#B66) ; [Lee et al., 2005](#B99) ; [Muramatsu et al., 2005](#B137) ), with mutations in *gyrB* ( [Lee et al., 2005](#B99) ; [Muramatsu et al., 2005](#B137) ; [Schwartz et al., 2006](#B190) ) and *parE* ( [Lee et al., 2005](#B99) ; [Rejiba et al., 2008](#B178) ) less common.

### Efflux

Four members of the RND family of multidrug efflux systems, MexAB-OprM, MexCD-OprJ, MexEF-oprN, and MexXY-OprM are known to accommodate FQs ( [Poole, 2000](#B165) ) and these efflux systems have been implicated in FQ resistance in clinical isolates ( [Poole, 2000](#B165) ; [Wolter et al., 2004](#B225) ; [Zhanel et al., 2004](#B232) ; [Reinhardt et al., 2007](#B177) ). Expression of *mexAB-oprM* is controlled directly or indirectly by three repressors, MexR ( [Srikumar et al., 2000](#B200) ), NalD ( [Morita et al., 2006](#B132) ) and NalC ( [Cao et al., 2004](#B19) ), and mutations in *mexR* ( [Henrichfreise et al., 2007](#B64) ), *nalC* ( [Henrichfreise et al., 2007](#B64) ) and *nalD* ( [Tomas et al., 2010](#B208) ) have been reported in FQ-resistant clinical isolates. *mexCD-oprJ* expression is controlled by a single known regulator, the NfxB repressor ( [Poole et al., 1996](#B171) ), and lab ( [Poole et al., 1996](#B171) ) and clinical ( [Jalal et al., 2000](#B77) ; [Higgins et al., 2003](#B66) ; [Henrichfreise et al., 2007](#B64) ) isolates expressing this efflux system and resistant to FQs invariably contain mutations in *nfxB* ( [Jalal et al., 2000](#B77) ; [Higgins et al., 2003](#B66) ; [Henrichfreise et al., 2007](#B64) ). Still, *mexCD-oprJ* -expressing mutants appear to be rare in a clinical setting ( [Jeannot et al., 2008](#B78) ; [Kiser et al., 2010](#B91) ). Unlike the other FQ-exporting RND-type efflux systems, expression of *mexEF-oprN* is regulated by a transcriptional activator, MexT ( [Köhler et al., 1999](#B92) ; [Ochs et al., 1999](#B142) ). Unusually, many wild type stains carry inactivating mutations in *mexT* ( [Maseda et al., 2000](#B121) ), with *mexEF-oprN* expression and resistance resulting from reversion of these mutations ( [Maseda et al., 2000](#B121) ). These so-called *nfxC* mutants ( [Köhler et al., 1997](#B93) ), which have been described in the clinic ( [Fukuda et al., 1995](#B46) ; [Jalal et al., 2000](#B77) ), also show resistance to carbapenems such as imipenem, though not because MexEF-orpN accommodates these agents but because of a coordinate, MexT-dependent reduction of OprD in such mutants ( [Köhler et al., 1999](#B92) ; [Ochs et al., 1999](#B142) ). Hyperexpression of this efflux system (and reduction in OprD production) is also seen in lab isolates disrupted in the *mexS* gene encoding a putative oxidoreductase (a. k. a qrh; [Köhler et al., 1999](#B92) ) of unknown function ( [Sobel et al., 2005](#B199) ). Expression of *mexXY* is controlled by a single known regulator, the MexZ repressor ( [Matsuo et al., 2004](#B123) ), and *mexZ* mutations have been reported in lab-selected FQ-resistant isolates hyperexpressing *mexXY* ( [Hocquet et al., 2008](#B68) ). *mexXY* -hyperexpressing FQ-resistant isolates lacking mutations in *mexZ* have also been described although the mutation(s) responsible were not identified ( [Hocquet et al., 2008](#B68) ). Despite its ability to accommodate FQs, however, MexXY-OprM has seldom been linked to FQ resistance in clinical isolates ( [Wolter et al., 2004](#B225) ).

## Resistance to Aminoglycosides

A number of aminoglycosides are commonly used in the treatment of *P. aeruginosa* infections (e. g., tobramycin, gentamicin, amikacin; [Gilbert et al., 2003](#B49) ; [Bartlett, 2004](#B7) ), particularly pulmonary infections in patients with cystic fibrosis (CF) where amikacin and, in particular, tobramycin are routinely employed ( [Canton et al., 2005](#B18) ; [Taccetti et al., 2008](#B203) ). Their use is, however, linked to resistance development, with acquired aminoglycoside-modifying enzymes (AMEs) and rRNA methylases, and endogenous efflux mechanisms typically responsible ( [Poole, 2005](#B169) ).

### Aminoglycoside-Modifying Enzymes

Aminoglycoside modification leading to antibiotic inactivation typically involves their phosphorylation (by aminoglycoside phosphoryltransferases, APHs), acetylation (by aminoglycoside acetyltransferases, AACs), or adenylation (by aminoglycoside nucleotidyltransferases, ANTs; aka. aminoglycoside adenylyltransferase, AAD; see [Ramirez and Tolmasky, 2010](#B176) for a recent review of these modifying enzymes). AMEs are common determinants of aminoglycoside resistance in *P. aeruginosa* (reviewed in detail in [Poole, 2005](#B169) ) except in CF isolates where these mechanisms are almost unknown ( [Shawar et al., 1999](#B194) ; [Henrichfreise et al., 2007](#B64) ; [Islam et al., 2009](#B74) ). Genes for AMEs are typically found on integrons with other resistance genes ( [Poole, 2005](#B169) ; [Ramirez and Tolmasky, 2010](#B176) ) and, as such, AME-haboring isolates are often multidrug-resistant.

#### Aminoglycoside acetyltransferases

Acetylation of aminoglycosides can occur at 1-, 3-, 6′-, and 2′-amino groups and involve virtually all medically useful compounds (e. g., gentamicin, tobramycin, and amikacin; [Ramirez and Tolmasky, 2010](#B176) ). Enzymes that modify the 3 [3- *N* -aminoglycoside acetyltransferases, AAC(3)] ( [Biddlecome et al., 1976](#B9) ) and 6′ [6′- *N* -aminoglycoside acetyltransferases, AAC(6′)] ( [Haas et al., 1976](#B58) ) positions are the most common acetyltransferases ( [Ramirez and Tolmasky, 2010](#B176) ) and, with ANT(2”) (see below) the most common enzymes providing for aminoglycoside resistance in this organism ( [Poole, 2005](#B169) ; [Shahid and Malik, 2005](#B192) ; [Dubois et al., 2008](#B35) ). The AAC(3) family, of which five subfamilies have been described in *P. aeruginosa* (I, II, II, IV, and VI; [Kim et al., 2008](#B90) ; [Zhao et al., 2009](#B234) ; [Ramirez and Tolmasky, 2010](#B176) ), is a common determinant of gentamicin resistance in this organism, less commonly contributing to tobramycin resistance (subfamilies II, III, and VI; [Poole, 2005](#B169) ). The AAC(6′) family, of which two major subfamilies have been described in *P. aeruginosa* (I and II; and many variants of the I subfamily; [Ramirez and Tolmasky, 2010](#B176) ), is the major AAC family contributing to aminoglycoside resistance in *P. aeruginosa* , with subfamily II predominating ( [Poole, 2005](#B169) ). AAC(6′) enzymes are major determinants of resistance to tobramycin and amikacin (subfamily I) and tobramycin and gentamicin (subfamily II; [Poole, 2005](#B169) ), although some subfamily I variants lack activity against amikacin (e. g., Ib, Ib′; [Galimand et al., 1993](#B47) ; [MacLeod et al., 2000](#B115) ). Owing to irregularities in AAC(6′) nomenclature, several of these enzymes that have been reported in *P. aeruginosa* lack a roman numeral subclass designation (e. g., AAC(6′)-29a, -29b, -30, -32, -33; [Ramirez and Tolmasky, 2010](#B176) ) and of these AAC(6′)-29a and -29b provide resistance to amikacin and tobramycin ( [Poirel et al., 2001](#B162) ) while AAC(6′)-30 exists as part of a bifunctional AAC(6′)-30/AAC(6′)-Ib′ enzyme that promotes resistance to tobramycin and only reduced susceptibility to amikacin and gentamicin ( [Mendes et al., 2004](#B127) ). A novel aminoglycoside acetyltransferase that exhibits FQ-acetylating activity, AAC(6′)-Ib-cr, has also been described in *P. aeruginosa* ( [Libisch et al., 2008](#B103) ).

#### Aminoglycoside nucleotidyltransferases

The most prevalent nucleotidyltransferase in *P. aeruginosa* is the ANT(2′)-I enzyme which inactivates gentamicin and tobramycin but not amikacin and is, thus, found in gentamicin- and tobramycin-resistant clinical isolates ( [Poole, 2005](#B169) ). A less common nucleotidyltransferases associated with aminoglycoside resistance in *P. aeruginosa* is ANT(4′)-II which provides resistance to tobramycin and amikacin ( [Poole, 2005](#B169) ; [Ramirez and Tolmasky, 2010](#B176) ). Two variants of this enzyme, ANT(4′)-IIa ( [Shaw et al., 1993](#B193) ) and -IIb ( [Sabtcheva et al., 2003](#B183) ) have been described in amikacin-resistant clinical isolates and there is a report of an *ant(4* ′ *)-I* gene in *P. aeruginosa* although its contribution to resistance was not established ( [Jin et al., 2009](#B80) ). While there are a number of reports of the ANT(3′) nucleotidyltransferase in *P. aeruginosa* ( [Ramirez and Tolmasky, 2010](#B176) ) this enzyme is active against streptomycin and none of the clinically used anti-pseudomonal aminoglycosides.

#### Aminoglycoside phosphoryltransferases

Aminoglycoside phosphoryltransferases found in *P. aeruginosa* are almost invariably 3′ enzymes that act on the 3-OH of target aminoglycosides and generally provide resistance to aminoglycosides not typically used to treat *P. aeruginosa* infections (kanamycin, neomycin, and streptomycin; [Poole, 2005](#B169) ). APH(3′)-II predominates in clinical isolates resistant to kanamycin (and neomycin; [Miller et al., 1994](#B128) ; [Poole, 2005](#B169) ) and, indeed, a chromosomal *aphA* -encoded APH(3′)-II type enzyme, APH(3′)-IIb ( [Hachler et al., 1996](#B59) ) is likely responsible for the general insensitivity of *P. aeruginosa* to kanamycin. APH enzymes that provide resistance to other aminoglycosides have also been described in *P. aeruginosa* and include APH(3′)-VI (amikacin; [Kettner et al., 1995](#B89) ; [Kim et al., 2008](#B90) ; [Jin et al., 2009](#B80) ), APH(3′)-IIb-like (amikacin, weakly; [Riccio et al., 2001](#B179) ), and APH(2”) (gentamicin and tobramycin; [Kettner et al., 1995](#B89) ).

### Efflux

Aminoglycoside resistance independent of inactivating enzymes has been known for some time in *P. aeruginosa* ( [Bryan et al., 1976](#B15) ). Characterized by resistance to all aminoglycosides and often associated with reduced aminoglycoside accumulation ( [Bryan et al., 1976](#B15) ) such resistance, particularly common in CF isolates (reviewed in [Poole, 2005](#B169) ), was attributed to reduced uptake owing to reduced permeability and, as such, was typically referred to as impermeability resistance. It is now known, however, that this resistance was likely due to efflux mediated by the MexXY-OprM multidrug efflux system. Indeed, this efflux system has been implicated in aminoglycoside resistance in clinical isolates, particularly CF isolates, in a number of studies ( [Sobel et al., 2003](#B198) ; [Hocquet et al., 2006](#B69) ; [Henrichfreise et al., 2007](#B64) ; [Islam et al., 2009](#B74) ).

The MexXY-OprM system is encoded by the *mexXY* operon that is under the control of the MexZ repressor ( [Matsuo et al., 2004](#B123) ) and the *oprM* gene of the *mexAB-oprM* multidrug efflux operon. Mutations in *mexZ* are common in pan-aminoglycoside-resistant CF isolates of *P. aeruginosa* expressing *mexXY* ( [Poole, 2005](#B169) ; [Hocquet et al., 2006](#B69) ; [Henrichfreise et al., 2007](#B64) ; [Islam et al., 2009](#B74) ; [Feliziani et al., 2010](#B41) ) with *mexZ* , in fact, identified as the most commonly mutated gene in CF isolates ( [Smith et al., 2006](#B197) ; [Feliziani et al., 2010](#B41) ). A number of studies highlight, however, the absence of mutations in *mexZ* or the *mexXY* promoter region in *mexXY* -expressing aminoglycoside-resistant CF isolates ( [Sobel et al., 2003](#B198) ; [Hocquet et al., 2006](#B69) ; [Islam et al., 2009](#B74) ), indicating that additional genes/mutations are linked to expression of this efflux locus in *P. aeruginosa* . A recent report of an *in vitro* -selected *mexXY* -expressing aminoglycoside-resistant mutant lacking a *mexZ* mutation identified a novel gene, *parR* , as the site of mutation ( [Muller et al., 2010](#B136) ). *parR* forms part of a two-gene operon, *parRS* , encoding a two-component regulatory systems that impacts expression of several antimicrobial resistance determinants in *P. aeruginosa* (e. g., *oprD* ), including *mexXY* . Significantly, mutations in *parR* are present in some clinical isolates that express *mexXY* but lack mutations in *mexZ* ( [Muller et al., 2010](#B136) ).

### 16S rRNA Methylases

A more recently discovered aminoglycoside resistance mechanism involves methylation of the 16S rRNA of the A site of the 30S ribosomal subunit, which interferes with aminoglycoside binding and so promotes high-level resistance to clinically relevant aminoglycosides like gentamicin, tobramycin, and amikacin (reviewed in [Doi and Arakawa, 2007](#B28) ). A number of different pan-aminoglycoside resistance-promoting 16S rRNA methylases have been described in *P. aeruginosa* , including RmtA ( [Yamane et al., 2004](#B229) ; [Jin et al., 2009](#B80) ), RmtB ( [Zhou et al., 2010](#B236) ), RmtD ( [Doi et al., 2007](#B29) ; [Lincopan et al., 2010](#B104) ), and ArmA ( [Gurung et al., 2010](#B55) ; [Zhou et al., 2010](#B236) ). RmtD is frequently co-produced with the SPM-1 MLB that predominates in Brazil ( [Doi et al., 2007](#B29) ; [Lincopan et al., 2010](#B104) ) and co-carriage of ArmA and the IMP-1 MBL has also been reported in *P. aeruginosa* isolates from Korea ( [Gurung et al., 2010](#B55) ).

## Resistance to Polycationic Antimicrobials

Owing to the increased prevalence of multidrug-resistant *P. aeruginosa* , “ older” antimicrobials like the polymyxins (polymyxin B and colistin) are back in favor, with earlier issues surrounding nephrotoxicity largely dealt with ( [Zavascki et al., 2007](#B230) ; [Molina et al., 2009](#B129) ). While these agents, and colistin in particular, are quite efficacious in the treatment of multidrug-resistant *P. aeruginosa* infections ( [Montero et al., 2009](#B130) ; [Falagas et al., 2010](#B40) ) there are reports of resistance to both polymyxin B ( [Landman et al., 2005](#B98) ; [Abraham and Kwon, 2009](#B1) ; [Barrow and Kwon, 2009](#B6) ) and colistin ( [Johansen et al., 2008](#B81) ; [Matthaiou et al., 2008](#B124) ; [Samonis et al., 2010](#B188) ) in clinical isolates. While in many cases the mechanism(s) of clinical polymyxin resistance are unknown, substitution of LPS lipid A with aminoarabinose has been shown to contribute to polymyxin resistance in *P. aeruginosa in vitro* ( [Moskowitz et al., 2004](#B133) ) and in CF isolates ( [Ernst et al., 1999](#B39) ). This modification is carried out by the products of the *arnBCADTEF* - *ugd* locus (a. k. a. *pmrHFIJKLM-ugd* and PA3552–59) that is regulated both by PhoPQ ( [Macfarlane et al., 2000](#B113) ) and a second two-component regulatory system, PmrAB ( [McPhee et al., 2003](#B126) ; [Moskowitz et al., 2004](#B133) ), with mutations in *phoQ* and *pmrB* shown to promote ArnBCADTEF-dependent polymyxin B resistance in clinical isolates ( [Abraham and Kwon, 2009](#B1) ; [Barrow and Kwon, 2009](#B6) ). A third two-component system, ParRS, also controls *arnBCADTEF* - *ugd* expression ( [Fernandez et al., 2010](#B42) ), with a mutation in *parR* linked to ArnBCADTEF-mediated polymyxin resistance in a lab isolate ( [Muller et al., 2010](#B136) ). *parR* (and *parS* ) mutations have been noted in clinical isolates, although there was no indication that the *arn* locus was upregulated, and the polymyxin resistance of these isolates was minimal ( [Muller et al., 2010](#B136) ).

## Biofilm Resistance

Biofilms, surface-attached three-dimensional structures in which bacteria are imbedded in a matrix comprised of polysaccharide, protein, and DNA, are increasingly recognized as the preferred mode of bacterial growth in nature and infectious disease ( [Lopez et al., 2010](#B112) ). This is true of *P. aeruginosa* ( [Harmsen et al., 2010](#B61) ), particularly in the case of pulmonary infections in patients with CF ( [Wagner and Iglewski, 2008](#B216) ; [Davies and Bilton, 2009](#B25) ). An important consequence of *P. aeruginosa* biofilm growth and one that is particularly relevant in a clinical context is marked resistance to antimicrobial agents ( [Davies and Bilton, 2009](#B25) ; [Hoiby et al., 2010](#B73) ). Antimicrobial resistance of *P. aeruginosa* biofilms appears to be complex, multifactorial, and in many instances not well understood ( [Drenkard, 2003](#B31) ; [Hoiby et al., 2010](#B73) ). Some studies indicate that *P. aeruginosa* within biofilms are metabolically less active and grow more slowly than cells at the biofilm periphery (owing to limited access to nutrients and oxygen; [Werner et al., 2004](#B222) ), which may contribute to increasing biofilm tolerance to antimicrobials since antimicrobials often target metabolically active cells ( [Pamp et al., 2008](#B150) ). Certainly, the suggestion that biofilm-grown *P. aeruginosa* from CF patients are anaerobic ( [Hassett et al., 2009](#B62) ) is likely to be significant in the context of antimicrobial resistance since many agents are inactive or less active under anaerobiosis ( [Schobert and Tielen, 2010](#B189) ). Oxygen limitation has, in fact, been shown to contribute significantly to the antimicrobial resistance of *in vitro* -grown *P. aeruginosa* biofilms ( [Borriello et al., 2004](#B11) ).

One explanation for biofilms being generally refractory to antimicrobial chemotherapy is the presence, in biofilms, of a highly resistant sub-population of cells called persisters ( [Lewis, 2008](#B100) ). Intriguingly, “ late” isolates of *P. aeruginosa* in CF (those recovered later in infection) produce increased levels of drug-tolerant persister cells, which may be the primary “ mechanism” for surviving chemotherapy and, so, may explain the general recalcitrance of *P. aeruginosa* infections in CF ( [Mulcahy et al., 2010](#B134) ). The idea of a sub-population of biofilm cells displaying different patterns of antimicrobial susceptibility is supported by a recent study showing that only the mobile cells responsible for forming the “ cap” component of the typical *P. aeruginosa* biofilm mushroom structures exhibited tolerance to colistin, as a result of colistin triggering PmrAB-dependent expression of the *arn* LPS modification locus ( [Haagensen et al., 2007](#B57) ; [Pamp et al., 2008](#B150) ). While the details of persister formation and the mechanism(s) responsible for persister resistance remain unknown, a preliminary screen of a transposon insertion mutant library for mutants showed altered persister formation identified several genes whose disruption either increased or decreased persister formation ( [De Groote et al., 2009](#B27) ).

Aminoglycosides have been shown to induce biofilm formation by *P. aeruginosa* , in a process that requires a gene, *arr* (aminoglycoside response regulator; [Hoffman et al., 2005](#B72) ). *arr* encodes a phosphodiesterase that impacts the levels of bis-(3′, 5′)-cyclic-di-guanidine monophosphate (c-di-GMP; [Hoffman et al., 2005](#B72) ), a second messenger known to influence biofilm formation ( [Harmsen et al., 2010](#B61) ) and lack of *arr* compromises biofilm resistance to aminoglycosides ( [Hoffman et al., 2005](#B72) ). Given that c-di-GMP production is generally correlated with biofilm formation ( [Harmsen et al., 2010](#B61) ) it is unclear how Arr-promoted turnover of this second messenger would promote biofilm formation. A second gene linked to biofilm-specific resistance to aminoglycosides in some strains only, *ndvB* , is involved in the synthesis of periplasmic (and intracellular) glucans that bind aminoglycosides (tobramycin), suggestive of a mechanism of resistance whereby aminoglycosides are sequestered and prevented from reaching their targets in the cytosol ( [Mah et al., 2003](#B116) ). These glucans, which have recently been purified and identified as highly glycerol-phosphorylated β-(1 → 3) glucans, actually form part of the biofilm matrix where they do, indeed, bind aminoglycosides ( [Sadovskaya et al., 2010](#B185) ). A tripartite ABC-family efflux system that is preferentially expressed in biofilm vs. planktonic cells, PA1875-PA1876-PA1877, has also been linked to biofilm-specific aminoglycoside résistance ( [Zhang and Mah, 2008](#B233) ). Efflux (mediated by MexCD-OprJ) has also been linked to biofilm-specific resistance to azithromycin in *P. aeruginosa* ( [Gillis et al., 2005](#B50) ; [Mulet et al., 2009](#B135) ).

## Hypermutation and Resistance

Hypermutable (or mutator) *P. aeruginosa* exhibiting increased mutation rates are common in chronic infections such as those that occur in the lungs of CF patients (see [Oliver, 2010](#B144) ; [Oliver and Mena, 2010](#B147) ; for reviews of hypermutation in CF isolates). The hypermutation phenotype of mutator stains results from defects in DNA repair, predominantly in the mismatch repair (MMR) system ( [Oliver, 2010](#B144) ), with mutations in *mutS* ( [Oliver et al., 2002](#B145) ; [Macia et al., 2005](#B114) ; [Feliziani et al., 2010](#B41) ), *mutL* ( [Oliver et al., 2002](#B145) ; [Feliziani et al., 2010](#B41) ), and *uvrD* (a. k. a *mutU* ; [Oliver et al., 2002](#B145) ) typically responsible. Significantly from an antimicrobial resistance standpoint, mutator strains show higher rates of antimicrobial resistance development than non-mutator strains ( [Oliver et al., 2000](#B146) ; [Ferroni et al., 2009](#B44) ), with the mutator phenotype of CF isolates often correlating with antimicrobial, including multidrug, resistance ( [Macia et al., 2005](#B114) ; [Waine et al., 2008](#B217) ; [Ferroni et al., 2009](#B44) ; [Feliziani et al., 2010](#B41) ; [Tam et al., 2010](#B205) ; reviewed in [Oliver, 2010](#B144) ).

A second DNA repair system less commonly linked to the mutator phenotype in *P. aeruginosa* is the DNA oxidative repair (GO) system charged with repairing and preventing incorporation into DNA of an oxidatively damaged form of guanosine (8-oxo-2′-deoxyguanosine, 8-oxodG; [Oliver and Mena, 2010](#B147) ). *In vitro* studies have shown that knockouts in the GO genes *mutT* and *mutY* yield increased mutation rates concomitant with increased oxidative damage of DNA ( [Mandsberg et al., 2009](#B118) ), with *mutT* ( [Mandsberg et al., 2009](#B118) ; [Morero and Argarana, 2009](#B131) ) and *mutY* ( [Mandsberg et al., 2009](#B118) ) strains also showing higher rates of antimicrobial resistance. Given that the characteristically chronically inflamed CF lung is an environment rich in reactive oxygen species (ROS) that can damage DNA, the potential for ROS-promoted hypermutability owing to defects in the GO system is certainly real. Although uncommon, mutator strains with lesions in *mutT* and *mutY* have been recovered from CF patients ( [Mandsberg et al., 2009](#B118) ).

## Concluding Remarks

Rates of infection and resistance are increasing in *P. aeruginosa* ( [Talbot et al., 2006](#B204) ; [Kerr and Snelling, 2009](#B88) ), and with reports of colistin-only sensitive *P. aeruginosa* and the presence of colistin-resistance in this organism the untreatable *P. aeruginosa* infection may be imminent. Compounding the increasing lack of effective anti-pseudomonal agents is the paucity of new drugs being developed that are active against *P. aeruginosa* and, indeed, the absence of any late-stage agents effective against pan-resistant *P. aeruginosa* ( [Talbot et al., 2006](#B204) ; [Boucher et al., 2009](#B12) ; [Page and Heim, 2009](#B148) ). The few novel agents with anti-pseudomonad activity (e. g., the siderophore–monobactam hybrid, BAL30072, the anti-pseudomonal cephalosporin CXA-101, and the MBL inhibitor ME1071) are, unfortunately, negatively impacted by known resistance mechanisms ( [Page and Heim, 2009](#B148) ). While the lack of classical antimicrobial options has prompted research into novel anti-pseudomonal strategies/agents, including a humaneered anti- *P. aeruginosa* Fab antibody fragment, KB001, cationic antimicrobial peptides, efflux pump inhibitors, modulators of virulence ( [Page and Heim, 2009](#B148) ; [Veesenmeyer et al., 2009](#B212) ), and phage therapy ( [Wright et al., 2009](#B227) ), only KB001 is in later stage clinical trials ( [Page and Heim, 2009](#B148) ). Clearly, more therapeutic options are needed. Given the resistance armamentarium available to *P. aeruginosa* and the observation that drug use begets resistance, more also needs to be done in the areas of antimicrobial stewardship, resistance surveillance, and infection control ( [Kerr and Snelling, 2009](#B88) ). With limited (and shrinking) options, and an environment where anti-infectives, generally, are not being developed and fewer and fewer resources are being devoted to this therapeutic area by the major pharmaceutical companies ( [Boucher et al., 2009](#B12) ) prudent management of available agents and more robust resistance monitoring and infection control practices are essential. While these will likely not prevent the rise of untreatable pan-resistant *P. aeruginosa* , hopefully their numbers and impact can be limited.

## Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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