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REVIEW

Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant *Pseudomonas aeruginosa* Infections

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SUMMARY In recent years, the worldwide spread of the so-called high-risk clones of multidrug-resistant or extensively drug-resistant (MDR/XDR) *Pseudomonas*

aeruginosa has become a public health threat. This article reviews their mechanisms of resistance, epidemiology, and clinical impact and current and upcoming therapeutic options. *In vitro* and *in vivo* treatment studies and pharmacokinetic and pharmacodynamic (PK/PD) models are discussed. Polymyxins are reviewed as an important therapeutic option, outlining dosage, pharmacokinetics and pharmacodynamics, and their clinical efficacy against MDR/XDR *P. aeruginosa* infections. Their narrow therapeutic window and potential for combination therapy are also discussed. Other "old" antimicrobials, such as certain β-lactams, aminoglycosides, and fosfomycin, are reviewed here. New antipseudomonals, as well as those in the pipeline, are also reviewed. Ceftolozane-tazobactam has clinical activity against a significant percentage of MDR/XDR *P. aeruginosa* strains, and its microbiological and clinical data, as well as recommendations for improving its use against these bacteria, are described, as are those for ceftazidime-avibactam, which has better activity against MDR/XDR *P. aeruginosa*, especially strains with certain specific mechanisms of resistance. A section is devoted to reviewing upcoming active drugs such as imipenem-relebactam, cefepime-zidebactam, cefiderocol, and murepavadin. Finally, other therapeutic strategies, such as use of vaccines, antibodies, bacteriocins, anti-quorum sensing, and bacteriophages, are described as future options.

KEYWORDS *Pseudomonas aeruginosa*

INTRODUCTION

There are several major reasons why the emergence and dissemination of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Pseudomonas aeruginosa* strains have recently become issues of public health concern. First, *P. aeruginosa* causes severe infections, particularly in health care settings and in immunocompromised patients. Second, it has an outstanding capacity for being selected and for spreading antimicrobial resistance *in vivo* (1, 2). Third, the successful worldwide spread of the so-called "high-risk" clones of *P. aeruginosa* poses a threat to global public health that needs to be studied and managed with urgency and determination (3).

The lack of therapeutic alternatives means that infections caused by these antibiotic-resistant bacteria pose a considerable threat regarding morbidity and mortality worldwide. The impact of inadequate therapy in these infections is significant; indeed, the World Health Organization reported in 2017 that carbapenem-resistant *P. aeruginosa* was listed in the "critical" group for which new antibiotics were urgently required (4).

Recent years have witnessed an increasing prevalence of MDR and XDR *P. aeruginosa* strains, with rates of between 15% and 30% in some geographical areas (5–7). Most countries in Europe report rates of resistance of more than 10% for all antimicrobial groups under surveillance (8). Combined resistance is also common in *P. aeruginosa*. In 2015, the European Centers for Disease Prevention and Control stated that 13.7% of *P. aeruginosa* isolates were resistant to at least three antimicrobial groups and 5.5% to all five antimicrobial groups under surveillance (EARS-Net) (8). According to data from the United States, MDR *P. aeruginosa* is the cause of 13% of severe health care-associated infections (9).

The solutions to this crisis are to allocate more resources to basic and clinical research and to infection control and antimicrobial stewardship, to develop new antimicrobials, and to optimize the use of those that are currently available. This article reviews the current definitions and mechanisms of multidrug resistance in *P. aeruginosa* and the epidemiology of high-risk clones disseminated worldwide. Based on the information available, current and upcoming therapeutic options are reviewed, including clinical studies and, where these are lacking, *in vitro* and animal studies. It should be noted that most clinical studies have methodological limitations and that interpretation of the evidence is difficult.

OVERVIEW OF *P. AERUGINOSA* RESISTANCE MECHANISMS

Intrinsic *P. aeruginosa* Resistance (Intrinsic Resistome)

P. aeruginosa has a remarkable array of mechanisms of antibiotic resistance in its arsenal, including multiple chromosomal determinants as well as the complex regulatory pathways involved in intrinsic and adaptive resistance (1, 2, 10–13). The mechanisms thought to have the greatest effect on the lower natural susceptibility of *P. aeruginosa* compared to other Gram-negative microorganisms are inducible AmpC cephalosporinase expression, constitutive (MexAB-OprM) and inducible (MexXY) efflux pump production, and low outer membrane permeability. Since the aminopenicillins and a number of cephalosporins (cefoxitin, in particular) are strong inducers of expression and are also efficiently hydrolyzed by AmpC, inducible β-lactamase production has a key role in the natural resistance of *P. aeruginosa* to these agents. Inducible AmpC expression plays a decisive role in the natural reduced susceptibility of *P. aeruginosa* to imipenem, since the hydrolytic stability of this antibiotic is to some degree affected by its high inducer potency. Two other chromosomal β-lactamases, the OXA enzyme OXA-50/PoxB (14, 15) and the more recently described imipenemase (PA5542) (16), may also have an impact on intrinsic β-lactam susceptibility levels, although their role in intrinsic and/or acquired resistance requires further elucidation. Constitutive expression of the MexAB-OprM efflux pump plays a major role in lower basal levels of susceptibility to the vast majority of β-lactams (except for imipenem) and fluoroquinolones, whereas inducible production of MexXY has a major effect on the intrinsic low-level resistance to aminoglycosides (17). In addition to these well-known resistance determinants, an analysis of mutant libraries resulting from whole-genome screening has revealed a large set of genes, referred to collectively as the intrinsic resistome, which have an effect on antibiotic susceptibility (2, 16, 18, 19).

Acquisition of Resistance through Chromosomal Gene Mutations (Mutational Resistome)

Apart from its vast intrinsic resistome, *P. aeruginosa* shows an outstanding ability to develop further antimicrobial resistance to all available antibiotics via the acquisition of chromosomal mutations. Table 1 provides a summary of the main genes known to increase resistance levels and thus shape the *P. aeruginosa* mutational resistome (3).

Overproduction of chromosomal AmpC cephalosporinase, involving a broad range of genes belonging to the complex regulatory cell wall recycling pathways, is probably the most common mutation-driven β-lactam resistance mechanism. It has been detected in over 20% of *P. aeruginosa* clinical isolates (13, 20, 21). Mutational inactivations of *dacB* (which encodes PBP4) and *ampD* (which encodes an *N*-acetylmuramyl-L-alanine amidase) are known to be the most common mechanisms of *ampC* hyperproduction and β-lactam resistance (21, 22). Inactivation of PBP4 has also been demonstrated to activate the CreBC/BlrAB two-component system, increasing resistance levels further (21). Specific mutations leading to modification of the conformation of the transcriptional regulator AmpR, which regulates *ampC* overexpression and β-lactam resistance, have also been detected in clinical strains. These mutations include D135N, documented in species other than *P. aeruginosa*, and the R154H mutation, associated with the epidemic MDR/XDR ST175 high-risk clone (13). Mutations in various other genes have been found to upregulate *ampC*, including those encoding other amidases (AmpDh2/AmpDh3), other penicillin-binding proteins (PBP5 or PBP7), lytic transglycosylases (MltB and SltB1), MPL (UDP-*N*-acetylmuramate:L-alanyl-γ-D-glutamyl-*meso*-diaminopimelate ligase), and NuoN (NADH dehydrogenase I chain N). Nevertheless, further analysis of their effect on β-lactam resistance in natural strains is still required (13).

Apart from AmpC hyperproduction, recent studies have highlighted the fact that mutations leading to the structural modification of AmpC may be the cause of resistance to β-lactams, including the novel β-lactam–β-lactamase inhibitor combinations ceftolozane-tazobactam and ceftazidime-avibactam (23–26). Another study detected several amino acid variants in AmpC in a small proportion (approximately 1%)

TABLE 1 Main genes known to be involved in *P. aeruginosa* mutational antibiotic resistance

Gene(s)	Resistance mechanism	Antibiotics affected
gyrA	Quinolone target modification (DNA gyrase)	Fluoroquinolones
gyrB	Quinolone target modification (DNA gyrase)	Fluoroquinolones
parC	Quinolone target modification (DNA topoisomerase IV)	Fluoroquinolones
parE	Quinolone target modification (DNA topoisomerase IV)	Fluoroquinolones
pmrA, *pmrB*, *phoQ*, *cprS*, *colR*, *colS*	Lipopolysaccharide modification (addition of the 4-amino-4-deoxy-L-arabinose moiety to the lipid A portion)	Polymyxins
parR	Lipopolysaccharide modification (addition of the 4-amino-4-deoxy-L-arabinose moiety to the lipid A portion)	Polymyxins
	OprD downregulation	Imipenem, meropenem
	MexEF-OprN hyperproduction	Fluoroquinolones
	MexXY hyperproduction	Fluoroquinolones, aminoglycosides, cefepime
parS	Lipopolysaccharide modification (addition of the 4-amino-4-deoxy-L-arabinose moiety to the lipid A portion)	Polymyxins
	OprD downregulation	Imipenem, meropenem
	MexEF-OprN hyperproduction	Fluoroquinolones
	MexXY hyperproduction	Fluoroquinolones, aminoglycosides, cefepime
mexR, *nalC*, *nalD*	MexAB-OprM hyperproduction	Fluoroquinolones, ceftazidime, cefepime, piperacillin-tazobactam, meropenem, ceftazidime-avibactam
nfxB	MexCD-OprJ hyperproduction	Fluoroquinolones, cefepime
mexS	MexEF-OprN hyperproduction	Fluoroquinolones
	OprD downregulation	Imipenem, meropenem
mexT	MexEF-OprN hyperproduction	Fluoroquinolones
	OprD downregulation	Imipenem, meropenem
cmrA, *mvaT*, *PA3271*	MexEF-OprN hyperproduction	Fluoroquinolones
mexZ, *PA5471.1*, *amgS*	MexXY hyperproduction	Fluoroquinolones, aminoglycosides, cefepime
oprD	OprD porin inactivation	Imipenem, meropenem
ampC	AmpC structural modification	Ceftolozane-tazobactam, ceftazidime-avibactam
ampD, *ampDh2*, *ampDh3*, *ampR*, *dacB*, *mpl*	AmpC hyperproduction	Ceftazidime, cefepime, piperacillin-tazobactam
ftsI	β-Lactam target modification (PBP3)	Ceftazidime, cefepime, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem
fusA1	Aminoglycoside target modification (elongation factor G)	Aminoglycosides
glpT	Inactivation of transporter protein GlpT	Fosfomycin
rpoB	Rifampin target modification, RNA polymerase β-chain	Rifampin

of *P. aeruginosa* clinical isolates that were linked to ceftolozane-tazobactam and ceftazidime-avibactam resistance (27). To date, over 300 *Pseudomonas*-derived cephalosporinase (PDC) variants have been reported, some of which confer increased ceftolozane-tazobactam and ceftazidime-avibactam resistance. An updated database of PDC variants is available free from Antonio Oliver's laboratory at https://arpbigidisba.com. In addition to β-lactamases, there is growing evidence of the role of PBP modification in β-lactam resistance, especially mutations in PBP3 (encoded by *ftsI*). Recent data from cystic fibrosis (CF) patients (28, 29), epidemic strains (30, 31), and *in vitro* studies (32, 33) have shown that specific mutations in PBP3 play a role in the emergence of β-lactam resistance. Those most frequently reported are R504C/R504H and F533L, located in domains involved in the stabilization of the β-lactam–PBP3 inactivation complex (34).

Loss of the carbapenem-specific porin OprD may be the result either of inactivating mutations/insertion sequences in the *oprD* gene or of remote mutations that upregulate efflux system MexEF-OprN or CzcCBA with concomitant downregulation of *oprD*

expression. Mutational inactivation or downregulation of the OprD porin (along with inducible AmpC production) drives imipenem resistance and decreased meropenem susceptibility. The prevalence of imipenem resistance is frequently above 20%, and most of the isolates involved are OprD deficient (20, 35). OprD inactivation frequently acts synergistically with AmpC overexpression to drive resistance to all the classic antipseudomonal β-lactams (36). Mutational overexpression of one of the four major efflux pumps of *P. aeruginosa* also plays a major role in mutation-driven resistance (17, 20, 37, 38). Overexpression of MexAB-OprM and MexXY is common (10% to 30%) among clinical isolates, whereas the prevalence of MexCD-OprJ and MexEF-OprN overexpression is considerably lower ($<$5%). MexAB-OprM has the widest substrate spectrum, and mutation-driven overexpression of this efflux pump results in reduced susceptibility to fluoroquinolones and all β-lactams (except imipenem). The combination of MexAB-OprM overexpression and OprD inactivation is one of the major causes of resistance to meropenem among clinical strains (35). Apart from its role in intrinsic aminoglycoside resistance, mutation-driven hyperproduction of MexXY is a common driver of resistance to cefepime in clinical strains (39). MexCD-OprJ or MexEF-OprN hyperproduction is less prevalent and mainly affects fluoroquinolones, although the mutations (*mexT*/*mexS*) that drive MexEF-OprN hyperproduction also determine resistance to imipenem due to the repression of *oprD* (40). Overexpression of MexCD-OprJ, which is particularly prevalent in chronic infections, also drives increased cefepime MICs, despite determining increased susceptibility to several β-lactams and aminoglycosides (41).

Apart from efflux pump overexpression, *P. aeruginosa* fluoroquinolone resistance frequently arises from mutations in DNA gyrases (GyrA and GyrB) and type IV topoisomerases (ParC and ParE) (42). The prevalence of fluoroquinolone resistance varies according to geography but is over 30 to 40% in multiple countries. Studies have recently shown that, in addition to MexXY overexpression and horizontally acquired mechanisms (see below), aminoglycoside resistance may result from mutations in *fusA1*, encoding elongation factor G, and indeed, specific FusA1 mutations have been shown to confer aminoglycoside resistance *in vitro* (43, 44) and in clinical strains, particularly among CF patients (29, 44, 45). The role of specific *fusA1* mutations in resistance has also been demonstrated using site-directed mutagenesis (46).

Finally, while the prevalence of colistin resistance remains relatively low ($<$5%), it has grown recently, possibly because of increased use of colistin as a last-resort agent for the treatment of infections caused by MDR/XDR strains. Colistin resistance frequently results from the modification of the lipid A moiety of lipopolysaccharide (LPS) following the addition of 4-amino-4-deoxy-L-arabinose (47). The mutations involved are frequently linked to the two-component regulatory systems PmrAB and PhoPQ, which lead to activation of the *arnBCADTEF* operon. More recently, it has been shown that mutations in the ParRS two-component regulator not only drive colistin resistance by activating the *arnBCADTEF* operon but also lead to an MDR profile through overexpression of MexXY and downregulation of OprD (12). Two other two-component regulators (ColRS and CprRS) are also known to be involved in polymyxin resistance (48).

Horizontally Acquired Resistance Mechanisms (Horizontally Acquired Resistome)

In addition to mutational resistance, which is relatively frequent, transferable resistance in *P. aeruginosa* is another area of increasing concern. Indeed, there is a growing prevalence worldwide of the most troublesome of transferable β-lactamases, the extended-spectrum β-lactamases (ESBLs) and carbapenemases (especially class B carbapenemases, or metallo-β-lactamases [MBLs]), although the distribution is not uniform and ranges from below 1% to nearly 50%, depending on the hospital and geographic area (49). Furthermore, the challenge of detecting transferable β-lactamases in *P. aeruginosa* may mean that their prevalence has been underestimated in several areas (50). The genes encoding ESBLs and carbapenemases are generally found in class 1 integrons along with determinants of aminoglycoside

resistance. These integrons are often inserted into transposable elements located on the bacterial chromosome, although the involvement of conjugative elements is increasingly reported (51–54). Transferable β-lactamases detected so far in *P. aeruginosa* were recently reviewed by Potron et al. (55). The most frequently reported ESBLs in *P. aeruginosa* include those in class D (such as OXA-2 or OXA-10 variants) and class A (PER, VEB, GES, BEL, and PME). Class A ESBLs typically documented in the order *Enterobacteriales* (such as TEM, SHV, or CTX-M β-lactamases) are infrequently documented in *P. aeruginosa*. With respect to the carbapenemases, MBLs are by far the most prevalent in *P. aeruginosa*, with the VIM and IMP types being the most frequent and the most geographically widespread. The SPM MBL is prevalent in Brazil, and NDM, GIM, and FIM are detected only occasionally. Finally, the worldwide prevalence of class A carbapenemases in *P. aeruginosa* is low, although GES and KPC enzymes have been detected in several countries (54).

Transferable aminoglycoside resistance is most frequently driven by aminoglycoside-modifying enzymes encoded in class 1 integrons. Those most commonly described in *P. aeruginosa* are acetyltransferases from the AAC(3′) (gentamicin) and AAC(6′) (tobramycin including amikacin or not) groups and nucleotidyltransferase ANT(2′)-I (gentamicin and tobramycin) (1). Nevertheless 16S rRNA methyltransferases (such as Rmt or Arm), which confer resistance to all aminoglycosides on the market, including the novel plazomicin, also represent major emerging threats (55). Transferable fluoroquinolone resistance driven mainly by Qnr determinants such as QnrVC1 has occasionally been detected (56). A very recent study has also reported the occurrence of plasmid-mediated quinolone resistance apparently driven by a novel phosphotransferase, CrpP (57).

The novel combinations ceftolozane-tazobactam and ceftazidime-avibactam are known to be relatively stable against AmpC hydrolysis (58, 59), relying on the stability of ceftolozane against hydrolysis by AmpC in the case of ceftolozane-tazobactam and on the inhibitory activity of avibactam against AmpC in the case of ceftazidime-avibactam. However, recent *in vitro* and *in vivo* data indicate that the development of resistance to both agents may be the result of a combination of mutations leading to hyperproduction and the structural modification of AmpC (23, 25–27). Available *in vitro* and *in vivo* data also suggest that specific PBP3 mutations may reduce susceptibility to both combinations. On the other hand, overexpression of different efflux pumps seems to affect ceftazidime-avibactam susceptibility more than that of ceftolozane-tazobactam (27, 60).

With respect to acquired β-lactamases, neither ceftolozane-tazobactam nor ceftazidime-avibactam shows activity against MBL-producing strains. However, ceftazidime-avibactam, but not ceftolozane-tazobactam, may show activity against isolates producing class A carbapenemases such as GES enzymes (61). Likewise, the activity of ceftolozane-tazobactam and ceftazidime-avibactam against ESBL-producing *P. aeruginosa* isolates is variable, but it is generally favorable in the case of ceftazidime-avibactam. Finally, extended-spectrum mutations in horizontally acquired OXA-type β-lactamases may lead to the emergence of resistance to both agents (25, 62, 63).

EPIDEMIOLOGY OF MULTIDRUG-RESISTANT *P. AERUGINOSA*: DEFINITIONS AND PREVALENCE

Over the last decades, various definitions of MDR *P. aeruginosa* profiles have been used, although the consensus definition that is probably most widely used at present is the one published by Magiorakos et al. (64) in 2012. Multidrug resistance (MDR) was defined as nonsusceptibility (intermediate plus resistant [I+R]) to at least one agent in at least 3 antibiotic classes, extensive drug resistance (XDR) as nonsusceptibility to at least one agent in all but 1 or 2 antibiotic classes, and pan-drug resistance (PDR) as nonsusceptibility to all agents in all classes. The following classes and antibiotics were recommended for testing: antipseudomonal cephalosporins (ceftazidime and cefepime), antipseudomonal penicillins plus β-lactamase inhibitors (ticarcillin-clavulanate and piperacillin-tazobactam), monobactams (aztreonam), antipseudomonal carbapenems

(imipenem, meropenem, and doripenem), aminoglycosides (gentamicin, tobramycin, amikacin, and netilmicin), fluoroquinolones (ciprofloxacin and levofloxacin), phosphonic acids (fosfomycin), and polymyxins (colistin and polymyxin B). While this proposal was certainly useful for the harmonization of definitions of *P. aeruginosa* resistance profiles, several other aspects remain to be considered. First, even if a single definition is used, the result will vary depending on whether EUCAST or CLSI breakpoints are used. Second, the comprehensive application of the proposed definition is limited by the lack of clinical breakpoints (both CLSI and EUCAST) for one of the agents (fosfomycin). Similarly, until 2019, EUCAST breakpoints for aztreonam considered *P. aeruginosa* intrinsically nonsusceptible to this agent and therefore not applicable to MDR/XDR/PDR definitions based on acquired resistance. Finally, the current definition does not consider recently introduced antipseudomonal agents such as ceftazidime-avibactam or ceftolozane-tazobactam.

Regardless of the question of definitions mentioned above and the mechanisms involved, the prevalence of MDR *P. aeruginosa* is probably increasing worldwide, although with major geographical differences. The prevalence of MDR *P. aeruginosa* has increased over the last few decades and is now within the 15 to 30% range in multiple areas (5–7, 56). Furthermore, a significant proportion of MDR strains also meet the criteria for classification as XDR, which further restricts the treatment options available. As an example, a recent (2017) large-scale (51 hospitals) multicenter study of *P. aeruginosa* infections performed in Spain showed that 26% of isolates were MDR and 65% of those (17% of all isolates) met the criteria for XDR, and most were susceptible only to colistin including amikacin or not (56). Indeed, in many hospitals worldwide, colistin-only-sensitive (COS) profiles are not uncommon and pan-drug resistance has already been documented (65, 66). However, resistance to the novel antipseudomonal agents ceftolozane-tazobactam and ceftazidime-avibactam was not considered in most of these studies. While the overall prevalence of resistance to these new therapeutic options is below 10%, there is considerable geographical variation depending on the prevalence of acquired β-lactamases such as ESBLs or carbapenemases (31, 66–70).

Epidemic High-Risk Clones

An analysis of the molecular epidemiology of *P. aeruginosa* isolates obtained from hospital-acquired infections, CF patients, or the environment typically reveals high clonal diversity, with most isolates being linked to unique genotypes, However, a closer look shows that this is true for antibiotic-susceptible isolates but not for those showing MDR/XDR phenotypes. Indeed, there have been multiple epidemic outbreak reports and alerts of MDR/XDR strains in the hospital environment for decades. More recent studies have provided further evidence of the MDR/XDR global clones, referred to as "high-risk" clones, disseminated in several hospitals worldwide (71). *P. aeruginosa* high-risk clones were recently reviewed (3). A map of the worldwide distribution of the most prevalent high-risk clones is provided in Fig. 1 and a summary of their characteristics in Table 2.

With regard to the prevalence and impact of high-risk clones, a 2008–2009 multicenter study of *P. aeruginosa* bacteremia carried out in Spain revealed that the vast majority of susceptible isolates were represented by single genotypes but that clonal diversity was much lower among MDR and, especially, XDR strains (72, 73). Seventy-three of 81 (90%) XDR isolates in fact were found to belong to just 3 clones, which were those of the major international MDR/XDR high-risk clones: ST175 (62), ST111 (9), and ST235 (5, 10). In a multicenter study performed 7 years later, ST175 continued to be the most common high-risk clone (68% of XDR isolates) (31). The same pattern was found in several studies worldwide, with most of the MDR/XDR isolates being linked to these and a few other clones (74–78). Of the three major high-risk clones, ST235, associated with serotype O11, is without doubt the most widespread, being found in many countries across all five continents (3, 79). ST111 (serotype O12) also has a worldwide distribution and has so far been documented on every continent except

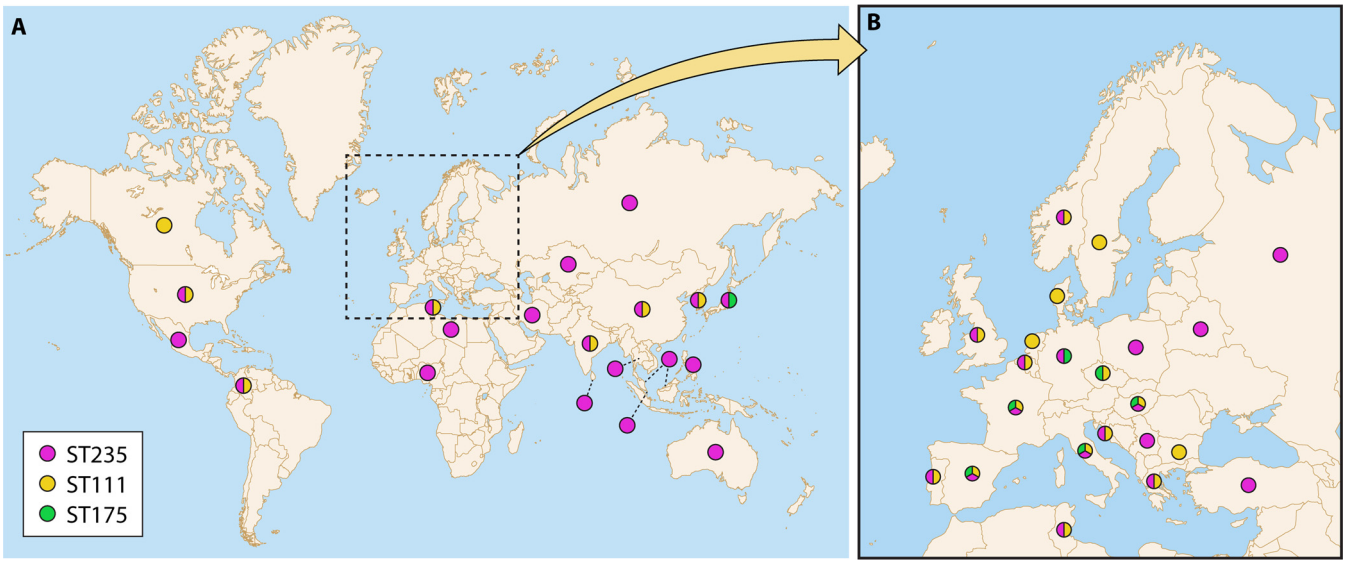

FIG 1 World distribution (A) and European distribution (B) of ST235, ST111, and ST175 based on published data. (Reproduced from reference 3 with permission from Elsevier.)

Oceania. Finally, ST175 (serotype O4) is widely distributed in several European countries. Interestingly, even though susceptible isolates have probably been studied less than MDR isolates, the available information suggests that these clones are infrequent among susceptible isolates. Apart from the 3 major high-risk clones, ST277 is of particular significance, being widely disseminated in Brazil (79). ST244 is also frequently detected in several countries but is not always linked to MDR/XDR profiles (72, 80). Other recently reported emerging high-risk clones include ST308 and ST395 (81, 82).

The link between high-risk clones and horizontally acquired resistance mechanisms is overwhelming, and most ESBL- or MBL-producing *P. aeruginosa* isolates belong to a few clones, with ST235 being the most frequent, followed by ST111 (3). A recent genomic analysis suggested that the specific presence in ST235 of DprA, a determinant involved in homologous recombination present in transformable species, likely increases the ability of this high-risk clone to acquire and maintain foreign resistance elements at a higher rate than other *P. aeruginosa* clones (79). A significant relationship between high-risk clones and mutation-driven resistance mechanisms has also been reported. For example, the mechanisms responsible for the XDR phenotype of the ST175 clone, which is widespread in Spanish and French hospitals, are combinations of specific mutations in AmpR (G154R), OprD (Q142X), and MexZ (G195E) and 3 quinolone-resistance determining region (QRDR) mutations (GyrA T83I and D87N and ParC S87W) (30). An analysis of the resistomes of large worldwide collections of *P. aeruginosa* strains also showed that mutation-driven mechanisms were frequent among ST111 and ST235 clones; most of them had QRDR mutations (frequently GyrA T83I and ParC S87L) and often showed a mutated *oprD* (31, 83, 84).

TABLE 2 Characteristics of the three major global *P. aeruginosa* high-risk clones

Characteristic	ST111	ST175	ST235
O-antigen serotype	O12	O4	O11
Type III secretion system	ExoS	ExoS	ExoU
Virulence[a]	++	+	+++
Worldwide distribution	++	+	+++
Transferable resistance	++	+	+++
Mutational resistance	++	+++	++

[a]Capacity to produce more severe and/or higher mortality in acute infections according to results from animal models and clinical experience (5, 60, 65, 85, 86).

The pathogenicity of epidemic high-risk clones is another major issue that should be taken into account (85). Current evidence suggests that virulence among the different high-risk clones is variable. We considered virulence as the capacity to produce more severe infections and/or higher mortality in acute infections according to results with animal models and clinical experience (5, 61, 66, 86, 87). These studies specifically show that the ExoU$^+$ ST235 high-risk clone is highly virulent and associated with very high mortality, whereas the virulence of ST175 appears to be particularly low. Apart from virulence, determining which factors drive the success of the high-risk clones is another major issue that certainly needs clarification. A recent study evaluated a panel of eight biological characteristics potentially associated with the success of these clones (73). Surprisingly, the three major high-risk clones (ST111, ST175, and ST235) were found to be defective in the three types of motility and pigment (pyoverdine and pyocyanin) production and also showed reduced fitness *in vitro*. On the other hand, high-risk clones displayed increased spontaneous mutant frequencies and biofilm growth. Other recent studies have demonstrated enhanced biofilm formation and decreased motility in high-risk clones (88). Hence, there are similarities between these biological markers defined for *P. aeruginosa* high-risk clones and those typically resulting from adaptation to chronic infection (73). Nevertheless, further analysis, including information from whole-genome sequencing (WGS) (30, 31, 73, 84, 89, 90), is needed for a more complete understanding of the factors driving the success of high-risk clones.

CLINICAL IMPACT OF MULTIDRUG RESISTANCE IN *P. AERUGINOSA*

One of the main consequences of multidrug resistance is the difficulty of selecting an appropriate empirical antibiotic treatment. Patients with infections due to MDR/XDR pathogens are at an increased risk of receiving inadequate initial antimicrobial therapy (91, 92). Delays in receipt of effective antibiotic therapy are associated with worse outcomes and higher mortality rates in patients with *P. aeruginosa* bloodstream infections (93–96), and MDR/XDR patterns are also associated with a greater likelihood of inadequate empirical treatment in these infections (97–100). Furthermore, directed therapies used for MDR/XDR infections are usually second- or third-line antimicrobial agents and are thus less effective than those used to treat infections caused by susceptible strains (85). Nevertheless, the direct relationship between multidrug resistance and clinical outcome remains unclear (97, 101, 102). Although it is generally assumed that infections caused by MDR bacteria are associated with poor outcomes (94, 97, 103–105), infection outcomes depend not only on delays in receiving adequate antimicrobial therapy or use of suboptimal directed therapy but also on factors associated with the host or the pathogen (5, 85, 98, 106–108). With respect to the host, MDR/XDR *P. aeruginosa* colonization and infection usually occur in patients with multiple underlying diseases, which may explain the worse outcome (109, 110). Consequently, mortality in these patients may be due to severe preexisting comorbidities (111, 112). With respect to the pathogen, the biological implications of antibiotic resistance for virulence in *P. aeruginosa* is currently a hot topic (85, 86). It is generally assumed that acquisition of resistance mechanisms is associated with fitness costs that lead to decreased virulence in MDR/XDR strains (86, 113–117). Nevertheless, it has also been reported that some resistance mutations are not associated with fitness costs (115, 118), and other reports have claimed that MDR strains would be able to develop compensatory or suppressor mutations that allow them to recover their initial fitness so that, in the end, they do not lose virulence (113–115, 119). As mentioned previously, *P. aeruginosa* has a large number of virulence factors (5, 85, 108, 120). One of the most important virulence determinants is the type III secretion system (TTSS) (5, 120–122), which injects effector cytotoxins (ExoS, ExoT, ExoU, and/or ExoT) into the host cells (5, 120, 122). ExoU is the most potent of the four effector exotoxins identified, and its expression correlates with a poor prognosis (5, 85, 120–123). A recent clinical study conducted in patients with *P. aeruginosa* bacteremia demonstrated that the *exoU*$^+$ genotype was associated with increased early mortality and suggested that it would be

a useful prognostic biomarker in *P. aeruginosa* infections (5). Apart from the TTSS, other virulence determinants of *P. aeruginosa* have recently been described, such as toxin ExlA, which induces plasma membrane disruption of host cells, conferring increased virulence to the bacterium (108, 124). The HigB/HigA toxin/antitoxin system may influence some virulence factors of *P. aeruginosa*, such as pyocyanin, swarming, and biofilm formation (125). With respect to the impact of multidrug resistance on the virulence of *P. aeruginosa*, Peña et al. (5) found an association between some TTSS genotypes and antibiotic resistance patterns, with the *exoU*$^+$ genotype being less frequent in MDR strains (5). Other studies also suggest an association between the TTSS and certain resistance profiles (115, 122, 123). The *exoU*$^+$ genotype is present in only one of the three most prevalent high-risk clones worldwide, ST235 (5, 86). As previously noted, this high-risk clone is more virulent than the other prevalent clones, ST175 and ST111 (85, 86) (Table 2). Several experimental and clinical studies, however, suggest potentially reduced virulence in MDR/XDR *P. aeruginosa* (5, 73, 86, 117, 126–129). Experimental *in vitro* studies have shown that MDR strains have a lower growth rate and are defective in virulence determinants such as bacterial motility or pigment production (73, 86, 117). Experimental *in vivo* animal models have demonstrated that MDR/XDR *P. aeruginosa* strains are less able to produce infection, an inflammatory response, and mortality than susceptible strains (86, 126, 127, 129). Clinical studies also support the impaired virulence of MDR *P. aeruginosa* strains (5, 100, 107, 111, 130), and some of them showed that infections caused by MDR/XDR strains were not associated with higher mortality, even though they were more frequently managed with delayed adequate therapy (5, 98–100, 111, 114, 131). Taking these studies into account, we conclude that XDR strains may be associated with fitness costs and reduced virulence, but the data should be interpreted with caution, because, as mentioned above, at least one of the international XDR high-risk clone strains maintains high virulence regardless of its resistance profile. More studies are needed to clarify this.

IN VITRO AND *IN VIVO* TREATMENT MODELS: ANTIMICROBIAL COMBINATION OPTIONS

In Vitro Models

Pharmacodynamic interactions between drugs and bacteria have been studied in several *in vitro* models. Static systems can be used for rapid determination of time-kill behavior (132). Dynamic models such as the one-compartment *in vitro* model (IVM) and the two-compartment hollow-fiber infection model (HFIM) provide information that allows the development of dosing regimens that improve therapeutic results (133). Studies of dose fractionation, the suppression of resistant mutants, combination therapy, and the magnitude of the index required to obtain a specific amount of bacterial kill can be performed with both systems (132). Compared with the one-compartmental model, the hollow-fiber model allows the bacterial load to remain constant, biohazardous organisms to be safely contained, and absorption and elimination curves and rapid half-lives ($t_{1/2}$s) to be modeled (133).

In vitro studies have been conducted to find "optimal treatment options" against MDR or XDR *P. aeruginosa*. Combination antibiotic therapy for MDR/XDR *P. aeruginosa* is generating interest because of the potential severity of these infections and the high risk of resistance selection with monotherapy. The possibilities of expanding the spectrum of coverage, achieving additive or synergistic antibacterial effects, and suppressing emerging resistance are all factors that favor the use of combination therapy (7).

Several studies have examined *in vitro* interactions between various antipseudomonal antibiotics (e.g., carbapenems, colistin and polymyxin B, fosfomycin, aminoglycosides, and quinolones). A number of methods of detecting synergy have been employed, including the microdilution checkerboard technique, gradient diffusion (Etest), time-kill curve assays (134, 135), and dynamic models. Reported synergistic drug combinations against MDR/XDR *P. aeruginosa* include colistin-ceftazidime (136),

colistin-rifampin (137), cefepime-tobramycin (138), ceftazidime-avibactam-amikacin (139), colistin-doripenem, imipenem, and meropenem (140–142), meropenem-levofloxacin (143), imipenem-levofloxacin and colistin-levofloxacin (144), meropenem-ciprofloxacin (145), polymyxin B-enrofloxacin (146), fosfomycin-amikacin (147), and even some double-β-lactam combinations (148). Table 3 provides a list of studies of different drug combinations against MDR/XDR *P. aeruginosa*, showing the *in vitro* study model used, type of drug interactions, and whether or not suppression of resistance was achieved. Nevertheless, these studies have not led to clear recommendations for clinical practice, and there is a lack of consensus about which antibiotic combinations should be used against these difficult-to-treat infections to improve the therapeutic response and reduce selection of resistant mutants (135).

The lack of antipseudomonal agents in the pipeline adds a further complication to this situation (149), although in recent years some progress has been made with the development of new molecules and new β-lactamase inhibitor combinations (150, 151). The new cephalosporin ceftolozane (formerly known as CXA-101) (58) in combination with tazobactam has shown promising characteristics for the treatment of *P. aeruginosa* infection (152). Since 2010, many *in vitro* studies of the role of ceftolozane against MDR and XDR *P. aeruginosa* have been carried out. VanScoy et al. (153) studied the effect of ceftolozane-tazobactam against two isolates of *P. aeruginosa*: an ATCC strain and a clinical isolate. Against the wild-type isolate (MIC of 0.5 mg/liter), resistance was not selected by any dose; against the clinical *P. aeruginosa* isolate (MIC of 4 mg/liter), however, although resistance was suppressed by a ceftolozane-tazobactam dose of 2 g/1 g every 8 h, resistance selection was observed with intermediate dosing regimens (125/62.5 through 1,000/500 mg) (153). For this reason, combination therapy is also starting to be studied for some MDR/XDR infections. Some recent studies have shown synergistic effects of ceftolozane-tazobactam with colistin and amikacin (154–156). Interestingly, in a hollow-fiber infection model, the combination therapy of ceftolozane-tazobactam plus meropenem had a synergistic effect on cell killing and also prevented resistance selection against XDR *P. aeruginosa* strains belonging to the ST175 clone (157).

Clinical trials are needed to confirm the results of these models, which are nonetheless very useful for deciding which trials should be developed.

In Vivo Models

There are few *in vivo* studies related to different antibiotic options and combinations against MDR/XDR *P. aeruginosa*. In a mouse model of pneumonia, intranasal colistin combined with rifampin was beneficial for synergistic antibacterial activity (158). High-dose colistin showed a 1.5-$\log_{10}$ CFU reduction against MDR *P. aeruginosa* infections in a neutropenic mouse thigh model (159). In the same study, the combination of high-dose colistin with aztreonam was even better, showing a 2.5-$\log_{10}$ CFU reduction. Yadav et al. recently demonstrated substantially enhanced killing *in vivo* against an MDR *P. aeruginosa* clinical isolate with an optimized imipenem-plus-tobramycin combination regimen (160).

CURRENTLY AVAILABLE ANTIMICROBIALS FOR THE TREATMENT OF MDR AND XDR *P. AERUGINOSA* INFECTIONS

Polymyxins

Increased bacterial resistance to antibiotics in conjunction with the lack of new drugs in the pipeline has become a major clinical and public health concern worldwide, which is especially worrisome in the case of MDR, XDR and PDR *P. aeruginosa* (3, 4). Although novel agents such as ceftolozane-tazobactam and ceftazidime-avibactam have expanded the therapeutic arsenal (67, 157, 161–165), polymyxins continue to represent the only therapeutic option in some cases.

Two polymyxins are available for clinical use: colistin (polymyxin E) and polymyxin B. They were released in the 1950s and were not subjected to the same drug development procedures and regulatory scrutiny that are needed for modern drugs, so

TABLE 3 *In vitro* and *in vivo* models in which combination therapy options against MDR/XDR *P. aeruginosa* have been studied

Drug combination (yr, reference)	*P. aeruginosa* type	Study model[a]	Type of drug interaction	Suppression of resistance[b]
Cefepime-aztreonam (1998, 148)	Strain 164, including wild-type, partially derepressed, and fully derepressed phenotypes	HFIM	Synergistic	—
Meropenem-levofloxacin (2010, 143)	Wild-type strain PAO1 and isogenic MexAB-OprM-overexpressing strain	HFIM	Synergistic	Yes
Colistin-doripenem (2011, 140)	Colistin-heteroresistant reference strain (ATCC 27853) and colistin-resistant MDR clinical isolate	IVM	Additive or synergistic	Emergence of colistin-resistant subpopulations of ATCC 27853 reduced and delayed with combination therapy
Cefepime-tobramycin (2012, 138)	Wild-type strain PAO1 and its isogenic AmpC stably derepressed mutant	HFIM	Additive	Yes
Colistin-doripenem (2014, 361)	MDR	HFIM	Synergistic	Yes
Imipenem-levofloxacin, colistin-levofloxacin (2015, 144)	MDR	IVM	Synergistic	—
Colistin-meropenem (2016, 142)	Wild-type strain (ATCC 27853) and a meropenem-resistant strain (ARU552)	PK/PD model	Synergistic	Yes
Fosfomycin-amikacin (2017, 147)	Strain PA SAT 290	HFIM	Synergistic	Yes
Ceftolozane-tazobactam- meropenem (2018, 157)	Strain ST175	HFIM	Synergistic	Yes
Ceftolozane-tazobactam-colistin or -amikacin (2018, 154)	MDR	IVM	Synergistic	Yes
Ceftolozane-tazobactam-amikacin (2018, 155)	5 strains, 3 with OprD mutation and AmpC overexpression	IVM	Additive	Yes
Enrofloxacin-polymyxin B (2018, 16)	Strain 12196	IVM and HFIM	Synergistic	Yes
Meropenem-tobramycin (2018, 362)	PAO1 wild-type strain and its isogenic hypermutable PAO Δ*mutS* strain	HFIM	Synergistic	—
Ceftazidime-avibactam-amikacin (2018, 139)	3 carbapenem-resistant *P. aeruginosa* isolates with ceftazidime-avibactam MICs of 4/4 to 8/4 μg/ml and AMK-I MICs of 8 to 64 μg/ml	Chemostat model	Quicker killing with the combination	—
Meropenem-ciprofloxacin (2018, 145)	Hypermutable	HFIM	Synergistic at high doses	Yes
Ceftolozane-tazobactam- meropenem and ceftazidime, alone and in combination with colistin (continuous infusion) (2019, 151)	MDR-HUB1 (ceftolozane-tazobactam and meropenem-susceptible), XDR-HUB2, (ceftolozane-tazobactam susceptible and meropenem resistant), MDR-HUB3 (ceftolozane-tazobactam resistant and meropenem-susceptible)	Pharmacodynamic *in vitro* model of biofilm	Combinations of colistin plus ceftolozane-tazobactam and meropenem were the most appropriate treatments for biofilm-related infections caused by XDR and MDR *P. aeruginosa* strains, respectively	Yes
Colistin-rifampin (2009, 158)	MDR	AM	Synergistic	Yes
Colistin-aztreonam (2017, 159)	MDR	AM	Synergistic	Yes
Imipenem-tobramycin (2017, 238)	MDR	AM	Synergistic	Yes

[a]IVM, *in vitro* one-compartment model; HFIM, hollow-fiber infection model; AM, animal model.
[b]—, not evaluated.

our underlying pharmacological knowledge of these two polymyxins has until relatively recently been less than reliable (166–168). In recent years, however, a significant amount of preclinical and clinical data about these "old drugs" has emerged (169–173). The chemistry of polymyxins is very important for their antibacterial activity. Polymyxins are positively charged, enabling them to interact with phosphate groups in lipid A of the lipopolysaccharide (LPS) that are negatively charged (168). Polymyxins also have hydrophobic regions that can interact with the LPS (174). The result of these interactions is disruption of the bacterial cell membrane (174–176), which is the first step in the mechanism of action. Nevertheless, the final mechanism involved in bacterial cell death remains unknown (168). Recent studies performed on *P. aeruginosa* have argued against the traditional idea that colistin exerts its bactericidal effect by creating holes in the cytoplasmic membrane (177–179). New studies should explore other hypotheses, such as that bacterial killing is due to phospholipid exchange between the outer and cytoplasmic membranes, inhibition of respiratory enzymes, and/or formation of reactive oxygen species (179).

Since colistin and polymyxin B differ by only a single amino acid in the peptide ring (174), it is not surprising that they have similar antibacterial spectra, mainly against Gram-negative bacilli (174). In spite of their similar chemical structures, however, they are used in different forms when administered to patients parenterally. Polymyxin B is administered directly as an active antibiotic, whereas colistin is administered as an inactive prodrug, colistin methanesulfonate (CMS) (168, 176), which must be converted into colistin after administration (180). The use of one or the other polymyxin varies according to geographical area. In Europe and Australia, the only available form is colistin (in the form of CMS), whereas in the United States, Brazil, Malaysia, and Singapore, clinicians can use either colistin or the polymyxin B parenteral formulation (168).

Intravenous colistin dosing is controversial. Initially, low doses of CMS were used in clinics, based on the manufacturer's instructions (181–183), but thanks to more recent pharmacokinetic and pharmacodynamic (PK/PD) data from population studies, it is now possible to provide an update of recommended dosages (171, 172, 184, 185). Some clinical studies evaluated the efficacy of parenteral colistin at higher doses (4.5 IU administered every 12 h), following a loading dose of 9 million IU (186, 187), although there are no clinical data available for the outcomes for patients receiving doses based on the equation proposed by Garonzik et al. (170) and updated by Nation et al. (171, 172) in 2016. In an attempt to translate PK/PD knowledge to clinical practice, Sorlí et al. studied the impact of colistin plasma concentrations on clinical outcome in 91 patients with infections caused by MDR/XDR *P. aeruginosa* (188). The mean colistin plasma concentrations in this cohort of patients were 1.67 ± 1.42 mg/liter, which is lower than those proposed in other studies and in the recent polymyxin use guidelines (170–172, 185). Nevertheless, 79.9% of patients achieved clinical cure, and colistin plasma concentrations were not observed to be statistically related to clinical cure (188). The same group demonstrated that a high plasma concentration of colistin was an independent risk factor for nephrotoxicity (183, 189). In conclusion, although PK/PD studies have concluded that higher doses of colistin should be used, there is a lack of clinical studies on the outcomes for patients treated according to more recent recommendations (171, 172, 185). In the case of urinary tract infections, colistin is a good option because concentrations of formed colistin in urine are high (185). Moreover, and because of this, in urinary tract infections the colistin dose could be lower than in other invasive infections (190). However, no clinical data are available to confirm this option.

There are several published clinical studies focused on colistin for treating MDR/XDR *P. aeruginosa* infections. The majority are single-center retrospective series with low numbers of patients, with two exceptions comprising more than 100 patients (182, 183) and with very different patient profiles (intensive care unit [ICU], cancer, hematologic, pneumological, etc.). The most frequent infectious source was low respiratory tract infection. Colistin doses were variable and adjusted for renal function. Combination

therapy was administered to 51 to 100% of patients in these series. The clinical response at different time points varied between 52% and 79% and was higher than 70% in half of the studies. Mortality (at different time points) was between 11% and 61%. No information about resistance selection was given in these studies (181, 182, 188, 191–201) (Table 4).

The question of whether combination therapy might improve patient outcomes is another major issue to be considered for the use of polymyxins in the treatment of MDR/XDR *P. aeruginosa* infections. Data from PK studies confirm that colistin plasma concentrations following the dosing suggestions of the European Medicines Agency (EMA) and FDA are low and inadequate for the treatment of MDR/XDR *P. aeruginosa* infections (165–167, 178, 182, 183). These findings highlight the importance of considering colistin combination therapy for MDR/XDR *P. aeruginosa* infections. Zusman et al. (202) recently published a systematic review about polymyxins in combination or as monotherapy against carbapenem-resistant Gram-negative bacteria (GNB) and showed that polymyxin combined with carbapenems or tigecycline and/or aminoglycosides had an unadjusted association with survival, but when biased studies were excluded from the analysis, there was no association between combination therapy and survival. The majority of the studies did not include *P. aeruginosa* infections (202). In a cohort of patients with pneumonia due to XDR *P. aeruginosa*, Khawcharoenporn et al. showed that combination therapy with 2 active drugs was associated with better survival than active monotherapy, including colistin in the majority of cases (Table 4) (203). Interestingly, a recent prospective clinical series of bone and joint infections due to MDR/XDR *P. aeruginosa* also showed better clinical outcomes with colistin in combination therapy, in comparison with β-lactam or colistin as monotherapy (204) (Table 4). Larger clinical series and randomized clinical trials with invasive MDR/XDR *P. aeruginosa* infections are needed to confirm these data. Until then, the recent expert-panel guidelines for optimal use of polymyxins recommend that for the treatment of MDR/XDR *P. aeruginosa* infections, polymyxin should be used in combination with one or more additional agents to which the pathogen displays a susceptible MIC (185).

With respect to polymyxin B, there is limited clinical experience with MDR/XDR *P. aeruginosa* infections (166, 205–209). The studies are retrospective series with low numbers of patients, except for one with 126 cases (208). Bacteremia and pneumonia were the predominant indications. Clinical response is insufficiently studied, and mortality rates are worryingly high (Table 4).

Nephrotoxicity is a common adverse effect of systemically administered polymyxins (210, 211). This adverse effect is dose-limiting for both polymyxins (colistin and polymyxin B), although polymyxin B seems to be less nephrotoxic (205). In the case of colistin, plasma concentrations associated with renal damage overlap those required for a bacterial effect (212). Colistin plasma concentrations have been demonstrated to be the most important risk factor for the development of acute kidney injury (AKI). An average steady-state plasma colistin concentration of greater than $\sim$2 mg/liter is considered to be an independent risk factor for colistin-associated nephrotoxicity (183, 189, 213). These data highlight the narrow therapeutic window of colistin. In this scenario, therapeutic drug monitoring could be a useful clinical tool to maximize clinical goals while minimizing potential nephrotoxicity (185).

Both polymyxin B and CMS have been administered as inhalation therapy for the treatment of pneumonia, bronchiectasis, and chronic *P. aeruginosa* infection and for pulmonary exacerbations in patients with cystic fibrosis. Once again, most of the studies of inhaled administration were performed with CMS. A recent meta-analysis focused on the use of inhaled colistin monotherapy for respiratory infections in non-CF patients (214). The analysis included 10 studies of patients diagnosed with pneumonia and 2 studies of those with ventilator-associated tracheobronchitis. Overall all-cause mortality was 33.8% and the clinical success rate was 70.4% (214). The authors of this meta-analysis concluded that the outcomes for patients receiving therapy with inhaled CMS as monotherapy were encouraging and deserved further consideration for the

TABLE 4 Clinical studies providing outcome information for infections due to MDR/XDR *P. aeruginosa* treated with systemic antimicrobial therapy[a]

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
Polymyxin B							
2007, Furtado et al., 209	Single-center retrospective case series	Brazil, 79, MDR *P. aeruginosa*, nosocomial PNEU	Treatment with i.v. polymyxin B. Dosing was as follows: for CL_{CR} of ≥80 ml/min, 1.5–2.5 mg/kg/day; for CL_{CR} of 30–79, 1–1.5 mg/kg/day; for CL_{CR} of <30, 1–1.5 mg/kg every 2–3 days for anuric patients, 1–1.5 mg/kg every 5–7 days. Total daily dose administered by continuous infusion over 24 h.	None	EOT favorable outcome (complete or partial resolution of signs/symptoms) for 35 patients (47%)	Variables associated with unfavorable outcome were acute respiratory syndrome and septic shock (multivariate analysis)	–
2010, Elias et al., 208[c]	Single-center retrospective cohort study	Brazil, 126, MDR *P. aeruginosa* infections	Treatment for at least 3 days with i.v. polymyxin B	None	All-cause in-hospital mortality, 74 patients (59%)		–
2015, Rigatto et al., 206[c]	Multicenter retrospective cohort study	Brazil, 18 ICU patients, XDR *P. aeruginosa*, "severe" infections	15 patients received at least 2 days i.v. polymyxin B. Dosing was as follows: 1.5–3.0 mg/kg (in 2 doses).	3 patients receiving polymyxin B + an antimicrobial lacking *in vitro* activity	30-day all-cause mortality, 14 patients (93%) in the monotherapy group and 0 (0%) in the combined treatment group ($P < 0.01$)		–
2015, Nelson et al., 207[c]	Single-center retrospective cohort study	USA, 17, carbapenem-resistant *P. aeruginosa* BSI I	Treatment for at least 2 days with i.v. polymyxin B	None	30-day all-cause mortality, 8 patients (47%)		–
Colistin							
2003, Markou et al., 192	Single-center retrospective case series	Greece, 19 critically ill patients, XDR *P. aeruginosa* sepsis (6 coinfected with other pathogens), 11 VAP (55%), 3 CLABSI, 3 primary BSI, 1 sinusitis, 1 UTI, 1 thoracic empyema	Treatment with i.v. COL + a β-lactam AB (despite documented resistance) (also patients surviving >48 h after initiating COL). COL dosing was as follows: 3 MU/8 h (adjusted by CL_{CR}).	None	Clinical response (abatement of fever for at least 48 h + improvement of vital signs) for 13 patients (68%) 30-day all-cause mortality, 9 patients (47%)		–
2003, Linden et al., 193	Single-center retrospective case series	USA, 23 critically ill solid-organ recipients and other general surgery patients, XDR *P. aeruginosa* infection, 18 PNEU (78%), 8 BSI, 6 IAI, 3 wound, 1 IE, 5 multiple simultaneous infection types	Treatment: for at least 3 days with i.v. COL. Dosing was as follows: for Cr of 1.6–2.5 mg/dl, 5 mg/kg/day (in 2 doses); for Cr of 2.6–4, 2.5 mg/kg/day (1 dose); for Cr of >4 or HD, 1 mg/kg/day (1 dose). 13 patients (57%) received antipseudomonal combination treatment.	None	14 patients (61%); 3 patients with favorable response experienced relapse EOT microbiological eradication for 10 /17 patients (59%) EOT all-cause mortality, 7 patients (30%) All-cause in-hospital mortality, 14 patients (61%)	There was no difference in response rate between patients with COL monotherapy (6 [60%]) and combined therapy (8 [62%]). A variable associated with clinical failure was bacteremia (univariate analysis)	–

(Continued on next page)

TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2005, Reina et al., 194[c]	Single-center prospective cohort study	Argentina, 80, ICU-acquired *P. aeruginosa* infections (19 with XDR *P. aeruginosa* infections), 48 VAP (54%), 21 BSI	19 patients with XDR *P. aeruginosa* treated with i.v. COL (COL-only-susceptible strains). Dosing was as follows: for Cr of <1.2 mg/dl, 5 mg/kg/day (in 3 doses); for Cr of 1.3–1.5, 2.5–3.8 mg/kg/day (in 2 doses); for Cr of 1.6–2.5, 2.5 mg/kg/day (in 1–2 doses); for Cr of ≥2.6, 1.5mg/kg/36 h (single dose); for HD, 1 mg/kg/day (single dose).	61 patients with *P. aeruginosa* treated with an antipseudomonal non-COL-containing regimen (according to susceptibility; 81% of patients treated with carbapenems)	All-cause in-hospital mortality, 7 patients in the COL group (37%) and 17 patients in the non-COL group (28%) ($P = 0.65$) No cases of renal failure (Cr of ≥2 m/dl, reduction in CL_{CR} of ≥50%, or renal replacement therapy requirement)		–
2005, Michalopoulus et al., 195[c]	Single-center retrospective case series	Greece, 35, ICU-acquired XDR *P. aeruginosa* infections, 24 PNEU (69%), 20 VAP (57%), 11 BSI, 3 CLABSI, 2 UTI, 2 SSSI, 1 sinusitis, 10 multiple simultaneous infection types	Treatment for at least 2 days with i.v. COL. Dosing was as follows: for Crs of ≤1.2, 1.3–1.5, 1.6–2.5, and ≥2.6 mg/dl, 3 MU every 8, 12, 24, and 36 h, respectively; for dialysis, 1 MU after dialysis.	None	All-cause in-hospital mortality. 10 patients (29%)		–
2007, Hachem et al., 191	Single-center retrospective cohort study	USA, 95 cancer patients, MDR *P. aeruginosa* infection, 47 PNEU (49%), 37 BSI, 7 UTI, 5 wound	31 patients treated with i.v. COL. Dosing was as follows: 5 mg/kg/day (in 2–4 doses); for HD, 1.5mg/kg/36 h. 13 patients (42%) received antipseudomonal combination treatment.	64 patients treated with another antipseudomonal AB (according to susceptibility); 29 patients (45%) received antipseudomonal combination treatment	6-day clinical response, 16 (52%) in the COL group vs 20 (31%) in the control group ($P = 0.055$) EOT clinical response, 16 (52%) in the COL group vs 22 (34%) in the control group ($P = 0.11$) 6-day microbiological eradication, 15 (48%) in the COL group vs 25 (39%) in the control group ($P = 0.39$) EOT microbiological eradication, 15 (48%) in the COL group vs 26 (41%) in the control group ($P = 0.47$) EOT infection-related mortality, 8 (26%) in the COL group vs 11 (17%) in the control group ($P = 0.33$) EOT all-cause mortality, 19 (61%) in the COL group vs 30 (47%) in the control group ($P = 0.19$) Nephrotoxicity, 7 (23%) in the COL group vs 14 (22%) in the control group ($P = 0.94$)	There was a significantly higher clinical response rate in patients who received COL ($P = 0.026$) but no difference in the microbiologic response rate ($P = 0.24$) (multivariate analysis). Independent predictors of infection-related deaths were underlying diagnosis of hematologic malignancy (vs solid tumor) and ICU stay during infection	–

(Continued on next page)

TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2009, Montero et al., 182	Single-center retrospective case series	Spain, 121, XDR *P. aeruginosa* infection, 59 RTI (48.8%), 20 PNEU, 16 BSI, 13 UTI, 11 STI, 1 otitis, 1 arthritis	Treatment for at least 3 days with i.v. COL. Dosing was as follows: 2.5–5 mg/kg/day in 3 doses/day. 35 patients (29%) received i.v. + nebulized COL; 84 patients (69%) received systemic antipseudomonal combination treatment.	None	Clinical success (resolution/improvement of fever, leukocytosis, and local signs) for 87 patients (72%): UTI, 11 (85%); RTI, 43 (73%); SSTI, 8 (73%); PNEU, 13 (65%); BSI, 10 (63%) Microbiological eradication for 31 patients of 89 (35%) All-cause in-hospital mortality, 20 patients (17%) (higher mortality for PNEU or BSI [36%] than for other infections [8.2%] [$P = 0.004$]) Attributable in-hospital mortality, 15 patients (12%) Nephrotoxicity for 10 patients (8%)		−
2010, Cheng et al., 196[c]	Single-center retrospective case series	Taiwan, 38, MDR *P. aeruginosa* infection	Treatment with i.v. COL. Dosing was as follows: for CL_{CR} of ≥80 ml/min, 5 mg/kg/day; for CL_{CR} of 30–79, 2.5–3.8 mg/kg/day; for CL_{CR} of <30, 2.5 mg/kg/day; for HD, 2.5mg every other day after dialysis.	None	3-day clinical response (improvement of symptoms/signs) for 22 patients (58%)		−
2010, Falagas et al., 197[c]	Single-center retrospective cohort study	Greece, 68, MDR *P. aeruginosa* infection	13 patients received at least 3 days of treatment with i.v. COL monotherapy.	55 patients treated with COL + another systemic antipseudomonal AB	Clinical cure for 51 patients (75%): COL monotherapy, 10/13 (77%); COL + MER, 24/24 (86%); COL + PIP/TAZ, 6/10 (60%); COL+ other agents, 11/17 (65%)		−
2011, Durakovic et al., 198	Single-center retrospective matched cohort study	Croatia, 52 patients with hematologic malignancy, MDR *P. aeruginosa* infection with sepsis, 40 with bacteremia (77%)	26 patients received treatment with i.v. COL. Dosing was as follows: 3 MU/8 h; for Cr of 105–140 μmol/liter, 2.5–3.8 mg/kg/12 h; for Cr of 141–220, 2 mg/kg/24 h; for Cr of >221, 1.5 mg/kg/48 h. 23 patients (88%) received antipseudomonal combination treatment.	26 patients (matched by site of isolation, age, gender, hematologic disease and treatment) were treated with another antipseudomonal AB (according to susceptibility); 22 patients (85%) received antipseudomonal combination treatment (all with dual therapy)	EOT clinical success (resolution of fever and signs/symptoms) for 20 (77%) in the COL group and 17 (65%) in the control group ($P = 0.36$) Mortality, 3 patients (11%) in the COL group and 3 (11%) in the control group Renal failure (Cr of >150 μmol/liter or an increase of ≥50% from the baseline value ([patients with prior renal failure]) for 3 patients (11%) in the COL group and 0 (0%) in the control group ($P = 0.07$)		+

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2011, Naesens et al., 199	Single-center retrospective cohort study	Belgium, 20 ICU patients, MDR *P. aeruginosa* PNEU (6 VAP)	9 patients received >2 days treatment with i.v. + inhaled COL. Dosing of i.v. COL and inhaled COL, respectively, was as follows: 62,500 IU/kg daily (in 3–4 doses) and 2 MU/8 h.	6 patients treated with inhaled COL 5 patients treated with i.v. COL	EOT favorable clinical response (resolution of signs/symptoms) for 7 patients (78%) in the i.v. + inhaled COL group, 6 patients (100%) in the inhaled COL group, and 2 patients (40%) in the i.v. COL group Mortality, 3 patients (33%) in the i.v. + inhaled COL group, 0 patients (0%) in the inhaled COL group, and (100%) 5 patients in the i.v. COL group		−
2013, Sorlí et al., 183	Single-center prospective cohort study	Spain, 102, MDR GNB infection, 89 (90%) MDR *P. aeruginosa* infection	Treatment for at least 4 days with i.v. COL. Dosing was as follows: 3–9 MU daily (in 3 doses).	None	Clinical response (resolution of signs/symptoms and laboratory parameters) for 79 patients (78%) 30-day all-cause mortality. 33 patients (32%) Nephrotoxicity (≥1.5-fold Cr increase and/or ≥25% decrease in the GRF (RIFLE criteria of AKI) for 53 patients (52%) at any time during treatment, 26 (26%) patients at day 7, and 50 (49%) of patients at EOT	Independent variables associated with 30-day mortality were EOT-AKI and APACHE score. Independent variables associated with EOT-AKI were Charlson score, ≥2 nephrotoxic drugs, and COL plasma trough concentration.	+
2013, Vicari et al., 200[c]	Single-center retrospective cohort study	USA, 32, monomicrobial carbapenem-resistant *P. aeruginosa* BSI	Treatment for at least 3 days with i.v. COL; dosing was decided by the treating clinician.	None	7-day microbiological success for 19 patients (59%)		−
2016, Benattar et al., 181[c]	Multicenter prospective cohort study	Israel, 89, carbapenem-resistant *P. aeruginosa* infection	Treatment with i.v. COL for at least 3 days or until death. Dosing was as follows: first period (2006–2009), 3–6 MU/day; second period (2012–2015), 9-MI loading dose followed by 4.5 MU/12 h.	None	28-day all-cause mortality, 37 patients (42%)		+
2017, Sorlí et al., 188	Single-center prospective cohort study	Spain, 91, XDR *P. aeruginosa* infection, 24 PNEU (25%), 22 UTI, 11 SSTI, 10 SSI, 6 BSI, 18 others	Treatment for at least 3 days with i.v. COL. Dosing was as follow: 3–9 MU daily (in 3 doses), decided by the treating clinician. 46 patients (51%) received antipseudomonal combination treatment.	None	Clinical cure (resolution of symptoms/signs) for 72 patients (79%) All-cause in-hospital mortality, 28 patients (31%) Attributable in-hospital mortality, 13 patients (14%) Nephrotoxicity (RIFLE criteria of AKI) for 30 patients (33%) at day 7 and 49 patients (54%) at EOT	Independent variables associated with all-cause mortality were APACHE II and McCabe scores and EOT-AKI.	+

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
Ceftolozane-tazobactam							
2017, Castón et al., 282	Multicenter retrospective case series	Spain, 12, MDR *P. aeruginosa* infection with septic shock, 6 PNEU (50%), 4 IAI, 1 CLABSI, 1 otomastoiditis	Treatment with TOL/TZ as salvage therapy. 4 patients (33%) received a high dose[d]	None	30-day cure (resolution of signs/symptoms and radiologic findings) for 9 patients (75%); 1 of these 9 patients (otomastoiditis) had a late recurrence 30-day microbiological eradication for 8/11 (73%), although 2 of the 8 patients had a late recurrence with TOL/TZ-resistant *P. aeruginosa* (18%); persistence for 3/11 (27%) 30-day all-cause mortality, 3 patients (25%)		–
2017, Haidar et al., 26	Single-center retrospective case series	USA, 21, MDR *P. aeruginosa* infection (6 had coinfections with other pathogens), 16 PNEU (76%), 2 RTI, 1 cIAI, 1 BSI, 1 cUTI	Treatment with TOL/TZ. Among 12 patients: 5 patients (24%) received a high dose. 16 patients (76%) received antipseudomonal combination treatment.	None	90-day clinical success for 15 (71%); for the 6 patients with clinical failure, there were 4 attributable deaths and 2 patients with recurrent infection 90-day recurrent colonization and emergence of resistance for 4 patients (19%) with recurrent colonization and 3 patients (14%) with emergence of TOL/TZ resistance 30- and 90-day all-cause mortality, 2 patients (10%) and 10 patients (48%), respectively 30- and 90-day attributable mortality, 1 patient (5%) and 4 patients (19%), respectively (attributable mortality was due to persistent or recurrent PNEU)	There was use of previous antipseudomonal AB in 20/21 (95%) patients. The only variable associated with clinical failure was SAPS II score (univariate analysis).	–
2017, Munita et al., 283	Multicenter retrospective case series	USA, 35, carbapenem-resistant *P. aeruginosa* infection, 18 PNEU (51%), 5 BJI, 5 abscesses, 2 LAVD, 2 SSI, 1 CLABSI, 1 UTI	At least 3 days of treatment with TOL/TZ. There was wide variation of TOL/TZ dosing. 8 patients (23%) received antipseudomonal combination treatment.	None	In-hospital clinical success (survival, resolution of signs/symptoms, no recurrence) for 26 cases (74%), including 70% when used as monotherapy and 87% when used with another AB No 3-day microbiological failure for 25 evaluable patients All-cause in-hospital mortality, 8 patients (23%)	There was use of previous antipseudomonal AB in 31/34 (91%) patients. Treatment was unsuccessful in the 4 cases with TOL/TZ MIC of >4 mg/liter.	–

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2018, Gallagher et al., 281	Multicenter retrospective cohort study	USA, 205, MDR *P. aeruginosa* infection, 121 PNEU (59%) (58 VAP), 28 UTI, 26 wound, 20 IAI, 16 BJI BSI	Treatment for at least 24 hours with TOL/TZ. 97 patients (47%) received a high dose; 81 patients (40%) received antipseudomonal combination treatment.	None	EOT clinical success for 151 patients (74%) EOT microbiological cure for 150 patients (71%) All-cause 30-day and inpatient mortality, 39 patients (19%); patients with VAP had the worst outcome (22 patients with VAP [40%] died)	Initiation of TOL/TZ within 4 days of culture collection was an independent predictor of survival and clinical and microbiological success.	–
2018, Hakki and Lewis, 284	Single-center retrospective case series	USA, 6 HCT recipients or patients with hematologic malignancies, 7 MDR *P. aeruginosa* infections, 3 PNEU (50%), 2 primary BSI, 1 SSTI	Treatment with TOL/TZ monotherapy; 7 courses of treatment (100%) were high dose.	None	Clinical success for 5 episodes of 7 (71%); there were 2 recurrences of infection after ending TOL/TZ treatment and 1 patient (14%) with emergence of TOL/TZ resistance 30-day all-cause mortality, 0 (0%)		–
2017, Dinh et al., 285	Multicenter retrospective case series	France, 15, XDR *P. aeruginosa* infection, 6 PNEU (40%), 3 UTI, 2 IAI, 1 RTI, 1 BJI, 1 meningitis, 1 vascular graft infection	Treatment with TOL/TZ as salvage therapy. 7 patients (47%) received a high dose, and 6 patients (40%) received antipseudomonal combination treatment.	None	In-hospital clinical cure for 10 patients (67%) 28-day or hospital discharge clinical cure for 8/9 patients (NA for 6 patients) In-hospital microbiological cure for 6/8 evaluable patients In-hospital all-cause mortality, 4 patients (27%)		–
2018, Xipell et al., 165	Single-center retrospective case series	Spain, 23 patients/24 episodes, MDR *P. aeruginosa* infections, 19 (79%) of them XDR *P. aeruginosa*, 8 RTI (35%): 4 PNEU, 7 UTI, 5 SSI, 3 IAI	Treatment for at least 3 days with TOL/TZ. 3 patients (13%) received a high dose, and 22 patients (92%) received combined antipseudomonal treatment.	None	In-hospital clinical success for 21 of 24 episodes (88%) Microbiological eradication for 14/16 evaluable episodes; 1 patient (4%) had emergence of TOL/TZ resistance 6-week all-cause mortality, 5 patients (22%)	There was use of previous antipseudomonal AB in 21/24 (88%) episodes. 3/3 patients with RTI received TOL/TZ at 3 g/8 h and were cured, while 3 of 5 patients with RTI receiving 1.5 g/8 h died.	–
2018, Díaz-Cañestro et al., 62	Single-center prospective case series	Spain, 58, *P. aeruginosa* infection, 56 of them MDR *P. aeruginosa*, 50 XDR *P. aeruginosa*, 35 RTI (60%), 10 UTI, 4 IAI, 3 BSI, 2 BJI, 4 other	Treatment for at least 48 hours with TOL/TZ. 27 patients (47%) received 1.5 g/8 h, 24 patients (41%) received a high dose, and 37 patients (64%) received antipseudomonal combination treatment.	None	7-day clinical cure for 37 patients (64%) (XDR *P. aeruginosa*, 21/50 patients [42%]; MDR *P. aeruginosa*, 6/6 patients [100%]) 30-day microbiological cure (negative-control culture) and emergence of TOL/TZ resistance for 21 of 30 evaluable patients (70%); 8 patients (14%) with emergence of TOL/TZ resistance 30-day all-cause mortality, 16 patients (28%)	Variables associated with clinical failure (univariate analysis) were ventilator-dependent respiratory failure, SOFA, molecular type ST175, XDR *P. aeruginosa*, and TOL/TZ resistance development. The only independent risk factor for clinical failure was ventilator-dependent respiratory failure.	–

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2018, Escolà-Vergé et al., 286	Single-center retrospective case series	Spain, 38, XDR *P. aeruginosa* infection, 14 RTI (37%); 7 PNEU, 6 SSTI, 6 UTI, 4 BJI, 4 IAI, 3 primary BSI, 1 mediastinitis	Treatment for at least 3 days with TOL/TZ. 23 patients (61%) received a high dose, and 22 patients (58%) received antipseudomonal combination treatment.	None	EOT clinical response for 33 patients (87%) 90-day clinical response for 26 patients (68%) 90-day clinical failure for 12 patients (32%) (clinical recurrence, 7 [18%], attributable mortality, 4 patients; persistent infection, 1 patient) Microbiological recurrence for 12 patients; 4 patients (11%) with emergence of TOL/TZ resistance 90-day all-cause mortality, 5 patients (13%)	Variables associated with clinical cure at 90 days (univariate analysis) were adequate infection source control and lower TOL/TZ MIC.	−
2018, Dietl et al., 287	Single-center retrospective case series	Spain, 7 patients at high risk or with preexisting renal impairment, XDR *P. aeruginosa* BJI and SSTI, 4 BJI (1 PJI), 2 SSTI	Treatment with TOL/TZ. All patients received FDA-approved dosages.	None	90-day clinical cure for 6 patients (86%); 1 patient with recurrence (new infection at the same site after EOT) 7-day microbiological eradication for 4 of 4 evaluable 30-day postdischarge and all-cause inpatient mortality, 0 (0%)	There was use of previous antipseudomonal AB in 2/6 (33%) patients.	−
2018, Bassetti et al., 288	Multicenter retrospective case series	Italy, 101, 18 (17.8%) MDR, 51 (50.5%) XDR, 2 (2.0%) PDR *P. aeruginosa*, 32 PNEU (31.7%), 21 SSTI, 14 cUTI, 13 cIAI, 9 BJI, 6 primary BSI	Treatment with TOL/TZ. 31 (31%) received a high dose, and 36 (37%) received antipseudomonal combination therapy.	None	EOT clinical success for 84 patients (83%): XDR-PDR *P. aeruginosa*, 43/53 (81%) (vs MDR, 14/18 [78%] vs no-MDR *P. aeruginosa*, 27/30 [90%]), monotherapy, 54/65 (83%) vs combination therapy, 30/36 (83%), cITU or cIAI, 85% (vs primary BSI [100%] vs SSTI [91%] vs BJI [89%] vs RTI [75%]); 3 patients (3%) had emergence of TOL/TZ resistance	Independent predictors of clinical failure were sepsis and receipt of continuous renal replacement therapy.	−
Ceftazidime-avibactam							
2016, Carmeli et al., 308[e]	Multicenter randomized clinical trial	16 countries worldwide, 21 patients with ceftazidime-resistant *P. aeruginosa* cUTI or cIAI	Treatment with CAZ-AVI (ceftazidime, 2 g/8 h).	Treatment with BAT	Clinical cure at the test-of-cure visit (7–10 days after end of therapy) for patients with cUTI (12 of 14 patients [86%] in the CAZ-AVI group vs 5/5 patients [100%] in the BAT group and patients with cIAI (1 of 1 patient in the CAZ-AVI group vs 1/1 patient in the BAT group) Favorable microbiological response at the test-of-cure visit for 11 of 14 patients (79%) with cUTI in the CAZ-AVI group vs 3/5 patients (60%) in the BAT group		++

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2018, Rodríguez-Núñez et al., 163	Single-center retrospective case series	Spain, 8, MDR *P. aeruginosa* infection, 7 (88%) of them XDR *P. aeruginosa*, 4 PNEU (50%), 1 RTI, 1 CLABSI, 1 BJI, 1 meningitis	Treatment for at least 3 days with CAZ-AVI (ceftazidime, 2 g/8 h). 6 patients (75%) received antipseudomonal combination treatment.	None	30-day clinical cure (survival, resolution of symptoms/signs, and absence of relapse) for 4 patients (50%) (all failures were in patients with RTI [4/5 patients]) 30-day all-cause mortality, 1 patient (13%) 90-day all-cause mortality, 3 patients (38%)		–
Aminoglycosides							
2016, Brasseur et al., 250[c]	Single-center retrospective case series	Belgium, 11 ICU patients, MDR *P. aeruginosa* infections with sepsis/septic shock, 5 tertiary peritonitis, 4 VAP, 1 postesophagectomy, 1 empyema, 1 necrotizing pancreatitis	Treatment with high-dose aminoglycoside therapy coupled with high-flow (>45-ml/kg/h) continuous venovenous hemodiafiltration as salvage therapy. The loading dose was 25–30 mg/kg for amikacin and 8–10 mg/kg for gentamicin and tobramycin. 7 patients were treated with amikacin, 3 with gentamicin, and 1 with tobramycin.	None	EOT clinical response for 7 patients (65%)		–
Monotherapy vs combination therapy							
2015, Ribera et al., 204	Single-center retrospective cohort study	Spain, 34, MDR *P. aeruginosa* BJI (23 XDR *P. aeruginosa* BJI)	19 patients were treated in monotherapy: 14 with a β-lactam intermittent bolus, 4 with COL, and 1 with β-lactam continuous infusion.	Treatment with combination therapy of 15 patients: 10 COL + β-lactam continuous infusion, 3 COL + β-lactam intermittent bolus, 1 amikacin + β-lactam intermittent bolus. COL dosing was 2 MU/8 h. The antipseudomonal β-lactam with the lowest MIC value was used.	12-month clinical cure (absence of clinical failure) for 6 patients (32%) in the monotherapy group and 11 patients (73%) in the combined treatment group ($P = 0.02$)		–

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TABLE 4 (Continued)

Drug and yr, authors, reference	Study design	Patients (country, no., condition)	Intervention/exposure	Comparison group(s)	Outcome	Comments	Quality of the study[b]
2018, Khawcharoenporn et al., 203	Single-center retrospective cohort study	Thailand, 136, monomicrobial XDR *P. aeruginosa* PNEU (50 VAP)	22 patients received inactive therapy: 10 PIP-TAZ, 10 nonactive carbapenem, 2 nonactive FOS + nonactive carbapenem.	74 patients received treatment with active monotherapy: 40 COL + nonactive carbapenem, 22 COL, 6 COL + nonactive FOS, 4 FOS + nonactive carbapenem 40 patients received combined therapy: 22 COL + FOS, 12 DOR + FOS, 6 COL + DOR. Dosing was as follows: for COL, 300 mg loading followed by 150 mg/12 h; for DOR, 1 g over 4 h/8 h (MIC, 4–8 mg/liter); for FOS, 4 g over 4 h/8 h. Nebulized COL was used in 28 patients with monotherapy (42%) vs 10 patients with combination therapy (39%).	EOT microbiological cure (no growth in sputum or BAL fluid 14 days after therapy) for 0 patients (0%) in the inactive therapy group, 30 patients (54%) in the active monotherapy group, and 36 patients (90%) in the active combined 2-drug therapy group ($P \leq 0.01$ 14-day all-cause mortality, 20 patients (91%) in the inactive therapy group, 26 patients (35%) in the monotherapy group, and 4 patients (10%) in the combined 2-drug therapy group ($P \leq 0.01$) 28-day all-cause mortality, 22 patients (100%) in the inactive therapy group, 36 patients (49%) in the monotherapy group, and 4 patients (10%) in the 2-drug therapy group ($P \leq 0.01$)	Independent variables associated with 28-day mortality were inactive therapy and no ID consultation. Independent predictors of 28-day mortality in patients with at least 1 active AB were monotherapy and no ID consultation.	−
Other combinations							
2012, Apisarnthanarak and Mundy, 258	Single-center retrospective cohort study	Thailand, 49, carbapenem-resistant *P. aeruginosa* PNEU (29 VAP)	25 patients treated with high-dose (1-g) 4-h infusions of DOR (MIC, 4–8 mg/liter) + FOS for at least 2 days	24 patients treated with COL (5 mg/kg/day in 2 doses) + FOS for at least 2 days	EOT or in-hospital clinical cure for 15 patients (60%) in the DOR+FOS group and 14 patients (58%) in the COL+FOS group EOT or in-hospital microbiological cure for 18 patients (72%) in the DOR+FOS group and 18 patients (55%) in the COL+FOS group EOT or in-hospital all-cause mortality, 10 patients (40%) in the DOR+FOS group and 10 patients (42%) in the COL+FOS group		−

[a]Abbreviations: AB, antibiotic; AKI, acute kidney injury; BAL, bronchoalveolar lavage; BAT, best available therapy; BJI, bone and joint infection; BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; cIAI, complicated intra-abdominal infection; COL, colistin; Cr, plasma creatinine concentration; CL_{CR}, creatinine clearance; cUTI, complicated urinary tract infection; CLABSI, central line-associated bloodstream infection; DOR, doripenem; EOT, end of treatment; GRF, estimated glomerular filtration rate; IE, infective endocarditis; FDA, Food and Drug Administration; FOS, fosfomycin; HCT, hematopoietic cell transplant; IAI, intra-abdominal infection; ID, infectious diseases; LAVD, left ventricular assist device; MDR, multidrug resistant; MU, millions of international units; NA, not applicable; PIP-TAZ, piperacillin-tazobactam; PJI, prosthetic joint infection; PNEU, pneumonia; SSI, surgical site infection; RIFLE, risk, injury, failure, loss, and end-stage kidney disease; RTI, respiratory tract infection (other than pneumonia or not specified); SAPS-II, simplified acute physiology score; SSTI, skin and soft tissue infection; TOL/TZ, ceftolozane-tazobactam; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

[b]++, high quality; +, acceptable; −, low quality. Adapted from the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/methodology.html).

[c]Study including patients with MDR *Acinetobacter* spp., MDR *P. aeruginosa*, and/or other MDR GNB infections; only specific information available on *P. aeruginosa* infections is reported.

[d]High dose, TOL/TZ dose of 3 g/8 h (2 g ceftolozane + 1 g tazobactam every 8 h) or the equivalent after adjusting for renal function.

[e]The study includes infections due to ceftazidime-resistant Gram-negative pathogens and not specifically multidrug-resistant Gram-negative pathogens.

treatment of respiratory tract infections caused by MDR GNB. Another recent meta-analysis analyzed the combination of inhaled and intravenous (i.v.) colistin. The studies used low-quality data, which suggested that the combination does not lower mortality in patients with MDR Gram-negative infections except when a low i.v. colistin dose is administered. The results for MDR/XDR *P. aeruginosa* infections were not specifically extracted (215).

Regarding studies performed in patients with infections caused by *P. aeruginosa*, Athanassa et al. performed a pharmacokinetic study of inhaled CMS in mechanically ventilated critically ill patients (216). The study included 8 patients with *P. aeruginosa* infection receiving 80 mg of CMS every 8 h. Colistin concentrations in epithelial lining fluid (ELF) were 5-fold higher than those achieved in serum, although ELF concentrations at 4 and 8 h were below the EUCAST breakpoints. Based on these data, the authors concluded that inhaled colistin can achieve high drug concentrations in the lungs, although a dose of 80 mg every 8 h may not be suitable for the treatment of infections caused by MDR GNB (216). Lu et al. (217) compared the clinical outcomes for 122 patients with ventilator-associated pneumonia (VAP) caused by *P. aeruginosa* and *Acinetobacter baumannii* strains susceptible to β-lactams, aminoglycosides, or quinolones and treated with i.v. antibiotics for 14 days with those for patients with VAP caused by MDR *P. aeruginosa* or *A. baumannii* treated with nebulized colistin (5 million IU every 8 h) either in monotherapy ($n = 28$) or in combination with i.v. aminoglycosides. With several methodological limitations, they concluded that nebulized CMS was noninferior to intravenous β-lactams associated with aminoglycosides or quinolones (217). With respect to the use of CMS in patients with ventilator-associated tracheobronchitis, Maskin et al. demonstrated in a study of 17 patients infected with MDR *P. aeruginosa* that inhaled CMS was able to reduce the volume of tracheal secretions, purulence, and bacterial load (218).

There is little clinical information about the use of nebulized polymyxin B. A recent study of inhaled polymyxin B against *P. aeruginosa* in a mouse lung infection model highlighted the advantage of pulmonary delivery of polymyxin B over intravenous administration for achieving high levels of drug exposure in ELF (219). A clinical study performed by Pereira et al. that focused on the use of nebulized polymyxin B as salvage therapy for pneumonia and initial treatment of tracheobronchitis caused by MDR GNB (220) concluded that inhaled polymyxin B was useful as salvage therapy for hospital-acquired pneumonia caused by MDR GNB that failed i.v. treatment and also when used alone in the treatment of *P. aeruginosa* tracheobronchitis. Taking all these results into account, we consider that inhaled polymyxins should be considered for the treatment of lower respiratory tract infections caused by MDR/XDR *P. aeruginosa*. The evidence is not strong enough to consider inhaled therapy alone for pneumonia, where a combination of intravenous and inhaled polymyxins would be a good option. In the case of tracheobronchitis, inhaled therapy alone could be used, although more dosage studies and clinical series are needed.

Another scenario in which polymyxins can play an important role is in the treatment of central nervous system infections (CNS) due to MDR/XDR bacteria. When MDR organisms are the cause of infection, CNS mortality has been reported to be as high as 71% (221). This is partly due to the fact that only a proportion of the intravenous antibiotic dose reaches the site of infection in these difficult-to-treat infections (222–224). Hence, high intravenous doses are required to achieve bacterial killing. Peripheral administration of colistin, however, is neither effective nor safe for CNS infection, due to extensive renal reabsorption and the risk of colistin-associated nephrotoxicity (225). To overcome this problem, intrathecal or intraventricular delivery of polymyxins has generally been used in clinical practice and has become the only therapeutic option for the treatment of MDR GNB CNS infections that are resistant to all other antibiotics. Although most clinical experience with this administration route has been reported for infections caused by *Acinetobacter baumannii*, there are some reports of infections caused by MDR/XDR *P. aeruginosa* (226–233) that have had good clinical outcomes. Even though the intrathecal route in this setting is mandatory, intrathecal polymyxin

therapy has never been optimized according to PK/PD indices (225). The current IDSA guidelines suggest an intrathecal dose of 10 mg of CMS or 5 mg of polymyxin B once daily (234). The recent international consensus guidelines on the use of polymyxins recommend an intraventricular or intrathecal dose of 125,000 IU CMS (~4.1 mg colistin base activity) or 5 mg (50,000 IU) polymyxin B per day (185).

In clinical practice and even in the guidelines, both the dose and the duration of treatment of CNS infections are chosen empirically, since no PK/PD targets have so far been established. For this reason, and as Nation et al. pointed out, it is important in the near future to define optimal targets for the optimization of dosage regimens for the administration of polymyxins by the intrathecal route (169).

Carbapenems

Like all β-lactam antibiotics, carbapenems exhibit time-dependent antibacterial activity. Different *in vitro* and *in vivo* studies have identified the PK/PD parameter most predictive of efficacy as the percentage of the dosing interval that unbound or free serum drug concentrations exceed the MIC for the pathogen ($fT > MIC$). Old *in vitro* and *in vivo* PK/PD studies initially defined an $fT > MIC$ of ≥40% as the optimal value for the bactericidal activity of carbapenems (235). A similar value was identified in a murine thigh model infected with *P. aeruginosa* strains overexpressing MexA-MexB-OprM efflux pumps at both standard and high inocula (236).

With the currently approved antibiotic doses and short-term infusion regimens, the probability of achieving optimal PK/PD target exposures across all patient populations and susceptible pathogens is greater than 80% (http://www.eucast.org/documents/rd/; accessed 25 October 2018). This probability is considerably reduced, however, in the case of infections caused by less susceptible or even resistant pathogens, such as MDR or PDR *P. aeruginosa*. New strategies aimed at achieving the desired targets are therefore required. In this scenario, numerous studies have assessed new dosing strategies, such as increasing the dose or using prolonged infusion administration.

Various studies aimed at defining the optimal carbapenem dose for these difficult-to-treat *P. aeruginosa* infections in different special populations show that high doses may be needed.

One pharmacodynamic study used Monte Carlo simulation to evaluate different dosage regimens of meropenem administered in intermittent or extended (3-h) infusions against populations of *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter* species with different susceptibilities. MIC data and distributions were derived from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC), a multicenter, longitudinal surveillance program in 14 American centers. A total of 276 isolates of *P. aeruginosa* were included, 22.1% of them with MIC values of >4 mg/liter. A meropenem dosage of 1 g/8 h in extended infusion, or 2 g/8 h in intermittent/extended infusion, was required for exposure of 50% $fT > MIC$ against all susceptible *P. aeruginosa* isolates (MIC values of ≤4 mg/liter). However, for organisms considered intermediate-resistant to meropenem (MIC = 8 mg/liter), only the higher-dose regimen of 2 g/8 h in extended infusion achieved adequate bactericidal exposure. The authors suggested the highest dose of meropenem (2 g/8 h) administered by extended infusion for treatment of intermediate or resistant *P. aeruginosa* (237).

An *in vitro* infection model also using Monte Carlo simulation evaluated the optimal dosage of imipenem combined with tobramycin against carbapenem- and aminoglycoside-resistant *P. aeruginosa* clinical isolates. The simulated doses that obtained the best antibacterial activity were imipenem at 4 or 5 g/day in continuous infusion combined with tobramycin (238). The same group confirmed the adequacy of this dosage regimen in a neutropenic mouse thigh model of XDR *P. aeruginosa* infection (160). In one study of bloodstream infections that included 237 isolates of *P. aeruginosa* with reduced susceptibility to carbapenems, different carbapenem dosing regimens were tested: imipenem at 0.5 to 1 g/6 h by 0.5- and 3-h infusion, meropenem at 1 to 2 g/8 h by 0.5- and 3-h infusion, and doripenem at 0.5 to 2 g/8 h by 1- and 4-h infusion. A $T > MIC$ of 40% was considered to be the optimal PK/PD ratio. The results showed that meropenem at

2 g/8 h infused over 3 h and doripenem at 1 g/8 h infused over 4 h showed the best efficacy against *P. aeruginosa* with reduced susceptibility to carbapenems (239). Interestingly, in a case report of a critically ill double-lung transplant patient with pneumonia due to MDR *P. aeruginosa* with a meropenem MIC of 32 mg/liter who received meropenem in continuous infusion (8 g meropenem/24 h), a clinical cure was achieved (240).

Other Classical Antipseudomonal β-Lactams

There are very few data regarding the role of some classical antipseudomonal β-lactams such as cefepime, ceftazidime, piperacillin-tazobactam, and aztreonam in monotherapy against MDR/XDR *P. aeruginosa* infections.

Aztreonam could be a possible option for the treatment of Ambler class B MBL-producing Gram-negative bacteria, including *P. aeruginosa*. One series assessed its clinical efficacy in MBL-producing *P. aeruginosa* infections. In that study, the mortality rate was 30%, but most cases involved combination therapy, and the sample size was too small to be able to draw definitive conclusions (241). Another series included nine patients with MBL-producing *Pseudomonas* infections receiving i.v. colistin combined with aztreonam or piperacillin-tazobactam, and seven (77.8%) of these patients had favorable outcomes and survived (242).

A case report described an immunocompromised patient with an MDR *P. aeruginosa* wound infection who was successfully treated with high-dose aztreonam administered in continuous infusion (8.4 g/day) (243). Another case report described a patient undergoing hemodialysis who developed MDR *P. aeruginosa* bacteremia with a cefepime MIC of 16 mg/liter and was successfully treated with an extended-infusion regimen (3 h) of this antibiotic (244).

A severely immunodepressed patient with MDR *P. aeruginosa* bacteremia with a ceftazidime MIC of 64 mg/liter was treated with high-dose ceftazidime administered in continuous infusion (6.5 to 9.6 g/day) with clinical success (243).

As previously mentioned, some *in vitro* combination assays, such as those with cefepime-tobramycin (138) and cefepime-aztreonam (148), have shown additive or synergistic effects against MDR *P. aeruginosa*.

Based on the type of strain and resistance phenotype and genotype, a possible strategy in individual cases could be to use one of these drugs at high doses administered in prolonged infusion in a combination therapeutic regimen.

Aminoglycosides

Some aminoglycosides remain active against several MDR/XDR *P. aeruginosa* strains (245, 246). Although they can be used in monotherapy in urinary tract infections (247), aminoglycosides could be used in combination with other antimicrobials for the treatment of more severe infections caused by MDR/XDR *P. aeruginosa*.

With respect to their pharmacodynamics, numerous *in vitro* and *in vivo* studies have demonstrated that aminoglycosides have concentration-dependent antibacterial activity and that a peak concentration (maximum concentration [C_{max}]/MIC) of ≥8 to 10 is the best PK/PD predictor of efficacy (248). This value should be reached during the first 24 to 48 h of treatment. This PK/PD index was associated with better clinical cure rates in a retrospective clinical study performed in patients with *P. aeruginosa* bacteremia that was not specifically caused by MDR or XDR *P. aeruginosa* strains (249).

A few studies in recent years have set out to optimize dosing regimens to combat MDR GNB such as *P. aeruginosa*. One PK model, cited above, evaluated the optimal dose of tobramycin and imipenem against carbapenem- and aminoglycoside-resistant *P. aeruginosa* clinical isolates (238). The authors concluded that a 7-mg/kg dose of tobramycin every 24 h, given in 0.5-h infusions, combined with imipenem was needed to achieve adequate bacterial killing and prevent regrowth at 48 h.

One strategy used to treat infections caused by XDR *P. aeruginosa* was to administer very high doses of aminoglycosides combined with continuous renal clearance tech-

niques to prevent renal toxicity. The results showed high survival rates, although the number of included patients was limited (250, 251).

In the case of severe or deep infections such as pneumonia or meningitis due to MDR or XDR *P. aeruginosa*, other routes of administration can be used for aminoglycosides. For the treatment of pneumonia, inhaled amikacin allows high drug concentrations to be achieved at the site of infection (e.g., ELF) and prevents high systemic exposures that can potentially cause systemic toxicity. The use of inhaled antibiotics (polymyxins or aminoglycosides), however, is currently recommended only as adjunctive therapy for infections caused by Gram-negative bacilli susceptible only to aminoglycosides or polymyxins, and in combination with other systemically administered agents (252).

Meningitis is another difficult-to-treat infection. The efficacy of intravenous aminoglycosides is limited due to poor penetration into the central nervous system, which leads to low and inadequate concentrations at the site of infection. In cases of this kind, administration of intraventricular aminoglycosides may be needed. A recent case of postsurgical meningitis caused by PDR *P. aeruginosa* was successfully treated with a combination of intravenous cefepime administered by continuous infusion and combined with intravenous and intraventricular amikacin (253). Although the strain had an MIC for amikacin of 32 mg/liter, the achievement of concentrations of 200 mg/liter in the central nervous system was sufficient for resolution of infection.

Fosfomycin

Because of its excellent *in vitro* bactericidal activity against a wide spectrum of organisms, including MDR *P. aeruginosa*, intravenous fosfomycin in combination with other antimicrobials has reemerged for the treatment of infections caused by MDR bacteria (254, 255). One proposed therapeutic option is to use fosfomycin with carbapenems, a combination that has shown good synergistic activity against different *P. aeruginosa* isolates. This combination has also demonstrated better clinical outcomes, especially when the carbapenem is administered in extended infusion (256–258).

Other experiments have assessed the use of fosfomycin in combination with β-lactams, aminoglycosides, or colistin (259). In one of these, fosfomycin was administered to 5 patients undergoing orthotopic liver transplantation, 3 of whom had infections due to XDR *P. aeruginosa* with a MIC for fosfomycin of $<$16 mg/liter and another due to XDR *Klebsiella pneumoniae* and *P. aeruginosa* with MICs of 32 mg/liter (259). In two of the patients, the infection was eradicated, but in the other three, treatment failed (in two the clinical response was poor, and the third developed a superinfection).

This so-called "old" antibiotic has also been associated with new antimicrobials, such as ceftazidime-avibactam or ceftolozane-tazobactam (260, 261). A patient with XDR *P. aeruginosa* meningitis was successfully treated with a 3-g/8-h dose of ceftolozane-tazobactam associated with a 4-g/6-h dose of fosfomycin (261). Nevertheless, the doses of fosfomycin used in these cases varied considerably, which provides evidence that the optimal dose of this antibiotic for the treatment of difficult-to-treat infections is yet to be defined.

In a systematic review of the clinical and microbiological effectiveness of fosfomycin for the treatment of MDR, XDR, or PDR nonfermenting Gram-negative bacterial infections, the fosfomycin dose for *P. aeruginosa* infections ranged from 2 g/12 h to 5 g/8 h in combination with other antimicrobials (254).

Several studies have evaluated different dosage regimens of fosfomycin in combination with carbapenems for the treatment of non-MDR and MDR *P. aeruginosa* clinical isolates based on PK/PD target attainment. In one of these, Monte Carlo simulation was used to calculate the probability of target attainment for different fosfomycin and carbapenem doses and infusion times (262). In the case of non-MDR *P. aeruginosa* isolates, prolonged infusion of a carbapenem combined with fosfomycin in continuous infusion at 16 to 24 g/day obtained the best PK/PD ratios. However, for the MDR *P. aeruginosa* isolates, none of the fosfomycin and carbapenem combinations achieved

the PK/PD targets. It should be borne in mind that the clinical isolates tested in this study, which was carried out in Thailand, had very high fosfomycin MIC values, and the results cannot be extrapolated to other settings (262).

More clinical series and trials are needed to define the future role of fosfomycin in these infections, including the optimal dose and possible combinations.

NEW ANTIMICROBIALS AGAINST MDR AND XDR *P. AERUGINOSA*

Although a clear distinction has often been made between old and new antipseudomonal antibiotics (263, 264), two antibiotics resulting from the combination of old and new drugs have been released in recent years (265, 266).

Ceftolozane-Tazobactam

Ceftolozane-tazobactam is an effective combination against several MDR Gram-negative bacilli, especially MDR/XDR *P. aeruginosa*. Ceftolozane is one of the most active antipseudomonals. Its activity against *P. aeruginosa* exceeds that of the rest of the antipseudomonal β-lactams by between 20% and 25% (267). Ceftolozane inhibits PBPs and non-ESBL TEM and SHV variants and AmpC enzymes, while tazobactam targets class A serine β-lactamases and ESBLs. Ceftolozane also acts against non-ESBL class D oxacillinases, but it lacks activity against carbapenemases (268).

In a number of studies, MDR/XDR *P. aeruginosa* susceptibility to ceftolozane-tazobactam has been shown to be variable, with rates varying between 55% and 96.6% depending on the series and countries (31, 67, 150, 245, 246, 269–274). The data from these studies are shown in Table 5.

With respect to its PK/PD indices, the bactericidal efficacy of ceftolozane-tazobactam, as with other cephalosporins, is correlated with the percentage of time the plasma drug concentration is above the MIC for the target organism (%T $>$ MIC) (151). Monte Carlo simulations have been performed to study ceftolozane-tazobactam dosing regimens and to define the optimal dose of this drug against infections caused by MDR *P. aeruginosa* with MIC values of between 4 and 32 mg/liter, testing different doses, infusion times, and renal function statuses (275). The multiple scenarios simulated identified the current ceftolozane-tazobactam dose of 1/0.5 g as optimal for MICs of $\leq$32 mg/liter (creatinine clearance [CL_{CR}], 15 to 50 ml/min), $\leq$16 mg/liter (CL_{CR}, 51 to 120 ml/min), and $\leq$8 mg/liter (CL_{CR}, 121 to 180 ml/min). In simulations of augmented renal clearance across infections with MICs of 4 to 32 mg/liter, extended infusions of 4 to 5 h had a higher probability of target attainment (PTA) than shorter and continuous infusions (275). Another study simulated four ceftolozane-tazobactam doses ranging from 250/125 mg to 2/1 g every 8 h, with infusion durations of 1 to 7 h and continuous infusions. The PTA target was defined as 40% *f*T$>$ MIC (276). The results showed that the current dose of 1/0.5 g was optimal for MICs of $\leq$32 mg/liter and different renal function values. In patients with augmented renal clearance, however, extended infusions of 4 to 5 h provided higher PTAs than intermittent infusions. On the other hand, another population PK study in patients with pneumonia, which included kinetics in the ELF, also simulated different dosage regimens and concluded that a dose of 2 g/1g was necessary to achieve a $>$90% PTA (actual, 98%) in ELF against pathogens with MICs of $\leq$8 mg/liter (277). As with other β-lactam antibiotics, administration of the drug over a prolonged period by extended or continuous infusion is a potential strategy for improving the probability of attaining the PK/PD target. Until recently, however, very little evidence of evaluations of extended or continuous infusion of ceftolozane-tazobactam has been available. One case report described a patient with urinary tract infection caused by MDR *P. aeruginosa* who was successfully treated with no adverse events in an outpatient setting with a 4/0.5-g dose of ceftolozane-tazobactam every 24 h given as continuous infusion (278). Another case report evaluated the pharmacokinetics of this antibiotic in a critically ill patient with an MDR *P. aeruginosa* prosthetic hip joint infection receiving continuous venovenous hemofiltration who was treated with a 1/0.5-g dose of ceftolozane-tazobactam every 8 h administered as extended infusion over 4 h (279). An outpatient with a lung abscess caused by carbapenem-

TABLE 5 Ceftolozane-tazobactam activity against resistant strains of *P. aeruginosa*

Authors (journal, yr, reference)[a]	Total no. of centers (country[ies])	Total no. of *P. aeruginosa* strains	Susceptibility[b]			Comments
			Type of strain	No.	%	
Giani et al. (JAC, 2018, 68)	20 (Italy)	935	Resistant to rest of β-lactams	183	59.6	Ceftolozane-tazobactam retained activity against 64 (46.8%) of the strains that were resistant to all other agents except colistin
Humphries et al. (AAC, 2017, 271)	3 (USA)	309	Resistant to rest of β-lactams	105	55	55 (29%) strains analyzed were susceptible to ceftazidime-avibactam
Pfaller et al. (JAC, 2017, 272)	17 (European countries)	603	4 resistance phenotypes (ceftazidime, cefepime, meropenem, piperacillin-tazobactam)	CFZ NS,139; CP NS, 124; MER NS, 126; TZP NS, 162	CFZ NS, 65.5; CP NS, 61.3; MER NS, 65.9; TZP NS, 70.4	91.7% of the strains analyzed were globally susceptible
Del Barrio-Tofiño et al. (AAC, 2017, 31)	9 (Spain)	150	XDR	101	68.7	MIC_{90}, >64 mg/liter
Walkty et al. (JAC, 2018, 246)	10–15 (Canada)	3,229	MDR	462	90.5	MIC_{90}, 4 mg/liter
			XDR	84	78.6	MIC_{90}, 16 mg/liter
Pfaller et al. (IJAA, 2017, 245)	14 (Asia-Pacific, minus China, Australia, and New Zealand)	489	MDR	134	67.2	MIC_{90}, >32 mg/liter
Sader et al. (JAC, 2014, 269)	31 (13 European countries)	2,191	MDR	698	57.4	MIC_{90}, ≤8 mg/liter
			XDR	538	46.3	
Buehrle et al. (AAC, 2016, 150)	1 (USA)	38	Meropenem resistant	38	92	Median MIC_{90} (range): ceftolozane-tazobactam, 1 (0.25–64) mg/liter; ceftazidime-avibactam, 4 (2–>32) mg/liter
Grupper et al. (AAC, 2017, 273)	34 (USA)	290	Meropenem, aztreonam, cefepime, piperacillin-tazobactam NS	103	91	
Livermore et al. (JAC, 2018, 67)	Not specified (UK)	1,384	AmpC derepressed	147	96.6	94.6% of the strains analyzed were susceptible to ceftazidime-avibactam
Tato et al. (IJAA, 2015, 274)	10 (Spain)	500	MDR	34	64.7	MIC_{90}, >64 mg/liter

[a]JAC, *Journal of Antimicrobial Chemotherapy*; AAC, *Antimicrobial Agents and Chemotherapy*; IJAA, *International Journal of Antimicrobial Agents*.
[b]CFZ, ceftazidime; CP, ciprofloxacin; MER, meropenem; TZP, piperacillin-tazobactam; NS, nonsusceptible.

TABLE 6 Suggested antimicrobial therapy options for the most prevalent resistance profiles of MDR/XDR *P. aeruginosa*[a]

Resistance profile	Resistance mechanism(s)	High-risk clones where they are more frequent	Treatment options[b]
PTZ R, CAZ R, ATM R, MER R, TOL/TZ S, CAZ/AVI S, AMK S COL S	AmpC overexpression + OprD deficiency	ST175	COL, POLY-B, TOL/TZ, CAZ/AVI, AMK
PTZ R, CAZ R, ATM S, MER R, TOL/TZ R, CAZ/AVI R, AMK S COL S	MBL production	ST235, ST111 (ST175)	COL, POLY-B, ATM, AMK
PTZ R, CAZ R, ATM R, MER R, TOL/TZ R, CAZ/AVI S, AMK S COL S	Class A carbapenemase (such as GES enzymes) or combinations of certain ESBLs with OprD deficiency	ST235	COL, POLY-B, CAZ/AVI

[a]Abbreviations: PTZ, piperacillin-tazobactam; CAZ, ceftazidime; ATM, aztreonam; MER, meropenem; TOL/TZ, ceftolozane-tazobactam; CAZ/AVI, ceftazidime-avibactam; AMK, amikacin; COL, colistin; POLY-B, polymyxin B.

[b]Administration of β-lactams in extended or continuous infusion and/or combination with intravenous colistin, polymyxin B, or amikacin should be considered in severe infections. Amikacin or colistin in monotherapy is acceptable for urinary tract infection. Therapeutic drug monitoring of colistin or amikacin is recommended. Nebulized colistin (2 to 5 MU/8 h) as adjunctive therapy in lower respiratory tract infections should be considered.

resistant *P. aeruginosa* with a ceftolozane-tazobactam MIC_{90} of 2 mg/liter obtained favorable clinical results after 3 g/1.5 g of ceftolozane-tazobactam administered in continuous infusion (280). In these last two cases, the serum concentration analysis confirmed that these dosing regimens were adequate for the achievement of the desired PK/PD target (279, 280).

Some series of clinical experience with ceftolozane-tazobactam in MDR/XDR *P. aeruginosa* infections have been published (Table 4). These studies are mainly retrospective, with short series of patients, except for a study of 205 patients (281). The main indication in these series was respiratory tract infection, and different doses of ceftolozane-tazobactam were used, sometimes in combination therapy. Cure rates were close to 70%, with emergence of resistance of 4 to 14% in some studies and mortality rates, measured at different times, ranging from 0% (in small series of cases) to 27% (26, 62, 165, 281–288).

In summary, ceftolozane-tazobactam might be a good option for the treatment of MDR/XDR *P. aeruginosa* infections that are susceptible to this drug, but it should be used with caution and with optimization of dosing and, probably, infusion times. Combination therapy could be considered for high-inoculum infections in order to prevent selection of resistance *in vivo* (Table 6). However, more clinical studies are needed to fully confirm these statements. Specifically, observational studies on the use of this drug and on the possible selection of resistant mutants in the real world, clinical trials comparing monotherapy with combination therapy, and larger series of MDR/XDR *P. aeruginosa* infections would be useful in the near future.

Ceftazidime-Avibactam

Avibactam contains a diazabicyclooctane nucleus and acts as a broad-spectrum inhibitor that is effective against enzymes with a nucleophilic serine residue (289). It has no activity against MBL-producing strains (290). The addition of avibactam to ceftazidime protects the cephalosporin from enzymatic degradation caused by *P. aeruginosa* strains (mainly due to Amp-C enzymes but also due to ESBLs and class A carbapenemases such as GES enzymes) and leads to decreased MICs of ceftazidime, which is more marked when combined with higher doses of avibactam (291).

Several *in vitro* studies have demonstrated that ceftazidime-avibactam displays good activity against large collections of MDR/XDR *P. aeruginosa* strains collected in different parts of the world and at different times, with inhibition rates varying between 66.1% and 86.5% (162, 292–295) (Table 7). In another series including 5,716 strains of *P. aeruginosa* collected in the INFORM study, ceftazidime-avibactam showed 92.4% activity against all the strains tested (296). Although its activity was low against MBL-positive strains, it was the second most active agent after colistin. Likewise, in another *in vitro* study, several *P. aeruginosa* strains with different levels of resistance were exposed to β-lactam antibiotics and 74.1% of pan-β-lactam-resistant isolates were susceptible to ceftazidime-avibactam with an MIC_{90} of 16 mg/liter (59). Similarly, activity against strains of *P. aeruginosa* from patients with urinary tract infections in U.S.

TABLE 7 Ceftazidime-avibactam activity against MDR and XDR *P. aeruginosa*

Authors (journal, yr, reference)[a]	Total no. of centers (country or continents)[b]	Total no. of strains	MDR strains			XDR strains			Comments
			No.	%	MIC_{90} (mg/liter)	No.	%	MIC_{90} (mg/liter)	
Sader et al. (IJAA, 2015 292)	71 (USA)	3,082	436	80.7	≤8	247	74.5	≤8	Susceptibility rates for ceftazidime, piperacillin-tazobactam and meropenem, 8.5%–22.9% (MDR strains) and 2.0%–13.4% (XDR strains)
Sader et al. (AAC, 2015, 293)	75 (USA)	3,902	338	81.0	16	338	73.7	32	Colistin efficacy against MDR and XDR strains (EUCAST), 99.7%
Stone et al. (JAC, 2018, 162)	? (Europe, North and South America, Asia, and Africa)	565	56	66.1	64				Data from adult phase III clinical trials
Sader et al. (AAC, 2017, 295)	INFORM study (USA)	7.868	1,562	86.5	16	717	75.9	32	Amikacin efficacy, 87.1% (MDR strains) and 80.8% (XDR strains); colistin efficacy, >99% (both types of strains)
Sader et al. (AAC, 2017, 294)	? (USA)	3,402	613	82.7	16	365	76.2	32	Colistin was the most active antibiotic (99.6% susceptibility)

[a]JAC, *Journal of Antimicrobial Chemotherapy*; AAC, *Antimicrobial Agents and Chemotherapy*; IJAA, *International Journal of Antimicrobial Agents*.
[b]A question mark indicates that the total number of centers was not given in the indicated article.

hospitals showed a MIC_{90} of 32 mg/liter for strains resistant to ceftazidime, meropenem, or piperacillin-tazobactam (297). The INFORM 2012–2014 study analyzed the activity of ceftazidime-avibactam against 7,062 strains of *P. aeruginosa* and found that 563 (8%) of them showed resistance to this antibiotic. Half of these were explained as due to possession of genes encoding MBLs (298). Another study assessed ceftazidime-avibactam activity against clinical isolates, 41 of them *P. aeruginosa*, in a phase III trial of complicated urinary tract infections. The range of MICs for these strains was 4 to 16 mg/liter (299).

In order to analyze the emergence of *P. aeruginosa* resistance to ceftazidime-avibactam, a study was developed to assess the evolution of this microorganism after exposure to the antibiotic. Interestingly, the studied strains developed mutants resistant to ceftazidime-avibactam, mainly through the efflux pumps PA14_45890 and PA14_45910 (60).

Regarding PK/PD parameters, after multiple doses of ceftazidime-avibactam at 2 g/0.5g, the C_{max} was 113.0/15.0 mg/ml and the area under the curve (AUC) was 348.2/42.2 mg · h/liter. With respect to the PK/PD properties of ceftazidime-avibactam, a new ratio has been proposed that can be calculated *in vitro* or *in vivo*, defined as %*f*T > CT, with CT being the "concentration threshold" for avibactam (300). In an HFIM, several CT values were tested to determine which one best correlated with efficacy against ceftazidime-resistant *P. aeruginosa* strains (MICs of 32 to 128 mg/liter for ceftazidime and 2 to 16 mg/liter for ceftazidime-avibactam) (301).

A PK/PD study was designed to evaluate the predictive performance of the susceptibility cutoff points established by the regulatory agencies for ceftazidime-avibactam against different bacteria (161). The results were consistent in the case of susceptible *P. aeruginosa* strains, but the cutoff points were challenged when strains resistant to several antibiotics included in clinical trials were considered. The model was considered unreliable for the analysis of ceftazidime-avibactam activity against resistant *P. aeruginosa*, probably because these strains had mechanisms of resistance that could not be reversed by adding avibactam to ceftazidime.

Various *in vitro* and *in vivo* PK studies have evaluated the PK/PD parameters of ceftazidime-avibactam against different Gram-negative microorganisms. An *f*T > MIC for at least 50% of the dosing interval has been shown to achieve the maximum bacterial kill (302). For avibactam, which does not have antibacterial activity at clinically relevant concentrations, a minimum free avibactam concentration (threshold concentration [fC_T]) needed to achieve sufficient β-lactamase inhibition to restore the activity of ceftazidime was defined. The estimated critical concentration threshold (C_T) was

≤0.15 mg/liter (303). In a neutropenic mouse lung and thigh infection model of ceftazidime-resistant *P. aeruginosa* expressing AmpC and/or TEM-24 β-lactamase, achievement of a free T > C_T of 40% to 50% and an fC_T of 1 mg/liter for avibactam exceeded the exposures associated with stasis, 1-$\log_{10}$ kill, and 2-$\log_{10}$ kill of *P. aeruginosa* (300). Another *in vitro* study evaluated the bactericidal activity of ceftazidime-avibactam against 18 *P. aeruginosa* isolates and 15 *Enterobacteriaceae* isolates, including wild-type isolates and ESBL, KPC, and/or AmpC producers (304). At 6 h, the authors observed time-dependent and bactericidal activity against all *Enterobacteriaceae* isolates and a lower degree of initial killing against all *P. aeruginosa* isolates. At 24 h, ceftazidime-avibactam did not have any bactericidal activity, and bacterial regrowth was detected in both species.

Based on this PK/PD target, the optimal dose for its achievement has been evaluated in population PK models, and a dose of 2/0.5 g ceftazidime-avibactam every 8 h administered intravenously over 2 h has been recommended for patients with normal renal function. This selected dose allows the PK/PD target to be achieved against *Enterobacteriaceae* and *P. aeruginosa* isolates using the ceftazidime-avibactam breakpoints of ≤8/4 mg/liter (305). These population PK models of ceftazidime-avibactam were built using PK data from five phase III trials in patients with complicated intra-abdominal infections, complicated urinary tract infections, and nosocomial (including ventilator-associated) pneumonia (306). This clinical dose was further validated in an HFIM and in neutropenic and immunocompetent mouse thigh infection models against different *P. aeruginosa* isolates with ceftazidime-avibactam MICs of 4 to 16 mg/liter (307).

Clinical studies with ceftazidime-avibactam in MDR/XDR *P. aeruginosa* infections are scarce and contain low numbers of patients. Doses used were 2/0.5 g/8 h, sometimes prescribed in combination. The cure rates were close to 80%, and most failures occurred in respiratory tract infections. There is limited information on mortality, microbiological eradication, recurrence, or the emergence of resistance (163, 308). Related to this, and rather worryingly, ceftazidime-avibactam-resistant *P. aeruginosa* isolates were identified in 9/355 (2.5%) of microbiologically evaluable patients in a phase III clinical trial that compared ceftazidime-avibactam with meropenem in nosocomial pneumonia (309).

In summary, *in vitro* studies have shown that ceftazidime-avibactam might be a good option for the treatment of MDR/XDR *P. aeruginosa* infections, but clinical experience is currently limited. Depending on the underlying mechanisms of resistance, ceftazidime-avibactam could be the best option for some MDR/XDR *P. aeruginosa* strains, such as those harboring Class A carbapenemases (such as GES enzymes) or combinations of certain ESBLs with OprD deficiency (Table 6). Larger series of MDR/XDR *P. aeruginosa* infections treated with ceftazidime-avibactam are needed.

CRITICAL EVALUATION OF CLINICAL STUDIES PROVIDING INFORMATION ON OUTCOMES OF INFECTIONS DUE TO MDR/XDR *P. AERUGINOSA*

Table 4 provides a summary of clinical studies including 5 or more patients that have analyzed the outcomes for patients with MDR/XDR *P. aeruginosa* infections treated with different systemic antibiotic regimens. Although some studies addressed only MDR/XDR *P. aeruginosa* infections, many others considered them jointly with other MDR GNB infections, including those caused by *A. baumannii* and/or *Enterobacteriaceae*. Among these, only those that specifically detail any outcome for patients with MDR/XDR *P. aeruginosa* infections are included here. The design and quality of the studies were evaluated according to the Scottish Intercollegiate Guidelines Network (SIGN) method (https://www.sign.ac.uk/methodology.html).

Most publications have analyzed patients treated with colistin (180–188, 299, 300) and, more recently, with ceftolozane-tazobactam (26, 62, 165, 281–287). There are some articles about patients treated with polymyxin B (207–209), ceftazidime-avibactam (163, 308), and aminoglycosides (250) or with different combinations of antimicrobials (203, 204, 206, 258). Overall, the number of studies is limited. Most are retrospective studies

of case series or cohorts and have all the limitations inherent to this type of design, as well as small sample sizes. At the same time, most studies have other significant limitations. First, they include patients with heterogeneous baseline characteristics (age, comorbidities, and immunocompetence), infection sites, percentages of polymicrobial infections (often not provided), and severity at presentation, differences in pathogen susceptibility (MDR and XDR *P. aeruginosa*) and MICs of the antimicrobials (frequently not provided), use of different antimicrobial doses or dose adjustments according to the patient's degree of renal dysfunction (especially in the case of colistin), delays in time to effective therapy, use of different antimicrobial combinations in an unplanned way, use of the antibiotic being studied after failure of initial (empirical and/or directed) antimicrobial therapy, a variety of treatment durations, and different amounts of information, or none at all, about source control. Despite this heterogeneity, outcomes are usually presented in aggregated form, making them difficult to interpret. Furthermore, in the few studies comparing different antibiotics, doses, or antimicrobial combinations, the invariably small sample sizes make it difficult to adjust for all other variables affecting the outcomes. Second, the included studies do not use a unanimous definition of multidrug-resistant *P. aeruginosa*. Third, the outcomes considered in different studies (clinical and microbiological responses and mortality) are frequently defined in different ways and/or are evaluated at different time points during clinical evolution. In the particular case of colistin and ceftolozane-tazobactam, an additional problem is that different studies have used different doses, with a tendency to increase them over time, which makes it difficult to compare results between publications.

As previously mentioned, until very recently, colistin was the only alternative for many cases of MDR *P. aeruginosa* infection. The use of this drug is complicated due to its narrow therapeutic window and frequent nephrotoxicity and by the fact that an adequate dosage has not yet been properly determined. More recently, the availability of ceftolozane-tazobactam and ceftazidime-avibactam represents a major step forward, mainly because they are active against several MDR/XDR *P. aeruginosa* strains, with limited side effects. However, it is difficult to use published data as a basis for comparing outcomes with these antimicrobials against those with colistin. There is a lack of clinical studies with ceftazidime-avibactam. In the case of ceftolozane-tazobactam, some clinical studies allow for some comparisons. With respect to 28- to 30-day all-cause mortality, a 32% to 47% rate was reported for colistin in 3 studies (181, 183, 192) and a 10% to 28% rate for ceftolozane-tazobactam in 4 studies (26, 62, 281, 282). As a result of the limitations of the studies that have been mentioned already, these apparent differences should be interpreted with caution. The emergence of resistant *P. aeruginosa* mutants during treatment with ceftolozane-tazobactam is of particular concern. This fact supports the use of ceftolozane-tazobactam at high doses, preferably in extended or continuous infusion, and also raises the question of the possible advantages of combining antibiotics in difficult-to-treat and high-inoculum infections, at least in the first days of treatment. Several studies have addressed the potential advantages of combination therapy (203, 204, 206, 258) and suggested possible alternatives: the use of β-lactams in extended or continuous infusion (in the case of MICs classified as intermediate) combined with colistin, as well as different dual therapies of combinations including doripenem (with intermediate MICs) in extended infusion, fosfomycin, or colistin. In 3 studies, the combinations showed better results than monotherapy (203, 204, 206). Nevertheless, the limitations of these studies prevent definitive conclusions from being drawn. Only one well-designed clinical trial has addressed this issue, with a comparison of the colistin-plus-meropenem combination versus colistin alone (187). Unfortunately, the study lacked enough power to reach conclusions in the case of MDR *P. aeruginosa*.

Another aspect that has led to several publications is the possible usefulness or advantage of administration of inhaled versus intravenous colistin or of a combination of both of them in the case of respiratory infections. Two recent meta-analyses addressed this question in patients with MDR GNB (214, 215), although the studies do

not provide specific results for MDR/XDR *P. aeruginosa* infections. Only studies that explicitly detail the outcomes for patients with MDR *P. aeruginosa* respiratory infections are included here (199, 217). No definitive conclusions can be reached from these studies. This is another of the many questions in the treatment of these complex infections that remain unresolved. However, based on data on other MDR GNB infections, nebulized colistin seems acceptable as adjuvant therapy when treating MDR/XDR *P. aeruginosa* respiratory infections.

Considering all of the reviewed studies and data, we have defined some general therapeutic recommendations based on the most prevalent resistance profiles of MDR/XDR *P. aeruginosa* (Table 6).

INVESTIGATIONAL AGENTS WITH ACTIVITY AGAINST MDR/XDR *P. AERUGINOSA*

Imipenem-Relebactam

Relebactam is an active β-lactamase inhibitor of class A and class C β-lactamases (310), and in combination with imipenem (plus cilastatin), it can restore imipenem activity against resistant strains, including AmpC-producing *P. aeruginosa* (311). One study set out to assess the *in vitro* activity of imipenem-relebactam against 3,143 clinical strains of non-*Proteus Enterobacteriaceae* and *P. aeruginosa* collected at 21 U.S. hospitals participating in the SMART program (312). Of all *P. aeruginosa* strains tested, 94.4% (846/896) were susceptible to this antibiotic, compared with 74.7% (669/896) that were susceptible to imipenem. The *in vitro* activities of the imipenem-relebactam combination were 78% against imipenem-resistant *P. aeruginosa* strains and 82.2% against MDR *P. aeruginosa* strains. Only colistin and amikacin showed activity similar or superior to that of imipenem-relebactam. Another study evaluated its *in vitro* activity against strains in the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) group, which includes MDR *P. aeruginosa* (313). Imipenem-relebactam showed activity against 94% (796/845) of *P. aeruginosa* strains, in contrast to 70.3% (594/845) in the case of imipenem. Additionally, 80.5% of the strains of these imipenem-resistant microorganisms (MIC_{90}, 16 μg/ml) were susceptible to imipenem-relebactam with a MIC_{90} of 2 μg/ml. Only amikacin showed activity comparable to that of imipenem-relebactam, with 95.6% susceptibility.

A double-blind, phase I clinical trial evaluated the pharmacokinetics and safety of relebactam, administered alone or in combination with imipenem-cilastatin (314). Administration of a single dose of relebactam over a dose range of 25 to 1,150 mg showed a terminal half-life ($t_{1/2}$) of between 1.3 and 1.8 h, with pharmacokinetics similar to those of imipenem, which supports combination with this antibiotic given with the same frequency of infusion. The AUC and C_{max} increased exponentially with the dose. The AUC target of 13.1 mg · h/liter was obtained with a 125-mg dose of relebactam administered with imipenem, but the AUC reached higher values when relebactam was administered as the sole drug. The pharmacokinetics of imipenem-cilastatin were similar when administered as standard combination therapy or together with relebactam. Administration of a single 125-mg dose of relebactam with 500 mg imipenem showed AUC values for relebactam that were 22% and 25% higher in adult and elderly women, respectively, than in men in each age group. Both elderly men and women had 41% and 45% higher mean plasma concentrations than the corresponding group of adult men. Relebactam was excreted almost completely in the urine, with the percentages ranging between 94.7% and 100% in the 24 h after administration of a single dose. The PK parameters for imipenem were comparable across all the groups studied. Tolerability was good, with drowsiness being the most frequently observed adverse effect. In study 2, 7-day administration of multiple doses of 125 mg of relebactam with 500 mg of imipenem showed similar $t_{1/2}$ values on days 1 and 7, and accumulation of relebactam did not occur. The AUC target of 13.1 mg · h/liter was again reached with the same doses of relebactam. Again, when the compounds were administered at the described doses, the drug was generally well tolerated.

A phase II clinical trial evaluated different doses of relebactam combined with imipenem-cilastatin in patients with complicated intra-abdominal infections (315). Both

the 125-mg and 250-mg doses of relebactam combined with 500 mg of imipenem showed 100% microbiological eradication in patients with *P. aeruginosa* infections. Of a total of 5 strains of imipenem-resistant *P. aeruginosa*, 3 showed susceptibility to the combination with relebactam. To date, no clinical experiences with imipenem-relebactam and MDR/XDR *P. aeruginosa* infections have been published. However, considering its characteristics and antimicrobial activity, this drug could play an important role in the near future in therapy against MDR/XDR *P. aeruginosa*.

Cefiderocol

Cefiderocol is a siderophore cephalosporin with activity against multiple Gram-negative organisms, including strains that are resistant to other antibiotics (316). Cefiderocol acts by binding to ferric iron, which enables it to use bacterial iron transporters to penetrate the external bacterial membrane. It also has high stability against β-lactamases, including serine-dependent β-lactamases and MBLs (317, 318). The ability of cefiderocol to neutralize AmpC overproduction, its stability against these enzymes, and its ability to induce AmpC in *Enterobacter cloacae* and *P. aeruginosa* have been studied (318). While the MICs of ceftazidime and cefepime for the *P. aeruginosa* PAO1 strain increased 4- to 16-fold due to the inactivation of AmpD and DacB, cefiderocol MICs were only slightly affected. The effect of AmpC inactivation on the MICs of these antibiotics was very limited. Similar results were observed when the effect on AmpC overproduction was studied. Hence, cefiderocol was found to be a very stable cephalosporin against these enzymes.

Another *in vitro* experiment evaluated the activity of cefiderocol against 1,873 clinical isolates of Gram-negative organisms from 52 countries (319). A total of 262 strains of MDR *P. aeruginosa* were exposed to various antibiotics; the MIC_{90} values of colistin and cefiderocol were 1 mg/liter, versus >8 mg/liter for ciprofloxacin and >64 mg/liter for meropenem, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam. The same finding was also observed when the activities of several antibiotics against 100 strains of imipenem-resistant *P. aeruginosa* were studied (320). The MIC_{90} of cefiderocol was 1 mg/liter, and this drug was the most active of all the antipseudomonal antibiotics studied.

A mouse model of infection was used to determine the PK/PD characteristics of this antibiotic against different strains of *P. aeruginosa* with cefiderocol MICs in the range of 0.063 to 0.5 mg/liter (321). When the %*f*T> MIC was calculated for the different strains, it was observed that the probability of achieving the therapeutic target was 100% against all strains tested at a dose of 166 mg/kg/8 h. While the results of ongoing clinical trials and other clinical studies are awaited, this drug holds great promise for the treatment of MDR/XDR *P. aeruginosa* infections.

Murepavadin

The need to find antibiotics with new mechanisms of action has given rise to certain agents that are able to interact with external bacterial membranes composed of phospholipids and lipopolysaccharides (322). Murepavadin is able to interact with the membrane protein LptD of *P. aeruginosa* as a peptidomimetic antibiotic with specific activity against this microorganism. It would therefore be the first microorganism-specific antimicrobial molecule (323). The activity of murepavadin against 785 strains of XDR *P. aeruginosa* has been studied and compared with those of other antibiotics, such as colistin, ceftolozane-tazobactam, and tobramycin (324). The activity of this antibiotic was excellent, since it inhibited 97.8% of isolates studied at concentrations of <2 mg/liter and showed 8 times higher activity than colistin.

A phase I study aimed to assess the PK behavior of murepavadin in healthy volunteers after a single dose ranging from 0.05 mg/kg to 4.5 mg/kg and after multiple doses ranging from 1 mg/kg to 5 mg/kg every 12 h (325). The AUCs ranged between 12,500 ng · h/ml for the lowest multiple dose and 74,500 ng · h/ml for the highest, with a mean $t_{1/2}$ of between 6.17 h and 7.15 h, respectively. A further study compared the PKs of this antibiotic in patients with different degrees of renal function (326). The mean

values ranged between 71.13 and 27.52 ng · h/ml for AUC, between 2.4 and 7 liters/h for clearance, between 1.4 and 7.8 h for $t_{1/2}$, and between 80.9 and 76.3 liters for the volume of distribution in patients with the worst renal function (mean creatinine clearance of 25.5 ml/min) versus healthy volunteers, respectively. In healthy volunteers, the ELF/plasma ratio for this antibiotic was practically 1.

In a phase II study in patients with ventilator-associated pneumonia, murepavadin showed a clinical cure in 10 of the 12 patients with confirmed *P. aeruginosa* infection (327). Likewise, the mortality rate was 8%, a value that should be interpreted with caution due to the low number of patients included in the study. Murepavadin, the first microorganism-specific antipseudomonal molecule, is a promising therapeutic alternative due to its excellent antimicrobial activity and PK data.

Cefepime-Zidebactam

Zidebactam, like avibactam, is a non-β-lactam drug belonging to the diazabicyclooctane group and has a high affinity for the PBP2 locus of Gram-negative microorganisms as well as a high capacity for β-lactamase inhibition (328). A study assessed the activity of zidebactam alone or combined with cefepime against several species of Gram-negative microorganisms, including 50 strains of *P. aeruginosa* (329). Zidebactam showed activity against two strains of NDM-positive *P. aeruginosa* at concentrations of 8 and 32 mg/liter. An analysis of the *in vitro* behavior of this drug against 1,291 strains of *P. aeruginosa* was performed, which included 43 strains of MDR *P. aeruginosa*: 10 strains that are susceptible to cefepime, 21 strains with overexpression of AmpC or efflux pumps, and 12 MBL-producing strains (330). The MIC_{90} of the combination against cefepime-susceptible strains was 2 mg/liter, versus 4 mg/liter for cefepime. For strains with overexpression of AmpC or efflux pumps, the 1:1 combination had a cefepime-zidebactam MIC of 8 mg/liter, versus 16 mg/liter for the 2:1 combination and 64 mg/liter and 32 mg/liter for cefepime and zidebactam alone, respectively. Finally, for the MBL-producing strains, the MICs of the 1:1 and 2:1 combinations were 8 mg/liter and 16 mg/liter, respectively. These values show the very high *in vitro* activity of this new antibiotic against MDR/XDR *P. aeruginosa*.

A study evaluated the plasma and intrapulmonary pharmacokinetics of multiple doses of 2 g cefepime and 1 g zidebactam administered to healthy volunteers and also carried out a safety analysis (331). After the seventh dose, the mean plasma PK values of cefepime were a C_{max} of 139.5 μg/ml and an AUC of 327.0 mg · h/liter, while those of zidebactam were a C_{max} of 60.0 mg/liter and an AUC of 139.5 mg · h/liter. The mean concentrations of cefepime and zidebactam in ELF were reached at 1.25 h after administration, with values of 35.24 mg/liter and 14.61 mg/liter, respectively, and a plasma/ELF ratio of 2.41. In the case of alveolar macrophages, the highest mean concentrations of cefepime and zidebactam were 16.99 mg/liter at 8 h and 2.06 mg/liter at 6 h, respectively. One volunteer presented a moderate hypersensitivity reaction that was drug related. These data, together with the very high *in vitro* activity of this new antibiotic against MDR/XDR *P. aeruginosa*, define it as an excellent future option for these infections.

Bacteriophages

Bacteriophages were developed more than a century ago but were superseded by antibiotics, largely because phage activity is frequently limited to particular strains; now, however, they are being reinvestigated due to their activity against difficult-to-treat strains (332). Phage therapy has a special place in Eastern Europe, notably Russia, Georgia, and Poland. There is limited experience regarding the effectiveness of phage use. They have mostly been used in phage mixtures with activity against different resistant strains of *P. aeruginosa* for the treatment of infections and have shown promising results, some of them pending publication.

A review showed that the number of studies with phages for the treatment or prevention of *P. aeruginosa* infection is limited, and most or all have been developed in patients with cystic fibrosis and used as inhaled therapy (333). Given that some

infections in this population are produced by mucoid strains of MDR *P. aeruginosa*, the phages used should have activity against both biofilm-producing and non-biofilm-producing strains. Combination therapy with active antibiotics and phages could be a possible option that should be evaluated in future studies. One study used an *in vitro* model and two mouse models to determine the activity of a combination of 6 phages against biofilm-producing MDR *P. aeruginosa* strains in patients with cystic fibrosis (334). The results with the bacteriophage cocktail used were encouraging and showed good capacity of the phages in reducing bacterial load and biofilm formation. This could be a useful strategy for local treatment of deep infections, such as bone and joint infections caused by XDR *P. aeruginosa* (335). Another study was based on the isolation of different *P. aeruginosa* phages from hospital sewage samples, specifically SL1, SL2, and SL4 (336). The 5 strains of MDR *P. aeruginosa* were affected by at least one of the phages studied, and no bacterial regrowth was observed. Phage SL2 showed the highest activity against planktonic strains, while SL4 was the best against the biofilm model. The highest survival rate was achieved with SL1. However, the activity of the phage cocktail was not better than that of the most active phage used individually.

The use of inhaled antibiotics is currently spreading, and one study set out to evaluate three different types of nebulizer for administering bacteriophage PEV44, which is active against *P. aeruginosa* (337). The authors concluded that the Omron NE22 nebulizer best maintained phage viability. The efficacy and safety of inhaled administration of *P. aeruginosa* phage therapy were evaluated in a mouse model of pulmonary infection caused by MDR *P. aeruginosa* (338). The results demonstrated that intratracheal administration of dry phage powder significantly reduced the bacterial load of MDR *P. aeruginosa* in the lungs of the mice and resulted in minimal damage to the lung tissue.

Another strategy that has been studied for the treatment of infections caused by resistant microorganisms is the use of phages combined with antibiotics (339). Phage-drug combination therapy has been shown to be superior to the activity of each agent separately. Phage-antibiotic synergy (PAS) was studied in an *in vitro* model in which phages of the family *Myoviridae*, genus *Pbunavirus*, showed synergy with multiple antibiotics, and in the case of the phage active against *P. aeruginosa*, with piperacillin and ceftazidime (340).

Bacteriocins

Bacteriocins are substances with antimicrobial activity that are produced by some bacteria. It has been proposed that they could be used clinically for the treatment for infections caused by multidrug-resistant microorganisms (341). One study assessed the activity of three R-type pyocins produced by strains of *P. aeruginosa* against clinical isolates of this microorganism in patients with cystic fibrosis (342). These substances showed potential therapeutic activity that should be considered in future clinical studies.

Anti-Quorum-Sensing Strategies

Quorum-sensing molecules are regulators of virulence mechanisms that are present in diverse microorganisms, including MDR/XDR *P. aeruginosa* (343, 344). These regulators are also involved in the formation of biofilm and in the regulation of gene expression that underlies collective behaviors in cellular populations. Interfering with these molecules has been proposed as an alternative or complementary tool against MDR bacteria by inhibiting their pathogenicity and biofilm formation (345). The strategies to interfere with quorum sensing are directed against the biosynthesis, accumulation, and detection of the signals derived from small molecules that act as self-inductors of the propagation of quorum sensing (346). Among the strategies to inhibit quorum sensing are the interference with transcriptional factors related to DNA transcription and signal interference of the quorum sensing once it has been detected, as has been applied successfully with *P. aeruginosa* (347), as well as the inhibition of

bacterial enzymes related to this process in different bacteria, including *P. aeruginosa* (348).

Vaccines and Monoclonal Antibodies

One of the strategies for combating infections caused by MDR/XDR microorganisms involves the use of vaccines or monoclonal antibodies, which are emerging as novel tools for preventing the acquisition of MDR *P. aeruginosa* infections in high-risk patients (349). Some vaccines, namely IC43, KB001-A, and KBPA-101, have already been tested in critically ill patients (350). A study performed in ventilated critically ill patients confirmed the immunogenicity of IC43 vaccination in this population (351).

With respect to antibodies, new active targets aimed at neutralizing virulence factors such as the *P. aeruginosa* type III secretion system (TTSS) are under development as monoclonal antibodies and vaccines (352). PcrV is an essential protein for TTSS activity and the one that has been used mostly as a target. The aim of one study was to develop monoclonal antibodies that neutralize the virulence of the TTSS by acting on the PcrV protein (353). In a clinical study, KB001-A, a pegylated antibody that inhibits the function of the PcrV protein, was administered to cystic fibrosis patients infected with *P. aeruginosa*. Although the endpoint of clinical efficacy was not achieved, possible benefits in the regulation of infection and inflammation in these patients were observed (354). KBPA-101 is another human monoclonal antibody obtained from healthy volunteers who were given a polysaccharide conjugate vaccine with *P. aeruginosa* toxin A (355). This antibody showed linear pharmacokinetics in healthy volunteers and no adverse effects. Consequently, it has been proposed for future use as an alternative for the prevention of *P. aeruginosa* infections (356). Another monoclonal antibody (V2L2MD) showed very good prophylactic protection in several mouse models of *P. aeruginosa* infection. In a rabbit model of pneumonia, MEDI3902, a selective monoclonal antibody against PcrV proteins, and Psl exopolysaccharide showed a highly protective effect against a highly virulent *P. aeruginosa* strain (357). This protective activity was observed in another experiment that demonstrated the high specificity of this monoclonal antibody against the PcrV epitopes of most of the *P. aeruginosa* strains studied, as well as maintenance of its protective effect (358). These results led to a phase I study in healthy volunteers (359) that demonstrated the efficacy and tolerability of this drug. At present, this antibody has been included in a phase II proof-of-concept trial for evaluating the prevention of nosocomial pneumonia in patients colonized by *P. aeruginosa* (360).

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