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Manuel Pina-Sánchez[1]
Marta Rua[1,2]
José Luis Del Pozo[1,2,3]

Present and future of resistance in *Pseudomonas aeruginosa*: implications for treatment

[1]Department of Clinical Microbiology, Clínica Universidad de Navarra, Pamplona, Spain
[2]Infectious Diseases Division, Clínica Universidad de Navarra, Pamplona, Spain
[3]Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain

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ABSTRACT

Pseudomonas aeruginosa is a pathogen that has a high propensity to develop antibiotic resistance, and the emergence of multidrug-resistant strains is a major concern for global health. The mortality rate associated with infections caused by this microorganism is significant, especially those caused by multidrug-resistant strains. The antibiotics used to treat these infections include quinolones, aminoglycosides, colistin, and β-lactams. However, novel combinations of β-lactams-β-lactamase inhibitors and cefiderocol offer advantages over other members of their family due to their better activity against certain resistance mechanisms.

Selecting the appropriate empiric antibiotic treatment requires consideration of the patient's clinical entity, comorbidities, and risk factors for multidrug-resistant pathogen infections, and local epidemiological data. Optimizing antibiotic pharmacokinetics, controlling the source of infection, and appropriate collection of samples are crucial for successful treatment.

In the future, the development of alternative treatments and strategies, such as antimicrobial peptides, new antibiotics, phage therapy, vaccines, and colonization control, holds great promise for the management of *P. aeruginosa* infections.

Keywords: *Pseudomonas aeruginosa*; antibiotic resistance; Metallo-β-lactamases; Ceftolozane-tazobactam; Ceftazidime-avibactam; Cefiderocol; Imipenem-Relebactam; Meropenem-vaborbactam

Correspondence:
José Luis Del Pozo
Department of Clinical Microbiology, Clínica Universidad de Navarra, Pamplona, Spain
E-mail: jdelpozo@unav.es

PSEUDOMONAS AERUGINOSA: A VERSATILE PATHOGEN

P. aeruginosa is an extremely versatile pathogen with three key characteristics (Figure 1). Firstly, it has a high adaptive capacity resulting from its ability to generate mutations at a high rate, its genomic plasticity, its ability to form biofilms and enter a *persister* state, and its *quorum* sensing communication mechanisms. Secondly, it has a large arsenal of virulence factors, such as pigments, exotoxins, proteases, secretory systems, and biofilm formation. Thirdly, it has a high potential to generate and transmit antibiotic resistance [1].

This bacterium is responsible for a wide variety of infections at different anatomical levels, but it is important to note two aspects when studying these infections. Firstly, it is primarily considered an opportunistic pathogen, so there are patient-specific criteria that must be met for a P. aeruginosa infection to occur, and the severity of the infection is modulated by factors such as the patient's level of immunosuppression, exposure to medical devices, length of hospital stay, and location in the hospital [1].

Biofilm formation is implicated in infections caused by P. aeruginosa, with classical examples being chronically infected cystic fibrosis or ventilator-associated pneumonia. Hypermutant strains have been described within the biofilm, which may generate and share resistance mechanisms [2].

PSEUDOMONAS AERUGINOSA: THE PARADIGM OF ANTIBIOTIC RESISTANCE

The antibiotic resistance mechanisms of this bacterium can be categorized as innate and acquired. Innate mechanisms, such as low outer membrane permeability, Mex-type efflux pumps, and AmpC cephalosporinase, are common features of this species. Acquired mechanisms can be acquired through

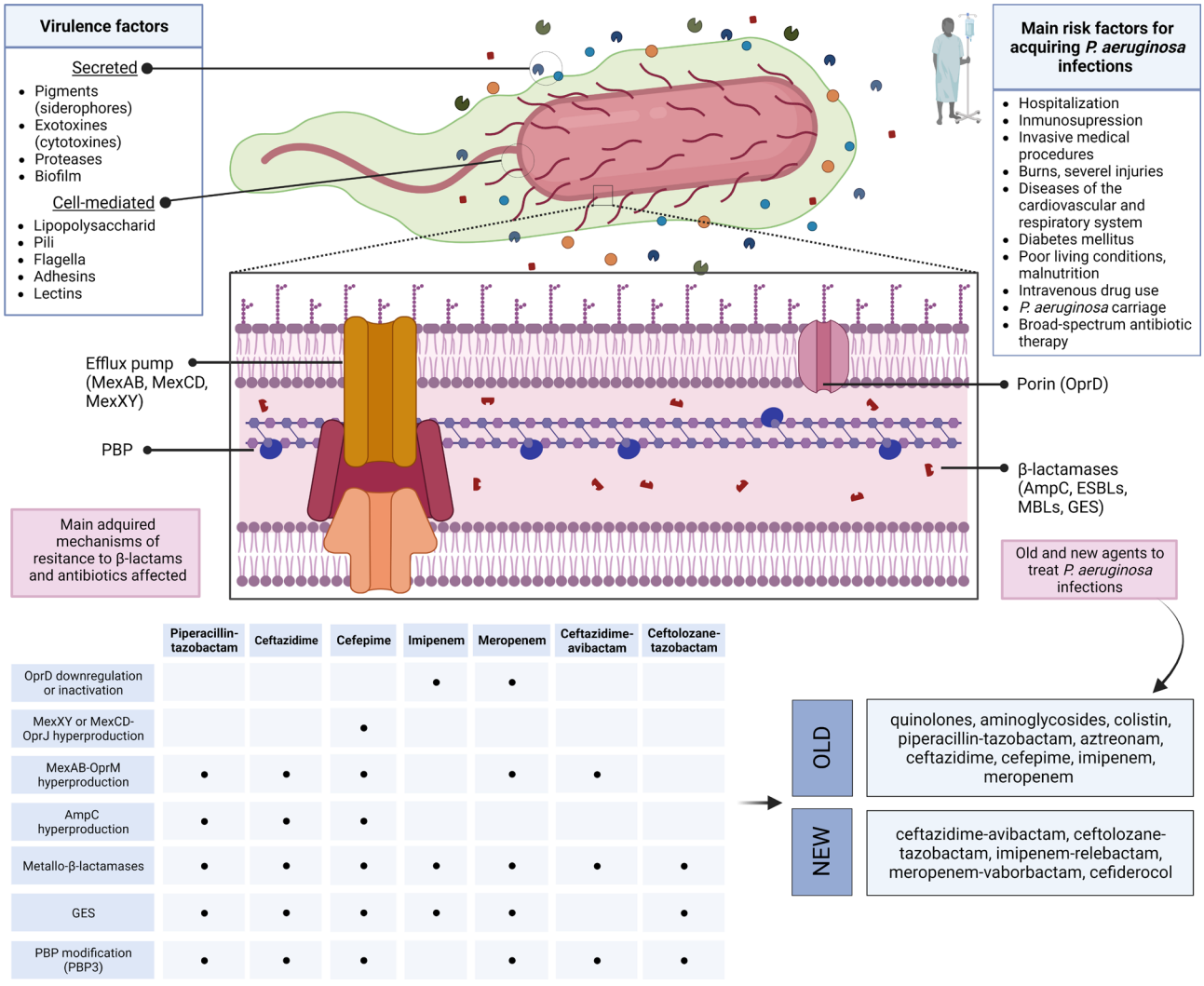

Figure 1 | **Virulence factors, risk factors for acquiring infection, scheme of β-lactam resistance mechanisms and agents to treat *Pseudomonas aeruginosa* infections.**

ESBLs: extended-spectrum β-lactamases, MBLs: metallo-β-lactamases, GES: Guiana extended-spectrum β-lactamase. Created with BioRender.com

chromosomal gene mutations or horizontal transfer. Some of the most frequent mechanisms of acquired resistance through mutations include overproduction of chromosomal AmpC cephalosporinase, loss of the carbapenem-specific OprD porin, and mutational overexpression of efflux pumps. In the case of horizontally acquired resistance, extended-spectrum β-lactamases and carbapenemases are of special concern. Metallo-β-lactamases are by far the most prevalent carbapenemases in P. aeruginosa [3].

Many of these mechanisms can lead to resistance to the same class of antibiotics. For instance, resistance to carbapenems can be mediated by loss of OprD porin expression, overexpression of efflux pumps, and production of metallo-β-lactamases. The combined action of these resistance mechanisms makes treating infections with P. aeruginosa especially challenging.

MULTIDRUG-RESISTANT *PSEUDOMONAS AERUGINOSA* (MDRPA): DIMENSION OF THE PROBLEM

The World Health Organization (WHO) published a priority list of antibiotic-resistant bacteria in 2017, which includes carbapenem-resistant *P. aeruginosa*. Taconelli et al. ranked the bacteria on the list based on several factors, including mortality, health burden, prevalence of resistance, resistance trend, community burden, transmissibility, preventability in healthcare and community settings, treatability, and drug develop-

ment. *P. aeruginosa* placed second on the list, following carbapenem-resistant *Acinetobacter baumannii* [4].

Moreover, *P. aeruginosa* is the sixth pathogen with the highest number of deaths attributable to bacterial antimicrobial resistance, according to 2019 data [5]. This is particularly notable since other bacteria higher on the list, such as *Escherichia coli*, *Staphylococcus aureus*, or *Klebsiella pneumoniae*, cause more infections in the community, ultimately affecting a larger number of individuals than *P. aeruginosa*.

MDRPA IN SPAIN: WHERE ARE WE?

According to the ECDC 2022 data, the rate of carbapenem-resistant *P. aeruginosa* in Spain ranges between 10% and 25% [6]. A nationwide survey conducted in 2017 with 1454 strains showed that 9% of them were multidrug-resistant, 17% were extensively drug-resistant, and 0.1% were pandrug-resistant [7]. However, it is important to bear in mind that these data are pre-pandemic and the impact of the COVID-19 pandemic on the previous distribution should be assessed. For those strains, colistin, amikacin, ceftolozane-tazobactam, and ceftazidime-avibactam showed the highest susceptibility rates. The MIC90 for the latter two was 2 and 8, respectively [7]. This reflects that the most active β-lactam against P. aeruginosa is ceftolozane-tazobactam. It is important to note that this study was conducted before the release of cefiderocol.

Among the extensively drug-resistant *P. aeruginosa* strains, 61% were found to have OprD deficiency, and 65% displayed overproduction of AmpC [7]. This reflects that the most active β-lactam against *P. aeruginosa* is Ceftolozane-tazobactam. It is important to notice that this study is before cefiderocol release.

Among the extensively drug-resistant *P. aeruginosa* strains, 61% were found to be OprD deficiency, and 65% displayed overproduction of AmpC It is worth noting the intervariability between hospitals. Clonal diversity is much lower among multidrug-resistant and especially extensively drug-resistant strains. High-risk clones have been identified, which are linked to hospital outbreaks worldwide, and all of them possess the ability to develop and transfer resistance [3]. For instance, the ST175 clone accounts for 40.9% of all extensively drug-resistant isolates in Spain [7].

Certain extensively drug-resistant clones, such as ST175, ST111, and ST235, are frequently linked to particular resistance mechanisms, which in turn are related to a resistance profile. In other words, the observed susceptibility profile should make us suspect the resistance mechanism and the clone we are dealing with because the therapeutic options will vary accordingly [3]. Therefore, MDRPA should not be uniformly treated with the same antimicrobial approach.

The IDSA guidelines recommend the use of ceftolozane-tazobactam to treat MDRPA if susceptible, when the infection is moderate to severe, or when source control is poor [8]. However, a previous multicenter study in Spain reflected that in 150 MDRPA, 68.7% were susceptible to ceftolozane-tazobactam [9]. These results support that antibiotic treatment does not end with guideline recommendations.

MORTALITY ASSOCIATED WITH MDRPA INFECTIONS

The mortality rate associated with infections caused by this bacterium is extremely high, exceeding that of S. aureus in certain types of infections, such as bloodstream infections [10]. MDRPA infections are associated with higher mortality compared to non-MDRPA infections. Inappropriate empiric treatment has been shown to increase mortality [11]. However, it should be noted that other variables might account for this outcome, such as more virulent strains or debilitated patients.

MDRPA: THERAPEUTIC OPTIONS

Quinolones are the only group of antibiotics that can be orally administered to treat P. aeruginosa infections. Aminoglycosides are used intravenously in monotherapy only for uncomplicated urinary tract infections, otherwise they are administered in combination with other antibiotics. Colistin is reserved as a last resort due to its side effects. β-lactam antibiotics are available in different levels of potency, with piperacillin-tazobactam, ceftazidime, and cefepime as the first level, followed by carbapenems in the second level, novel β-lactams-β-lactamase inhibitors in the third level, and cefiderocol in the highest level.

Avibactam is a β-lactamase inhibitor with inhibitory activity against several types of β-lactamases, including class C, class A, and certain class D enzymes. However, ceftazidime-avibactam has limitations, including vulnerability to efflux pumps and lack of activity against metallo-β-lactamases. Ceftolozane is a stable antibiotic against AmpC-type β-lactamases and efflux pumps of *P. aeruginosa*, with less potential for resistance development compared to ceftazidime. However, ceftolozane has its own limitations, including a lack of activity against metallo-β-lactamases and class A carbapenemases. [12]. During the COVID-19 pandemic, the increased use of ceftazidime-avibactam led to a rise in resistance rates to both ceftolozane-tazobactam and ceftazidime-avibactam due to a cross-resistance phenomenon induced by either antibiotic [12]. This effect should be considered when developing antibiotic rotation strategies in hospitals.

Relebactam restores imipenem activity against strains expressing AmpC overproduction and OprD deficiency, and is stable against efflux pumps and some β-lactamases (class A and D). However, it has no activity against metallo-β-lactamases and induces cross-resistance to the previously mentioned antibiotic combination.

Meropenem-vaborbactam is weaker against strains with decreased expression of OprD porins and those with efflux pumps. It also has no activity against class B β-lactamases. Its role is mainly related to KPC-producing enterobacteria rather than MDRPA [12].

Cefiderocol, as an iron chelator, enters the periplasm through active iron transporters and porins like other β-lactams, where it binds to PBPs. It has increased stability against serine- and metallo-β-lactamases and extended spectrum of activity against other non-fermentative Gram-negative bacilli. However, there is limited data on its activity against class D β-lactamases, such as *P. aeruginosa* chromosomal OXA-50. Cefiderocol has no cross-resistance with other β-lactams, although minimum inhibitory concentrations may increase [12].

MDRPA: SOME CONSIDERATIONS FOR TREATMENT CHOICE

Choosing appropriate empirical treatment for infection requires consideration of various factors, such as the clinical entity, comorbidities, and the presence of risk factors for multidrug-resistant pathogens. Local epidemiological data should be used to ensure effective treatment. [13]. Timely collection of an appropriate sample is critical for identifying the causative microorganism and facilitates appropriate antibiotic de-escalation. In addition to selecting the appropriate antibiotic, optimizing pharmacokinetics is crucial for successful treatment. [14].

Adequate control of the source of infection is key to overcoming the infection, even with optimal management of antimicrobial therapy [15].

The use of combined empirical treatment remains unclear, and the decision should be evaluated on a case-by-case basis. Although a meta-analysis showed no difference in mortality between combined antimicrobial therapy and monotherapy [16], a retrospective study reported a favorable effect of combination therapy in treating *P. aeruginosa* bacteraemia in neutropenic patients. [17]. Therefore, empirical combination therapy might be more effective than monotherapy in certain cases. The three main objectives of using more than one antibiotic are to expand the spectrum, increase the bactericidal activity during high bacterial load, and reduce the development of resistance.

The duration of treatment should not differ based on whether the infection is caused by MDRPA or a sensitive strain. If oral sequencing is possible, it should be done if the isolate is sensitive to an oral option, the patient is haemodynamically stable, there is good control of the focus, and the patient can absorb the drug to be sequenced [8].

MDRPA: THE FUTURE

Colonization by healthcare-associated pathogens often precedes infection, and the protective microbiota plays a crucial role in preventing this. Successfully decolonizing a patient or preventing colonization altogether could potentially avoid future infections. One strategy to achieve this is studying the microbiome and modifying it [18].

Furthermore, alternative treatments such as antimicrobial peptides, new antibiotics, phage therapy, nanoparticles, anti-inflammatory agents, gene editing tools, and vaccines are being developed, showing great promise for the future management of *P. aeruginosa* infections. These novel approaches offer a wide range of potential options to combat and control this pathogen [19].

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

1. Behzadi P, Baráth Z, Gajdács M. It's Not Easy Being Green: A Narrative Review on the Microbiology, Virulence and Therapeutic Prospects of Multidrug-Resistant *Pseudomonas aeruginosa*. Antibiot (Basel, Switzerland). Switzerland; 2021 Jan;10(1).
2. López-Causapé C, Rojo-Molinero E, Macià MD, Oliver A. The problems of antibiotic resistance in cystic fibrosis and solutions. Expert Rev Respir Med. England; 2015 Feb;9(1):73–88.
3. Horcajada JP, Montero M, Oliver A, Sorlí L, Luque S, Gómez-Zorrilla S, et al. Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant Pseudomonas aeruginosa Infections. Clin Microbiol Rev. United States; 2019 Sep;32(4).
4. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. United States; 2018 Mar;18(3):318–27.
5. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet (London, England). England; 2022 Feb;399(10325):629–55.
6. for Disease Prevention EC, Control, for Europe WHORO. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. World Health Organization. Regional Office for Europe; 2022. xxi, 136 .
7. Del Barrio-Tofiño E, Zamorano L, Cortes-Lara S, López-Causapé C, Sánchez-Diener I, Cabot G, et al. Spanish nationwide survey on Pseudomonas aeruginosa antimicrobial resistance mechanisms and epidemiology. J Antimicrob Chemother. England; 2019 Jul;74(7):1825–35.
8. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis an Off Publ Infect Dis Soc Am. United States; 2022 Aug;75(2):187–212.

9. Del Barrio-Tofiño E, López-Causapé C, Cabot G, Rivera A, Benito N, Segura C, et al. Genomics and Susceptibility Profiles of Extensively Drug-Resistant Pseudomonas aeruginosa Isolates from Spain. Antimicrob Agents Chemother. United States; 2017 Nov;61(11).
10. Thaden JT, Park LP, Maskarinec SA, Ruffin F, Fowler VGJ, van Duin D. Results from a 13-Year Prospective Cohort Study Show Increased Mortality Associated with Bloodstream Infections Caused by Pseudomonas aeruginosa Compared to Other Bacteria. Antimicrob Agents Chemother. United States; 2017 Jun;61(6).
11. Morata L, Cobos-Trigueros N, Martínez JA, Soriano A, Almela M, Marco F, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of Pseudomonas aeruginosa bacteremia. Antimicrob Agents Chemother. United States; 2012 Sep;56(9):4833–7.
12. Canton R, Doi Y, Simner PJ. Treatment of carbapenem-resistant Pseudomonas aeruginosa infections: a case for cefiderocol. Expert Rev Anti Infect Ther. England; 2022 Aug;20(8):1077–94.
13. Montravers P, Bassetti M. The ideal patient profile for new beta-lactam/beta-lactamase inhibitors. Curr Opin Infect Dis. United States; 2018 Dec;31(6):587–93.
14. Lodise TPJ, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis an Off Publ Infect Dis Soc Am. United States; 2007 Feb;44(3):357–63.
15. Moise PA, North D, Steenbergen JN, Sakoulas G. Susceptibility relationship between vancomycin and daptomycin in Staphylococcus aureus: facts and assumptions. Lancet Infect Dis. United States; 2009 Oct;9(10):617–24.
16. Paul M, Leibovici L. Editorial commentary: combination therapy for Pseudomonas aeruginosa bacteremia: where do we stand? Vol. 57, Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. United States; 2013. p. 217–20.
17. Kim YJ, Jun YH, Kim YR, Park KG, Park YJ, Kang JY, et al. Risk factors for mortality in patients with Pseudomonas aeruginosa bacteremia; retrospective study of impact of combination antimicrobial therapy. BMC Infect Dis. England; 2014 Mar;14:161.
18. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. England; 2021 Jan;19(1):55–71.
19. Qin S, Xiao W, Zhou C, Pu Q, Deng X, Lan L, et al. Pseudomonas aeruginosa: pathogenesis, virulence factors, antibiotic resistance, interaction with host, technology advances and emerging therapeutics. Signal Transduct Target Ther. England; 2022 Jun;7(1):199.