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Editorial

Multidrug-resistant *Pseudomonas aeruginosa*: A pathogen with challenging clinical management

Pseudomonas aeruginosa multirresistente: un patógeno de difícil manejo clínico

In the 21st century we expect to find ourselves facing different healthcare challenges and among the most worrying, antibiotic resistance is at forefront.[1] *Pseudomonas aeruginosa* is a pathogen of great concern due to its ability to develop resistance to several classes of antibiotics[2] and because it produces severe infections, particularly in healthcare settings and in immunocompromised patients, with high mortality rates.[3]

In the recent years, the spread of extensively drug-resistant (XDR) *P. aeruginosa* has become a public health concern and currently there are limited therapeutic options with low level of evidence of their efficacy and potential of selection of resistant mutants.[4]

P. aeruginosa is inherently resistant to many antibiotics due to its low permeability outer membrane, active efflux pumps, and production of several resistance mechanisms, including beta-lactamases, aminoglycoside-modifying enzymes, and quinolone resistance mechanisms.[4] The expression of efflux pumps, which are involved in the active extrusion of antibiotics from the bacterial cell are an important mechanism of resistance. The most well-characterized efflux pumps in *P. aeruginosa* are the MexAB-OprM, MexCD-OprJ, and MexEF-OprN systems. These efflux pumps are involved in resistance to a wide range of antibiotics, including beta-lactams, fluoroquinolones, and aminoglycosides.[5] Another mechanism of resistance in *P. aeruginosa* is the production of beta-lactamases, which hydrolyze beta-lactam antibiotics such as penicillins, cephalosporins, and carbapenems. The AmpC beta-lactamase is the most expressed beta-lactamase in *P. aeruginosa* and is chromosomally encoded, while some strains can also acquire carbapenemases through horizontal gene transfer.[6] *P. aeruginosa* can also produce aminoglycoside-modifying enzymes, which are enzymes that modify aminoglycosides, rendering them ineffective. These enzymes include acetyltransferases, adenyltransferases, and phosphotransferases. Finally, *P. aeruginosa* can also develop resistance through the mutation of target genes, such as the mutations in the *gyrA* and *parC* genes that confer fluoroquinolone resistance[7]

Overall, the complex and multifaceted mechanisms of resistance in *P. aeruginosa* make it a challenging pathogen to treat and underscore the importance of appropriate antibiotic use and infection control actions to prevent the emergence and spread of multidrug-resistant rods.

Moreover, dissemination of high-risk clones (MDR/XDR clones) has been reported worldwide in hospitals. Among them, ST (sequence type) 235, ST111, and ST175 have been found to be the most prevalent.[4] A multicentric study performed in Spain showed that clonal diversity of *P. aeruginosa* isolated from blood cultures was much lower among MDR and XDR strains than in wild-type strains. Most XDR isolates belonged to the fore mentioned high-risk clones. Although resistance in XDR *P. aeruginosa* is especially mutation-mediated like in the case of ST175, some of these high-risk clones have been associated to transferable resistance mechanisms, particularly acquired β-lactamases.[6] As a result of this, the treatment of XDR *P. aeruginosa* infections could be challenging due to the limited number of effective antibiotics.

Several classes of antibiotics have been used to treat infections caused by *P. aeruginosa* as first line agents. Antipseudomonal antibiotics include β-lactams acting by inhibiting bacterial cell wall synthesis, namely penicillins (piperacillin, ticarcillin, carbenicillin alone or in combination with a β-lactamase inhibitor), cephalosporins (ceftazidime and cefepime), monobactams (aztreonam), and carbapenems (imipenem, and meropenem). Other antipseudomonal antibiotics are fluoroquinolones (ciprofloxacin and levofloxacin) and aminoglycosides (amikacin, tobramycin, and gentamicin) that block DNA synthesis and protein synthesis, respectively.[4,8,9] Colistin and polymyxin B have been reintroduced in the clinics to treat infections caused by MDR/XDR bacilli. Despite being an effective agent against XDR *P. aeruginosa,* its clinical use has been limited by its associated side effects (particularly nephrotoxicity).[8,9]

Combination therapy, in which two or more antibiotics are used together, is often recommended for the treatment of XDR *P. aeruginosa* infections.[10] However, there is lack of clinical evidence of the usefulness of combined therapy, even it may not be effective in some cases.[10,11] In fact, the current European guidelines do not recommend in favor or against combination therapy for MDR/XDR *P. aeruginosa* infections.[12,13]

In the context of growing prevalence of XDR *P. aeruginosa* isolates showing resistance to all first-line agents, new molecules with antipseudomonal action have been developed, as well as new associations with beta-lactamase inhibitors: ceftolozane–tazobactam (C/T), ceftazidime–avibactam (CZA), imipenem–relebactam and cefiderocol.

Ceftolozane inhibits PBPs present in *P. aeruginosa* and is not affected by non-extended spectrum beta-lactamases class D oxacil-

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linases and AmpC β-lactamases, while tazobactam inhibits class A serine β-lactamases and extended spectrum beta-lactamases (ESBL). With these features, C/T is a broad spectrum antimicrobial and also a very active antipseudomonal agent, including activity against non-carbapenemase producing MDR/XDR *P. aeruginosa* strains.[14] Currently C/T is approved at a dose of 1.5 g every 8 h as a 1 h rate of infusion (ceftolozane 1 g and tazobactam 0.5 g) for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in combination with metronidazole, and 3 g every 8 h (ceftolozane 2 g and tazobactam 1 g) for hospital-acquired pneumonia including ventilator-associated bacterial pneumonia (HABP/VABP) caused by Gram-negative organisms. However, the severity of MDR/XDR *P. aeruginosa* strains has led physicians to off-label use of C/T and it is generally reserved for the use against MDR/XDR *P. aeruginosa* strains. C/T has shown promising results for the treatment of infections caused by multidrug-resistant *P. aeruginosa* in some observational clinical series.[15,16] However, more studies are needed to further evaluate the efficacy and safety of ceftolozane/tazobactam in different patient populations and settings. In the current EIMC issue, a multicenter Portuguese real-life study shows that C/T was effective in treating a variety of infections mostly due to XDR *P. aeruginosa* (85.9%), including severe patients with important comorbidities as cancer (32%) and neutropenia (12.5%). Respiratory tract infections were the most frequent (28.1%). C/T was mostly used as targeted therapy (98.4%) and as monotherapy (72.7%). The study showed high rates of microbiological (79.2%) and clinical (78.7%) success. However in-hospital mortality was quite high (34%), probably due to the comorbidity of included patients. Selection of resistance was detected in 5 (7.8%) patients with difficult to treat infections. This study somehow reinforces the results of the initial pivotal studies where, as usual, there are few patients with severe infections caused by XDR *P aeruginosa*.[17]

Ceftazidime–avibactam is a combination of the antipseudomonal cephalosporin, ceftazidime, with avibactam, a new beta-lactamase inhibitor. This combinations shows an improvement in activity against beta-lactamases belonging to classes A and C, as well as some enzymes of class D, but is not active against metallo-betalactamase producers.[18] Avibactam reduces the minimum inhibitory concentrations of ceftazidime against *P. aeruginosa* by preventing it from being degraded by *P. aeruginosa* AmpC enzymes, but also by ESBLs, KPC, OXA-48 and class A carbapenemases such GES enzymes if they are present.[19] CZA has an important activity against XDR *P. aeruginosa* and it is an important addition to the armamentarium of antibiotics for the treatment of these infections. However, like with all antibiotics, its use should be judicious and optimized to prevent the emergence of resistance.[20] In the last five years, there have been several studies and publications on CZA and its use in the treatment of XDR *P. aeruginosa* infections.[21,22] Overall, these studies suggest that this durg is a promising option for the treatment of XDR *P. aeruginosa* infections, with high clinical cure rates and a favorable safety profile.[23]

Imipenem–relebactam is a combination of imipenem with a new beta-lactamase inhibitor, relebactam. The *in vitro* spectrum of activity includes class C beta-lactamases, including AmpC and *Pseudomonas*-derived cephalosporinases found in MDR *P. aeruginosa.* Moreover, this combination is unaffected by OprD deletions or efflux pump-mediated resistance in *P. aeruginosa.*[24] Therefore, this new drug is an interesting potential agent for the treatment of XDR *P. aeruginosa* infections. However clinical data on the experience of imipenem-relebactam in these infections is scarce. Data from small clinical series show promising results.[25]

Cefiderocol is a novel siderophore cephalosporin with abundant penetration capacity into the periplasmic space using the iron transport system and with a high stability to hydrolysis by all Ambler B-lactamases classes. It has become the first agent with activity against bacteria carrying class B β-lactamases (metallo-betalactamases).[26] It was introduced recently by the US Food and Drug Administration (FDA) in November 2019[27] and by the European Medicines Agency (EMA) in May 2020.[23] *In vitro*, preclinical, and clinical studies have shown expanded activity of cefiderocol against MDR bacteria including XDR *P. aeruginosa*, compared to other commercialized antibiotics.[28,29] The efficacy of cefiderocol has been tested in two randomized controlled trials compared with carbapenems in complicated urinary tract infections (APEKS-cUTI) and nosocomial pneumonia (APEKS-NP) with non-inferiority results.[30,31] In another randomized control trial, the CREDIBLE-CR study, its efficacy was demonstrated in the treatment of CRGNB compared with best available therapy.[30,31] However, in this study, the prevalence of *P. aeruginosa* in the cefiderocol group was only 15%. Real-life studies exploring this specific setting are currently limited. But given the need to look for new therapeutic options, although there are some cases reports and small case series published, more information is needed related to the use of cefiderocol in XDR *P. aeruginosa* infections.[32–36]

Other alternative therapies, such as phage therapy, immunotherapy, have also been studied for the treatment of *P. aeruginosa* infections.[37] These therapies have shown some promise in preclinical studies, but more research is needed to determine their effectiveness and safety in clinical settings.[38]

P. aeruginosa is a major problem in healthcare settings worldwide. The limited number of effective antibiotics and the ability of *P. aeruginosa* to rapidly develop resistance make it difficult to treat these infections. New antibiotics are being developed and studied and have undoubtedly improved the outlook, but more clinical data are needed, including randomized control trials with these new drugs. The search for alternative therapies continues and much remains to be done to win this difficult battle.

Conflicts of interest

MMM has received consulting fees and participated in educational activities from Pfizer, MSD, Shionogi, and Biomerieux.

JPH has received consulting fees from Gilead, Tillots, Menarini and TFF Pharmaceuticals, and participated in educational activities from MSD, Pfizer and Angelini.

References

1. Tacconelli E, Pezzani MD. Public health burden of antimicrobial resistance in Europe. Lancet Infect Dis. 2019;19:4–6, http://dx.doi.org/10.1016/S1473-3099(18)30648-0.
2. Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? Clin Infect Dis. 2002;34:634–40, http://dx.doi.org/10.1086/338782.
3. Oliver A, Mulet X, López-Causapé C, Juan C. The increasing threat of *Pseudomonas aeruginosa* high-risk clones. Drug Resist Updat. 2015;21–22:41–59, http://dx.doi.org/10.1016/J.DRUP.2015.08.002.
4. 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. 2019;32:e00031-19, http://dx.doi.org/10.1128/CMR.00031-19.
5. Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clin Microbiol Rev. 2015;28:337–418, http://dx.doi.org/10.1128/CMR.00117-14.
6. del Barrio-Tofiño E, López-Causapé C, Oliver A. *Pseudomonas aeruginosa* epidemic high-risk clones and their association with horizontally-acquired β-lactamases: 2020 update. Int J Antimicrob Agents. 2020;1:56, http://dx.doi.org/10.1016/j.ijantimicag.2020.106196.
7. Kos VN, Déraspe M, McLaughlin RE, Whiteaker JD, Roy PH, Alm RA, et al. The resistome of *Pseudomonas aeruginosa* in relationship to phenotypic susceptibility. Antimicrob Agents Chemother. 2015;59:427–36, http://dx.doi.org/10.1128/AAC.03954-14.
8. Sorlí L, Luque S, Grau S, Berenguer N, Segura C, Montero MM, et al. Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis. 2013;13:380, http://dx.doi.org/10.1186/1471-2334-13-380.

9. Luque S, Grau S, Berenguer N, Horcajada JP, Sorlí L, Montero MM, et al. Shedding light on the use of colistin: still gaps to be filled. Enferm Infecc Microbiol Clin. 2011;29:287–96, http://dx.doi.org/10.1016/j.eimc.2011.02.003.
10. Montero MM, Montesinos IL, Knobel H, Molas E, Sorlí L, Siverio-Parés A, et al. Risk factors for mortality among patients with *Pseudomonas aeruginosa* bloodstream infections: what is the influence of XDR phenotype on outcomes? J Clin Med. 2020;9:514, http://dx.doi.org/10.3390/JCM9020514.
11. Peña C, Gómez-Zorrilla S, Suarez C, Dominguez MA, Tubau F, Arch O, et al. Extensively drug-resistant *Pseudomonas aeruginosa*: risk of bloodstream infection in hospitalized patients. Eur J Clin Microbiol Infect Dis. 2012;31:2791–7, http://dx.doi.org/10.1007/s10096-012-1629-3.
12. Paul M, Carrara E, Retamar P, Tängdén T, Bitterman R, Bonomo RA, et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine). Clin Microbiol Infect. 2022;28:521–47, http://dx.doi.org/10.1016/J.CMI.2021.11.025.
13. Executive summary of the diagnosis and antimicrobial treatment of invasive infections due to multidrug-resistant Enterobacteriaceae. Guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) [Internet]. https://www.elsevier.es/es-revista-enfermedades-infecciosas-microbiologia-clinica-28-pdf-S0213005X14003978 [cited 17th 2023].
14. Zhanel GG, Chung P, Adam H, Zelenitsky S, Denisuik A, Schweizer F, et al. Ceftolozane/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant Gram-negative bacilli. Drugs. 2014;74:31–51, http://dx.doi.org/10.1007/s40265-013-0168-2.
15. Ford H, Henry H, Health F, Holger DJ, Rebold NS, Alosaimy S, et al. Impact of ceftolozane–tazobactam vs. best alternative therapy on clinical outcomes in patients with multidrug-resistant and extensively drug-resistant *Pseudomonas aeruginosa* lower respiratory tract infections. Infect Dis Ther. 2022;11:1965–80, http://dx.doi.org/10.1007/s40121-022-00687-9.
16. Pogue JM, Pogue JM, Kaye KS, Veve MP, Patel TS, Gerlach AT, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant *Pseudomonas aeruginosa*. Clin Infect Dis. 2020;71:304–10, http://dx.doi.org/10.1093/cid/ciz816.
17. Leitão IL, Mimoso Santos C, André P, Lino S, Lemos M, Froes F. Ceftolozane/tazobactam for the treatment of *Pseudomonas aeruginosa* infections: a multicenter case series analysis. Enferm Infecc Microbiol Clin (English Ed). 2023, http://dx.doi.org/10.1016/J.EIMCE.2021.12.017. S2529-993X(22)00311-2.
18. Li H, Estabrook M, Jacoby GA, Nichols WW, Testa RT, Bush K. In vitro susceptibility of characterized β-lactamase-producing strains tested with avibactam combinations. Antimicrob Agents Chemother. 2015;59:1789–93, http://dx.doi.org/10.1128/AAC.04191-14.
19. Sy SKB, Zhuang L, Beaudoin M-E, Kircher P, Tabosa MAM, Cavalcanti NCT, et al. Potentiation of ceftazidime by avibactam against β-lactam-resistant *Pseudomonas aeruginosa* in an in vitro infection model. J Antimicrob Chemother. 2017;72:1109–17, http://dx.doi.org/10.1093/jac/dkw535.
20. Lopez-Montesinos I, Montero MM, Domene-Ochoa S, López-Causapé C, Echeverria D, Sorlí L, et al. Suboptimal concentrations of ceftazidime/avibactam (CAZ-AVI) may select for CAZ-AVI resistance in extensively drug-resistant *Pseudomonas aeruginosa*: in vivo and in vitro evidence. Antibiotics. 2022;11:1–12, http://dx.doi.org/10.3390/antibiotics11111456.
21. Jorgensen SCJ, Trinh TD, Zasowski EJ, Lagnf AM, Simon SP, Bhatia S, et al. Real-world experience with ceftolozane–tazobactam for multidrug-resistant Gram-negative bacterial infections. Antimicrob Agents Chemother. 2020;64:e02291-19, http://dx.doi.org/10.1128/AAC.02291-19.
22. Vena A, Giacobbe DR, Castaldo N, Cattelan A, Mussini C, Luzzati R, et al. Clinical experience with ceftazidime–avibactam for the treatment of infections due to multidrug-resistant Gram-negative bacteria other than carbapenem-resistant enterobacterales. Antibiotics (Basel). 2020;9:71, http://dx.doi.org/10.3390/ANTIBIOTICS9020071.
23. Zhen S, Wang H, Feng S. Update of clinical application in ceftazidime–avibactam for multidrug-resistant Gram-negative bacteria infections. Infection. 2022;50:1409–23, http://dx.doi.org/10.1007/s15010-022-01876-x.
24. Young K, Painter RE, Raghoobar SL, Hairston NN, Racine F, Wisniewski D, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa*. BMC Microbiol. 2019;19:1–14, http://dx.doi.org/10.1186/S12866-019-1522-7/TABLES/4.
25. Rebold N, Morrisette T, Lagnf AM, Alosaimy S, Holger D, Barber K, et al. Early multicenter experience with imipenem–cilastatin–relebactam for multidrug-resistant Gram-negative infections. Open Forum Infect Dis. 2021;8:ofab554, http://dx.doi.org/10.1093/ofid/ofab554.
26. Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and in vivo profiles of a novel siderophore cephalosporin. Clin Infect Dis. 2019;69:S538–43, http://dx.doi.org/10.1093/cid/ciz826.
27. FDA approves new antibacterial drug to treat complicated urinary tract infections as part of ongoing efforts to address antimicrobial resistance. Case Med Res. 2019, http://dx.doi.org/10.31525/cmr-21c764f.
28. El-Lababidi RM, Rizk JG. Cefiderocol: a siderophore cephalosporin. Ann Pharmacother. 2020;54:1215–31, http://dx.doi.org/10.1177/1060028020929988.
29. European Medicines Agency – EMA|European Union [Internet]. https://european-union.europa.eu/institutions-law-budget/institutions-and-bodies/institutions-and-bodies-profiles/ema_en [cited 10th 2023].
30. Nordmann P, Shields RK, Doi Y, Takemura M, Echols R, Matsunaga Y, et al. Mechanisms of reduced susceptibility to cefiderocol among isolates from the CREDIBLE-CR and APEKS-NP clinical trials. Microb Drug Resist. 2022;28:398–407, http://dx.doi.org/10.1089/mdr.2021.0180.
31. Timsit JF, Paul M, Shields RK, Echols R, Baba T, Yamano Y, et al. Cefiderocol for the treatment of infections due to metallo-B-lactamase-producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. Clin Infect Dis. 2022;75:1081–4, http://dx.doi.org/10.1093/cid/ciac078.
32. Marcelo C, de Gea Grela A, Palazuelos MM, Veganzones J, Grandioso D, Díaz-Pollán B. Clinical cure of a difficult-to-treat resistant *Pseudomonas aeruginosa* ventriculitis using cefiderocol: a case report and literature review. Open Forum Infect Dis. 2022;9:ofac391, http://dx.doi.org/10.1093/OFID/OFAC391.
33. Meschiari M, Volpi S, Faltoni M, Dolci G, Orlando G, Franceschini E, et al. Real-life experience with compassionate use of cefiderocol for difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-P) infections. JAC Antimicrob Resist. 2021;3:dlab188, http://dx.doi.org/10.1093/JACAMR/DLAB188.
34. Stevens RW, Clancy M. Compassionate use of cefiderocol in the treatment of an intraabdominal infection due to multidrug-resistant *Pseudomonas aeruginosa*: a case report. Pharmacotherapy. 2019;39:1113–8, http://dx.doi.org/10.1002/PHAR.2334.
35. Gras J, Villar-Fernandez S, Baylac P, Xhaard A, Valade S, Camelena F, et al. Successful cefiderocol therapy of severe infections due to difficult-to-treat *Pseudomonas aeruginosa* in two allogeneic hematopoietic stem cell transplantation recipients. Ann Hematol. 2022;101:1365–7, http://dx.doi.org/10.1007/S00277-021-04737-Z.
36. Weber C, Schultze T, Göttig S, Kessel J, Schröder A, Tietgen M, et al. Antimicrobial activity of ceftolozane–tazobactam, ceftazidime–avibactam, and cefiderocol against multidrug-resistant *Pseudomonas aeruginosa* recovered at a German University Hospital. Microbiol Spectr. 2022;10:e0169722, http://dx.doi.org/10.1128/SPECTRUM.01697-22.
37. Chegini Z, Khoshbayan A, Taati Moghadam M, Farahani I, Jazireian P, Shariati A. Bacteriophage therapy against *Pseudomonas aeruginosa* biofilms: a review. Ann Clin Microbiol Antimicrob. 2020;19:45, http://dx.doi.org/10.1186/S12941-020-00389-5.
38. Shao X, Xie Y, Zhang Y, Liu J, Ding Y, Wu M, et al. Novel therapeutic strategies for treating *Pseudomonas aeruginosa* infection. Expert Opin Drug Discov. 2020;15:1403–23, http://dx.doi.org/10.1080/17460441.2020.1803274.

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