Intensive Care Med (2020) 46:350–352
https://doi.org/10.1007/s00134-019-05905-6

UNDERSTANDING THE DISEASE

Understanding resistance in *Pseudomonas*

George Dimopoulos[1*], Murat Akova[2], Jordi Rello[3,4] and Garyphalia Poulakou[5]

Pseudomonas aeruginosa (PA) is the most common multi-drug resistance (MDR) pathogen in hospitalized patients, increases duration of hospitalization, and, despite the appropriate treatment, has an attributable mortality of 13.5% [1]. Risk factors for PA acquisition in the ICU are advanced age, length of mechanical ventilation, previous antibiotic exposure, transfer from a medical unit or ICU, and admission to a ward with high incidence [2]. PA can develop an MDR phenotype through a complex genome including several intrinsic and acquired mechanisms to several antibiotics depicted in Supplementary Fig. 1 [3–5]. It is widely believed that acquiring several resistance elements by PA and other pathogenic bacteria may lead a negative fitness and a less virulent pathogen. However, this concept has been challenged recently, indicating that resistance genes may provide a survival advantage with increased in vivo fitness [6]. In turn, this may have serious implications in the clinical setting that virulent strains with MDR phenotypes may settle as the primary pathogens in infected, high-risk patients. Fever/hypothermia, PIRO score > 2, vasopressors at infection onset, and recent antipseudomonal cephalosporin exposure have been found to be independent predictors of MDR-PA infections [7, 8].

The arsenal of antibiotics against MDR/XDR *P. aeruginosa* is awaiting promising molecules (Supplementary Table 1) [5, 9–11]. Two molecules in late-stage of development are quite promising in the treatment of XDR *P. aeruginosa*, because they retain activity in the presence of metallo-enzymes; cefiderocol and cefepime–zidebactam due to their extended spectrum, encompassing all current mechanisms of resistance in MDR and XDR *P. aeruginosa* [5, 9, 10]. Although results from clinical trials are pending, murepavadin holds promise in the treatment of XDR strains (it was used as single antipseudomonal agent or combined with a standard antipseudomonal antibiotic). However, early in vitro reports revealed mutations indicative of a resistance mechanism shared with colistin, indicating that pre-existing colistin resistance involving lipopolysaccharide modifications could impede activity of murepavadin.

Alternatives to antimicrobial strategies, include new delivery methods (nebulization and encapsulation of antibiotics), vaccines—monoclonal antibodies (MA), and modulation of patient's immune response. Nebulization of antibiotics (mostly of colistin and aminoglycosides) has been used in heterogeneous dosage regimens and indications, ranging from ventilation-associated pneumonia (VAP) and ventilator-associated tracheobronchitis (VAT) to colonization by resistant *P. aeruginosa* strains. Their use is hampered by the lack of standardization and broad experience [12]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggests the administration of antibiotics by aerosolisation in mechanically ventilated adults as a practice restricted to salvage therapy in VAP by difficult-to-treat organisms under a strict protocol of administration [13]. New delivery methods such as encapsulation of antibiotics in nanocarriers improve the drug diffusion, protect the drug from undesired degradation, control drug release, and increase uptake in the infected site [14]. These methods use anionic liposomes (with positive results in a model of pneumonia caused by *P. aeruginosa* in the absence of any additional antibiotic treatment), polyacid nanoparticles, water-soluble oligosaccharide conjugates, polymeric nanocomposites, or solid lipid nanoparticles. Ciprofloxacin, meropenem, and aminoglycosides have already been encapsulated into liposomes or loaded into nanoparticles [14].

Therapeutic approaches through modulation of patient's response or the pathogenicity of *P. aeruginosa* are quite promising. The vaccine IC43, a recombinant

*Correspondence: gdimop@med.uoa.gr
[1] Department of Critical Care, University Hospital ATTIKON, National and Kapodistrian University of Athens, 1 Rimini str. Haidari, 12462 Athens, Greece
Full author information is available at the end of the article

outer membrane protein (Opr) targeting the Oprs of *P. aeruginosa,* completed a phase II trial, in which no significant difference was found in *P. aeruginosa* infection rates, although it was associated with a lower mortality rate [14]. Despite evident immunogenicity between days 7 and 14, *P. aeruginosa* infection occurred prior to the development of IgG immune response. ExoU is the most important virulence mechanism with impact on outcomes, although research efforts have been focused in blocking PcrV [14]. KB001, a pegylated anti-PcrV MA fragment to the type III secretion system (TTSS) of *P. aeruginosa* involved with the release of exotoxins, failed to show improvement in lung inflammation and reduction in colonization in patients with cystic fibrosis [14]. Other MAs include IgY avian polyclonal antibody (phase III clinical trial—NCT01455675 completed—results pending) and MEDI3902 binding to PcrV and Psl-mediating cytotoxicity (in phase II trial NCT02696902 in mechanically ventilated patients as of writing of this review) [14]. Modulators of bacterial cell wall, transport, signaling, or virulence have also been used against *Pseudomonas* spp. infections. Inhibitors of quorum sensing have demonstrated activity against biofilm formation and secretion of virulence factors (elastase—Las, rhamnolipids—Rhl, and *Pseudomonas* quinolone signal systems—PQS) [14]. However, until now, none of them has been evaluated in clinical practice. In the ICU, only macrolides were associated with a trend to prevent VAP and reduction of quorum sensing-regulated virulence factors activation [14]. Neutralization of virulence effectors inhibit *P. aeruginosa* LasB elastase targeting the ability of bacteria to evade the immune system, while Gallium, an iron mimetic, inhibits in vitro *P. aeruginosa* growth and biofilm formation [14]. Bacteriophages prevent damage to normal flora, do not infect the eukaryotic cells, and are not associated with rapid proliferation inside the host bacteria. The use of monophage vs cocktail treatment, the genomic identification (to minimize the risk of horizontal gene transfer to bacteria), and stability to reach the site of infection remain important challenges for the future [14].

An antagonistic interaction to the yeast between *Candida* spp. and *Pseudomonas aeruginosa* and the role of cell wall components, quorum sensing molecules, phenazines, fatty acid metabolites, and competition for iron are well described [15]. The role of newly identified elements of *P. aeruginosa* QS network, oxylipin production by both species, as well as the genetic and phenotypic plasticity of those pathogens reflect suggested future perspectives. The prevention of *P. aeruginosa* resistance deals with microbiological monitoring, antimicrobial stewardship, and infection control programs (environmental cleaning/disinfection, hand hygiene, and education of personnel), while the discrimination between colonization and infection is crucial (supplementary text).

In-depth understanding of the pathogenicity and resistance mechanisms of *P. aeruginosa* and its interactions with the host led to the development of several non-antibiotic approaches. Future treatments of *P. aeruginosa* infections, particularly by XDR strains, will probably adopt the aforementioned advancements with or without the addition of antibiotics.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05905-6) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Critical Care, University Hospital ATTIKON, National and Kapodistrian University of Athens, 1 Rimini str. Haidari, 12462 Athens, Greece. [2] Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey. [3] Ciberes, Instituto Salud Carlos III & Vall D'Hebron Research Institute (VHIR), Barcelona, Spain. [4] Scientific Collaborator, Clinical Research in ICU, CHU Nîmes, University Montpellier, Montpellier, France. [5] 3rd Department of Internal Medicine, SOTIRIA Hospital, National and Kapodistrian University of Athens, Athens, Greece.

Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

Publisher's Note

Received: 15 October 2019 Accepted: 19 December 2019
Published online: 20 January 2020

References

1. Rello J, Jubert P, Vallés J, Artigas A, Rué M, Niederman MS (1996) Evaluation of outcome for intubated patients with pneumonia due to *Pseudomonas aeruginosa*. Clin Infect Dis 23(5):973–978
2. Venier AG, Gruson D, Lavigne T, Jarno P, Lhériteau F, Coignard B, Savey A, Rogues AM (2011) Identifying new risk factors for *Pseudomonas aeruginosa* pneumonia in intensive care units: experience of the French national surveillance, REA-RAISIN. J Hosp Infect 79(1):44–48. https://doi.org/10.1016/j.jhin.2011.05.007
3. Roux D, Danilchanka O, Guillard T, Cattoir V, Aschard H, Fu Y et al (2015) Fitness cost of antibiotic susceptibility during bacterial infection. Sci Transl Med 7(297):297ra114
4. Potron A, Poirel L, Nordmann P (2015) Emerging broad-spectrum resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: mechanisms and epidemiology. Int J Anticrob Agents 45:568–585. https://doi.org/10.1016/j.ijantimicag.2015.03.001
5. Horcajada JP, Montero M, Oliver A, Sorlí L, Luque S, Gómez-Zorilla S, Benito N, Grau S (2019) Epidemiology and treatment of multi-drug resistant and extensively-drug resistant *Pseudomonas aeruginosa* infections. Clin Microbiol Rev 32:e00031-19. https://doi.org/10.1128/CMR.00031-19
6. Maurice NM, Bedi B, Sadikot RT (2018) *Pseudomonas aeruginosa* biofilms: host response and clinical implications in lung infections. Am J Resp Cell Mol Biol 58:428–439. https://doi.org/10.1165/rcmb.2017-0321TR
7. Micek ST, Wunderink RG, Kollef MH, Chen C, Rello J, Chastre J et al (2015) An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. Crit Care 19:219. https://doi.org/10.1186/s13054-015-0926-5

8. Borgatta B, Lagunes L, Imbiscuso AT, Larrosa MN, Luján M, Rello J (2017) Infections in intensive care unit adult patients harboring multidrug-resistant *Pseudomonas aeruginosa*: implications for prevention and therapy. Eur J Clin Microbiol Infect Dis 36(7):1097–1104. https://doi.org/10.1007/s10096-016-2894-3
9. Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G (2019) The "old" and the "new" antibiotics for MDR gram-negative pathogens: for whom, when, and how. Front Public Health 7:151. https://doi.org/10.3389/fpubh.2019.00151
10. Bassetti M, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A (2017) Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 43:1464–1475. https://doi.org/10.1007/s00134-017-4878-x
11. Romano KP, Warrier T, Poulsen BE, Nguyen PH, Loftis AR, Saebi A, Pentelute BL, Hung DT (2019) Mutations in pmrB confer cross-resistance between the LptD Inhibitor POL7080 and colistin in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 63:e00511-19. https://doi.org/10.1128/AAC.00511-19
12. Solé-Lleonart C, Roberts JA, Chastre J, Poulakou G, Palmer LB, Blot S, Felton T, Bassetti M, Luyt CE, Pereira JM, Riera J, Welte T, Qiu H, Rouby JJ, Rello J, Investigators ESGCIP (2016) Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines. Clin Microbiol Infect 22:359–364. https://doi.org/10.1016/j.cmi.2015.12.016
13. Rello J, Rouby JJ, Sole-Lleonart C, Chastre J, Blot S, Luyt CE, Riera J, Vos MC, Monsel A, Dhanani J, Roberts JA (2017) Key considerations on nebulization of antimicrobial agents to mechanically ventilated patients. Clin Microbiol Infect 23:640–646. https://doi.org/10.1016/j.cmi.2017.03.018
14. Tümmler B (2019) Emerging therapies against infections with *Pseudomonas aeruginosa*. F1000 Res 8(F1000 Faculty Rev):1371
15. Fourie R, Poihi CH (2019) Beyond antagonism: the interaction between *Candida* species and *Pseudomonas aeruginosa*. J Fungi 5:34. https://doi.org/10.3390/jof5020034