Enferm Infecc Microbiol Clin. 2019;37(10):623–625

Enfermedades Infecciosas y Microbiología Clínica

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Editorial

Optimizing the management of *Pseudomonas aeruginosa* infections with tools for the detection of resistance mechanisms and pharmacokinetic/pharmacodynamic (PK/PD) analysis

Optimizando el manejo de las infecciones por *Pseudomonas aeruginosa* mediante la utilización de herramientas para la detección de mecanismos de resistencia y el análisis farmacocinético/farmacodinámico (PK/PD)

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Pseudomonas aeruginosa is one of the most important opportunistic pathogens, being for instance the main cause of ventilator-associated pneumonia and burn wound infections in hospitalized patients. It is also the first etiologic agent of chronic respiratory infections in patients with chronic underlying diseases such as cystic fibrosis or chronic obstructive pulmonary disease.[1] The success of this species to develop this pathogenic lifestyle is supported by its great adaptability, in turn based on its extensive genome. It encodes a plethora of genes sustaining its notable metabolic versatility, an outstanding set of virulence factors, and finally, a great potential for antibiotic resistance development.[2] This is probably the most striking feature of *P. aeruginosa*, which supports the worldwide growth on the prevalence of resistant isolates. In fact, the isolation of multidrug-resistant, extensively drug-resistant and even pan-resistant strains of *P. aeruginosa* is not exceptional but the contrary, mainly in developing countries of Asia, Middle East and Latin America.[3] The *P. aeruginosa* resistance can be achieved through mutations in chromosomal genes, mainly driving to porins' loss, hyperexpression of efflux pumps or of the chromosomal cephalosporinase AmpC, or to the alteration of the antibiotics' targets.[4,5] Besides, *P. aeruginosa* is very often reported to harbor horizontally-acquired resistance determinants usually encoded in class I integrons, in turn located in transferable plasmids. Among these transmitted determinants the most relevant is the almost endless array of acquired β-lactamases, including extended spectrum and/or carbapenemases (topic that will be addressed below), so that virtually no β-lactam escapes from their hydrolytic spectrum.[4] This outstanding capacity for resistance development makes of *P. aeruginosa* infection a clinical-epidemiological problem of paramount importance, making the infections caused by this species highly life-threatening and increasing the length of hospital admissions, which has obvious economic implications. To curb down this growing menace of *P. aeruginosa*, research has been forced to play a prominent role in the last years. Fortunately, very substantial advances to understand the antibiotic resistance mechanisms of *P. aeruginosa* have been achieved, and for instance today we almost completely understand the genetics and molecular basis for the AmpC hyperproduction, the most important resistance mechanism of this species.[5] An obvious consequence of this knowledge is the development of new antipseudomonal formulations usually including β-lactamase inhibitors (e.g. cefiderocol, ceftazidime–avibactam, ceftolozane–tazobactam, meropenem–vaborbactam, zidebactam, etc.), that although show encouraging activity, do not completely solve the problem of *P. aeruginosa* resistance since it has been shown to be capable of becoming resistant also to them.[6] But in parallel to all these advances achieved during the last decades, the fight against *P. aeruginosa* has been and needs to be approached from other points of view, such as the epidemiological works of resistances' prevalence, i.e. antimicrobial susceptibility surveillance studies. Many of them have been published dealing with *P. aeruginosa* since several years ago, which shows once more the epidemiological threat that *P. aeruginosa* resistance supposes.[3] Of course, these retrospective works have interest to look to the past, but they will be always a need in future, to see the evolution of resistance to the new compounds as those mentioned above. They are also needed to assess if the measures in terms of antibiotic stewardship, dissemination limitation strategies, etc. applied in a certain area and lapse of time are working. In addition and obviously, they provide a fast idea of the local epidemiology of resistance, and thus, they constitute an indispensable tool to determine the empirical treatments more suitable for each context. However, these studies gain considerable scope if they are complemented with molecular epidemiology (i.e. clonal relatedness, MLST typing, etc.) and/or resistance mechanisms characterization,[7,8] data

See related articles: https://doi.org/10.1016/j.eimc.2019.02.004, https://doi.org/10.1016/j.eimc.2019.02.009

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obviously very helpful to draw more appropriate empirical treatments. In fact, thanks to this last kind of works it has been identified the existence of globally spread *P. aeruginosa* successful clones (also called high-risk clones), characterized by several features mainly related with resistance mechanisms, explaining their outstanding success and dissemination.[9]

In this same context, the combination of the local antimicrobial susceptibility data with other additional parameters, namely pharmacokinetic/pharmacodynamics (PK/PD), is a novel perspective that has been scarcely approached in the past,[10–12] and that greatly enhances the potential of the studies on epidemiology of resistance and surveillance. Since many years ago it is known that PK/PD parameters [e.g. the maximum concentration/minimal inhibitory concentration (MIC), time above the MIC, area under the time-concentration curve, etc.] define the requirements of an antimicrobial to successfully clear a given infection. In fact, each group of antibiotics display a particular behavior regarding these parameters, and for instance, the aminoglycosides are concentration-dependent drugs, whereas beta-lactams effectiveness rely on the time above the MIC.[13–15] On its turn, additional factors such as the location of the infection, the half-life of the drug, its binding capacity to the serum proteins, etc. are those which finally determine the PK/PD values, and thus, have to be considered in order to evaluate the success' possibilities of a specific treatment.

Either way, the work of Valero and colleagues included in the current number of EIMC[16] is an excellent example of study combining different approaches to manage *P. aeruginosa* challenge, because not only provides information regarding the raw susceptibility/resistance, but also introduces information of PK/PD data from a retrospective analysis of 18 years from a tertiary Spanish Hospital (excluding ICU patients). The combination of the mentioned epidemiological and PK/PD data together with Monte Carlo simulations to model the possible infection outcome without knowledge of the specific isolate's susceptibility, through the determination of the so-called cumulative fraction of response (CFR), definitively provides great interest to this study. It allows to see changes in the predicted drugs' effectiveness that would not be visible by only considering the local MIC distributions, and besides, it also displays the trends of these parameters during the last years in the specific geographic area. In fact, the work suggests that certain drugs with relatively low local susceptibility values, such as carbapenems (mainly meropenem) could be more effective than suspected, and thus their therapeutic value could be reconsidered. Contrary results (relatively high percentages of susceptibility but low CFRs) for certain antibiotics such as cefepime are also shown by Valero and co-workers. Thus, this work indicates that the correlation between raw susceptibility and the predicted success probability (estimated through CFR) is not always clear and direct, and hence, they must be used as complementary tools, in accordance with the work of Zelenitsky and colleagues in Canada: the raw MICs data were shown to be overestimating the ciprofloxacin capacity, for instance.[10] Hence, these results also support the previous work of Valero and colleagues with strains from critically ill patients, in which the raw susceptibility data were shown to be insufficient to detect changes in CFR in certain cases.[12] The use of Monte Carlo simulations to determine the probabilities of target attainment in order to optimize the empiric treatments has been proposed before,[17] but its combination with such large amount of data of raw MICs (18 years period) is innovative, enhancing the scope of the study of Valero et al.[16]

In parallel to these approaches, the diagnosis of the resistance mechanisms in the laboratory routine is another essential point of the fight against *P. aeruginosa*, and is often closely related with the local epidemiology of resistance. The diagnostic tools gain even more importance when referred to the detection of transferable mechanisms (obviously because of their dissemination risk), mostly if we have into account the growing prevalence of *P. aeruginosa* strains harboring horizontally-acquired carbapenemases, and the increasing diversification (in terms of amino-acid variants) of these enzymes. In fact, it has been reported in *P. aeruginosa* the isolation of carbapenemases from classes A: GES and KPC enzymes; B: also called Metallo-β-lactamases, from IMP, VIM, GIM, NDM, SIM, SPM types and the recently described CAM-1; and C: OXA-40 and OXA-198. Among these carbapenemases, the IMP and VIM types are those more worldwide disseminated and displaying more variants by far: more than 30 different IMP and 25 different VIM variants have been found in *P. aeruginosa*, although the number of different enzymes within each type is even greater (almost double) if we consider the rest of species. Although several of the amino acid variants do not entail any advantage, some of them have been described to provide significant changes in the hydrolytic spectrum of the enzyme, which enforces the idea for the need of reliable detection tests.[18–20] In the specific case of the featured study of Gutiérrez and colleagues,[21] who assess the validity of the carbapenem inactivation method (CIM) to detect the carbapenemase-producing *P. aeruginosa*, they used an extensive collection of carbapenem-resistant strains proceeding from Colombia, a country in which the presence of transferable carbapenemases is not negligible at all. In fact, carbapenem-resistant *P. aeruginosa* mediated by KPC- and/or VIM-type enzymes is considered endemic in this country. Besides, Colombia was the first place in which a KPC-type carbapenemase (very likely proceeding from the massive dissemination of these enzymes in Colombian *Klebsiella pneumoniae*) was first detected in *P. aeruginosa*.[22] Thus, although the percentages of carbapenem-resistant isolates in Colombia are significantly lower than in some other Latin America countries,[23,24] the active and reliable detection of acquired carbapenemases in the daily practice is indispensable to improve the empiric treatments and to limit the horizontal dissemination of the strains and/or determinants in this and other countries. In their interesting work, Gutiérrez et al. conclude that, although limited by the relatively long time required to obtain results and the lack of capacity to identify the specific carbapenemase, the use of imipenem instead of meropenem significantly improves the accuracy of the CIM test in terms of sensitivity and specificity (reaching 99.4 and 98.9% respectively).[21] Although the CIM was first introduced to detect carbapenemases only in *Enterobacteriaceae*, the further modifications introduced allowed to apply the test to *P. aeruginosa*. Some additional changes have been subsequently introduced, in terms of incubation time and/or mediums, resulting in the so-called modified CIM (mCIM) and the CIMTris. These modifications, shown to increase the sensitivity (reaching 100%) have the inconvenient of decreasing the specificity.[25,26] Of course, other phenotypic diagnostic methods (boronic acid, modified Hodge test, modified Carba NP test, Epsilon test, etc.), are widely used, but since they usually require the use of specific/expensive reagents that are not always available in the clinical laboratories in Latin America, and more importantly, since they have been shown to not clearly improve the performance of the carbapenemase detection,[26,27] the use of CIM is envisaged as an inexpensive, relatively quick and reliable test to be mainly used in laboratories with limited resources. Mainly if having into account two additional points, (i) the significant improvement that the use of imipenem supposes, as shown by Gutiérrez et al., and (ii) in Colombia the diversity of carbapenemases is quite limited (as told before, the great majority of identified enzymes belong to VIM or KPC types), and for this reason, the identification of the specific type through the use of more expensive tests such as multiplex PCR could be expendable by now.[28,29]

Thus, the works of Valero and colleagues and Gutiérrez and coworkers published in the current number of EIMC[16,21] are two excellent examples of the type of studies we need to combine with basic research, in order to progressively gain ground in the

fight against *P. aeruginosa*. Only departing from a multi-disciplinary attack including the maximum number of approaches as those presented here, we will make steps in that direction against this fearsome adversary.

Conflict of interest

None to declare.

Acknowledgement

CJ wish to thank Dr Antonio Oliver for revising the manuscript.

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