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Editorial

Surveillance studies on antimicrobial susceptibility, from international to local studies

Estudios de vigilancia de la sensibilidad a los antimicrobianos, de los estudios internacionales a los estudios locales

Epidemiological surveillance studies of microorganisms' antimicrobial susceptibility are essential parts of the plans established to combat the resistance of bacteria to this group of drugs. The World Health Organization (WHO), the United Nations (UN), the European Center for Disease Prevention and Control (ECDC) in Europe or the Centers for Disease Control and Prevention (CDC) in the U.S. remark their relevance in the analysis and monitoring of the results both globally and at local level.[1]

Although there are several gaps that need to be addressed, epidemiological surveillance studies have proven to be useful in analyzing the evolution and trends of antimicrobial resistance, detecting the emergence of new resistance mechanisms, correlating the impact of the use of antimicrobials on the ecology of microorganisms, as well as providing effectiveness to actions taken in stewardship programs (*Programas de Optimization del uso de Antimicrobianos*, PROA).[1–3] There are currently surveillance programs funded by government agencies such as GLASS, from WHO,[4] EARS-net, from ECDC,[5] or NARMS, from CDC.[6,7] Unfortunately, the information included in these surveillance studies is reduced to that of a limited number of microorganisms, in general those with an impact on Public Health, and few antimicrobials are monitored.[8] However, there are also surveillance programs promoted by the pharmaceutical industry in response to regulatory aspects necessary for the commercialization of antimicrobials that enlarge their information. In fact, the European Medicines Agency (EMA) requires the pharmaceutical companies to provide epidemiological surveillance data on microorganisms from infections included in their indication for the process of marketing authorization of new antimicrobials.[9] These companies are also obliged to make a temporary surveillance of the susceptibility of the antimicrobials that they commercialize after their introduction in the market, including also comparator antibiotics used in the target infections thereof. Thanks to this, different international surveillance programs have been developed, such as SENTRY, SMART, or LEADER. Some of them were initiated more than two decades ago, allowing temporary analysis of antimicrobial resistance and complementing the information provided by the epidemiological surveillance studies of governmental agencies. Also, thanks to all these data, the program of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which allows the distribution of the minimun inhibitory concentration (MIC) values of the different microorganisms used for the calculation of epidemiological cut-off values (ECOFFs), enlarges the information included in this program.[10]

Programs that passively collect susceptibility testing data from the laboratory informatics systems (LIS) have been highlighted as an important tool for surveillance.[8,11,12] Some examples of these programs are RedMIVA in the Comunidad Valenciana in Spain[13] or AURA in Australia.[12] The National Plan against Antibiotic Resistance (PRAN) of the Ministry of Health in Spain, coordinated by the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) reflects the need to create a global system that allows adding susceptibility data in real time with common and homogeneous indicators.[14]

Faced with these initiatives that collect susceptibility testing information in a global way, there are also studies that address data collection at the local level. Their intention is to highlight specific problems in pathogens due to the introduction of new antimicrobials or to sensitize about the development of resistance in specific pathogens, which are not always covered in the surveillance studies discussed above. In this sense, in the present issue of Enfermedades Infecciosas y Microbiología Clínica, two Spanish studies describe the evolution of antimicrobial resistance from different pathogens: AmpC β-lactamase-producing-*Enterobacterales* causing urinary tract infections (UTIs) and *Pseudomonas aeruginosa* responsible for invasive infections, respectively.[15,16] Both studies represent excellent examples of regional and local surveillance studies over time using different targets and final objectives.

In the first one, Jiménez-Guerra et al.[15] address, in a non-interventionist study, the epidemiological evolution of antibiotic resistance with the main purpose to know contemporary values of resistance in order to help in the establishment of the most adequate empiric treatment among the population at risk of UTIs in a single center, focussing in AmpC β-lactamase-producing *Enterobacterales*. Several antimicrobials routinely tested were recorded. The time period was 11 prospective years (2006–2016) and comprised a total of 736 isolates of the following microorgan-

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isms (CESPM Group) (percentages are rounded): *Enterobacter cloacae* (30.6%); *Morganella morganii* (23.5%); *Klebsiella aerogenes* (20.4%); *Citrobacter freundii* (10.3%); *Serratia marcescens* (8.8%); and *Providencia stuartii* (6.4%) recovered from ambulatory and hospitalized patients attending both the Virgen de las Nieves hospital in Granada, Spain. The 4 most represented wards (figures are rounded) were emergency unit (30%), urology (14%), nephrology (12.8%) and pediatrics (9%). Samples' collection, microbiology processing, identification, antimicrobial susceptibility testing (AST), and reporting of the results were performed following standardized routine procedures. Interpretation of AST results was done according to Clinical and Laboratory Standards Institute (CLSI) guidelines. A statistical analysis was performed and the evolution of resistance was addressed using the Pearson's χ^2 Test. *E. cloacae*, *K. aerogenes* and *M. morganii* were the most frequently recovered species. Interestingly, a global decrease in susceptibility was observed over the period of study.

The authors stress that, when considering the figures from the "extremes" of the period studied (2006 and 2016), *E. cloacae* exhibited the most pronounced decrease in its susceptibility to all antibiotics tested: piperacillin/tazobactam (85–66%), cefepime (90–69%), gentamicin (100–76%), tobramycin (100–72%), fosfomycin (90–48%), nitrofurantoin (75–28%), ciprofloxacin (95–72%), and trimethoprim/sulfamethoxazole (95–55%). The lowest decrease in susceptibility occurred with imipenem (100–93%). The authors mention that a VIM-producing *E. cloacae* was recovered in 2015 from a patient attending the nephrology unit.

It is to be noted that, globally, and when recording the total of the mean values obtained for all antibiotics and all the species, cefepime, imipenem, ciprofloxacin, and gentamicin were the most active agents with an 80% or even higher percentages of susceptible isolates. Finally, when addressing the issue of empiric treatments against UTIs caused by AmpC β-lactamase-producing-*Enterobacterales*, it is quite important to know which are the limitations of use of many of the recommended (frequently orally administered) antibiotics against other bacterial species, because in the so-called CESPM group (target of the present study), certain compounds have lost their activity, making almost unadvisable their empiric administration. However, the authors indicate that, although the directed treatments with cefepime or imipenem are effective and reliable, there still exist and adequate number of other antibiotics with good and preserved activity. So, coming back to the possibility of an empiric treatment against these species, gentamicin and ciprofloxacin (with the exception of ESBL-producers, frequently resistant) could be a good alternative to spare carbapenems' use.

The second study is a retrospective work, from Fernández-Cuenca et al.,[16] whose objective is to know the actual resistance rates and to describe the evolution of resistance of 1341 clinical *Pseudomonas aeruginosa* isolates responsible for invasive infections, occurring in a wide region in southern Spain. This work comprised a multicentre study involving 20 hospitals from Andalucia (14), Extremadura (5), and Ceuta (1). Isolates recovered between 2012 and 2017 were submitted for routine susceptibility testing, and data were later retrieved to analyze the evolution of resistance. Main variables of the study were the type of AST method used, the guidelines followed for interpretation of the results, either EUCAST or CLSI, and percentages of resistance. Several antimicrobials with antipseudomonal activity and routinely tested in the participant laboratories were analyzed. Statistical analysis of qualitative variants' discrepancies was done using the Chi Square Test or the Fisher's Test, if required.

The 4 most represented wards were medical units (47%), surgical units (26%), intensive care units (ICUs) (22%) and emergency units (4%). In the case of clinical samples, 27% were from the respiratory tract, 25% were urines, 24% were blood, and 23% were from abdominal origin. Automated systems for AST used were MicroScan (58%), Vitek2 (24%), Wider (15%) and Phoenix (2%). Disk diffusion (0.7%) and MIC gradient strips (0.3%) were also used. At the time of the study, a total of 52% of the centers followed CLSI and 48% followed the EUCAST guidelines. A progressive use of EUCAST was observed starting from 2014. Resistance rates were analyzed after defining two groups of isolates: non-susceptible (including resistant and intermediate category) and resistant (excluding the intermediate category).

Among resistant isolates, and according to EUCAST-2019 criteria, resistance rates ranged between 25% to ciprofloxacin and 4% to colistin, while such rates were 19% to both ciprofloxacin and imipenem and 3% to amikacin, when following CLSI-2019 criteria. When considering the non-susceptible isolates, overall resistance rates varied from 25% to ciprofloxacin and 4% to colistin when using EUCAST, and between 28% to aztreonam and 6% to colistin when following CLSI guidelines. Statistically significant differences in resistance rates between the two defined groups (see above) were observed for amikacin: 9% of resistant and 13% of non-susceptible isolates, and for meropenem: 15% of resistant and 20% of non-susceptible, when using EUCAST. Significant differences, when following CLSI were: 3% of resistant and 7% of non-susceptible isolates to amikacin, and 15% of resistant and 20% of non-susceptible isolates to meropenem. The highest resistance rates were observed among respiratory tract isolates particularly to ciprofloxacin (40%), amikacin (12%) and colistin (10%). A total of 14% of multidrug-resistant (MDR) and 7% of extensively drug-resistant (XDR) isolates were observed at the end of the study (2017).

The authors underscore that the use of different guidelines (EUCAST or CLSI) has an important effect at the time of recording global resistance rates and, as expected, this situation might have an important clinical impact when treatment is established. According to the results obtained in their study, differences were particularly significant for piperacillin-tazobactam, cefepime, amikacin, and ciprofloxacin for which higher resistance rates were observed when using EUCAST breakpoints. Ciprofloxacin was the less active compound (resistance rates 25% EUCAST and 19% CLSI), being colistin, amikacin and tobramycin the most active ones, with $\leq$10% of resistance rates. The main conclusion of this study was that antimicrobial resistance rates in *P. aeruginosa* were stable throughout the study period and that these rates are not particularly high in the south of Spain.

In both studies, the authors used routine laboratory data mainly obtained from an automatic system. This approach has the advantage of reflecting AST results obtained in real life and reported to the clinicians. Nevertheless, it might have the disadvantage of recording data that has been considered inconsistent when obtained from these automatic systems, such as colistin,[17] or the obvious absence of antimicrobials recently introduced in therapeutics. Additionally, a limitation of both studies is the lack of retrieving a phenotypic analysis of the resistance mechanisms that are obtained with an interpretive reading approach of the antibiograms.[18] Authors analyzed resistance trends but not inferred antimicrobial resistance mechanisms regarding the analysis of the resistance phenotypes, which might help a better selection of antimicrobials or the establishment of guidelines at local level. For this approach it is important the selection of the antibiotics and concentrations tested.[19] Also, in the second study[16] there is a lack of uniform AST method in all participating laboratories and, moreover, in all of them, the absence of molecular techniques, such as PFGE or MLST to avoid the inclusion of clonal or identical isolates, that might impact when calculating resistance rates. The inclusion of these techniques in daily practice is not feasible but might impact the rates of susceptibility or resistance. In the second study, only the first isolate was included. This approach, widely used in surveillance

studies, might underestimate the real rates of resistance or the presence of multidrug-resistant isolates, particularly when patients receive several courses of antimicrobials and have a long length of stay.[20,21] These patients are considered at high-risk for developing resistance, and secondary isolates are normally multidrug-resistant but are not included in the analysis.

On the other hand, the criterion of expressing susceptibility rates is also relevant. The concept of non-susceptible (intermediate plus resistant isolates) was used in the study of Fernández-Cuenca et al.[16] EUCAST have recently changed the definitions of susceptibility testing categories, and the new definition, particularly for the "intermediate"(I) category indicates that it can be considered as "susceptible" if the exposure to the agent is increased by adjusting the dosing regimen or according to the concentration that it reaches at the site of infection.[22] As a consequence of this change, EUCAST recommends to merge the susceptible (S) with the I (former intermediate) category rather than the I with the resistant (R) category in AST cumulative reports and surveillance studies when reflecting data of susceptibility. The main reason for this recommendation is to reflect percentages of treatable infections/microorganisms rather than the detection of resistance mechanisms.

It is clear that surveillance and monitoring of antimicrobial susceptibility have clear implications in the plans of containment antimicrobial resistance and in the implementation of stewardship programs.[2,3] Future efforts in surveillance should be done to assure massive and passive retrieve of AST data from routine clinical microbiology laboratories and to implement machine-learning analysis in a real time scenario. Also, the implementation of molecular tools, such as whole genome sequencing, will enlarge the interest of surveillance studies.[23] With this approach it will be possible to detect new resistance mechanisms and better monitor the different actions implemented to curtail antimicrobial resistance. All these aspects reinforce the importance of microbiology laboratories as a first step to obtain information regarding antimicrobial resistance and the relevance of the analysis performed in the articles published in this issue.[15,16]

Conflict of interest

The authors declare the absence of conflict of interest.

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