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Editorial

The endless increase of antibiotic resistance in Enterobacteriaceae and the activity of new compounds to face the challenge[☆]



El continuo aumento de la resistencia antibiótica en las enterobacterias y la actividad de nuevos compuestos para hacer frente a este desafío

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Multidrug-resistance in Enterobacteriaceae is a concerning problem in clinical environments both the hospital and the ambulatory setting.^{1,2} The global dispersion of this trait threatens the possibility to treat infectious diseases, endangering the effectiveness of current antibiotics and their recognized success. Resistance, which occurs naturally over time, is accelerated by the misuse and overuse of antibiotics making this circle impossible to be curtailed.³ Moreover, the shortage of novel treatment options put in evidence that the need of new antibiotics does not yet cover the increasing prevalence of antibiotic-resistant bacterial infections.⁴ Another aspect to be considered is the economic burden of antibiotic resistance (lengthier stays in hospitals and more intensive care required), which increases health care costs making stewardship efforts mandatory.^{5,6}

In this issue of *Enfermedades Infecciosas y Microbiología Clínica*, four Spanish studies address the increase of resistance in Enterobacteriaceae affecting different antibiotic groups and the activity of the newly introduced ceftazidime/avibactam against multidrug-resistant Enterobacteriaceae expressing combined mechanisms of resistance.

Arana et al.⁷ publish a study that analyses the evolution of multidrug resistance (amoxicillin, gentamicin, ciprofloxacin, and trimethoprim-sulfamethoxazole) along 12 years (2003–2014) among a total of 39,980 isolates of *Escherichia coli* and *Klebsiella pneumoniae* causing urinary tract infections (UTI) from community and hospitalized patients in a city located in the southern area of Madrid. Resistance evolution and the global trend observed for the whole studied period clearly aware about the increase of resistance among the most common enterobacterial species causing UTI. Considering the end point year (2014), percentage of

multidrug-resistant (MDR)-*E. coli* causing UTI from hospitalized patients was 8.2 and 4.5 from those of ambulatory origin, respectively, being gentamicin and ciprofloxacin mainly responsible for this augment. When considering *K. pneumoniae*, 9.6% of isolates from hospital and 3.8% from outpatients were MDR. Notably, these figures represent a 4-fold and an 8-fold increment, respectively, when compared with values from previously recorded periods. In this latter case, ciprofloxacin, gentamicin and trimethoprim-sulfamethoxazole were involved in the multiresistant phenotype. Another approach was done to evaluate the incidence of extended-spectrum beta-lactamases (ESBL) among MDR isolates, being of 10.3% for *E. coli* (hospitalized patients), and 5.7% (ambulatory patients). As awaited, figures for *K. pneumoniae* were higher; 15% of MDR harboured an ESBL (inpatients), being of 5.5% among outpatients' isolates. This percentage represents a 5-fold increase compared with a previous survey ended at 2010. The worrying increase of resistance in community-recovered isolates could be partially explained by the amount of antibiotic prescription among ambulatory patients in Spain, a practice that should be immediately stopped establishing strict stewardship programs in this setting.⁸ In addition, susceptibility to fosfomycin, meropenem and amoxicillin-clavulanate was analysed. Although slowly increasing, resistance to fosfomycin in *E. coli* was of 14–18% (out and inpatients, respectively). On the contrary, a significant resistance rate to amoxicillin-clavulanate was observed, being of 52–47% in *E. coli*. A 16.4% of resistance was found among ambulatory *K. pneumoniae* isolates but, surprisingly, the total (100%) of isolates from the hospital setting was resistant to this compound. This could be explained by the expansion of a clonal isolate in the institution. No resistance to meropenem was observed which means a surprising absence of carbapenemases, considering their incidence in most Spanish hospitals.⁹

The increase in resistance to third generation cephalosporins, imipenem and co-resistance in 7140 blood isolates of *K. pneumoniae* (2010–2014), according to the Spanish EARS-Net (European Antimicrobial Resistance Surveillance Network) database, is analysed by Aracil et al.¹⁰ This system has been implemented for the antimicrobial resistance surveillance in Europe and public access is available (ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2015).

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Data submitted by 41 Spanish hospitals of different complexity corresponding to *K. pneumoniae* causing bacteraemia, exhibiting resistance percentages to cefotaxime (15.8), ceftazidime (13.7), imipenem (1.7), tobramycin (14.1), gentamicin (10.4), amikacin (1.9), and ciprofloxacin (20.1), were recorded, as well as those from amoxicillin–clavulanate (23.3), piperacillin–tazobactam (13.1), and cotrimoxazole (22.4). Statistics analysis of antibiotic resistance trends demonstrated a non-stop increase of antibiotic resistance (between 2010 and 2014). Global percentage of resistance to 3rd generation cephalosporins (ESBL and/or carbapenemase producers) rose from 9.8–10.2% to 19–20% using CLSI or EUCAST criteria, respectively. For aminoglycosides, these figures were of 8.8%–14.8%, being tobramycin the most affected. Ciprofloxacin diminished a 4.2% of its activity (15.4%–19.6% of resistance increase). It is certainly worrying that imipenem resistance showed nearly a 13-fold increment (0.27%–3.46%). Moreover, coresistance involving 3rd generation cephalosporins, ciprofloxacin and aminoglycosides was nearly of 10% (9.7%) but, of greatest concern is that 90.7% (almost all) of imipenem resistant isolates belonged to this group isolates. As expected, this *K. pneumoniae* isolates were carbapenemase producers, OXA-48 (75), VIM (13), KPC (9), IMP (6), and GES (1), in many cases involved in outbreaks.

In the case of the study performed by Machuca et al.,¹¹ the authors study the underlying quinolone-resistance mechanisms, both chromosomally encoded and plasmid-mediated, as well as their prevalence, in Enterobacteriaceae producing either acquired plasmid-mediated AmpC and/or carbapenemases. A total of 289 isolates (*E. coli*, *K. pneumoniae*, *Proteus mirabilis*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Citrobacter koseri*, *Proteus penneri*, and *Salmonella enterica*), submitted from 35 Spanish hospitals between February and July 2009 were evaluated.

Plasmid-mediated quinolone resistance (PMQR) genes were detected in 31.8% (92 out of 289) of the total isolates. From these 92 isolates, 77 have only one PMQR and 15 have two PMQR. The observed *qnr* genes were *A1*, *B4*, *B19*, *D*, *S1*, *S2* and the other plasmid mediated determinant found was *aac(6')-Ib-cr* gene. The *qnrB4* gene was the most prevalent *qnr* gene detected (20%), mostly associated with DHA-1 plasmid-mediated AmpC. Interestingly, and also important from the laboratory point of view, 14.6% of isolates with ciprofloxacin MICs of 0.5 mg/L or higher showed no mutations in *gyrA* or *parC*, but PMQR genes were detected in 90% of such isolates. This aspect stresses the necessity to keep in mind that quinolone MIC values included in the clinical susceptibility breakpoint may harbour plasmid-mediated resistance determinants, with the consequent possibility of spreading in the hospital environment.^{12,13} The prevalence of PMQR genes (all types) among carbapenemase-producing isolates was 39% (11 out of 28) and 31.4% (83 out of 264) among those encoding a plasmid-mediated AmpC. Novel or relevant findings concerning chromosomal quinolone-resistance mechanisms was not observed. It is important to stress that PMQR determinants, in association with other chromosomal-mediated quinolone resistance mechanisms, different to mutations in *gyrA* and *parC*, (increased energy-dependent efflux, altered lipopolysaccharide or porin loss), could lead to ciprofloxacin MIC values that exceed clinical susceptibility breakpoints, otherwise, the sole presence of certain PMQR mechanisms could remain undetected.¹³

The study performed by López-Hernández et al.¹⁴ evaluates the *in vitro* activity of ceftazidime–avibactam (CAZ-AVI), a novel β -lactam/ β -lactamase combination against a total of 250 Enterobacteriaceae with various resistance phenotypes. The antimicrobial spectrum of activity of this compound comprises multidrug-resistant gram-negative bacteria, including *Pseudomonas aeruginosa*, producing ESBL and AmpC, being also active against carbapenem-resistant isolates that produce

class A and D carbapenemases. However, avibactam does not inactivate metallo- β -lactamases.^{15,16} Tested isolates were ESBL-producing *Escherichia coli*, ESBL-producing *K. pneumoniae*, these latter were grouped according to their outer membrane protein profile (POR+/-) and the production of plasmid AmpC [AACBLs (AACBL+/-)] and ESBLs (ESBL+/-). Isolates classified as POR-lacked both outer membrane proteins, OmpK35 and OmpK36. All ESBL-producing isolates that were resistant to ceftazidime (>90%, EUCAST criteria) were susceptible to CAZ-AVI with MICs $\leq$ 1 mg/L. Moreover, CAZ-AVI exhibited excellent activity against *K. pneumoniae* (AACBL+/-) and (ESBL+/-)-phenotypes irrespective of porin status. CAZ-AVI also exhibited full activity (MIC $\leq$ 2 mg/L) against the different species of AACBL-producing Enterobacteriaceae (all resistant to ceftazidime), including *P. mirabilis*, *K. oxytoca*, *C. koseri*, *E. cloacae*, and *S. enterica*.

Resistance is nowadays a global problem, worsened by the continuous selective pressure exerted not only by the use, but also by the overuse and misuse of huge antibiotic quantities in all environments in which human interventions are present. Many different mechanisms had led to the spread of resistance (mainly by mobilization through horizontal gene transfer) leading to the notorious phenomenon of multidrug resistance. The evolving resistance trends, particularly in hospital settings, hampers most available treatment options against different infections in the health care system. However, compounds like ceftazidime–avibactam are newly options that give certain relief to the resistance panorama. Anywhere, it is extremely necessary to emphasize that imprudent use of antibiotics must be stopped if we don't want to loose the scarce options available to curb the growing threat of antibiotic resistance.

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