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Practical approach by type of pathogens

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Changes in bacterial hospital epidemiology

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ABSTRACT

Antibiotics' use and prescription requires a profound review, as their inadequate administration has been one of the main forces leading to resistance as a result of overuse and misuse. Resistance is particularly challenging in nosocomial environments in which there has been a gradual change in bacterial epidemiology owing to the continuous increase of multi-drug-resistant isolates, which imply a threat to prevent and cure infections. Expertise at the time of using antibiotics, development of new diagnostic tools and the possibility of having new antimicrobials are required to stay ahead of evolving resistance. Moreover, surveillance is also relevant to monitor antimicrobial resistance.

Key words: multi-drug-resistance, nosocomial environment, resistance prevalence

Cambios en la epidemiología bacteriana en el hospital

RESUMEN

El uso y la prescripción de antibióticos requiere una revisión profunda ya que la administración inadecuada ha sido una de las causas más importantes de la resistencia, como resultado del empleo excesivo e inadecuado de los mismos. La resistencia es un problema particularmente desafiante en el ambiente hospitalario en el cual ha habido un cambio gradual de la epidemiología bacteriana debido al aumento continuo de aislamientos multirresistentes, lo que implica una amenaza para la prevención y curación de las infecciones. El conocimiento adecuado de los antibióticos, el desarrollo de nuevas técnicas de diagnóstico y la posibilidad de disponer de nuevos antimicrobianos son necesarios para adelantarnos a la evolución de la resistencia. Asimismo, los estudios de vigilancia son relevantes para la monitorización de la resistencia a los antimicrobianos.

Palabras clave: multirresistencia, ambiente hospitalario, prevalencia de resistencia

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INTRODUCTION

The concept of "One Health" is a worldwide strategy promoted by health authorities that recognizes the link between human and animal health, as well as the ecosystem integrity in the fight again antimicrobial resistance [1]. Achievement of this goal requires the collaboration between physicians, veterinarians, and environmental specialists. Moreover, it requires also the involvement of health authorities, politicians and population in general [2].

An outstanding part of this "One health" action is devoted to fight against antimicrobial resistance through the joint of educational, communications, surveillances, new diagnostic methods implementation as well as prevention and control of antimicrobial resistance emergence and dispersion. With this aim, various regional, national and international action plans have been proposed and are nowadays in progress. The European Union (EU) directs efforts to shape a worldwide strategy to fight against resistance, as this is an interconnected problem requiring coordinated global control measures [3].

The High-level Meeting on Antimicrobial Resistance that was held on 2016 at the General Assembly of the United Nations posed the problem and the possible solutions to be addressed on this respect by all member states. The most outstanding among them obviously coincide with those measures proposed by the EU and can be summarized as the mandatory sanitation, hygiene and infection control as well as the easy of access to better antimicrobials worldwide, the education and implementation of stewardship programmes and the research in new molecules and strategies of treatment as well as the availability of rapid diagnostic tools [4].

FACING THE PROBLEM OF MULTIDRUG RESISTANT BACTERIA

Incidence of hospital-acquired infection varies among countries and even more, among different hospitals from the same country, as complexity of large hospitals is inevitable high, requiring strict control measures of infection containment, which is not always successful. Moreover, not infrequently, patients colonized or infected with nosocomial pathogens are transferred between countries, regions and health care centres, and this may have consequences for the care of patients [5].

Nosocomial infection affects huge number of patients globally, increasing mortality rate and financial losses significantly. Prevalence of nosocomial infections varies according to the economic status with estimated ranges of 3.5-12% in high-income countries whereas it varies between 5.7% and 19.1% in middle and low-income ones [6]. According to the Study of Prevalence of Nosocomial Infections in Spain (EPINE, "Estudio de Prevalencia de las Infecciones Nosocomiales en España"), in 2017, the overall incidence of nosocomial infections was 7.7% (313 hospitals surveyed and 61,673 patients). Percentages of the most frequent nosocomial infections were as follows: surgical, 26%, urinary, 20%; respiratory, 19%; bacteraemia and catheter-related infection, 16%; and other infections, 19%.

Microbiology results reported by EPINE in 2017 are shown in table 1**.** When compared the prevalent organisms reported in this study with those considered by the WHO [7], life-threatening species with growing antimicrobial resistance, a strong coincidence exists between both sources (table 2). Moreover, most of them belong to the so-called ESKAPE group. This acronym was initially defined by Rice [8] to gather those species particularly resistant that currently cause the majority of hospital infections and effectively "escape" the effects of currently used antibacterial drugs. Nowadays, the organisms included are vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus,* multi-drug-resistant *Klebsiella pneumoniae,* multi-drug-resistant *Acinetobacter baumannii,* fluoroquinolone-resistant *Pseudomonas aeruginosa*, and multi-drug-resistant *Enterobacter* spp. The epidemiologic variations observed in the last years highlighted the need of a change from the initial proposed acronym ESKAPE to ESCAPE to accommodate *Clostridium difficile* (*E. faecium*, *S. aureus*, *C. difficile*, *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae) [9].

Microorganisms included in the Critical Category are particularly threatening in hospitals, nursing homes, and among patients whose care requires ventilators and blood

Table 1 **Bacterial pathogens depicted according to their relative frequency (Higher than 1%) in nosocomial infections in Spain (EPINE-2017)**

MICROORGANISM	N	Percentage
Escherichia coli	712	15.8
Pseudomonas aeruginosa	434	9.6
Staphylococcus aureus	434	9.6
Klebsiella pneumoniae	359	8.0
Enterococcus faecalis	310	6.9
Staphylococcus epidermidis	284	6.3
Enterococcus faecium	182	4.03
Enterobacter cloacae	146	3.2
Proteus mirabilis	146	3.2
Clostridium difficile	108	2.4
Acinetobacter baumannii	81	1.8
Morganella morganii	61	1.3
Stenotrophomonas maltophilia	61	1.3
Serratia marcescens	59	1.3
Klebsiella oxytoca	52	1.1
Enterobacter aerogenes	47	1.0

Table 2 **WHO classification of "Priority pathogens" for which new antibiotics are urgently needed**

PRIORITY	MAIN RESISTANCE FEATURE
Critical	
Pseudomonas aeruginosa	Carbapenems
Acinetobacter baumannii	Carbapenems
Multi-drug-resistant *Enterobacteriaceae*	Carbapenems and 3rd. gen. cephalosporins
High	
Staphylococcus aureus	Methicillin, intermediate vancomycin
Enterococcus faecium	Vancomycin
Helicobacter pylori	Clarithromycin
Campylobacter spp.	Fluoroquinolones
Salmonella enterica	Fluoroquinolones
Neisseria gonorrhoeae	3rd. gen. cephalosporins, fluoroquinolones
Medium	
Streptococcus pneumoniae	Penicillin
Haemophilus influenzae	Ampicillin
Shigella spp.	Fluoroquinolones

catheters. They can cause severe infections such as bloodstream infections and pneumonia. "High" and "Medium" categories include an important number of various species with increasingly drug-resistance trend. Surprisingly, *Clostridium difficile* is not included in the WHO list although the epidemiology of *C. difficile* infections (CDI) has dramatically changed since the early 2000s, with an increasing incidence and severity across Europe. This is partly due to the emergence and rapid worldwide spread of the hypervirulent and epidemic PCR ribotype 027 [10]. Moreover, *Mycobacterium tuberculosis*, whose resistance to traditional treatment is growing, particularly in some countries, was excluded in this list because it is subject of other control programmes conducted by this organization.

Concerning antimicrobial use, when comparing previous and present data from EPINE, the prevalence of patients receiving antibiotics rose from 36.8% in 2000 to 46.1% in 2017, entailing almost 10% increase in a decade. This augment of the antimicrobial load in the hospital environment inevitably leads to an increase in pressure and selection of resistant variants that tend to persist in the nosocomial setting, able to emerge when both patient's and environment's conditions are favourable.

THE PERFECT STORM: EPIDEMIOLOGY OF INVASIVE ISOLATES IN EUROPEAN UNION (EU) HOSPITALS, THE CASE OF SPAIN

For most bacterial species reported to the EARS-net (2016), resistance percentages varied across Europe, being generally higher in southern than in northern countries; as a consequence, mean values are reported. Evolution of resistance (2013-2016) in the most significant pathogens associated with nosocomial infections are briefly exposed [11].

Carbapenemase-producing *Klebsiella pneumoniae*. The highest EU mean resistance percentage in 2016 was reported for third-generation cephalosporins (25.7%, the majority due to ESBLs), followed by fluoroquinolones (24.6%), aminoglycosides (19.0%) and carbapenems (6.1%). A total of 2.4% of all reported *K. pneumoniae* isolates in EU were resistant to colistin. The majority of these were reported from Greece and Italy but a low number of isolates had been tested against this antimicrobial, so these findings should be interpreted with caution and may not be representative for Europe as a whole. However, emergence of colistin resistance mediated by plasmid-mediated *mcr-1* to *mcr-7* genes is undoubtedly alarming, not only due to the rapid and ease of its dispersion but to its presence in highly drug-resistant Enterobacteriaceae isolates harbouring plasmids encoding carbapenemase genes [12,13]. Dispersion of carbapenemase producing *K. pneumoniae* has been associated with high-risk clones.

Carbapenemase-producing *Escherichia coli*. Combined resistance to fluoroquinolones, third-generation cephalosporins (mainly due to ESBLs) and aminoglycosides increased significantly during the period 2013-2016. Up till 2016, a low percentage of 0.1% of carbapenems resistance was reported. However, there is a growing threat to resistance to these compounds in *E. coli* mediated by a range of carbapenemases. The increasing prevalence of carbapenemase producing *E. coli* depict a complex alarming situation as this organism might be responsible for carbapenemase transmission to other Enterobaceriaceae as occurred with CTX-M enzymes.

Multidrug-resistant *Pseudomonas aeruginosa*. Resistance to many important antimicrobial groups including carbapenems was common in *P. aeruginosa* in many European countries in 2016. Moreover, *P. aeruginosa* is intrinsically resistant to several antimicrobials complicating treatment of serious infections. However, a slight decreased (13% to 10.3%) in combined resistance including piperacillin-tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems was recorded. However, in Spain, this situation is different and combined resistance rose from 12.2% to 14.5%. In the case of carbapenems, 17.6% of isolates were resistant in 2013 while this value was of 21.4% in 2016.

Multidrug-resistant *Acinetobacter baumannii*. In this species, mean percentage for combined resistance to fluoroquinolones, aminoglycosides and carbapenems was 31.7% in 2016 being of 44.3% among Spanish isolates. In the case of carbapenem-resistant *A. baumannii*, reports published in 2016 concluded that the epidemiological situation in parts of Europe has worsened in the past years, like Spain, in which reported resistance for invasive isolates is higher than 50%. Although reports on colistin resistance are scarce (probably due to difficulties in reliable susceptibility testing), in some countries like Greece and Italy percentage of resistance varies between 2-4%.

Methicillin-resistant *Staphylococcus aureus* (MRSA). A decrease in percentage of MRSA occurred in the EU between 2013-2016. Despite this trend (18.1% *vs*.13.75%), a percentage above 25% remains in one third of the reporting countries including Spain, in which this resistance rose from 22.6% (2013) to 25.8% (2016). Methicillin resistance coded solely by the *mecA* gene along many years has recently "added" to new genes, *mecC*, a variant of *mecA*, and also *mecB*, a plasmid-encoded transferable gene previously found in *Macrococcus caseolyticus* [14,15]. *mecB* gene is present in a multi-drug-resistance transferable plasmid that harbours genes encoding additional resistances. The presence of plasmid-encoded methicillin resistance in *S. aureus* in a healthcare setting reveals a novel level of risk of the transfer of broad β-lactam resistance in staphylococci [15].

Vancomycin-resistant *Enterococcus faecium*. Global European percentages varied from 9% (2013) to 11.8% (2016). In Spain, these figures are low 0.9% (2013) and 2.1% (2016).

Either *vanB* or *vanA* may account for this resistance profile and their distribution is variable depending on local epidemiological landscape [16]. The dispersion of the CC17 in many hospitals is responsible for the added resistance to ampicillin and penicillin in these isolates. The spectrum is worsened by the less activity of daptomycin in this enterococcal species, as the MIC_{90} is 4 mg/L.

CONCLUSIONS

EARS-Net data for 2016 show that antimicrobial resistance remains a serious threat to public health in Europe. For invasive bacterial infections, treatment with effective antimicrobial agents is necessary to reduce the risk of a fatal outcome. The high percentages of isolates with resistance to key antimicrobial groups reported from many countries are therefore of great concern. In addition to increased mortality rates, multi-drug-resistant Gram- negative infections are also associated with a higher economic burden due to their greater severity and increased resource utilization; longer hospital stays and increased hospital and antimicrobial therapy costs. Prudent antimicrobial use, comprehensive infection prevention and control strategies are the key of effective intervention to prevent the selection and transmission of bacteria resistant to antimicrobial agents.

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