Enfermedades Infecciosas y Microbiología Clínica

Editorial

Prudent use of antibacterial agents: are we entering in an era of infections with no effective antibacterial agents? What can we do?

Uso prudente de los agentes antibacterianos: ¿estamos iniciando una era de infecciones sin agentes antibacterianos eficaces? ¿qué podemos hacer?

Jordi Vila [a,*], Jesús Rodríguez-Baño [b] and Domingo Gargallo-Viola [c]

[a] Department of Clinical Microbiology, Hospital Clinic, IDIBAPS, School of Medicine, University of Barcelona, Barcelona, Spain
[b] Hospital Virgen Macarena, Seville, Spain
[c] Ferrer Research and Development Center, Barcelona, Spain

In the last decade we have witnessed a dramatic increase in the number of bacterial pathogens presenting multi-resistance to antibacterial agents. In fact, several organizations such as the European Centre for Diseases Control and the World Health Organization are considering infections caused by multidrug resistant bacteria as an emergent disease. When we talk about multidrug resistant bacteria we should take into consideration not only the emergence but also the spread of multidrug resistant bacteria and the spread of genetic elements carrying resistant determinants. Emergence of microorganisms resistant to antibacterial agents, either by mutations or by the acquisition of new mobile genetic elements, may take place irrespective of the presence of antibacterial agents. It is the exposure to these drugs that provides an advantage to cells with the newly gained phenotype. Therefore, abuse in the use of antibacterials in several settings is the motivating force in the increase of antibacterial resistance. The first of these settings is the use of antibacterial agents in animals, as prophylaxis or treatment of infections.[1] The multidrug resistant bacteria selected in animals can arrive in humans through direct contact or through the food chain. However, it is also possible that our normal gut microbiota have gained antibiotic resistance from antibiotic-exposed food animals. It is important to highlight that pets have recently been reported as reservoirs of multidrug resistant bacteria such as ESBL-producing *Escherichia coli*.[2] Finally, the use of antibacterial agents in aquaculture has been associated with increased antibiotic resistance. The use of antibiotics in animals can also be a source of these compounds in the environment. Overall, it has been calculated that antibacterial agents are added to the environment at a rate of over a million pounds per week.[3] Antibacterial agents have several routes of entry into the environment. Studies have shown that introduction by these routes has changed the antibiotic susceptibility of the bacteria in these environments. First of all, the antibacterial agents that we take in are not all processed by our bodies. Some are expelled as waste and wind up in our waste water treatment plants. Of bacteria isolated from sludge remaining after wastewater treatment at one plant, 46.4% were resistant to multiple antibacterial agents. Sewage from hospitals has also been shown to contribute to antibiotic resistance in treatment plants. Rivers contaminated with urban effluent and agricultural runoff have also been shown to have larger antibiotic resistant bacterial populations than areas upstream from the contamination source. In addition, some antibacterial can be found in household products, including toothpastes. An important compound found in household products is triclosan. This compound can induce the overexpression of efflux pumps such as AcrAB-TolC found in Enterobacteriaceae, thereby generating multidrug resistance.[4] These products wind up in the sewage or landfill after being used in our households. Moreover, antibiotics are also sprayed on high-values crops such as fruit tress to prevent bacterial infections. This can select for resistant bacteria on our crops. Not all of the spray remains on the fruit. Most of the antibiotics are washed into the soil and eventually end up in the ground water. Therefore, microorganisms are becoming resistant to antibacterial agent due to environmental pollution.

In developing countries the biological driving forces behind widespread drug resistance are, in principle, the same as in developed countries. The additional factors, in the developing countries which can contribute to the emergence of resistance are: i. Less potent activity of some antibacterial agents; ii. Over-the-counter availability and, iii. Lack of diagnostic laboratories mostly in hospitals in rural areas.[5] Among the factors favouring the dissemination of multidrug resistant bacteria the following should be pointed out: 1. Global food commercialization; 2. International trips; and 3. Transfer of patients between hospitals.

Over the years we have seen important epidemiologic changes in drug-resistant bacteria. The explosive worldwide dissemination of extended-spectrum β-lactamases (ESBL) in Enterobacteriaceae (particularly *Escherichia coli*, *Klebsiella* spp., *Salmonella* spp, and *Enterobacter* spp.) is among the most relevant events recently occurring, from both clinical and social perspective.[6,7]

* Corresponding author.
  E-mail address: jvila@ub.edu (J. Vila).

A conjunction of variables at different levels explain why such dissemination has been so dramatically fast, conforming what can be called a "perfect storm" that is paradigm of the fact that resistance can overcome any previous expectations.

At the molecular level, the association of genes encoding these enzymes, particularly the CTX-M types of ESBLs, with very efficient mobile genetic elements has allowed the spread of these genes among diverse clones and species in different ecological sites (environment, animals and humans). At the clonal level, ESBLs have been introduced in previously disseminated clones of enterobacteria or have even facilitated their further spread. At the level of the hosts (animals and humans), the use of certain antibacterial agents, including cephalosporins and fluoroquinolones, is playing a decisive role by providing these bacteria with a selective advantage, to be added to the frequent horizontal transmission that occurs in some environments, such as family healthcare centres.

As a result, we are facing facts like these: In Spain, between 7% and 15% of all community-onset bloodstream infections due to *E. coli* are caused by ESBL-producing strains (the percentages being higher in nosocomial episodes); and most hospitals have been affected by outbreaks or endemic situations caused by ESBL-producing *Klebsiella* or *Enterobacter*, also affecting many long term care facilities.[8,9] Beyond the impact on morbidity and mortality, these facts have also had a great influence on antibiotic policies[10] since these organisms are resistant to most antibiotics previously recommended as empirical therapy for many infectious syndromes, and carbapenems are considered the drugs of choice for serious infections caused by these organisms.[6,7,11] Thus, we have been facing a challenging situation: carbapenems, although considered as "reserve antibiotics", should now very frequently be used as front line weapons. Even though there are some alternatives for certain clinical situations, it is a fact that the situation posed by ESBLs has lead to changes in treatment guidelines and local protocols for antibiotic therapy. The potential emergence of other transmissible mechanisms conferring resistance to cephalosporins, such as plasmid-mediated AmpC enzymes, can only worsen the situation.

In this situation, a predictable new problem has just emerged: carbapenem resistance. This is a multifaceted problem, because carbapenem resistance in *Pseudomonas aeruginosa*, *Acinetobacter baumannii* or the Enterobacteriaceae may be mediated by diverse resistance mechanisms. Among them, there is one which justifies alarm: the spread of plasmid-mediated carbapenemases, among which metallo-β-lactamases and KPC enzymes are leaders.[12,13] These carbapenemases, most important in *P. aeruginosa* and *Klebsiella pneumoniae* but also in other enterobacteria, are causing enormous problems in many hospitals in Greece, Italy, Israel and the USA, where they are endemic. To make things even worse, there is also a clear emergent phenomenon in Spanish hospitals.[14] In fact, the first KPC-producing *K. pneumoniae* have recently been reported in Spain.[15] In addition, strains of enterobacteriaceae producing a new metallo-β-lactamase, NDM-1, has recently been shown to cause infections in patients from United Kingdom that have been previously hospitalised in India or Pakistan where this carbapenemase is spread.[16]

The therapeutic alternatives for carbapenemase-producing organisms are extremely limited, and even isolates showing resistance to all know antibacterials are being increasingly described. Frequently, only colistin and tigecycline maintain "in vitro" activity against these isolates (tigecycline is not active against *P. aeruginosa* or enterobacteria from the Protease family). In the case of colistin, the appropriate dosing has not been established,[17] and some data suggest it is less efficacious than β-lactams for susceptible organisms.[18] In the case of tigecycline, there is still scarce experience in these pathogens.[19] The potential

usefulness of combinations including fosfomycin (for susceptible isolates of Enterobacteriaceae or *P. aeruginosa*), rifampicin or other antibacterial agents merits further studies, although we are not confident that they will solve the problem.

As mentioned above, bacterial populations have been shown to change due to exposure to antibacterial agents. We are seeing a rise in antibiotic resistance all around the world. Some diseases that were previously susceptible to a variety of antibiotics are now untreatable. According to the Center for Disease Control (CDC), approximately 70 per cent of infections acquired during hospitalization are now resistant to at least one antibiotic. The following measures can be taken to prevent the emergence and spread of antibacterial resistant bacteria: 1. Rational use of antibiotics; 2. Infection control in the nosocomial setting; 3. Development of rapid diagnostic tests; 4. Research on antibacterial resistance (novel genes, reservoirs and surveillance), and 5. Research and development on new antibacterial agents. Concerning the latter point and despite the urgent need to find new antibacterial products, many pharmaceutical companies, including most large companies, have abandoned this field of development. This undesirable situation prompts us to consider how to unite the different players involved-public health authorities, regulatory agencies, pharmaceutical companies and the scientific community in general-to tackle this challenge which affects us all.

Although in the future a larger proportion of the total antibacterial market will be based on the very high incidence of mild-to-moderate respiratory tract and skin and soft tissue infections, interest in the antibacterial area has seen a clear shift towards the development of therapies for severe infections. Drug developers have been dissuaded from searching for new community therapies for various reasons: cost constraints, diminishing market due to a reduction in antibiotic prescriptions, the large number of different drug classes and products with significant generic erosion. Moreover, there has been significant regulatory uncertainty concerning the approval process for novel antibacterial drugs.

A number of new therapies, such as telavancin[20] or ceftaroline[21] to treat infections caused by Gram-positive pathogens, are available or will soon be on the market. However, the development of drugs against Gram-negative pathogens has been unsuccessful. New classes of drugs providing adequate treatment against these deadly pathogens (Enterobacteriaceae, *K. pneumoniae*, *P. aeruginosa*, and *Acinetobacter* species) are needed. Possibly the most important challenge for antibacterial therapy in coming years will be to find ways to combat disease caused by these organisms. Nonetheless, development of treatments must also be accompanied by the development of a rapid and economic diagnosis, enabling doctors to determine the appropriate use and time limit of application. For such new drugs, efficacy is the most important factor. The most important objective is to improve the condition of the patients, many of whom will be seriously ill. Development of oral administration as an alternative for new intravenous drugs will also be important.

Although there is clear demand for new agents for severe infections arising from bacterial resistance to current therapies, most pharmaceutical companies approach the problem with caution. Several issues need to be considered. Antibacterial therapy is acute, not chronic. Novel antibacterial drugs should be reserved for patients unresponsive to conventional therapies. Rising bacterial resistance shortens drug lifecycles. Markets may not be large enough to generate adequate return on investment. Thus, despite important bacterial threats to public health, such as the growing incidence of severe infections caused by MDR strains or emerging pathogens, most large pharmaceutical companies have reduced their research efforts or have left the antibacterial marketplace to focus on more lucrative areas. Therefore, smaller companies have filled the resultant gap by identifying new

candidates from new drug discovery programs and by taking over clinical programs abandoned by big companies. However, the global financial crisis has increased pressure on the pharmaceutical industry, particularly affecting such small companies, and funding will remain an issue for biotechnology during the coming years.

Decreasing investment in antibacterial drug development, coupled with the increase in antibacterial resistance, is generating concern and real social alarm. The Infectious Diseases Society of America (IDSA) has initiated the 10×20 programme, designed to bring together resources to create a sustainable global antibacterial drug research and development enterprise with the power to develop new, safe, and effective antibiotics in the short-term.[22]

This is the way to proceed: partnership between private and public sectors. We know which organisms and patient types to treat. We know the profile of the products we need to use. All that is needed is for each player to contribute. Academics must develop knowledge for the drug industry to apply. Pharmaceutical companies must contribute resources and experience for the development of drugs. Regulatory agencies must facilitate the approval of such drugs taking into account that they will need to focus treatment on a limited group of patients. Finally, doctors and health authorities must prescribe the drugs appropriately. The problem is urgent. The outcome depends upon responsible action by everyone.

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