Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Special article

Antibiotics policy: The arrival of antimicrobial stewardship programmes☆

Política de antibióticos: irrupción de los programas de optimización del uso de antimicrobianos (PROA)

Josep M. Mòdol Deltell[a,b,c,*], Marlene Álvarez Martins[b,c,d], Maria Méndez Hernández[b,e], Montserrrat Giménez Pérez[b,c,f]

[a] Dirección Médica, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain
[b] Programa VINCat, Barcelona, Spain
[c] Programa asistencial de experiencia del Institut Català de la Salut (PROA PADEICS), Badalona, Spain
[d] Servicio de Farmacia, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain
[e] Servicio de Pediatría, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain
[f] Servicio de Microbiología, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain

ARTICLE INFO

Article history:
Received 9 October 2017
Accepted 13 October 2017
Available online xxx

Introduction

"A post-antibiotic era in which common infections are deadly once again, far from being an apocalyptic fantasy, is a very real possibility in the XXI century".[1] This overwhelming statement was issued by the World Health Organization (WHO). Why? After decades of abuse in antibiotic prescriptions, the phenomenon of antimicrobial resistance has emerged in recent years as a serious threat to public health.[2] The *European Center for Disease Control and Prevention*[3] and the White House, among others, have expressed similar concerns.[4] Some have established a parallel with the climate change phenomenon, although with less social and political awareness than the one that exists with global warming.[5]

It is estimated that infections caused by multiresistant bacteria cause about 25,000 deaths a year and involve an extra expense in health and loss of productivity of 1.5 billion euros[3] in Europe. The situation is not very different in the US, where 23,000 deaths are estimated, with global losses exceeding 50 billion dollars a year for this reason.[6]

To fight against this situation, besides the efforts of the different administrations to stimulate the pharmaceutical industry to develop new molecules and strengthening the nosocomial infection control teams, *antimicrobial stewardship*[7] programs have become popular in the last decade. These include the adequate selection, dosage, route of administration and duration of antibiotic treatment.[8] This term, which does not have an adequate translation into Spanish, has come to be called "programa de optimización (del uso) de los antimicrobianos", popularly known as PROA (Spanish acronym) (ASP in English, antimicrobial stewardship program).

Brief review of the introduction of antibiotics and the emergence of resistance

The natural evolution of bacteria contemplates the development of resistance mechanisms that are enhanced by the selective pressure exerted on them by antibiotics. In this way, the occurrence of each new antibiotic has been accompanied by the subsequent development of resistance to it (Fig. 1).

The antibiotic era starts with sulphonamides, the first class of antimicrobials manufactured and used on a large scale. Introduced in clinical practice in 1935, the first resistance was detected at the end of that decade.[9,10] Some years before, in 1928, Alexander Fleming discovered penicillin, the first beta-lactam antibiotic. Resistances were described in 1940,[11] prior to its being marketed, which took place in 1943.[10,12]

☆ Please cite this article as: Mòdol Deltell JM, Álvarez Martins M, Méndez Hernández M, Giménez Pérez M. Política de antibióticos: irrupción de los programas de optimización del uso de antimicrobianos (PROA). Med Clin (Barc). 2018. https://doi.org/10.1016/j.medcli.2017.10.038

* Corresponding author.
E-mail address: jmmodol.germanstrias@gencat.cat (J.M. Mòdol Deltell).

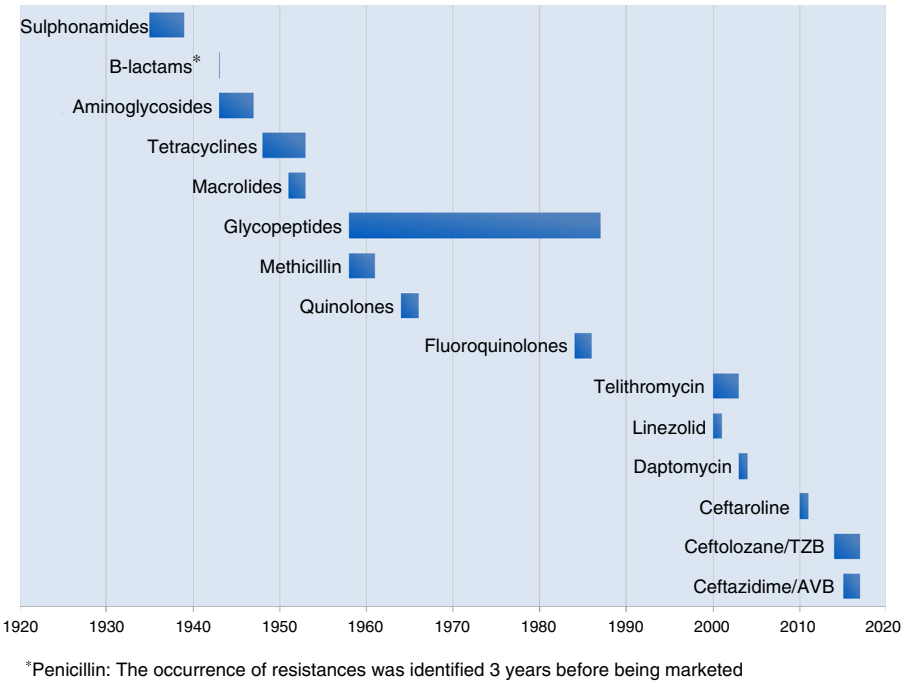

Fig. 1. Time between the introduction of antibiotics and the occurrence of resistance. AVB: avibactam; TZB: tazobactam. *Source*: Gould,[9] Davies and Davies,[10] and Aminov.[11]

During the 40s–60s of the last century, the so-called golden age of antimicrobial therapy followed, in which the classes of antimicrobials that are still used today were discovered: aminoglycosides, amphenicols, tetracyclines, macrolides, glycopeptides and quinolones, among others.[9] Within the group of beta-lactams, from the 1960s, cephalosporins were marketed, and carbapenems arose in the mid-1980s.[13] From then on, modifications were developed within the same classes of antimicrobials to try to mitigate the increasing occurrence of resistance, broaden the antimicrobial spectrum and improve the safety and pharmacokinetic profile. With the turn of the century new classes of antibiotics became available.

Linezolid was launched in 2000, an oxazolidinone active mainly against Gram-positive bacteria and with a low probability of developing resistances, as an alternative to glycopeptides. However, already in 2001 and 2002, the first cases of infections due to *Staphylococcus aureus*, *Enterococcus faecium* and *Enterococcus faecalis* who developed resistance during treatment were published.[14,15]

The first lipopeptide, daptomycin, was introduced to clinical practice in 2003. It was of great interest due to its activity against vancomycin and methicillin resistant Gram-positive bacteria. The first cases of resistance were diagnosed in 2004 and 2005, during the treatment of infections caused by methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *E. faecium*.[16]

The new systemic antibiotics that have appeared on the market in the last decade essentially belong to the families already described. In 2014 dalbavancin, the only second-generation glycopeptide or lipoglycopeptide currently available in Spain,[10] is active against gram-positive bacteria, including those resistant to methicillin and vancomycin, and provides advantages in the pharmacokinetic profile. Tedizolid was launched the same year, an oxazolidinone with a similar spectrum and activity against certain linezolid-resistant strains. Ceftaroline was launched in 2010 as part of the betalactams group, with activity against MRSA, ceftolozane/tazobactam in 2014 and ceftazidime/avibactam in 2015, with activity against multiresistant *Pseudomonas aeruginosa*. The latter is not yet marketed in Spain. Only bedaquiline, approved for the treatment of multidrug-resistant tuberculosis, belongs to a new class, diarylquinolines. Unfortunately, in line with what was described above, it did not take long for resistances them to appear. Already in 2011, ceftaroline-resistant MRSA strains were identified[13] and in 2013 a case of high level resistance with CMI >32 mg/l was detected.[17] This year, an emergency situation was reported involving ceftolozane/tazobactam resistance in infections caused by *P. aeruginosa*[18] and ceftazidime/avibactam in carbapenems-resistant *Klebsiella pneumoniae*.[19]

Development of new drugs

The period between the discovery of an antibiotic and its availability for clinical use is 10 years, on average, and it has been estimated that this process costs between 800 million and one billion dollars.[12] If we add to this the possibility of a short useful life due to the occurrence of resistances and the restriction of their use, they become unattractive products for the pharmaceutical industry. Most of the main companies have discontinued research in this field and, currently, less than 5% of the investigational drugs are antibiotics.[20] The concern for this situation has led international organizations to propose strategies to try to improve this trend.[20–22] WHO points to the need to separate the cost of investment in research and development from the sale price and volume and establishes an investment increase for new medicines as one of the objectives of its action plan 20. At global level, the authorities are taking initiatives in this regard: modification of the regulatory requirements for the approval of antibiotics, legislative changes to improve corporate incentives and public-private capital association formulas.[22]

Some considerations in relation to bacterial resistance

Knowledge of the mechanisms by which bacteria develop resistance to antibiotics is crucial to establish policies to optimize the use of antibiotics and control nosocomial infections.

Not all bacteria are initially sensitive to all antimicrobials. A certain bacterium may be resistant to an antibiotic without any mediating resistance acquisition. It would be in this case a *natural*