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Optimizing antimicrobial prescribing: a practical decalogue

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ABSTRACT

Increasing antibiotic resistance is one of the leading problems in the Public Agenda worldwide. In the last 20 years, the pace of antimicrobial drug development has markedly slowed leading to a dramatic world situation. Infections with antibiotic-resistant microorganisms have been associated with increased length of stay, mortality and costs. Improving antimicrobial prescribing is one of the tools in our hands to optimize the outcomes of patients with moderate to severe infections and control the emerging of resistance. Several clues to improve antimicrobial prescribing are provided as a key-messages decalogue.

Keywords: antibiotic prescribing, antimicrobial stewardship programs, antimicrobial resistance.

Optimización del uso de antibióticos: Decálogo práctico

RESUMEN

El incremento de resistencias antibióticas es uno de los problemas fundamentales al que nos enfrentamos en el manejo de infecciones en la actualidad. En los últimos 20 años, el desarrollo de nuevos fármacos se ha reducido de manera considerable conduciendo a una dramática situación mundial. Las infecciones por microorganismos multirresistentes se han asociado con un aumento de la estancia hospitalaria, de la mortalidad y de los costes. Para intentar cambiar esta situación, una de las estrategias que disponemos es mejorar el uso de antimicrobianos para disminuir la aparición de resistencias. En el texto se articulan en forma de decálogo mensajes claves para la optimización del uso de antibióticos.

Palabras clave: prescripción antibiótica, programas de optimización antimicrobiana, resistencia antimicrobiana.

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INTRODUCTION

We are witnessing a significant increase in antibiotic resistance to which antibiotic overuse and misuse has contributed. It has been consistently observed across several studies over the last decades that antimicrobials are often used inappropriately in up to 50% of prescriptions[1,2].

Antibiotics are unique drugs since its use in a given patient may impact on others (ecological impact) and, thus, prescribers should be aware of their responsibility in their use.

Antibiotic prescribing should be the result of an individualized, rational and methodical process, which must be conducted considering the available clinical, epidemiological, pharmacological and microbiological information and evidence.

Nevertheless, there are several factors that can negatively affect the prescribing process ("interferences"). First, as antibiotic may be prescribed by almost every physician, prescribers frequently lack the needed knowledge expertise in infectious disease and antimicrobial therapy. Other relevant interferences to the prescribing process are diagnostic uncertainty (for example, in respiratory infections it may be difficult to discern whether the etiological agent may be a virus or a bacteria), defensive medicine, poor perception of negative effects (both adverse effects and ecological impact) and logistical aspects. One significant barrier to the rational process of antimicrobial prescribing is that prescribing decisions are frequently made in an automated mode, omitting some of the critical steps in what it has been called "reflex" prescribing.

Furthermore, antibiotic therapy should be a dynamic process, requiring periodical reassessments. Figure 1 depicts how

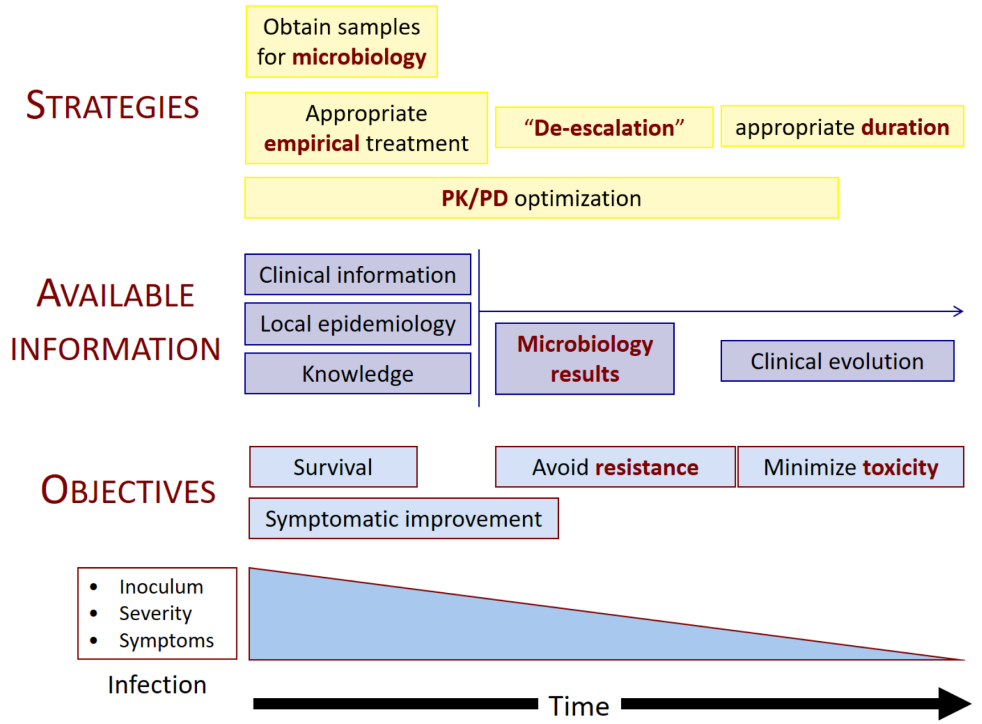

Figure 1 | **Therapeutic strategies according to the time of infection evolution. Adapted from J. Cobo.**

therapeutic strategies should be adapted to the goals and available information, which, indeed, change along the course of the infection.

In 2011, Public Health England outlined a campaign for appropriate antimicrobial use targeting prescribers ("Antimicrobial stewardship: Start smart - then focus") that included several evidence-based recommendations on antibiotic prescribing[3].

Antimicrobial stewardship programs (ASP) are institutional initiatives that aim to optimize antimicrobial prescribing in order to improve patient outcomes and to decrease antibiotic associated adverse effects, including their ecological impact using several strategies[4,5]. Since antibiotic prescribers are the workforce to achieve better antimicrobial use, educational activities targetting prescribers are among the most valuable resources of ASP.

In 2015, Hospital Universitario La Paz (Madrid, Spain) and Hospital Clínico Universitario "Lozano Blesa" (Zaragoza, Spain) ASPs launched a campaign to increase awareness of the main principles of antibiotic use among prescribers based on the Public Health England key messages. The campaing consisted of several vintage-looking posters, inspired in the golden antibiotic era (1940's-1950's) because if antimicrobials had been tought to be used more appropriately, currently antimicrobial resistance use would eventually be a less relevant problem. Every poster contained a key-message to foster appropriate antimicrobial use. Posters can be accessed at http://www. pantuas.com/usoantibioticos/. Overall, the posters conform a decalogue sharing a motto "Not less, not more. Your choice!" emphasizing at the same time prescriber responsibility and autonomy regarding antimicrobial prescribing (figure 2). This campaing has been adopted by the Spanish Agency of Medicines (AEMPS) as part of the Spanish National Plan against Antimicrobial Resistance.

PRACTICAL DECALOGUE

1. Assess your patient carefully before prescribing antibiotics. Antimicrobials should be avoided when there is no evidence or high likelihood of a bacterial/fungal infection. Thus, it is essential to carefully assess the patient in search of clues of an infectious disease that should be treated with antibiotics. Clinical assessment should ocasionally be complemented with laboratory (e.g. biomarkers such as white blood cell count, C-reactive protein and procalcitonin, lactate...) and imaging test in order to reduce uncertainty. Nevertheless, there are circumstances in which antibiotics should be started despite significant uncertainty, such as in patients with febrile neutropenia and in splenectomized patients with fever.

2. In severe infections, start FAST. The prompt initiation of effective antibiotic treatment has a high impact on morbidity and mortality in severe infections.The severity of an infection can be defined either by the degree of

Figure 2 | **Not less, not more. Your choice! Poster of Antimicrobial Stewardship Program campaing adopted by Spanish Agency of Medicines (AEMPS) as part of the Spanish National Plan against Antimicrobial Resistance.**

systemic involvement (sepsis, septic shock) or by its possible consequences/sequelae. In these situations, it is advisable to start the antibiotic as soon as possible, preferably within the first hour of diagnosis.

3. Choose empiric therapy considering local epidemiology and patients' individual factors. When choosing empirical antimicrobial therapy, prescriber needs to be systematic in order to anticipate the most likely etiological agents, their susceptibility patter and, finally the best antibiotic choice. In a didactic way, it can be summed up by the acronym **SAFEx**: **S**yndrome (infectious syndrome or site of infection), **A**cquisition (community, nosocomial or healthcare-associated), individual **F**actors (risk factors for multidrug-resistant microorganisms, colonization or previous infection), local **E**pidemiology (local pathogen prevalence and resistance profiles) and e**X**tra factors (allergies, comorbidities, immunodepression and drugs interactions). Local antibiotic treatment guidelines are of great help to choose empirical antimicrobial therapy since they already consider many of these factors in a wide variety of syndromes and circumstances.

4. Dosing matters, too. Antimicrobial dose optimization needs considering several factors such as those that have just mentioned in the former paragraph as well as the pharmacokinetic and pharmacodynamic properties of the antibiotic to be used.

PK/PD models can be used to predict clinical and bacteriological efficacy and to help identify the most suitable dosage. For instance, in time-dependent antibiotics, like beta-lactams, the bactericidal activity correlates with the percentage of time that the antimicrobial concentration is maintained above the minimum inhibitory concentration (MIC). However, fluoroquinolones and aminoglycosides are concentration-dependent drugs, being the peak concentration and area under the curve predictors of bactericidal effect.

Patients with renal failure might need dose adjustement of several antibiotics which have significant renal clearance. Of note, first dose should not be adjusted since it needs to fill the drug distribution volumen. In the case of antibiotics with a narrow therapeutic range such as vancomycin or aminoglycosides, it may be necessary to determine plasma levels.

5. Get the bug. Obtain samples for microbiological diagnosis before starting antibiotic treatment. Correct sampling of specimens for culture as well as its processing are essential to achieve an etiological diagnosis. Knowing the causative microorganism and its antibiotic susceptibility reduces diagnostic uncertainty and facilitates targeted therapy.

To increase the sensitivity of microbiologic diagnosis, samples shoud be obtained prior to commencing antibiotic, when possible. Nevertheless, do not delay treatment in patients with sepsis or life-threatening infections.

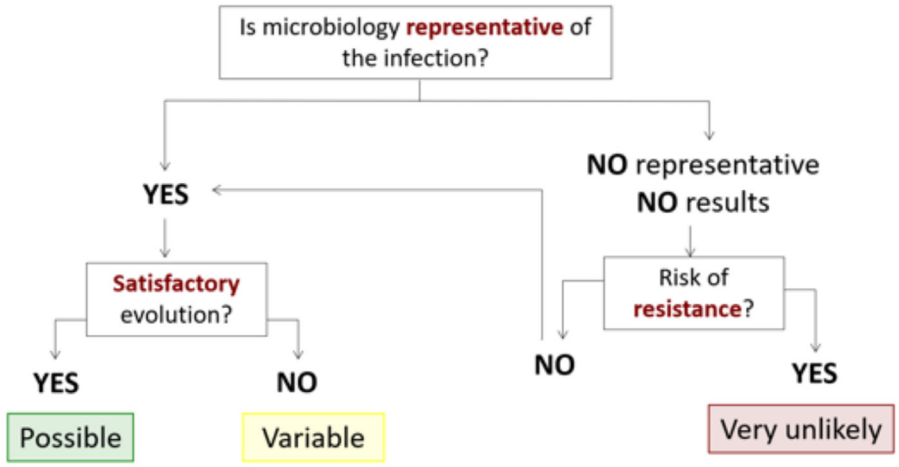

Figure 3 | **Algorithm for de-escalation antimicrobial therapy.**

6. Document in the chart your antibiotic plan: indication and expected duration. Documenting the antibiotic plan in the chart is among the most widely accepted quality indicators for antimicrobial prescribing[6,7]. In addition to helping other healthcare professionals to assist the patient, documenting the antibiotic plan works as a final check in the process of antibiotic prescribing. Prescriber can detect errors in this step of the prescribing process. Documenting the presumed duration of antimicrobial therapy serves as an anchor (heuristics) to guide therapy.

7. Reassess (and adjust) antibiotic therapy periodically. As antibiotic therapy is a dynamic process, it should be reassessed periodically. 48-72 hours after antibiotics have been started, microbiology results frequently become available. Moreover, the clinical course may provide further diagnostic information as well as more clues on the duration of therapy. Reassessing antimicrobial therapy each 48-72 hours facilitates targeted therapy and discontinuation of antibiotics when the evidence of infection is absent.

8. Target antimicrobial therapy when possible. Targeted therapy aims to treat the causative pathogenes, maximizing efficacy and minimizing antibiotic pressure and thus, ecological damage in the form of antibiotic resistance. As a rule of thumb, targeted therapy consists of chosing the antimicrobial with the highest efficacy and the lowest spectrum. Targetting antimicrobial therapy or streamlining is more easily achievable when a strong etiological diagnosis is available.

Nevertheless, streamlining or de-esacalating antimicrobial therapy is not always straightforward. A management algorithm, such as the one depicted by figure 3 can be of help. The most favorable scenario for de-escalation occurs when the microbiological sample is representative of the infection and the clinical response is favorable. In all other circumstances a more thorough approach is necessary.

9. Switch to po (oral route) when possible. Sequential antibiotic therapy (SAT) refers to the conversion of intravenous to oral treatment using an agent from the same or another antibiotic class. Several studies have demonstrated its advantages (safety, convenience and cost-saving). Nevertheless not all infections are suitable for oral antimicrobial therapy. Despite more and more syndromes are being progresively considered good candidates for SAT, there are still a number of infections that are still not, such as endocarditis, primary bacteremia (or endovascular focus), central nervous system infections, acute osteomyelitis, and non-drained visceral abscesses.

In those infectious syndromes in which it has been proven to be effective and safe, SAT should be considered when there the patient is clinically stable (absence of fever in the last 48-72 hours, clinical improvement, and tendency towards normalization of laboratory parameters), there is adequate oral intake and gastrointestinal absorption and adequate antibiotic bioavailability[8].

10. Don't go overtime with antibiotic duration. The duration of the antibiotic treatment should be the minimum that, adapted to the circumstances of each patient, warrants its cure with a minimum rate of recurrence. Too short a course of therapy risks treatment failure, whereas too long a course of therapy carries potential risks for the individual patient and to other patients through the emergence of resistant microorganisms. This requires individualization.

The standard guidelines for therapy often provide a range of appropriate durations, but optimal duration in many situa-

tions is uncertain. More and more evidence is available from clinical trials that shorter courses are as effective as prolonged courses for certain infections[9,10].

Nevertheless, very frequently infections are treated too long since antibiotics provide a false sense of security and the negative consequences derived from their use often go unnoticed or are undervalued. It is essential to increase awareness of the relevance of optimizing the duration of antimicrobial therapy, as well as to change duration framing, and to individualize.

CONCLUSIONS

We have herein summarized the key principles of antimicrobial prescribing that, if correctly applied, should contribute to obtain the best possible outcomes from antimicrobial therapy, minimizing the emergence of resistance, preserving antibiotics as a societal common. These principles should be applied by prescribers, a huge and heterogeneous number of physicians that are part of a complex healthcare system. As knowing does not equal acting, it is relevant to act on all those factors negatively influencing prescribing. Antimicrobial stewardship programs and all other institutional efforts are necessary to achieve this goal.

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