



# Enfermedades Infecciosas y Microbiología Clínica

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## A review of the factors influencing antimicrobial prescribing

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### ABSTRACT

#### Keywords:

Antimicrobial stewardship  
Antimicrobial prescribing process  
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Inappropriate prescribing  
Drug resistance

There are multiple benefits of appropriate antimicrobial prescribing: it has a direct impact on clinical outcomes, avoids adverse effects, is cost effective and, perhaps most importantly, it helps to prevent the emergence of resistance. However, any physician can prescribe antibiotics, which is not the case with other clinically relevant drugs. There is great variability in the prescribing physician's (PP) training, motivation, workload and setting, including accessibility to infectious diseases consultants and/or diagnostic techniques, and therefore there is a high risk of inappropriate prescription. Many antibiotic prescribing errors occur around the selection and duration of treatment. This includes a low threshold for the indication of antibiotics, delayed initiation of treatment when indicated, limited knowledge of local antimicrobial resistance patterns by the PPs, errors in the final choice of dose, route or drug and a lack of de-escalation. Similarly, the prescription of prophylactic antibiotics to prevent surgical site infections, despite being commonly accepted, is suboptimal. Factors that may explain suboptimal use are related to the absence of well-defined protocols, poor knowledge of prophylactic protocols, miscommunication or disagreement between physicians, logistical problems, and a lack of audits. A proper understanding of the prescribing process can guide interventions to improve the PP's practices. Some of the potential interventions included in a stewardship program are education in antimicrobial prescribing, information on the local resistance patterns and accessibility to a qualified infectious diseases consultant.

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### Revisión de los factores que influyen en la prescripción de antibióticos

#### RESUMEN

#### Palabras clave:

Optimización del uso de antibióticos  
Proceso de prescripción de antibióticos  
Determinantes del uso de antibióticos  
Prescripción inadecuada  
Resistencia al fármaco

La prescripción adecuada de antimicrobianos tiene un impacto directo sobre la evolución clínica del paciente, evita posibles efectos adversos, es coste-efectiva y contribuye a evitar la emergencia de resistencias. A diferencia de lo que ocurre con otros fármacos de interés clínico, cualquier médico puede prescribirlos. Esto significa que entre los médicos prescriptores (MP) hay una gran variabilidad en el grado de formación, motivación, carga de trabajo y especialidad, la accesibilidad a los consultores de enfermedades infecciosas y/o a técnicas de diagnóstico, lo que conlleva un alto riesgo de uso inadecuado. Muchos de los errores de la prescripción están relacionados con una mala selección o duración de los tratamientos antibióticos. Eso incluye un bajo umbral para la indicación, un retraso en el inicio, un conocimiento limitado de los patrones locales de resistencia, errores en la elección final de dosis, vía o fármaco y, por último, la falta de simplificación de los tratamientos empíricos. Del mismo modo, el uso de antibióticos profilácticos, a pesar de ser comúnmente aceptado, no es óptimo. Las razones fundamentales que explican esta situación están relacionadas con la ausencia de protocolos bien definidos o la falta de conocimiento de estos, la falta de comunicación entre los médicos y/o la existencia de problemas logísticos. Una comprensión adecuada del proceso de prescripción puede guiar las intervenciones para mejorar los hábitos de los MP. Algunas de las posibles intervenciones podrían ser medidas formativas, la difusión de las resistencias locales y la accesibilidad a un consultor experto.

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## Introduction

There are many benefits of appropriate antimicrobial prescribing: it has a direct impact on clinical outcomes, avoids adverse effects, is cost effective and, perhaps most importantly, helps to prevent the emergence of resistance.<sup>1,2</sup> However, antimicrobial prescription is a complex process involving multiple factors. Any physician can prescribe antibiotics, which is not the case with other clinically relevant drugs. There is great variability in the degree of training, motivation, settings, workload of the prescribing physician, accessibility to infectious diseases consultants and/or diagnostic techniques; therefore, there is a high risk of inappropriate use of antimicrobials. The solution to these problems may seem relatively straightforward: simply follow specific guidelines. However, real-life decisions on antimicrobial prescribing are not based on accurate clinical diagnoses, but on the nature and severity of the signs and symptoms. Antimicrobial prescribing is subjected to a certain degree of diagnostic uncertainty and is influenced by many factors related to the physician, the patient and the environment. In order to promote the appropriate use of antimicrobials, it is important to analyze the prescribing process, the prescribing physicians (PP) and other influencing factors. This review reflects on the elements related to the inappropriate prescribing of antibiotics in their empirical, directed or prophylactic use.

## Prescribing process

Many studies have used a qualitative approach to investigate aspects that determine the appropriate use of antimicrobials. According to these studies, the primary aspects can be grouped into factors related to the PP, factors related to the patients and factors related to the environment.

Fear of failure is one of the factors related to the PP. Diagnostic uncertainty, prognostic impact, multiple choices, inadequate training and difficulties in the doctor-patient relationship<sup>3</sup> generate tensions and anxieties for the PP. These anxieties tend to be mitigated by mimicry (do what others are doing) or by the consultation of guidelines. An additional problem related to the PP is that antimicrobial prescribing can occur in multiple settings: from areas with a high workload, comprised of patients with acute and potentially serious syndromes and difficult follow-up<sup>4</sup> (e.g., emergency services) to areas with high-risk and/or vulnerable patients, where the temptation is to use the best available strategies and drug options. Also, the lack of time for reflection on their prescription choices and the outcome feedback needed to evaluate these decisions plays a role.<sup>4</sup> Additional factors are economic considerations, particularly in private practice settings, and the lack of awareness of antimicrobial resistance as being a real problem. PPs tend to be more concerned for their individual patient than for the potential risk of bacterial resistance.<sup>5</sup> In fact, prescribing antibiotics unnecessarily is considered less inappropriate and causes less PP concern than the inappropriate prescription of antibiotics.<sup>6</sup> Previous negative experiences in handling infectious diseases with or without the use of antimicrobials and an altruistic attitude toward the patient are other factors that contribute to the misuse of antibiotics.

Environmental factors can also contribute to the misuse of antimicrobials. Numerous factors have been identified in this category, including lax regulations on the prescription and dispensing of antimicrobials; authorization of antimicrobial use for certain population groups with poor education on the impact of antimicrobial resistance; a lack of adequate resources for the etiological diagnosis of major infectious syndromes; institutional saving policies that induce a bias in prescribing criteria based on dubious evidence; and pressure from the pharmaceutical industry that influences the professionals' criteria, with little time for reflection and discussion.<sup>7</sup> The lack of institutional initiatives for improving the use of

antimicrobial agents in hospitals, the absence of a competitive environment and the poor compensation obtained from the PP's efforts result in a lack of motivation for additional training and professional improvement. On the other hand, the lack of specific targets adapted for each intervention (which greatly reduces their effectiveness), poor professional networks and the lack of joint committees (including external agents such as universities, scientific advisers, health institutions and private companies), make the development and design of objectives and strategies to establish the use of antimicrobial awareness in hospitals difficult.

## Empirical therapy

Empirical treatment requires interventions with a significant prognostic impact based on clinical and microbiological predictions, with complex treatment options. The need for improvement in the prognosis of serious infections has increased the tendency to prescribe broad-spectrum antibiotics following a logical and simplified strategy that prioritizes the clinical benefits over the potential negative consequences. The implementation of programs such as the "Sepsis Survival Campaign" has contributed to the extension of this strategy. The rationale and logic of this strategy hinders the possibilities of change and, until now, it has not been possible to successfully implement antimicrobial stewardship programs in this setting.

Many antibiotic prescribing errors occur around the selection of empirical treatments. This includes a low threshold for the indication of antibiotics (due to problems predicting the bacterial etiology), delayed initiation of treatment when indicated (caused by the difficulty in recognizing the severity of infections), a limited knowledge of local antimicrobial resistance patterns by the PPs and errors in the final choice of dose, route or drug (due to limited specific training in antibiotic use and to low awareness of the clinical guidelines). The potential interventions in empirical settings are difficult. After a long history of accumulated failure, current proposals to minimize exposure to antibiotics are mainly focused on strategies to reduce the duration of directed antimicrobial therapies. Nevertheless, empirical therapy has many opportunities for improvement and should remain a priority issue for the improvement programs. Possible interventions include the following: a) facilitating the recognition of serious infections (by means of strategies such as the "Sepsis Survival Campaign"), which would avert the delay of empirical therapy in critically ill patients and would reduce pressure on the use of drugs and intensive strategies in patients who are not severely ill; b) facilitating access to evidence-based guidelines incorporating local epidemiology and resistance patterns; c) the recommendation and requirement to conduct controlled cultures before starting antibiotic therapy; d) the implementation of strategies to promote de-escalation and the reduction of antibiotic therapy duration, as will be discussed below.

Effective antimicrobial stewardship programs can improve the PP's empirical prescribing through adapted protocols, electronic information, smart phone training sessions and prospective audits of antimicrobial use, performed by either infectious diseases physicians or clinical pharmacists with infectious disease training.<sup>8</sup>

## Directed therapy

Between the second and third day after starting empirical antibiotic treatment, the PP should always consider whether to make changes to the initial regimen to optimize it if possible.

Optimization pursues the administration of the most selective, effective and safe antibiotics against the infection being treated, at appropriate doses according to pharmacokinetic and pharmacodynamic parameters (PK/PD) and during the shortest possible time, all in accordance with the best available scientific evidence. Any changes

must be made based on the patient's clinical response and on the identification of the causative organism and its antibiotic susceptibility, when known.

If the clinical response is inadequate (e.g., worsening or persistent signs and symptoms of infection) and treatment failure can be explained by the results of microbiological tests, it is clear that the PP should establish a targeted antibiotic treatment according to the information received from the microbiology laboratory. When the microbiological data does not explain the therapeutic failure, the PP must rethink the diagnosis, investigate any complications that may explain the lack of response, repeat microbiological tests and ultimately change the treatment, if necessary.

In this scenario, it would be likely that the PP, concerned about the evolution of the patient, would seek the advice of microbiologists and infectious diseases specialists before making therapeutic changes, and would be receptive to the suggestions received.

If the clinical response is adequate, it is rare for the PP to consider the simplification of empirical therapy a priority. Often the PP thinks that a treatment that works should not be changed, and identifies broad-spectrum antimicrobials with more potency and a longer length of therapy with better cure rates. Furthermore, the PP's awareness of the global problem of antibiotic resistance and its epidemiological and clinical significance is usually low.

Although there are large differences between centers and wards, experience has shown that the change from empirical therapy to targeted therapy is often not considered and, when performed, a high proportion of treatments are inadequate (e.g., in the type of antibiotic selected, dose, route, duration). Although it is a well-known problem, in practice it is difficult to solve. There are many psychological, cultural, social, economic and behavioral implications that significantly affect the PP's final practice.<sup>9-11</sup> In relation to the inadequacy of targeted therapies, factors such as a lack of motivation, routine practice, the application of "defensive medicine" and the possible negative influences of the pharmaceutical industry have been frequently highlighted. However, although all these factors may contribute, the most important reason for inadequate therapy is the great and increasing difficulty for the non-specialist PP to use antibiotics in an optimal way. Indeed, an optimal antimicrobial prescribing process requires wide knowledge of the local epidemiology of bacterial resistance and, above all, specific and updated training in infectious diseases and antimicrobial therapy; a knowledge that non-specialist PPs do not necessarily possess.

In addition to international and local therapeutic guidelines, it may be very useful to have qualified consultants available to assist PPs in making prescribing decisions when necessary.

The primary issues to consider in the process of directed antibiotic therapy are as follows:

- **Microbiological diagnosis.** The information generated in the Microbiology laboratory is the basis for directed therapy. The PP should always obtain appropriate samples for culture and susceptibility testing and repeat them when indicated. The professionals involved in antibiotic stewardship programs, especially microbiologists, should emphasize the importance of cultures and susceptibility patterns, facilitating access to the results and evaluating the implementation of techniques (real-time PCR) that allow the rapid diagnosis of key resistance mechanisms. On the other hand, any positive culture results must be considered in relation to their clinical context, to avoid the mistake of treating patients with simple colonization status.
- **Optimization.** When the causative agent is known with certainty or high probability, the goal of targeted therapy is to choose the antimicrobial therapy with the highest activity and specificity. However, clinical interpretation of the susceptibility pattern is subject to multiple factors.<sup>12</sup> Furthermore, the rational selection of optimal treatment involves a number of critical factors related to

the characteristics of the patient, the type and site of the infection, as well as the pharmacokinetics and/or pharmacodynamics of the antibiotic. Wherever possible, the targeted treatment should result in a simplification of the empirical one. The PP can often choose from several options and should opt for the most effective, safe and cost-effective therapy.

In this sense, the list of antibiotics used as a second option in intensive care units should be diversified, to avoid excessive consumption of empirically used antibiotics, which are mostly beta-lactams. The choice should be consistent with the general guidelines set out by the local committee of antibiotics. It is desirable that the PPs be assisted by an infectious diseases consultant in the process of selecting the best-targeted therapy.

- **Sequential therapy.** A systematic plan for the switch from parenteral to oral antimicrobials with excellent bioavailability, when the patient's condition allows, can decrease the length of hospital stay and is associated with fewer nosocomial infections and lower healthcare costs. Sequential therapy is indicated in a wide spectrum of infections, although the degree of scientific evidence is limited. An early switch to oral antimicrobials is not routinely considered by the PP, usually due to a lack of information and due to previous personal experience. It is important that stewardship programs disseminate the concept of "clinical stabilization" and promote sequential treatment.

- **Length of therapy.** Recommendations on the length of antibiotic therapy are based on empiricism and experience, as evidence from randomized trials is scarce.<sup>13,14</sup> The general view is that the length of therapy in hospitals is excessive. This factor is important in order to reduce bacterial resistance and cost; shortening the duration of treatment is the most effective way to reduce the overall consumption of antimicrobials in a specific area or center. The PPs do not usually consider this problem, unless advised by the specialist consultant or as a result of an adverse effect. During educational interventions by qualified consultants, the best accepted recommendations are usually dose adjustments and oral route switching, whereas the most poorly accepted is treatment retrieval. Some useful concepts, such as the early mobilization of patients and switching to the oral route may contribute to shortening the total length of therapy, and should be emphasized.<sup>15</sup> In addition, the rational use of biomarkers, such as procalcitonin, may help to shorten the length of antibiotic therapy when clinical stability is reached.<sup>16,17</sup>

### Antimicrobial prophylaxis

Surgical site infections (SSIs) represent the second or third most common cause of nosocomial infections (NI), accounting for 14%-18% of the total.<sup>18,19</sup> The use of surgical prophylaxis aims to prevent SSIs, SSI-related morbidity and mortality, reduce the duration and cost of health care and minimize potential adverse effects, including the impact on the patient and the hospital microbiome.<sup>20</sup> The use of antimicrobial prophylaxis is recommended in those surgeries with a high incidence of SSIs (clean-contaminated, preferably), prosthetic surgeries or in surgeries where the development of an SSI can have disastrous consequences.<sup>18-21</sup>

Several studies have evaluated adherence to antimicrobial prophylaxis guidelines. In some surveys, over 90% of physicians recognize its importance and its evidence based value, and confirm their own adherence to recommendations.<sup>22</sup> However, despite increasing evidence of their effectiveness, the use of antimicrobial prophylaxis in this clinical setting is associated with inappropriate timing, selection and excessive duration of treatment. Poor completion rates for surgical prophylaxis recommendations range from 0% to 70%.<sup>23</sup> In a study conducted in thirteen Dutch hospitals, Van Kasteren et al.<sup>24</sup> found that antibiotic choice, duration, dose, dosing interval and timing of the first dose were concordant with hospital guidelines in 92%, 82%, 89%, 43% and 50% of procedures, respectively. Only 28% overall



adherence to guidelines was observed. Other authors have found an excessive duration of antimicrobial prophylaxis in up to 45.2% of procedures and a lack of intraoperative redosing of antimicrobial prophylaxis in 19.8% of procedures. The latter was identified as an independent risk factor associated with increased SSIs.<sup>25</sup>

The factors most commonly associated with the failure of antibiotic prophylaxis in surgery are varied. Simon et al.<sup>26</sup> found that the prescription of antimicrobial prophylaxis by a surgeon as compared with an anesthesiologist (RR: 3.4), a clean-contaminated surgery (RR: 2.2), traumatology surgery (RR: 1.87), digestive surgery (RR: 3.7) and head or neck-related surgery (RR: 11.4) were independent factors associated with non-compliance with guidelines for surgical antimicrobial prophylaxis. In general, the most commonly described factors are the absence of well-defined protocols, the lack of knowledge, miscommunication or disagreement between physicians, logistical problems and a lack of audits.

Finally, we must remark that multiple studies have shown that there is room to improve the adequacy of perioperative antibiotic prophylaxis.<sup>18,27</sup> In most studies, the control indicators recommended by the Surgical Infection Prevention and Surgical Care Improvement Projects were used (PSCIP).<sup>28</sup> In some studies, interventions promoted by the hospitals' pharmacy departments were prioritized.<sup>29</sup> In other studies, after a baseline intervention to identify common practice in certain surgery areas, educational interventions were conducted in the departments involved. These included measures for the development of specific prophylaxis kits for each type of intervention, computerized treatment retrievals, etc.<sup>30</sup>

With current knowledge, the most reasonable way to improve antibiotic prophylaxis is to launch a structured program of improvement with multidisciplinary involvement in hospitals. The development of local guidelines, with appropriate dissemination, educational programs, workshops, audits and a detailed review of all the logistics must be included. Dull et al.<sup>31</sup> accurately described a plan launched in two U.S. hospitals that achieved, within eighteen months, a 100% adherence to perioperative prophylaxis. A multidisciplinary team was formed, following a review of scientific evidence, and consensus guidelines for good clinical practice inspired by the PSCIP recommendations were developed for the selection, timing of administration and duration of prophylaxis. Well-defined strategies designed to facilitate the switch process and to ensure safety were considered in each of the sections. For instance, those responsible for each step of the process were clearly identified, in order to facilitate their involvement.

In summary, antimicrobial prescribing is a complex process involving many prescribers with varying degrees of training, motivation and knowledge of antimicrobial multi-resistance. Choosing the best antibiotic for a particular patient in an empirical or directed way is not easy, and adherence to the recommendations for prophylactic use in real life has proven challenging. Interventions aimed at improving antimicrobial use should consider multiple actions on the fundamental factors of the prescribing process: the prescribers' fears and limitations, the patients and the environment. A consultation with an infectious diseases expert during the prescribing process should be included in antimicrobial stewardship programs for the rational use of antimicrobial drugs.

### Conflicts of interest

EC has accepted grants, speaking engagements and conference invitations from Astellas, AstraZeneca, Novartis, Pfizer and MSD.

LA-R has accepted grants, speaking engagements and conference invitations from Pfizer and MSD.

FG has no conflicts of interest.

JP has received grants for consultancies, conferences, training and research, from Janssen, Novartis, Wyeth, MSD, Pfizer, AstraZeneca, Gilead, GSK, BMS, Roche, Boehringer Ingelheim and Abbott.

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