



# Enfermedades Infecciosas y Microbiología Clínica

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## Scientific evidence and research in antimicrobial stewardship

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### ABSTRACT

#### Keywords:

Antibiotic policy  
Antibiotic stewardship  
Antibiotic use  
Healthcare quality  
Epidemiologic designs  
Clinical research

Evaluating the impact of antibiotic stewardship programs is challenging. There is evidence that they are effective in terms of reducing the consumption and cost of antibiotics, although establishing their impact on antimicrobial resistance (beyond restrictive policies in outbreaks caused by specific antimicrobial resistant organisms) and clinical outcomes is more difficult. Proper definitions of exposure and outcome variables, the use of advanced and appropriate statistical analyses and well-designed quasi-experimental studies would more accurately support the conclusions. Cluster randomized trials should be used whenever possible and appropriate, although the limitations of this approach should also be acknowledged. These issues are reviewed in this paper. We conclude that there are good research opportunities in the field of antibiotic stewardship.

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### Evidencia e investigación científica en la optimización del uso de antibióticos

#### RESUMEN

#### Palabras clave:

Política de antibióticos  
Programas de antibioterapia  
Uso de antibióticos  
Calidad asistencial  
Diseños epidemiológicos  
Investigación clínica

La evaluación del impacto de los programas de optimización de uso de antibióticos supone un reto. A pesar de que hay evidencia de la eficacia de estos programas en la reducción del consumo y coste de los tratamientos antibióticos, establecer su impacto en la reducción de resistencias (más allá de determinadas intervenciones restrictivas en brotes causados por microorganismos resistentes concretos) y en mejorar los resultados clínicos es más difícil. Para poder establecer conclusiones sólidas se necesita, en general, una adecuada definición de las variables de exposición y resultado, el uso de técnicas de análisis avanzadas adecuadas al diseño y estudios cuasi-experimentales bien diseñados. Siempre que sea adecuado y factible debe intentarse realizar estudios aleatorizados de *clusters*, pero las limitaciones específicas de estos deben tenerse en cuenta. En este artículo se revisan estos aspectos, y se concluye que hay buenas oportunidades para la investigación en el área de los programas de optimización del uso de antibióticos.

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### The importance of research in antibiotic stewardship: opportunities and challenges

In recent years, the optimization of antimicrobial prescribing in hospitals in conjunction with parallel initiatives in the community setting has become a very important part of clinical activity in infectious diseases. Thus, in 2012, the Spanish Society of Infectious

Diseases and Clinical Microbiology (SEIMC), the Spanish Society of Hospital Pharmacy and the Spanish Society of Preventive Medicine, Public Health and Hygiene joined forces to release a consensus document on Programs for Optimizing the use of Antibiotics (PROA) in Spanish hospitals.<sup>1</sup> This was just the first step on the challenging path towards the goal of improving the quality of antimicrobial use. The efficacy and safety of antimicrobials should be measured as quality indicators, using both individual and population analyses to reflect their impact on the outcome of infection, the evolution of antimicrobial resistance and their economic impact on the health system.

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The various interventions in any antimicrobial stewardship program may be difficult to implement, because they have to change the long-established attitudes of a large number of professionals. In prevalence studies carried out in Spain, as many as 42% of hospitalized patients were receiving antimicrobials in 2010 and 2011,<sup>2</sup> reflecting the large number of physicians prescribing antimicrobials. At the same time, individual attitudes are difficult to change, because they are based on personal beliefs and behavior, and sometimes on antiquated knowledge. The recommendations of programs directed at optimizing antimicrobial use must be supported by the best available evidence, which comes from well-designed randomized clinical trials, cohort studies, studies of antimicrobial resistance mechanisms and their relationship with antimicrobial use. The recommendations must also be supported by the best possible organization of education and intervention activities and by defining quality indicators for antimicrobial use. These topics are analyzed in the manuscripts of this issue of *ENFERMEDADES INFECCIOSAS Y MICROBIOLOGÍA CLÍNICA*. An important way to support effective programs is by generating new knowledge on all the topics reviewed in this issue, particularly defining the best type of intervention in terms of clinical results and cost-effectiveness.

Infectious Diseases physicians and other clinicians who are experts in infectious diseases and antimicrobial use, microbiologists and pharmacists have the opportunity to contribute to improving their daily work and to general knowledge in the field through research on all the topics mentioned above. A PubMed Advanced Search (accessed April 29<sup>th</sup> 2013) that included the term “antimicrobial stewardship” OR “antimicrobial policy” found 1325 publications between 2001 and 2006, and 2350 from 2007 to 2012. Research in this field presents significant and specific challenges. Among these challenges are the need to develop multidisciplinary and multicenter studies that compare interventions, to carry out powered population studies, to include complementary approaches to answering the various research questions arising from real clinical practice, to explore the problem of antimicrobial resistance, to evaluate education programs, and to determine the sustainability of various interventional approaches.

### Scientific evidence for the effectiveness of activities aimed at improving the use of antibiotics

The fundamental goals of any antimicrobial stewardship program (ASP) are to monitor and direct antimicrobial use in healthcare institutions, thus providing a standard evidence-based approach to judicious antimicrobial use.<sup>2-4</sup> These goals should form part of the institutional strategies of hospitals and are greatly appreciated by professionals, administrators and society at large.<sup>5,6</sup>

The primary objectives of an ASP can be summarized as follows: 1) to improve the clinical outcomes of patients by reducing potentially adverse drug events (such as *Clostridium difficile*-associated disease [CDAD]), morbidity, mortality, length of hospitalization, and healthcare-related costs; and 2) to prevent and/or reduce antimicrobial resistance.<sup>1,6,7</sup> These objectives are achieved through improvements in the quality of antibiotic use and reductions in exposure to antimicrobials.

The relationship between inappropriate antimicrobial consumption and the development, persistence and spread of antibiotic resistance has been evaluated in numerous published scientific papers. It is clear, however, that the factors associated with antibiotic resistance are complex, often corresponding to multiple interrelated phenomena, which makes it difficult to attribute a significant change in antibiotic resistance exclusively to the particular ASP intervention. There are also significant methodological problems involved in analyzing the impact of ASP from a causal point of view.<sup>8</sup> In many interventions, the appropriate use or restriction of certain antibiotics is associated with widespread practices of infection

control, such as promoting hand hygiene among staff or preventing transmission, which provide an extra benefit of ASP interventions. On the other hand, if the ASP is not accompanied by adequate infection control standards, transmission of some resistant pathogens that are less influenced by antibiotic use may continue despite an improvement in the quality of prescriptions. However, numerous published experiences have shown that the application of an ASP can help to prevent or control the spread of some drug-resistant organisms, especially Gram-negative rods or glycopeptide-resistant enterococci<sup>9-14</sup> and *C. difficile*.<sup>15-18</sup>

The impact of appropriate antimicrobial use on improving the clinical outcomes of patients may seem obvious, yet the causal relationship is also difficult to prove. There have been numerous studies on the effectiveness of ASPs on clinical and microbiological outcomes in patients with bacteremia or Gram-negative rod infections. The appropriate use of antimicrobials has also been associated with a marked reduction in drug-related adverse events, particularly *Clostridium difficile*-associated disease (CDAD).<sup>9,15,19,20</sup> The most relevant marker for this important objective of an ASP is a reduction in mortality as a direct result of improved patient care and outcomes. The majority of the studies, however, were not designed to evaluate this indicator. To obtain strong evidence for this association, randomized, controlled multicenter studies are needed. Because ASPs are usually aimed at reducing antimicrobial exposure, it is also equally important to demonstrate that they are not associated with deleterious effects, which have been shown in various studies.<sup>21</sup>

A recent systematic literature review analyzed 66 studies of interventions (randomized controlled clinical trials, controlled before-and-after studies and interrupted time series studies), designed to improve antibiotic prescribing practices for hospital inpatients. The objective of the review was to assess the effectiveness of the interventions and to evaluate their impact on reducing the incidence of antimicrobial resistant pathogens or CDAD and clinical outcome. Fifty-one (77%) of the studies showed significant improvements in at least one of the objectives of the predetermined outcomes. In 60 studies, the aim was to reduce prescribed antibiotic treatment; 47 of them assessed a “drug outcome”, and 38 detected a significant improvement (81%); 16 studies evaluated a “microbiological outcome”, of which 12 (75%) improved significantly; in 9 studies, a “clinical outcome” was evaluated, in which only 2 (22%) showed a significant deterioration and 3 (33%) showed a significant improvement. The authors concluded that intervention programs for improving antimicrobial prescribing in hospitals are successful and can help reduce or control antibiotic resistant organisms and hospital-acquired infections, although the impact on variables associated with clinical outcomes is more moderate and difficult to assess.<sup>22</sup>

### Interventions that can be measured, confounders, and endpoints

Stewardship programs, like all quality programs, must be monitored using quality indicators that can be broken down into structure, procedure and outcome indicators. These indicators can also be used as endpoints for research studies. Changes in antimicrobial consumption, which is regarded as a procedure indicator, is one of the most common quality indicators measured in studies of stewardship programs. Consumption should be measured using generally accepted units, the most widespread of which is the defined daily dose (DDD). However there are others, such as the prescribed daily dose, which can be used as an alternative or a complement.<sup>1</sup> They should be calculated with a denominator such as 100 or 1000 patient-days and can be useful for benchmarking, although the challenges of case-mix differences are far from being resolved.<sup>1,23</sup> Other procedure indicators include the rate of adequate empirical therapy, the rate of adequate duration of antimicrobial therapy and the rate of de-escalation or optimized therapy (Table 1).

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