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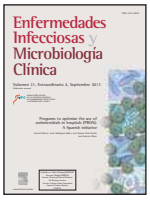

How to assist clinicians in improving antimicrobial prescribing: Tools and interventions provided by stewardship programs

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ABSTRACT

In the last decade, there has been an exponential increase in the microorganisms resistant to antimicrobials and a significant increase in the cost of these types of drugs. This phenomenon has increased interest in the development of interventions for counseling on and control of the use of antimicrobials, referred to as *stewardship programs*. In this article we review, from various points of view, the tools that have been developed with this purpose. First, we highlight the value of locally adapted guidelines and clinical pathways as an essential part of the operational process. Then we emphasize the importance of the relationship between microbiologists and clinicians for the accurate transmission of the information provided by blood cultures to make the most appropriate choice of antimicrobial for the patient's treatment. We also review the computerized tools that have facilitated the correct use of antimicrobials according to the controls established by the departments of pharmacy. Based on the previous tools, some programs based on "bedside recommendations" provided by multidisciplinary teams have been developed for optimizing the rational use of antimicrobials (PROA programs). Finally, we comment on the peculiarities of the programs targeting antifungals that have been developed in recent years.

Cómo ayudar a los clínicos a mejorar la prescripción de antimicrobianos: herramientas e intervenciones proporcionadas por los programas de optimización

Palabras clave:
PROA
Programas de optimización
Antimicrobianos
Antifúngicos

RESUMEN

En la última década se ha producido un aumento exponencial de los microorganismos resistentes a antimicrobianos y un notable aumento en el coste de estos fármacos. Esto ha hecho que aumente el interés por la aplicación de diferentes intervenciones de asesoramiento y control del tratamiento antimicrobiano. En este artículo se revisan, desde diferentes puntos de vista, las herramientas que se han desarrollado con este propósito. En primer lugar destacamos la importancia de las directrices y de las guías clínicas, adaptadas localmente, como pieza esencial de este tipo de programas. También destacamos la importancia de la relación entre microbiólogos y clínicos para una rápida transmisión de la información obtenida del resultado de los hemocultivos al clínico responsable para la adecuación del tratamiento antimicrobiano empírico. Se revisan las herramientas informáticas que han facilitado el empleo correcto de los antimicrobianos de acuerdo con el control establecido por los servicios de farmacia. Asentados sobre las herramientas citadas previamente se han desarrollado programas centrados en recomendaciones "a pie de cama" provistos por equipos multidisciplinarios, con el propósito de optimizar el tratamiento antimicrobiano (programas PROA). Por último se comentan las peculiaridades de los programas dirigidos al control de antifúngicos que se han desarrollado en los últimos años.

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Introduction

In the last decade, there has been an exponential increase in the microorganisms resistant to antimicrobials and a great increase in the cost of these types of drugs. This phenomenon has increased interest in the development of interventions for counseling on and control of the use of antimicrobials. In this article we review, from various points of view, the tools that have been developed with this purpose.

Programs based on guidelines and clinical pathways: The cornerstone of any antimicrobial stewardship program

The cornerstone of any effective program for optimizing the rational use of antimicrobials (PROA), also referred to as an antimicrobial stewardship program (ASP), is education using recognized professional sources, clinical pathways, practical guidelines and feedback to prescribers regarding their antimicrobial usage patterns.[1-4] Education is an essential part of the operational process.[5] The operational process refers to the actual implementation of a PROA at the desired level in a community or hospital. This process includes the successful implementation of guidelines and formularies; strategies to restrict the use of broad spectrum agents; measures that reduce the use of antibiotics or promote the use of appropriate antibiotics by way of de-escalation; parenteral to oral conversion strategies; and targeting redundant prescribing.[6] The PROA should include specific objectives based on measurable indicators and activities aimed at improving the use of antimicrobials, primarily through educational activities and interventions designed to train prescribers rather than to solely enact restrictive measures. Education on antimicrobial usage in healthcare facilities remains an important institutional function and underscores the need for formalized programs, especially in those clinical departments where 50%-75% of the patients receive prophylactic or therapeutic antimicrobials, and where studies have demonstrated that up to 50% of this use is inappropriate.[7]

Guidelines and clinical pathways are now available for several common infections, but the impact of these guidelines on prescribing is difficult to measure accurately. Nonetheless, a PROA could promote the use of clinical guidelines. The use of guidelines is more likely to be successful if they are tailored to match the local susceptibility patterns, and physicians are more likely to have confidence in the guidelines if they are aware of what these patterns are. Moreover, local guidelines must be periodically reviewed to take into account any changes in the susceptibility pattern of organisms. Practice guidelines are known to reduce antimicrobial usage, but studies have demonstrated that incorporating diagnostic strategies in the guidelines along with criteria for admission and discharge would assist in the overall implementation of guidelines and lead to better outcomes.[8,9] The guidelines also go hand in hand with systematic prior approval programs and automatic stop orders. Such hybrid strategies have been successfully implemented in American and Canadian hospitals.[10]

One of the advantages of guideline development as part of a PROA is that it provides the opportunity to incorporate many thought leaders within a hospital to develop hospital- or network-specific algorithms. Guidelines can use national recommendations but should incorporate local trends in antimicrobial resistance and hospital-specific targets for decreased use. Ibrahim et al.[11] demonstrated that the implementation of treatment guidelines for ventilator-associated pneumonia during a 2-year period doubled the rate of appropriate initial therapy, while decreasing the length of therapy and the recurrence of ventilator-associated pneumonia. Other studies of guidelines for ventilator-associated pneumonia have shown similar results.[12,13]

The broadcast and local implementation of clinical guidelines based on those developed by scientific societies can aid in the choice of the best antibiotic prescription. A great majority of studies have found better patient outcomes when the empirical treatment recommended in these guidelines has been applied, including cases of community-acquired pneumonia[14-16] and meningitis.[17] However, a recent study showed poorer results in cases of severe nosocomial pneumonia at risk of multi-resistant pathogens;[18] this study suggests that it is necessary to consider the applicability of the clinical guidelines depending on the local epidemiological context.

Although there are national clinical practice guidelines for many types of infection, successful clinical practice involves the careful consideration of local epidemiology, local formulary, and the clinical and epidemiological features of the individual patient. Furthermore, clinical decision-making must sometimes occur in the face of absent or ambiguous national guidelines. Therefore, institution-specific recommendations for commonly encountered, high-priority clinical syndromes can be an especially valuable resource provided by a PROA/ASP.

In 2007, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published joint guidelines for the development of programs to enhance antimicrobial stewardship in the institutional setting.[2] These guidelines provide the metrics for developing a customized program and may serve to facilitate discussions with administrators and key individuals whose support is needed to set up a program. Endorsement from the Society of Infectious Diseases Pharmacists, the Alliance for the Prudent Use of Antimicrobials, the Centers for Disease Control and Prevention and the World Health Organization emphasizes the common concern for antimicrobial stewardship, and global interest is developing.[19,20]

Several Spanish scientific societies have recently published a consensus document that defines the objectives, implementation measures, evaluation and feedback systems of programs such as the PROA guidelines.[21] The primary goals are to improve the clinical results of patients with infections, to minimize the adverse events associated with the use of antimicrobials (including the emergence and spread of antibiotic resistance) and to ensure the use of the most cost-effective treatments. The document also provides a set of recommendations for the implementation of these programs in Spanish hospitals. Multidisciplinary antibiotic teams should be formed under the auspices of the Infection Committees.

Perhaps more interesting is the development by each hospital of protocols for prophylaxis and empirical or directed antibiotic treatment. Unlike clinical practice guidelines, these protocols are more prescriptive or standardized in character and do not need to include recommendation levels based on scientific evidence. To implement these, one can use the guidelines of scientific societies, but a profound understanding of the local epidemiology is also essential. Multidisciplinary involvement is important, including the participation of all specialists involved in the process order, to promote its acceptability and subsequent monitoring. These protocols should also be regularly updated and adapted to changing patterns of resistance, including possible new therapeutic possibilities. It is recommended that each hospital develop its own specific protocols of empirical and directed treatment against infectious processes, which includes almost thirty infectious syndromes in some PROA programs. Protocols should include first-line treatment and at least one alternative treatment, taking into consideration frequent and special or individual situations, such as renal failure, hepatic dysfunction, beta-lactam allergy and pregnancy. In addition, the targeted therapy and duration should be considered. In the case of ventilator-associated pneumonia, there is evidence that the development and implementation of hospital protocols is associated with an increase in the adequacy of the empirical therapy and a reduction in the duration of antibiotic treatment, but none of these studies demonstrated a reduction in mortality.[12,22]

Institution-specific guidelines assist in the streamlining and standardizing of antibiotic decision-making and provide a basic resource for decision algorithms, one-to-one education and discussion between program team members and front-line providers. Example topic areas for institution-specific guidelines that may be targeted by a PROA include surgical prophylaxis, community-acquired pneumonia, urinary tract infection (UTI) and asymptomatic bacteriuria. Institutions can also create treatment pathways and algorithms to assist front-line clinicians with antimicrobial selection, dosing and duration for scenarios targeted by institution-specific guidelines. Empiric antibiotic choices for commonly encountered diagnoses, such as community-acquired pneumonia,[9] are especially amenable to this type of intervention.[23,24] Some computerized physician order entry systems provide link-out capabilities for antimicrobial stewardship decision support materials. Order entry itself can also incorporate specific elements, such as a predetermined stop date.[25] Information technology (IT) delivery systems provide an exciting area for growth and innovation in antimicrobial stewardship clinical decision support.[26] Personal digital assistant or smartphone applications and web-based systems create outlets for disseminating guidelines or local antibiograms through convenient, real-time media. As in the period before the antimicrobial has been prescribed, electronic systems can be developed to prompt providers with treatment recommendations in the period after prescription based on local patient and microbiological data.[25] Validated decision support systems have often led to improved compliance with practice guidelines, fewer adverse antimicrobial related reactions and improved antimicrobial choice and dosing.[27,28] A PROA can provide several different types of clinical decision support for clinicians, including protocols for de-escalation and recommendations for length of therapy. In some hospitals, appropriate uses of antimicrobial agents have been facilitated by the implementation of clinical pathways generated by an electronic medical record system.[29]

Programs based on the information provided by blood cultures: The importance of the microbiologist-clinician connection

Bloodstream infections (BSI) remain a leading cause of morbidity and mortality. Overall in-hospital mortality rates range between 12% and 21% in recent studies, but within specific populations there may be wide variability. The variables influencing mortality rates in bacteremic patients include the following: the intrinsic features of the patient (e.g., age, underlying diseases, immunosuppression and the severity of acute disease); the primary site of infection (e.g., urinary and biliary tract-related bacteremia are usually associated with a lower mortality rate than those that are pneumonia-related); the microorganism (e.g., *Staphylococcus aureus* bacteremia reaches higher mortality rates, between 20% and 40%); and presentation with sepsis, severe sepsis or septic shock.[30]

Another important variable influencing mortality rates is the treatment adequacy for BSI. As many as 40%-60% of all patients with BSI receive inadequate empirical therapy and, even after the final microbiological report is issued, 8%-20% of patients with BSI still receive inadequate antimicrobial treatment.[31,32] Many authors have compared sepsis-related mortality among patients given appropriate antibiotics with that among patients given inappropriate treatment, and the relationship of reduced mortality rate to appropriate antibiotic therapy was well documented in most of these studies.[32-34] While some authors did not confirm these results, they observed that the duration of hospitalization was longer and that charges for a given hospital stay increased with inappropriate therapy.[33,34]

Consultation with infectious disease specialists (IDS) has been shown to reduce the mortality of patients with BSI. Thus, the CDC and the IDSA, in conjunction with other organizations, have recently recommended consultation with IDS for the treatment of serious infectious diseases as well as the implementation of institutional programs providing advice on empirical antimicrobial treatment decisions, either directly through communication with clinicians and/or indirectly through the creation of institutional guidelines.[2,35] One of the advantages of using local guidelines is the ability to reach out to frontline professionals who are not IDS.[35] Epidemiological data are essential for the design of locally adapted guidelines that increase coverage against the most prevalent organisms, including those producing emergent antimicrobial resistance mechanisms.[30,35] The implementation of bacteremia programs requires a multi-pronged approach with multidisciplinary teams involving IDS and clinical microbiologists. The first goal is to work with health care practitioners to help each patient receive the most appropriate empirical therapy.[2,35]

Blood culture results are key to optimizing antimicrobial therapy for BSI, which emphasizes the potential benefit of applying testing methods involving rapid microbial detection. Even a rapidly reported gram stain result can have a dramatic impact on improving antibiotic therapy.[30,31,36] Several authors have shown that the active reporting of the gram stain findings immediately after the detection of microbial growth in the blood culture considerably increased the proportion of patients who received appropriate treatment.[31,36] In their study, Bouza et al. found that the active notification of the gram stain results, with written and oral reports and recommendations at bedside, led to suggestions regarding the alteration of therapy in 50% of cases. This author clearly shows that a delay until the final microbiological report of the blood culture becomes available is an independent risk factor for infection related mortality, with a risk of death 1.2 times greater each day until definitive microbiological information is available.[31] In one other prospective observational study of the management and outcome of bacteremia, Byl et al. showed the favorable impact of the IDS and the microbiology results on the quality of empirical and documented antimicrobial therapy and on the improved use of antimicrobial drugs.[36] Based on these results, an adequate intervention to meet the basic needs of a comprehensive bacteremic program include an active reporting of molecular results or gram stain results immediately after the detection of microbial growth in the blood culture, together with active recommendations for antibiotic therapy (e.g., drugs, doses, route) and other aspects of management (e.g., catheter removal, surgical drainage).[30,31,36]

Other complementary interventions include a post-prescription review and follow-ups, including tailoring antibiotics to subsequent definitive microbiological results, changing antibiotics from broad to narrower-spectrum (de-escalation), shortening the duration of antibiotic therapy and switching from intravenous to oral therapy. The rapid determination that a blood culture will not yield bacteria may also be used to shorten courses of empirical therapy and, in turn, reduce the risk of adverse events and the risk that resistant organisms will be selected if and when bacteremia does occur.[35] An added benefit of the programs is that they generally demonstrate cost savings because fewer doses of antibiotics are used and less expensive antibiotics are chosen.[2,35]

The success of these programs depends on the regular monitoring and evaluation of the outcomes of interest, namely the impact of these activities on the performance of blood cultures, the classification of BSI, the adequacy of empirical treatment, early source control, the adequacy of treatment after early reporting, definitive therapy, the switch to oral therapy, the duration of antimicrobial therapy, BSI mortality rates and cost savings. Quality standards in management need to be defined and applied locally, with an analysis of results to decide on interventions aimed at improving the management and the prognosis of patients with BSI.

Programs based on computerized programs: The pharmacist-clinician connection

Antibiotic treatment is initiated in many cases as empirical therapy. Appropriate treatment is critical in patients with

bloodstream infections and for patients hospitalized in a medical intensive care unit. However, we know that 30%-50% of patients are given inappropriate empirical antibiotic treatment.[37,38] The inappropriate use of these antimicrobials can contribute to the emergence of antibiotic-resistant organisms. Antimicrobial stewardship is important to address the problem of multi-resistant pathogens.[39,40] In several studies, computerized physician order entry (CPOE) has been shown to reduce medication errors.[37,41,42] During the last few years, healthcare organizations have been increasingly turning to clinical decision support systems (CDSS), which provide clinicians with patient-specific recommendations to aid clinical decision-making.

CDSS is any software that directly aids clinical decision making by matching the patient's characteristics to a computerized knowledge base for the purpose of generating patient-specific assessments or recommendations that are then presented to clinicians for consideration. These systems have been associated with improved antibiotic prescribing, compliance with clinical protocols and guidelines, reduction in total antibiotic use, reduced antimicrobial costs, shorter hospitalizations and a reduction in antibiotic-resistant organisms.[37,39,41]

Antibiotic CDSS may function as non-integrated (standalone) or integrated information systems. Integrated antibiotic CDSS are embedded within other applications such as pharmacy dispensing systems and CPOE. The use of combined CPOE and CDSS has demonstrated a substantial reduction in medical errors.[37,41] Some examples of these systems include alerts to critical laboratory results, alerts to discrepancies between prescribed antibiotics and culture susceptibility, drug interactions, CPOE with links to local protocols or electronic protocols, risk calculators and information on how to contact the CDSS team.[7,43]

Computerized systems have also been used to control antimicrobial prescriptions and costs. In a before-and-after study, the gradients in the use of third- and fourth-generation cephalosporins, glycopeptides, carbapenems, aminoglycosides and quinolones all fell after deployment, whereas extended-spectrum penicillin use increased.[44] In one hospital, simply adding the antimicrobial cost information to the antimicrobial susceptibility data resulted in a decrease in average monthly antimicrobial expenditures of $7,636 (17%).[2] In another hospital, during the first year of the CDSS implementation they observed a reduction of $181,000 in antibiotic expenditures.[41] In another study, a total of 2838 Gram-negative organisms were isolated from clinical sites from ICU patients during the study period. There was significant improvement in the susceptibility of *Pseudomonas* to imipenem 18.3%/year (95% confidence interval [CI]: 4.9–31.6; P=.009) and gentamicin 11.6%/year (95%CI: 1.8–21.5; P=.02) compared with the pre-intervention trend.[39]

Regarding empirical therapy, a computerized antimicrobial guidance program was developed based on the previous 5 years of laboratory culture data, augmented by knowledge from experts on infectious disease. The program was designed to assist physicians with the targeting of empiric antimicrobials for hospitalized patients by tracking pathogenic bacteria and their evolving antimicrobial resistance profiles. Physicians initiated effective empiric therapy in 150 of the 226 cases, for an effectiveness rate of 66%. The computer-guided therapy was effective in 195 of the 226 cases, for a rate of 86%.[45] In the randomized trial TREAT, these systems significantly improved the probability that the patients received appropriate antibiotics (odds ratio [OR]: 1.48; 95%CI: 1.03–2.11).[46,47]

In conclusion, to assist physicians with the appropriate choice of antibiotic therapy, investigators have developed computerized antibiotic decision support tools that query large databases of microbial cultures and resistance data and provide accurate suggestions for antibiotic therapy.

Intervention programs based on the recommendations of a multidisciplinary team

The primary aim of a PROA should be to start antibiotics as early and with as broad a spectrum as needed, according to severity and clinical suspicion, but also to reduce the spectrum and duration of antibiotic treatment when microbiological data and clinical course allow it, which is the difficult part of these programs. Previous experiences[48-51] and guidelines[2,21] from stewardship programs have been published. Empiric antibiotic treatment should follow local guidelines; these local guidelines should be evidence-based, relevant to the local healthcare setting and take into account local antibiotic resistance patterns. The development of these guidelines is another one of the PROA duties, in close collaboration with the infectious and pharmacy commissions.

These activities should be structured around a multidisciplinary team that should include an infectious diseases physician and a clinical pharmacist with infectious diseases training, at a minimum. According to hospital complexity and implication in the PROA, the team could also have a clinical microbiologist, an information specialist, an infection control specialist and a hospital epidemiologist. The PROA must always have the approval and support of the institution's authorities through commissions on infectious diseases and quality standards. PROA also needs the acceptance of all the clinical services that are going to be audited by the antibiotic team. One way to implement this is to include PROA objectives as a specific care quality objective of the service when negotiated with hospital managers. Before starting any PROA activities, an adequate diffusion and design of the activities should be undertaken. Special programs adapted to special services such as the intensive care unit could be designed in accordance with attending physicians.

One of the targets of this type of program is the streamlining or de-escalation of therapy. An appropriate empirical antibiotic treatment used at the beginning of an infectious episode, in accordance with local guidelines, could conflict with good stewardship to promote judicious use because continuing therapy that is excessively broad contributes to the selection of antimicrobial-resistant pathogens. This conflict can be resolved when microbiological culture results become available and when streamlining or de-escalating the antibiotic treatment to a targeted one of the narrowest reasonable spectrum is possible, taking into account its foci and penetrability. This can be applied to those infection episodes that are monomicrobial, such as primary or catheter-related BSI, UTI, meningitis and pneumonia. De-escalating when the culture results are negative is also possible, based on the clinical criteria and suspected foci.

Another frequent target of PROA is the conversion of parenteral to oral treatment. Antimicrobial therapy for patients with serious infections requiring hospitalization is generally begun with parenteral and empirical therapy, but as the clinical course improves, this first regimen can be switched to target treatment in accordance with microbiological data, as discussed previously, and change to an oral route, since multiple antimicrobials have good oral bioavailability. This change can result in a reduction in the length of hospital stay, health care costs and nosocomial complications due to intravenous access. The clinical criteria required are adequate oral tolerance and clinical stability. Antimicrobials such as fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole and voriconazole allow a switch to the oral route due to good bioavailability. Although this measure could be simple to implement, previous negotiation with the clinical team is always recommended.

Intervention is also possible over the duration of therapy. The duration of antibiotic treatment should be the minimum possible to obtain complete healing with the lowest risk of recurrence; this requires individualization of the decision according to each patient's

circumstances. Attempting to shorten the duration of antibiotic treatment calls for more dialogue with the attending physician before implementation, but increasing evidence and clinical guidelines can help with the decision. Before making the decision to stop antibiotic treatment, the proper evaluation of foci control, the implication of pathogens with high probability of recurrence such as *S. aureus* or *Candida* spp, and any other factor such as immunosuppression or prosthetic material that could predict recurrence should be taken into account. There is enough evidence to shorten the duration of treatment in several clinical entities; for example, non-complicated community-acquired pneumonia can be treated for 5 days if the patient is afebrile and has hemodynamic stability.[52] Ventilator-associated pneumonia not produced by non-fermenting gram-negative bacilli can be treated for as short as 7-8 days.[53] There is also experience in short treatments for exacerbation in Chronic Obstructive Pulmonary Disease,[54,55] non-complicated pyelonephritis[56] and catheter-associated UTI.[57]

Optimal antibiotic treatment is not only related to choosing the right drug but also taking into account the proper dose for the patient (e.g., age, weight, renal and hepatic function, plasma levels of proteins and albumin, volume of distribution), the type of infection (e.g., meningitis, endocarditis, prosthesis-related) and the causative organism itself. Pharmacokinetic (PK) and pharmacodynamic (PD) issues are also an important part of stewardship programs. For instance, taking into account PK/PD parameters, beta-lactams should be administered in prolonged infusions because their activity is related to the time that the drug concentration remains greater than the MIC, whereas the administration of aminoglycosides is preferable in a single dose because they are concentration-dependent agents.

New tools and new targets in antimicrobial stewardship: Programs targeting antifungals

The high cost, the risk of toxicity and interactions, and the subtle differences among many antifungals are good justifications for the development of antimicrobial stewardship programs targeting antifungals.[58] However, published experience with these intervention programs is scarce.

Some observational studies have been published. In 1996, Gutiérrez et al. communicated the results of a retrospective study involving 74 patients and 115 antifungal treatments in a British hospital.[59] Most of the antifungals were prescribed for the treatment of *Candida* infections. They found that 40% of the regimens were "unconventional," primarily because of the duration or indication of the treatment, according to "conventional practice." There was no intervention in this study.

More than a decade later, in 2008, Sutepvarnon et al.,[60] reported the results of a prospective observational study developed in a tertiary care hospital in Thailand. They found 42 out of 57 (74%) patients had been given inappropriate antifungal treatment. The suitability of the treatment was established according to the recommendations of a textbook on infectious diseases. The urinary tract as the site of isolation was a statistically significant risk factor for inappropriate treatment (P<.001), whereas consultation with an infectious disease specialist was associated with appropriate antifungal prescription (P<.001). Inappropriate prescriptions involved treatment with fluconazole in 64% of the cases and amphotericin B in 31% of the cases. The reasons detected for inadequate prescriptions were the following: treatment considered unnecessary (31%); lack of renal dose adjustment (29%); inappropriate dose or duration (7%); and other (33%). The authors emphasize in their conclusion the importance of educational interventions to improve these results.

Another observational and retrospective study developed in France was published in 2012.[61] The analysis of the prescription for antifungals was restricted to the intensive care units and the oncology and hematology wards. This included 199 prescriptions for 133 adult patients. Fluconazole accounted for 67% of the prescriptions. The indication and dosage were found to be inappropriate in 22% and 21% of the cases, respectively, and "debatable" in 13% and 17% of the cases, respectively. As a result of this study, a recommendation was made for a consultation with a physician with expertise in these types of infections in any case of invasive fungal infection within that hospital.

To the best of our knowledge, only two prospective studies reporting the results of an antifungal stewardship program have been published. The first was developed in the Thai hospital cited above; the prescriptions and expenses for antifungals targeting *Candida* were compared in the 18 months before and after the implementation of an educational and stewardship program.[62] A 59% reduction in the prescription of antifungals and a significant reduction in inappropriate prescription (from 71% to 24%) were achieved. Total cost savings were US$31,615 during the 1.5 year post-intervention period.

One study has been published describing a stewardship program targeting different families of antifungals (amphotericin B, azoles and equinocandins) used for the prevention and treatment of infections by both molds and yeasts.[50] In this prospective study, the prescriptions and expenses of antifungals during the development of a 12-month non-compulsory stewardship program were compared with those of the previous year. The program was based on face-to-face recommendations to the prescribing physician after a thorough review of every case (only 1% of the recommendations were not accepted). In this study, a change was recommended in 29% of the reviewed treatments. There was a 32% reduction in the prescription of intravenous voriconazole, an 8% increase of oral voriconazole, a 20% reduction in caspofungin (the only included equinocandin) and a 13% increase in the prescription of liposomal amphotericin B. There was an 11.8% reduction in the expenses for antifungals when compared with the previous year (net savings US$370,681.78). A significant difference was not detected between both periods regarding the incidence of candidemia, the percentage of persisting/relapsing candidemia, the incidence of filamentous fungal infections or the mortality of patients with this type of fungal infection. The authors highlight the importance of antifungal stewardship programs, of personal recommendations, of microbiological data as a measure of the quality of care provided and the possibility of a reduction in the adverse effects of antifungals when the study was developed.

A prospective study developed in another Spanish hospital has been recently reported, targeting all the families of antifungals.[63] This program was based on a "bedside intervention approach." Antifungal treatments were susceptible to optimization in 54% of the cases. De-escalation in the context of empirical treatment was one of the main interventions in this study. The intervention saved a mean of €25,000 per month.

As has been described for antibiotic stewardship programs, the challenge for programs targeting antifungals is to actively maintain them for long periods of time.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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