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Infection Prevention and Safety in Low and Middle Income Countries (AC Barossy, Section Editor)

Antifungal Stewardship in Low- and Middle-Income Countries

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Abstract

Purpose of review Antifungal stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antifungals by promoting the selection of the optimal antifungal drug regimen, dose, duration of therapy, and route of administration.
Recent findings The high mortality associated with invasive fungal diseases (IFDs), combined with suboptimal diagnostic tools, has driven the overuse of antifungal drugs. High drug costs and the toxicities of antifungal agents are the principal rationale for antifungal stewardship, while antifungal resistance is an emerging but less prevalent issue.
Summary This review assesses the situation of antifungal stewardship in low- and middle-income countries and provides basic tools for the development of antifungal stewardship (AFS) programs.

Introduction

Antimicrobial stewardship (AMS) is defined as a program with coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents, including antibacterials, antifungals, antivirals, and antiparasitics, by promoting the selection of the optimal antimicrobial drug regimen, including dose, duration of therapy, and route of administration [1••]. Antifungal stewardship (AFS) refers to a program or series of interventions for monitoring and directing antifungal (AF) use at a healthcare institution. These agents have been largely neglected, and the few published audits of antifungal drug use demonstrate clear deficiencies in prescribing behavior [2•]. The main problems are poor compliance with guidelines and a reluctance to de-escalate therapy when a seriously ill patient is improving on broad-spectrum treatment. In this sense, the main solutions for achieving a high level of quality in antifungal prescribing are on the basis of better mycological diagnosis and conformation by multidisciplinary teams of AFS [2•].

In the developing world, the use of antifungal drugs poses a daily challenge for professionals of many different specialties. Clinical manifestations of invasive fungal infections (IFI) may be non-specific, diagnostic tests for fungal diseases are often not done or not available, and many times antifungal drugs are not available [3]. This review will assess the situation of antifungal stewardship in low- and middle-income countries and provide basic tools for the development of antifungal stewardship (AFS) programs.

The importance of antifungal stewardship

The main reasons for developing AFS are the emergence of fungal resistance, the lack of access to more effective antifungals, the toxicity, and the cost of drugs.

The range of fungal pathogens along with the population at risk continues to expand [4••]. This is owing to the widespread adoption of aggressive immunosuppressive therapy among certain patient populations (e.g., chemotherapy, transplants) and the increasing use of invasive devices such as central venous catheters (CVCs). The use of new immune modifying drugs has also opened up an entirely new spectrum of patients at risk of IFIs.

Invasive fungal infections are associated with unacceptably high mortality rates (around 40%), and more than 90% of all reported fungal-related deaths result from species that belong to one of four genera: *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis* [4••]. Among the main reasons for IFI mortality are late diagnosis with a consequent delay in treatment and inappropriate selection of antifungal or an inappropriate dose.

Inappropriate antifungal use has contributed to the global increase in antifungal resistance and has played a role in the shift in the etiology of invasive fungal infections. In one study, antifungals were unnecessary in 16% of cases. Inadequacies in other aspects of antifungal prescription were drug selection, 31%; dosing, 16%; no switch from intravenous to oral administration, 20%; no adjustment after microbiological results, 35%; and length of therapy, 27% [5].

Data from several studies strongly suggest that agricultural azoles are responsible for medical treatment failure in azole-naïve patients in clinical settings [6]. *Candida glabrata* resistance may exceed 15% in some countries. *C. auris* is an emerging healthcare-associated pathogen associated with high mortality, and its antifungal resistance affects three continents [7, 8]. Breakthrough candidemia on echinocandins therapy and prophylaxis has been documented

in patients with prolonged use [9]. Triazole resistance in *Aspergillus fumigatus* has been described in both azole-naïve and azole-exposed patients.

Moreover, overuse of antifungals may also lead to higher toxicity associated with unnecessary medication exposure [10••, 11••].

Many regions in the world do not have some antifungals available for the treatment of invasive fungal infections. Approximately 481 million people in the world do not have access to amphotericin B and 5 fluocitocyne [4, 11••, 12].

Cost is one of the principal justifications for ASF. Studies of cost have reported that antifungal drugs contribute between 4 and 15% of the total treatment cost of patients with IFDs [12–14].

Differences between antibiotic stewardship and antifungal stewardship

The objectives of AMS programs are to reduce inappropriate use, improve results, reduce toxicity and resistance, and achieve a good cost-effectiveness ratio. In practice, antibiotics stewardship refers mainly to the use of antibiotics and AFS to antifungals. There are some differences between AMS and AFS programs such as the following [15]:

- AFS is mainly used in secondary or tertiary care hospitals, while AMS is used at all levels of complexity of the health system
- Fewer medical specialties participate in the AFS than in AMS, as for example, hemato-oncology, organ transplantation, critical care, gastrointestinal surgery, and respiratory.
- The antifungal treatments and prophylaxis are more prolonged than the antibacterial treatments.
- The pharmacokinetics of antifungals is more complex. Antifungals have more interactions and contraindications than antibiotics, and therapeutic drug monitoring is indicated for some azoles (voriconazole, posaconazole). In a recent study, a total of 83% of hospitalizations with posaconazole use, 61% with itraconazole use, and 82% with voriconazole use included the use of at least one drug that resulted in severe drug–drug interactions [16].

Barriers for the implementation of AFS programs

In the world, one of the main barriers to developing an AFS program is the knowledge of the prescribers about IFI management [15]. In a study about the knowledge of prescribing physicians, the mean score of adequate responses (± SD) was 5.8 ± 1.7 out of 10 points [17].

Access to modern diagnostic tools is frequently limited in developing countries [18, 19]. Microbiology labs at institutions may not be able to rapidly test and determine susceptibilities for fungal isolates. Therefore, clinicians are limited to distinguishing drug-resistant infections based only on clinical suspicion or comfort with de-escalating to a narrower spectrum of antifungals [20].

A recent study of patients with candidemia reported that less than 40% of echinocandin-treated patients with fluconazole-susceptible isolates were de-escalated to fluconazole and only 50% of patients with less severe disease or *C. albicans* underwent de-escalation [21].

Additionally, there is a lack of access to rapid, sensitive, and specific fungal diagnostics to facilitate accurate and timely diagnosis, leading to excessive empiric prescribing. *Histoplasma* spp. antigen, galactomannan, and b-D-glucan are not commercially available in most Latin American centers [18, 19, 22, 23]. There is a 20% increase in mortality of invasive candidiasis if therapy is delayed by > 12 h [24].

A goal is increase the number of clinical mycologists and decrease cost, time to result, and requirements for sensitivity and specificity [25].

Main elements to implement an AFS in low- and middle-income countries

Leadership commitment

An AFS intervention requires monitoring of other physicians' prescriptions, so empowerment by, and full support from, the hospital authorities are essential (hospital director, infection control commission, and heads of the main involved departments) [26].

Multidisciplinary team

The first step in the development of an antifungal stewardship program is to build a multidisciplinary team encompassing the necessary expertise in the management of IFD to develop and implement the AFS program [27••]. The core members of the AFS team should consist of individuals who possess sufficient knowledge of, and experience in, the clinical management of relevant patient populations, fungal epidemiology and susceptibility patterns, the laboratory diagnosis of invasive fungal disease (IFD), pharmacokinetics (PK) of antifungal drugs, dosing, and drug–drug interactions. The team should be constituted by an infectious diseases specialist, a clinical pharmacist, and a microbiologist. The other members should be chosen according to the local characteristics of the hospital (hematologist, ICU consultants, respiratory physicians, and surgeons) [27••].

Antifungal guidelines

As in the AMS programs, the guidelines are the starting point for the implementation of a program. There are several international guidelines for the management of fungal infections that should be adapted to the epidemiology and institutional situation to achieve greater adherence [28–30]. The main points to emphasize in the local guidelines are the initial empirical treatments in oncohematological patients, since it is in these clinical situations that more than 60% of the antifungal agents are prescribed [31]. Management bundles, for example for candidemias, should include appropriate empirical selection of antifungals, appropriate empirical dosing of antifungals, appropriate duration of treatment, removal of

existing CVCs, follow-up blood cultures until candidemia clearance, and ophthalmological examination [32, 33].

Basic interventions to improve antifungal use in low- and middle-income countries

Define policy

The are two main strategies in the AMS programs: preauthorization and restriction, where antimicrobials are made available through an approval process (formulary restrictions and preauthorization), and prospective audit, which provides advice or feedback to help physicians to prescribe properly. Both restriction and enabling techniques were successful in achieving effectiveness of the intervention and, when complemented by effective communication of the review results, could have considerable health service and policy impacts [34].

Antimicrobial or antifungal guidelines

Use guidelines adapted from national or regional guidelines that consider diagnostic methods, local susceptibilities, and empirical treatments recommended according to clinical situations.

Training

Training is one of the main starting points in the AMS programs and is widely justified action by increase in IFIs, population at risk, and appearance of new drugs [20, 35].

Improve the diagnosis of fungal infections

Early diagnosis of fungal infection is critical to perform effective treatment.

Clinical interventions

Daily coordination between clinicians, including specialists in infectious diseases and microbiologists (mycologists), is essential to manage fungal infections of individual patients. Indication, pathogen, site of infection, patient inmunological status, liver and renal function, and interactions must be considered [36].

Withdrawal or de-escalation of antifungals, especially during empirical therapy, should receive special attention. Even when susceptibility results are available to guide therapy, clinicians are often reluctant to de-escalate therapy when a seriously ill patient is improving on broad-spectrum treatment.

Measuring the performance of an AFS program

In order to evaluate the impact of antifungal stewardship, it is very important to define baseline indicators that measure the adequacy of prescriptions and expenditures. Demonstrating the continued benefit of an AFS program to hospital administrators, drug committees, and senior

clinicians relies on the cyclical monitoring of process, outcome, and structural measures relevant to the prevention and management of IFDs [2•, 5].

Conclusion

The current variability in antifungal use, inappropriate dosing, and delays in initiating appropriate therapy indicate a need for antifungal stewardship to improve the prevention, diagnosis, and management of IFIs. There is much less experience with AFS programs than with antibacterial initiatives.

In low- and middle-income countries, the main challenges are to make efforts to develop training programs in fungal infections, improve diagnosis of IFIs, and achieve access to antifungals.

Compliance with Ethical Standards

Conflict of Interest

Dr. Fernando Riera has received educational grants from Merck, Gilead, and TEVA.
Juan Pablo Caeiro declares that he has no conflict of interest.
Claudia Elena Sotomayor declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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