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Review

Antifungal stewardship: the Latin American experience

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Abstract

Antifungal stewardship is a critical component of healthcare management that focuses on optimizing the use of antifungal medications to improve patient outcomes, minimize resistance, and reduce healthcare costs. In resource-limited settings, the prevalence of fungal infections remains a significant health concern, often exacerbated by factors such as compromised immune systems, inadequate diagnostic capabilities, and limited access to antifungal agents. This paper reviews the current state of antifungal stewardship practices in developing countries, addressing the unique socioeconomic and healthcare landscape.

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Introduction

Antifungal use has steadily risen over time in concert with the increase in the number of immunocompromised adults and children at risk for invasive fungal infections (IFIs) and opportunistic fungal infections. Despite the growing concern, fungal infections receive very little attention and resources, leading to a paucity of quality data on fungal disease distribution and antifungal resistance patterns.[1]

The diagnosis and treatment of Invasive Fungal Diseases (IFDs) are challenged by limited access to quality diagnostics and treatment as well as emergence of antifungal resistance in many settings.[2]

People infected by a resistant microorganism or by microorganisms that are difficult to treat, such as fungi, have a higher risk of death by infection, prolonged stays, and more expensive hospital stays.[3]

Antimicrobial stewardship programs aim to improve utilization, achieve better patient outcomes, combat antibiotic resistance, and reduce costs.[3] These programs are an important tool to decrease the unnecessary and suboptimal use of antimicrobials. However, most current efforts have targeted antibiotic use, whereas antifungal stewardship has been relatively overlooked.[4,5]

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High drug costs and the toxicities of antifungal agents are the principal rationale for AFS while antifungal resistance is an emerging but less prevalent issue.[6,7]

The current literature on antifungal stewardship programs and the use of antifungals is scarce in Latin America, where access to diagnostic and treatment to IFI is difficult. This review summarizes the current status of antifungal stewardship programs in Latin America and highlights future development needs.

Fungal burden Latin America

Antifungal use is intimately linked to the burden of fungal disease. Epidemiology Latin America shares characteristics common to the rest of the world but also has its own regional characteristics. Serious fungal diseases can affect more than 2 million people annually in Central and South America and the Caribbean, of which more than 350 000 cases are life-threatening.[8]

Recently, the World Health Organization (WHO) published the first fungal priority pathogens list (WHO FPPL). The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance. The pathogens included were ranked and then categorized into three priority groups (critical, high, and medium) (Table 1).[1,2]

Regarding invasive candidiasis, regional data show a high incidence of candidemia; compared to the rest of the world, countries like Brazil and Colombia are the ones with the highest

Table 1. WHO fungal priority pathogens list (WHO FPPL)

Critical Priority Group	*Cryptococcus neoformans*, *Candida auris* *Aspergillus fumigatus* *Candida albicans.*
High Priority Group	*Nakaseomyces glabrata (Candida glabrata)*, *Histoplasma* spp. Eumycetoma causative agents Mucorales *Fusarium* spp *Candida tropicalis* *Candida parapsilosis*
Medium Priority Group	*Scedosporium* spp. *Lomentospora prolificans* *Coccidioides* spp *Pichia kudriavzevii (Candida krusei)* *Cryptococcus gattii* *Talaromyces marneffei* *Pneumocystis jirovecii* *Paracoccidioides* spp.
WHO fungal priority pathogens list to guide research, development, and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.	

incidence.[9,11] *C. parapsilosis* (5–49%) and *C. tropicalis* (9.7% and 39%) are the main non-albicans species in the region, and *Nakaseomyces glabrata (Candida glabrata)* is less common than in North America and Europe, but its frequency is increasing.[10,12] Overall, resistance rates to fluconazole increased from 0.4% to 1.2% among *C. albicans*, from 0.5% to 2.3% among isolates of *C. tropicalis*, and from 0 to 2.6% for *C. parapsilosis*.[8,10,11,13]

Echinocandin resistance remains rare, possibly related to the low use of echinocandins in the region and probably underestimated since most routine laboratories do not perform antifungal susceptibility tests.[9] Maldonado et al in Colombia in a study of 300 isolates of *Candida* found 7.3% and 7.7% resistance to anidulafungin and caspofungin, respectively, and found higher middle-income countries (MICs) for these echinocandins in almost all species.[12]

Candida auris is an emerging fungal pathogen that is associated with nosocomial infections and is considered a serious global health threat.[13] This species was detected in Latin America in 2013 and later spread in the región. Multiple cases have been reported in Venezuela,[10] Colombia,[14] Panama,[15] Brazil,[13] and, in 2022, Argentina.[16]

Aspergillus is the most common cause of IFI in patients with allogenic Hematopoietic Stem Cell Transplantation (HSCT) in Latin America, with a bimodal distribution (before posttransplant day 30 or after day 90), and it is the second most common cause in solid-organ transplant recipients.[17] Their frequency depends on the level of development of the health system and the availability of these procedures.[18] In addition, this fungus also affects patients recovered from TB (a very frequent infection in the region), with an estimated infection rate of around 10%.[19] Of concern and with very limited information, resistance to azoles has been identified in environmental isolates in the region, which may limit the use of these products.[20,21]

Fusarium is mainly observed in patients with leukemias or transplants. Isolations of these microorganisms have been relatively limited, and outbreaks caused by this type of microorganism have been observed in the region, especially in Brazil where it is more frequent than mucormycosis in this group of patients.[22–24] Voriconazole or a lipid formulation are the drugs selected for the primarytreatment of invasive fusariosis.[25]

Mucormycosis is an emerging disease, and its incidence has increased in hospitals over the years.[26–28] In a review of 143 cases in South America, the most common underlying conditions associated with mucormycosis were diabetes mellitus (42.0%) and penetrating trauma/burns (20.0%). Underlying conditions involving immunosuppression, including treatment of hematological malignancy, solid organ transplant, and corticosteroid use, also accounted for a large proportion of cases (45.5%).[27] Early diagnosis, control of the underlying disease, and prompt management may increase the survival rate.

Histoplasmosis and cryptococcosis are fungal infections mainly observed in patients with HIV, in advanced stages. According to epidemiological data, an incidence of more than 2% has been calculated in those living with HIV in Guatemala, Belize, Venezuela, Guyana, and Suriname, close to 1% in Guatemala, Costa Rica, Panama, Colombia, and Argentina, and less than 1% in the rest of the region.[29]

Data from Guatemala,[30] Argentina,[31] and Brazil[32] show that the incidence of cryptococcosis in patients with a recent diagnosis of HIV infection and CD4 counts below 100 cells per ml is greater than 5%, using screening strategies.

Availability of fungal pathogens diagnostic tests

To achieve favorable results in an antifungal stewardship program, the availability of appropriate diagnostic tools and a comprehensive drug armamentarium is essential.[6,33] Studies about diagnostic capabilities and access to antifungal drugs are scarce. Beyond two recent works recently published, which differ in the period, survey method, and scope, there are no other studies with a systematic evaluation of these questions in Latin America.[34–36]

In a survey directed to representatives of many institutions in Latin America and Caribbean, Falci and Pasqualotto aimed to design a snapshot of diagnostic and therapeutic capabilities of the region, and perceptions of fungal disease by the responders.[36] The authors classified the mycology laboratories of the institutions according to the European Confederation of Medical Mycology standards of excellence. Only 9% of the laboratories met the proposed standards. This study enrolled 129 institutions, mainly in Brazil (74%) and the majority reported third level of care complexity. Fundamental tools for antifungal stewardship, such as fungal identification and susceptibility tests, had shown to be lacking. The authors highlight that an incorrect identification and unawareness of antifungal resistance data can lead to inadequate treatments and unfavorable outcomes.[36] The use of MALDI-ToF was reported in only 20% of institutions. Another highly valuable resource for enhancing an antifungal stewardship program is the use of therapeutic drug monitoring,[32] was reported in less than 20% of responders. Voriconazole was the drug more frequently measured (16%), followed by itraconazole (10%) and posaconazole (4%).[36] Regarding antigen testing, the scenario was also not good, with a low proportion of responders reporting access to *Histoplasma* and beta-glucan antigen detection, and cryptococcal antigen availability was absent in around 25% of centers.[36] The galactomannan (GM) test, useful for an effective antifungal stewardship program, was reported in only 48% of institutions.[36] Moreover, beta-glucan testing was demonstrated

also to be a beneficial and cost-effective tool in stewardship strategies and its absence in most centers signifies a missed opportunity to reduce unnecessary drug use.[37]

A different approach, focusing only on the endemic mycoses, was recently published by Caceres and colleagues.[35] The authors describe the main findings of an analysis made by participants of the first International Meeting on Endemic Mycoses of the Americas. Representatives of 27 territories (divided into 9 regions) responded about availability of diagnostic methods and treatment for endemic mycoses. Moreover, a regional Strength, Weakness, Opportunities, and Threats analysis was performed by selected participants. This study reported that conventional tools for endemic diseases such as microscopy and culture were available, in at least one reference center per region. However, for other tools like serology and antigen detection, inequalities have been reported across the regions.[35]

Riera and colleagues, between June and August 2022, surveyed infectious disease, and clinicians from each of the 24 sites of Argentina were contacted to describe local access to fungal diagnostic tools and antifungal agents.[36] Thirty responses were collected from facilities throughout Argentina. Most institutions were governmental (77%). A mycology department was available in 83% of them. Histopathology was available in almost 93% of the sites, while automated methods and GM tests were available in 57%, each; 53% of the sites had access to MALDI-TOF-MS through regional reference laboratories, and polymerase chain reaction was present in 20% of the sites. Susceptibility testing was available in 63% of the laboratories.[36]

Antifungal drugs: consumption, availability, and use strategies reported for the region

The global consumption of antifungal agents is on the rise, especially in MICs, and certain life-saving antifungal agents indicated in severe fungal infections such as echinocandins and polyenes may be underutilized, especially in these countries.[38]

Falci and Pasqualotto reported access to flucytosine had the worst case, with less than 20% of access across the region. Echinocandins had variable availability, around 30–41%. Azoles like fluconazole and itraconazole, along with deoxycholate amphotericin B, were most accessible. Liposomal amphotericin and the newer azoles (including voriconazole) had uneven availability reported by the responders.[36]

Caceres and colleagues[35] reported access to sulfonamide, azoles (such as itraconazole and voriconazole), and deoxycholate amphotericin B in most territories. Nonetheless, in some regions liposomal amphotericin has limited availability, as well as the newer azoles (posaconazole and isavuconazole).[35]

Riera and colleagues found that fluconazole was the only antifungal agent available in all institutions. This was followed by amphotericin B deoxycholate (83%) and itraconazole (80%).[36] If an antifungal agent was not available onsite, then 60% of the patients could receive adequate antifungal treatment within the first 48 h upon request.[36]

Several studies have found that fluconazole is still the most frequently prescribed antifungal agent despite the market introduction of echinocandins and mold-active azoles.[37,39]

Quiros et al.[40] in a study included a network of hospitals from nine Latin American countries. In a study that included 84 Medical Surgical ICUs from tertiary-care hospitals in Latin America. Among the 426 systemic antifungal prescriptions, triazole drugs were the most frequently prescribed: 2.4% of total prescriptions for community acquired infections and 3.4% of total prescriptions of hospital acquired infections. The consumption of antifungals expressed in defined daily dose (DDD) every 100 patient days was: triazoles 7.4–7.9 DDD per 100 PD, amphotericin 2.2–3.4 DDD per 100 PD, and echinocandins 2.2–2.6 DDD/100 DDD per 100 PD.[40]

Table 2. Antifungal treatment strategies for invasive fungal infections

Prophylaxis	Administration of antifungal drugs to patients without signs or symptoms of IC but with risk factors for its development	Strategy frequently applied in specific subgroups of patients at risk Low specificity since it covers a population at risk, it does not require the use of complementary diagnostic methods at the beginning
Preemptive	Treatment triggered by evidence of fungal infection, basing on "surrogate marker" or non-culture diagnostic tests, without definitive microbiological identification of fungal pathogen (e.g., positive biomarkers 1-3 beta-D-glucan, mannan-antimannan antibodies, polymerase chain reaction assays)	This strategy aims to narrow the large target population of prophylaxis and to reduce the time of initiation of empiric treatment Intermediate specificity
Empiric therapy	The administration of antifungal drugs to patients presenting signs and symptoms of infection potentially due to fungi and at risk of IC development	Febrile neutropenic patients despite broad-spectrum antibiotics, septic patients with potential intra-abdominal focus of infection
Targeted therapy	Targeted treatment for identified pathogen	High specify

Cortegiani, A., Russotto, V., Raineri, S. M., Gregoretti, C., De Rosa, F. G., & Giarratano, A. (2017). *Untargeted Antifungal Treatment Strategies for Invasive Candidiasis in Non-neutropenic Critically Ill Patients: Current Evidence and Insights. Current Fungal Infection Reports, 11(3), 84–91.* doi:10.1007/s12281-017-0288-3

Regarding the strategies for the use of antifungals (prophylaxis, empiric therapy, preemptive to antifungal treatment directed by confirmed diagnosis),[41] regional data are scarce and the data come from closed immunocompromised patients (Table 2).[42]

Prophylaxis consists of the administration of antifungals in patients at high risk of IFI without an evidence of IFI. Fluconazole is the main drug used, aimed at the prevention of candidiasis, and voriconazole/posaconazole/isavuconazole are recommended to extend the prophylaxis of IFIs due to filamentous fungi.[42–44]

The use of antifungal prophylaxis in Latin America is reported in several studies. In a Brazilian hospital, it was identified that 38 (11.9%) of the prescriptions corresponded to prophylaxis, fluconazole being the most indicated; the study showed a low proportion of appropriate antifungal drug use; the dosage and drug–drug interactions criteria were the determining factors for the high percentage of non-adherence to treatment guidelines in the hospital.[45] There is reported experience of the use of prophylactic antifungals in a reference center in Peru,[46] in 47 children under 13 years of age; patients who received posaconazole showed an increase in transaminase values and the development of breakthrough fungal infections. The published data of 251 children with autologous or

Table 3. Antifungal core elements

Full support of hospital governance	Integrate antifungal stewardship into hospital strategic plans and policies Dedicate resources to support activities
Accountability and responsibility	Stewardship team should have in-depth knowledge and clinical experience managing invasive fungal disease
Expertise on infection management	Access to timely conventional and nonculture-based diagnosis, treatment, and monitoring
Education and practical training	Targeted educational programs to address diagnosis, treatment, and monitoring
Other actions aiming at responsible antimicrobial use	Infectious diseases consultation for patients with invasive fungal disease Develop treatment pathways and guidelines Postprescription and feedback
Monitoring and surveillance	Establish surveillance to support stewardship program initiatives Routine susceptibility and reports Medication screening by clinical pharmacist or clinician Therapeutic drug monitoring for triazole antifungals
Reporting and feedback	Track and benchmark antifungal drug use Access patient level outcomes Data feedback to prescribers

Johnson MD, Lewis RE, Dodds Ashley ES, Ostrosky-Zeichner L, Zaoutis T, Thompson GR, Andes DR, Walsh TJ, Pappas PG, Cornely OA, Perfect JR, Kontoyiannis DP. Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium. J Infect Dis. 2020 Aug 5;222(Suppl 3):S175-S198. doi: 10.1093/infdis/jiaa394. PMID: 32756879; PMCID: PMC7403757.

allogeneic HPCT in Argentina[46] describe that until 2006 they used fluconazole and then switched to voriconazole as IFI prophylaxis. During an experience at a children's hospital, which included the management of 139 HSCT recipients in Colombia,[47] reported that the results with the use of voriconazole prophylaxis, the frequency of IFI was 4.4 vs. 7.4% with use of other prophylactic antifungals, with no statistically significant difference (Table 3).

The clinical guidelines for the management of NF published in the region in 2005 recommend the use of empirical antifungal therapy to the extent that NF patients persist febrile on the 7th day despite appropriate antibacterial therapy. However, it is suggested to consider a study with GM and perform lung imaging at the time of its prescription.[48]

In a publication of a survey of NF therapy practices in 19 hospitals in Latin America, the use of empirical antifungals is the most frequent practice, indicating it as soon as possible in high-risk episodes, usually after 72 hours of persistence of fever, previously performing a chest CT scan in 89.62% of the centers and 70.37% performing a GM measurement, resulting in amphotericin use in some of its formulations being the most frequently prescribed antifungal.[49]

Regarding the use of antifungal in a preemptive strategy, Santolaya et al[50] compared the strategy of empirical vs preemptive. A total of 149 children were randomized, 73 to empirical therapy and 76 to preemptive therapy. Thirty-two of 76 (42%) children in the preemptive group received antifungal therapy. The median duration of antifungal therapy was 11 days in the empirical arm and 6 days in the preemptive arm ($P < 0.001$), with similar overall mortality (8% in the empirical arm and 5% in the preemptive arm, $P = 0.47$). IFD-related mortality was the same in both groups (3%, $P = 0.97$), as were the percentage of children with IFD (12%, $P = 0.92$) and the number of days of fever (9, $P = 0.76$). Preemptive antifungal therapy was as effective as empirical antifungal therapy in children with cancer, fever, and neutropenia, significantly reducing the use of antifungal drugs.[50] Obviously, to consider the preemptive strategy, it is essential to have quick access to GM measurement, images, BAL, among others.

Concerning the use of GM, in a study conducted in Brazil,[51] the reasons for requesting GM were evaluated during a 1-year period, including 245 samples corresponding to 158 patients, in which 60.1% were hemato-oncology patients, most of them due to diagnostic purposes 46.5%, followed by preemptive strategy surveillance 25.7% and therapeutic follow-up 15.1%.

Antimicrobial stewardship and antifungal stewardship in Latin America

The worldwide development and implementation of AMS programs vary considerably. In a 2015 survey, the availability of regional standards for antimicrobial stewardship in Latam was 30%.[52] The main barriers to implementing AMS programs described in this survey were perceived to be a lack of funding or personnel, a lack of information technology, and prescriber opposition.[52] Few hospitals in Latin America report having a structure or resources needed for a successful ASP and antimicrobial stewardship activities differ significantly among Latin American countries.[41]

Gamarra et al.[53] documented the unique experience of the Antifungal stewardship (AFS) in Latam, in this study evaluating the quality of antifungal prescriptions in a tertiary care hospital, and to test if a simple educational activity could improve the quality of prescriptions. Among 333 prescriptions, fluconazole was the most frequently (80.5%) prescribed agent. Hematology (26.7%), infectious diseases department (22.8%), internal medicine (15.9%), and intensive care unit (14.4%) were the units with most antifungal prescriptions. The researchers observed that 72.7% of prescriptions were considered inappropriate. With simple educational activity, a large proportion of inappropriate prescriptions was improved.

Conclusion

Current literature about AFS shows a difficult scenario in Latin America. There are substantial inequalities in the regional and local availability of antifungal agents. Treatment, accessibility of antifungal agents, and stewardship were some of those measures.[54]

These programs must be comprehensive and not forget the concept of One Health, since they are drugs used in crops and animals and influenced by changes in environment.[55]

Many decisions involved in the management of IFD must be instituted in a specific sequence over a short time frame to have maximal clinical impact. Clinical care pathways or treatment bundles are useful strategies, to maximize treatment effectiveness.[4]

ASPs centered on hospitalized patients may be an efficient strategy to optimize antifungal use in hospitals. The applicability in hospitals may have to be focused on critical care units and immunocompromised patients units, places where antifungals are used more frequently.[5–7,56] It is recommended that the professionals who carry out the task have special training in

mycology and in the management of antifungals given their special characteristics (prolonged use, toxicity, and interactions).[5,7]

We recommended four actionable core measures for antifungal stewardship programs[4]:

1. Full support of hospital governance.
2. Institution-wide education program.
3. Measures to support optimal antifungal utilization.
4. Measures to control antifungal prescribing, utilization, and resistance.

On the other hand, scientific societies should develop and update regional guides and stimulate the publication of experiences in the field to obtain more information. We still have a long way to go; efforts should be urgently made to improve diagnostic capabilities, equalize regional disparities, and qualify antifungal stewardship programs in Latin America.

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