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Treatment and Prevention of Hospital Infections (D Vilar-Compte, Section Editor)

Do We Need Antifungal Stewardship?

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Abstract

Purpose of review Invasive fungal infections (IFIs) are recognized as a significant health problem worldwide. Inappropriate use of antifungals contributes to antifungal resistance and emerging fungi. There is an urgent clinical need to limit inappropriate antifungal usage through judicious antifungal stewardship (AFS).
Recent findings The main goals of AFS are optimized care, de-escalation or withdrawal of antifungal therapy when appropriate, reduced costs, and reduced fungal resistance, with no negative impact in terms of morbidity or mortality. AFS should be tailored for each institution and health-care system, and should be performed by an experienced and trained multidisciplinary team, based on education, bedside interventions, and daily collaboration with the microbiology department and pharmacy team. Performance measures are needed to evaluate the impact of AFS. It is recommended that AFS be implemented in a stepwise manner, with modest initial goals to enable demonstration of success in the short term.
Summary Encouraging the appropriate use of antifungal drugs should help to decrease the incidence of IFIs, thereby reducing antifungal resistance.

Introduction

Invasive fungal infections (IFIs) are increasingly recognized as a significant health problem worldwide, associated with high costs and poor outcomes [1].

Mortality rates of 45–63% and 50% have been reported for invasive aspergillosis and invasive candidiasis, respectively [1]. In addition to high costs [2], several factors are associated with this high mortality, including diagnostic difficulties and delays in appropriate treatment, and excessive use of antifungal therapy [3]. It has been estimated that 57% of antifungal prescriptions are inappropriate, with 16% considered unnecessary [4, 5••]. Another problem with the use of antifungals is that systemic agents often have greater toxicity and potential for severe interactions than antibacterial drugs, and are

also related to emerging fungal pathogens and the global increase in antifungal resistance [3, 6]. Recent reports show that the emergence of resistance to fluconazole and echinocandins in some species of *Candida* are associated with unnecessary exposure [5••]. Multidrug-resistant *Candida auris* and azole-resistant *Aspergillus fumigatus* pose an alarming threat, which takes us to the urgency for implementation of effective antifungal stewardship (AFS) programs [5••, 7].

The complexity of patients who develop IFIs requires a multidisciplinary team with complementary skills to monitor and ensure an adequate clinical response. AFS efforts focused on empirical use in intensive care units (ICUs) and other critical care units, where most antifungal use takes place (e.g., oncology units), may have the greatest impact [8]. Antifungal administration by means of surveillance programs are important for increasing adherence and safety, thus improving clinical and microbiological response; these programs require consideration of the patient's risk factors, comorbidities, target organisms, biological markers, drug interactions, cost factors, and the likelihood of emergence and spread of resistance [9–11].

Encouraging the appropriate use of antifungal drugs should help to limit, and possibly reduce, the emergence of antifungal resistance [12].

Main factors related to overuse of antifungals

- Under-recognition of IFIs [5••]
- Lack of rapid, sensitive, and specific fungal diagnostics tools to facilitate accurate and timely diagnosis, leading to excessive empirical prescribing [2]
- Inadequate prescriber knowledge regarding the management of IFIs [2]
- Vulnerability of high-risk patient groups with high mortality attributable to IFI, even with appropriate treatment, often leading to reluctance to delay treatment [2]
- Difficult prescribing decisions due to the complexity of the evidence-based information supporting treatment and prophylaxis [2]
- Complex pharmacokinetics and pharmacodynamics of antifungals (inter- and intra-patient variations), and the need for individualized drug regimes in the context of patient comorbidities and drug–drug interactions [2]
- Adverse drug reactions, reported in 29% of hospitalized patients receiving antifungal agents [5••]

Definition of stewardship

Antimicrobial stewardship has been defined as coordinated interventions designed to improve and measure the appropriate use of antimicrobials in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae [4, 13–15]. The most effective antimicrobial programs incorporate multiple strategies simultaneously, in collaboration with the various specialties within a given health care facility, although interventions on a smaller scale to improve antimicrobial use are also valuable in some settings [14].

AFS refers to a program or series of interventions organized to monitor and direct the use of antifungal drugs in a health care institution, balancing the need to provide prompt, appropriate, effective therapy while avoiding the use of antifungals when not indicated [14–16].

Given the rarity of IFIs and the lower incidence of resistance relative to bacteria, AFS has received less attention than antibiotic stewardship [2].

There are some differences between the programs, as shown in Table 1.

Aims of antifungal stewardship

There are three main goals:

I. De-escalation of antifungal therapy when appropriate

- decreasing the number of prescriptions
- switching from intravenous to oral prescriptions
- stopping when unnecessary

II. Reduced costs and optimized care of patients with IFI

- shorter length of hospitalization
- fewer complications
- less use of antifungals

III. Reduced fungal resistance

Suggested components of AFS program

There are several steps involved in creating an adequate AFS program, and as there is no consensus about the order of these, we propose the following sequence: (Fig. 1)

Table 1. Differences between antimicrobial and antifungal stewardship. Adapted from [2]

	Antimicrobial	**Antifungal**
Setting	Primary and secondary care	Secondary care
Specialists involved	All specialists	Certain specialists: critical care, hemato-oncology, oncology, organ transplantation, gastrointestinal surgery, respiratory, internal medicine
Indication	Mainly treatment or single-dose prophylaxis	Prolonged prophylaxis and treatment
Diagnosis	CRP Procalcitonin Culture: Earlier	ß-D-glucan Galactomannan Computerized tomography Culture: Not early Difficult if deep-seated
Resistance	Increasing multidrug resistance reports	Reported mainly for *Candida glabrata*, *Candida auris*
Pharmacokinetics	Less complex—few interactions	Complex—many interactions and contraindications, therapeutic drug monitoring indicated (azoles)
Prophylactic measures	Defined	Not clearly defined
Tailored treatment	Developed	Not well developed
Consensus on treatment	Better	Needs to be improved

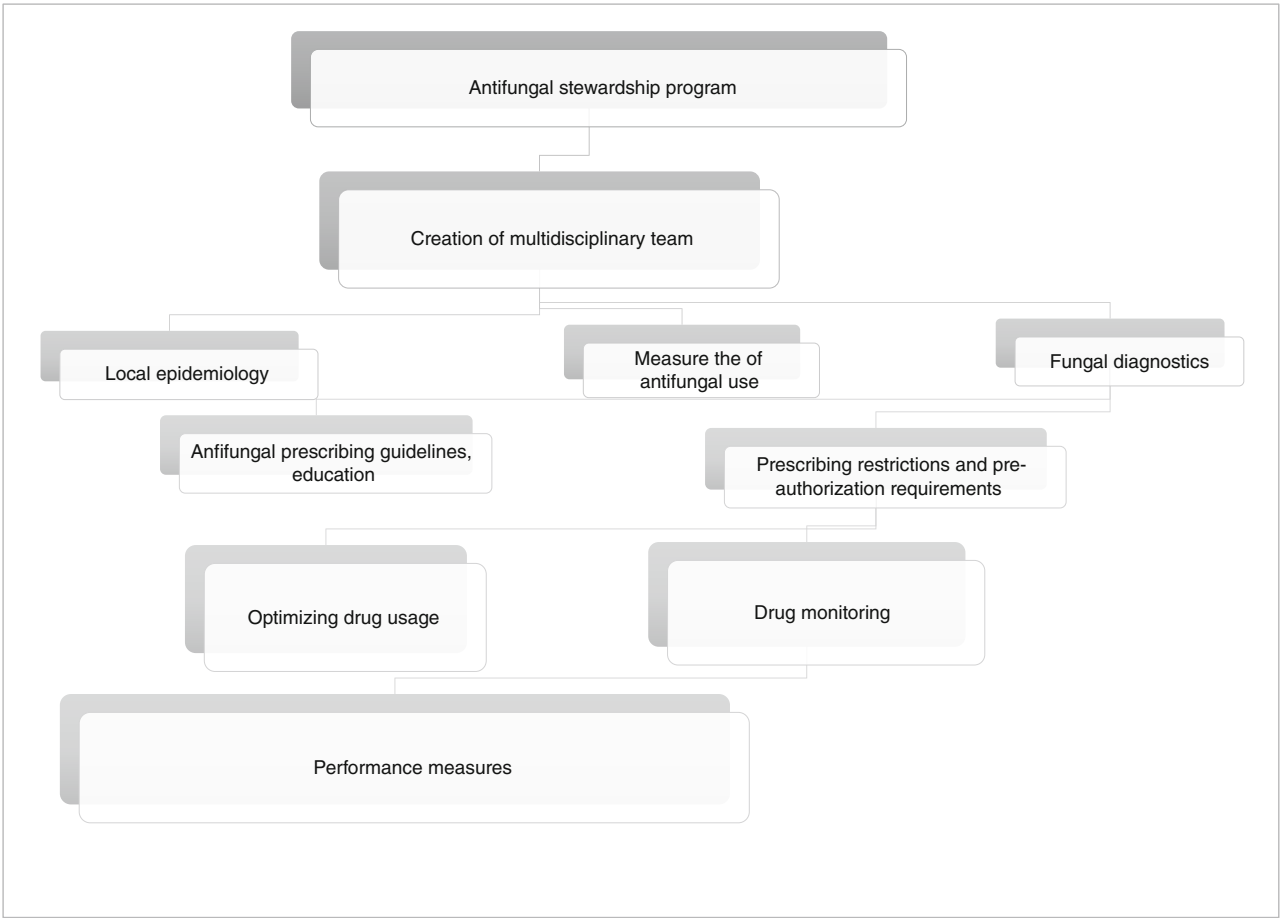

Fig 1. Recommended steps for the creation and implementation of an antifungal stewardship program.

a) Creation of a multidisciplinary team

One of the first steps is to organize a collaborative group that receives approval, empowerment, and support from hospital managers [18, 19••]. It is important to select a respected leader who can ensure clinical governance [18]. The specialty of the leader may differ among hospitals; essential characteristics include having a deep understanding of the diagnosis and management of fungal infections, contributing to post-prescription review and feedback, and having the capacity to coordinate the group [5••, 13, 18].

The suggested best leader is an infectious disease (ID) specialist who is trained to handle complicated or critical patients with multiple infections, with experience in evaluating clinical signs and symptoms in different types of patients and in treating associated complications [20]. ID physicians have experience in the evaluation of risk factors for the development of fungal infections and the selection of diagnostic studies that must be ordered to establish the diagnosis [5••]. They can also guide other physicians who treat patients with IFIs, in the selection and interpretation of diagnostic test results, recommendations regarding the retention or suspension of antifungals, and patient-specific- dosing and preventing the development of resistance [21•].

The other team members should be seen as local authorities and opinion leaders; it is suggested to include personnel from the ID and microbiology department, pharmacists, internists, a hospital epidemiologist, an infection control specialist, and a computer systems analyst. Also, hemato-oncology, organ transplantation, critical care, and gastrointestinal surgery specialists could be considered [4, 19••].

These members should work closely with the infection control committee and pharmacy team in order, supported by hospital administration and medical staff leadership. The multidisciplinary team should serve to maximize engagement with clinical specialties, develop and implement new interventions, and monitor performance [18].

b) Local epidemiology with continuous surveillance

Once human resources are ready, it is necessary to assess the magnitude of the problem and audit antifungal use to determine where, how, and by whom antifungals are prescribed [19••].

Local epidemiology should be collected from each center, specifying the methods used. A registry of all IFIs is necessary: the microbiology department must maintain records of isolates reflecting proven infections, in addition to an experienced physician who reviews each case and identifies clinically significant infections [1].

When an isolate is found by an automated system, its resistance should be confirmed by micro-broth dilution, as this is considered the gold standard [1]. The Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have published specific clinical cutoff points for triazoles and echinocandins, as well as specific epidemiological cutoff values for each of them, that help us determine susceptibility and potential resistance and to guide the choice and dosage of the proper antifungal drug [18]. It should be noted that clinical breakpoints of many antifungals are available for certain *Candida* species but not for molds, making the interpretation of some fungi very difficult [1]. Internal quality control and enrollment in national external quality control programs is recommended to ensure robust results [1].

c) Fungal diagnostics

The development of improved diagnostic methods is associated with reduced antifungal use [1].

The realization of cultures in specific media, guided by the clinical context of each case, improves the opportunity to obtain the correct diagnosis [14]. However, delay in the time to positive identification and lack of availability of susceptibility tests, as previously mentioned, results in low sensitivity and specificity of fungal cultures [1, 14]. It has been demonstrated that timely access to radiological investigations and bronchoscopy leads to optimal prescription decisions [2].

The adoption of a diagnostic-driven approach incorporating non-culture-based tests (NCBRs), such as galactomannan, beta-D-glucan, and *Aspergillus* polymerase chain reaction (PCR), can have excellent negative predictive value that can be harnessed to exclude IFIs [22].

Specifically, for candidemia, rapid diagnostic techniques such as peptide nucleic acid fluorescence in situ hybridization (PNA-FISH), T2*Candida* magnetic resonance, multiplex PCR, and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) have recently been developed and can aid the stewardship process

by improving the accuracy and timeliness of identification of *Candida* spp., enabling earlier tailoring of empirical therapy [2].

The use of NCBRs with traditional radiological tests has been associated with significantly reduced duration of antifungal treatment, and can guide discontinuation of empirical antifungal treatment in a safe, and cost-effective way, without increasing the risk of mortality [2, 5••, 23].

d) Antifungal prescribing guidelines, education, and feedback

There are significant geographical variations in fungal epidemiology and resistance; local trends must be monitored in order to develop guidelines for appropriate antifungal treatment [24, 25].

These guidelines should be drafted and agreed upon within the AFS group and updated at least every 2 years, incorporating the suggestions of prescribers, microbiologists, and pharmacists, as well as newly available knowledge [19••].

The development of accessible and easy-to-use guidelines has implications in the correct prescription of antifungals, accounting adherence, and patient related comorbidities [5••]. These guidelines should be applied during everyday care based on an understanding of those areas in which consensus has and has not been reached, but is important to understand that guidelines and education alone are unlikely to be successful, and must be combined with other strategies [21•, 25].

The multidisciplinary team must carry out periodic educational sessions, focused from the lower level of care to the most accurate, and not only for clinicians specialized in infectious diseases [26, 27]. An educational program is highly desirable in order to increase antifungal prescriber knowledge in diagnosing and managing IFIs [19••].

Before initiating education, is important to consider that there are inconsistencies and lack of knowledge in relation to adequate diagnosis, confusion between colonization and real infection, selection and appropriate dosing of drugs, available diagnostic methods, interpretation of the specific microbiological results for each drug, prophylaxis indications, and first-line therapy [18, 28]. These barriers should be considered in designing training strategies [5••].

Passive educational activities, such as lectures or informational pamphlets, should be used to complement other stewardship activities, but these are not recommended as the only educational tool [13].

e) Prescribing restrictions and preauthorization requirements

Restrictions on prescribing could be implemented using two types of interventions:

1. Restrictive (e.g. necessitating a limited formulary and requiring pre-approval for antifungal use by designated individuals) [18].

Advantages: Reduces initiation of unnecessary/inappropriate antifungals; optimizes empirical choices and influences downstream use; prompts review of clinical data/prior cultures at the time of initiation of therapy; reduces antibiotic costs; and allows direct control over antifungal use [18].

Disadvantages: Impacts on the use of restricted agents; loss of prescriber autonomy; delays in therapy; effectiveness depends on skill of approver; and addresses empirical use to a much greater degree than downstream use [18].

2. Persuasive and prospective (e.g. encouraging education, developing guidelines, improving access to experts to discuss cases or post-prescription bedside review for dosage optimization and sequential treatment) [29]. This

strategy requires more time and effort and a high level of expertise, but is believed to have better long-term acceptance than restrictive measures [18]. Involving prescribing physicians in the discussion of antifungal use is strategically crucial [19••].

Advantages: Can increase visibility of AFS and build collegial relationships; more clinicians available for recommendations, enhancing uptake by prescribers; greater flexibility in timing of recommendations; can be done on less than daily basis if resources are limited; provides educational benefit to clinicians; prescriber autonomy maintained; and can address de-escalation of antibiotics and duration of therapy [13, 21•].

Disadvantages: Participation is voluntary and typically labor-intensive; involves a great commitment; success depends on the method of sending information to prescribers; prescribers may be reluctant to change therapy if the patient is clinically stable; the identification of interventions may require support from information technology and/or the purchase of computerized surveillance systems; and more time is required to achieve reductions in the use of targeted antibiotics [13, 21•].

The choice of one of the two strategies can be based on the attitude, disposition, and adaptability to change on the part of the local health team [21•].

An electronic prescribing and approval system is a helpful tool, enabling new orders to be flagged automatically for expert AFS review, preventing delays in commencement of antifungals [5••].

f) Optimizing drug usage

- Choice of antifungal drug: In accordance with local guidelines and resistance patterns. Consider the pharmacokinetics-pharmacodynamics (PK/PD) of each drug [30]. Adjustment must be made based on the results of microbiological culture [30].
- Dosage adjustment considering clinical characteristics and other concomitant diseases of patients who develop fungal infections, such as weight, and renal or liver failure [30].
- The use of other medications requires analysis of potential drug–drug interactions [5••, 10, 31].
- De-escalation or step-down therapy is vital to antimicrobial stewardship programs, and it is also applicable for antifungal use [30, 32]. Antifungal de-scaling on day 10 has been carried out in different randomized clinical trials, but decisions should be based on the systemic inflammatory response syndrome (SIRS) criteria as an objective clinical evaluation to effect the treatment change safely, after improvement in clinical status, sterilization of blood cultures, and documented in vitro susceptibility of the causative yeast/mold [32].
- Switching from intravenous (IV) to oral (PO) route whenever possible [30, 32]. Elimination of the IV route prevents the development of other infections in the bloodstream [26].

g) Drug monitoring

- Proper monitoring of liver and/or kidney function tests [31].
- Therapeutic drug monitoring (TDM) is recommended by some guidelines as part of standard patient care, used as a tool to guide dosing,

in order to enhance the safety and efficacy of some antifungals [5••]. TDM is most relevant to triazole antifungals, which have varied and unpredictable pharmacokinetics, especially in severely ill adults and in children, and is important when managing patients on long-term therapy and those at risk of developing resistance [17]. TDM improves outcomes in the context of patient-related factors such as signs of malabsorption, drug interactions, and poor treatment response [5••, 33]. An important barrier to TDM use is its lack of availability in all hospitals, and thus few programs have included antifungal TDM as a feasible intervention [33].

h) Performance measures

Measuring antimicrobial use is an essential step in AFS programs in order to correlate antifungal prescribing quality with patient outcome and evaluate performance, and to justify resources over and above antifungal cost savings [5••, 8]. Some of the main activities include establishing goals and indicators, designing a written annual plan, and selecting the metrics that will be used to check whether the program is working [18].

Measures should include patient outcomes, costs, and consumption of antifungals, assessed via adherence to therapeutic advice by the AFS team and other quality indicators [5••, 34]. Some indicators may be recorded monthly. The number of indicators should be low [19••].

Quality indicators described include:

Antifungal quantitative metrics. This measure is suggested to be performed in the same hospital pre- and post-implementation of an appropriate AFS program (it may over- or underestimate the numbers if it is compared with other hospitals) [35]. Antifungal consumption is used as the primary measure; when it is used in specific units or teams, it can lead to the identification of higher users (e.g. hematology-oncology and ICU patients) [36]. Antifungal consumption could be measured by defined daily dose (DDD) adjusted for bed occupancy (e.g. 1000/ patient-days). This data is limited to inpatients, tends to overestimate usage for some drugs, and can have large fluctuations in small populations [36]. Days of therapy (DOT), adjusted for bed occupancy, is less sensitive to individualized antifungal dosing. Patient-level consumption data are necessary, and not feasible without electronic prescribing [5••, 37]. The results of DDD and DOT are adjusted for the costs of each antifungal.

Quality metrics. These include activities performed, recommendations by the AFS team with acceptance rates, availability of locally adapted antifungal guidelines, and prescriber education. These measures are important but do not directly assess the impact on antifungal consumption and patient outcomes [5••]. Audit tools for assessing compliance with international guidelines have recently been proposed; these tools may not consider nonadherence because of patient- and treatment-related factors [5••].

Patient outcomes and microbiological metrics. These are measures of the impact on patient outcomes such as incidence of IFIs, mortality, and adverse drug reactions from antifungals [5••].

Finally, all the information should flow in all directions, and every success must be shared with all the members of the multidisciplinary

team and with the involved departments [19••]. Unit-specific feedback is necessary and should be provided periodically [19••].

Several studies have shown that AFS programs are extremely effective in reducing the costs associated with the management of IFIs [6, 37, 38].

Conclusions

AFS and antibiotic stewardship programs share similar goals, but with distinctive clinical priorities. AFS should be tailored for each institution and health-care system, and performed by an experienced and trained multidisciplinary team, based on education, bedside interventions, and daily collaboration with the microbiology department and pharmacy. To achieve optimal results, AFS programs should be implemented in a stepwise manner, and the initial goals should be modest, enabling demonstration of success in the short term.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have 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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wattal C, Cakrabarti A, Oberoi JK, Donnelly JP, Barnes RA, Sherwal BL, et al. Issues in antifungal stewardship: an opportunity that should not be lost. J Antimicrob Chemother. 2016;72:969–74. https://doi.org/10.1093/jac/dkw506.
2. Whitney L, Bicanic T. Antifungal stewardhisp. In: Laundy M, Gilchrist M, Whitney L, editors. Antimicrobial stewardship. Oxford: University Press; 2016. p. 1–20.
3. Stanzani M, Sassi C, Battista G, Cavo M, Lewis RE. Improved radiographic imaging of invasive fungal disease: the cornerstone to antifungal stewardship in the hematology units? Curr Fungal Infect Rep. 2016. https://doi.org/10.1007/s12281-016-0258-1.
4. Azap OK, Ergönül O. Antifungal stewardship. In: Pulcini C, Ergönuül Ö, Beovic B, Can F, editors. Antimicrobial stewardship. Amsterdam: Elsevier; 2017. p. 147–63.
5.•• Urbancic KF, Thursky K, Kong DCM, Johnson PDR, Slavin MA. Antifungal stewardship: developments in the field. Curr Opin Infect Dis. 2018;31:490–8. https://doi.org/10.1097/QCO.0000000000000497
This very recent article very clearly describes the fundamental aspects of implementing a stewardship program.
6. Ramos A, Pérez-Velilla C, Asensio A, Ruiz-Antorán B, Folguera C, Cantero M, et al. Antifungal stewardship in a tertiary hospital. Rev Iberoam Micol. 2015;32:209–13. https://doi.org/10.1016/j.riam.2014.11.006.
7. Gamaletsou MN, Walsh TJ, Sipsas NV. Invasive fungal infections in patients with hematological malignancies: emergence of resistant pathogens and new antifungal therapies. Turk J Hematol. 2018;35:1–11. https://doi.org/10.4274/tjh.2018.0007.
8. Vallabhaneni S, Baggs J, Tsay S, Srinivasan AR, Jernigan JA, Jackson BR. Trends in antifungal use in US hospitals, 2006-12. J Antimicrob Chemother.

2018;73:2867–75. https://doi.org/10.1093/jac/dky270.

9. Hamdy RF, Zaoutis TE, Seo SK. Antifungal stewardship considerations for adults and pediatrics. Virulence. 2017;8:658–72. https://doi.org/10.1080/21505594.2016.1226721.
10. Valerio M, Vena A, Rodríguez-González CG, de Vega EC, Mateos M, Sanjurjo M, et al. Repeated antifungal use audits are essential for selecting the targets for intervention in antifungal stewardship. Eur J Clin Microbiol Infect Dis. 2018;37:1993–2000. https://doi.org/10.1007/s10096-018-3335-2.
11. Micallef C, Aliyu SH, Santos R, Brown NM, Rosembert D, Enoch DA. Introduction of an antifungal stewardship programme targeting high-cost antifungals at a tertiary hospital in Cambridge, England. J Antimicrob Chemother. 2015;70:1908–11. https://doi.org/10.1093/jac/dkv040.
12. Aguado JM, Silva JT, Bouza E. Conclusion and future perspectives on antifungal stewardship. J Antimicrob Chemother. 2016;71(suppl 2):ii43–4. https://doi.org/10.1093/jac/dkw396.
13. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuet AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51–77. https://doi.org/10.1093/cid/ciw118.
14. Ruhnke M. Antifungal stewardship in invasive Candida infections. Clin Microbiol Infect. 2014;20(Suppl 6):11–8. https://doi.org/10.1111/1469-0691.12622.
15. Nwankwo L, Periselneris J, Cheong J, Thompson K, Darby P, Leaver N, et al. A prospective real-world study of the impact of an antifungal stewardship program in a tertiary respiratory-medicine setting. Antimicrob Agents Chemother. 2018;62(10). https://doi.org/10.1128/AAC.00402-18.
16. Richardson MD. An introduction to antifungal stewardship. Antimicrob Chemother. 2016;71(suppl 2):ii3. https://doi.org/10.1093/jac/dkw390.
17. Perlin DS, Rautemaa-Richardson R, Alastruey-Izquierdo A. The global problem of antifungal resistance: prevalence, mechanisms, and management. Lancet Infect Dis. 2017;17:e383–92. https://doi.org/10.1016/S1473-3099(17)30316-X.
18. Muñoz P, Bouza E. The current treatment landscape: the need for antifungal programmes. J Antimicrob Chemother. 2016;71(Suppl 2):ii5–ii12. https://doi.org/10.1093/jac/dkw391.
19.•• Muñoz P, Valerio M, Vena A, Bouza E. Antifungal stewardship in daily practice and health economic implications. Mycoses. 2015;58(Suppl 2):14–25. https://doi.org/10.1111/myc.12329

This manuscript provides a step-by-step guides for the successful implementation of an AFS program.

20. Agrawal S, Barnes R, Brüggemann RJ, Rautemaa-Richardson R, Warris A. The role of the multidisciplinary team in antifungal stewardship. J Antimicrob Chemother. 2016;71(suppl 2):ii37–42. https://doi.org/10.1093/jac/dkw395.
21.• Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44:159–77. https://doi.org/10.1086/510393.

These are the guidelines issued by the IDSA which support programs for use of antimicrobials, including antifungals.

22. Pfaller MA, Castanheira M. Nosocomial candidiasis: antifungal stewardship and the importance of rapid diagnosis. Med Mycol. 2016;54:1–22. https://doi.org/10.1093/mmy/myv076.
23. Rouzé A, Loridant S, Poissy J, Dervaux B, Sendid B, Cornu M, et al. Biomarker-based strategy for early discontinuation of empirical antifungal treatment in critically ill patients: a randomized controlled trial. Intensive Care Med. 2017;43:1668–77. https://doi.org/10.1007/s00134-017-4932-8.
24. Hull CM, Purdy NJ, Moody SC. Mitigation of human-pathogenic fungi that exhibit resistance to medical agents: can clinical antifungal stewardship help? Future Microbiol. 2014;9:307–25. https://doi.org/10.2217/fmb.13.160.
25. Miyazaki T, Kohno S. Current recommendations and importance of antifungal stewardship for the management of invasive candidiasis. Expert Rev Anti-Infect Ther. 2015;13:1171–83. https://doi.org/10.1586/14787210.2015.1058157.
26. Shah DN, Yau R, Weston J, Lasco TM, Salazar M, Palmer HR, et al. Evaluation of antifungal therapy in patients with candidaemia based on susceptibility testing results: implications for antimicrobial stewardship programmes. J Antimicrob Chemother. 2011;66:2146–51. https://doi.org/10.1093/jac/dkr244.
27. Cornely OA, Koehler P, Arenz D, Mellinghoff SC, et al. EQUAL Aspergillosis Score 2018: an ECMM score derived from current guidelines to measure QUALity of the clinical management of invasive pulmonary aspergillosis. Mycoses. 2018;61:833–6. https://doi.org/10.1111/myc.12820.
28. Rzewuska M, Charani E, Clarkson JE, Davey PG, Duncan EM, Francis JJ, et al. Prioritizing research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper. Clin Microbiol Infect. 2019;25:163–8. https://doi.org/10.1016/j.cmi.2018.08.020.
29. Valerio M, Muñoz P, Rodríguez CG, Caliz B, Padilla B, Fernández-Cruz A, et al. Antifungal stewardship in a tertiary-care institution: a bedside intervention. Clin Microbiol Infect. 2015;21:492.e1–9. https://doi.org/10.1016/j.cmi.2015.01.013.
30. Valerio M, Rodriguez-Gonzalez CG, Muñoz P, Caliz B, Sanjurjo M, Bouza E, et al. Evaluation of antifungal use in a tertiary care institution: antifungal stewardship

urgently needed. J Antimicrob Chemother. 2014;69:1993–9. https://doi.org/10.1093/jac/dku053.
31. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother. 2014;69:1162–76. https://doi.org/10.1093/jac/dkt508.
32. Bal AM, Shankland GS, Scott G, Imtiaz T, Macaulay R, McGill M. Antifungal step-down therapy based on hospital intravenous to oral switch policy and susceptibility testing in adult patients with candidaemia: a single centre experience. Int J Clin Pract. 2014;68:20–7. https://doi.org/10.1111/ijcp.12231.
33. Lempers VJ, Brüggemann RJ. Antifungal therapy: drug-drug interactions at your fingertips. J Antimicrob Chemother. 2016;71:285–9. https://doi.org/10.1093/jac/dkw159.
34. Barnes RA, Stocking K, Bowden S, Poynton MH, White PL. Prevention and diagnosis of invasive fungal disease in high-risk patients within an integrative care pathway. J Infect. 2013;67:206–14. https://doi.org/10.1016/j.jinf.2013.04.020.
35. Morii D, Ichinose N, Yokozawa T, Oda T. Impact of an infectious disease specialist on antifungal use: an interrupted time-series analysis in a tertiary hospital in Tokyo. J Hosp Infect. 2018;99:133–8. https://doi.org/10.1016/j.jhin.2018.01.003.
36. Ananda-Rajah MR, Slavin MA, Thursky KT. The case for antifungal stewardship. Curr Opin Infect Dis. 2012;25:107–15. https://doi.org/10.1097/QCO.0b013e32834e0680.
37. Bienvenu AL, Argaud L, Aubrun F, Fellahi JL, Guerin C, Javouhey E, et al. A systematic review of interventions and performance measures for antifungal stewardships programmes. J Antimicrob Chemother. 2018;73:297–305. https://doi.org/10.1093/jac/dkx388.
38. López-Medrano F, Juan RS, Lizasoain M, Catalán M, Ferrari JM, Chaves F, et al. A non-compulsory stewardship programme for the management of antifungals in a university-affiliated hospital. Clin Microbiol Infect. 2013;19:56–61. https://doi.org/10.1111/j.1469-0691.2012.03891.x.

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