Title

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium

Journal

The Journal of Infectious Diseases, 222(Supplement_3)

ISSN

0022-1899

Authors

Johnson, Melissa D
Consortium, for the Mycoses Study Group Education and Research
Lewis, Russell E
et al.

Publication Date

2020-08-05

DOI

10.1093/infdis/jiaa394

Peer reviewed

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Core Recommendations for Antifungal Stewardship: A Statement of the Mycoses Study Group Education and Research Consortium

Melissa D. Johnson,[1,a] Russell E. Lewis,[2,a] Elizabeth S. Dodds Ashley,[1,a] Luis Ostrosky-Zeichner,[3] Theoklis Zaoutis,[4] George R. Thompson III,[5] David R. Andes,[6] Thomas J. Walsh,[7] Peter G. Pappas,[8] Oliver A. Cornely,[9,10,11,12] John R. Perfect,[1] and Dimitrios P. Kontoyiannis[13]; for the Mycoses Study Group Education and Research Consortium

[1]Division of Infectious Diseases and International Health, Duke University Medical Center, Durham, North Carolina, USA, [2]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, [3]Division of Infectious Diseases, Laboratory of Mycology Research, McGovern Medical School, Houston, Texas, USA, [4]Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [5]Division of Infectious Diseases, Department of Internal Medicine, University of California, Davis, Sacramento, California, USA, [6]Department of Medicine and Department of Medical Microbiology and Immunology, University of Wisconsin–Madison, Madison, Wisconsin, USA, [7]Transplantation-Oncology Infectious Diseases, Weill Cornell Medicine of Cornell University, New York, New York, USA, [8]Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA, [9]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [10]German Centre for Infection Research, partner site Bonn-Cologne, Cologne, Germany, [11]CECAD Cluster of Excellence, University of Cologne, Cologne, Germany, [12]Clinical Trials Center Cologne, University Hospital of Cologne, Cologne, Germany, and [13]Department of Infectious Diseases, Infection Control and Employee Health, MD Anderson Cancer Center, Houston, Texas, USA

In recent years, the global public health community has increasingly recognized the importance of antimicrobial stewardship (AMS) in the fight to improve outcomes, decrease costs, and curb increases in antimicrobial resistance around the world. However, the subject of antifungal stewardship (AFS) has received less attention. While the principles of AMS guidelines likely apply to stewarding of antifungal agents, there are additional considerations unique to AFS and the complex field of fungal infections that require specific recommendations. In this article, we review the literature on AMS best practices and discuss AFS through the lens of the global core elements of AMS. We offer recommendations for best practices in AFS based on a synthesis of this evidence by an interdisciplinary expert panel of members of the Mycoses Study Group Education and Research Consortium. We also discuss research directions in this rapidly evolving field. AFS is an emerging and important component of AMS, yet requires special considerations in certain areas such as expertise, education, interventions to optimize utilization, therapeutic drug monitoring, and data analysis and reporting.

Keywords. stewardship; antifungal; candidiasis; aspergillosis; guidelines; diagnostics.

Invasive fungal diseases (IFDs) afflict mostly critically ill or immunocompromised patients with complex underlying disease states and are associated with significant morbidity, mortality, and costs. These attributes, combined with the limited sensitivity of current fungal diagnostic tools, often leads to unnecessary and inappropriate prescribing of antifungal agents [1–4]. Nearly 3% of all hospital admissions and 7.7% of intensive care unit (ICU) admissions in the United States (US) are associated with the prescription of systemic antifungals [5, 6]. As much as 30%–50% of antifungal prescriptions could be optimized or are inappropriate [3, 7–10]. Overprescribing of antifungal agents puts patients at greater risk for drug toxicities and drug interactions, and has the potential to select for resistant fungi [11]. Antifungal agents are also among the costliest anti-infective agents on hospital formularies, and "at risk" populations continue to grow and to present with more IFDs. As such, antifungal prescribing has come under greater scrutiny, in keeping with the expansion of antimicrobial stewardship (AMS) programs to include antifungal agents and IFD management [12]. This document builds upon prior reports of building capacity and improving antifungal stewardship (AFS) programs [12, 13].

> **Recommendation:** Antifungal stewardship activities are an essential part of any comprehensive stewardship approach in facilities where antifungals are used.

Designing stewardship programs that incorporate standard principles, often called core elements, is widely accepted as a best practice [14, 15]. While the principles of AMS are essential to AFS, substantial differences exist in terms of the patient population at risk for IFD and diagnostic approaches. Globally, most nations are seeing increased growth of AMS programs [16]. Yet European surveys have suggested that relatively few hospitals have formal AFS programs [17], even though many of the established interventions used in AMS have been shown to be effective at improving the quality of antifungal prescribing and reducing costs [18–22]. Application of the core elements for AFS depends on the resources and expertise available

[a]M. D. J., R. E. L., and E. S. D. A. contributed equally to this work.

Correspondence: Dimitrios Kontoyiannis, MD, ScD, PhD (Hon), Division of Internal Medicine, Department of Infectious Diseases, Infection Control and Employee Health, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1460, Houston, TX 77030 (dkontoyi@mdanderson.org).

The Journal of Infectious Diseases® 2020;222(S3):S175–98

DOI: 10.1093/infdis/jiaa394

in the local institution, as well as support at the national and global level.

An international consensus panel developed a set of core elements that should universally apply to AMS programs. These elements seek to unify various nationally described best practices and reflect the current "state of the art" in optimizing antimicrobial use [12, 14, 23]. The identified elements are (1) engagement of the senior hospital management leadership toward AMS; (2) accountability and responsibilities; (3) available expertise on infection management; (4) education and practical training; (5) actions aiming at responsible use; (6) monitoring and surveillance; and (7) reporting and feedback [14].

In this document, we highlight specific challenges unique to AFS with respect to these core elements and provide recommendations on how these challenges can be addressed. The recommendations will primarily focus on AFS as it relates to the 2 most common IFDs (invasive candidiasis and invasive aspergillosis), although the general principles are applicable to the management of a wide range of invasive mycoses. Although our recommendations will focus mostly on institutional approaches and applications of AFS, these may naturally and necessarily extend to other care settings such as the community, ambulatory care clinics, urgent care clinics, and nursing homes.

CORE ELEMENT 1: ENGAGEMENT OF SENIOR MANAGEMENT LEADERSHIP TOWARD ANTIMICROBIAL STEWARDSHIP

> **Recommendation:** Antimicrobial stewardship and antifungal stewardship goals should be integrated into hospital strategic plans and policies with senior leadership engagement, accountability, and dedicated resources to support these activities.

Senior leadership support has been shown to be a critical component of quality improvement programs, similar to AMS and infection prevention [24–28]. Over time, there has been increasing recognition of the value of senior leadership in hospital quality and safety. Leadership can both empower the stewardship programs to enact necessary changes and support expansion of stewardship goals throughout the organization by promoting engagement and awareness. In a 2013 systematic review of 122 publications, Millar and colleagues noted that high-performing hospital organizations in the US were more likely to have boards with a dedicated quality committee and have written policies, tools such as dashboards and scorecards, and established goals of quality improvement for the organization [29]. The largest hospital accreditation body in the US, The Joint Commission, has called for hospital leaders to establish a culture of safety as well as establish AMS programs as an organizational priority [30, 31]. These executive advocates should ensure that stewardship maintains a key place as part of organizational priorities as evidenced by inclusion in budgets, strategic plans, performance improvement priorities, job descriptions, and annual institutional goals. In addition, sufficient resources should be allocated to support achievement of these goals including personnel, operational resources, and information technology systems.

A recent survey of National Health Service (NHS) acute-care hospitals in England found that >50% of responding hospitals were lacking in the senior leadership component of the core elements [32]. Similarly, data from the 2015 National Healthcare Safety Network (NHSN) survey of 4569 acute and critical access hospitals in the US indicated that only 48.1% met all 7 Centers for Disease Control and Prevention (CDC) Core Elements of Antimicrobial Stewardship, and that Leadership Commitment had the second-lowest compliance rate of the core elements (67.7%). In multivariate analysis, having a written statement of commitment from the facility's leadership was the strongest predictor of meeting all 7 CDC core elements [33].

AFS should be prominent in stewardship discussions with leadership, as antifungal use often involves key "at risk" patient populations, is expensive, and may help leverage other stewardship activities including diagnostic stewardship. Administrators are frequently faced with the challenge of prioritizing the funding of multiple competing programs that similarly aim to optimize patient care, and cost-effectiveness may not necessarily translate into dollars saved for the institution. While cost reductions should not be the primary aim of any stewardship program, cost savings may be an added benefit to the healthcare system as antimicrobial use is optimized. A compelling argument may be that the AMS program will result in cost savings but also optimize patient care [34]. A recent study reported that antifungal expenditures in the United States exceeded $9.37 billion for the years 2005–2015, and direct healthcare costs associated with fungal diseases in the US exceeded $7.2 billion in 2017 [35, 36]. Given the high cost of many antifungal agents, it is possible that cost savings realized with AFS would likely offset much of the overall costs of running an entire AMS program and help make the business case for the entire program [22, 37]. Assessing the institutional impact of AFS within the overall AMS program could be an essential and potentially influential component of discussions with leadership. Similarly, working with leadership of service lines responsible for key areas of antifungal use, such as those responsible for oncology services, may prove more successful given their influence on providers and protocols governing day-to-day utilization of these agents.

It is possible that within an organization, depending on the frequency of fungal infections encountered and complexity of the patient population, AFS might not require extensive resources over and above that dedicated to AMS already. In some cases, the natural place for AFS may be as an extension of the AMS committee. However, the AFS needs of the individual facility should be evaluated carefully and resourced accordingly. In a recent survey of AFS programs at acute-care NHS Trusts in

England, 11% of participating centers reported having a dedicated AFS program, while 43% indicated that AFS was included as part of their AMS program and 26% stated that they did not have a dedicated AFS program but monitor antifungal utilization [17]. Twenty percent did not have a dedicated AFS program at all, and 27 of 34 responding facilities stated they would increase AFS activities if they could. Facilities not performing AFS indicated that this was most often due to a lack of resources such as staff time (67%) and competing priorities (48%). These barriers, as well as a lack of financial resources, have been cited repeatedly in the AMS literature.

Our authorship believes that hospital leadership should ensure an appropriate level of staffing and personnel to carry out AFS activities, where feasible and within the scope of individual institutional profiles. In an attempt to address this, several groups have published staffing models for AMS with considerations specific to healthcare settings (eg, inpatient, outpatient, long-term care) [38]. As of 2017, only 5 nations had standards for AMS staffing [39]. However, these staffing models and standards do not specifically differentiate AFS vs AMS needs and there is considerable variability in what are considered core AMS activities [38]. This remains an area of need for future investigations.

CORE ELEMENT 2: ACCOUNTABILITY AND RESPONSIBILITIES

Stewardship success hinges on having a highly functioning multidisciplinary team. This is not unique to AFS, but the team may need uniquely qualified members to incorporate the complex aspects of antifungal management. As previously mentioned, antifungal agents are often critical components of treatment protocols under the leadership of other specialties such as stem-cell or solid organ transplant and/or hematology/oncology. In addition to having defined and identified AMS leadership, engaged representatives from other areas of frequent antifungal use should be identified and incorporated as key stakeholders for AFS. Coordinating these various disciplines and the silos of care that exist is critical to the success of AFS.

As an example, antifungal prophylaxis in high-risk populations extends beyond acute hospitalization, and issues regarding antifungal drug access and acquisition in the outpatient setting become paramount in a successful therapeutic course. In these cases, failure to provide antifungal drug coverage can lead to the devastating consequence of a new IFD. Therefore, having team members that span the inpatient and outpatient settings is important. Similarly, antifungal therapy also involves many drug–drug interactions with essential treatments for underlying disease states, such as immunosuppressive agents following transplant. Any modifications desired by the AFS team should only be made after careful consideration of these other therapies and management strategies, and in consensus with the individual services. In the case of these high-risk populations, responsibility for the care of the patient lies with the primary specialties; stewarding of these antifungal agents should be included in those formal responsibilities.

> **Recommendation:** Core members of the stewardship team should have in-depth knowledge and clinical experience in the management of invasive fungal disease (IFD) in pertinent patient populations, including fungal epidemiology and susceptibility patterns; laboratory diagnosis of IFD; spectrum and pharmacokinetics of antifungal drugs; strategies for optimizing antifungal dosing and duration; fungal surveillance; and anticipating, interpreting, and managing drug–drug interactions, antifungal toxicities, and their management, as well as interpretation of therapeutic drug monitoring. This would include, whenever possible, infectious diseases (ID) physician(s) and ID-trained pharmacist(s).

As mentioned previously, the formation of a multidisciplinary team with the necessary expertise is essential to AFS activities. Core members of the stewardship team should have in-depth knowledge and clinical experience in the management of IFD in pertinent patient populations, including fungal epidemiology and susceptibility patterns; laboratory diagnosis of IFD; spectrum and pharmacokinetics (PK) of antifungal drugs; strategies for optimizing antifungal dosing and duration; fungal surveillance; and anticipating, interpreting and managing drug–drug interactions, antifungal toxicities, and their management as well as interpretation of therapeutic drug monitoring (TDM) [40]. Involvement of knowledgeable ID consultants is important [41]. However, such expertise may not always be available within the institution and guidance may need to be obtained from outside sources. In a recent US survey, 31% of 528 responding hospitals did not have an ID physician on the stewardship committee and only 52% had an ID-trained pharmacist [42].

Similar to generalized AMS where the definition of stewardship expertise remains unclear, AFS is subject to significant challenges due to the lack of AFS-specific training programs. In limited-resource settings, it may be possible to increase involvement of ID leadership in local AFS activities by (1) contracting or resource-sharing with other hospitals for ID-trained personnel; (2) utilizing resources within a health system network, recognizing that local needs and personnel must be taken into consideration at the network level; (3) using collaborative organizations to share data and resources (eg, private/commercial consulting organizations, statewide groups in the US, or national networks in many countries); or (4) engaging telehealth support for stewardship efforts at the local level [43]. A supplemental or alternative approach when ID expertise is not available would be to identify and train local personnel in AFS principles and best practices.

> **Recommendation:** We recommend that antifungal stewardship teams develop ongoing collaborative strategies

to engage key practitioners who most frequently manage invasive fungal disease (eg, weekly clinical rounds), or include clinical specialists from high-prescribing specialties as core team members in stewardship discussions involving antifungal therapies.

Engagement with clinical specialties that involve the most frequent prescribing of antifungal therapy, either by routinely attending clinical rounds or through high visibility in key units, builds trust and communication and is key to successful stewardship of these agents [44]. Unsolicited patient care recommendations are more likely to be accepted when colleagues are viewed as team members rather than external auditors who lack direct knowledge of the patient or are unwilling to accept direct responsibility for medical decisions [40]. Many transplant physicians, intensivists, hematologists, and transplantation-oncology ID physicians acquire significant expertise in the management of IFDs and should play important roles in the AFS programs [40]. Their participation is critical for the development of effective care bundles and making daily decisions for patient management. AFS programs should engage these clinical specialists or identify "champions" within these specialties with an interest in improving the management of IFD.

Regarding implementing routine stewardship activities, the effectiveness of stewardship interventions is improved if a team member has opportunities to discuss the patient's clinical history and plans for future surgery, transplant, and/or chemotherapy, and the potential impact of antifungal treatment on the individualized treatment regimen of their underlying disease. For example, in patients with acute myeloid leukemia, mold disease increases not only short-term mortality risk but also long-term risk of disease relapse due to disruption of therapeutic plans scheduled after complete remission achievement (eg, consolidation chemotherapy, transplantation) [45–47]. Additionally, azole antifungals may have severe drug–drug interactions with many of the small-molecule kinase inhibitors used as targeted chemotherapy in consolidation regimens or to bridge patients to hematopoietic stem cell transplantation [48]. Therefore, decisions regarding antifungal prophylaxis should not be made in a "vacuum," but rather following multidisciplinary discussions to understand the patient's prognosis for relapse and the future treatment approaches, in order to maintain remission of the underlying malignancy.

Frequently, these practitioners are best positioned to provide optimal diagnostic approaches and to incorporate advances in their field into the management of IFD. For example, radiologic findings often drive decisions with regard to antifungal prescribing in patients with suspected invasive pulmonary aspergillosis, even though characteristic findings of the disease on chest computed tomography (CT) (eg, nodular opacities with or without a halo sign) are neither sensitive nor specific for mold disease and may drive unnecessary empiric antifungal prescribing [49, 50]. Improvement in the specificity and sensitivity of radiological detection of fungal lesions will likely improve AFS performance. Stanzani and colleagues reported that improved radiologic assessment using CT pulmonary angiography, which can distinguish angioinvasive fungal disease from more common bacterial pneumonia or other non-angioinvasive processes in the lung, supported reduction in empiric antifungal use among high-risk hematology populations with European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG)–defined possible aspergillosis [51]. Similarly, fluorodeoxyglucose positron emission tomography/CT may detect occult or undiagnosed disseminated IFD in more than one-third of patients and detect resolution of the infection sooner than conventional CT, possibly supporting earlier discontinuation of antifungal therapy [52–55].

CORE ELEMENT 3: AVAILABLE EXPERTISE ON INFECTION MANAGEMENT

As discussed above, it is important to have individuals with antifungal expertise as AMS committee members. Although not previously specifically addressed, expertise in fungal diagnostics is equally important to optimal AFS.

Recommendation: We recommend that centers that frequently manage patients with invasive fungal disease have access to timely conventional and non-culture-based diagnostic testing for *Candida* and *Aspergillus* species.

Early and accurate diagnosis of IFD is one of the most important factors influencing outcomes of fungal diseases and appropriate prescribing of antifungal therapy. Over the last 2 decades, non-culture-based tests (NCBTs) such as galactomannan, *Aspergillus* polymerase chain reaction (PCR), mannan, antimannan antibody, and (1→3)-β-D-glucan (BDG) have become essential tools for early detection of IFD in both neutropenic and nonneutropenic patients (Table 1). These tests have been incorporated in diagnostic criteria for IFD that can be managed through diagnostic-driven pathways in some centers that rely on early detection of biomarkers plus radiological or clinical signs (CT imaging findings, persistent fever, localizing symptoms) as a trigger for starting antifungal therapy [56, 57].

The high negative predictive values (NPVs) of NCBTs are valuable for de-escalation of empiric antifungal therapy, but require careful interpretation by clinicians with expertise in managing IFDs [68–71]. Although routine discontinuation of antifungal agents in patients with negative NCBTs has not been widely endorsed in treatment guidelines to date [57, 72, 73], negative tests provide useful microbiological evidence as part of a broader clinical and/or radiological assessment that could support discontinuation of empirical antifungal therapy. However, the performance of NCBTs can vary depending on

Table 1. Comparison of United States Food and Drug Administration–Approved Non-Culture-Based Diagnostic Tests for *Candida* and *Aspergillus*

Parameter	Serum (1→3)-β-D-Glucan (*Candida*) [58–60]	Serum Mannan/ Antimannan (*Candida*) [61]	Blood T2Candida (*Candida*) [62, 63]	PCR (*Candida*) [64]	Galactomannan (*Aspergillus*) [65]	Serum (1→3)-β-D-Glucan (*Aspergillus*) [66, 67]
Sensitivity	80%	58%	91%	73%	71%	81%
Specificity	80%	93%	98%	95%	89%	78%
PPV/NPV at 2% prevalence (screening[a])	9%	12.5%	0.5%	16.7%	8%	8%
	>99%	99%	>99%	99%	99%	>99%
PPV/NPV at 10% prevalence (screening[a])	30%	50%	81%	50%	41%	29%
	97%	95%	99%	94%	96%	97%
PPV/NPV at 30% prevalence (diagnosis[b])	<63%	77%	96.4%	74%	72%	62%
	90%	83%	96%	81%	87%	91%

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

[a]Screening: asymptomatic patients without localized signs of infection.

[b]Diagnosis: symptomatic patients with suspected infection.

the host, type of underlying immunosuppression, test sample (ie, serum vs bronchoalveolar lavage fluid), and concomitant medications or treatments [57, 74–76].

Diagnostic stewardship is becoming an important component of any anti-infective stewardship program. Judicious use of NCBTs requires the ordering practitioner to consider the pretest probability of IFD in the presenting patient. Disease likelihood relies on multiple factors, with the most common being the underlying disease risk factors for IFD, persistent fever on broad-spectrum antibiotic therapy, and the presence of any signs or symptoms consistent with IFD. The pretest probability for IFD in an individual patient may be estimated with institutionally validated prognostic risk models or risk scores, such as those reported for invasive candidiasis [77–80] and invasive aspergillosis [81]. However, such risk scores often must be adapted and validated to the local clinical context before broad institutional use [82]. Thus, it is more common in many medical centers to generally classify patients to be at high, low, or intermediate risk for developing IFD. Policies for diagnostic stewardship should be developed in conjunction with institutional colleagues from clinical microbiology laboratories and ID, particularly those with expertise in medical mycology.

As a general rule, NCBTs for IFDs have limited clinical utility if the pretest probability of IFD falls below 10% [83] or if a positive test does not increase the probability of disease above a threshold that would be considered for prophylaxis or therapy (ie, >15%–30%). Given that the global rate of invasive candidiasis in many ICUs ranges between 1.8% and 7.8% [80] and rates of probable or proven mold disease in the total hematology population are typically <3% [81], special attention should be paid by AFS programs to the use of NCBTs for screening in asymptomatic patients. Currently approved tests that measure galactomannan antigen and BDG are subject to frequent false-positive results and could trigger unnecessary antifungal therapy or diagnostic procedures if frequently used in patient populations with a low pretest probability of IFD. For example, Duarte and colleagues [84] reported that routine galactomannan screening in patients receiving posaconazole prophylaxis was more frequently associated with a false-positive result (13.8%) rather than true disease, resulting in increased unnecessary diagnostic studies (chest CT) in asymptomatic patients.

A number of rapid diagnostic tests for invasive candidiasis, including matrix-assisted laser desorption/ionization–time of flight spectrometry, multiplex PCR, peptide nucleic acid fluorescent in situ hybridization, and T2 magnetic resonance detection panels, have been introduced over the last 2 decades (Table 2). The clinical impact of these rapid tests, particularly their ability to reduce time to appropriate antifungal therapy or reduction in antifungal usage, has been consistently shown to be improved when results are reported in coordination with AFS activities [85–90]. Although they are still being investigated, non-culture-based biomarkers hold promise for early diagnosis of mucormycosis [91, 92].

CORE ELEMENT 4: EDUCATION AND PRACTICAL TRAINING

> **Recommendation:** We recommend the development of targeted educational programs as part of a multifaceted antifungal stewardship program to address knowledge gaps in the interpretation of microbiology laboratory results, differentiation of colonization vs infection, indications for prophylaxis vs empiric therapy, and antifungal therapy dosing and monitoring.

Education alone is not considered to be an effective AFS intervention [12]. However, several studies have documented frequent gaps in prescribers' knowledge with respect to differentiating fungal colonization from disease and indications for prophylaxis vs empirical antifungal treatment [102].

Numerous studies have surveyed inappropriate antifungal use in hospitals and have shown significant gaps in the knowledge of appropriate antifungal prescribing. For example, Nivoix et al found that 40% of antifungal use in a French hospital was inappropriate with respect to either indication, dosage, risk of

Table 2. Comparison of United States Food and Drug Administration–Approved Commercial Rapid Identification Systems for *Candida* Species From Blood

Method (Brand Name[s], Manufacturer[s])	Organisms Identified	Hands-on Time, min	Turnaround Time[a], min	Recovery From Blood[a]	Reference
MALDI-TOF (VITEK MS, bioMérieux; MALDI Biotyper CA, Bruker Corp)	Bacteria and yeasts, >200 spp	1	5	Indirect	[85, 94]
Multiplex PCR (Film Array Blood Culture Identification, BioFire Diagnostics; ePLEX BCID-FP panel, GenMark Diagnostics)	19 bacteria and 5 *Candida* spp	2	60	Indirect	[95, 96]
	11 *Candida* spp including *C. auris*, also: *Cryptococcus*, *Fusarium*, and *Rhodotorula*; gram-positive and gram-negative bacteria panels	<2	90		
FISH (*C. albicans/C. glabrata* PNA FISH, AdvanDx; Yeast Traffic Light PNA FISH, AdvanDx; Accelerate Pheno BC Test Kit, Accelerate Diagnostics)	*Candida, 2* spp	5	90	Indirect	[87, 88, 97–99]
	Candida, up to 5 spp 14 bacteria, 2 *Candida* spp (*C. albicans* and *C. glabrata*)	<10	90		
T2MR (T2 *Candida* Panel, T2 Biosystems)	*Candida*, 5 spp	<5	180–300	Direct	[100, 101]

Table adapted and modified from Hamdy et al [93].

Abbreviations: MALDI-TOF, matrix-assisted laser desorption/ionization–time of flight; PCR, polymerase chain reaction; PNA FISH, peptide nucleic acid fluorescent in situ hybridization; T2MR, T2 magnetic resonance.

[a]T2MR is currently the only United States Food and Drug Administration–approved rapid molecular diagnostic system that identifies *Candida* spp directly from blood and that can be performed before positive blood culture; other methods are performed only after growth on blood culture has been noted.

drug–drug interactions, or antifungal susceptibility results [7]. The most common reasons for inappropriate prescribing were use of prophylaxis for nonapproved indications, lack of weight-based dosing of fluconazole, and lack of dose reduction according to renal function. In a retrospective cohort study of 305 hospitalized patients at 4 US medical centers, Jacobs and colleagues found that roughly half of patients with asymptomatic candiduria received antifungal therapy despite data suggesting the value of no treatment [9]. A recent PK point-prevalence study reported that antifungal agents, particularly fluconazole, were routinely underdosed in one-third of patients with sepsis [103], a previously reported independent risk factor for patient death [104]. The finding of relatively high prevalence of fluconazole underdosing is noteworthy as many AFS programs do not monitor fluconazole prescribing because of the relatively low cost of this medication [17, 20, 105, 106], even though it is still the most widely prescribed antifungal agent (often inappropriately for candiduria or yeast in respiratory specimens). The predictive value of *Candida* in the urine or respiratory secretions for invasive candidiasis is very low, even in severely neutropenic patients [107, 108]. Misuse of fluconazole may profoundly influence the epidemiology of *Candida* bloodstream infections and is associated with increased rates of antifungal resistance [109, 110].

Valerio et al evaluated prescriber knowledge of IFD diagnosis and treatment and identified several key knowledge gaps in the areas of interpretation of microbiological results, antifungal selection, and dosing [102]. Knowledge gaps identified in the prescriber survey were then used to design an interactive training strategy that was incorporated into a multifaceted AFS program with patient bedside interventions [22]. Hence, education plays an important complementary role with other AFS initiatives to improve appropriateness of antifungal prescribing.

Recent trends in integrating stewardship principles into the curricula of a variety of healthcare and postgraduate training programs is encouraging and essential to improving the knowledge of our workforce; these programs should also include elements of AFS.

CORE ELEMENT 5: OTHER ACTIONS AIMING AT RESPONSIBLE ANTIMICROBIAL USE

Recommendation: We recommend, whenever possible, that infectious diseases consultation be performed for patients with invasive fungal diseases such as fungemia, invasive aspergillosis, mucormycosis, and cryptococcal meningitis.

The complexity of patients who acquire IFDs is well recognized, and mortality rates associated with these infections are among the highest of all infectious diseases. Several recent studies have demonstrated the impact of ID consultation on outcomes in patients with candidemia and cryptococcosis and have shown improvement in the performance of quality measures and/or lower mortality [111–119]. This is especially important in hematology units with high prevalence of resistant fungi or presence of non-*Candida* opportunistic yeasts as causes of fungemia, where general guideline-based recommendations for preemptive antifungal use might not be optimal [120]. Data are lacking for other individual IFDs, but ID consultation for these other infections may be embedded in a comprehensive approach to care [121], and specialized infection management will likely be critical. While face-to-face consultation is commonplace in the US and may be preferable, it is not always readily available in all circumstances and resource-limited settings. In these situations, it may be especially important to implement other pathways and stewardship interventions to optimize care [42, 43, 122, 123]. A recent study evaluated published data on outcomes of telemedicine vs in-person ID consultation, but the variety of methods

and outcomes used in the primary literature hampered meta-analysis [123]. This is an evolving area deserving of further study.

Recommendation: We recommend the development of institutional care pathways or treatment bundles as well as guidelines to improve the probability that diagnostic and therapeutic interventions for invasive fungal disease are delivered in a timely and logical sequence to maximize patient outcomes and provider education.

Prescriber education and the development of local guidelines are often the first steps for implementing AFS programs [44]. National or international guidelines are available for treatment and prevention of common IFDs and provide expert evaluation of published evidence concerning the best diagnostic and therapeutic approaches. Several noncontrolled studies have suggested that patients are more likely to have early consultation by an ID specialist, earlier source control, timely diagnostic examinations, and appropriate antifungal therapy selection and treatment duration when prescribers adhere to treatment guidelines during the management of invasive candidiasis [112, 116, 124–128]. However, the adherence rates to treatment guidelines may be relatively low outside large-high volume tertiary care or university-affiliated medical centers [129, 130]. More recently, quality scoring systems have been proposed to provide metrics of prescriber adherence to international guidelines for invasive candidiasis [131], invasive aspergillosis [132], cryptococcosis [133], and mucormycosis [134], although it is still unknown whether such quality scores are associated with improved patient outcomes.

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 another useful strategy to ensure that critical diagnostic tests and source control procedures are performed in a timely fashion when antifungal therapy is started, in order to maximize treatment effectiveness. These bundles must be available at the point of care, whether embedded in computer decision support systems or linked to expert prescribers such as ID physicians or clinical pharmacists, in order to facilitate earlier consultation for questions concerning optimal drug selection, dosing, or management of drug interactions in medically complex or critically ill patients. Even without ID consultation, treatment bundles for candidemia developed and implemented by members of the AMS team have been shown to improve performance of elements such as antifungal therapy utilization and duration, ophthalmological examination, and removal of central venous catheters [135]. Algorithms have been proposed for preemptively treating cryptococcal infection on the basis of cryptococcal antigen screening in asymptomatic patients with newly diagnosed human immunodeficiency virus in resource-limited areas [136–138]. While the optimal antifungal therapy has yet to be defined for this situation, it demonstrates another way to facilitate prompt diagnosis and treatment of a serious fungal infection in a high-risk population where there is a lack of readily available ID consultants.

Most treatment bundles are not an exhaustive list of precise protocols, but rather a set of 3–5 steps that local experts believe are critical to execute at the time antifungal therapy has started and while monitoring response to treatment. Examples of typical bundle elements for invasive candidiasis and invasive aspergillosis are shown in Table 3.

Takesue and colleagues developed a 9-component management bundle for invasive candidiasis based on Infectious Diseases Society of America (IDSA) guidelines that focused on 3 elements at the start of antifungal therapy and 6 elements for follow-up after antifungal therapy was started [126]. The bundle was implemented in 11 regional medical centers and was used to manage 648 nonneutropenic patients with candidemia. The investigators found a significant difference in clinical outcomes between patients with and without bundle compliance (92.9% vs 75.8%, $P = .011$). Independent elements of the bundle that contributed to clinical success of candidemia treatment included central venous catheter removal within 24 hours after confirmation of a positive blood culture, assessment of the clinical efficacy after 3–5 days of antifungal therapy to consider the necessity of alternative treatments, and continuation of antifungals at least 2 weeks after clearance of *Candida* from the bloodstream. Vena and colleagues demonstrated that a more exhaustive bundled approach for patients with candidemia was associated with lower 14- and 30-day mortality [139]. Admittedly, there may be some disagreement regarding the merits of individual aspects of these treatment bundles [144–148], but the data suggest that, overall, treatment bundles can be a very effective approach toward improving antifungal prescribing and improving patient outcomes.

Recommendation: Ongoing interventions such as "handshake stewardship rounds" or postprescription review and feedback should be considered an essential part of a comprehensive antifungal stewardship approach.

Expert postprescription review and feedback (PPRF) has been identified as the most valuable intervention for improving antifungal prescribing and reducing antifungal consumption and costs [12, 106]. PPRF focuses on the identification of target patient populations when pathogens are identified or a target (typically high-cost) antifungal is prescribed. These triggers lead to an evaluation of the IFD management by one member of the AFS team (eg, ID physician, pharmacist, and/or clinical microbiologist) who can advise the prescriber about patient-specific clinical and microbiological issues to improve care.

Recent studies have reported the benefit of newer interventions such as "handshake stewardship rounds" that engage providers in an ongoing discussion about rational antimicrobial prescribing. In a children's hospital setting, this approach was

Table 3. Sample Care Bundles for Invasive Candidiasis and Invasive Aspergillosis

Bundle	
Invasive candidiasis management bundle	
At the time therapy is being started	Perform 2 high-volume blood cultures (40 mL) prior to starting therapy
	Removal of existing CVCs within 24 h of diagnosis
	Initial appropriate selection and dosing of antifungals considering local epidemiology started within 12 h of culture
	Ophthalmological exam within the first week of diagnosis
After starting therapy	Follow-up blood cultures daily until clearance of candidemia is documented
	Echocardiography in patients with persistent fungemia, fever, or new cardiac symptoms
	Assessment of clinical efficacy 3–5 d after starting therapy and evaluating the need for alternative therapy based on culture identification and susceptibility results are available
	Administration of at least 2 wk of therapy after clearance of blood cultures (longer with organ involvement)
	Step-down to oral fluconazole therapy in patients with a favorable clinical course and an isolate with documented susceptibility
Invasive aspergillosis management bundle	
At the time therapy is being started	Serum galactomannan test repeated twice in patients not on mold-active azole prophylaxis
	CT imaging of chest and/or sinus/brain in patients with symptoms localized at these signs
	Early bronchoscopy (within 48 h) with cytology examination and culture of BAL fluid, measurement of galactomannan antigen titer in BAL; transbronchial biopsy if feasible
	Initial appropriate selection and dosing of antifungal agents considering previous antifungal exposure and local epidemiology
	Systematic screening for drug interactions using a computerized drug interactions database for any patient starting or stopping a triazole antifungal agent
After starting therapy	Periodic (eg, weekly) testing of serum galactomannan (if aspergillosis) as an adjunct criterion to assess treatment response
	TDM of voriconazole and posaconazole and possibly isavuconazole serum levels to document adequate drug exposures
	Assessment of therapy appropriateness based on microbiological, culture, or histological results
	Repeat chest CT imaging after 3–4 wk and periodically based on response, to assess infection status and/or progression
	Step-down to oral triazole therapy in patients with a favorable clinical course

Sources: [116, 126, 131, 132, 139–143].

Abbreviations: BAL, bronchoalveolar lavage; CT, computed tomography; CVC, central venous catheter; TDM, therapeutic drug monitoring.

associated with a 12.1% decrease in antifungal days of therapy (DOT) per 1000 patient-days (131 to 109 DOT/1000 patient-days) [149]. Similarly, academic detailing rounds have been reported to increase concordance with AMS recommendations even in the challenging setting of solid organ transplantation [150]. This conceptually simple, yet time- and resource-intensive type of stewardship intervention is recognized as an effective and sustainable stewardship practice and is worthy of further consideration [151]. These and other AFS activities are outlined in Table 4.

Other methods such as preauthorization may be used, but in at least 2 recent studies have been shown to be less effective for AMS [153, 154]. PPRF was associated with more pharmacist interactions with clinicians, identification of more instances of inappropriate antimicrobial use, and improved de-escalation than preauthorization. Strict preauthorization may also be challenging to implement owing to the difficulty in ensuring a thorough and timely review of antimicrobial utilization by a member of the AMS team prior to the first dose [154].

Recommendation: We recommend that facilities evaluate the quality of antifungal prescribing on a systematic basis, and use data-driven strategies to further optimize antifungal stewardship interventions.

Data-driven approaches have been shown to aid stewardship programs in optimizing antimicrobial use. Conducting medication-utilization evaluations or disease state–based evaluations can be an important part of this work, as these illuminate potential areas for improvement [155]. Examples of performance measures and outcomes that could be assessed are shown in Table 5. Several tools have also been developed to help AFS teams in evaluating antifungal use and quality of care for patients with fungal infections [3, 131–134]. These tools have not yet been widely utilized, but are a promising area to support data-driven AFS efforts.

Recommendation: Additional research is needed to develop and evaluate new tools to facilitate antifungal stewardship, so that interventions have maximal impact and require minimal resources.

Table 4. Essential, Achievable, and Aspirational Antifungal Stewardship Activities

Stewardship Activity Level	Description
Essential	Development of institutional treatment pathways or bundles for antifungal prophylaxis and empiric therapy
	Development of targeted education programs for appropriate diagnosis and treatment
	Antifungal prescription review for drug–drug interactions
	Handshake rounds or postprescription review and feedback
	Intravenous to oral transition program
	Local surveillance and reporting of IFD to prescribers
Achievable	Rapid non-culture-based diagnostic tests for *Candida* and *Aspergillus* spp communicated to AFS team/clinicians
	Provide timely antifungal susceptibility testing results provided and communicated in a timely manner to AFS team/clinicians
	Specific comments to guide therapy and antifungal dosing recommendations are provided on microbiology reports
	Cumulative antifungal susceptibility reports reported to prescribers
	Timely TDM reported to AFS team and clinicians
	Review of autopsy reports and patient outcomes systematically to assess for undiagnosed IFDs and/or underutilization of antifungal agents
Aspirational	Participate in regional or national surveillance systems
	Individualized patient risk assessment (eg, institutional risk model, genetic risk factor screening)
	Optimize use of point-of-care microbiological tests, when available
	Utilize personalized TDM-dose adaptation (such as Bayesian methods) for antifungal therapy
	Incorporate advanced radiologic approaches for invasive aspergillosis (CT pulmonary angiography, FDG PET/CT)

Table adapted and modified from Morency-Potvin et al [152].

Abbreviations: AFS, antifungal stewardship; CT, computed tomography; FDG PET/CT, fluorodeoxyglucose positron emission tomography/computed tomography; IFD, invasive fungal disease; TDM, therapeutic drug monitoring.

In the future, additional innovative methods for AFS may be employed. These include the use of artificial intelligence to better identify opportunities for optimizing fungal infection diagnosis and antifungal prescribing. One recent study described such an approach, which used machine learning algorithms to identify invasive fungal pneumonia through review of CT scan reports from patients with hematologic malignancies [156]. Medical record reviews were subsequently performed to verify proven/probable invasive mold disease and identify potential areas of process improvement for the hospital, such as selection and administration of appropriate antifungal prophylaxis, attainment of therapeutic concentrations of prophylactic antifungals, and delays in performance of diagnostic testing. While there are several limitations to this approach (eg, its independent impact on AFS and the sensitivity, specificity, positive predictive value [PPV], and NPV of natural language in different types of high-risk patients where radiologic findings might be due to several other causes such as extramedullary leukemia or coinfection), this is an intriguing area where additional development could potentially result in new tools that will help facilitate AFS activities.

In addition, novel methods such as time-series analyses and linear regression have been used to identify periods of over- and underutilization of antibiotics within a given hospital, allowing for identification of "antimicrobial use outbreaks" [157]. These methods effectively and necessarily control for seasonality and baseline expected antimicrobial utilization associated with a certain level of patient acuity within a facility, and similar approaches have been effectively utilized by infection prevention programs for many years. A pattern of unexpected antimicrobial and/or antifungal use can be identified and investigated more rapidly, adding efficiency to the work of the stewardship team. These methods could be potentially applied to AFS as a way of generating more meaningful internal data for action by stewards.

Table 5. Example Performance Measures for Antifungal Stewardship Evaluations

Performance Measure
Mortality (or for prophylaxis, fungal-free survival)
Length of stay
Clinical response (treatment success, stable disease, failure)
Appropriate choice of antifungal agent, dose, route, duration
Time to (targeted/optimal) therapy
Adherence with practice guidelines
Persistent culture positivity/time to culture resolution
Recurrent or breakthrough infection
Performance of quality measures (ie, ophthalmologic examination, galactomannan testing, follow-up cultures performed)
Therapeutic drug monitoring performed/achievement of therapeutic levels

CORE ELEMENT 6: MONITORING AND SURVEILLANCE

> **Recommendation:** We recommend that all centers that manage patients with invasive fungal disease establish or adapt local surveillance systems for fungal infections to support antifungal stewardship program initiatives.

Adherence to treatment guidelines is enhanced when evidence-based treatment recommendations are adapted to local circumstances, epidemiology, and care pathways with input from local expert clinicians [44]. This requires institutions to

have adequate surveillance systems in place to measure the IFD burden and epidemiological trends that help direct stewardship strategies. Continuous surveillance in hospitals is also essential for detecting and containing emerging threats such as multidrug-resistant *Candida auris* [158, 159].

The key elements of this surveillance should include (1) standardized case definitions for IFD [160]; (2) defined patient populations identified for continuous monitoring; (3) identification of cultured fungal pathogens to the species level whenever possible; (4) established mechanisms for real-time reporting, analyzing, and disseminating data to prescribers; and (5) incentives for conducting surveillance [158].

Surveillance of IFD is inherently challenging as traditional culture-based methods for case diagnosis have limited sensitivity, so many patients treated with systemic antifungals may be missed. An increasingly larger percentage of cases are diagnosed by NCBTs. Distinguishing colonization from infection can be difficult for *Candida* species, and in the case of *Aspergillus* species may require histopathological evidence of tissue or organ invasion by fungi [160], which is often difficult in critically ill or severely pancytopenic patients. Even in the era of more sensitive fungal biomarkers, many clinically significant IFDs are missed [161]. As many immunocompromised patients with diagnostic imaging features of invasive mold infection on chest CT scan receive empirical antifungal therapy in the absence of positive cultures or NCBT results, such cases may not be detected in a routine AFS monitoring program.

Recommendation: We recommend that centers routinely managing invasive fungal diseases have access to timely antifungal susceptibility testing.

Antifungal susceptibility testing is recommended in both US and European treatment guidelines during the management of invasive candidiasis to guide treatment selection and support stepdown therapy to oral triazoles [140, 141], especially in nonneutropenic patients. Its contribution is less clear in high-risk neutropenic patients with cancer where azole-resistant species are quite common [162, 163]. The role of in vitro susceptibility testing in the management of invasive aspergillosis and other molds is less well established [142,143,164], but is likely to increase in the near future with reports of increasing triazole resistance in *Aspergillus* species, the emergence of resistant non-*Aspergillus* molds, and the potential future approval of new antifungal classes [11, 165]. The Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing have developed standardized microdilution broth antifungal susceptibility testing methods with associated clinical breakpoints for most common fungal species and frequently prescribed antifungals [166, 167]. A number of other commercial testing methods (eg, agar diffusion tests [disk and gradient strips], commercial microbroth dilution tests, or the semiautomated VITEK system [bioMérieux, Marcy l'Etoile, France]) are available. All of these tests can reliably detect triazole and echinocandin resistance; however, local validation and expertise in antifungal susceptibility testing are important for interpretation [168].

An emerging area of research in this regard involves identifying predictors of antifungal resistance among at-risk populations [169–173]. Further development and validation of predictive models may aid in AFS efforts to optimize antifungal selection and utilization in these populations where antifungal resistance is more commonly encountered.

Recommendation: Although there are limited data evaluating their utility for antifungal stewardship, we recommend that centers that perform routine antifungal susceptibility testing develop cumulative antifungal susceptibility reports.

Susceptibility data can be used to generate cumulative antimicrobial susceptibility reports (CASRs) to serve as an epidemiological surveillance tool and to assess the effectiveness of different stewardship interventions. Antibacterial CASRs help prescribers select effective therapy when culture results are pending and aid ASPs in informing and updating local guidelines for empirical treatment of common infection syndromes including recommendations for prophylaxis [152]. CASRs also provide the rationale for antimicrobial formulary selection, surveying local resistance and benchmarking for collateral impact of antibiotic use in the institution (eg, incidence of fluoroquinolone or carbapenem resistance), as well as identifying targets for stewardship interventions.

Few hospitals currently report fungal susceptibilities in CASRs, and unlike antibacterial agents [174], no specific standards have been proposed on how to construct or analyze such reports for antifungals. Nevertheless, a number of studies have demonstrated correlations between antifungal usage and the emergence of resistance in *Candida* species [173, 175, 176]. Current guidelines for antibiotic CASRs recommend testing only diagnostic (not surveillance) first isolates [174]. Additional analysis of follow-up cultures may be necessary to fully understand the presence of resistant organisms within a facility [169, 177]. For *Aspergillus* species, surveillance of triazole resistance may also require environmental surveillance; expert recommendations have discouraged empiric triazole use for *Aspergillus* in high-risk patients when environmental triazole resistance rates exceed 10% [178].

Antifungal CASRs also provide useful year-to-year epidemiological data that are important for analyzing susceptibility trends and evaluating the utility of new antifungals currently in development with unique spectra of activity. Given the small number of isolates at some centers, it is likely that susceptibility data from multiple years will need to be combined to provide a reliable picture of susceptibility rates. Shifts in patient mix or factors predisposing to IFDs among a facility's population may also impact susceptibility over time and should be considered [172, 179].

Recommendation: We recommend that antifungal stewardship promote rational diagnostic testing and that the results of both fungal culture and non-culture-based tests are communicated to antifungal stewardship teams to facilitate "real-time" interventions.

Generally, the high NPV of BDG, mannan–anti-mannan, or T2 magnetic resonance results should support decisions to withhold antifungal therapy in most patients with an estimated pretest prevalence of invasive candidiasis ranging from 0.4% to 10% [180]. However, the routine use of such tests in patients already at low risk for invasive candidiasis (ie, <5%) minimally reduces the already low probability of infection and is not cost-effective [181]. On the other hand, in some subsets of critically ill patients with intra-abdominal candidiasis, the NPV threshold of NCBT may not be sufficiently low (ie, ~ 6% of infection) to withhold antifungal therapy in a severely ill patient without an alternative diagnosis [180]. However, at least one group integrated both the NPV of the BDG test with a designated "champion for stewardship" within an ICU to reduce both antifungal consumption and patient mortality [182]. This strategy reduced inappropriate initiation of antifungal therapy by 90%. These types of biomarker-based strategies may work best within a team concept with multilayer controls.

Positive NCBTs must be carefully interpreted and can have unintended consequences of driving unnecessary antifungal prescribing. Specifically, positive NCBTs in patients with a very low pretest probability of disease are associated with a low PPV and are probably insufficient to justify treatment. A positive NCBT is most useful in patient populations with a reasonable baseline probability of disease (ie, 5%–15%) where a positive result would significantly upgrade infection likelihood and the justification for starting antifungal therapy [180]. Discrepant positive NCBT results in patients with negative cultures can be particularly challenging to interpret in some high-risk populations and can drive overprescription of antifungals and spurious reporting of hospital infection rates [180]. Thus, expertise in fungal diagnostics is required to understand both the strengths and limitations of NCBTs, and how the results should be interpreted.

Recommendation: We recommend that all patients have their medication record screened by a clinical pharmacist or clinician to carefully assess for antifungal drug interactions. This should also be performed when starting and stopping concomitant medications.

Drug–drug interactions are frequently encountered in patients requiring antifungal agents, and have been reported in approximately 88% of hospitalizations where mold-active triazoles were administered [183]. These interactions have potentially serious consequences including increased risk of QTc prolongation/cardiac arrhythmias, seizures, leukopenia or nephrotoxicity, and interference with the metabolism of chemotherapy, anesthetic agents, or cardiovascular medications as well as subtherapeutic antifungal concentrations. The complexity of patients commonly requiring antifungal therapy increases the likelihood of polypharmacy and the potential of such interactions occurring.

Frequently, severe drug–drug interactions may be identified without clear recommendations or medical guidance. In these cases, clinical expertise in managing IFD and drug–drug interactions in consultation with primary teams is important in developing an individualized strategy that minimizes risks to the patient while maintaining effective therapeutic regimens—for example, alternative prophylaxis regimen, TDM, or reduction of immunosuppressive drug dosage, such as with voriconazole and sirolimus.

Recommendation: We recommend that centers routinely managing patients with invasive fungal disease have access to timely therapeutic drug monitoring for triazole antifungal agents.

Triazole antifungals are the most frequently prescribed class of antifungal agents and subject to considerable intra-and interpatient PK variability [184], potentially putting patients at risk for subtherapeutic or toxic drug exposures [185–187]. TDM is the most direct way to identify patients who are at increased risk for treatment failure or toxicity due to altered PK. The availability of in-house TDM has been reported to shorten time to drug concentration results and attainment of therapeutic drug concentrations [187, 188]. However, the resources and expertise for in-house analysis may not be available in all centers or may only be available as a send-out test to an outside reference laboratory with associated delay before results are available. As a result, the role and application of TDM will vary from center to center.

TDM should be considered for patient populations who are likely to have unpredictable oral drug absorption if receiving oral triazoles, such as those with severe mucositis with diarrhea, vomiting, or who may have altered antifungal PK such as pediatric, obese, or critically ill patients with altered organ function or extracorporeal circuits including dialysis or extracorporeal membrane oxygenation [103, 189]. TDM has been specifically recommended for the majority of patients receiving voriconazole, posaconazole, itraconazole, and flucytosine [140, 184, 188]. However, even for fluconazole, subtherapeutic exposures have been observed in one-third of critically ill patients [10]; patients on high-volume renal replacement therapy [10, 103, 190] or pediatric patients with febrile neutropenia [191] may be particularly susceptible to lower exposures. Isavuconazole is a newer triazole and, in analysis of data from primary treatment of invasive aspergillosis (SECURE) trial and real world experience at one diagnostic laboratory, appeared to have relatively low inter- and intrapatient variability [192, 193]. Others have reported moderate variability in concentrations achieved in certain populations such as solid organ transplant recipients [194, 195]. Emerging data on echinocandins and

other antifungal agents in special populations may also support broader TDM requirements in certain populations [196–198].

Other scenarios where TDM may provide useful information include patients with suspected drug concentration–related toxicities (ie, central nervous system disturbance or hypokalemia with hypertension); intravenous to oral transitioning of therapy in patients with documented IFD; during the management of drug–drug interactions; or in patients with breakthrough IFD [184, 199]. In the latter case TDM helps establish whether breakthrough infection occurred in the presence of "therapeutic" triazole concentrations or may be attributed to inadequate drug exposures [200]. Decisions about the need to use TDM for particular antifungals may also fall under the umbrella of diagnostic stewardship and require consideration of local factors as well [93, 201]. Inherent to the success of TDM is a pharmacokinetically sound approach to the adjustment of dosages. This may be challenging in drugs with nonlinear, saturation, Michelis–Menten type PK, such as voriconazole. The AFS should include or have readily available the PK expertise to manage pharmacokinetically complex antifungal agents.

CORE ELEMENT 7: REPORTING AND FEEDBACK

Recommendation: All facilities should have a mechanism to track antifungal drug use.

Reporting and feedback can be one of the most powerful tools to drive change in AFS programs. The first and most widely used metric for any AMS is drug use. Available metrics for measuring antifungal drug use are largely the same as those available for antibacterial agents and will be familiar to the AMS team [202]. In general, measures of antifungal drug use that expand beyond expenditures and represent actual patient drug exposure are preferred. The 2 primary metrics used for this are DOT [203] and defined daily dose (DDD) [204]. While the former is the preferred metric in the US and the standard used for national inpatient antibiotic use measurement, the latter is widely used in Europe. There are advantages and disadvantages to each, related to the ability of each technique to be used widely (including in pediatric populations and in patients with significant hepatic and/or renal function) as well as to differences in collection method; DOT requires access to data from an electronic medication administration record, whereas DDD can be calculated from a variety of different data sources and approximate an average daily dose an adult patient would receive. A detailed review of these metrics including their advantages and disadvantages in special populations has been described elsewhere. These concepts apply to both antibacterial and antifungal agents [205].

To account for differences in patient volumes, a normalizing denominator such as patient-days, patient admissions, days present (a novel method described by the US CDC), or inhabitants for a given geographic area is typically applied [203, 206, 207]. The denominators can be used with either estimate of total drug use and have even been applied to normalize overall treatment costs (eg, antifungal cost per patient day). Each of these provides a way to compare data based on patient volumes and can readily be calculated at the level of the entire facility for a specific unit, ward, or type of ward within the facility.

However, there are certain factors that make quantifying and reporting on the quantity of antifungal drug use distinctly different than that of antibacterial use. First, the overall quantity of antifungal drug utilization at the facility level is on a different level of magnitude than that of antibacterial use. Interpretation of antibacterial use is aided by the sheer large quantity that is observed. For example, in US hospitals, approximately 50% of all hospitalized patients will receive some antibacterial agent while hospitalized [208]. As a result, even the smallest of facilities will be able to measure thousands of antimicrobial administrations each day. In contrast, <3% of all US inpatients will receive an antifungal agent during admission [6], meaning that use in some hospitals may be limited to very small patient populations, making aggregate summary data of overall antifungal use difficult to interpret. In fact, for the smallest of hospitals, variations in antifungal use can be attributed to a single patient with a suspected or confirmed fungal infection. These fluctuations can make stewardship interventions targeting antifungal drug use difficult to measure.

Conversely, in other cases, significant use of antifungal agents can obscure some use trends that might be of interest. This includes oncology units, where certain patient populations receiving antifungal prophylaxis may make it appear that there is 100% antifungal coverage (demonstrated as 1000 or >1000 DOT/1000 patient-days). When such a large proportion of patients are receiving continuous antifungal therapy, it can be difficult for data trends to emerge such as potentially unnecessary combination antifungal therapy warranting stewardship intervention.

Recommendation: Benchmarking antifungal use can aid in antifungal stewardship work.

Given the variation in antifungal drug use that can be seen based on hospital size and patient population, finding similar hospitals with which to compare data can be one of the best ways to begin identifying targets for AFS interventions based on consumption data. However, finding a source for benchmarking can be difficult. Both the US and Europe have mechanisms to benchmark and compare antifungal drug use.

In the US, the NHSN, administered by the CDC, has developed risk-adjusted metrics for antimicrobial use. In the 2019 update of these methods, antifungal agents targeting invasive candidiasis were included for the first time, permitting hospitals to compare antifungal use in adult and pediatric medical, surgical, and combined medical and surgical wards and ICUs as well as adult step-down and hematology/oncology units [203, 209]. Adult antifungal use in DOT per 1000 days present is risk-adjusted for several facility-level factors, including location type, facility type, total number of hospital as well as ICU

beds, and average length of hospital stay. Facility use is reported as a ratio of the observed DOT compared to the risk-adjusted expected DOT. The reported ratio is referred to as the standardized antibiotic administration ratio (SAAR), with values >1 representing more use than predicted. A SAAR was also recently developed for neonatal fluconazole use and can be used for neonatal critical care units and step-down nurseries [209].

These larger national and regional comparisons are relatively new, and not all facilities are able to report the data needed for these benchmark reports. As a result, more informal benchmarking groups including provincial, state, and regional stewardship collaboratives that are willing to share data have also formed; this collaboration can also happen with select drug purchasing groups. While there are no specific standards that have been developed for these informal collaboratives, there are some key principles that should be followed. First, data should be obtained from the same source: Even when using a metric such as a DDD, if it is calculated by some partners using purchasing data and others using administration data, there may be a significant difference in what is observed due to the data source alone. There are several reasons why purchasing data do not reflect actual patient exposure owing to the practices and complexities of health system drug acquisition. Second, comparator hospitals with similar patient populations should be included, and this is especially true for facilities with oncology and solid organ transplant populations. Finally, data collection practices at the hospitals should be similar. There may be variability in results due to inclusion of certain areas in the hospital such as perioperative areas, where in some hospitals antimicrobial prophylaxis is recorded in the operating room (possibly in a separate electronic record) and in others attributed to the inpatient ward. Inclusion of alternate routes of administration can also influence results and should be consistent across hospitals. For example, in one stewardship collaborative, great variability was observed in overall antifungal use that was ultimately attributed to some facilities only reporting data regarding oral nystatin administration (unpublished data, Duke Antimicrobial Stewardship Outreach Network). Therefore, as with all benchmarking data, these data should be interpreted with caution to ensure that accurate and fair comparisons are being made.

Recommendation: Antifungal stewardship programs should ideally assess patient-level outcomes where possible.

In addition to quantifying antifungal drug use, stewardship programs should employ measures that assess the overall effectiveness of interventions. As a primary goal of any stewardship program, including those targeting antifungal use, appropriateness of prescriptions remains a metric of much interest. It has proven difficult to best define appropriate antimicrobial use [210, 211]. Consensus opinions have concluded that it is best to assess appropriateness of use by comparing patterns of use with locally accepted guidelines for best practices that are adjusted and refined to local patient prescribing practices and epidemiology of infection [202, 210]. Just as important may be examination of patient outcomes such as mortality, via autopsy studies and/or medical record reviews to assess for undiagnosed IFDs [212–214]. These endeavors may help to identify areas where antifungals have been underutilized or employed too late in the disease process, and may generate another actionable item for quality improvement activities as part of the AFS program.

Other indicators for measuring antifungal drug use that may be useful to AFS programs include the process measures of how often planned stewardship interventions are performed. Examples of these are described above for implementation of candidemia bundles [124] and can also include conversion from intravenous to oral therapies, the number of cases reviewed, the number of guidelines developed, and so forth [211]. In fact, measuring that a process was actually implemented is vitally important to measuring the impact of a program and should not be overlooked when planning stewardship interventions [93, 202, 205, 215].

There is a desire to capture more patient-centered metrics where possible. At present, data supporting AFS program impact on overall mortality, hospital length of stay, and ICU length of stay are largely limited to single-center experiences with variable outcomes [44, 93]. These may be challenging targets to influence with stewardship interventions given the complexity of underlying disease and the various factors that contribute to healthcare resource utilization. The prominent role of antifungal therapy in prophylaxis at many institutions provides the ability to track some novel outcomes such as infection-free prophylaxis courses and balancing measures such as breakthrough-resistant infections. These are important program outcomes that should be considered when defining AFS-related metrics [44, 106].

Recommendation: All antifungal stewardship programs should have a mechanism for direct data feedback to prescribers.

The CDC Core Elements of Stewardship promote using stewardship data to drive change by ensuring it is widely disseminated [15]. This is also vitally important to AFS efforts. As is the case with AMS, direct feedback to front-line prescribers either at the individual, service, or unit level has been described as a key factor for success for many antifungal-based stewardship interventions [3, 93, 216]. A plan to disseminate data to prescribers should be a part of any AFS program. These data may need to be different from information used to report stewardship program interventions to leadership, as it should be in a format to allow prescribers to easily interpret and apply to local practices, whereas leadership often receives data regarding AFS initiatives in aggregate.

CONCLUSIONS

This document addresses how the global consensus of core elements for AMS can be applied to antifungal therapy and

provides specific recommendations for developing coordinated interventions to measure and improve appropriate use of antifungal agents. Stewardship and its formal elements and principles attempt to put structure around utilization of antimicrobial agents, and it is clear that this effort can and should extend to antifungal agents and the prevention and management of IFDs. Given the high rates of inappropriate antifungal use in many institutions, the development of AFS programs provides a foundation for improved communication, diagnosis, and management of IFDs, while optimizing patient outcomes and increasing cost-effectiveness. Many of these recommendations are based on global utilization, but adoption

Table 6. Questions for Future Antifungal Stewardship–Related Clinical Research as Related to Each of the Core Elements

Core Element/Research Need
Leadership
• What are the conditions/data to support dedicated resources for AFS as it relates to type/volume of hospital practice?
• What are the minimal/optimal staffing requirements for a successful AFS program?
Accountability and responsibilities
• Silos of care vs team-based approach to AFS
• How to best deal with outlier or reluctant prescribers in specialty units (eg, hematology units)
• Core criteria for AFS Centers of Excellence
• Interface of infection prevention and AFS
• Impact of development and implementation of AFS training programs
Available expertise on infection management
• Better define what a credible local expert is and best communication practices with key stakeholders
• Evaluate the impact of telemedicine and AFS, particularly in resource-limited settings
• What are the barriers to implementing NCBTs for common IFDs and what is the AFS impact of implementing these strategies?
Education and practical training
• Best educational practices for sustained impact in AFS
Other actions aiming at responsible antimicrobial use
• Development/optimization of patient education and adherence strategies during chronic antifungal use as part of AFS efforts
• Side effects/allergies to antifungals and AFS
• Non-blood-based biomarkers (eg, volatile compounds, urine antigens), innovative radiology tests (eg, PET/CT, CT angiography), artificial intelligence/natural language processing as AFS accelerators
• When to stop antifungals as major component of AFS in invasive mold disease
• Outpatient AFS, AFS in primary care, nursing homes
• Relevance of guideline (mostly constructed based on RCT) on clinical practice
• Pediatric specific issues in AFS
• Use of co-primary outcomes to evaluate an AFS intervention
• EHR-generated checklists as a way for culture change of provider's antifungal use habits
• New antifungals pipeline and impact on future AFS
• When to do patient-level audits? At first antifungal prescription and discharge?
• Identify and develop new tools to improve efficiency of daily AFS operations
• Develop pathways to guide implementation of diagnostic stewardship in challenging situations (such as rejection of orders for *Aspergillus* galactomannan tests in patients on mold-active prophylaxis with sufficient drug levels)
• Best AFS practices in the ambulatory setting
Monitoring and surveillance
• Impact of nonprescription antifungal use (including agricultural agents) on AFS resistance metrics
• Artificial intelligence, natural language processing, and AFS
• Impact of AFS in mycobiome
• Effect of volume of IFD and profile of the hospital in AFS
• Susceptibility testing for resistant fungi: in vitro phenotypic vs genotypic assays and AFS
• How cyclicity in epidemiology of IFD, changes in oncology treatment affect AFS metrics?
Reporting and feedback
• Clinical scorecards for predictions of resistance
• Develop/utilize quality scoring systems to evaluate and report prescriber adherence to international guidelines
• Role of antibiotic or antiviral stewardship on key outcome measure/metrics of AFS
• Postimplementation QI projects as drivers of AFS refinement
• AFS apps for the clinician
• Optimal interval for assessing AFS impact: is it dependent on what we measure?
• Systematic study of "failures" in AFS: Is it unit specific? Effects of local culture of primary prescribers

Abbreviations: AFS, antifungal stewardship; CT, computed tomography; EHR, electronic health record; IFD, invasive fungal disease; NCBT, non-culture-based test; PET/CT, positron emission tomography/computed tomography; QI, quality improvement; RCT, randomized controlled trial.

of these principles will require some tailoring at the local level based on the differences between healthcare systems and practices. Although many intriguing questions specifically relating to AFS remain (Table 6), the practice of AFS is expanding and its continued growth will be necessary for us to optimize our care of patients at risk of or afflicted with IFDs.

Notes

Acknowledgments. D. P. K. acknowledges the Texas 4000 Distinguished Professorship for Cancer Research and the National Cancer Institute (National Institutes of Health) Cancer Center (CORE support grant number 16672).

Supplement sponsorship. This supplement is sponsored by the Mycoses Study Group Education and Research Center (MSGERC).

Potential conflicts of interest. M. D. J. reports personal fees from Astellas, Paratek, Shionogi, Cidara and UpToDate, and grants from Astellas, Scynexis, Charles River Laboratories, and Merck & Co, outside the submitted work. R. E. L. reports grants from Merck, and personal fees from Gilead and Cidara Therapeutics, outside the submitted work. E. S. D. A. reports personal fees from The Joint Commission Resources and UptoDate, outside the submitted work. L. O.-Z. reports personal fees from Astellas, Cidara, Gilead, Pfizer, F2G, Mayne, Stendhal, and Biotoscana, and grants from Astellas, Cidara, Scynexis, Real Time, and Amplyx, outside the submitted work. T. Z. reports personal fees from Pfizer, outside the submitted work. G. R. T. reports grants from Astellas, Amplyx, Cidara, Mayne, Scynexis, and F2G, and other from Astellas, Amplyx, Cidara, Mayne, Scynexis, Pfizer, and F2G, during the conduct of the study. D. R. A. reports other from Amplyx, Fedora, Roche, and Matinas, and grants from Amplyx, Fedora, and Merck, outside the submitted work. T. J. W. has received grants for experimental and clinical antimicrobial pharmacology and therapeutics to his institution from Allergan, Amplyx, Astellas, Lediant, The Medicines Company, Merck, Scynexis, and Tetraphase, and has served as consultant to Amplyx, Astellas, Allergan, ContraFect, Gilead, Lediant, Medicines Company, Merck, Methylgene, Pfizer, and Scynexis, outside the submitted work. P. G. P. reports grants from Merck, Astellas, Scynexis, IMMY, Cidara, and Amplyx, and personal fees from Cidara and Amplyx, outside the submitted work. O. A. C. is supported by the German Federal Ministry of Research and Education; is funded by the Deutsche Forschungsgemeinschaft (German Research Foundation) under Germany's Excellence Strategy–CECAD, EXC 2030–390661388; has received research grants from Actelion, Amplyx, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Janssen Pharmaceuticals, The Medicines Company, MedPace, Melinta Therapeutics, Merck/MSD, Pfizer, and Scynexis; is a consultant to Actelion, Allecra Therapeutics, Amplyx, Astellas, Basilea, Biosys UK Limited, Cidara, Da Volterra, Entasis, F2G, Gilead, Matinas, MedPace, Menarini Ricerche, Roche Diagnostics, Merck/MSD, Nabriva Therapeutics, Octapharma, Paratek Pharmaceuticals, Pfizer, PSI, Rempex, Scynexis, Seres Therapeutics, Tetraphase, and Vical; and has received lecture honoraria from Astellas, Basilea, Gilead, Grupo Biotoscana, Merck/MSD, and Pfizer. J. R. P. reports grants from Astellas, Pfizer, Minnetronix, and Amplyx; advisory board honoraria from Merck, F2G, Ampili, and Matinas; and advisory board/consulting honoraria from Scynexis, outside the submitted work. D. P. K. reports research support from Astellas Pharma and honoraria for lectures from Merck & Co, Gilead, and United Medical; has served as a consultant for Astellas Pharma, Cidara, Amplyx, Astellas, Pulmocide, and Mayne; and is a member of the data review committee of Cidara.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

REFERENCES

1. des Champs-Bro B, Leroy-Cotteau A, Mazingue F, et al. Invasive fungal infections: epidemiology and analysis of antifungal prescriptions in onco-haematology. J Clin Pharm Ther **2011**; 36:152–60.
2. Muñoz P, Valerio M, Vena A, Bouza E. Antifungal stewardship in daily practice and health economic implications. Mycoses **2015**; 58(Suppl 2):14–25.
3. Valerio M, Rodriguez-Gonzalez CG, Muñoz P, Caliz B, Sanjurjo M, Bouza E; COMIC Study Group (Collaborative Group on Mycoses). Evaluation of antifungal use in a tertiary care institution: antifungal stewardship urgently needed. J Antimicrob Chemother **2014**; 69:1993–9.
4. Azoulay E, Dupont H, Tabah A, et al. Systemic antifungal therapy in critically ill patients without invasive fungal infection. Crit Care Med **2012**; 40:813–22.
5. Stultz JS, Kohinke R, Pakyz AL. Variability in antifungal utilization among neonatal, pediatric, and adult inpatients in academic medical centers throughout the United States of America. BMC Infect Dis **2018**; 18:501.
6. 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.
7. Nivoix Y, Launoy A, Lutun P, et al. Adherence to recommendations for the use of antifungal agents in a tertiary care hospital. J Antimicrob Chemother **2012**; 67:2506–13.
8. Islahudin F, Mohd SFR. Evaluation of appropriate use of antifungal therapy in a tertiary care hospital. Asian J Pharm Clin Res **2015**; 8:195–9.
9. Jacobs DM, Dilworth TJ, Beyda ND, Casapao AM, Bowers DR. Overtreatment of asymptomatic candiduria among hospitalized patients: a multi-institutional study. Antimicrob Agents Chemother **2018**; 62:e01464-17.

10. Sinnollareddy MG, Roberts JA, Lipman J, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: data from multinational Defining Antibiotic Levels in Intensive Care Unit (DALI) patients Study. Crit Care **2015**; 19:1.
11. Lamoth F, Chung SJ, Damonti L, Alexander BD. Changing epidemiology of invasive mold infections in patients receiving azole prophylaxis. Clin Infect Dis **2017**; 64:1619–21.
12. Urbancic KF, Thursky K, Kong DCM, Johnson PDR, Slavin MA. Antifungal stewardship: developments in the field. Curr Opin Infect Dis **2018**; 31:490–8.
13. Gohlar G, Hughes S; Royal Pharmaceutical Society. How to improve antifungal stewardship. **2019**. https://www.pharmaceutical-journal.com/cpd-and-learning/learning-article/how-to-improve-antifungal-stewardship/20206772.article. Accessed 23 March 2020.
14. Pulcini C, Binda F, Lamkang AS, et al. Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clin Microbiol Infect **2019**; 25:20–5.
15. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis **2014**; 59(Suppl 3):S97–100.
16. Howard P, Pulcini C, Levy Hara G, et al; ESCMID Study Group for Antimicrobial Policies (ESGAP); ISC Group on Antimicrobial Stewardship. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. J Antimicrob Chemother **2015**; 70:1245–55.
17. Micallef C, Ashiru-Oredope D, Hansraj S, et al. An investigation of antifungal stewardship programmes in England. J Med Microbiol **2017**; 66:1581–9.
18. Standiford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. Infect Control Hosp Epidemiol **2012**; 33:338–45.
19. Apisarnthanarak A, Yatrasert A, Mundy LM; Thammasat University Antimicrobial Stewardship Team. Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol **2010**; 31:722–7.
20. 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.
21. Mondain V, Lieutier F, Hasseine L, et al. A 6-year antifungal stewardship programme in a teaching hospital. Infection **2013**; 41:621–8.
22. Valerio M, Muñoz P, Rodríguez CG, et al. Antifungal stewardship in a tertiary-care institution: a bedside intervention. Clin Microbiol Infect **2015**; 21:492.e1–9.
23. Barlam TF, Cosgrove SE, Abbo LM, 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.
24. Sinkowitz-Cochran RL, Burkitt KH, Cuerdon T, et al. The associations between organizational culture and knowledge, attitudes, and practices in a multicenter Veterans Affairs quality improvement initiative to prevent methicillin-resistant *Staphylococcus aureus*. Am J Infect Control **2012**; 40:138–43.
25. Saint S, Kowalski CP, Banaszak-Holl J, Forman J, Damschroder L, Krein SL. The importance of leadership in preventing healthcare-associated infection: results of a multisite qualitative study. Infect Control Hosp Epidemiol **2010**; 31:901–7.
26. Murray E, Holmes A. Addressing healthcare-associated infections and antimicrobial resistance from an organizational perspective: progress and challenges. J Antimicrob Chemother **2012**; 67(Suppl 1):i29–36.
27. Jiang HJ, Lockee C, Bass K, Fraser I. Board engagement in quality: findings of a survey of hospital and system leaders. J Healthc Manag **2008**; 53:121–34; discussion 135.
28. Jiang HJ, Lockee C, Bass K, Fraser I. Board oversight of quality: any differences in process of care and mortality? J Healthc Manag **2009**; 54:15–29; discussion 29–30.
29. Millar R, Mannion R, Freeman T, Davies HT. Hospital board oversight of quality and patient safety: a narrative review and synthesis of recent empirical research. Milbank Q **2013**; 91:738–70.
30. Joint Commission on Accreditation of Healthcare Organizations. Leadership committed to safety. Sentinel Event Alert **2009**:1–3.
31. Joint Commission on Hospital Accreditation. Approved: new antimicrobial stewardship standard. Jt Comm Perspect **2016**; 36:1, 3–4, 8.
32. Scobie A, Budd EL, Harris RJ, Hopkins S, Shetty N. Antimicrobial stewardship: an evaluation of structure and process and their association with antimicrobial prescribing in NHS hospitals in England. J Antimicrob Chemother **2019**; 74:1143–52.
33. O'Leary EN, van Santen KL, Webb AK, Pollock DA, Edwards JR, Srinivasan A. Uptake of antibiotic stewardship programs in US acute care hospitals: findings From the 2015 National Healthcare Safety Network Annual Hospital Survey. Clin Infect Dis **2017**; 65:1748–50.
34. Spellberg B, Bartlett JG, Gilbert DN. How to pitch an antibiotic stewardship program to the hospital C-suite. Open Forum Infect Dis **2016**; 3:ofw210.

35. Fitzpatrick MA, Suda KJ, Evans CT, Hunkler RJ, Weaver F, Schumock GT. Influence of drug class and healthcare setting on systemic antifungal expenditures in the United States, 2005–15. Am J Health Syst Pharm **2017**; 74:1076–83.
36. Benedict K, Jackson BR, Chiller T, Beer KD. Estimation of direct healthcare costs of fungal diseases in the United States. Clin Infect Dis **2019**; 68:1791–7.
37. Nwankwo L, Periselneris J, Cheong J, 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:e00402–18.
38. Greene MH, Nesbitt WJ, Nelson GE. Antimicrobial stewardship staffing: how much is enough? Infect Control Hosp Epidemiol **2019**; 41:1–11.
39. Pulcini C, Morel CM, Tacconelli E, et al. Human resources estimates and funding for antibiotic stewardship teams are urgently needed. Clin Microbiol Infect **2017**; 23:785–7.
40. 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.
41. Mulanovich V, Kontoyiannis DP. Acute myeloid leukemia and the infectious diseases consultant. Leuk Lymphoma **2018**; 59:1284–91.
42. Vaughn VM, Greene MT, Ratz D, et al. Antibiotic stewardship teams and *Clostridioides difficile* practices in United States hospitals: a national survey in The Joint Commission antibiotic stewardship standard era. Infect Control Hosp Epidemiol **2020**; 41:143–8.
43. Stenehjem E, Hyun DY, Septimus E, et al. Antibiotic stewardship in small hospitals: barriers and potential solutions. Clin Infect Dis **2017**; 65:691–6.
44. Ananda-Rajah MR, Slavin MA, Thursky KT. The case for antifungal stewardship. Curr Opin Infect Dis **2012**; 25:107–15.
45. Michallet M, Bénet T, Sobh M, et al. Invasive aspergillosis: an important risk factor on the short- and long-term survival of acute myeloid leukemia (AML) patients. Eur J Clin Microbiol Infect Dis **2012**; 31:991–7.
46. Even C, Bastuji-Garin S, Hicheri Y, et al. Impact of invasive fungal disease on the chemotherapy schedule and event-free survival in acute leukemia patients who survived fungal disease: a case-control study. Haematologica **2011**; 96:337–41.
47. Girmenia C, Micozzi A, Piciocchi A, et al. Invasive fungal diseases during first induction chemotherapy affect complete remission achievement and long-term survival of patients with acute myeloid leukemia. Leuk Res **2014**; 38:469–74.
48. Weis TM, Marini BL, Bixby DL, Perissinotti AJ. Clinical considerations for the use of FLT3 inhibitors in acute myeloid leukemia. Crit Rev Oncol Hematol **2019**; 141:125–38.
49. Arendrup MC, Bille J, Dannaoui E, Ruhnke M, Heussel CP, Kibbler C. ECIL-3 classical diagnostic procedures for the diagnosis of invasive fungal diseases in patients with leukaemia. Bone Marrow Transplant **2012**; 47:1030–45.
50. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis **2011**; 52:1144–55.
51. Stanzani M, Sassi C, Lewis RE, et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. Clin Infect Dis **2015**; 60:1603–10.
52. Douglas AP, Thursky KA, Worth LJ, et al. FDG PET/CT imaging in detecting and guiding management of invasive fungal infections: a retrospective comparison to conventional CT imaging. Eur J Nucl Med Mol Imaging **2019**; 46:166–73.
53. Vos FJ, Donnelly JP, Oyen WJ, Kullberg BJ, Bleeker-Rovers CP, Blijlevens NM. 18F-FDG PET/CT for diagnosing infectious complications in patients with severe neutropenia after intensive chemotherapy for haematological malignancy or stem cell transplantation. Eur J Nucl Med Mol Imaging **2012**; 39:120–8.
54. Xu B, Shi P, Wu H, Guo X, Wang Q, Zhou S. Utility of FDG PET/CT in guiding antifungal therapy in acute leukemia patients with chronic disseminated candidiasis. Clin Nucl Med **2010**; 35:567–70.
55. Sharma P, Mukherjee A, Karunanithi S, Bal C, Kumar R. Potential role of 18F-FDG PET/CT in patients with fungal infections. AJR Am J Roentgenol **2014**; 203:180–9.
56. Drgona L, Colita A, Klimko N, Rahav G, Ozcan MA, Donnelly JP. Triggers for driving treatment of at-risk patients with invasive fungal disease. J Antimicrob Chemother **2013**; 68(Suppl 3):iii17–24.
57. Marchetti O, Lamoth F, Mikulska M, Viscoli C, Verweij P, Bretagne S; European Conference on Infections in Leukemia (ECIL) Laboratory Working Groups. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant **2012**; 47:846–54.
58. He S, Hang JP, Zhang L, Wang F, Zhang DC, Gong FH. A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-β-D-glucan for invasive fungal infection: focus on cutoff levels. J Microbiol Immunol Infect **2015**; 48:351–61.
59. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, Michalopoulos A, Rafailidis PI, Falagas ME. β-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis **2011**; 52:750–70.
60. Onishi A, Sugiyama D, Kogata Y, et al. Diagnostic accuracy of serum 1,3-β-D-glucan for *Pneumocystis jiroveci* pneumonia, invasive candidiasis, and invasive aspergillosis:

systematic review and meta-analysis. J Clin Microbiol **2012**; 50:7–15.
61. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C; Third European Conference on Infections in Leukemia Group. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. Crit Care **2010**; 14:R222.
62. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: a clinical trial. Clin Infect Dis **2015**; 60:892–9.
63. Mylonakis E, Zacharioudakis IM, Clancy CJ, Nguyen MH, Pappas PG. Efficacy of T2 magnetic resonance assay in monitoring candidemia after initiation of antifungal therapy: the serial therapeutic and antifungal monitoring protocol (STAMP) trial. J Clin Microbiol **2018**; 56:e01756-17.
64. Avni T, Leibovici L, Paul M. PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. J Clin Microbiol **2011**; 49:665–70.
65. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis **2006**; 42:1417–27.
66. White PL, Price JS, Posso RB, Barnes RA. An evaluation of the performance of the Dynamiker Fungus (1-3)-β-D-glucan assay to assist in the diagnosis of invasive aspergillosis, invasive candidiasis and *Pneumocystis pneumonia*. Med Mycol **2017**; 55:843–50.
67. Lamoth F. Galactomannan and 1,3-β-D-glucan testing for the diagnosis of invasive aspergillosis. J Fungi (Basel) **2016**; 2:22.
68. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis **2005**; 41:1242–50.
69. Barnes RA, White PL, Bygrave C, Evans N, Healy B, Kell J. Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients. J Clin Pathol **2009**; 62:64–9.
70. Morrissey CO, Chen SC, Sorrell TC, et al; Australasian Leukaemia Lymphoma Group and the Australia and New Zealand Mycology Interest Group. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. Lancet Infect Dis **2013**; 13:519–28.
71. Hebart H, Klingspor L, Klingebiel T, et al. A prospective randomized controlled trial comparing PCR-based and empirical treatment with liposomal amphotericin B in patients after allo-SCT. Bone Marrow Transplant **2009**; 43:553–61.
72. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis **2009**; 48:1042–51.
73. Girmenia C, Micozzi A, Gentile G, et al. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. J Clin Oncol **2010**; 28:667–74.
74. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. Clin Infect Dis **2005**; 40:1762–9.
75. Lamoth F, Calandra T. Early diagnosis of invasive mould infections and disease. J Antimicrob Chemother **2017**; 72:i19–28.
76. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis **2009**; 49:1688–93.
77. Bruyère R, Quenot JP, Prin S, et al. Empirical antifungal therapy with an echinocandin in critically-ill patients: prospective evaluation of a pragmatic *Candida* score-based strategy in one medical ICU. BMC Infect Dis **2014**; 14:385.
78. León C, Ruiz-Santana S, Saavedra P, et al; Cava Study Group. Usefulness of the "Candida score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. Crit Care Med **2009**; 37:1624–33.
79. Hermsen ED, Zapapas MK, Maiefski M, Rupp ME, Freifeld AG, Kalil AC. Validation and comparison of clinical prediction rules for invasive candidiasis in intensive care unit patients: a matched case-control study. Crit Care **2011**; 15:R198.
80. Ostrosky-Zeichner L, Pappas PG, Shoham S, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. Mycoses **2011**; 54:46–51.
81. Stanzani M, Vianelli N, Cavo M, Kontoyiannis DP, Lewis RE. Development and internal validation of a model for predicting 60-day risk of invasive mould disease in patients with haematological malignancies. J Infect **2019**; 78:484–90.
82. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med **2015**; 162:W1–73.
83. Maertens J, Theunissen K, Lodewyck T, Lagrou K, Van Eldere J. Advances in the serological diagnosis of invasive *Aspergillus* infections in patients with haematological disorders. Mycoses **2007**; 50(Suppl 1):2–17.
84. Duarte RF, Sánchez-Ortega I, Cuesta I, et al. Serum galactomannan-based early detection of invasive

aspergillosis in hematology patients receiving effective antimold prophylaxis. Clin Infect Dis **2014**; 59:1696–702.
85. Huang AM, Newton D, Kunapuli A, et al. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis **2013**; 57:1237–45.
86. Banerjee R, Teng CB, Cunningham SA, et al. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. Clin Infect Dis **2015**; 61:1071–80.
87. Forrest GN, Mankes K, Jabra-Rizk MA, et al. Peptide nucleic acid fluorescence in situ hybridization-based identification of *Candida albicans* and its impact on mortality and antifungal therapy costs. J Clin Microbiol **2006**; 44:3381–3.
88. Heil EL, Daniels LM, Long DM, Rodino KG, Weber DJ, Miller MB. Impact of a rapid peptide nucleic acid fluorescence in situ hybridization assay on treatment of *Candida* infections. Am J Health Syst Pharm **2012**; 69:1910–4.
89. Nguyen MH, Wissel MC, Shields RK, et al. Performance of *Candida* real-time polymerase chain reaction, β-D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. Clin Infect Dis **2012**; 54:1240–8.
90. Bilir SP, Ferrufino CP, Pfaller MA, Munakata J. The economic impact of rapid *Candida* species identification by T2Candida among high-risk patients. Future Microbiol **2015**; 10:1133–44.
91. Dadwal SS, Kontoyiannis DP. Recent advances in the molecular diagnosis of mucormycosis. Expert Rev Mol Diagn **2018**; 18:845–54.
92. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al; Mucormycosis ECMM MSG Global Guideline Writing Group. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis **2019**; 19:e405–21.
93. Hamdy RF, Zaoutis TE, Seo SK. Antifungal stewardship considerations for adults and pediatrics. Virulence **2017**; 8:658–72.
94. Tan KE, Ellis BC, Lee R, Stamper PD, Zhang SX, Carroll KC. Prospective evaluation of a matrix-assisted laser desorption ionization-time of flight mass spectrometry system in a hospital clinical microbiology laboratory for identification of bacteria and yeasts: a bench-by-bench study for assessing the impact on time to identification and cost-effectiveness. J Clin Microbiol **2012**; 50:3301–8.
95. MacVane SH, Nolte FS. Benefits of adding a rapid PCR-based blood culture identification panel to an established antimicrobial stewardship program. J Clin Microbiol **2016**; 54:2455–63.
96. Huang T-D, Melnik E, Bogaerts P, Evrard S, Glupczynski Y. Evaluation of the ePlex blood culture identification panels for detection of pathogens in bloodstream infections. J Clin Microbiol **2019**; 57:e01597–18.
97. Alexander BD, Ashley ED, Reller LB, Reed SD. Cost savings with implementation of PNA FISH testing for identification of *Candida albicans* in blood cultures. Diagn Microbiol Infect Dis **2006**; 54:277–82.
98. Harris DM, Hata DJ. Rapid identification of bacteria and *Candida* using PNA-FISH from blood and peritoneal fluid cultures: a retrospective clinical study. Ann Clin Microbiol Antimicrob **2013**; 12:2.
99. Pancholi P, Carroll KC, Buchan BW, et al. Multicenter evaluation of the accelerate PhenoTest BC Kit for rapid identification and phenotypic antimicrobial susceptibility testing using morphokinetic cellular analysis. J Clin Microbiol **2018**; 56:e01329-17.
100. Patch ME, Weisz E, Cubillos A, Estrada SJ, Pfaller MA. Impact of rapid, culture-independent diagnosis of candidaemia and invasive candidiasis in a community health system. J Antimicrob Chemother **2018**; 73(Suppl 4):iv27–30.
101. Walker B, Powers-Fletcher MV, Schmidt RL, Hanson KE. Cost-effectiveness analysis of multiplex PCR with magnetic resonance detection versus empiric or blood culture-directed therapy for management of suspected candidemia. J Clin Microbiol **2016**; 54:718–26.
102. Valerio M, Vena A, Bouza E, et al; COMIC Study Group (Collaborative Group on Mycosis). How much European prescribing physicians know about invasive fungal infections management? BMC Infect Dis **2015**; 15:80.
103. Sinnollareddy M, Peake SL, Roberts MS, Lipman J, Roberts JA. Using pharmacokinetics and pharmacodynamics to optimise dosing of antifungal agents in critically ill patients: a systematic review. Int J Antimicrob Agents **2012**; 39:1–10.
104. Labelle AJ, Micek ST, Roubinian N, Kollef MH. Treatment-related risk factors for hospital mortality in *Candida* bloodstream infections. Crit Care Med **2008**; 36:2967–72.
105. Reed EE, West JE, Keating EA, et al. Improving the management of candidemia through antimicrobial stewardship interventions. Diagn Microbiol Infect Dis **2014**; 78:157–61.
106. Bienvenu AL, Argaud L, Aubrun F, et al. A systematic review of interventions and performance measures for antifungal stewardship programmes. J Antimicrob Chemother **2018**; 73:297–305.
107. Kontoyiannis DP, Reddy BT, Torres HA, et al. Pulmonary candidiasis in patients with cancer: an autopsy study. Clin Infect Dis **2002**; 34:400–3.

108. Georgiadou SP, Tarrand J, Sipsas NV, Kontoyiannis DP. Candiduria in haematologic malignancy patients without a urinary catheter: nothing more than a frailty marker? Mycoses **2013**; 56:311–4.
109. Playford EG, Marriott D, Nguyen Q, et al. Candidemia in nonneutropenic critically ill patients: risk factors for non-albicans *Candida* spp. Crit Care Med **2008**; 36:2034–9.
110. Chander J, Singla N, Sidhu SK, Gombar S. Epidemiology of *Candida* blood stream infections: experience of a tertiary care centre in North India. J Infect Dev Ctries **2013**; 7:670–5.
111. Lee RA, Zurko JC, Camins BC, et al. Impact of infectious disease consultation on clinical management and mortality in patients with candidemia. Clin Infect Dis **2019**; 68:1585–7.
112. Farmakiotis D, Kyvernitakis A, Tarrand JJ, Kontoyiannis DP. Early initiation of appropriate treatment is associated with increased survival in cancer patients with *Candida glabrata* fungaemia: a potential benefit from infectious disease consultation. Clin Microbiol Infect **2015**; 21:79–86.
113. Mejia-Chew C, O'Halloran JA, Olsen MA, et al. Effect of infectious disease consultation on mortality and treatment of patients with *Candida* bloodstream infections: a retrospective, cohort study. Lancet Infect Dis **2019**; 19:1336–44.
114. Jones TM, Drew RH, Wilson DT, Sarubbi C, Anderson DJ. Impact of automatic infectious diseases consultation on the management of fungemia at a large academic medical center. Am J Health Syst Pharm **2017**; 74:1997–2003.
115. Menichetti F, Bertolino G, Sozio E, et al; GISA (Italian Group for Antimicrobial Stewardship) Candidemia Study Group. Impact of infectious diseases consultation as a part of an antifungal stewardship programme on candidemia outcome in an Italian tertiary-care, university hospital. J Chemother **2018**; 30:304–9.
116. Cook G, Advani S, Rab S, Kandiah S, Patel M, Wong J. Treatment bundle improves outcomes in the management of candidemia at large urban academic medical center. Open Forum Infect Dis **2017**; 4(Suppl 1):S89.
117. Ishikane M, Hayakawa K, Kutsuna S, Takeshita N, Ohmagari N. The impact of infectious disease consultation in candidemia in a tertiary care hospital in Japan over 12 years. PLoS One **2019**; 14:e0215996.
118. Spec A, Olsen MA, Raval K, Powderly WG. Impact of infectious diseases consultation on mortality of cryptococcal infection in patients without HIV. Clin Infect Dis **2017**; 64:558–64.
119. Tascini C, Bertolino G, Sozio E, Sbrana F, Ripoli A, Carmignani C. Antifungal stewardship programs and candidemia. Clin Infect Dis **2020**; 70:1522–3.
120. Kontoyiannis DP. Echinocandin-based initial therapy in fungemic patients with cancer: a focus on recent guidelines of the Infectious Diseases Society of America. Clin Infect Dis **2009**; 49:638–9; author reply 639–40.
121. Dai Y, Walker JW, Halloush RA, Khasawneh FA. Mucormycosis in two community hospitals and the role of infectious disease consultation: a case series. Int J Gen Med **2013**; 6:833–8.
122. Coombes CE, Gregory ME. The current and future use of telemedicine in infectious diseases practice. Curr Infect Dis Rep **2019**; 21:41.
123. Burnham JP, Fritz SA, Yaeger LH, Colditz GA. Telemedicine infectious diseases consultations and clinical outcomes: a systematic review and meta-analysis protocol. Syst Rev **2019**; 8:135.
124. Rac H, Wagner JL, King ST, Barber KE, Stover KR. Impact of an antifungal stewardship intervention on optimization of candidemia management. Ther Adv Infect Dis **2018**; 5:3–10.
125. Antworth A, Collins CD, Kunapuli A, et al. Impact of an antimicrobial stewardship program comprehensive care bundle on management of candidemia. Pharmacotherapy **2013**; 33:137–43.
126. Takesue Y, Ueda T, Mikamo H, et al; ACTIONs Project. Management bundles for candidaemia: the impact of compliance on clinical outcomes. J Antimicrob Chemother **2015**; 70:587–93.
127. Popovich K, Malani PN, Kauffman CA, Cinti SK. Compliance with Infectious Diseases Society of America guidelines for ophthalmologic evaluation of patients with candidemia. Infect Dis Clin Pract **2007**; 15:254.
128. Patel M, Kunz DF, Trivedi VM, Jones MG, Moser SA, Baddley JW. Initial management of candidemia at an academic medical center: evaluation of the IDSA guidelines. Diagn Microbiol Infect Dis **2005**; 52:29–34.
129. Mellinghoff SC, Hartmann P, Cornely FB, et al. Analyzing candidemia guideline adherence identifies opportunities for antifungal stewardship. Eur J Clin Microbiol Infect Dis **2018**; 37:1563–71.
130. Pagano L, Caira M, Offidani M, et al. Adherence to international guidelines for the treatment of invasive aspergillosis in acute myeloid leukaemia: feasibility and utility (SEIFEM-2008B study). J Antimicrob Chemother **2010**; 65:2013–8.
131. Mellinghoff SC, Hoenigl M, Koehler P, et al. EQUAL *Candida* score: an ECMM score derived from current guidelines to measure quality of clinical candidaemia management. Mycoses **2018**; 61:326–30.
132. Cornely OA, Koehler P, Arenz D, C Mellinghoff S. 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.
133. Spec A, Mejia-Chew C, Powderly WG, Cornely OA. EQUAL *Cryptococcus* score 2018: a European confederation of medical mycology score derived from current guidelines to measure quality of clinical cryptococcosis management. Open Forum Infect Dis **2018**; 5:ofy299.
134. Koehler P, Mellinghoff SC, Lagrou K, et al. Development and validation of the European Quality (EQUAL) score for mucormycosis management in haematology. J Antimicrob Chemother **2019**; 74:1704–12.
135. Murakami M, Komatsu H, Sugiyama M, et al. Antimicrobial stewardship without infectious disease physician for patients with candidemia: a before and after study. J Gen Fam Med **2018**; 19:82–9.
136. Jarvis JN, Govender N, Chiller T, et al. Cryptococcal antigen screening and preemptive therapy in patients initiating antiretroviral therapy in resource-limited settings: a proposed algorithm for clinical implementation. J Int Assoc Physicians AIDS Care (Chic) **2012**; 11:374–9.
137. Temfack E, Bigna JJ, Luma HN, et al. Impact of routine cryptococcal antigen screening and targeted preemptive fluconazole therapy in antiretroviral-naive human immunodeficiency virus-infected adults with CD4 cell counts <100/μL: a systematic review and meta-analysis. Clin Infect Dis **2019**; 68:688–98.
138. World Health Organization. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva, Switzerland: WHO, **2018**.
139. Vena A, Bouza E, Corisco R, et al; COMIC Study Group. Efficacy of a "checklist" intervention bundle on the clinical outcome of patients with candida bloodstream infections: a quasi-experimental pre-post study. Infect Dis Ther **2020**; 9:119–35.
140. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 62:e1–50.
141. Cornely OA, Bassetti M, Calandra T, et al; ESCMID Fungal Infection Study Group. ESCMID guideline for the diagnosis and management of *Candida* diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect **2012**; 18(Suppl 7):19–37.
142. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect **2018**; 24(Suppl 1):e1–38.
143. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **2016**; 63:e1–e60.
144. Breazzano MP, Day HR Jr, Bloch KC, et al. Utility of ophthalmologic screening for patients with *Candida* bloodstream infections: a systematic review. JAMA Ophthalmol **2019**; 137:698–710.
145. Vinikoor MJ, Zoghby J, Cohen KL, Tucker JD. Do all candidemic patients need an ophthalmic examination? Int J Infect Dis **2013**; 17:e146–8.
146. Vena A, Muñoz P, Padilla B, et al; CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI. Is routine ophthalmoscopy really necessary in candidemic patients? PLoS One **2017**; 12:e0183485.
147. Raad I, Hanna H, Boktour M, et al. Management of central venous catheters in patients with cancer and candidemia. Clin Infect Dis **2004**; 38:1119–27.
148. Seidelman J, Fleece ME, Yang WZ, et al. Invasive ocular candidiasis: who is really at risk? Open Forum Infect Dis **2019**; 6(Suppl 2):S617–8.
149. Baker DW, Hyun D, Neuhauser MM, Bhatt J, Srinivasan A. Leading practices in antimicrobial stewardship: conference summary. Jt Comm J Qual Patient Saf **2019**; 45:517–23.
150. So M, Morris AM, Nelson S, Bell CM, Husain S. Antimicrobial stewardship by academic detailing improves antimicrobial prescribing in solid organ transplant patients. Eur J Clin Microbiol Infect Dis **2019**; 38:1915–23.
151. MacBrayne CE, Williams MC, Levek C, et al. Sustainability of handshake stewardship: extending a hand is effective years later. Clin Infect Dis **2020**; 70:2325–32.
152. Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the microbiology laboratory can right the ship. Clin Microbiol Rev **2017**; 30:381–407.
153. Tamma PD, Avdic E, Keenan JF, et al. What is the more effective antibiotic stewardship intervention: preprescription authorization or postprescription review with feedback? Clin Infect Dis **2017**; 64:537–43.
154. Anderson DJ, Watson S, Moehring RW, et al; Antibacterial Resistance Leadership Group. Feasibility of core antimicrobial stewardship interventions in community hospitals. JAMA Netw Open **2019**; 2:e199369.
155. Valerio M, Vena A, Rodríguez-González CG, et al; COMIC Study Group (Collaborative Group on Mycoses). 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.
156. Baggio D, Peel T, Peleg AY, et al. Closing the gap in surveillance and audit of invasive mold diseases for

antifungal stewardship using machine learning. J Clin Med Res **2019**; 8:1390.
157. Scheetz MH, Crew PE, Miglis C, et al. Investigating the extremes of antibiotic use with an epidemiologic framework. Antimicrob Agents Chemother **2016**; 60:3265–9.
158. Ellis D, Marriott D, Hajjeh RA, Warnock D, Meyer W, Barton R. Epidemiology: surveillance of fungal infections. Med Mycol **2000**; 38(Suppl 1):173–82.
159. Benedict K, Richardson M, Vallabhaneni S, Jackson BR, Chiller T. Emerging issues, challenges, and changing epidemiology of fungal disease outbreaks. Lancet Infect Dis **2017**; 17:e403–11.
160. De Pauw B, Walsh TJ, Donnelly JP, et al; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis **2008**; 46:1813–21.
161. Multani A, Allard LS, Wangjam T, et al. Missed diagnosis and misdiagnosis of infectious diseases in hematopoietic cell transplant recipients: an autopsy study. Blood Adv **2019**; 3:3602–12.
162. Antoniadou A, Torres HA, Lewis RE, et al. Candidemia in a tertiary care cancer center: in vitro susceptibility and its association with outcome of initial antifungal therapy. Medicine (Baltimore) **2003**; 82:309–21.
163. Gamaletsou MN, Walsh TJ, Zaoutis T, et al. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. Clin Microbiol Infect **2014**; 20:O50–7.
164. Lionakis MS, Lewis RE, Chamilos G, Kontoyiannis DP. *Aspergillus* susceptibility testing in patients with cancer and invasive aspergillosis: difficulties in establishing correlation between in vitro susceptibility data and the outcome of initial amphotericin B therapy. Pharmacotherapy **2005**; 25:1174–80.
165. Georgiadou SP, Kontoyiannis DP. The impact of azole resistance on aspergillosis guidelines. Ann N Y Acad Sci **2012**; 1272:15–22.
166. Clinical and Laboratory Standards Institute. M27-A3: reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard—3rd ed. Wayne, PA: CLSI, **2008**.
167. Arendrup MC, Meletiadis J, Mouton JW, et al. EUCAST technical note on isavuconazole breakpoints for *Aspergillus*, itraconazole breakpoints for *Candida* and updates for the antifungal susceptibility testing method documents. Clin Microbiol Infect **2016**; 22:571.e1–4.
168. Eschenauer GA, Nguyen MH, Shoham S, et al. Real-world experience with echinocandin MICs against *Candida* species in a multicenter study of hospitals that routinely perform susceptibility testing of bloodstream isolates. Antimicrob Agents Chemother **2014**; 58:1897–906.
169. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in *Candida glabrata*: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis **2013**; 56:1724–32.
170. Shields RK, Nguyen MH, Press EG, et al. The presence of an FKS mutation rather than MIC is an independent risk factor for failure of echinocandin therapy among patients with invasive candidiasis due to *Candida glabrata*. Antimicrob Agents Chemother **2012**; 56:4862–9.
171. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis **2005**; 41:60–6.
172. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis **2005**; 191:1350–60.
173. Lortholary O, Desnos-Ollivier M, Sitbon K, Fontanet A, Bretagne S, Dromer F; French Mycosis Study Group. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. Antimicrob Agents Chemother **2011**; 55:532–8.
174. Clinical and Laboratory Standards Institute. M39-A4 analysis and presentation of cumulative antimicrobial susceptibility test data; approved guideline—4th ed. Wayne, PA: CLSI, **2014**.
175. Kim SH, Shin JH, Kim EC, et al. The relationship between antifungal usage and antifungal susceptibility in clinical isolates of *Candida*: a multicenter Korean study. Med Mycol **2009**; 47:296–304.
176. Fournier P, Schwebel C, Maubon D, et al. Antifungal use influences *Candida* species distribution and susceptibility in the intensive care unit. J Antimicrob Chemother **2011**; 66:2880–6.
177. Lewis JS 2nd, Wiederhold NP, Wickes BL, Patterson TF, Jorgensen JH. Rapid emergence of echinocandin resistance in *Candida glabrata* resulting in clinical and microbiologic failure. Antimicrob Agents Chemother **2013**; 57:4559–61.
178. Verweij PE, Ananda-Rajah M, Andes D, et al. International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. Drug Resist Updat **2015**; 21–22:30–40.

179. Lortholary O, Renaudat C, Sitbon K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010). Intensive Care Med **2014**; 40:1303–12.
180. Clancy CJ, Nguyen MH. Non-culture diagnostics for invasive candidiasis: promise and unintended consequences. J Fungi (Basel) **2018**; 4:27.
181. Jung DS, Farmakiotis D, Jiang Y, Tarrand JJ, Kontoyiannis DP. Uncommon *Candida species* fungemia among cancer patients, Houston, Texas, USA. Emerg Infect Dis **2015**; 21:1942–50.
182. Rautemaa-Richardson R, Rautemaa V, Al-Wathiqi F, et al. Impact of a diagnostics-driven antifungal stewardship programme in a UK tertiary referral teaching hospital. J Antimicrob Chemother **2018**; 73:3488–95.
183. Andes D, Azie N, Yang H, et al. Drug-drug interaction associated with mold-active triazoles among hospitalized patients. Antimicrob Agents Chemother **2016**; 60:3398–406.
184. 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.
185. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis **2012**; 55:1080–7.
186. Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob Agents Chemother **2012**; 56:5503–10.
187. McCreary EK, Bayless M, Van AP, et al. Impact of triazole therapeutic drug monitoring availability and timing. Antimicrob Agents Chemother **2019**; 63:e01245–19.
188. John J, Loo A, Mazur S, Walsh TJ. Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients. Expert Opin Drug Metab Toxicol **2019**; 15:881–95.
189. Watt KM, Benjamin DK Jr, Cheifetz IM, et al. Pharmacokinetics and safety of fluconazole in young infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J **2012**; 31:1042–7.
190. Muhl E, Martens T, Iven H, Rob P, Bruch HP. Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol **2000**; 56:671–8.
191. van der Elst KCM, Pereboom M, van den Heuvel ER, Kosterink JGW, Schölvinck EH, Alffenaar J-WC. Insufficient fluconazole exposure in pediatric cancer patients and the need for therapeutic drug monitoring in critically ill children. Clin Infect Dis **2014**; 59:1527–33.
192. Andes D, Kovanda L, Desai A, Kitt T, Zhao M, Walsh TJ. Isavuconazole concentration in real-world practice: consistency with results from clinical trials. Antimicrob Agents Chemother **2018**; 62:e00585-18.
193. Kaindl T, Andes D, Engelhardt M, Saulay M, Larger P, Groll AH. Variability and exposure-response relationships of isavuconazole plasma concentrations in the Phase 3 SECURE trial of patients with invasive mould diseases. J Antimicrob Chemother **2019**; 74:761–7.
194. Wu X, Clancy CJ, Rivosecchi RM, et al. Pharmacokinetics of intravenous isavuconazole in solid-organ transplant recipients. Antimicrob Agents Chemother **2018**; 62:e01643–18.
195. Kabulski GM, MacVane SH. Isavuconazole pharmacokinetics in a patient with cystic fibrosis following bilateral orthotopic lung transplantation. Transpl Infect Dis **2018**; 20:e12878.
196. Yang Q, Wang T, Xie J, et al. Pharmacokinetic/pharmacodynamic adequacy of echinocandins against *Candida* spp. in intensive care unit patients and general patient populations. Int J Antimicrob Agents **2016**; 47:397–402.
197. Autmizguine J, Hornik CP, Benjamin DK Jr, et al. Pharmacokinetics and safety of micafungin in infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J **2016**; 35:1204–10.
198. Jullien V, Azoulay E, Schwebel C, et al; EMPIRICUS Trial Study Group. Population pharmacokinetics of micafungin in ICU patients with sepsis and mechanical ventilation. J Antimicrob Chemother **2017**; 72:181–9.
199. Nguyen M-VH, Davis MR, Wittenberg R, et al. Posaconazole serum drug levels associated with pseudohyperaldosteronism [manuscript published online ahead of print 12 August 2019]. Clin Infect Dis **2020**; 70:2593–8.
200. Lionakis MS, Lewis RE, Kontoyiannis DP. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. Clin Infect Dis **2018**; 67:1621–30.
201. Bassetti M, Giacobbe DR, Vena A, Brink A. Challenges and research priorities to progress the impact of antimicrobial stewardship. Drugs Context **2019**; 8:212600.
202. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES; Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel. Expert consensus on metrics to assess the impact of patient-level antimicrobial stewardship interventions in acute-care settings. Clin Infect Dis **2017**; 64:377–83.

203. Centers for Disease Control and Prevention. National Healthcare Safety Network. https://www.cdc.gov/nhsn/. Accessed 27 October 2019.
204. World Health Organization Collaborating Centers. ATC/DDD Index. https://www.whocc.no/atc_ddd_index/. Accessed 27 October 2019.
205. Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. Curr Treat Options Infect Dis **2014**; 6:101–12.
206. Adriaenssens N, Coenen S, Versporten A, Muller A, Vankerckhoven V, Goossens H. European Surveillance of Antimicrobial Consumption (ESAC): quality appraisal of antibiotic use in Europe. J Antimicrob Chemother **2011**; 66(Suppl 6):vi71–7.
207. European Centre for Disease Prevention and Control. Antimicrobial consumption database (ESAC-Net). https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database. Accessed 17 February 2020.
208. Magill SS, Edwards JR, Beldavs ZG, et al. Prevalence of antimicrobial use in US acute care hospitals, May-September 2011. JAMA **2014**; 312:1438–46.
209. Centers for Disease Control and Prevention. National Healthcare Safety Network. ACH surveillance for antimicrobial use and antimicrobial resistance options. https://www.cdc.gov/nhsn/acute-care-hospital/aur/index.html. Accessed 17 February 2020.
210. Spivak ES, Cosgrove SE, Srinivasan A. Measuring appropriate antimicrobial use: attempts at opening the black box. Clin Infect Dis **2016**; 63:1639–44.
211. Kallen MC, Prins JM. A systematic review of quality indicators for appropriate antibiotic use in hospitalized adult patients. Infect Dis Rep **2017**; 9:6821.
212. Ruangritchankul K, Chindamporn A, Worasilchai N, Poumsuk U, Keelawat S, Bychkov A. Invasive fungal disease in university hospital: a PCR-based study of autopsy cases. Int J Clin Exp Pathol **2015**; 8:14840–52.
213. Dignani MC. Epidemiology of invasive fungal diseases on the basis of autopsy reports. F1000Prime Rep **2014**; 6:81.
214. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses **2013**; 56:638–45.
215. Khadem TM, Dodds Ashley E, Wrobel MJ, Brown J. Antimicrobial stewardship: a matter of process or outcome? Pharmacotherapy **2012**; 32:688–706.
216. Al Balushi KA, Alzaabi MA, Alghafri F. Prescribing pattern of antifungal medications at a tertiary care hospital in Oman. J Clin Diagn Res **2016**; 10:FC27–30.