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Antifungal Stewardship Interventions in Patients with Hematologic Malignancies

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Abstract

Purpose of Review Antifungal stewardship has been recognized as a significant component of any antimicrobial stewardship program. In this article, we aim to provide a review of recommendations and antifungal stewardship interventions in hematologic patients.

Recent Findings Core elements of antibiotic stewardship programs can be applied to antifungal stewardship practices. Engagement of high-prescribing specialists, timely access to fungal diagnostics, screening for drug-drug interactions, and therapeutic drug monitoring are recommended practices that specifically pertain to antifungal stewardship. Tools recently developed in assessing adherence to guidelines can prove useful in evaluating prescribing practices. The most common longitudinal metrics are likely to hinge on measuring antifungal consumption. However, many of the parameters to measure antifungal stewardship activity and performance are extremely challenging to obtain.

Summary A multifaceted antifungal stewardship approach is required to improve antifungal use among hematologic patients in an efficient and sustainable manner.

Keywords Antifungal stewardship · Hematology candidiasis · Aspergillosis · Guidelines · Metrics

Introduction

Antimicrobial stewardship refers to the implementation of coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents [1]. Antifungal stewardship has been increasingly recognized as a significant component of any antimicrobial stewardship program. Invasive fungal infections (IFIs) are associated with significant morbidity and mortality posing a serious public health threat. In the USA, candidemia carries a substantial burden that represents only a portion of the burden of invasive candidiasis [2]. Alarmingly, rates of hospitalization for invasive aspergillosis and mucormycosis have been increasing [3]. The World Health Organization released a fungal priority pathogens list in an effort to strengthen the global response to fungal infections and antifungal resistance [4]. Based on that list, *Candida auris* and *Aspergillus fumigatus* are considered critical priority pathogens. In many ways, addressing the threat of antifungal resistance is similar to the public health efforts in combating antibiotic resistance.

Patients with hematologic malignancies are vulnerable to infectious complications due to both their underlying disease and chemotherapy-associated immunosuppression. In the past decade, increasingly immunosuppressive treatment regimens have been developed and, at the same time, older and frailer patients are being accepted for the treatment of leukemia and myelodysplastic syndromes. These practices are poised to increase the risk of fungal infections. In addition, ibrutinib and other tyrosine kinase inhibitors that have revolutionized the management of B-cell hematologic malignancies have been associated with increased

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risk of pulmonary and extrapulmonary IFIs [5]. The number of individuals receiving hematopoietic stem cell transplants (HSCTs) has been growing, specifically with a notable increase in the transplantation of adults over the age of 70 [6]. Finally, the introduction of chimeric antigen receptor (CAR) T-cell therapy has been associated with invasive mold infections in the setting of prolonged neutropenia and high-dose corticosteroid use [7].

Herein, we provide an overview of recommendations and antifungal stewardship interventions in the management of patients with hematologic malignancies, HSCT recipients, and CAR-T-cell recipients.

Core Elements and Recommendations on Antifungal Stewardship

We believe that cancer centers and hospitals with a high census of Hematology-Oncology patients should have a dedicated antifungal stewardship program. Depending on the burden of antifungal use and available resources, this may be integrated within or structurally report to the antimicrobial stewardship program. Members of the antifungal stewardship team should have expertise in the management of IFIs and antifungal drug use, as well as a thorough understanding of common stewardship implementation practices.

In 2019, the Center for Disease Control (CDC) updated the Core Elements of Hospital Antibiotic Stewardship Programs [8]. These Core Elements can be applied to antifungal stewardship practices in the inpatient setting, as outlined in the following.

Commitment: Hospital leadership should dedicate adequate human, financial, and information technology resources in support of the antifungal stewardship program.

Accountability: A leader and co-leader (ideally, physician and pharmacist) should be responsible for the management of the antifungal stewardship program.

Pharmacy expertise: A pharmacist with expertise in antifungal use should lead implementation efforts.

Action: Antifungal stewardship interventions should be implemented. Priority interventions include pre-authorization, prospective audit and feedback, and development of hospital-specific recommendations/guidelines.

Tracking: Antifungal prescribing and the impact of interventions should be tracked in order to assess program outcomes.

Reporting: Provider- and institution-level data should be reported to prescribers and hospital leadership.

Education: Prescribers and pharmacists should be educated on appropriate antifungal use with both passive and active educational strategies, including academic detailing, case-based education, and/or structured lectures.

We believe that all the above elements are important components of any antifungal stewardship program. Hospital leadership commitment and appointment of responsible program leaders are essential. For centers that do not have an established antifungal stewardship program, emphasis should be placed on developing both horizontal and vertical stewardship interventions addressing specific areas, such as de-escalation from echinocandin to azole therapy in candidemia, *Pneumocystis* prophylaxis for at-risk individuals, and duration of treatment for aspergillosis. As the program expands, additional interventions may be implemented to optimize antifungal use depending on institutional needs. Formulary restrictions/pre-authorization and prospective audit can provide an opportunity for immediate feedback in the form of case-specific, informal prescriber education (i.e., academic detailing). Formal educational sessions on antifungal use can be eventually implemented. Tracking and reporting will allow personnel to refine the interventions, identify new opportunities for optimization, and advance the program.

In 2020, a statement on core recommendations was published by an expert panel of the Mycoses Study Group Research and Education Consortium (MSGERC) [9••]. Expectedly, there is some overlap between the CDC and MSGERC statements. Additional specific recommendations formulated by MSGERC include the following: (i) engagement of high-prescribing specialists (such as hematologists), (ii) access to timely diagnostics and antifungal susceptibility testing, (iii) screening for drug-drug interactions and therapeutic drug monitoring (TDM). In our opinion, access to timely diagnostics is the cornerstone of any successful stewardship program, as this not only allows for timely initiation of effective antifungal treatment but, equally important, can support withholding or early cessation of treatment where biomarkers and imaging are not indicative of IFI.

In 2021, consensus guidelines were published by the Australasian Antifungal Guidelines Steering Committee [10••]. Key antifungal stewardship interventions include integration of local guidelines into prescriber workflows, educational efforts in departments with high-volume systemic antifungal use, post-prescription review and feedback, and antifungal prescription audit. These guidelines also provide a framework pertaining to antifungal use metrics.

The European Confederation of Medical Mycology has established best practice recommendations for Centers of Excellence. In the field of Microbiology/Mycology, these include the following: direct microscopy of fluids, direct fluorescent-antibody staining or PCR for *Pneumocystis*, cerebrospinal fluid India ink staining or *Cryptococcus* antigen testing, availability of cultures that support fungal growth, identification of fungi to the species complex level, appropriate processing of respiratory samples, *Aspergillus* galactomannan testing on bronchoalveolar lavage fluid, serum

beta-D-glucan screening, PCR testing of biopsy specimens (when fungal hyphae are detected), *Aspergillus*-specific IgG and IgE testing, antifungal susceptibility testing for *Candida* and *Aspergillus* spp., TDM for itraconazole, voriconazole, posaconazole, and flucytosine. In our opinion, testing for applicable dimorphic fungi (serology and antigen) should also be available in endemic areas. We consider all the above diagnostic modalities essential for the success of antifungal stewardship programs. If testing is not available on site, centers should have a process for timely processing and shipment of samples to reference laboratories.

Besides processing and reporting by the microbiology laboratory, prompt collection of specimens is key to timely diagnosis. Procedures such as bronchoscopy, lumbar puncture, and aspiration of abscesses should ideally be performed within 24–48 h after ordering. For example, a patient with symptoms consistent with respiratory tract infection and new nodular consolidations on chest CT imaging should be promptly evaluated and scheduled for bronchoscopy with bronchoalveolar lavage and possibly transbronchial biopsy. This requires coordination between the primary service and the pulmonary department.

The antifungal stewardship team should consist of individuals with expertise in the management of both hematologic malignancies and fungal infections. The team should include a hematologist, an infectious disease physician, a clinical microbiologist, and a clinical pharmacist. We anticipate that inclusion of a hematologist will increase the acceptance rate for recommendations provided to primary prescribers working within the specialty of Hematology-Oncology. We previously published on the role of members of the multidisciplinary team in antifungal stewardship [11]. In Table 1, we provide an updated framework of roles and responsibilities. For hospitals with pediatric units, specialists with expertise in pediatric care should be included.

In most instances, we anticipate that infectious disease-trained physicians and pharmacists will be involved in day-to-day stewardship interventions. Hematologists and Clinical Microbiologists will have an advising role on the overarching goals of the program and development of institutional guidelines or diagnostic algorithms. The antifungal stewardship team can liaise with other physicians, such as hospitalists, pulmonologists, intensivists, and radiologists.

US hospitals have implemented inpatient antibiotic stewardship programs in response to regulatory requirements. Most recently, outpatient antibiotic stewardship interventions have been launched to meet standards set by accreditation bodies. We believe that integration of antifungal stewardship metrics into existing regulatory efforts or similar standalone regulations on antifungal stewardship should be implemented in cancer centers and large hospitals (> 500 beds).

Adherence to Guidelines

Effective antibiotic stewardship practices are summarized by the 5Ds: right diagnosis, right drug, right dose, right duration, and timely de-escalation. In Table 2, we apply these concepts to antifungal stewardship and provide examples of common challenges.

Professional societies have published guidelines on the management of candidiasis [12, 13], aspergillosis [14, 15],

Table 1 Roles and responsibilities of members of the antifungal stewardship team

Hematologist	• Evaluating the impact of chemotherapy on host immune responses • Advising on duration of neutropenia/lymphopenia • Risk stratification based on hematopoietic stem cell transplant type • Assessing the degree of immunosuppression conferred by regimens administered for prophylaxis/treatment of graft-versus-host disease • Advising on implications of antifungal use in patients participating in hematology trials • Estimating overall cancer prognosis
Infectious Disease/ Clinical Microbiology Specialist	• Evaluating significance of organisms recovered by conventional culture methods or molecular diagnostics (colonization versus infection) • Incorporating fungal biomarkers and microbial cell-free DNA sequencing in the diagnosis of infection • Evaluating appropriateness of antifungal prophylaxis based on underlying hematologic disease • Evaluating appropriateness of antifungal treatment (selected regimen, duration of treatment) and role of secondary prophylaxis • Assessing response to treatment and need for therapy modification • Incorporating use of novel antifungal agents (under clinical trial or expanded access program)
Pharmacist	• Reviewing drug-drug interactions • Addressing pharmacokinetic issues in specific patient populations • Incorporating pharmacogenomics in clinical care • Advising on route of administration and appropriate dosing • Adjusting dose based on therapeutic drug monitoring • Evaluating potential side effects of antifungal agents • Proposing alternative therapeutic regimens (convenience, safety profile, treatment failure) • Developing metrics to monitor stewardship interventions and outcomes

Table 2 The 5 Ds of antifungal stewardship

Description	Main challenges with examples	Proposed stewardship interventions
Diagnosis Does the condition require antifungal therapy?	-Determining the etiology of clinical/radiographic findings (Cause of febrile neutropenia, pulmonary nodules) -Differentiating colonization from infection (sputum culture with growth of *Aspergillus* spp.)	-Availability of non-culture-based diagnostics (including PCR and microbial cell-free DNA sequencing)
Drug Is the antifungal appropriate for the treatment of the fungal infection?	-Choice of empiric treatment for presumed fungal infection (Targeting *Aspergillus* vs *Mucor* or other mold) -Drug choice for pathogen-directed therapy in the setting of rising antifungal resistance (azole-resistant *Candida*, azole-resistant *Aspergillus* spp.)	-Antibiograms for hematologic patients -Provider education -Pre-authorization for high-cost antifungals -Post-prescription review
Dose What is the recommended dose and route of administration?	-Dosage adjustments for weight, renal function, site of infection (dosing in obesity, acute kidney injury, central nervous system infection) -Route of administration (administration via gastric/enteral feeding tubes)	-Electronic order sets -Computerized decision support tools
Duration What is the recommended duration of antifungal treatment?	-Duration of prophylaxis or treatment in the setting of ongoing immunosuppression (upcoming chemotherapy, chronic graft-versus-host disease) -Gaps in *Pneumocystis* prophylaxis	-Local guidelines on appropriate duration of prophylaxis -Multidisciplinary review with input from Hematology specialist
De-escalation Can treatment be deescalated to a narrow-spectrum antifungal?	-Need for induction therapy (timing of transition from amphotericin B to azole therapy in cryptococcosis and endemic mycoses) -Timely antifungal susceptibility testing (step-down from echinocandin to azole therapy in candidiasis)	-Provider education -Post-prescription review in the outpatient setting -Joint Infectious Disease and Hematology clinics

cryptococcosis [16], and mucormycosis [17, 18]. We note that guidelines provide best practice recommendations; however, healthcare professionals must make treatment decisions on a case-by-case basis using clinical judgment and expertise. Clinicians should also be familiar with the latest available evidence, which may not have been included in the guidelines at the time of their drafting. As an example, the findings of a phase 3, randomized, non-inferiority study comparing posaconazole and voriconazole for the primary treatment of invasive aspergillosis are not included in the guidelines that preceded the publication of the trial [19].

Assessing adherence to guidelines can be challenging. One of the first studies in this area deemed that the overall rate of inappropriate antifungal use in the intensive care units and the Hematology-Oncology department of a French tertiary care hospital was 40% in 2007 [20]. Simple tools have been designed by the European Confederation of Medical Mycology (ECMM QUALity or EQUAL Scores). These can be used for audit purposes. Scoring is based on the strength of recommendations published in the guidelines. For candidemia, obtaining initial blood cultures (40 mL volume), *Candida* species identification, treatment with an echinocandin, and central venous catheter removal within 24 h are assigned a score of 3 [21]. Antifungal susceptibility testing, step-down to fluconazole, and treatment for 14 days after the first negative culture are assigned a score of 2. Echocardiography and ophthalmoscopy receive a score of 1. A maximum score is calculated by adding individual scores. In a multicenter, observational study of patients with culture-proven candidemia, lower adherence rates to guideline recommendations (reflected by lower EQUAL Candida scores) was an independent predictor of mortality [22•]. Similar scoring systems have been developed for aspergillosis [23], cryptococcosis [24], mucormycosis [25], scedosporiosis [26], and trichosporonosis [27].

Lessons Learned from Antifungal Stewardship Interventions

Over the last decade, several articles have been published on antifungal stewardship interventions. Interventions addressing the management of candidemia typically target all hospitalized patients [28–34]. In the following paragraphs, we will review interventions primarily implemented in hematology patients that have addressed both yeast and mold infections. We highlight important findings and the knowledge gained by each study. We believe that antifungal stewardship interventions should be targeted toward all prescribers (i.e., staff physicians, advanced practice providers, and trainees). Furthermore, stewardship efforts can be enhanced by addressing antifungal use in ambulatory patients, particularly pertaining to the duration of prophylaxis or treatment.

A Multifaceted Approach Can Result in Reduced Drug Use Without Compromising Patient Care. One of the most comprehensive antifungal stewardship studies outlined antifungal utilization improvement efforts in a Spanish university hospital [35]. The main prescribing department was Hematology. In the first year of the intervention, pocket-size treatment guidelines were distributed to prescribers, an order entry tool for antifungals was incorporated into the electronic medical record, and interactive training courses were developed. An audit of antifungal prescriptions enabled practice assessment. In the second year of the intervention, all antifungal prescriptions were prospectively audited by infectious disease specialists. Feedback was provided to prescribers. There are three important findings from this study: incidence of and mortality secondary to candidemia was reduced, the number of defined daily doses of antifungals decreased, and the program led to significant cost savings. The sustainability of the intervention was demonstrated up to 36 months after implementation.

Stewardship Interventions for Mold-Active Antifungals Are Associated with Significant Cost Savings. An antifungal stewardship program was launched in a university hospital in England. A consultant microbiologist and an antimicrobial pharmacist prospectively audited high-cost antifungal use and provided direct feedback to prescribers. Half of the interventions were made in hematologic patients, and the most common indication was aspergillosis. The 12-month observational study demonstrated high intervention rates for patients receiving micafungin, voriconazole, and liposomal amphotericin B and a significant cost reduction without compromise in patient care [36].

Most Studies Demonstrate a High Acceptance Rate of Recommendations Made by the Antifungal Stewardship Team. In a French tertiary-care center, antifungal stewardship included several interventions. As with other studies, most orders were placed by hematologists. Compliance with feedback by the stewardship team was 88% [37]. Of note, care optimization, as recommended by the antifungal stewardship team, also included removal of central catheters in patients with candidemia, an intervention not directly related to antifungal drug use but which may improve clinical outcomes.

Stewardship Interventions Are Feasible in the Pediatric Population. In a Spanish hospital, protocols were developed by the antifungal stewardship team for Hematology-Oncology patients [38]. In addition, prescribing pediatricians attended a course on antifungal use. Knowledge gaps in the areas of epidemiology, pharmacology, and antifungal prophylaxis were identified. Following the interventions, a significant decrease in inappropriate antifungal use was observed.

Antifungal Stewardship Interventions Can Be Integrated into the General Antimicrobial Stewardship Program.

In a 904-bed tertiary-care teaching hospital in the USA, restricted antimicrobials, including some antifungals (i.e., amphotericin B formulations, itraconazole, posaconazole, voriconazole, and micafungin) required prior approval by Infectious Disease staff. Controlled and restricted antimicrobials were reviewed ≥ 48 h after the initial order. The antimicrobial pharmacist made recommendations with input from the Infectious Disease physician. This intervention combined pre-authorization and post-prescription audit and feedback. Antifungal use (defined by defined daily doses per 1000 patient-days) was decreased by 71% [39]. Similarly, general antimicrobial stewardship interventions implemented in smaller hospitals led to reduced antifungal consumption and are summarized in a review by Hart et al. [40].

In Certain Settings, a Single Intervention May Be Successfully Implemented. In a British university hospital, most IFI diagnoses have been categorized as possible by EORTC/MSGERC criteria. In this setting, patients treated with posaconazole had a follow-up chest CT scan at 4 weeks after the initial diagnosis. Decision on duration of antifungal treatment was made based on neutrophil recovery, ongoing need for corticosteroid treatment, and follow-up radiographic findings. Overall treatment duration was reduced with this simple intervention [41].

Metrics in Antifungal Stewardship

As observed above, metrics used to measure the success of antifungal stewardship efforts have varied widely and included clinical outcomes, appropriateness, intervention rates, cost avoidance, and antifungal consumption. Though of obvious benefit, the practice of routinely tracking clinical outcomes pertaining to antifungal stewardship activities may be arduous and difficult to directly correlate with changes in antifungal use practices. Similarly, appropriateness of therapy represents a challenging metric for stewardship programs given the ambiguity around the definition of "appropriate" and the labor-intensive nature of collecting such data outside of point prevalence assessments [42]. Appropriateness is often defined using adherence to guidelines; however, for reasons noted above, this may be fraught with limitations. Tracking and reporting intervention rates is common amongst stewardship programs and may offer insight into opportunities for improvement in types, services, and methodologies of recommendations provided [43].

Cost avoidance has long been measured by antimicrobial stewardship teams, which also applies to antifungal stewardship [35, 36, 40]. However, the chief goal of antimicrobial stewardship is to optimize patient outcomes and minimize unintended consequences of antimicrobial use, with promotion of cost-effective care following suit. Many antifungals, both new (e.g., isavuconazole) and old (e.g., flucytosine), are costly agents. Therefore, tracking cost expenditures may be of value to program leaders, and especially to hospital administration. Should improvements in cost expenditure be observed as a direct result of stewardship activities, this may serve to increase the allocation of resources to stewardship efforts. Though not recommended as a primary metric, cost of care may augment standard consumption metrics.

The most common longitudinal metrics for antifungal stewardship programs are likely to hinge on measuring antifungal consumption [35, 39, 40]. Several utilization metrics exist for measuring antifungal agent consumption. Older data often utilizes defined daily doses (DDD) per 1000 patient days. This metric adds the total dosage of a product administered within an institution and then divides that value by the dose determined by the World Health Organization (WHO) to be the typical daily dose [44]. This value is then, most commonly, normalized per 1000 patient days. This consumption metric is limited by applicability and/or variability in patient populations unlikely to receive the WHO defined dose (e.g., renal impairment, prophylaxis, pediatric populations, etc.). Additionally, the DDD would not account for loading doses and, therefore may provide a skewed view in agents such as caspofungin or voriconazole. As such, guidelines pertaining to the implementation of antimicrobial stewardship programs published by the Infectious Diseases Society of America recommend using days of therapy (DOT) per 1000 days present as the standard metric in antimicrobial stewardship programs [45]. A DOT is defined as any day on which a minimum of one dose of a given agent is administered. This metric is less susceptible to variation in populations receiving doses outside of the WHO DDD and provides a more consistent determinant of relative use [46]. Yet, the DOT is not without limitations. It does not assign a value to days between doses for agents being given on a q48h or less frequent dosing schedule (e.g., hemodialysis adjustments for fluconazole or flucytosine). Given that the relative use of most antifungals would be well captured by this metric, we would advocate that DOT per 1000 days present be considered the standard consumption metric for antifungal use.

Lastly, in the USA, the CDC has begun calculating standardized antimicrobial administration ratios (SAAR) for some classifications of anti-infectives reported through the antimicrobial use and resistance module with the National Healthcare Safety Network [47]. One category receiving a SAAR is antifungal agents predominantly used for invasive candidiasis (i.e., anidulafungin, caspofungin, micafungin, and fluconazole). The SAAR represents a ratio of an institution's observed DOT per 1000 days present to expected DOT per 1000 days present. The expected value is calculated using a negative binomial regression model accounting for certain institutional features (e.g., bed size, facility type, teaching status, intensive care unit bed size, and average facility length of stay). Patient care

locations within an institution, including intensive care units and general hematology/oncology units, are also assigned a unit-level SAAR. Use of the SAAR in antifungals may be hampered by a lack of model considerations for the institutional prevalence of IFI, lack of inclusion of several antifungal agents, and lack of inclusion of transplant center status as a consideration in the binomial regression. Therefore, the precise utility of this value's accuracy and implication pertaining to antifungal use is currently limited at best. Further study of SAAR implications in antifungal stewardship is warranted.

Practical Considerations

The evaluation of an antifungal stewardship program is critical to understanding what has been done and its associated effectiveness. The outputs will guide the development of future antifungal stewardship activities, provide key data to feedback to the prescribing physicians, and support their engagement, as well as direct where improvements are needed. There remains uncertainty around defining optimal programmatic metrics and the feasibility of obtaining the required information. Nevertheless, detailed metrics have been proposed [10••, 48, 49], and here we present those we regard as important.

Number of Antifungal Drug Prescriptions Reviewed. This should specify whether the prescription was for prophylactic, empirical, or targeted therapy; was it compliant with local guidelines, and was it appropriate for the clinical context? Number of episodes where antifungal prophylaxis was not prescribed (even though recommended by local guidelines) should also be reported.

Number of Stewardship Recommendations Made. This should specify their nature (cessation or change of drug; changes in dosing, route of administration; ordering or interpreting diagnostic tests, including TDM; drug-drug interactions), and, ideally, the proportion of recommendations accepted and implemented.

Incidence of IFI. Presented as a percentage both of total patients and total episodes of hospital admission. Each episode should be classified by EORTC/MSGERC criteria as possible, probable, or proven, and no evidence of IFI [50]. This should be contrasted with the rate of antifungal treatment (empirical and targeted) for both the total patients and total episodes of hospital admission. Fungal species and susceptibility testing should also be reported (when available).

IFI Incidence Rates. The species and antifungal susceptibility results should be reported.

Therapeutic Drug Monitoring. The proportion of episodes where TDM was performed and, for individual results, the percentage within the therapeutic range.

IFI Outcomes. For cases with objective evidence of IFI, decreasing biomarker values and resolving changes on imaging should be reported. The IFI status on cessation of antifungal therapy should be recorded.

Many of the parameters to measure antifungal stewardship activity and performance are extremely challenging to obtain [48]. The reasons for this are multifactorial and include resource limitations, lack of relevant information in hospital information systems (particularly drug details), the challenges of linking patient-level data with respect to clinical parameters, drug prescribing, and laboratory and imaging results, as well as the complexity of this patient population.

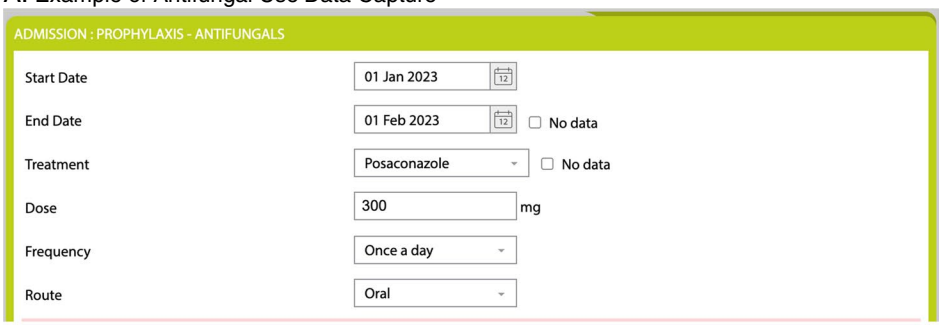
To aid clinical management, we have developed an online, novel information technology system at Barts Health NHS Trust. This is functioning as both clinical support and audit tool for Hematology-Oncology inpatients. The aim was to combine clinical parameters, antimicrobial drug prescribing, and laboratory and imaging results in one repository to give a complete picture of a patient's infection management. At the same time, departmental cumulative data would also be available. Figure 1 shows examples of data fields.

Demographic data points captured include patient age, gender, date of admission, primary diagnosis, and date of diagnosis. Data points related to admission include baseline renal and liver function tests, disease status, chemotherapy type and cycle, and presence of a central venous catheter. Antimicrobial data include the indication, drug, dose, route of administration, and start/stop dates (Fig. 1A). The reason for stopping a drug is recorded, with a drop-down menu allowing multiple selections as appropriate (Fig. 1B). The software requires a comment for every antibacterial and antifungal prescription on guideline compliance (Yes/No), as well as a stewardship team evaluation of the appropriateness of the antimicrobial use (Fig. 1C). A drop-down menu provides a list of options if the drug usage is deemed "inappropriate" (Fig. 1D). Only positive results for blood culture (the organism and peripheral versus central source), other cultures, and bronchoscopy are recorded, while all fungal biomarker results are collected.

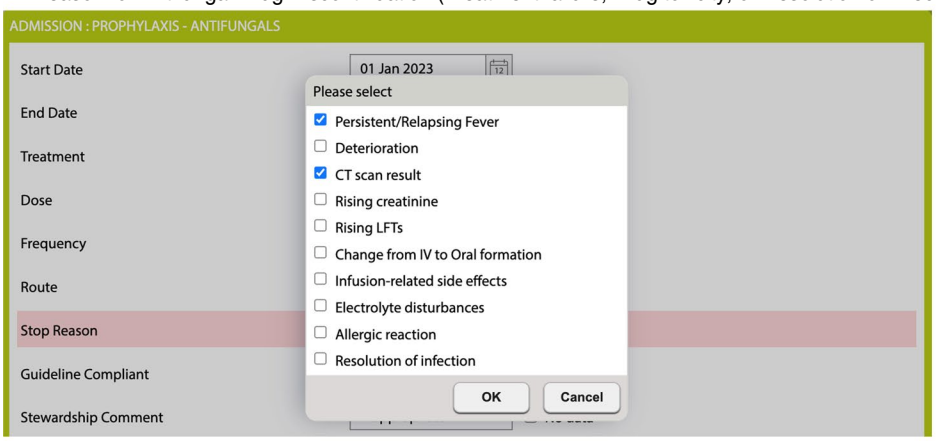
Future Directions

Several novel antifungal agents are being studied in clinical trials and may be available for compassionate use through expanded access programs. In that context, a novel antifungal may be considered the "right drug" for patients who have been intolerant of or have failed standard treatment. Given their mechanism of action, these novel antifungal agents may be active against strains that exhibit resistance to the currently marketed agents. Ibrexafungerp is an orally bioavailable glucan synthase inhibitor that shares a similar target to the echinocandins [51]. Olorofim inhibits pyrimidine synthesis, thus affecting the fungal cell wall and resulting in cell lysis [52]. Fosmanogepix inhibits the trafficking and

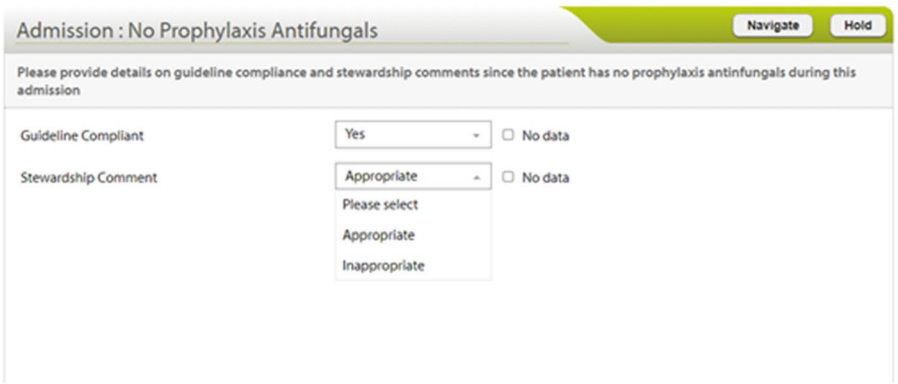
A. Example of Antifungal Use Data Capture



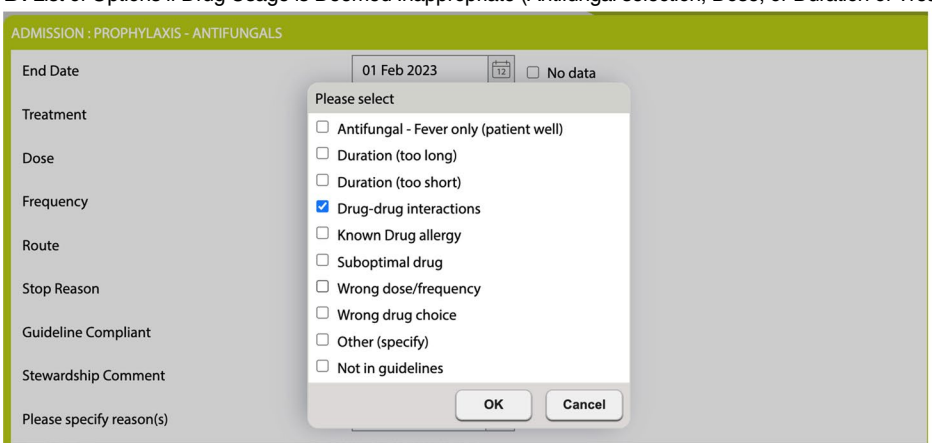
B. Reason for Antifungal Drug Discontinuation (Treatment failure, Drug toxicity, or Resolution of Infection)



C. Example of Data Capture in Relation to Guideline Compliance and Appropriate Antifungal Use



D. List of Options if Drug Usage is Deemed Inappropriate (Antifungal selection, Dose, or Duration of Treatment)



◂**Fig. 1** An online, information technology system to capture antifungal use **A**. Example of antifungal use data capture, **B**. Reason for antifungal drug discontinuaton (Treatment failure, drug toxicity, or resolution of infection), **C**. Example of data capture in relation to guideline compliance and appropriate antifungal use, **D**. List of options if drug use is deemed inappropriate (Antifungal selection, dose, or duration of treatment)

anchoring of mannoproteins to the cell membrane and outer cell wall leading to a reduction in hyphal formation and cell malformation [53]. Opelconazole (formerly PC945) is an inhaled azole that may have a role in both prophylaxis and treatment of aspergillosis [54].

Incorporation of clinical trials in the management of patients with IFIs can be coordinated, or contributed to, by the antifungal stewardship team. Site principal investigators can liaise with the stewardship team to ensure the timely enrollment of qualifying participants. For patients participating in cancer trials at the time of diagnosis of fungal infection, further input from Hematology will be required. These discussions can be facilitated by an established multidisciplinary stewardship team.

Conclusions

Effective stewardship interventions can aid clinicians in selecting appropriate antifungal therapy, which, in turn, will improve patient outcomes and decrease healthcare expenditures. Institutional leadership should provide adequate resources in support of stewardship interventions. Those involved in antifungal stewardship should possess the necessary knowledge and experience in managing fungal infections in at-risk individuals. Hematologists, infectious disease physicians, clinical microbiologists, and pharmacists involved in stewardship should raise awareness and educate other healthcare professionals on appropriate antifungal use. We anticipate that antifungal stewardship programs will expand in the coming years, and the knowledge gained will allow clinicians to further improve their practices and optimize patient care.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Paschalis Vergidis has received research funding from Cidara, Scynexis and Ansun, and has served on the DSMB for AbbVie (all fees have been paid to Mayo Clinic). Ryan Stevens has no conflict of interest. Samir Agrawal has received funding from Gilead, meeting support from Hikma, and honoraria from Shionogi and NAPP/Mundipharma. He has served on the advisory board for Pfizer.

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•• Of major importance

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