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The Emerging Threat of Antifungal Resistance in Transplant Infectious Diseases

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Abstract

Purpose of Review The global emergence of antifungal resistance among *Candida* spp. and *Aspergillus* spp. will disproportionately affect transplantation recipients, who are prone to invasive fungal disease.

Recent Findings Invasive candidiasis is increasingly caused by non-*albicans Candida* species with reduced susceptibility to first-line antifungals. Echinocandin resistance in *Candida glabrata* is increasing in some settings. *Candida auris* has rapidly emerged as a global concern due to multidrug resistance and efficient nosocomial spread in healthcare settings. Azole-resistant *Aspergillus fumigatus* is already an important concern in some European countries and is increasingly reported elsewhere, possibly driven by agricultural use of triazole fungicides.

Summary Antifungal resistance is anticipated to expand among these and other common fungal pathogens. Culture-independent detection methods will become more important for rapid diagnosis and to guide empiric therapy. Antifungal stewardship is of critical importance to conserve our limited antifungal armamentarium for transplantation recipients and other vulnerable patients.

Keywords *Candida* · *Aspergillus* · Azole · Echinocandin · Antifungal susceptibility · Solid organ transplant · Hematopoietic stem cell transplant · Stewardship

Introduction

Invasive fungal diseases are important causes of morbidity and mortality following solid organ and hematopoietic stem cell transplantation. Progress in prevention and management of invasive fungal disease following transplantation has improved outcomes but may be threatened by the emergence of antifungal resistance among common fungal pathogens.

The incidence and microbiology of invasive fungal disease are influenced by a number of factors, including geography, type of transplantation, and use of prophylaxis [1]. In general, the most common causes of invasive fungal disease following solid organ transplantation are *Candida* spp. and *Aspergillus* spp., responsible for 50–60 and ~ 20–25% of such infections, respectively [1, 2]. Less common causes of invasive fungal disease in this group are *Cryptococcus* spp., non-*Aspergillus* molds, and the agents of the endemic mycoses [2]. Among hematopoietic stem cell transplantation recipients, *Aspergillus* spp. predominate, followed by *Candida* spp.; these fungi were responsible for 43 and 28% of invasive fungal disease, respectively, in a large multicenter study [3].

Survival of invasive fungal disease among transplant recipients has dramatically improved thanks largely to effective therapy [1]. Recently, however, an increasing number of reports have raised concern about invasive fungal disease caused by strains resistant or less susceptible to available antifungals [4, 5•]. Given the risk of invasive fungal disease in transplantation recipients and the selection of antifungal resistant organisms by antifungal treatment and/or prophylaxis routinely used following transplantation, clinicians should be aware of emerging antifungal resistance and how this may affect these patients. In this paper, we review the epidemiology and mechanisms of antifungal resistance among *Aspergillus* and *Candida* spp., the status of laboratory methods for detection of antifungal resistant strains, and management of these complex cases. Finally, we highlight the

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importance of antifungal stewardship to limit or reverse these alarming trends.

Mechanisms of Antifungal Activity and Resistance

There are three major classes of antifungals, and their mechanisms of action are relevant for understanding resistance. The azoles include fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole. Azoles interfere with synthesis of ergosterol, an essential component of fungal cell membranes, via inhibition of lanosterol 14α-demethylase; this target protein is encoded in yeasts by *ERG11* and in molds by *cyp51* [6]. Azole resistance in *Candida* spp. can arise from point mutations at *ERG11*, of which > 140 are described [6]. Upregulation of *ERG11* gene expression can result from gain of function mutations in the transcription gene *UPC2* [7]. In addition, drug efflux appears to be an important mechanism of azole resistance in *Candida albicans* and *Candida glabrata* [6]. In *Aspergillus* spp., mutations of the promoter region *cyp51A* can lead to azole resistance by altering the target site for these agents. A number of mutations have been reported that lead to phenotypic resistance and clinical treatment failure [8, 9]. The resistance mechanism most frequently encountered in clinical and environmental isolates of azole-resistant *Aspergillus fumigatus* is a 34-base pair (b.p.) tandem repeat (TR_{34}) in *cyp51A*, in combination with an amino acid substitution of leucine-to-histidine in position 98 (L98H). TR_{34}/L98H leads to pan-azole resistance [10•]. Other *cyp51A* mutations leading to phenotypic resistance reported in environmental and clinical isolates include a 46-b.p. tandem repeat (TR_{46}) combined with tyrosine-to-phenylalanine substitution at codon 121 (Y121F) and threonine-to-alanine substitution at codon 289 (T289A); TR_{46}/Y121F/T289A leads to high level in vitro resistance to voriconazole and isavuconazole [11, 12]. Additional less common mutations include a 53-b.p. tandem repeat (TR_{53}) and the point mutations G54, G138, and M220 [10•, 13]. Alternatively, mechanisms of azole-resistant *A. fumigatus* not involving mutations to *cyp51A* appear important in some settings; for example, a study from the UK reported that 43% of azole-resistant *A. fumigatus* isolates did not have *cyp51A* mutations; the mechanisms in these isolates were not proven [14].

The echinocandins include caspofungin, micafungin, and anidulafungin; these inhibit synthesis of β-(1,3)-D-glucan, a component of fungal cell walls, by non-competitively binding to FKS subunits of β-(1,3)-D-glucan synthase [15]. Echinocandin resistance is conferred by target site alteration [5•]. Some *Candida* spp., like *Candida parapsilosis* species complex, have naturally occurring polymorphisms at *FKS1* that increase echinocandin minimum inhibitory concentrations (MICs) [16]. Resistance may also arise in *Candida* spp. from mutations at highly conserved "hot spot" sites on the *FKS1* gene and/or the *FKS2* gene in *C. glabrata* [17]. Less is known about mechanisms of echinocandin resistance in *Aspergillus* spp. [18]. One recent report identified a mutation of *FKS1* in a clinical isolate of *A. fumigatus* from a patient with chronic pulmonary aspergillosis [19]. However, the extent of this mechanism among resistant isolates is unknown.

Amphotericin B, the sole agent in the polyene class of antifungals, binds to ergosterol, leading to porous cell membranes and cell death [6]. Mechanisms of resistance are less clear than for other antifungals. In *Candida* spp., acquired resistance is associated with mutations that affected sterol synthesis [5•]. Resistance in *Aspergillus flavus* is associated with alterations in cell wall composition [20]. In *Aspergillus terreus*, reduced ergosterol wall content was reported in one resistant isolate [21] but not in another, which was noted to have increased catalase production, suggested to reduce the oxidizing ability of amphotericin B [22].

Candida spp. and Invasive Candidiasis

Invasive candidiasis comprises candidemia and other deep-seated infections caused by *Candida* spp. Antifungal resistance among *Candida* spp. has become an important clinical and public health concern [5•].

Antifungal resistance can be acquired by *Candida* spp. while on therapy [23, 24]. In addition, some *Candida* spp. are intrinsically resistant or less susceptible to specific antifungals [25•]. Among *C. albicans*, antifungal resistance is uncommon: epidemiological surveillance studies have suggested that resistance to fluconazole and echinocandins is generally below 2 and 1%, respectively [26–28]. Alternatively, antifungal resistance is more common in some non-*albicans Candida* species [5•, 28]. For instance, the rates of fluconazole and echinocandin resistance among *C. glabrata* isolates in epidemiological surveys are 14 and 2–4%, respectively [28, 29], although the latter figure underestimates the published experiences of some US centers [30–32]. *Candida krusei* isolates are intrinsically resistant to fluconazole [33]; *C. parapsilosis* isolates are resistant to fluconazole in up to 7.5% [18] and may have reduced susceptibility to echinocandins; fluconazole resistance is reported in up to 9 and 22% of *C. tropicalis* isolates from the USA and Europe, respectively [18]; and among clinical isolates of *Candida auris*, resistance to fluconazole, amphotericin B, and echinocandins occurs in > 90, 40–50, and ~ 5% of isolates, respectively [34].

Shifts in the Distribution of *Candida* Species Causing Invasive Candidiasis

Invasive candidiasis is increasingly reported to be caused by non-*albicans Candida* spp. that are intrinsically less susceptible or resistant to antifungals [25•, 35]. The relative attribution of invasive candidiasis to different *Candida* species is

influenced by geography [36]. Globally, *C. albicans* is the most common cause of candidemia, causing between 36 and 70% of cases [35]. In North America and Northern Europe, the next most common species is typically *C. glabrata*, accounting for 18.1–40.7 and 8.5–31.0% of cases of candidemia, respectively [18]. In Latin America, Spain, and South Africa, *C. parapsilosis* is more common [35, 37, 38]. Alternatively, *C. tropicalis* is the second most common cause of candidemia in Asia, causing 25.4% of cases [39]; there, fluconazole-resistant *C. tropicalis* is a concern, comprising 15% of isolates from Taiwan, for example [40]. Perhaps most concerning given the attributes of frequent multidrug resistance, the ability to persist in environments, and efficient nosocomial transmission, *C. auris* is increasing as a cause of invasive candidiasis. For example, *C. auris* is reported to cause up to 30% of cases of candidemia in some centers in India [41].

The prevalence of invasive candidiasis caused by various species is also affected by patient factors, such as age, comorbidities, hospitalization, and use of, class of, and duration of antifungal prophylaxis [33, 42]. Fluconazole prophylaxis leads to a decrease in invasive candidiasis due to *C. albicans* and an increase due to *C. glabrata* and *C. krusei* [33, 43–45]; similarly, when echinocandins are used for prophylaxis, more cases are attributable to *C. parapsilosis* [44]. In addition, one report found that among patients with candidemia, being the recipient of a solid organ or hematopoietic stem cell transplantation is an independent risk factor for being infected with a fluconazole non-susceptible isolate [46]. Among solid organ transplantation recipients, a large prospective surveillance study that included 17,000 solid organ transplantation recipients from 15 transplantation centers (representing 15% of solid organ transplantations performed in the USA) found that invasive candidiasis was caused by *C. albicans* in 46.3% of cases, *C. glabrata* in 24.4% of cases, and *C. parapsilosis* in 8.1% [45]. In fact, 39% of invasive candidiasis episodes represented breakthrough disease (usually by non-*albicans Candida* species) in patients receiving antifungal prophylaxis [45].

Echinocandin Resistance in *C. glabrata*

Echinocandin resistance occurs most frequently in *C. glabrata*, although it can also occur less frequently with other *Candida* spp. [17]. Echinocandin resistance appears to be increasing in some settings, including some transplantation centers [30, 31]. A retrospective 10-year survey of *C. glabrata* isolates at the Duke University Medical Center reported that echinocandin resistance increased from 4.9% in 2001 to 12.3% in 2010 [30]. Pittsburgh University Medical Center reported 8% of *C. glabrata* isolates from cases of invasive candidiasis were echinocandin-resistant; moreover, this figure increased to 32% when considering only patients with prior echinocandin exposure [31]. Another series, from the Texas Medical Center in Houston, reported that 18% of bloodstream *C. glabrata* isolates harbored *FKS1* or *FKS2* mutations, which were associated with prior echinocandin exposure [47]. Importantly, *FKS* mutations are associated with clinical failure of echinocandin therapy [30, 31, 47]. In addition, fluconazole resistance also occurs in over a third of echinocandin-resistant *C. glabrata* isolates, limiting treatment options [29].

Candida auris

In 2009, a new species of *Candida* was identified from the ear of a Japanese patient [48]; since then, *C. auris* has rapidly emerged in at least 17 countries on five continents as a serious threat to public health [49]. In addition to a propensity for otomycosis [50, 51], *C. auris* causes invasive candidiasis [52], and its virulence approaches that of *C. albicans* [53]. Antifungal resistance in *C. auris* is a major concern: fluconazole resistance is nearly universal, amphotericin B resistance occurs in nearly half of all isolates, and echinocandin resistance is documented in 5–7% of isolates [54]. A striking degree of clonality within geographically clustered isolates hints at efficient horizontal transmission [41, 54]. Indeed, *C. auris* has been implicated in large outbreaks in healthcare settings, including in the UK and the USA [55, 56]. The nosocomial potential of *C. auris* may partly be because of the ability of this organism to persist on patients and environmental surfaces for prolonged periods [55, 57, 58]; moreover, *C. auris* can be misidentified using phenotypic identification methods [59], which may delay implementation of appropriate infection prevention and control measures [49].

Identification of *Candida* Species

Because of differences in patterns of antifungal susceptibilities, correct fungal identification to species level can be imperative for guiding clinical decisions in patients with invasive fungal disease. This concept has been highlighted most dramatically by the recent emergence of *C. auris*, which is managed differently because of inherent antifungal resistance and potential for nosocomial transmission [60]. *C. auris* is frequently misidentified (most often as *Candida haemulonii* or *Rhodotorula glutinis*) by automated identification systems in wide use in clinical microbiology laboratories [59]. Correct identification of *C. auris* can be made using research use-only databases of matrix-assisted laser desorption ionization-time of flight mass spectrometry instruments (MALDI-TOF MS) and by genetic sequencing, usually of the internal transcribed spacer (ITS) region of the fungal rRNA gene or D1-D2 regions of the 28S rDNA [61].

Detection of Antifungal Resistance in *Candida* spp.

Clinical practice guidelines for candidiasis from the Infectious Diseases Society of America (IDSA) recommend azole susceptibility testing for all clinically relevant *Candida* isolates and echinocandin susceptibility testing for clinically relevant isolates of *C. glabrata*, *C. parapsilosis*, and other *Candida* spp. where patients have been recently exposed to echinocandins [62]. The latter caveat underscores the importance of dialogue between clinicians and the clinical microbiology laboratory.

Currently recommended antifungal susceptibility testing practices are based on phenotypic response of cultured fungi to selected antifungals [63]. Standardized methods have been prescribed by the Clinical Laboratory Standard Institute (CLSI) and European Union Committee on Antimicrobial Susceptibility Testing (EUCAST) using broth microdilution. In addition, commercial assays widely used in clinical microbiology laboratories include *E-test* (Biomerieux, Hazelwood, MO), automated testing platforms (e.g., *Vitek-2* [Biomerieux]), and colorimetric tests like *YeastOne Sensititre* (Thermo Fisher Scientific, Waltham, MA) [5•]. Clinical breakpoints associated with treatment outcome have been defined for some *Candida* spp., but these are imperfect at predicting patient response [64].

Phenotypic antifungal susceptibility testing does have some important limitations. Firstly, isolation of the pathogen is required, but cultures are negative in up to half of patients with invasive candidiasis [65]. Secondly, phenotypic methods are limited by delays in turnaround, dictated by the growth rate of the organism [63]. Consequently, interest has turned to culture-independent methods of predicting antifungal susceptibility, including molecular detection of genetic mutations associated with resistance [63, 64]. Such assays are most feasible when there are few mechanisms of resistance associated with few mutations. Azole resistance in *Candida* spp., for example, is governed by several mechanisms (i.e., target alteration, target overexpression, efflux) associated with a vast array of mutations, which likely make molecular or proteomic determination of susceptibility challenging.

On the other hand, echinocandin resistance in *Candida* spp. may be a good candidate for culture-independent detection methods because resistance is driven by a dominant mechanism (target site alteration) caused by few mutations (at *FKS1* and/or *FKS2*) that reliably lead to phenotypic resistance associated with poor outcomes [64]. Molecular and proteomic assays have been evaluated for the detection of *FKS* mutations in order to predict echinocandin susceptibility [66, 67]. Further validation is required before such assays are commercially available and can be recommended.

Although not specific for antifungal resistant strains, *T2Candida* (T2 Biosystems, Lexington, MA) is another culture-independent diagnostic assay that may be useful in rapid diagnosis of candidemia and guiding appropriateness of early antifungal therapy. This assay uses nuclear magnetic resonance spectroscopy combined with PCR for rapid detection of five dominant *Candida* species, grouped by typical patterns of susceptibility: *C. albicans/C. tropicalis*, *C. glabrata*/*C. parapsilosis*, and *C. krusei* [68]. In a clinical trial, the assay detected and identified these *Candida* spp. in whole blood in 4.4 ± 1.0 h, with a sensitivity of 91.1% and a specificity of 99.4% compared to culture as the gold standard [69]. While not supplanting culture and susceptibility testing, this commercially available test may help in the selection of empiric antifungal therapy—based on local patterns of resistance—while susceptibility testing is pending.

Management

Management of invasive candidiasis often necessitates empiric treatment, in part because a significant portion of cases are not microbiologically proven [65], and because of the delays inherent to culture and susceptibility testing [64]. Current clinical practice guidelines recommend echinocandins as first-line therapy for candidemia. Fluconazole is considered an acceptable alternative in patients who are stable and not considered to be at risk of infection due to fluconazole-resistant *Candida* spp. [62]. Consequently, an echinocandin would be the appropriate first-line agent in transplant recipients or other patients with breakthrough invasive candidiasis in the setting of fluconazole prophylaxis, whereas empiric treatment with a lipid formulation of amphotericin B would be reasonable in patients taking echinocandin prophylaxis. In non-neutropenic patients treated with echinocandins, transition to fluconazole or voriconazole should be considered if the patient is clinically stable, repeat blood cultures document clearance of infection, and if the pathogen is susceptible to the desired azole [62]. There are no clinical practice guidelines available for the management of *C. auris*, although empiric treatment with an echinocandin would be appropriate given reported susceptibility patterns [54].

Aspergillus spp. and Aspergillosis

Aspergillus spp. are ubiquitous environmental molds. Infection is acquired by inhalation of environmental conidia by susceptible hosts and can lead to a spectrum of disease which includes allergic bronchopulmonary aspergillosis, aspergilloma, chronic pulmonary aspergillosis, and invasive aspergillosis, the most devastating form, and of main concern for immunocompromised hosts [2].

Reduced antifungal susceptibility among *Aspergillus* spp. is a growing concern [70]. Methodologies for antifungal susceptibility testing suggested by CLSI and EUCAST differ. Clinically validated breakpoints have not been established

by CLSI for molds. Instead, epidemiological cutoff values (ECVs) are used to distinguish wild-type isolates from those that demonstrate higher MICs or mean effective concentrations (which are used for quantifying in vitro effect of echinocandins on molds) [71]. ECVs do not incorporate clinical outcome data in their determination, so the extrapolation of treatment success or failure based on these should be done with caution. Nonetheless, isolates with MIC/mean effective concentrations greater than ECVs will be referred to here as "resistant." Clinical breakpoints for itraconazole, voriconazole, and posaconazole against *Aspergillus* spp. have been suggested by CLSI and EUCAST [72]. ECVs have been reported for isavuconazole [73, 74] and echinocandins [75]. Breakpoints for amphotericin B against *Aspergillus* spp. were suggested by EUCAST, but clinical outcome data to support them is limited [76].

Azole Resistance

Triazoles are the first-line therapy for most patients with aspergillosis, including invasive aspergillosis [77]. However, azole-resistant *A. fumigatus* isolates have been reported with increasing frequency in some centers. A large global survey reported 3.2% of clinical *A. fumigatus* isolates to be azole resistant [78]; however, in some European countries, resistance rates are even higher. For instance, a multicenter survey from the Netherlands reported itraconazole resistance in up to 6.0% of clinical *A. fumigatus* isolates [79]. While in-host resistance mutations have been observed in patients receiving azole treatment for chronic aspergillosis syndromes [80], over 90% of clinical azole-resistant *A. fumigatus* isolates are thought to have gained resistance mutations in the environment as a consequence of fungicidal use of azoles in agriculture [81–83].

A survey from the Netherlands reported the proportion of *A. fumigatus* isolates resistant to itraconazole ranged from 1.7 to 6.0% since 2000 [79]; for > 90% of these isolates, the mechanism was TR_{34}/L98H. Some infected patients had been azole-naïve, and since *A. fumigatus* is not communicable between people, this finding raised the possibility that a resistant strain was acquired from the environment [13, 79]. Indeed, the investigators soon reported the detection of environmental *A. fumigatus* strains harboring TR_{34}/L98H [81]. The authors hypothesized that cross-resistance to medically important azole antifungals was occurring in the environment in response to widespread agricultural use of azole fungicides [82]. In retrospect, the first known azole-resistant *A. fumigatus* isolate with TR_{34}/L98H from the Netherlands appeared within a few years of the approval of triazoles for agricultural use [13]. TR_{34}/L98H mutation has since been identified in clinical and environmental *A. fumigatus* isolates from six continents [12, 78, 84–89]. In addition to de novo mutations, intercountry spread of azole-resistant *A. fumigatus* isolates can occur unintentionally from the transfer of agricultural products. For instance, azole-resistant *A. fumigatus* were identified among tulip bulbs transferred from the Netherlands to Ireland [90].

van der Linden et al. first reported voriconazole-resistant *A. fumigatus* isolates harboring TR_{46}/Y121F/T289A among clinical and environmental samples from the Netherlands. These isolates retained susceptibility to itraconazole and posaconazole [11]. Clinical or environmental *A. fumigatus* isolates harboring TR_{46}/Y121F/T289A have since been reported from five continents [18].

Invasive aspergillosis caused by azole-resistant *A. fumigatus* is associated with high mortality. At least five case series of patients with invasive aspergillosis due to azole-resistant *A. fumigatus* have evaluated outcomes: four from Europe and one from the USA. Three European series each included eight patients: deaths occurred in seven (88%), seven (88%), and four (50%) patients, respectively [8, 11, 91]. In a fourth study of patients in an intensive care unit in the Netherlands diagnosed with invasive aspergillosis, death occurred in 10/10 (100%) patients in whom disease was caused by azole-resistant *A. fumigatus* compared to 23/28 (82%) in whom disease was caused by azole-susceptible strains [92]. A retrospective case-control study of patients with hematological malignancies or hematopoietic stem cell transplantations with invasive aspergillosis reported no difference in outcome per triazole susceptibility of *A. fumigatus* isolates, although the numbers were small ($n = 19$ resistant isolates) [32].

Echinocandin and Polyene Resistance Among *Aspergillus* spp.

Although ECVs been suggested for echinocandins against *Aspergillus* spp. [75], testing suffers from problems with reproducibility and lack of clinical validation [93]. Consequently, the prevalence of echinocandin resistance is unclear.

Intrinsic amphotericin B resistance is uncommon among *A. fumigatus*. However, elevated MICs are observed more frequently with some other *Aspergillus* spp., including *A. terreus* [94], *A. flavus* [95], *A. lentulus* [96], *A. calidoustus* [97], *A. alliaceus*, and *A. nidulans* [98].

Identification

Antifungal susceptibility profiles of some cryptic species of *Aspergillus* may differ from sibling species within species complex [99]. Consequently, identification to species level may be helpful in some cases. However, routine species-level identification of *Aspergillus* spp. is not currently practical in most clinical laboratory settings and is not recommended in current clinical practice guidelines from IDSA [77]. Species identification using molecular methods should be

considered if isolates demonstrate atypical growth or if there is concern for resistance [77].

Detection of Antifungal Resistance in *Aspergillus* spp.

In contrast to the recommendations for candidiasis, IDSA clinical practice guidelines for the diagnosis and management of aspergillosis do not recommend routine antifungal susceptibility testing of *Aspergillus* spp. Rather, antifungal susceptibility testing is recommended when azole-resistant *A. fumigatus* is suspected or in patients who fail to response to triazole therapy [77]. Partly, this is because antifungal susceptibility testing is not universally available in the USA [100]. Alternatively, an international group of experts on the diagnosis and management of aspergillosis caused by azole-resistant *A. fumigatus* recommended that antifungal susceptibility be routinely performed on clinical isolates from patients who require antifungal therapy [101•]. Moreover, it was recommended that up to five colonies be tested because of the possibility of heterogeneous *A. fumigatus* populations in a sample [101•]. The group further recommended that molecular determination of resistance mechanism be undertaken for epidemiological purposes if azole-resistant *A. fumigatus* is detected [101•].

An important limitation in the most widely used detection methods for azole-resistant *A. fumigatus* is the need for pathogen recovery. In some high-risk patients, the yield of culture from non-invasive specimens is low and reduced further by pre-emptive treatment with antifungals. In addition to culture-based techniques for determining antifungal resistance, several PCR assays have been developed for the culture-independent detection of *cyp51A* mutations in clinical samples [102]; in fact, some assays, such as *AsperGenius PCR* (Pathognostic, Maastrich, the Netherlands) [103] and *MycoGENIE A. fumigatus real-time PCR kit* (Ademtech, Pessac, France) [104], are already commercially available in Europe. Prospective studies evaluating the impact of these are pending [102].

Management

Clinical practice guidelines recommend voriconazole as first-line therapy for most patients with aspergillosis [77]. The international expert group for aspergillosis caused by azole-resistant *A. fumigatus* has recommended that voriconazole be reconsidered as first-line monotherapy when ≥ 10% of environmental *A. fumigatus* isolates are azole-resistant; in this case, voriconazole should be combined with an echinocandin or replaced with a lipid formulation of amphotericin B alone until antifungal susceptible testing is available for clinical isolates [101•]. When environmental resistance rates were between 5 and < 10%, there was no consensus on optimal empiric management. A practical limitation to this approach is the fact that data regarding prevalence of resistance among environmental *A. fumigatus* isolates is rarely available for most areas.

Conclusion

Tracking the emergence and spread of antifungal resistance requires that some challenges be overcome. Firstly, access to antifungal susceptibility testing should be improved. A recent survey of US infectious diseases physicians found that 21% of respondents lacked access to antifungal susceptibility testing [100]. Secondly, there should be consensus on how to enumerate cases and define prevalence of antifungal resistance [105]. For instance, repeated culture of resistant *A. fumigatus* from a patient with chronic aspergillosis could, in the absence of standardized reporting, be counted by a laboratory many times more than a single isolate from a patient with a hematological malignancy [105]. Additionally, although a group of international experts recommended clinical decisions regarding empiric management of aspergillosis be guided by the prevalence of resistance among environmental isolates of *Aspergillus* spp. [101•], such data are rarely available to clinicians. Thirdly, there should be standardization in the detection techniques. Fourthly, antifungal resistance should ideally be tracked by active surveillance to minimize the problem of referral bias; although, national-level programs [106] are uncommon and in many areas (including the USA), only passive surveillance is performed [107]. Even where resistance is infrequently encountered, robust international surveillance data can help guide patient-level decisions regarding treatment and—in the case of *C. auris*—infection control measures in an age of increasing global travel and medical tourism [51].

The observed increase in invasive fungal disease caused by antifungal resistant pathogens can be expected to continue unless human behaviors are modified to reduce selective pressures favoring resistant strains of clinical and environmental fungi. While the value of antibiotic stewardship for antibacterial therapy is widely appreciated, there has been less emphasis on the need for systematic efforts to ensure conservation of medically useful antifungals. In addition to judicious antifungal use by clinicians, a multifaceted approach is required that includes the critical appraisal of the use and selection of agricultural fungicides. These measures will be essential for ensuring that effective antifungals are available when needed for the prevention and treatment of fungal disease in the most vulnerable patients.

Compliance with Ethical Standards

Conflict of Interest Dr. Schwartz has nothing to disclose.

Dr. Patterson reports personal fees from Astellas, Basilea, Gilead, Merck, Scynexis, Toyama, and Pfizer.

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