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CURRENT MANAGEMENT OF FUNGAL INFECTIONS (S JACOBS, SECTION EDITOR)

Updates on the Treatment of Non-*Aspergillus* Hyaline Mold Infections

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Abstract
Purpose of Review This review summarizes both the recent and relevant studies about the treatment of non-*Aspergillus* hyaline molds.
Recent Findings Given the rarity of these infections, there have been no large randomized clinical trials regarding the most effective antifungal therapy.
Summary Although there are more data for the treatment of *Fusarium* and *Scedosporium*, there are limited data with case reports that address the other rare hyalohyphomycetes. As we develop improved diagnostic techniques and larger fungal registries, we may be able to determine efficacious treatment modalities. We hope that future research will focus on implementing clinical trials with the new antifungals and ongoing development of novel fungal agents.

Keywords Hyaline molds · Hyalohyphomycetes · Emerging fungal infections · Antifungal therapy · *Fusarium* · *Scedosporium*

Introduction

Treatment of invasive infections due to non-*Aspergillus* hyaline molds (hyalohyphomycetes) is challenging. These molds are of particular concern due to their intrinsic resistance to many standard antifungal drugs and their potential for causing devastating disease. The most common infections are due to *Fusarium* spp. and *Scedosporium/Lomentospora*, followed by *Paecilomyces* spp., *Acremonium* spp., *Scopulariopsis* spp., *Trichoderma* spp., and *Rasamsonia* spp. These filamentous fungi have branching septate hyphae that lack pigment and are often confused with *Aspergillus.* It can also be difficult to determine whether their presence in clinical specimen is reflective of colonization or invasive disease. Consequently, accurate diagnosis and institution of proper treatment is often delayed. In this article, we will briefly touch on the epidemiology of hyalohyphomycoses and then transition to a review of their treatment drawing from the published literature and from our own experiences.

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Background and Epidemiology

Hyalohyphomycetes, which are normally present in soil, water, and vegetation, are increasingly recognized as causes of infection. Reasons for this include a growing population of at-risk patients, broad use of prophylaxis effective against other organisms (e.g. *Aspergillus, Candida*, bacteria), and improved fungal diagnostic techniques [1, 2].

Data regarding hyalohyphomycoses are available from epidemiology studies in the USA and Australia. The US based Transplant-Associated Infection Surveillance Network (TRANSNET) identified 1208 invasive fungal infections in solid organ transplantations (SOT) and 983 invasive fungal infections in hematopoietic stem cell transplantations (HSCT) from 2001 to 2006. Of those, 169 (8%) were due to non-*Aspergillus* molds, with *Fusarium* accounting for 22% and *Scedosporium* for 16% [3, 4]. By contrast, an Australian study of non-*Aspergillus* mold infections found that 33% were due to *Scedosporium* spp., 8% *Fusarium* spp., and 2% *Paecilomyces* spp., indicating that epidemiology may differ by locale [5].

Fusarium species are grouped into ten phylogentic species complexes [6]. Most infections are probably due to *F. solani* species complex [7]. In the TRANSNET data set, *F. solani* accounted for 27% of *Fusarium* infections, but almost 60% were reported as unspecified *Fusarium* spp. [4]. Clinical manifestations in non-immunocompromised patients are most frequently keratitis and onychomycosis. In immunocompromised patients, infectious sites also include the skin, sinuses, lower respiratory tract, and bloodstream [7]. Diagnosis is typically made by tissue or blood cultures with MALDI-TOF and PCR assays increasingly used to assist with identification of the organism [7–9]. With regard to fungal biomarkers, *Fusarium* can cross-react with the galactomannan assay and the beta-d-glucan assay has variable reactivity [10–13].

The *Scedosporium* genus is primarily comprised of the *Scedosporium apiospermum* complex (*S. apiospermum sensu stricto*, *S. boydii*, and *Pseudallescheria angusta*). There are other rare species including *S. aurantiacum*, *S. dehoogii*, and *S. minutisporum* [14]. *S. prolificans* is phylogenetically distinct from other *Scedosporium* spp. and has been renamed *Lomentospora prolificans* [15]. The teleomorph (sexual state) of *S. apiospermum* is known as *Pseudallescheria apiosperma* [7]. *P. boydii* was initially classified as the teleomorph but has since been determined to be a different species [14].

Scedosporium/Lomentospora spp. tolerate anaerobic and high saline environments and can be found in sewage, manure, and swamps. *L. prolificans* and *S. aurantiacum* are primarily found in hot and dry climates and are particularly localized to Australia, Spain, and Southern US, whereas *S. apiospermum* species complex is found in temperate climates and distributed worldwide [16•]. Most infections occur in immunocompromised patients. Of the 27 *Scedosporium* infections in the TRANSNET data set, *S. apiospermum* accounted for 70% and *L. prolificans* for 30% [4]. In immunocompetent patients, infection may occur following traumatic injury or near drowning in contaminated water. Typical sites of infection include the sinuses, lower respiratory tract, central nervous system (CNS), and bloodstream [7]. Similar to *Fusarium*, *Scedosporium* is best diagnosed with tissue or blood cultures. Molecular assays are increasingly used, but are still experimental [7, 8]. There may be a role for beta-d-glucan and galactomannan index in diagnosing *Scedosporium/Lomentospora*, but utility of those assays is inconsistent [17, 18].

Basic Principles of Treatment

Hyalohyphomycoses should be considered in patients with compatible exposures, host factors, and clinical features. Clues include a history of exposures to soil, dust, vegetation, and water that is suspected or known to be contaminated with fungal spores. *Fusarium* is typically associated with tropical and subtropical climates and *Scedosporium* with more temperate climates and certain geographic locales (e.g., Australia). Major host factors to consider are immunodeficiency states such as hematological malignancy, solid organ transplant (especially lung), and bone marrow transplant. Abnormal pulmonary architecture and mucosal defects can predispose to colonization with fungi such as *Fusarium* spp., *Scedosporium* spp., *Purpureocillium lilacinum*, and *Paecilomyces variotii*, which can then progress to infection. In that regard, predisposing conditions such as skin breakdown and trauma, and lung diseases with bronchiectasis (e.g., cystic fibrosis) are important host factors. Given that these molds may be resistant to multiple antifungal agents, infections that break through prophylaxis or initial empiric therapy with a mold active agent should raise concern for hyalohyphomycoses.

Infection vs Colonization?

The decision to treat is straightforward when culture is obtained from a sterile site (e.g., tissue or blood) and when there is histopathologic evidence of invasive infection. More challenging are circumstances when organism is retrieved from non-sterile site specimen such as a sinus aspirate, sputum, bronchoalveolar lavage fluid, or urine. Cultures obtained from these sites do not necessarily indicate infection. This is particularly true for patients with bronchiectasis such as those with cystic fibrosis (CF) and non-immunocompromised patients with chronic sinusitis. Distinguishing between infection and colonization requires consideration of host vulnerability, clinical signs and symptoms, results of non-culture techniques (e.g., beta glucan, galactomannan, nucleic acid amplification), and radiographic findings.

When to Pursue Surgical Versus Medical Management Alone?

As a general rule, surgical debridement/drainage of affected areas should be considered in non-pulmonary hyalohyphomycoses. This is especially true when there is localized skin or soft tissue infection, brain involvement, or pleural disease. Antifungal therapy should be guided by susceptibility, with the caveat that Clinical and Laboratory Standards Institute (CLSI) breakpoints have not yet been established for these fungi. Surgical intervention should be strongly considered for *L. prolificans* given its resistance to virtually all available antifungals. For bloodstream infections (e.g., with *Fusarium*), removal of central venous catheters may be required [7, 19••, 20•]. There is sometimes a role for resection of fungal lung lesions [21], especially if there is no improvement with medical management alone, but the decision to operate is often complicated by the high morbidity associated with such procedures.

Immunomodulation

Immunosuppression should be reduced to the extent feasible to assist with restoration of the immune system. Resolution of neutropenia when present is important. In that regard, granulocyte-colony stimulating factor (G-CSF) is helpful [20•, 22••, 23]. In cases that prove refractory to antifungals, immunomodulatory therapy such as interferon-γ (IFN-γ) may have a role [24, 25]. The evidence for checkpoint inhibitor induced immuno-stimulation as a potential modality for non-*Aspergillus* hyalohyphomycosis is extrapolated from experience with invasive candidiasis in mice and invasive mucormycosis in a single patient who responded to a combination of nivolumab and interferon gamma after surgery and antifungal therapy were unable to control the infection [26, 27]. Using checkpoint inhibitors and T-cell activation as an adjunctive modality merits further study.

Duration of Therapy

Length of therapy is individualized and based on site and extent of infection, whether source control has been attained, the patient's net state of immunosuppression, and safety considerations. As a general rule, treatment should be for several months or longer. Exceptions are localized skin or soft tissue infection that has been managed with thorough debridement (or amputation), which may require little or no additional antifungal therapy. Treatment for pulmonary, sinus, CNS, and disseminated infection should be continued at least until radiographic and clinical signs of infection have resolved. For patients with anticipated prolonged immunodeficiency, such as those with hematologic malignancies and HSCT, antifungal therapy should be maintained until substantial improvement of immune function.

Drug Toxicity

Voriconazole, posaconazole, and amphotericin B (AmB) products are the most commonly used drugs for hyalohyphomycoses and all are associated with potential for toxicity and/or drug-drug interactions. Isavuconazole is occasionally used; however, there have been no robust clinical trials to support its use. The echinocandins have less toxicity, but also have a smaller role in therapy.

Posaconazole comes in IV and oral forms, although many hospitals do not have the IV formulation readily available. For oral posaconazole, both delayed release tablets and suspension are available. The tablets are preferred as they have superior absorption and drug levels compared with the suspension. Trough levels should be obtained 5–7 days after initiation and checked weekly thereafter, with a goal trough of ≥ 0.7–1 mcg/mL [28, 29]. With the oral suspension, effective drug levels may not be achieved for many days (or at all) despite increasing dosage. This is particularly problematic in patients with high BMI, severe mucositis, malabsorption, and inability to consume high fat meals.

Voriconazole is available in IV and oral formulations. Voriconazole has complicated non-linear pharmacokinetics that lead to unpredictable drug levels and significant drug-drug interactions through the CYP450 system. Trough levels should be obtained 5–7 days after initiation and checked weekly thereafter, with a goal trough of 2–5.5 mcg/mL (though some recommend 1.5–4.5 mcg/mL). Levels below 1 mcg/mL are associated with clinical failure and levels above 5.5 mcg/mL with toxicity [30–33].

Isavuconazonium sulfate (prodrug of isavuconazole) is available in IV and oral formulations. There are certain laboratories that will check isavuconazole levels, although there is no data to suggest that a specific isavuconazole trough level is therapeutic. In contrast to the other triazoles, isavuconazole shortens the QTc interval, which should be avoided in patients with familial short QT syndrome.

Posaconazole, isavuconazole, and voriconazole are inhibitors and substrate of P-glycoprotein and CYP450 enzymes and can impact serum concentrations of co-administered drugs metabolized via these pathways (e.g., sirolimus, tacrolimus, cyclosporine, warfarin). It is crucial to adjust the doses of such medications when azoles are started or stopped. Liver and cardiac toxicities are important in both. Hepatic enzymes should be monitored either weekly or biweekly and a baseline EKG should be obtained to measure the QTc (except for isavuconazole, which shortens the QTc). If it is > 450 ms (men) or > 460 ms (women), a follow-up EKG should be obtained daily for the first 48–72 h after initiation. If the QTc is > 500 ms at baseline, then an alternative therapy should be considered if possible. Posaconazole tablets can cause abdominal pain in some patients. Voriconazole may cause visual hallucinations and photosensitivity with short-term therapy. Skin cancers and periostitis are associated with long-term voriconazole therapy.

The most common side effects with AmB are infusion-related reactions, renal toxicity, and electrolytic disturbances. These are less common with lipid formulations, which are the treatment of choice if using an AmB product. Careful monitoring of renal function and electrolytes is mandatory. Salt loading (e.g., infusion of 0.9% NaCl × 0.5 to 1.0 L/day) reduces renal toxicity. The echinocandins are generally very well tolerated, though occasionally can cause infusion-related reactions and hepatic enzyme elevations.

Treatment of Specific Fungi

Fusarium

**primary recommendation: voriconazole (Table 1).

The treatment of choice is voriconazole with consideration of adding lipid formulation amphotericin-B (AmB) as initial

Table 1 Recommended therapy of non-*Aspergillus* hyaline mold infections

Fungal pathogen	Initial antifungal therapy	Alternative therapy
Fusarium	Voriconazole	AmB + voriconazole may be considered pending susceptibility Posaconazole *F. solani* may be resistant to voriconazole and require AmB
Scedosporium	Voriconazole	Voriconazole + AmB or echinocandin may be considered pending susceptibility
Lomentospora prolificans	Voriconazole + terbinafine Voriconazole + echinocandin +/− inhaled AmB	
Purpureocillium lilacinum (formerly known as *Paecilomyces lilacinus*)	Voriconazole or posaconazole	
Paecilomyces variotii	Posaconazole or AmB	
Acremonium (formerly known as *Cephalosporium*)	AmB, voriconzole or posaconazole	
Scopulariopsis and *Microascus*	Terbinafine + voriconazole or posaconazole Caspofungin + voriconazole or posaconazole	Based on in vitro data, can consider posaconazole + caspofungin + terbinafine (but this showed antagonism with *S. candida*)
Trichoderma	Voriconazole	Voriconazole + echinocandin may be considered pending susceptibility
Rasamsonia argillacea (formerly known as *Geosmithia argillacea*)	Posaconazole + echinocandin	posaconazole + echinocandin + AmB may be considered pending susceptibility

In all cases consider: (1) surgical debridement when feasible and especially for non-pulmonary sites of infection, (2) reduction of immunosuppression, (3) addition of G-CSF when there is neutropenia. Granulocyte infusion and interferon gamma can be considered in refractory cases

therapy in deeply invasive disease [19••, 20•, 22••, 34••]. While the minimum inhibitory concentrations (MICs) of azole antifungals for *Fusarium* spp. tend to be high, the clinical significance of this is unclear. For most *F. solani* species, complex isolates MICs are low for AmB (1 mg/L), but higher for azoles. In a multicenter Australian study, only AmB had consistently favorable MICs (1–2 mg/L) for *Fusarium solani* species complex, while those for all other commonly used antifungal agents were ≥ 2 mg/L [35]. More favorable (although still variable) triazole MICs are observed with *F. verticilloides*, *F. oxysporum*, and *F. proliferatum* [36–38].

The best outcomes are with *Fusarium verticillioides* [22••]. Clinical outcomes with voriconazole are often better than would be expected based on the in vitro results. In several case series, some level of response (either partial or complete) was reported in 50% of patients on voriconazole, with worse outcomes if patients were neutropenic (5–36%) [22••, 39, 40]. There are limited data on posaconazole for *Fusarium*, although it has been used as salvage therapy in HSCT, with 48% of patients having either partial or complete response [7, 40, 41]. Additionally, there are data on isavuconazole from two clinical trials (SECURE and VITAL). In these trials, nine patients with *Fusarium* infections (3 *F. solani*, 4 *Fusarium* NOS; 2 *Fusarium* plus another mold) received isavuconazole as primary therapy with four patients demonstrating stable or positive response [42].

Combination therapy is controversial due to risk of antagonism and differences in responses between *Fusarium* species [43]. Retrospective studies and case series show mixed results [39]. Combinations that have shown clinical improvement include AmB with caspofungin, voriconazole, or terbinafine and voriconazole with terbinafine [44–50]. A retrospective analysis of 233 *Fusarium* cases comparing treatment outcomes between two time periods (1985–2000 and 2001–2011) showed increases in use of voriconazole, combination therapies, and survival rates during the latter time period. Combinations included voriconazole plus AmB (17 patients), voriconazole plus terbinafine (2 patients), and posaconazole plus AmB (2 patients) [51]. A recent report summarized treatment of 26 *Fusarium* infections in SOT recipients. Most were of skin and soft tissue (42%), followed by the lower respiratory tract (35%). Azole monotherapy (usually voriconazole) was used in 42% of patients followed by AmB monotherapy in 27% and combination (typically AmB with voriconazole or an echinocandin) in 19%. Overall mortality was 30% but reached 60% in the lung transplant population [52•].

Scedosporium

**primary recommendation: *Scedosporium* spp.- voriconazole (Table 1)

L. prolificans – voriconazole + terbinafine (Table 1)

Scedosporium/Lomentospora spp. are resistant to multiple antifungal agents. This is particularly problematic for *L. prolificans*, which is resistant to virtually every available antifungal agent. A survey of over 300 clinical and environmental isolates demonstrated S. *apiospermum* to have more favorable MICs to voriconazole as compared to other antifungals [53]. In a multicenter global study evaluating clinical experience of voriconazole for treatment of *Scedosporium*, 57% of patients responded successfully to therapy, especially

those with superficial or localized infections. Mortality rates were higher in those with CNS involvement, disseminated infections, hematologic malignancy, HSCT, and infection with *L. prolificans* [54].

L. prolificans is essentially a pan-resistant mold [16•, 20•, 34••]. Voriconazole is the most active agent, although its MIC is higher when compared to MICs for *S. apiospermum*. Despite attempts at antifungal optimization, there are high mortality rates with CNS and disseminated infections, as mentioned above. In an experimental mouse model of disseminated and CNS infection, almost all mice infected with *Scedosporium* isolates having voriconazole MIC ≤ 2 mg/L responded to that drug, whereas only 33% of mice challenged with strains having MIC ≥ 4 mg/L responded. This suggests that an MIC ≤ 2 mg/L can be predictive of a favorable outcome in disseminated infections [55].

In vitro analyses of isavuconazole against *Scedosporium* spp., *S. apiospermum*, and *L. prolificans* show drastic differences in susceptibilities, with isavuconazole having favorable MICs against *S. apiospermum* but higher ones against *L. prolificans* [53, 56–58]. Although isavuconazole has broad-spectrum mold activity, clinical experience in *Scedosporium* spp. is limited and additional data are needed before it can be broadly recommended.

Current guidelines recommend using voriconazole plus consideration of AmB or an echinocandin for *Scedosporium* spp. [19••, 20•, 22••, 34••, 59, 60], and a combination of voriconazole and terbinafine to treat *L. prolificans* infections based on evidence of in vitro synergy and case reports [19••, 22••, 34••, 61–67]. Clinical data suggests that patients who receive voriconazole-based therapy have favorable outcomes [68]. One study utilizing the FungiScope registry and a review of the literature since 2000 identified 208 *Scedosporium* and 56 *L. prolificans* infections. For *Scedosporium* infections, voriconazole (as compared with AmB) was associated with lower mortality in both localized and disseminated disease. For *L. prolificans* infections, voriconazole was also associated with lower mortality when compared to other antifungals (53% vs 69%, respectively). Of note, despite potential for in vitro synergism, the addition of terbinafine to voriconazole did not improve outcomes [69•]. This is likely due to low terbinafine tissue concentration at the site of infection.

Limited data are available for triple therapy. Animal data suggested synergy with voriconazole plus AmB plus an echinocandin [70]. In a multicenter German study of 31 CF patients with *Scedosporium*/*Lomentospora* lung infections (15/31 had *S. apiospermum* and 3/31 had *L. prolificans*), combination therapy with voriconazole and an echinocandin +/− inhaled AmB was more effective than voriconazole alone in improving FEV1, respiratory symptoms, and radiographic changes. While there were no differences between triple and dual therapy with respect to FEV1 and respiratory symptoms, patients with triple therapy had more radiographic improvement [71•].

Other Hyalohyphomycetes

Paecilomyces

**primary recommendation: *P. lilacinum* – voriconazole or posaconazole (Table 1)

P. variotii – posaconazole or AmB

Purpureocillium lilacinum (formerly known as *Paecilomyces lilacinus*) is increasingly recognized as a pathogen. Clinical manifestations include skin, soft tissue, and ocular infections [72]. This species is generally resistant to many antifungals, including AmB, itraconazole, fluconazole, and echinocandins, but tends to be susceptible to voriconazole and posaconazole [72–77]. *Paecilomyces variotii* is another clinically relevant species in the genus and tends to have lower susceptibility to voriconazole [78]. Several authors have reported voriconazole resistance and treatment failure [79–82]. Posaconazole has favorable MICs and its use has led to successful treatment [79, 81]. Isavuconazole has also shown favorable MICs [53, 57]. Guidelines do not make strong recommendations on antifungal therapy, but note that *P. lilacinum* is resistant to AmB but susceptible to triazoles, whereas *P. variotii* is susceptible to AmB and posaconazole [19••, 22••, 34••].

Acremonium

**primary recommendation: AmB or posaconazole or voriconazole (Table 1)

Acremonium spp. (previously known as *Cephalosporium*) typically cause infections in immunocompromised patients [83]. Clinical presentations include skin and nail infections, mycetoma, peritonitis in peritoneal dialysis patients and fungemia. Disseminated infections are associated with high mortality rates. In vitro data and case reports have favored using AmB, voriconazole, or posaconazole, depending on susceptibilities [84–87]; however, in vitro MICs are high for all antifungal agents except terbinafine [88]. In one report, a renal transplant recipient's subcutaneous infection resolved with surgical debridement and reduction in immunosuppression without need for antifungal therapy [89]. Guidelines recommend using AmB, posaconazole, or voriconazole [19••, 22••].

Scopulariopsis and *Microascus*

**primary recommendation: terbinafine/caspofungin + voriconazole or posaconazole (Table 1)

The genus *Scopulariopsis* encompasses both hyaline and melanized molds that are phylogenetically close to *Scedosporium*. The most common species are *S. brevicaulis*, *S. gracilis*, and *S. brumptii* (renamed as *Microascus gracilis* and *Microascus paisii*, respectively), *S. candida*, *M. cirrosus*, and *M. cinereus*. Infections occur mostly in immunocompromised patients and include superficial sites (e.g., skin, cornea) and invasive disease such as pneumonia, endocarditis, and cerebral abscesses [90, 91]. These infections are resistant to many antifungals and result in high mortality rates. Antifungal susceptibility testing should be performed. In vitro data suggest that *S. brevicaulis* is resistant to all available antifungal agents [92, 93]. In a murine model of infection, voriconazole, posaconazole, and AmB were effective against *S. brumptii*/*M. paisii*, but not *S. brevicaulis* [94]. Micafungin has favorable MIC for *S. brevicaulis*, but the significance of this is unclear and clinical failure with it has been reported [95]. Data regarding combination therapy are limited. A study of 27 clinical isolates observed synergy with caspofungin, posaconazole, and terbinafine with *Scopulariopsis* and *Microascus* spp. but antagonism for *S. candida* [96].

Various treatment combinations have been used with some clinical success. These include posaconazole or voriconazole with an echinocandin or terbinafine (or both), surgery and terbinafine, and in one report a combination of voriconazole, caspofungin, terbinafine, and aerosolized AmB [97–104]. Current guidelines recommend combination therapy with either voriconazole/posaconazole plus terbinafine or caspofungin [34••]. Unfortunately, given its resistance profile, successful outcome is rarely achieved with medical therapy alone. Treating physicians should strongly consider surgical debridement and restoration of host immunity when feasible.

Trichoderma

**primary recommendation: voriconazole (Table 1)

Trichoderma spp. may cause infections in immunocompromised hosts [105, 106]. Data to guide antifungal recommendations are sparse. In a study of 73 human and animal isolates (mostly *T. longibrachiatum*), voriconazole had the lowest MICs, while posaconazole and itraconazole showed no activity. Although some isolates were susceptible to AmB, most had high MICs. Echinocandins in general showed favorable MICs to *Trichoderma* spp. Of note, all the *Trichoderma* spp. showed similar susceptibility patterns [107]. With respect to clinical success, most reports suggest voriconazole with consideration of adding an echinocandin [108, 109, 110, 111•]. In a 2018 case report and review of *T. longibrachiatum* infections, the authors identified 14 cases with a survival rate of 64%. AmB susceptibilities were variable although tended to have higher MICs. The MICs of both voriconazole and caspofungin were low and favorable [111•]. Based on these limited data, recommendations should be to use voriconazole with consideration of adding an echinocandin.

Rasamsonia

**primary recommendation: posaconazole + echinocandin (Table 1)

Infections due to *Rasamsonia* spp. (most common in this genus, *Rasamsonia argillacea*, previously known as *Geosmithia argillacea*) are increasingly recognized [112–114]. While it may be difficult to distinguish these organisms phenotypically from *Paecilomyces* and *Penicillium* spp., identification is now easier with improved molecular testing [113, 115, 116]. The *Rasamsonia argillacea* complex includes *R. argillacea*, *R. aegroticola*, *R. eburnea*, and *R. piperina* [117]. Infections have been reported in patients with chronic granulomatous disease (CGD), CF, and graft versus host disease (GVHD) [112, 114, 116–122]. Infections involve the lungs and brain. Mortality rates may reach 50% despite aggressive antifungal and surgical interventions. The most effective antifungal regimen is not known, although combination therapy is preferred given the organism's resistance profile. Isolates are usually resistant to itraconazole and voriconazole [114, 117]. Generally, isolates have favorable MICs to posaconazole, echinocandins, with variable MICs to AmB [114, 117, 122]. A study of 47 isolates showed very favorable MICs for echinocandins, variable MICs for posaconazole and AmB, and clearly high MICs for both voriconazole and isavuconazole [123]. This susceptibility pattern was also seen in eight in vivo clinical isolates of CF patients [124]. There are limited data with respect to clinical and in vivo efficacy. Guidelines and case reports support the use of an echinocandin plus posaconazole with consideration of adding AmB [22••, 112, 114, 116, 119]

Novel and Future Therapies

Several new agents with activity against hyalohyphomycetes are currently in the developmental pipeline. APX001A (manogepix; formerly E1210) inhibits the fungal enzyme Gwt1, which in turn blocks the inositol acylation during synthesis of glycosylphosphatidylinositol (GPI)-anchored proteins of the cell wall. This agent and has activity against *Candida*, *Aspergillus*, and *Fusarium* [125]. A recent study showed APX001A to have potent in vitro activity against a range of hyalohyphomycetes including *Scedosporium*, *Fusarium*, *Paecilomyces*, *Lomentospora prolificans*, *Rasamsonia*, and *Trichoderma* [126•]. F901318 (olorofim) is an inhibitor of dihydroorotate dehydrogenase, a key enzyme in pyrimidine biosynthesis. It has very favorable in vitro activity against several *Scedosporium* spp. and *Lomentospora* spp., but less so against *Fusarium* [127, 128]. N-

chlorotaurine (NCT), an oxidant developed in topical and inhaled formulations, has shown fungicidal activity against *Scedosporium* and *Lomentospora* spp. [129, 130]. Additionally, hemofungin, an inhibitor of ferrochelastase, has in vitro activity against several fungi, including *Fusarium* spp. [131].

Conclusion

The non-*Aspergillus* hyaline molds are rare and emerging causes of infections with potential to cause significant morbidity and mortality. With the growing population of immunosuppressed patients, we are seeing more patients at risk for such infections, which are challenging to diagnose and treat. We have reviewed the recent literature and current guidelines on treatment and have summarized our recommendations. Several novel antifungal agents currently in development may have a role in treatment of these infections. It will be necessary to investigate these novel drugs in clinical trials given the limitations of our current antifungal therapies.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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