Emerging Fungal Infections in Solid Organ Transplantation

S. Huprikara,*, S. Shohamb and the AST Infectious Diseases Community of Practice

a Transplant Infectious Diseases Program, Icahn School of Medicine at Mount Sinai, New York, NY
b Transplant and Oncology Infectious Diseases Program, Johns Hopkins University School of Medicine, Baltimore, MD
* Corresponding author: Shirish Huprikar, shirish.huprikar@mssm.edu

Key words: fungal, transplant, emerging, zygomycosis, Scedosporium, Fusarium, dematiaceous

Abbreviations: AmBd, amphotericin B deoxycholate; L-AmB, lipid formulation of amphotericin B.

Introduction

Infections due to a variety of generally innocuous fungi are increasingly recognized as a problem in solid organ transplant (SOT) recipients (1–5). These organisms include filamentous fungi such as members of the Zygomycetes class (order Mucorales), Fusarium, Scedosporium, yeast-like organisms such as Trichosporon, Malessezia and Rhodotorula and the dematiaceous fungi (a collective term referring to a variety of darkly pigmented fungi) (6–13). Diseases caused by these diverse fungi are collectively known as “emerging” or “rare” fungal infections. The clinical manifestations and diagnosis of emerging and rare fungal infections are summarized in Table 1. Since these fungi cause a minority of infections in SOT, data regarding treatment options are limited. All of the treatment recommendations in these guidelines are derived from small case series, anecdotal experiences, and joint center reviews and are summarized in Table 2 (evidence grade III). Data gleaned from non-SOT populations, such as patients with hematological malignancies and/or HSCT, further inform decisions regarding these infections (6,14–18). Since data are quite limited, distinctions between adult and pediatric patients are not addressed in these guidelines.

Epidemiology and Risk Factors

Emerging fungal infections represent approximately 7–10% of fungal infections in SOT recipients and should be considered whenever invasive aspergillosis is suspected (12,13). These infections are rare and their incidence depends upon type of transplant. Lung and liver transplant recipients are at greatest risk. For example, mucormycosis, which is caused by Zygomycetes (order Mucorales) and is the best characterized of these infections, accounts for approximately 2% of fungal infections in SOT recipients. The overall incidence is 0.07% at 1 year after transplant, but twice that rate for liver and lung recipients (12,13,19).

Exposure to the emerging fungi is generally presumed to be from direct contact or inhalation from environmental sources, such as soil, vegetation, water, sewage or air. These organisms are encountered worldwide, but rates of infection may vary by geographic locale and intensity of environmental exposure (20). Most infections start in the respiratory tract or skin, but can then disseminate to multiple organs including the central nervous system. The size of airborne fungal propagules often dictates modes of transmission and clinical manifestations. For example Aspergillus fumigatus conidia are ideally suited by size for deposition in the alveoli, and tend to cause pneumonia. On the other hand, the larger conidia of Fusarium and the Zygomycetes can get trapped in the upper airways and sinuses and are more likely to cause sinus infections or infections at sites of direct inoculation.

As a general statement, major host risk factors for infection with these emerging fungi in organ transplant recipients include prolonged and profound immunodeficiency, breaks in skin integrity, and chronic respiratory disease (e.g. cystic fibrosis and bronchiectasis) (14,16,18,21). In the latter group, the underlying pulmonary architectural distortion and mucosal defects predispose patients to chronic colonization and infection with Scedosporium, Zygomycetes, and dematiaceous molds before and after lung transplantation (6,7,22). Exposure to selective antifungal agents, specifically azole prophylaxis or therapy, may select for less common fungi and contribute to shifts in incidence of infection with the emerging fungi. For example, voriconazole usage has been associated with mucormycosis in hematopoietic stem-cell transplant (HSCT) recipients in some medical centers (23–25). Much less commonly, infection may be transmitted during the transplantation process via contamination of the preservation fluid or from the organ itself. Transmission of Scedosporium and Zygomycetes has been reported in such circumstance and is associated with high rates of graft loss and mortality (26,27). Donors exposed to contaminated water such as near-drowning may be at particular risk for transmitting mucormycosis.
### Table 1: Clinical manifestations and diagnosis of emerging and rare fungal infections in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Fungal pathogen (references)</th>
<th>Clinical manifestations</th>
<th>Diagnosis</th>
</tr>
</thead>
</table>
| **Zygomycetes (order Mucorales) (30,31)** | • Pulmonary disease (most common)  
• Rhino-orbital cerebral  
• Disseminated disease (most common in liver transplant recipients)  
• Primary cutaneous disease (frequently at sites of medical or surgical interventions)  
• Bronchial anastomosis infections in lung transplant recipients  
• Gastrointestinal | • Broad, ribbonlike, nonseptate hyphae in tissue with calcofluor, PAS, or GMS silver staining  
• Growth in culture usually within 24–48 hours  
• Molecular techniques in development |
| **Fusarium** | • Pulmonary disease  
• Superficial and deep cutaneous disease  
• Disseminated (usually involves lung and skin)  
• Fungemia  
• Sinusitis  
• Osteomyelitis  
• Keratitis  
• Peritonitis  
• Endocarditis | • Blood cultures may be positive  
• Histopathologic appearance is similar to *Aspergillus* (77) |
| **Scedosporium (32,38,71,76)** | • Lung infection  
• Disseminated infection  
• CNS infection  
• Skin (less common)  
• Bone and joint infection  
• Ocular infection  
• Hepatosplenic infection  
• Peritonitis  
• Endovascular infection | • Histopathologic appearance is similar to *Aspergillus* |
| **Paecilomyces** | • Insidious cutaneous and subcutaneous infections:  
  • Cellulitis in areas of trauma  
  • Erythematous, violaceous, or crusted ulcers, plaques, nodules, and papulopustular lesions  
  • Sporotrichoid pattern (78–81)  
• Sternal wound infection in a lung transplant recipient with pretransplant respiratory colonization (82)  
• Other manifestations: sinus disease, osteomyelitis, keratitis, endophthalmitis, and disseminated infection (78) | • Reference laboratory should be consulted for confirmation  
• Irregular septate hyphae in tissue with PAS or GMS silver stain can be confused with other molds.  
• Suppurative and/or granulomatous inflammation in tissue  
• Molecular techniques in development |
| **Trichoderma (Hyalohyphomycosis) (83)** | • Perihepatic abscesses in liver transplant recipients  
• Pleuropulmonary disease in lung transplant recipients  
• Disseminated infection involving brain in kidney transplant recipients | • Fine hyaline septate hyphae in tissues with positive cultures  
• Molecular techniques in development |
| **Scopulariopsis** | • Disseminated infection with cutaneous, pleuropulmonary, cardiac, and brain involvement with nearly universal mortality (84–87) | • Branched and septate hyphae with GMS silver stain |
| **Acremonium** | • Mycosis (88) | • Septate hyphae with GMS silver stain  
• Fontana-Masson staining highlights the presence of melanin in the dematiaceous fungi |
| **Dematiaceous fungi (Exophiala, Alternaria and Bipolaris species are most common) (89–91)** | • Subcutaneous nodules and less commonly as skin abscesses, pustular lesions, or purulent ulcerations | • Pigmented sclerotic bodies with H&E stain  
• Septate hyphae with lactophenol alanine blue stain |
| **Chromoblastomycosis** | • Chronic cutaneous disease most frequently in the tropical and subtropical areas (92) | • Blood cultures are typically positive  
• Budding yeast in tissue |
| **Trichosporon** | • Disseminated infection (93–96) | |
Invasive mucormycosis is a potentially devastating complication in SOT recipients with an overall case fatality rate of 40–50% (28–30). Like invasive aspergillosis, infection may be associated with hemorrhagic necrosis, vascular thrombosis, and tissue infarction and can extend locally to infect adjacent structures or disseminate to other sites. Traditional risk factors for mucormycosis include uncontrolled diabetes mellitus, corticosteroids and neutropenia. In addition to diabetes mellitus, risk factors uniquely described in SOT recipients include renal failure and prior voriconazole and/or caspofungin use (31). Cases typically develop within 3–6 months of transplant but may occur much later except in liver transplant recipients where disease frequently occurs in the first month after transplant (31).

Approximately 25% of non-Aspergillus mold infections are caused by Scedosporium, which represent 1% of all fungal infections in SOT recipients (13,19). The genus Scedosporium includes several potently pathogenic species including S. apiospermum (and the related Pseudallescheria boydii), S. prolificans and the newly described S. auranticum (32). The evolving taxonomy of these fungi can confuse the reader when reviewing the literature, and some authors refer to Scedosporium species as dematiaceous fungi. Acquisition of Scedosporium occurs via direct or inhalational contact with contaminated water, soil, or from unknown sources in many cases (33). Risk factors for infection in SOT include pretransplant colonization (frequently encountered in cystic fibrosis), prior receipt of amphotericin B (to which Scedosporium species are generally resistant) and enhanced immunosuppression with treatment for organ rejection (34,35). The most common infecting species is S. apiospermum and the majority of infections are in lung transplant recipients (13). Median time to infection is approximately 3–4 months after transplantation but can vary, particularly in lung transplant recipients (2,36–38).

Fusariosis accounts for approximately 13% of non-Aspergillus mold infections and 0.6% of all fungal infections in SOT recipients (13,19). Fusarium solani, F. proliferatum, F. oxysporum, F. moniliforme, and F. sacchari have been implicated as causative agents of infections in SOT recipients (39,40). Fusarium is acquired from environmental sources, air, tap water, sinks and showerheads (41). The portal of entry is usually the skin or respiratory tract. Risk factors include persistent neutropenia, profound T-cell depletion and previous fungal infections.

The dematiaceous fungi are less commonly described in SOT recipients but transplant ID clinicians should be aware of them. This group of diverse fungi includes Alternaria, Bipolaris, Cladosporium, Cladophialophora bantiana, Curvularia, Exophiala, Ochroconis and Rhinocladiella mackenziei (42). In the context of the transplant patient, the most important conditions caused by these fungi are allergic respiratory tract and sinus diseases and invasive infections, such as cutaneous, subcutaneous, respiratory tract, CNS and disseminated infections. Collectively, these diseases are termed phaeohyphomycoses. Presence of such fungi in respiratory tract or sinus culture does not necessarily indicate invasive disease. For example, Cladosporium is rarely pathogenic and Curvularia and Bipolaris are frequently associated with allergic, rather than invasive sinusitis. However, identification of a dematiaceous fungus from a clinical specimen should not be carelessly dismissed as such fungi are increasingly recognized as important causes of infections in SOT recipients.

**Table 1:** Continued

<table>
<thead>
<tr>
<th>Fungal pathogen (references)</th>
<th>Clinical manifestations</th>
<th>Diagnosis</th>
</tr>
</thead>
</table>
| Malassezia                  | - Pityriasis or tineaversicolor, folliculitis (97)  
- Onychomycosis             | - KOH preparation and/or culture |
| Rhodotorula                 | - Peritonitis in a liver transplant recipient (99)  
- Fungemia in a liver-kidney transplant recipient (100) | - Budding yeast |
| Penicillium marneffei       | - Endemic in Southeast Asia, southern China, Taiwan, and Hong Kong  
- Disseminated infections (101–105) | - Dimorphic fungus |
| Paracoccidioides            | - Endemic to Latin America  
- Pulmonary involvement with or without disseminated disease (106–108) | - Dimorphic fungus |
| Sporothrix                  | - Infection is primarily initiated by trauma to the skin resulting in cutaneous infections marked by suppurative and granulomatous nodules that spread along lymphatic channels  
- Disseminated infection (109)  
- Pulmonary infection in a heart transplant patient (110) | - Dimorphic fungus |

**Diagnosis**

Colonization with one of the emerging fungi may occur in the recipient before or after transplantation. The presence of an emerging fungal species in cultures obtained from nonsterile sources does not necessarily indicate infection. This is a particularly relevant issue in lung transplant recipients in whom a variety of emerging fungi including the...
### Table 2: Recommended treatment of emerging and rare fungal infections in solid organ transplant recipients

<table>
<thead>
<tr>
<th>Fungal Pathogen (references)</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **Zygomycetes (order Mucorales)** | • Surgical excision or debridement is recommended whenever feasible  
(1) L-AmB is the treatment of choice  
(2) Combination of an echinocandin + L-AmB may be considered based on animal studies and retrospective reports (111–113).  
(3) Posaconazole may be considered for salvage therapy in patients intolerant to or failing AmB (114–116)  
• Maintenance antifungal therapy:  
  (1) Posaconazole  
  (2) L-AmB in patients who are clinically unstable or unable to tolerate oral intake  
• AmB deoxycholate was historically the drug of choice and remains the only approved agent in the United States but is associated with substantial nephrotoxicity and generally avoided in the current era (67,117,118) |
| **Fusarium** | • Surgical excision or debridement is recommended whenever feasible  
• Antifungal susceptibility is necessary to guide therapy  
• Combination therapy (AmB + voriconazole) may be considered pending final identification and susceptibility data  
• F. solani and F. verticillioides (119)  
  o High dose AmB  
• Other Fusarium species  
  o Either AmB or voriconazole1 (119) |
| **Scedosporium** | • Surgical excision or debridement is recommended whenever feasible  
• S. apiospermum  
  o Voriconazole1 (71,72)  
  o Combination of an echinocandin + voriconazole may be considered  
  o AmB, 5-flucytosine and terbinafine should not be used (72)  
• S. prolificans  
  o Surgical debridement should be considered primary therapy (resistant to virtually all of the available antifungal agents (72)  
• Combination antifungal options:  
  o Echinocandin + AmB or voriconazole (73)  
  o Voriconazole + terbinafine (74,75) |
| **Paecilomyces (79,120)** | • Surgical excision or debridement is recommended whenever feasible and may be sufficient for isolated cutaneous disease  
• Voriconazole (or posaconazole) for more extensive disease |
| **Trichoderma (83,121)** | • Surgical excision or debridement is recommended whenever feasible  
• Antifungal susceptibility is necessary to guide therapy  
• Combination of AmB + voriconazole or posaconazole may be considered until susceptibility data available |
| **Scopulariopsis** | • Surgical excision or debridement is recommended whenever feasible  
• Antifungal susceptibility is necessary to guide therapy  
• Combination therapeutic options based on in vitro synergy data  
  o Terbinafine + voriconazole or posaconazole  
  o Caspofungin + voriconazole or posaconazole |
| **Acremonium** | • Surgical excision or debridement is recommended  
• Antifungal susceptibility is necessary to guide therapy  
• Voriconazole, posaconazole or itraconazole are first line agents  
• Echinocandins may be considered based on in vitro data  
• Potential combination therapeutic options based on in vitro synergy data  
  o AmB + flucytosine  
  o Itraconazole + flucytosine |
| **Phaeohyphomycosis** |  
• Surgical excision or debridement is recommended whenever feasible and may be sufficient for isolated cutaneous disease  
• Antifungal susceptibility is necessary to guide therapy  
• Voriconazole, posaconazole or itraconazole are first line agents  
• Echinocandins may be considered based on in vitro data  
• Potential combination therapeutic options based on in vitro synergy data  
  o AmB + flucytosine  
  o Itraconazole + flucytosine |
| **Exophiala (89,91)** |  
• Surgical excision or debridement is recommended whenever feasible  
• Antifungal susceptibility is necessary to guide therapy  
• Voriconazole, posaconazole or itraconazole are first line agents  
• Echinocandins may be considered based on in vitro data  
• Potential combination therapeutic options based on in vitro synergy data  
  o AmB + flucytosine  
  o Itraconazole + flucytosine |

*Continued*
dematiaceous molds (e.g. Exophiala, Scedosporium, the Basidiomycetes, the Zygomycetes, Cladosporium, Fusarium, Paecilomyces and Penicillium) can colonize the respiratory tract before or after transplantation (43–46). Both the colonizing species and rate of colonization are dependent on the underlying condition and geographic locale. Evidence demonstrating a direct correlation to post-transplant fungal infection has varied among transplant centers (39,47–50). Likewise, pulmonary colonization after lung transplantation does not necessarily lead to invasive infection, even in the absence of antifungal therapy. In the clinical setting, distinguishing colonization from invasive infection can be challenging and often requires tissue examination. In renal transplant recipients, isolation of Trichosporon species in urine cultures is usually a benign finding and rarely associated with invasive or deep-seated infection (51,52).

Infection due to emerging molds and yeasts can be difficult to diagnose. Clinical signs and symptoms can be nonspecific and indistinguishable from more common fungal infections. A comprehensive diagnostic approach that includes invasive procedures (e.g. bronchoalveolar lavage, biopsies), careful specimen collection and processing, utilization of specific culture media, and select histological staining techniques is usually necessary for establishing the diagnosis (8). Histopathologic analysis of biopsy specimens that demonstrate septate hyphae on hematoxylin and eosin (H&E) staining may be seen with Aspergillus, Fusarium, and Scedosporium (17). In contrast, Zygomycetes typically appear as broad, nonseptate, ribbonlike hyphae by H&E staining. Fontana-Masson staining can be valuable for identifying dematiaceous fungi in tissue. Delayed or incorrect identification may lead to the initiation of incorrect treatment and result in further tissue destruction and/or dissemination of disease. Close communication between the transplant team and the mycology and pathology laboratory is essential. Final identification and susceptibility testing frequently requires referral to a reference laboratory. Once the fungus has been identified, distinguishing colonization from active infection is a potentially challenging but essential component of the pre- and posttransplant evaluation (3,36). Radiographic studies can demonstrate pathologic changes in tissue, particularly the lung, and help distinguish disease from colonization; however, imaging findings are not specific.

Note: None of these treatments are FDA-approved except where noted. L-AmB, lipid formulation of amphotericin B; AmBd, amphotericin B deoxycholate.

1 Voriconazole is FDA-approved for Scedosporium apiospermum and Fusarium infections when intolerant or refractory to other agents.
2 Amphotericin B deoxycholate is FDA-approved for Sporothrix infections.

Standard antifungal dosing is recommended (L-AmB 5 mg/kg daily; AmBd 1–1.5 mg/kg daily; voriconazole 6 mg/kg intravenous q12h × 2 loading dose followed by 4 mg/kg intravenous q12h or 200–300 mg orally twice daily; itraconazole 200 mg twice daily; posaconazole 200 mg four times daily or 400 mg twice daily; caspofungin 70 mg loading dose followed by 50 mg daily; micafungin 100 mg daily; anidulafungin 200 mg loading dose followed by 100 mg daily).
Although currently available molecular fungal diagnostic assays are unlikely to be of significant value in the specific diagnosis of emerging and rare fungal infections, it should be noted that assays that detect galactomannan are reported to be positive in cases of *Penicillium*, mucormycosis, *Fusarium*; and miscellaneous hyaline molds and yeast (53–58). Furthermore, assays that detect betaglucan may be effective at early detection of *Fusarium* and *Trichosporon* although the assay lacks specificity for any fungal pathogen (59,60).

The clinical manifestations and diagnosis of the emerging fungal infections are summarized in Table 1.

**Treatment**

Treatment of emerging fungal infections can be very challenging. Data regarding the optimal type and dosage of antifungal therapy are limited due to the absence of randomized controlled trials. Duration of treatment tends to be very prolonged, and many of the antifungal agents are extraordinarily costly and have the potential for drug interactions and/or substantial toxicity. In general, we recommend the following approach (III except where noted):

1. Therapy with an agent that has proven activity against the fungus should be administered as early as possible (II-3).
2. Immunosuppression should be reduced when clinically feasible. To date, immune reconstitution inflammatory syndrome has not been described with emerging or rare fungal pathogens and should not be a concern.
3. Surgical debridement (sometimes repeatedly) of the affected areas should be performed whenever feasible (II-2).
4. Antifungal therapy should be adjusted based on susceptibility testing at a reference laboratory. Although clinically validated antifungal susceptibility breakpoints are lacking, it is reasonable for clinicians to apply knowledge of general antifungal susceptibility patterns in guiding therapy.
5. Clinicians should closely monitor for renal toxicity with amphotericin B (AmB) products.
6. Clinicians should closely monitor for Q-T interval prolongation, drug interactions, hepatotoxicity and neuropsychiatric side effects with azoles (61,62). Therapeutic drug monitoring of voriconazole and posaconazole should be considered to guide dose adjustments although data for emerging fungal infections are lacking. Target voriconazole trough levels between 1.5–4.5 µg/mL are associated with the optimal balance of maximizing efficacy and minimizing toxicity (63). Based on very limited data in the prophylactic setting the target posaconazole trough levels should be at least 0.5 µg/mL (64).
7. Adjuvant therapy with interferon-gamma and/or granulocyte-macrophage colony stimulating factor is not routinely recommended but may be considered with caution in cases refractory to standard antifungal therapy based on case reports (65,66).

The recommended treatment of mucormycosis, *Fusarium*, *Scedosporium* and the other emerging fungal infections is summarized in Table 2. Although clinical data to guide assessing the response to therapy are lacking, antifungal therapy should be continued at least until all clinical and radiographic signs of infection have resolved.

**Mucormycosis**

Surgical resection or debridement is associated with treatment success in SOT recipients and its significance in the management of most cases of mucormycosis cannot be overemphasized (67). For bronchial anastomotic infections in lung transplant recipients, bronchoscopic or surgical debridement is essential (68). Medical therapy alone can be attempted in patients with pulmonary mucormycosis unless there is extensive necrosis or disease threatening major vascular structures. Lipid formulations of AmB are the drugs of choice for mucormycosis. Posaconazole may be considered for maintenance therapy once clinical stability has been achieved.

**Fusarium**

Surgical resection alone may be effective for limited cutaneous or sinus disease. Antifungal therapy is recommended for deeper sites of infection (e.g. lungs) or disseminated disease (69). Antifungal susceptibility can vary by species and *in vitro* testing should guide choice of antifungal therapy. *In vitro*, *Fusarium* species are often resistant to AmB and have a wide range of susceptibilities to voriconazole (70).

**Scedosporium**

Response to therapy is highly dependent on site of infection, extent of dissemination, and host factors (38). Outcomes are better when the infection is localized to the skin or lung and substantially worse with disseminated disease. Surgical excision is typically required. Outcomes tend to be better with *S. apiospermum* infection, which may be related to better response to antifungal agents (71,72). *In vitro*, voriconazole has the most potent activity against *S. apiospermum*. The echinocandins are also active, but AmB, 5-flucytosine and terbinafine have limited to no activity against *S. apiospermum* (72). Medical management of *S. prolificans* is extremely challenging and surgery is typically required to control infection. This species is resistant to virtually all of the available antifungal agents (72). Based on animal studies, combination therapy including an echinocandin and either AmB or voriconazole may be effective (73). *In vitro* and anecdotal reports suggest that combining voriconazole with terbinafine may be effective (74,75).
Prevention and Prophylaxis

The most common mechanism for colonization or infection is via environmental exposure. Patients should be instructed to avoid visiting construction sites and poultry farms, manipulating air-conditioning filters, and contact with sewage or decaying material. To reduce the risk of invasive fungal infection due to transmission during the transplantation process, care should be taken in accepting organs from near drowning victims. Organ procurement agencies should report all fungal isolates from a donor to the recipient center. Not all patients with fungal colonization require prophylaxis. Certain colonizing fungi are very rarely pathogenic (e.g. Cladosporium, Paecilomyces and Penicillium species other than P. marneffei) and their presence generally does not require prophylaxis. By contrast, the Zygomycetes and Scedosporium have been associated with disseminated infection in highly immunocompromised patients. Prophylaxis may be considered in such patients and in recipients of donor lungs that are colonized with these fungi (34,50,76).

Future Directions

Although it may be challenging to conduct randomized controlled trials, collaborative prospective studies should be performed to gain more information regarding the epidemiology, clinical manifestations, treatment strategies, and outcomes associated with mucormycosis, Fusarium and Scedosporium in SOT recipients. Furthermore, clinicians are encouraged to publish case reports and case series of the other emerging fungal infections.

Acknowledgment

This manuscript was modified from a previous guideline written by Bernard M. Kubak and Shirish S. Huprikar published in the American Journal of Transplantation 2009; 9(Suppl 4): S208–S228, and endorsed by the American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. Dr. Huprikar has served on advisory boards for Merck and Gilead. Dr. Shoham receives research funding from Astellas, Merck and Pfizer. He is also a member of the Merck Scientific Advisory Board.

References