Mold Infections in Solid Organ Transplant Recipients

Tracy L. Lemonovich, MD

KEYWORDS

• Antifungal • Aspergillosis • Invasive fungal infections • Fusariosis • Mucormycosis • Transplant

KEY POINTS

- Mold infections in solid organ transplant (SOT) recipients are a significant cause of morbidity with a high 12-week mortality of 29%.
- The most common and serious mold infections in SOT recipients include invasive aspergillosis, mucormycosis, fusariosis, scedosporiosis, and phaeohyphomycosis.
- Diagnosis of mold infections can be challenging and usually requires histopathologic and/or microbiologic criteria, often obtained by biopsy and culture of affected tissues. Blood cultures are positive in about half of the patients with disseminated *Fusarium* species or *Lomentospora prolificans* infections.
- Treatment of mold infections often necessitates combined antifungal therapy and surgical excision or debridement for localized disease.

INTRODUCTION

Mold infections are an important cause of morbidity and mortality in the solid organ transplant (SOT) population. These infections carry a significant clinical and economic burden.[1–3] Mold infections include invasive aspergillosis (IA) and other emerging fungal pathogens, such as mucormycosis (zygomycosis), *Fusarium*, *Scedosporium*, and the dematiaceous fungi (dark molds), among others. Diagnosis and management of these patients are challenging, often requiring invasive diagnostic methodologies and a multidisciplinary approach to treatment. IA is the most common mold infection and second most common invasive fungal infection (IFI) (after *Candida*) in SOT recipients, accounting for 19% to 25% of all IFIs, with non-Aspergillus molds making up 7% to 10%.[4–7] Risk factors for infection include immunosuppressive therapy, loss of skin or mucosal integrity, and risks specific to organ transplant type, such as chronic lung disease or anatomic disruptions.[6,8] The 12-week overall mortality of mold infections in SOT recipients is overall high at 29% but varies by organ transplant type, with the

Disclosure Statement: The author has served on a medical affairs advisory board for Allergan.
Department of Medicine, Division of Infectious Diseases and HIV Medicine, UH Cleveland Medical Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106, USA
E-mail address: tracy.lemonovich@UHhospitals.org

Infect Dis Clin N Am 32 (2018) 687–701
https://doi.org/10.1016/j.idc.2018.04.006
id.theclinics.com

highest mortality in liver transplant recipients.[5,9] This article reviews the epidemiology, risk factors, microbiology, diagnostic, and treatment approach to mold infections in SOT recipients.

ASPERGILLOSIS

IA is generally acquired via inhalation of conidia, making pulmonary infection the most common site of infection. Infections may be localized (pulmonary or extrapulmonary including surgical wound infections) or disseminated. Lung transplant recipients can be at risk for tracheobronchitis or infection of the bronchial anastomosis. IA occurs in 1% to 15% of SOT recipients.[10] Mortality in a recent series of SOT recipients was reported at 22%, which appears improved from historical cohorts, wherein mortality has been as high as 92% in some SOT populations.[11–13] The most common species causing human disease is *Aspergillus fumigatus*; *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* are also frequently encountered.

Diagnosis of IA, like other IFI, requires microbiologic and/or histopathologic criteria to define proven infection by European Organization for Research and Treatment of Cancer/Mycoses Study Group revised definitions.[14] Acquisition of adequate specimens is crucial for early diagnosis; bronchoscopy with bronchoalveolar lavage (BAL) is recommended for patients with suspected invasive pulmonary aspergillosis (IPA) with consideration of transbronchial biopsy or percutaneous needle biopsy depending on radiographic site of lesion.[15] Staining shows narrow septate hyphae with acute angle branching (**Fig. 1**). Recommended radiographic imaging should include chest computerized tomography (CT) scan for suspected IPA. Typical CT findings include nodules, consolidative lesions, or wedge-shaped infarcts. The classic halo sign, a nodule surrounded by a perimeter of ground glass opacity reflecting hemorrhage, may be seen particularly in neutropenic patients. An air crescent, or cavity in a mass or nodule, is usually a late CT finding.[15] Biomarkers such galactomannan (GM) and (1-3)-β-D-glucan from the serum may be considered but have low sensitivity in SOT recipients. Serum GM sensitivity has been reported to be only 20% to 30% in SOT populations.[16,17] However, testing of BAL for GM may improve sensitivity to 67% to 100% in SOT recipients.[10] Molecular testing with Aspergillus polymerase chain reaction (PCR) shows promise with high sensitivity for diagnosis of IA in some studies,

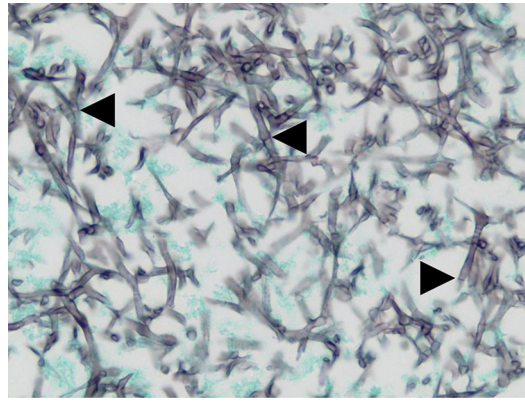

Fig. 1. *Aspergillus* narrow septate hyphae (*arrowheads*) (GMS stain, oil magnification ×1000). (*Courtesy of* Dr Daniel Rhoads and Dr Wissam Dahoud, UH Cleveland Medical Center, Cleveland, OH; with permission.)

but its exact role in diagnosis and management of SOT recipients (and other patient populations) is still not established.[15,18] Blood cultures with *Aspergillus* species usually are consistent with contamination and are rarely associated with IA even in high-risk patients.[19]

Early initiation of antifungal treatment of strongly suspected IA is recommended while conducting diagnostic testing to limit progression of disease.[15] Voriconazole, a triazole, is considered the drug of choice for primary therapy in all patient populations, including SOT recipients. This recommendation is based on a randomized trial of voriconazole compared with amphotericin B deoxycholate for treatment of IA in mostly hematopoietic stem cell transplant recipients and patients with hematologic malignancies showing improved survival with voriconazole[20] and has been supported by additional studies of voriconazole treatment, including those in SOT recipients.[10] Alternative antifungal therapies include liposomal or other lipid formulations of amphotericin and isavuconazole. A randomized trial showed noninferiority of isavuconazole compared with voriconazole in the treatment of IPA.[21] In general, *Aspergillus* azole resistance in the United States is low (<3%), and routine antifungal susceptibility testing (AFST) for initial infection is not recommended except in the patient in whom azole resistance is suspected or who is unresponsive to antifungal therapy.[15] Resistance to the echinocandins is also uncommon, as is amphotericin resistance with the exception of particular species such as *A terreus*.[15] Combination therapy (usually voriconazole plus an echinocandin) appears promising particularly for use in severe disease and has shown reduced mortality in some SOT recipients.[22] Tracheobronchial aspergillosis (TBA) occurs primarily in lung transplant recipients, affecting 4% to 6% of this patient population usually within 3 to 6 months posttransplant.[15,23] Risk factors for TBA include exposure of the lung allograft to the environment, *Aspergillus* colonization pretransplant and posttransplant, high degree of immune suppression, impaired mucociliary clearance, and pulmonary denervation.[24] Recommended treatment of TBA includes a mold-active triazole and adjunctive inhaled amphotericin, given associated anastomotic endobronchial ischemia or ischemic reperfusion injury due to airway ischemia.[15] Duration of therapy is usually 6 to 12 weeks for IPA depending on disease response to treatment and degree of immune suppression, at least 3 months for TBA or until resolution of infection.[10,15] Adjunctive therapies for IA include reduction in immune suppression, surgery for localized disease, and colony-stimulating factors or granulocyte infusions for neutropenic patients.[15] Although an optimal prophylaxis strategy has not been defined for SOT recipients, prophylaxis for IA is indicated for certain high-risk SOT populations. **Table 1** summarizes a prophylaxis strategy for high-risk SOT recipients.

MUCORMYCOSIS

Invasive mucormycosis (IM) is caused by Zygomycetes (order Mucorales) and is rare, making up only 2% of fungal infections in SOT recipients with overall incidence of 0.07% at 1 year posttransplant.[25] However, this infection has a high fatality rate with 90-day survival of only 50% to 60%.[26] Traditional risk factors for IM include uncontrolled diabetes mellitus, corticosteroids, and neutropenia as well as renal failure, reactivation of immunomodulating herpesviruses, malnutrition, and prior voriconazole and/or caspofungin use in SOT recipients.[27,28] Clinically important species of Zygomycetes include *Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, *Absidia*, *Apophysomyces*, and *Myocladus*.[7] Clinical disease spectrum includes pulmonary disease as the most common, but can also include rhino-sino-orbital (including extension to the brain), disseminated, gastrointestinal, and primary cutaneous

Table 1
Prophylaxis recommendations for invasive aspergillosis in solid organ transplant recipients

Organ Type	Risk Factors	Antifungal Prophylaxis	Duration
Lung	• Colonization with Aspergillus pretransplant or posttransplant • Mold infection in explanted lungs • Fungal infections in the sinuses • Single lung recipients	• Systemic triazole (voriconazole or itraconazole) OR inhaled amphotericin B product • For patients with listed risk factors, systemic voriconazole or itraconazole is preferred	• 3–4 mo posttransplant • Reinitiation of antifungal prophylaxis should occur if receiving thymoglobulin, aletuzumab, or high-dose corticosteroids
Liver	• Retransplantation • Renal failure, particularly requiring dialysis • Transplantation for fulminant hepatic failure • Reoperation	• Lipid formulation of amphotericin B OR an echinocandin	• Initial hospital stay or 4 wk posttransplant
Heart	• Pretransplant Aspergillus colonization • Reoperation • Cytomegalovirus disease • Posttransplant renal failure requiring hemodialysis • Presence of IA in the transplant program within 2 mo or transplant	• Itraconazole OR voriconazole	• 50–150 d

Adapted from Singh N, Husain S. AST infectious diseases community of practice. Aspergillosis in solid organ transplantation. Am J Transplant 2013;13(suppl 4):230; with permission.

disease.[6,29,30] Lung infection may present with consolidation/mass lesions, nodules, or cavities.[29] Disseminated infection can involve essentially any organ, including the lungs, heart, brain, liver, esophagus, stomach, small and large bowel, kidney, retroperitoneum, thyroid, and skin.[7] Primary cutaneous infection can occur at sites of surgical incisions or drains, intravenous catheter sites, and after skin trauma. Lesions may present with black necrosis with surrounding cellulitis, thrombophlebitis, or extension to deeper structures.[28] Lung and liver transplant recipients appear to be at highest risk for IM with infections occurring at a median of 6 months after transplant, but may occur as early as the first month post-ransplant in liver transplant recipients.[29]

Diagnosis typically requires an invasive procedure such as biopsy, fine-needle aspiration, bronchoscopy, endoscopy, or surgical exploration.[28] CT chest imaging may show a reverse halo sign, an area of ground glass opacity with a ring of consolidation. Staining shows broad, ribbonlike, nonseptate hyphae with irregular walls and 90° angle branching (**Figs. 2** and **3**). Diagnosis may be made by histology, culture, or both.[28,31] PCR testing is being increasingly used for diagnosis of mucormycosis and appears to be highly sensitive.[32] PCR testing of circulating DNA in serum may be a useful tool for both early detection and treatment monitoring.[33,34] Treatment of

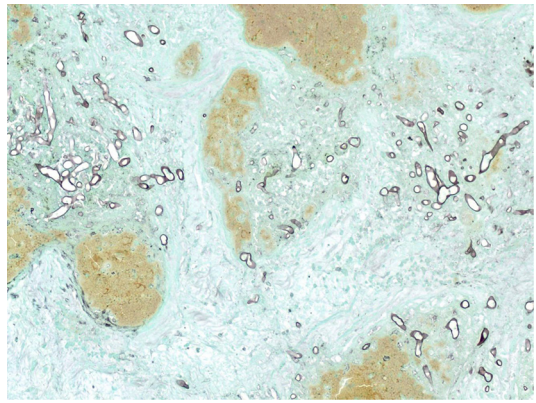

Fig. 2. Zygomycete in sinus vessel (GMS stain, magnification ×200). (*Courtesy of* Dr Daniel Rhoads and Dr Wissam Dahoud, UH Cleveland Medical Center, Cleveland, OH; with permission.)

mucormycosis often requires surgical treatment with excision or debridement of necrotic tissues combined with antifungal therapy. Recommended induction therapy is with lipid formulation amphotericin B.[35] Isavuconazole is also now a first-line treatment option based on a recent single-arm open-label trial with case-control analysis showing efficacy similar to amphotericin B.[36] Use of combination therapy with an echinocandin and lipid amphotericin B has been described in animal models and retrospective reports.[37–39] The combination of isavuconazole with micafungin has also been recently studied in murine models and in vitro studies showing synergy.[40,41] Posaconazole can be used for salvage therapy in patients intolerant to or failing amphotericin B or as maintenance antifungal therapy.[42–44] Isavuconazole can also be considered for maintenance and salvage therapy and has been reported to be successfully used for salvage in SOT patients.[45–47]

Fusarium

Fusariosis accounts for less than 1% of IFIs in SOT recipients and may occur late in the posttransplant period with a median time to infection of 365 days.[7,8] *Fusarium solani* is the most common species causing infection; other common species include *Fusarium oxysporum* and *Fusarium verticillioides*.[48] Exposure to fungi occurs by inhalation of airborne conidia or direct contact with contaminated material, such as soil, plants, or other organic matter.[7] The clinical spectrum of fusariosis includes superficial cutaneous infection, localized infections especially of the respiratory tract and sinuses, and disseminated infection.[49,50] Risk of infection can vary by transplant type, but lung transplant recipients appear particularly vulnerable to pulmonary fusariosis.[51] Primary skin infection due to direct inoculation may present with skin nodules, ulcers, cellulitis, or subcutaneous abscesses that can resemble ecthyma gangrenosum.[49] Localized infections are most common in the respiratory tract and sinuses, but can also include septic arthritis, endophthalmitis, osteomyelitis, cystitis, and brain abscess.[52] Disseminated infection occurs when 2 or more noncontiguous sites/organs are affected and may involve the gastrointestinal tract, liver, heart valves, kidneys, lungs, central nervous system (CNS), and skin.[7] Disseminated infection often is associated with characteristic skin lesions that may appear as targetoid red or violaceous painful nodules, which often ulcerate with an eschar.[52,53]

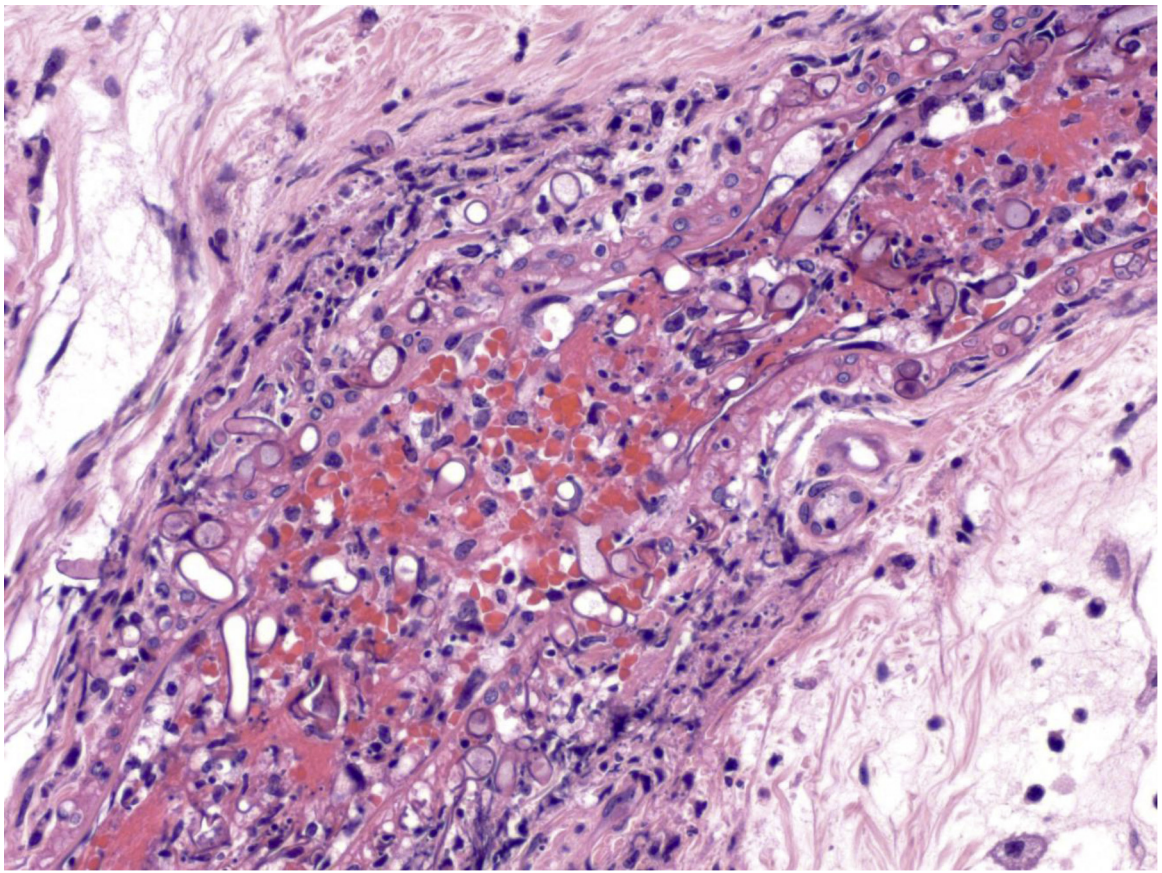

Fig. 3. Zygomycete in sinus vessel (hematoxylin and eosin stain, magnification ×400). (*Courtesy of* Dr Daniel Rhoads and Dr Wissam Dahoud, UH Cleveland Medical Center, Cleveland, OH; with permission.)

Diagnoses of fusariosis can be made by skin biopsy in cases of cutaneous involvement. Unlike many other mold infections, *Fusarium* frequently grows from blood cultures in disseminated infections and has been reported to be positive in 40% of cases.[54] Histopathologic appearance is similar to *Aspergillus* with acute branching septate hyphae. Culture testing should involve identification to the species level and AFST whenever possible to help guide therapy.[55,56] Nonculture biomarkers, such as GM and (1-3)-β-D-glucan, may be helpful adjuncts to diagnosis, but their exact role has not been defined.[7,57] Molecular PCR testing appears promising but has not been standardized for diagnosis.[55] Treatment of fusariosis depends on the site and extent of infection, the specific *Fusarium* species and its antifungal susceptibilities, as well as underlying host factors.[51] Surgical excision or debridement should be considered when feasible particularly for primary cutaneous and localized infections. Antifungal therapy is often guided based on species and antifungal susceptibilities. Amphotericin B, including lipid formulations and voriconazole, is first-line therapy for fusariosis; *F solani* appears to be more susceptible to amphotericin than the triazoles.[51] Posaconazole also has been used for primary and salvage therapy.[58,59] Combination therapy with amphotericin B and voriconazole or another triazole should be considered while awaiting identification and susceptibility data and/or in severe infection.[6,60] Overall mortality of fusariosis remains high with estimates ranging from 44% to 67% in various series, but lung transplant recipients appear to have a higher mortality at 67%.[48,51,61] SOT recipients with localized infection tend to have a better outcome than patients with hematological malignancies or bone marrow transplant.[50]

Scedosporium/Pseudallescheria

Scedosporium and *Pseudallescheria* species are found in soil and water, with infections usually occurring by inhalation of spores or by direct contact. Predominant species causing infection include *Scedosporium apiospermum*, *Pseudallescheia boydii*, and *L prolificans*. *S apiospermum* had previously been considered the asexual state of *P boydii* but is now considered a distinct species.[62] Lung transplant recipients are at risk for infection, particularly in cystic fibrosis (CF) patients, who are often colonized before transplant.[63,64] Other SOT recipients can also be affected, with clinical spectrum including localized infections of respiratory tract, sinuses, surgical site, and skin as well as disseminated infections involving the brain/CNS, eye, blood vessels, heart, bone, and joints.[65–67] Median time to infection after transplant is reported to be 4 months.[67] Diagnosis is by biopsy of affected tissues with culture and pathology, and histopathologic appearance is similar to *Aspergillus*.[6] Blood cultures may be positive in greater than 50% of *L prolificans* disseminated infections due to hematogenous spread.[55] Antifungal treatment of scedosporiosis should be directed by species identification and AFST of clinical isolates due to variable susceptibility to antifungal agents, with many species resistant to amphotericin B.[55,68] Voriconazole is usually considered first-line therapy and appears to be associated with better survival in transplant recipients than other therapies.[55,69,70] Surgical debridement should be considered whenever feasible and may be the primary therapy in *L prolificans* infections in which the organism may be resistant to all antifungals.[71] Combination therapy of voriconazole plus an echinocandin or terbinafine should be considered in severe or resistant infections.[55,72] CF patients known to be colonized with *Scedosporium* pre–lung transplant should be given antifungal prophylaxis, usually with a triazole.[64] Mortality from scedosporiosis is high, ranging from 58% to 72% in transplant recipients.[67,69]

Table 2
Summary of important fungal pathogens in solid organ transplant recipients

Fungal Pathogen	Important Species	Risk Factors/Transplant Type	Clinical Manifestations	Diagnosis	Treatment
Aspergillus	*A fumigatus*, *A flavus*, *A niger*, *A terreus*	Neutropenia Lung, liver, heart	IPA (most common) TBA (lung transplant) Disseminated	Narrow, septate hyphae with acute angle branching	Voriconazole
Zygomycetes	Rhizopus, Mucor, Rhizomucor, Absidia, Cunninghamella, Apophysomyces, Myocladus	Uncontrolled DM Corticosteroids Neutropenia Renal failure Immunomodulating viruses Malnutrition Prior voriconazole/ caspofungin use Liver, lung, kidney	Pulmonary (most common) Rhino-sino-orbital Disseminated Primary cutaneous Gastrointestinal Bronchial anastomosis (lung transplant)	Broad, ribbonlike, nonseptate hyphae Molecular testing	Lipid formulation amphotericin Surgical debridement when feasible
Fusarium	*F solani*, *F oxysporum*, *F verticillioides*	Lung, liver	Pulmonary Primary cutaneous Disseminated (often involving skin) Sinusitis Osteomyelitis/septic arthritis Endophthalmitis Brain abscess	Histopathology similar to Aspergillus Blood cultures may be positive	Amphotericin B or voriconazole Surgical debridement when feasible

Scedosporium/ pseudallescheria	*S apiospermum*, *P boydii*, *Lomentospora prolificans*	Lung	Pulmonary Sinusitis Surgical site Skin Disseminated	Histopathology similar to Aspergillus Blood cultures may be positive with *L prolificans*	Voriconazole Combination therapy Surgical debridement when feasible
Dematiaceous fungi (dark molds)	Alternaria, Exophiala, Curvularia, Cladosporium, Ochroconis, Bipolaris	All SOT types	Skin (nodules, abscesses, ulcers) Pulmonary Disseminated	Septate hyphae with GMS silver stain Fontana-Masson staining with melanin	Surgical excision of cutaneous lesions Triazoles
Paecilomyces		Heart, lung	Skin and soft tissue Peritonitis Sternal wound infection	Irregular septate hyphae	Voriconazole or posaconazole Surgical debridement when feasible

Abbreviation: DM, diabetes mellitus.
Adapted from Refs.[6,7,10]

Dematiaceous Fungi (Dark Molds)

The dematiaceous, or dark-pigmented, molds can cause the invasive infections phaeohyphomycosis, chromoblastomycosis, or mycetoma.[73] Primary cutaneous infections are the most common clinical presentation in SOT recipients and can cause subcutaneous nodules, abscesses, pustules, or purulent ulcerations.[6,74] Other sites of infection include the lungs and disseminated infection with CNS involvement. The most important pathogens causing infection in this group include *Alternaria*, *Exophiala*, *Curvularia*, *Cladosporium*, *Ochroconis*, and *Bipolaris.*[7,73] Time to infection posttransplant can be long, ranging from 2 months to 11 years with a median of 685 days.[73,74] Diagnosis is usually by biopsy with histopathology and culture; septate hyphae are present with silver stain, and Fontana-Masson staining can demonstrate the presence of melanin.[6] Surgical excision is the mainstay of treatment of primary cutaneous lesions and may not require antifungal therapy.[75] AFST should be used to guide therapy. First-line antifungal treatment includes voriconazole, posaconazole, and itraconazole; echinocandins and amphotericin B may also be useful.[7,76] Combination antifungal therapy may be considered for CNS or disseminated infections.[76]

PAECILOMYCES

Paecilomyces is a rare pathogen in SOT recipients and tends to cause localized skin and soft tissue infections, sometimes associated with other fungi or mycobacteria.[77–79] Case reports have also described peritonitis in a liver transplant recipient and sternal wound infection in a lung transplant recipient.[80,81] Histopathology of tissues may show irregular septate hyphae with Periodic acid-Schiff or Grocott's methenamine silver (GMS) stains but may appear similar to other molds.[6] Surgical excision and debridement are recommended and may be sufficient for cutaneous infection; voriconazole or posaconazole can be used for more extensive disease, but antifungal susceptibilities may help guide therapy.[6,7]

OTHER FUNGI

Numerous other fungi are rare but potentially emerging causes of mold infection in SOT recipients. These fungi include *Scopulariopsis*, *Trichoderma*, and *Acremonium* species in which various localized and disseminated infections have been described.[82–84] Treatment generally involves surgical excision when possible and antifungal therapy based on susceptibility testing.[6,7]

Table 2 summarizes the clinical manifestations, diagnosis, and treatment of important mold infections in SOT recipients.

SUMMARY

Mold infections remain an important cause of infection in SOT recipients, and a high level of clinical suspicion and vigilance are required for diagnosis and management. Advancements in diagnostics, such as molecular testing, may improve diagnosis in the future. The role of routine AFST for mold infections and the microbiologic definitions of antifungal resistance are still being determined. More data are needed regarding a correlation between antifungal susceptibilities and clinical outcomes.[85] The role of newer antifungal therapies, such as isavuconazole, in primary and salvage treatment is still evolving. Further research into the epidemiology, clinical manifestations, diagnosis, approach to prophylaxis, treatment, and outcomes of these infections is needed.

REFERENCES

1. Kontoyiannis DP, Yang H, Song J, et al. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. BMC Infect Dis 2016;16(1):730–5.
2. Menzin J, Meyers JL, Friedman M, et al. The economic costs to United States hospitals of invasive fungal infections in transplant patients. Am J Infect Control 2011;39(4):e15–20.
3. Menzin J, Meyers JL, Friedman M, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am J Health Syst Pharm 2009;66(19):1711–7.
4. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 2010;50(8):1101–11.
5. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis 2010; 12(3):220–9.
6. Huprikar S, Shoham S, AST Infectious Diseases Community of Practice. Emerging fungal infections in solid organ transplantation. Am J Transplant 2013;13(Suppl 4):262–71.
7. Shoham S. Emerging fungal infections in solid organ transplant recipients. Infect Dis Clin North Am 2013;27(2):305–16.
8. Crabol Y, Lortholary O. Invasive mold infections in solid organ transplant recipients. Scientifica (Cairo) 2014;2014:821969.
9. Neofytos D, Treadway S, Ostrander D, et al. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. Transpl Infect Dis 2013;15(3):233–42.
10. Singh N, Husain S, AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. Am J Transpl 2013;13(Suppl 4):228–41.
11. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 2012;65(5): 453–64.
12. Morgan J, Wannemuehler KA, Marr KA, et al. Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program. Med Mycol 2005;43(Suppl 1): S49–58.
13. Singh N, Arnow PM, Bonham A, et al. Invasive aspergillosis in liver transplant recipients in the 1990s. Transplantation 1997;64(5):716–20.
14. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.
15. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;63(4):e1–60.
16. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia Aspergillus galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transpl 2004;4:796–802.
17. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006;42:1417–27.

18. Imbert S, Gauthier L, Joly I, et al. Aspergillus PCR in serum for the diagnosis, follow-up and prognosis of invasive aspergillosis in neutropenic and nonneutropenic patients. Clin Microbiol Infect 2016;22(6):562.e1-8.
19. Simoneau E, Kelly M, Labbe AC, et al. What is the clinical significance of positive blood cultures with Aspergillus sp in hematopoietic stem cell transplant recipients? A 23 year experience. Bone Marrow Transpl 2005;35(3):303–6.
20. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 2002;347:408–15.
21. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387:760–9.
22. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation 2006;81:320–6.
23. Husain S, Paterson DL, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. Am J Transpl 2006;6:3008–16.
24. Horvath J, Dummer S, Loyd J, et al. Infection in the transplanted and native lung after single lung transplantation. Chest 1993;104:681–5.
25. Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001–2006. Emerg Infect Dis 2011;17(10):1855–64.
26. Abidi MZ, Sohail MR, Cummins N, et al. Stability in the cumulative incidence, severity and mortality of 101 cases of invasive mucormycosis in high-risk patients from 1995 to 2011: a comparison of eras immediately before and after the availability of voriconazole and echinocandin-amphotericin combination therapies. Mycoses 2014;57(11):687–98.
27. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. J Infect Dis 2009;200(6):1002–11.
28. Almyroudis NG, Sutton DA, Linden P, et al. Zygomycosis in solid organ transplant recipients in a tertiary transplant center and review of the literature. Am J Transpl 2006;6(10):2365–74.
29. Sun HY, Aguado JM, Bonatti H, et al, Zygomycosis Transplant Study Group. Pulmonary zygomycosis in solid organ transplant recipients in the current era. Am J Transpl 2009;9(9):2166–71.
30. Sun HY, Forrest G, Gupta KL, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. Transplantation 2010;90(1):85–92.
31. Song Y, Qiao J, Giovanni G, et al. Mucormycosis in renal transplant recipients: review of 174 reported cases. BMC Infect Dis 2017;17(1):283–8.
32. Salehi E, Hedayati MT, Zoll J, et al. Discrimination of aspergillosis, mucormycosis, fusariosis, and scedosporiosis in formalin-fixed paraffin-embedded tissue specimens by use of multiple real-time quantitative PCR assays. J Clin Microbiol 2016;54(11):2798–803.
33. Millon L, Larosa F, Lepiller Q, et al. Quantitative polymerase chain reaction detection of circulating DNA in serum for early diagnosis of mucormycosis in immunocompromised patients. Clin Infect Dis 2013;56(10):e95–101.
34. Millon L, Herbrecht R, Grenouillet F, et al, French Mycosis Study Group. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French

Surveillance Network of Invasive Fungal Infections (RESSIF). Clin Microbiol Infect 2016;22(9):810.e1-e8.
35. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect 2014;20(Suppl 3):5–26.
36. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al, VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 2016;16(7):828–37.
37. Reed C, Bryant R, Ibrahim AS. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis 2008;47(3):364–71.
38. Ibrahim AS, Gebremariam T, Fu Y, et al. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother 2008;52(4):1556–8.
39. Spellberg B, Fu Y, Edwards JE Jr, et al. Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice. Antimicrob Agents Chemother 2005;49(2):830–2.
40. Gebremariam T, Wiederhold NP, Alqarihi A, et al. Monotherapy or combination therapy of isavuconazole and micafungin for treating murine mucormycosis. J Antimicrob Chemother 2017;72(2):462–6.
41. Katragkou A, McCarthy M, Meletiadis J, et al. In vitro combination of isavuconazole with micafungin or amphotericin B deoxycholate against medically important molds. Antimicrob Agents Chemother 2014;58(11):6934–7.
42. Kim JH, Benefield RJ, Ditolla K. Utilization of posaconazole oral suspension or delayed-released tablet salvage treatment for invasive fungal infection. Mycoses 2016;59(11):726–33.
43. Vehreschild JJ, Birtel A, Vehreschild MJ, et al. Mucormycosis treated with posaconazole: review of 96 case reports. Crit Rev Microbiol 2013;39(3):310–24.
44. Alexander BD, Perfect JR, Daly JS, et al. Posaconazole as salvage therapy in patients with invasive fungal infections after solid organ transplant. Transplantation 2008;86(6):791–6.
45. Miceli MH, Kauffman CA. Isavuconazole: a new broad-spectrum triazole antifungal agent. Clin Infect Dis 2015;61(10):1558–65.
46. Natesan SK, Chandrasekar PH. Isavuconazole for the treatment of invasive aspergillosis and mucormycosis: current evidence, safety, efficacy, and clinical recommendations. Infect Drug Resist 2016;9:291–300.
47. Martin MS, Smith AA, Lobo M, et al. Successful treatment of recurrent pulmonary mucormycosis in a renal transplant patient: a case report and literature review. Case Rep Transplant 2017;2017:1925070.
48. Muhammed M, Anagnostou T, Desalermos A, et al. Fusarium infection: report of 26 cases and review of 97 cases from the literature. Medicine (Baltimore) 2013;92(6):305–16.
49. Halpern M, Balbi E, Carius L, et al. Cellulitis and nodular skin lesions due to Fusarium spp in liver transplant: case report. Transplant Proc 2010;42(2):599–600.
50. Sampathkumar P, Paya CV. Fusarium infection after solid-organ transplantation. Clin Infect Dis 2001;32(8):1237–40.
51. Carneiro HA, Coleman JJ, Restrepo A, et al. Fusarium infection in lung transplant patients: report of 6 cases and review of the literature. Medicine (Baltimore) 2011;90(1):69–80.

52. Gupta AK, Baran R, Summerbell RC. Fusarium infections of the skin. Curr Opin Infect Dis 2000;13(2):121–8.
53. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. Clin Microbiol Rev 2007;20(4):695–704.
54. Dignani MC, Anaissie E. Human fusariosis. Clin Microbiol Infect 2004;10(Suppl 1):67–75.
55. Tortorano AM, Richardson M, Roilides E, et al, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, European Confederation of Medical Mycology. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect 2014;20(Suppl 3):27–46.
56. Espinel-Ingroff A, Colombo AL, Cordoba S, et al. International evaluation of MIC distributions and epidemiological cutoff value (ECV) definitions for fusarium species identified by molecular methods for the CLSI broth microdilution method. Antimicrob Agents Chemother 2015;60(2):1079–84.
57. Tortorano AM, Esposto MC, Prigitano A, et al. Cross-reactivity of Fusarium spp. in the Aspergillus galactomannan enzyme-linked immunosorbent assay. J Clin Microbiol 2011;50:1051–3.
58. Horn DL, Freifeld AG, Schuster MG, et al. Treatment and outcomes of invasive fusariosis: review of 65 cases from the PATH Alliance(®) registry. Mycoses 2014;57(11):652–8.
59. Raad II, Hachem RY, Herbrecht R, et al. Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions. Clin Infect Dis 2006;42(10):1398–403.
60. Liu JY, Chen WT, Ko BS, et al. Combination antifungal therapy for disseminated fusariosis in immunocompromised patients: a case report and literature review. Med Mycol 2011;49(8):872–8.
61. Stempel JM, Hammond SP, Sutton DA, et al. Invasive fusariosis in the voriconazole era: single-center 13-year experience. Open Forum Infect Dis 2015;2(3): ofv099.
62. Lackner M, de Hoog GS, Yang L, et al. Proposed nomenclature for Pseudallescheria, Scedosporium and related genera. Fungal Divers 2014;1:1–10.
63. Abela IA, Murer C, Schuurmans MM, et al. A cluster of scedosporiosis in lung transplant candidates and recipients: the Zurich experience and review of the literature. Transpl Infect Dis 2018;20(1):12792–810.
64. Parize P, Boussaud V, Poinsignon V, et al. Clinical outcome of cystic fibrosis patients colonized by Scedosporium species following lung transplantation: a single-center 15-year experience. Transpl Infect Dis 2017;19(5):12738–44.
65. Johnson LS, Shields RK, Clancy CJ. Epidemiology, clinical manifestations, and outcomes of Scedosporium infections among solid organ transplant recipients. Transpl Infect Dis 2014;16(4):578–87.
66. Troke P, Aguirrebengoa K, Arteaga C, et al, Global Scedosporium Study Group. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob Agents Chemother 2008;52(5):1743–50.
67. Castiglioni B, Sutton DA, Rinaldi MG, et al. Pseudallescheria boydii (Anamorph Scedosporium apiospermum). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine (Baltimore) 2002; 81(5):333–48.
68. Lackner M, de Hoog GS, Verweij PE, et al. Species-specific antifungal susceptibility patterns of Scedosporium and Pseudallescheria species. Antimicrob Agents Chemother 2012;56(5):2635–42.

69. Husain S, Muñoz P, Forrest G, et al. Infections due to Scedosporium apiospermum and Scedosporium prolificans in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. Clin Infect Dis 2005; 40(1):89–99.
70. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection 2011;39(3):201–10.
71. Cortez KJ, Roilides E, Quiroz-Telles F, et al. Infections caused by Scedosporium spp. Clin Microbiol Rev 2008;21(1):157–97.
72. Rodríguez MM, Calvo E, Serena C, et al. Effects of double and triple combinations of antifungal drugs in a murine model of disseminated infection by Scedosporium prolificans. Antimicrob Agents Chemother 2009;53(5):2153–5.
73. Schieffelin JS, Garcia-Diaz JB, Loss GE Jr, et al. Phaeohyphomycosis fungal infections in solid organ transplant recipients: clinical presentation, pathology, and treatment. Transpl Infect Dis 2014;16(2):270–8.
74. McCarty TP, Baddley JW, Walsh TJ, et al. Phaeohyphomycosis in transplant recipients: results from the Transplant Associated Infection Surveillance Network (TRANSNET). Med Mycol 2015;53(5):440–6.
75. Santos DW, Camargo LF, Gonçalves SS, et al. Melanized fungal infections in kidney transplant recipients: contributions to optimize clinical management. Clin Microbiol Infect 2017;23(5):333.e9-e14.
76. Chowdhary A, Meis JF, Guarro J, et al, European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group, European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of systemic phaeohyphomycosis: diseases caused by black fungi. Clin Microbiol Infect 2014;20(Suppl 3):47–75.
77. Muñoz P, Maddalena G, Vena A, et al. Mold infections in solid organ transplant recipients. In: Ljungman P, Snydman D, Boeckh M, editors. Transplant infections. 4th edition. Switzerland: Springer International Publishing; 2016. p. 719–56.
78. Lavergne RA, Cassaing S, Nocera T, et al. Simultaneous cutaneous infection due to Paecilomyces lilacinus and Alternaria in a heart transplant patient. Transpl Infect Dis 2012;14(6):E156–60.
79. Kim JE, Sung H, Kim MN, et al. Synchronous infection with Mycobacterium chelonae and Paecilomyces in a heart transplant patient. Transpl Infect Dis 2011; 13(1):80–3.
80. Polat M, Kara SS, Tapısız A, et al. Successful treatment of Paecilomyces variotii peritonitis in a liver transplant patient. Mycopathologia 2015;179(3–4):317–20.
81. Lee J, Yew WW, Chiu CS, et al. Delayed sternotomy wound infection due to Paecilomyces variotii in a lung transplant recipient. J Heart Lung Transplant 2002; 21(10):1131–4.
82. Pate MJ, Hemmige V, Woc-Colburn L, et al. Successful eradication of invasive Scopulariopsis brumptii in a liver transplant recipient. Transpl Infect Dis 2016; 18(2):275–9.
83. Chouaki T, Lavarde V, Lachaud L, et al. Invasive infections due to Trichoderma species: report of 2 cases, findings of in vitro susceptibility testing, and review of the literature. Clin Infect Dis 2002;35(11):1360–7.
84. Geyer AS, Fox LP, Husain S, et al. Acremonium mycetoma in a heart transplant recipient. J Am Acad Dermatol 2006;55(6):1095–100.
85. Eschenauer GA, Carver PL. The evolving role of antifungal susceptibility testing. Pharmacotherapy 2013;33(5):465–75.