Respiratory Fungal Infections in Solid Organ and Hematopoietic Stem Cell Transplantation

Oveimar De La Cruz, MD⁹, Fernanda P. Silveira, MD, MS⁸, *

INTRODUCTION

Respiratory fungal infections are a significant cause of morbidity and mortality in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) recipients. Among fungal infections, it is particularly the invasive mold infections that contribute to mortality. Although fungal organisms can cause different organ involvement and even disseminated disease, the lungs are the most common organ involved, in as many as 80% of the cases,¹ and are often the organ in which disease first manifests. Changes in immunosuppressive regimens and antifungal prophylactic strategies alter the epidemiology and timeline of infections, which also differ according to the type of transplant performed. This article reviews the most common respiratory fungal infections in SOT and HSCT recipients, highlighting recent changes in epidemiology, common presentations, advances in diagnostics, and current prophylactic and treatment strategies. Although candidiasis is the most common fungal infection in SOT and HSCT recipients, it is not discussed here, as it is not a common cause of respiratory infection.

ASPERGILLUS INFECTIONS

Epidemiology and Risk Factors in Solid Organ Transplantation

Invasive aspergillosis (IA) is the most common mold infection and the most common fungal...
respiratory infection in SOT recipients. In a prospective multicenter cohort study of invasive fungal infections (IFIs) in SOT recipients from 15 centers, the cumulative incidence (CI) estimate of IA at 12 months following transplantation was 0.7%. The incidence of IA varies according to the transplanted organ. Lung transplant recipients have the highest risk of IA, heart and liver recipients have moderate risk, and kidney recipients are considered low risk. In a prospective multicenter surveillance study, the 12-month CI of IA was found to be 2.4% after lung transplantation, 0.8% after heart transplantation, 0.3% after liver transplantation, and 0.1% after kidney transplantation. Aspergillus fumigatus is the most common species causing IA in SOT and HSCT recipients. The 12-month survival of IA in SOT is 59%. Among SOT recipients, liver transplant recipients have greater mortality than other organ recipients. In one study, the 12-week mortality from IA in liver recipients was 61%, compared with 19% in lung transplant recipients.

The net state of immunosuppression, environmental exposure, and cytomegalovirus (CMV) infection are risk factors for IA that are common to all organ transplant recipients.

**Epidemiology and Risk Factors in Hematopoietic Stem Cell Transplantation**

IA is the most common IFI in HSCT. The prevalence of IA is higher in HSCT than in SOT, with rates as high as 64%. The 1-year incidence of all IFIs is higher in allogeneic mismatched related donor (MMRD) HSCT (8.1%), followed by matched unrelated donor (MUD) (7.1%), matched related donor (MRD) (5.8%), and autologous HSCT (1.7%). IA occurs sooner after HSCT than after SOT, at a median of 99 days. The overall 12-month survival of IA in HSCT is approximately 25%. Table 1 summarizes the specific risk factors, prevalence, incidence, timing, and survival of IA in HSCT and SOT.

**Clinical Presentation**

Aspergillus can cause a wide spectrum of disease. The most common clinical presentations in SOT and HSCT recipients are airway colonization, tracheobronchitis, pulmonary aspergillosis, and disseminated disease.

Aspergillus colonization is most relevant in lung transplantation, where it occurs in 20% to 50% of patients, with rates in patients with cystic fibrosis (CF) higher than in patients without CF. It is characterized by the isolation of the organism in bronchoalveolar lavage (BAL) obtained during surveillance bronchoscopy in a patient who is asymptomatic and without any signs of tissue invasion.

Tracheobronchitis is almost exclusively found in lung transplantation. It is characterized by involvement of the airways and bronchi without extension to the lungs. It typically occurs in the first 3 months posttransplantation, usually involving the anastomotic site. The pathologic features include necrosis, ulceration, and pseudomembrane formation. Diagnosis is suspected based on bronchoscopic appearance and confirmed by pathology and culture. If untreated, it may extend to the lung parenchyma.

Most cases of IA are pulmonary. The clinical manifestations and radiographic findings of pulmonary aspergillosis in SOT and HSCT recipients are distinct and listed in Table 2. The halo sign (Fig. 1), an important early radiological finding of pulmonary aspergillosis in neutropenic and HSCT recipients, is often absent in SOT recipients. Macronodules are more common in HSCT recipients, whereas peribronchial consolidation, ground-glass opacities, and micronodules with tree-in-bud are more common in SOT (Fig. 2). The sinuses, with or without extension to the central nervous system, are other sites of IA. Aspergillus also can cause a fungus ball, known as an aspergilloma, in the sinuses. This is characterized by the lack of tissue invasion. It may be difficult to distinguish between a fungus ball and invasive disease based only on imaging, and endoscopic examination, and often surgery with debridement and pathology specimens is required.

Aspergillus may disseminate to any organ, but it has a predilection for the central nervous system. Fewer cases of disseminated disease are seen in the current era, likely due to earlier diagnosis and the use of calcineurin inhibitors and target of rapamycin inhibitors, which have in vitro activity against Aspergillus. It is also possible that a change in induction regimens, with a shift toward less use of lymphocyte-depleting agents, has contributed to fewer cases of disseminated disease; however, this has not yet been demonstrated.

**Diagnosis**

The diagnosis of IA is difficult. Signs and symptoms are nonspecific and no single microbiological test can yield a definitive diagnosis. A definitive diagnosis of aspergillosis requires visualization of hyphal invasion on tissue and growth of
### Table 1
Specific risk factors, prevalence, incidence, and survival of invasive aspergillosis in HSCT and SOT

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HSCT</th>
<th>Lung</th>
<th>Heart</th>
<th>Liver</th>
<th>Kidney</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
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<tr>
<td>Aspergillus airway colonization pretransplant or early posttransplant single lung transplant</td>
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<tr>
<td>Aspergillus colonization</td>
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<tr>
<td>Pretransplant fulminant hepatic failure</td>
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<tr>
<td>Anastomotic complications</td>
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<tr>
<td>Graft ischemia</td>
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<tr>
<td>Hypogammaglobulinemia</td>
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<tr>
<td>Bronchiolitis obliterans</td>
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<tr>
<td>Airway stents</td>
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<tr>
<td>Pretransplant reoperation</td>
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<tr>
<td>Primary allograft failure or severe dysfunction</td>
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<tr>
<td>Retransplantation</td>
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<tr>
<td>Need for dialysis</td>
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<tr>
<td>High transfusion requirement</td>
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</table>

<table>
<thead>
<tr>
<th>Prevalence, %</th>
<th>43–64</th>
<th>44–63</th>
<th>23–25</th>
<th>7–11</th>
<th>11–14</th>
<th>5–10</th>
</tr>
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<tbody>
<tr>
<td>1-y Cl, %</td>
<td>1.6</td>
<td></td>
<td></td>
<td>0.7</td>
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<td>Time after transplantation, median, d</td>
<td>99</td>
<td>184</td>
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<tr>
<td>12-mo survival, %</td>
<td>25.4</td>
<td></td>
<td>59</td>
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</tbody>
</table>

**Abbreviations:** CI, cumulative incidence; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; MMRD, mismatched related donor; MUD, matched unrelated donor; SOT, solid organ transplant.

*Data from Refs.8,15,18,56–65*
Aspergillus in culture of the same tissue. However, in most cases obtaining tissue samples for a definitive diagnosis is not feasible due to cytopenias or the patient’s clinical condition. The diagnosis of aspergillosis requires a combination of clinical and radiographic findings, culture results, histopathologic findings and nonculture diagnosis assays such as galactomannan (GM) and 1–3 β-D-glucan (BG).

A computerized tomography (CT) scan of the chest is indicated whenever there is a clinical suspicion of invasive pulmonary aspergillosis, independent of the findings on chest radiograph. Bronchoscopy with BAL should be attempted, whenever possible, in all patients with suspected pulmonary involvement. If nodules are present, obtaining percutaneous or endobronchial biopsies increases the diagnostic yield.¹⁷

Aspergillus is ubiquitous in the air, so a positive culture result must be interpreted with caution, as it can be due to colonization or contamination of the plate.

Serum GM is a useful tool for the screening and diagnosis of IA in HSCT recipients, but not in SOT.¹⁷,¹⁸ The major limitation of the serum GM test is its reduced sensitivity in non-neutropenic individuals. In a meta-analysis, the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical and radiographic manifestations of invasive pulmonary aspergillosis in HSCT and SOT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td><strong>HSCT</strong></td>
</tr>
<tr>
<td>Lung involvement</td>
<td>74%–93%</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>Fever (often high), dry cough, hemoptysis, pleuritic chest pain</td>
</tr>
<tr>
<td></td>
<td>Lung transplant recipients:</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Radiologic features</td>
<td>Preengraftment:</td>
</tr>
<tr>
<td></td>
<td>Peribronchial consolidation</td>
</tr>
<tr>
<td></td>
<td>Diffuse bronchopulmonary infiltrate</td>
</tr>
<tr>
<td></td>
<td>Pulmonary nodules with or without “halo sign”</td>
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<tr>
<td></td>
<td>Postengraftment:</td>
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<tr>
<td></td>
<td>Air crescent sign</td>
</tr>
<tr>
<td></td>
<td>Cavitation</td>
</tr>
</tbody>
</table>

**Abbreviations:** HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant.

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**Fig. 1.** “Halo sign,” an area of ground-glass opacity surrounding a pulmonary nodule, in a patient with invasive pulmonary aspergillosis.

**Fig. 2.** Area of consolidation in a patient with invasive aspergillosis.
sensitivity of serum GM was 82% in a hematological population, as compared with 22% in SOT recipients.\textsuperscript{19} This test can be used for the early diagnosis of IA in neutropenic individuals. In this patient population, routine testing can be performed and detection of positive results, especially in 2 consecutive samples, provides strong evidence for the diagnosis of IA, as long as patients are not receiving antifungal prophylaxis or therapy with antimold activity.\textsuperscript{17} Serum longitudinal GM assays are also valuable for monitoring treatment response and predicting survival in HSCT.

GM can also be detected in BAL. In a meta-analysis of 30 diagnostic studies that evaluated the performance of the BAL GM assay for diagnosing IA, BAL GM had higher sensitivity (0.86) and lower specificity (0.86) than serum GM assays. BAL GM had higher sensitivity and similar specificity when compared with polymerase chain reaction (PCR)-based assays. Notably, test performance varied by patient population.\textsuperscript{20} There is preliminary data suggesting that BAL GM can be used to guide preemptive antifungal therapy in lung transplant recipients.\textsuperscript{21} False positive results in serum and BAL can occur, but are not common.

The BG assay can be used for diagnosis in HSCT, but results should be interpreted with caution, as the assay is not specific for Aspergillus.\textsuperscript{17}

The use of PCR in the blood in the diagnosis of IA is not currently recommended for routine use in clinical practice due to lack of conclusive validation for commercially available assays and the variety of methodologies in the literature.\textsuperscript{17} PCR of BAL specimens has a high negative predictive value for invasive pulmonary aspergillosis and can be considered in selected cases.\textsuperscript{17}

**Therapy**

Two major factors will affect the outcomes of patients diagnosed with aspergillosis: the extension of disease and the underlying degree of immunosuppression. Immunosuppression should be tapered or removed, whenever possible.

Voriconazole remains the first-line therapy for treatment of all forms of invasive aspergillosis,\textsuperscript{22} and liposomal amphotericin and isavuconazole are alternative options for primary therapy.\textsuperscript{17,23} The inclusion of isavuconazole in the first-line armamentarium against IA is an update in the most recent guidelines by the Infectious Diseases Society of America. Posaconazole, itraconazole, echinocandins, and amphotericin B lipid complex can be used for salvage therapy when the primary therapy fails.\textsuperscript{17}

Combination therapy including a formulation of amphotericin or an azole with echinocandins has shown an additive or synergist effect in most studies, when compared with monotherapy. Studies have varied significantly in design and some even showed antagonism. Combination therapy is currently not routinely recommended, but can be considered in certain situations.\textsuperscript{17}

Colony-stimulating factors can be used in neutropenic patients. Surgical resection or debridement should be considered for localized disease that is easily accessible, such as when there is invasive sinusitis.\textsuperscript{17}

In lung transplant recipients with tracheobronchitis, the use of adjunctive inhaled amphotericin is recommended, to increase antifungal delivery to areas of the anastomosis with endobronchial ischemia or ischemia reperfusion injury.\textsuperscript{17,18} Bronchoscopic debridement of the airway lesion also should be considered.

Therapeutic drug monitoring once steady state is reached is recommended when an azole is being used for therapy. Antifungal susceptibility testing should be reserved for patients with history of prolonged azole exposure, those unresponsive to antifungal therapy, or those with suspicion of having an azole-resistant isolate.\textsuperscript{17}

**Prophylaxis**

Anti-Aspergillus prophylaxis is recommended for patients at high risk for IA, as summarized in Table 3.\textsuperscript{5,17,18,24–26}

**ZYGOMYCETES INFECTIONS**

**Epidemiology and Risk Factors**

Zygomycosis is the second most common mold infection in HSCT and SOT recipients, with reported prevalences of 5% to 8% and up to 3% in HSCT and SOT, respectively.\textsuperscript{1,2,7} Fifty percent of the cases are attributed to Rhizopus, followed by Mucor and Rhizomucor. Infection occurs earlier in HSCT than SOT, with a median of 135 and 321 days, respectively. Zygomycosis is a deadly disease with a 12-week survival of 36% in HSCT and 44% in SOT.\textsuperscript{2,6,7,27,28}

The incidence of zygomycosis seems to be increasing in HSCT. Factors that have been associated with this change in epidemiology include the use of newer reduced toxicity conditioning regimens that allow transplantation of older patients and
patients with comorbid conditions, and extended use of voriconazole. Table 4 summarizes the specific risk factors, prevalence, incidence, timing, and survival of zygomycosis in HSCT and SOT.

**Clinical Presentation**

Zygomycetes are angioinvasive molds leading to rapid tissue necrosis and disseminated infection. Sinopulmonary, rhinocerebral, cutaneous, and disseminated disease are associated with HSCT and SOT.

Table 3

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Indication for Prophylaxis</th>
<th>Recommended Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCT</td>
<td>Allogeneic high risk (conditioning regimen containing antithymocyte globulin OR diagnosis of AML, ALL, MDS, aplastic anemia, T-cell lymphoma OR SCID OR cord blood) Significant GVHD, defined as: 1. prednisone ≥1 mg/kg/d if acute GVHD OR 2. Prednisone ≥0.8 mg/kg every other day if chronic GVHD OR 3. Antithymocyte globulin or TNF inhibitor (ie, etanercept, infliximab) use OR 4. Combination of ≥2 immunosuppressive agents IA before transplant</td>
<td>Posaconazole delayed release tablets</td>
<td>Not well defined. Until immune reconstitution (6–12 mo), depending on status of GVHD Alternatives: voriconazole OR itraconazole OR amphotericin B OR echinocandin</td>
</tr>
<tr>
<td>Lung</td>
<td>All patients in the early posttransplant period Beyond the early posttransplant period (&gt;6 mo): Rejection therapy with alemtuzumab or antithymocyte globulin OR isolation of pathogenic mold OR presence of airway stent</td>
<td>Inhaled amphotericin B (deoxycholate or liposomal) OR voriconazole OR itraconazole</td>
<td>4–6 mo 1–4 mo, depending on indication</td>
</tr>
<tr>
<td>Heart</td>
<td>Aspergillus in respiratory cultures Reoperation CMV disease Posttransplant hemodialysis IA episode in the program 2 mo prior or after heart transplant</td>
<td>Voriconazole OR itraconazole OR posaconazole</td>
<td>1–4 mo</td>
</tr>
<tr>
<td>Liver</td>
<td>Retransplantation Renal replacement therapy Reoperation involving thoracic or abdominal cavity</td>
<td>Voriconazole OR liposomal amphotericin OR echinocandin</td>
<td>Initial hospital stay or for 4 wk posttransplant</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; SCID, severe combined immunodeficiency; TNF, tumor necrosis factor. 

a Isavuconazole is a possible alternative but studies are lacking. 
b Inhaled amphotericin B preferred. 
c A systemic azole is preferred in patients with pretransplant mold colonization, recipients of single lung transplant, and those with evidence of mold infection in the explanted lungs.

Symptoms of rhinocerebral disease can be nonspecific, like facial pressure, headache, nasal congestion, presence of necrotic ulcers, or eschars at nasal mucosa or palate. New neurologic deficits should be a warning sign of cerebral extension leading often to epidural, subdural abscess, and cavernous sinus thrombosis. Orbital edema, ptosis, proptosis, or ophthalmoplegia are usually seen once sinus wall erosion occurs with periorbital fat compromise.

Pulmonary clinical manifestations are similar to and may be indistinguishable from IA. Fevers
refractory to broad-spectrum antibiotics, nonproductive cough, pleuritic chest pain, and rapidly progressive dyspnea can be observed. Parenchymal necrosis can ultimately lead to cavitation and hemoptysis, which could be fatal.31

Cutaneous manifestations and soft tissue infections present as wound infection with necrotic ulceration. Gastrointestinal disease is rare, but can manifest as gastric or bowel perforation, typhlitis, or ileal or appendiceal mass. Disseminated disease occurs in 9% to 13% in kidney transplantation, 11% to 20% in heart transplantation, 11% to 25% in lung transplantation, and 26% to 55% in liver transplantation.32 Most patients with disseminated disease have lung involvement with extension to other organs by contiguity or hematogenous dissemination. Mortality in disseminated disease can be as high as 96%.33

**Diagnosis**

The gold standard of diagnosis is histopathologic evidence of fungal tissue invasion. Hyphae morphology is characteristic with 90-degree angle at irregular interval and are pauciseptate. Most recently, molecular techniques are increasingly used for identification, including sequencing of PCR products. GM and BG are not useful for the diagnosis of zygomycosis due to the limited amounts of either on the fungal cell walls.34

**Therapy**

Survival is enhanced with prompt surgical debridement and adequate antifungal therapy. In a study, survival with combined approach was 70% as compared with 57% if either surgery or amphotericin B were used alone.35 The standard antifungal therapy is liposomal amphotericin B, with some investigators recommending doses as high as 10 mg/kg per day. Isavuconazole was recently approved for treatment of mucormycosis. Posaconazole is currently indicated for salvage therapy. Combination therapy has not shown clear benefit in several studies.36

**Prophylaxis**

Posaconazole prophylaxis is currently recommended only for neutropenic patients at risk for graft-versus-host disease (GVHD) in an outbreak scenario.36

**CRYPTOCOCCUS INFECTIONS**

**Epidemiology and Risk Factors**

Cryptococcosis is the third most common IFI in SOT recipients, with a prevalence rate ranging from 0.26% to 8.0%2 and 12-month CI of 0.2%.2 Cryptococcosis occurs late in the posttransplant course, with most cases occurring 1 year after transplantation.2,37 The 12-month survival is 73%.

The only known risk factor for cryptococcosis is the use of immunosuppression. Receipt of steroids, particularly at higher doses, seems to be especially important. Recently, a single-center

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HSCT</th>
<th>Lung</th>
<th>Heart</th>
<th>Kidney</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td>5–8</td>
<td>2–3</td>
<td>2–3</td>
<td>1–2</td>
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<tr>
<td>Severe GVHD</td>
<td></td>
<td>&lt;0.3</td>
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<td>0.2</td>
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<tr>
<td>Corticosteroid use</td>
<td></td>
<td>135</td>
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<td>312</td>
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<tr>
<td>Older</td>
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</tr>
<tr>
<td>DM</td>
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<td>CMV</td>
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<td></td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Myelodysplasia</td>
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<td>Voriconazole exposure</td>
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</tbody>
</table>

**Abbreviations:** CI, cumulative incidence; CMV, cytomegalovirus; DM, diabetes mellitus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant.

Data from Refs.28,66,67
study demonstrated an increase in the CI of cryptococcosis that was associated with receipt of 2 or more doses of antilymphocyte globulin or alemtuzumab. Because the risk for cryptococcosis is determined by the degree of immunosuppression, cryptococcosis is less common after HSCT, with a prevalence of 0.6%. This section will focus on SOT; however, the same principles apply to HSCT.

**Clinical Presentation**

Cryptococcosis most often presents with central nervous system involvement, with or without associated pulmonary involvement; however, isolated pulmonary cryptococcosis occurs in approximately 40% of SOT recipients. Isolated pulmonary cryptococcosis can be asymptomatic and diagnosed after the incidental finding of nodular pulmonary infiltrates. When symptoms are present, they are often mild and can be nonspecific. The presence of acute respiratory failure, pleural effusion and bilateral infiltrates has been identified as predictors of mortality in patients with cryptococcal pneumonia.

Immune reconstitution syndrome (IRS) can occur in as many as 14% of SOT recipients being treated for cryptococcal infection, typically between 4 and 6 weeks after initiation of antifungal therapy. It should not be confused with failure of therapy. Patients will have worsening of their clinical manifestations but with negative diagnostic studies. IRS occurs due a shift from a predominantly Th2 response to a Th1 proinflammatory response in the setting of antifungal therapy and reduction in immunosuppression. Central nervous system (CNS) disease and discontinuation of calcineurin inhibitor have been identified as independent predictors of IRS. IRS has been associated with graft loss and rejection, but not with increased mortality.

**Diagnosis**

Cryptococcal infection can be diagnosed by isolation of *Cryptococcus* sp in culture, visualization in direct microscopic examination, or detection of the polysaccharide antigen in serum or cerebrospinal fluid. If *Cryptococcus* is isolated in the sputum of asymptomatic transplant recipients, it should be considered a pathogen and investigation of invasive pulmonary disease should be pursued. A negative serum cryptococcal antigen does not exclude cryptococcal infection. Negative results can occur in approximately one-third of SOT recipients with isolated pulmonary disease and even in patients with CNS involvement.

**Therapy**

The treatment of cryptococcosis depends on the sites involved and the severity of the disease and is summarized in Table 5.

**Prophylaxis**

Routine primary or secondary prophylaxis for cryptococcosis is not recommended in transplant recipients.

**FUSARiUM**

**Epidemiology and Risk Factors**

Infections caused by *Fusarium* are rare and occur mainly in HSCT recipients, with sporadic cases in SOT, mostly lung recipients. This section is focused on HSCT. In the Transplant-Associated Infection Surveillance Network (TRANSNET), fusariosis occurred in 31 of 983 cases of invasive mold infections (IMIs) in HSCT and 6 of 1208 IMIs in SOT. When *Fusarium* is identified to the species level, *Fusarium solani* is the most commonly isolated. Among all IMIs in HSCT, fusariosis is associated with the lowest 1-year survival, only 6.3%. Risk factors for fusariosis include prolonged neutropenia, mismatched or

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Treatment of cryptococcosis in SOT and HSCT</th>
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<tbody>
<tr>
<td><strong>Site and Severity of Disease</strong></td>
<td><strong>Recommended Therapy</strong></td>
</tr>
<tr>
<td>CNS infection</td>
<td>Induction: liposomal amphotericin B and flucytosine for at least 2 wk, followed by</td>
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<tr>
<td>Consolidation: high dose fluconazole (400–800 mg/d) for 8 wk, followed by</td>
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<tr>
<td>Maintenance: fluconazole 200–400 mg for 6–12 mo</td>
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</tr>
<tr>
<td>Moderately severe to severe non-CNS or disseminated disease</td>
<td>Same as CNS infection</td>
</tr>
<tr>
<td>Mild to moderate non-CNS infection</td>
<td>Fluconazole 400 mg/d for 6–12 mo</td>
</tr>
</tbody>
</table>

*Abbreviations: CNS, central nervous system; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant. The use of flucytosine may not be possible due to side effects. When this happens, therapy with liposomal amphotericin should be extended to at least 4 to 6 wk.*
unrelated transplant, severe GVHD, corticosteroid use, and multiple myeloma. A Brazilian cohort identified antithymocyte globulin therapy, smoking, hyperglycemia, and acute myelogenous leukemia as risk factors for fusariosis early posttransplant.

Clinical Presentation

Usually, invasive fusariosis presents with fevers and papular nodular skin lesions with or without central necrosis. Thirty-nine percent to 54% of patients may have pneumonia with similar presentation as IA; with angioinvasion, lung infarction, and pulmonary nodules with or without halo signs (Fig. 3). Radiologic appearance can vary from nonspecific infiltrates on 50% of patients, to nodules or interstitial infiltrates. Disseminated disease is frequent, ranging from 22% to 79% in some reports. Skin lesions are common. Fungemia occurs in more than half of patients. Invasive sinusitis is described in 12% of patients.

Diagnosis

Definitive diagnosis is reached by identification of hyaline acute branching septated hyphae in tissue. Characteristic banana-shaped macroconidia will render genus identification. Different from other IMIs, blood cultures are positive in two-thirds of patients, with median time to positivity of 3 days. Immunochemistry stains and in situ hybridization also can be used to enhance diagnostic yield. Rapid molecular identification via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) is available in several hospitals. BG is often positive, but is not specific for fusariosis and false-positives can occur.

Fig. 3. Nodular infiltrates in an HSCT recipient with invasive fusariosis.

Therapy

There is lack of randomized trials to support a specific agent and outcome is poor despite treatment. Most successfully treated patients received either voriconazole at standard doses or liposomal amphotericin. Posaconazole has variable in vitro activity and susceptibility testing is often clinically unreliable. Echinocandins have no activity against Fusarium. Evidence supporting combination therapy is also poor. Surgical debridement and immune reconstitution appear to have a critical role on outcome.

Prophylaxis

The evidence to support primary or secondary prophylaxis is limited. Extended-spectrum azoles can be used in specific situations when patients with prior fusariosis will receive increased immunosuppression.

ENDEMIC MYCOSES

The endemic mycoses are more common in SOT, where they occur in approximately 5% of patients, than in HSCT, where they are seen in fewer than 1% of patients. The causative agents are geographically restricted, so incidence rates are higher in endemic areas. Most infections are due to Histoplasma capsulatum. The discussion on endemic mycoses will focus on SOT recipients, but principles can be applied to HSCT.

Histoplasmosis

Histoplasma capsulatum occurs in the Mississippi and Ohio River valleys, Central and South America, and certain areas of Africa and Asia. Disease can be due to primary infection, reactivation, or donor-derived infection. Histoplasmosis occurs later after SOT, at a median of 27 months after transplantation. The most common form of presentation is disseminated disease, with multiple organ involvement. Pulmonary symptoms are usually subacute and prolonged fever is a common feature.

Diagnosis can be established with culture, fungal stains of affected tissue, or detection of antigen in serum or urine. The most sensitive diagnostic test in SOT is detection of Histoplasma antigen in urine. Cross-reaction can occur with other endemic mycoses, such as penicilliosis, paracoccidioidomycosis, and blastomycosis. Antigen levels can be measured to assess response to therapy and to monitor for relapse once therapy is completed.

The choice of therapy will depend on the severity of disease and sites involved. Disease...
that is severe, disseminated, or involves the CNS, should be treated with liposomal amphotericin B for the first 4 to 6 weeks, followed by itraconazole for a total of at least 12 months. Lifelong suppressive therapy with itraconazole may be considered in some patients who will remain immunosuppressed and in patients who experienced relapse despite having received appropriate therapy.

A history of histoplasmosis or suggestion of old infection (presence of calcified hilar and mediastinal lymph nodes, splenic calcifications or a positive Histoplasma serology) are not a contraindication to transplantation and the risk of reactivation is low. Prophylaxis is not recommended, however, in such patients, histoplasmosis should be considered in the differential diagnosis of a febrile illness in the posttransplant period.

### Coccidioidomycosis

Coccidioidomycosis is endemic in the southwestern United States and northern Mexico. Infection can be primary, due to reactivation, or donor-derived. Approximately 50% of infections are believed to be due to reactivation, and most occur in the first year posttransplant. Mortality can be as high as 70%. Risk factors for coccidioidomycosis in SOT are prior history of coccidioidomycosis, positive serology, evidence of active infection at the time of transplant, and treatment of acute rejection.

The most common presentation is with pulmonary symptoms, which can be indistinguishable from a bacterial pneumonia, with acute onset of fever, productive cough, and dyspnea. Dissemination to any organ can occur.

Diagnosis can be established with culture, visualization of spherules in clinical specimens, serologic tests, or detection of Coccidioides antigen in serum, urine, BAL, or cerebrospinal fluid.

The choice of therapy depends on the severity of disease and sites involved. HSCT and SOT recipients with acute or chronic pulmonary coccidioidomycosis who are clinically stable should be treated with fluconazole. Patients with severe and/or rapidly progressing acute pulmonary or disseminated disease should initiate therapy with liposomal amphotericin, followed by fluconazole once the disease stabilizes. Reduction of immunosuppression is recommended in severe and disseminated disease. The treatment recommendations for extrapulmonary infection are the same as in the nontransplant population, with fluconazole being the drug of choice. Lifelong suppressive therapy with fluconazole is recommended to prevent relapse.

Patients with a prior history of coccidioidomycosis undergoing SOT should receive lifelong prophylaxis with fluconazole. Patients without a history of coccidioidomycosis undergoing SOT in an endemic area should receive primary prophylaxis with fluconazole for 6 to 12 months.

### Blastomycosis

Blastomycosis occurs in the southeastern, south central, and midwestern United States and the Canadian provinces that border the Great Lakes and the St Lawrence Seaway. It is the least common endemic mycoses and is rare after HSCT and SOT. It is primarily a pulmonary infection, but dissemination may occur, especially to skin, bones, and the genitourinary system.

Diagnosis can be established with culture, visualization of the organism in clinical specimens, serology, or antigen detection.

The recommended therapy for blastomycosis in patients who are immunosuppressed is with liposomal amphotericin B for at least 1 to 2 weeks or until clinical improvement, followed by itraconazole for a total of at least 12 months. Lifelong suppression may be required in patients who remain immunosuppressed or who experience relapse.

### OTHER MOLDS

Infections caused by non-Aspergillus molds, although still infrequent, have become more common. It is believed that this change in epidemiology reflects changes in antifungal prophylaxis and type and potency of immunosuppressive drugs. Most of these infections are caused by the Zygomycetes and Fusarium, which were discussed previously. However, Scedosporium and the dematiaceous molds are pathogens that one should know. Scedosporiosis can be caused by Scedosporium apiospermum and Scedosporium prolificans. These organisms are characterized by their level of resistance to the available antifungal drugs, particularly to amphotericin. Infection often disseminates and is associated with high mortality. The optimal therapy is not known but involves the use of triazole antifungals, usually voriconazole. Reduction in immunosuppression and adjunctive surgery should be considered.

The dematiaceous molds include Exophiala, Alternaria, Cladophialophora, Curvularia, Ochroconis, and others. Most data come from case reports. Infection usually occurs late and prognosis is good if diagnosis occurs before dissemination.
SUMMARY

Respiratory fungal infections are an important cause of morbidity and mortality in HSCT and SOT. Despite the availability of non–culture-based diagnostics, such as GM, diagnosis remains challenging. These infections carry a higher risk of dissemination in HSCT and SOT, which directly impacts outcomes. The advent of new antifungal agents, such as voriconazole, posaconazole, isavuconazole, echinocandins, and liposomal formulation of amphotericin, changed the therapeutic choice for these infections given its broader spectrum of activity and better safety profile. Despite that, the mortality associated with fungal respiratory infections remains high. As we continue to transplant a larger number of patients, and immunosuppressive therapies evolve, it is essential to continue to observe the epidemiology of these infections and adjust monitoring and prophylactic practices.

REFERENCES


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