Respiratory Fungal Infections in Solid Organ and Hematopoietic Stem Cell Transplantation

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KEYWORDS

• Fungal pneumonia • Solid organ transplant • Hematopoietic stem cell transplant • Fungal infection • *Aspergillus*

KEY POINTS

- Severity of invasive fungal infection (IFI) in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients is determined by inoculum size, degree of immunosuppression, and integrity of the immunologic defense mechanisms.
- Epidemiology and risk factors may differ in HSCT and SOT recipients.
- Diagnosis of fungal infections is difficult due to low yield of available testing. Every effort should be made to confirm the diagnosis, to guide treatment decisions.
- Aggressive and prompt treatment is required due to high mortality from IFI in transplant recipients.
- New prophylaxis strategies are changing the epidemiology of fungal infections in HSCT and SOT recipients.

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

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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%.[2] 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.[1–3] 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.[4] *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.[1]

The net state of immunosuppression, environmental exposure, and cytomegalovirus (CMV) infection are risk factors for IA that are common to all organ transplant recipients.[5]

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%.[6,7] 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%).[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%.[6,7] **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,[8,9] 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.[10] 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.[1,2,11] 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.[12,13] Macronodules are more common in HSCT recipients, whereas peribronchial consolidation, ground-glass opacities, and micronodules with tree-in-bud are more common in SOT[14] (**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,[1,2] likely due to earlier diagnosis and the use of calcineurin inhibitors and target of rapamycin inhibitors, which have in vitro activity against *Aspergillus*.[15] 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.[16]

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