Published in final edited form as:

Infect Dis Clin North Am. 2016 March ; 30(1): 277–296. doi:10.1016/j.idc.2015.10.001.

Approach to the Solid Organ Transplant Patient with Suspected Fungal Infection

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Keywords

Solid organ transplant; Invasive fungal infection; Candida; Aspergillus; Endemic fungi; Cryptococcus; Mold

INTRODUCTION

In solid organ transplant (SOT) recipients, invasive fungal infections (IFIs) are associated with significant morbidity and mortality. Detection of IFIs can be difficult because the signs and symptoms are similar to those of viral or bacterial infections or noninfectious illness, and diagnostic techniques have limited sensitivity and specificity. As a result, to aid in the diagnosis of IFI, clinicians often must rely on knowledge of the patient's risk factors for fungal infection.

In this article, an approach to diagnosis of IFIs is described on the basis of the SOT patient's clinical presentation and risk factors. Specifically, the spectrum of suspected IFIs that may be present in patients who present with clinical syndromes is outlined, including respiratory illness, neurologic illness, cutaneous manifestations, and a sepsis syndrome. Relevant fungal pathogens associated with these clinical syndromes, an initial diagnostic approach, and considerations for empiric antifungal therapy are discussed.

EPIDEMIOLOGY OF INVASIVE FUNGAL INFECTIONS AFTER SOLID ORGAN TRANSPLANTATION

The timing and incidence of IFIs vary by the organ transplanted and the use of antifungal prophylaxis. Candidiasis and aspergillosis have historically caused—and continue to cause

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Disclosure Statement: Dr J.A. Anesi has nothing to disclose; Dr J.W. Baddley consults for Merck, Astellas, and Pfizer.

—most IFIs in SOT recipients, although there are increasing reports of non-*albicans* *Candida* and non-*Aspergillus* molds complicating SOT in recent years^{1–5} (Table 1).

There have been 2 recent multicenter, observational studies describing the epidemiology of IFIs in SOT patients.^{6,7} The first, by Pappas and colleagues,⁶ analyzed data from the Transplant-Associated Infection Surveillance Network. The group described 1208 IFIs among 1063 SOT recipients (kidney, liver, pancreas, lung, heart, and small bowel) over a follow-up period of up to 5 years. The overall incidence of IFIs was 3.1%.⁶ The second study, by Neofytos and colleagues,⁷ used data collected from the Prospective Antifungal Therapy Alliance registry. In this study, 515 IFIs among 429 SOT recipients (liver, lung, kidney, heart, small bowel, islet cell, and pancreas) were described, with a follow-up time of up to 3 years. Both studies revealed similar IFI epidemiology: the most common IFIs were invasive candidiasis, invasive aspergillosis, and cryptococcosis. Invasive candidiasis was the most common IFI in all transplant types except in lung recipients, where aspergillosis was most common. Non-*Aspergillus* molds, endemic fungi, zygomycosis, and pneumocystosis were less commonly observed.^{6,7}

Timing of Invasive Fungal Infections After Solid Organ Transplant

In general, invasive candidiasis is an early complication of SOT, and other IFIs are more likely late complications, although the timing may vary based on antifungal prophylaxis and transplant type (Fig. 1).^{1,6–8} With current antifungal prophylaxis strategies, the time to onset of invasive candidiasis ranges between 3 and 6 months.^{6,7} The timing of aspergillosis is dependent on the site of infection: tracheobronchial or anastomotic *Aspergillus* infections typically occur within 90 days, whereas other forms of invasive aspergillosis occur later (6–12 months).^{6,7,9,10}

Zygomycosis and other non-*Aspergillus* mold infections tend to present later after SOT, with average time to onset of 312 to 467 days (10–14 months).^{6,7} Of note, a study reported time to mold infection of 81 days (2.7 months) in liver recipients, but 533 days (1.5 years) for nonliver SOT recipients, suggesting that liver recipients are an outlier with much earlier onset of both *Aspergillus* and non-*Aspergillus* mold infections.¹¹ This phenomenon of early mold infections after liver transplantation has been described in other studies as well.¹²

Endemic fungi also tend to be a late complication following SOT, with a median time to onset of 343 days (11.4 months), although one study found that the timing may be bimodal with 40% of infections occurring within the first 6 months after transplant and 34% occurring between 2 and 11 years after transplant.^{6,13}

Pneumocystosis is now predominantly a late complication of SOT. Before the advent of prophylaxis, it generally occurred between 3 and 6 months after transplant. Studies in the era of widespread prophylaxis, however, have shown that it now occurs typically more than 180 days (6 months) after transplant, after prophylaxis has been discontinued. Most cases occur within 1 year of transplant.¹⁴

Cryptococcosis is one of the latest infectious complications after SOT, with a median time to onset between 1.5 and 5 years after SOT.^{6,7}

Risk Factors for Invasive Fungal Infections Following Solid Organ Transplant

Knowledge and recognition of risk factors for IFI play an important role in evaluation of the patient with suspected IFI. Risk factors for IFI vary by the organ transplanted (Table 2). In liver recipients, the major risk factors associated with IFIs are predominantly surgical factors, as increased technical complexity, prolonged operation time, greater transfusion requirements, Roux-en-Y biliary anastomosis, retransplantation, and bleeding complications requiring reoperation have been associated with increased risk of IFIs.^{15–18} Nonsurgical factors that are associated with increased risk for IFIs in liver recipients include hepatic and renal dysfunction, particularly when requiring hemodialysis,^{19,20} and immunomodulatory viral infections, including cytomegalovirus (CMV) and human herpesvirus-6 (HHV-6).^{15,21–23}

In lung recipients, airway colonization with *Aspergillus* has been associated with increased risk for subsequent invasive aspergillosis.²⁴ Other risk factors for invasive aspergillosis include CMV infection, ischemia of the anastomosis, receipt of a single lung transplant, hypogammaglobulinemia, and augmented immunosuppression; it remains controversial whether allograft rejection is a significant risk factor.^{19,25–28}

In kidney recipients, the major risk factors for IFIs include diabetes, prolonged pre-transplant dialysis, allograft rejection, the use of tacrolimus, and graft failure requiring reinitiation of hemodialysis.²⁹ An increased risk for invasive aspergillosis specifically has been associated with high dose and prolonged duration of corticosteroids, and graft failure requiring hemodialysis and enhanced immunosuppression.^{19,30,31}

In heart transplant recipients, invasive candidiasis has been associated with use of broad-spectrum antibiotics, prolonged duration of antibiotic use, presence of central-venous catheters, and need for hemodialysis.^{1,8} Invasive aspergillosis has been associated with isolation of *Aspergillus* on bronchoalveolar lavage (BAL), reoperation, CMV disease, and posttransplant hemodialysis.^{32–34} The use of extracorporeal membrane oxygenation (ECMO) is also associated with increased risk for IFIs.³⁵

Risk factors for IFIs in pancreas recipients include increased donor age, enteric drainage (rather than bladder drainage), pancreas transplantation after kidney transplantation, preoperative peritoneal dialysis, and pancreatic retransplantation.³⁶

With small bowel transplantation, patients are thought to be particularly high risk for IFIs, especially candidiasis, when there is graft rejection or dysfunction, enhanced immunosuppression, anastomotic disruption, abdominal reoperation, and multivisceral transplantation.³⁷ Infections with non-*albicans* *Candida* species have been associated with the use of fluconazole prophylaxis.³

RECOGNITION OF INVASIVE FUNGAL INFECTIONS BY CLINICAL SYNDROME

Given the lack of diagnostic tests with high sensitivity and specificity for detecting IFIs, the diagnosis of an IFI in an SOT recipient is often made based on the patient's clinical

presentation, knowledge of fungal infections by site, and patient risk factors. In this section, suspected IFI by clinical syndrome is approached. Specifically discussed are patients who present with pulmonary symptoms, neurologic symptoms, cutaneous eruptions, and sepsis syndrome without localizing symptoms.

Pulmonary Fungal Infections

When a transplant recipient presents with respiratory symptoms, pulmonary fungal infections should be considered, particularly if the patient is more than 6 months after transplantation. Patients with pulmonary mycosis often present with nonspecific symptoms such as cough (either dry or productive) and fever. They may also endorse hemoptysis, dyspnea, and systemic symptoms of weight loss and fatigue.

Among transplant recipients, fungi are much less common causes of pneumonia than are bacteria or viruses—fungi account for approximately 6% of all pneumonias.³⁸ Molds, especially *Aspergillus* species, cause the greatest number of pulmonary fungal infections in SOT recipients.^{38,39} Less commonly, *Fusarium*, *Scedosporium*, agents of mucormycosis, and dematiaceous fungi may be causative. *Cryptococcus*, and the dimorphic endemic fungi, such as *Histoplasma*, *Blastomyces*, and *Coccidioides*, should be considered on the basis of clinical presentation and geography. In studies conducted before the widespread use of prophylaxis, the incidence of *Pneumocystis jiroveci* pneumonia (PJP) varied between 5% and 15% depending on the organ type and immunosuppressive regimen; in the era of prophylaxis, the incidence of PJP within the first year after SOT is estimated to be less than 1%, although higher rates (up to 15%) have been reported after 1 year.^{40–43}

Initial evaluation of the transplant patient with suspected pulmonary mycosis typically involves chest imaging. Radiographic findings, especially subcentimeter lesions, may be difficult to appreciate on chest radiograph alone, so chest computed tomographic scan is the best imaging modality.⁴⁴ Imaging may reveal nodular or masslike opacities (with or without the halo sign), which may progress to cavitary lesions. Ground-glass opacities (GGOs) and lobar infiltrates can also be seen with some types of fungal infections.^{45–47} It is not uncommon to have concurrent bacterial or viral pulmonary infection in patients with a pulmonary fungal infection, sometimes complicating radiographic interpretation. The following sections highlight suspected fungal infections on the basis of imaging findings (Table 3).

Pulmonary nodules or masses—Nodules are the most common radiographic findings of pulmonary fungal infections.^{48,49} In SOT recipients, aspergillosis should be considered strongly when nodular opacities are seen, because it is the most common cause of nodular pneumonia.^{38,50,51} The halo sign is much less sensitive for aspergillosis in SOT patients than for neutropenic patients with hematologic malignancy.⁵² Specific risk factors that should increase suspicion for pulmonary aspergillosis include retransplantation, reoperation, renal failure, and transplantation for fulminant liver failure in liver recipients^{53–57}; single lung transplants, early airway ischemia, CMV infection, *Aspergillus* colonization, acquired hypogammaglobulinemia, and rejection in lung recipients^{25–28,58–60}; colonization of the respiratory tract with *Aspergillus*, reoperation, CMV disease, and posttransplant

hemodialysis in heart recipients^{32–34}, and graft failure requiring hemodialysis, and prolonged duration of corticosteroid exposure in renal recipients.^{19,30,31}

Endemic fungi can also cause nodular pneumonias in SOT recipients. Although endemic fungi may rarely occur outside of the typical geographic regions, donor-derived infection can be another cause of endemic fungal infections outside of the endemic regions and should always be considered. Histoplasmosis is endemic to the Ohio and Mississippi River Valleys. Patients with exposures to bats, caves, and construction sites are at increased risk. In the southwest United States and parts of Mexico, *Coccidioides* infection may result in nodular pneumonia in SOT patients.^{61,62} Risk factors for coccidioidomycosis among SOT recipients include treatment of acute rejection and African American race.^{62,63}

Nodular pneumonia is the most common presentation of cryptococcosis in SOT patients.^{49,64} Patients receiving calcineurin-inhibitor immunosuppression are at increased risk of pulmonary cryptococcosis.⁶⁵ Other risk factors include corticosteroids, alemtuzumab, and antithymocyte use.^{66–70} Concomitant meningitis may also be a clue to cryptococcal infection.

The agents of mucormycosis, *Fusarium*, and phaeohyphomycoses may cause pneumonia that manifests with nodular opacities. These emerging fungi are most common among liver and lung transplant recipients.⁶ Other risk factors include breaks in skin integrity, chronic respiratory disease, and prior exposure to azoles (that may select for less common fungi).^{71–77}

Pulmonary ground-glass opacities—PJP often presents with diffuse interstitial infiltrates and GGOs on chest imaging. Lung and combined heart-lung recipients are at higher risk for PJP than other organ types.⁴³ Other risk factors for PJP include prolonged corticosteroid courses, antilymphocyte therapy, alemtuzumab therapy, CMV disease, allograft rejection, and lack of PJP prophylaxis.^{78–81} Other fungal infections that may present with GGOs include aspergillosis, histoplasmosis, and coccidioidomycosis.^{46,61,82}

Diagnostic evaluation for pulmonary fungal infections—Diagnosis of pulmonary IFI in SOT patients is difficult, because clinical signs and radiographic changes may be nonspecific. Historically, microscopy of clinical specimens from sputum or bronchoscopy has been useful, specifically for diagnosis of PJP.⁸³ Culture of clinical specimens remains an important method of diagnosis, but many fungi are difficult to grow in culture, and thus, the utility in establishing a diagnosis is limited.^{84,85} Even when there is growth on culture, there may be difficulties in identification on the basis of macroscopic and microscopic morphologic characteristics.

Serologic testing has become a useful adjunct for diagnosing pulmonary IFI in SOT recipients. Serologic testing is used frequently for cryptococcosis, histoplasmosis, aspergillosis, and coccidioidomycosis.⁸³ Serum cryptococcal antigen testing can detect both *Cryptococcus neoformans* and *Cryptococcus gattii*; the serum test has a relatively high sensitivity for detecting cryptococcal meningitis but has a lower diagnostic yield for isolated pulmonary cryptococcosis in SOT patients (approximately 50%).⁸⁶ *Histoplasma* urine

antigen testing has a sensitivity of 92% for patients with disseminated disease, 80% with diffuse pulmonary disease, 34% with subacute pulmonary disease, and 14% with chronic pulmonary disease.^{87–89} The antibody test for *Coccidioides* may be positive in 50% to 70% of patients with pneumonia and can also be falsely positive in the setting of histoplasmosis.^{90,91}

Serum or BAL galactomannan testing may aid in the diagnosis of aspergillosis, but the sensitivity and specificity have not been reliable in SOT patients. For example, a recent meta-analysis showed a sensitivity of 22% and specificity of 84% in SOT recipients.⁹² β -D-Glucan, a nonspecific marker of fungal infection, was found to have a marginal positive predictive value when used in lung transplant patients, although the negative predictive value was high.⁹³

Thus, despite laboratory advances, the clinical presentation, chest imaging, and clinical suspicion on the basis of risk factors and epidemiology are essential to the diagnosis of pulmonary IFI. If an SOT recipient presents with fever, cough, and chest imaging concerning for fungal pneumonia, relevant serologic studies should be obtained early in the process. In addition, bronchoscopy should be considered early in the process.

Central Nervous System Fungal Infections

Fungal infections of the central nervous system (CNS) in SOT patients are associated with significant mortality, necessitating careful evaluation of the patient with suspected CNS infection. IFIs may cause meningitis, brain abscesses, and frontal lobe destruction associated with sinus disease (Table 4). Patients may present with headache, neck stiffness, focal neurologic deficits, altered mental status, somnolence, cranial nerve palsy, or seizures; they may not have fever. The most common fungal infection of the CNS in SOT patients is cryptococcal meningitis, occurring in 0.2% to 5% of SOT patients.⁶⁴ Less commonly, *Candida* species, molds, and endemic fungi can infect the CNS and may result in a variety of lesions on brain imaging.

Meningitis—Cryptococcal meningitis may present with minimal abnormalities on brain imaging particularly in early disease, although later in the disease process meningeal enhancement is expected, along with gelatinous pseudocyst formation in the basal ganglia and findings of hydrocephalus.⁹⁴ In advanced disease, cryptococcomas may be seen, particularly with *C. gattii* infection.^{94,95} Lumbar puncture (LP) should be performed when symptoms of meningitis are present. It is of critical importance that an opening pressure be measured when performing the LP, because elevated intracranial pressure is associated with poor outcomes.⁶⁴ Cerebrospinal fluid (CSF) testing should include measurement of cell counts, protein, glucose, as well as aerobic/anaerobic cultures, mycobacterial culture, fungal culture, and cryptococcal antigen testing. The CSF cryptococcal antigen assay is more sensitive and specific than fungal culture or India ink staining.^{65,96,97} A serum cryptococcal antigen assay has a sensitivity approaching 90% for detection of CNS disease and can be sent as an adjunct.⁹⁷

Rarely, endemic fungi including *Coccidioides* and *Histoplasma* cause meningitis, with headache, altered mental status, and minimal changes on brain imaging.^{94,98–100} Serologic

testing is often required to diagnose *Coccidioides* meningitis. The detection of *Coccidioides* antibodies in the CSF is nearly as specific as recovery of the organism on culture; alternatively, this diagnosis can be inferred from CSF with a lymphocytic pleocytosis in the setting of known coccidioidomycosis.¹⁰⁰ Urine antigen or serum antibody testing is often required for diagnosing *Histoplasma*. The *Histoplasma* antigen and antibody tests can be tested on CSF, although the sensitivity of the antigen test is estimated to be around 38%, and the specificity around 96%.^{101–103} The serum antibody test for *Histoplasma* has been shown to detect the organism in about 80% of cases (not specifically with CNS disease), although it may be less accurate in the SOT population.^{87,101,104}

Brain abscess—Candidiasis may cause fungal brain abscesses. Typically, there are multiple small abscesses (often <3 mm) at the gray-white junction or perforating arterial zones.⁹⁴ As it is generally from hematogenous spread, risk factors for candidemia should be considered, and blood cultures should be performed. Candidal infections with dissemination to the CNS usually occur within the first 3 months after transplant, in contrast to other IFIs, which tend to occur later after transplant.^{1,8,105,106}

When there is a single large brain abscess, molds including *Aspergillus*, agents of mucormycosis, and dematiaceous fungi should be considered as causes, particularly in the more profoundly immunocompromised SOT recipients.^{107–111} *Aspergillus* can also cause multifocal hemorrhagic lesions with associated infarcts, in addition to nodules.⁹⁴ Endemic fungi, in particular *Coccidioides*, *Blastomyces*, and *Histoplasma*, can also cause abscesses, although it is an uncommon presentation for each of these causes. Aspiration of the abscess is often necessary in order to establish these diagnoses.

Frontal lobe lesions with sinus disease—Frontal lobe lesions should prompt an evaluation of the sinuses as a possible source of fungal infection due to direct extension. Typically, there is evidence of bony erosion on imaging, and the orbits and optic nerves may also be affected. Molds, in particular *Aspergillus* and the agents of mucormycosis, should be considered in these cases.^{112,113} Other molds that may cause rhino-orbital cerebral infection include *Fusarium* and *Scedosporium*. Invasive mucormycosis among SOT patients has been reported to be particularly prevalent in patients who also have diabetes mellitus, renal failure, and prior voriconazole or caspofungin use.¹¹³ Diagnosis is usually made via endoscopic sinus evaluation with histopathologic evaluation and culture of biopsies.

Cutaneous Manifestations of Invasive Fungal Infections

Dermatologic diseases are common in SOT patients. Because of immune suppression and lack of inflammatory response in tissues, the typical morphology of skin lesions may be altered, making diagnosis difficult. Unusual pathogens should always be considered, even when skin lesions appear typical. For example, cryptococcal cellulitis may be indistinguishable from cellulitis caused by pathogens such as *Staphylococcus* or *Streptococcus*. Definitive diagnosis of fungal skin lesions is often made by skin biopsy with routine examination, special staining, and tissue cultures.

Fungal infections are among the most common skin infections in SOT patients and may be present in up to 50% of patients.^{114,115} However, most are superficial infections and are not

described herein. There are several scenarios wherein cutaneous fungal infections may occur: (1) primary skin infections such as tinea infections; (2) primary skin infections caused by opportunistic pathogens, which may remain localized or invade; and (3) secondary skin infections caused by dissemination from other sites. This section reviews skin manifestations of selected invasive mycoses in SOT recipients (Table 5).

Aspergillosis—Cutaneous aspergillosis may present as primary or secondary skin lesions. A recent review of a prospective multicenter aspergillosis database in France identified approximately 1% (15/1410) of patients having cutaneous infections: 5 with primary infection and 10 with secondary infection (cutaneous plus disseminated aspergillosis).¹¹⁶ Of these, 3 were SOT recipients. Primary skin infection with aspergilli may occur as a result of burns, trauma, or infected catheters.^{116–118} Typical skin lesions appear as erythematous papules and plaques. Lesions may become necrotic or develop hemorrhagic eschar.^{116–118} In primary disease, extensive surgical debridement is often required.

Secondary infections usually result from hematogenous spread or direct spread from other foci of infection, both of which are associated with high mortality. Lesions may present as cellulitis, pustules, nodules, subcutaneous abscesses, ulcerations, or hemorrhagic blisters.¹¹⁶ Skin biopsy may show blood vessel involvement and branching, septate hyphae.

Cryptococcosis—Skin involvement occurs in up to 20% of SOT patients with cryptococcosis and may manifest as primary or secondary infection.^{119–122} There may be a variety of lesions, including pustules, papules, purpura, ulcers, cellulitis, superficial granulomas or plaques, abscesses, and sinus tracts.^{119,120,123} Cases of necrotizing cellulitis have also been described in SOT recipients.^{124,125} Cellulitis not responding to routine antibacterial agents should prompt evaluation for cryptococcal infection or other unusual pathogens. Cryptococcal cellulitis is often present in patients receiving systemic corticosteroids or other immunosuppressive therapy and is characterized by prominent erythema and induration; development of blisters or ulcerations may also occur.^{126,127} Skin biopsy for routine examination and culture is the most sensitive test for the diagnosis of cryptococcal skin disease.

Mucormycosis—SOT patients comprise fewer than 10% of patients with mucormycosis.^{128,129} Cutaneous disease is seen in approximately 20% of cases.¹³⁰ Primary cutaneous mucormycosis results from inoculation of the fungus into the skin and often occurs at the site of external catheters.¹³¹ Secondary cutaneous mucormycosis is seen after dissemination from pulmonary sites of infection but is very rare among patients with pulmonary mucormycosis.¹³² Cutaneous mucormycosis typically presents with a necrotic eschar and surrounding erythema.¹³¹ Other less common lesions include cellulitis with necrosis, erythematous macules or nodules, and plaques.^{133,134}

Phaeohyphomycosis—There are more than one hundred species of dematiaceous, or pigmented, fungi that cause human disease. Common causative species in SOT patients include *Alternaria*, *Exophiala*, *Cladophialophora*, and *Ochroconis*.^{5,135} Among transplant patients with phaeohyphomycosis, skin and soft tissue infections are present in most cases.^{5,135} Lesions are frequently on the extremities and result from traumatic inoculation, but

lesions as a result of dissemination are also common. Manifestations are quite variable and may include nodules, cysts, cellulitis, plaques, eschars, and ulcerations.^{5,136} Skin biopsy for routine examination and culture, with special staining (Gomori-Methenamine silver or Fontana-Masson), will identify pigmented fungal forms.

Invasive Fungal Infections Causing a Sepsis Syndrome

SOT recipients often present with a sepsis syndrome but without any localizing symptoms. In these cases, it is important to consider IFIs, particularly candidemia/candidiasis.

Candidiasis is more common among small bowel, pancreas, and liver transplant recipients than among kidney, heart, or lung recipients.⁶ The risk for disseminated candidiasis is also increased in patients who have received prolonged courses of antimicrobials, parenteral nutrition, those who have had a prolonged ICU stay, recent CMV disease, primary graft failure, or early surgical re-exploration, and those with diabetes or on renal replacement therapy.^{137,138} When assessing for candidiasis, at least 2 sets of blood cultures should be obtained, because *Candida* species can be grown on routine blood cultures, although the sensitivity remains around 70% even with newer techniques.¹³⁹ Another diagnostic tool to consider is the β -D-glucan assay, which has a sensitivity of 70% and specificity of 87% among patients with invasive candidiasis.^{140–142}

In addition to candidiasis, another IFI to consider in the setting of a sepsis syndrome is progressive disseminated histoplasmosis (PDH), which may include extrapulmonary infection with gastrointestinal disease, hepatitis, mucosal/skin abnormalities, and hepatosplenomegaly.¹⁴³ The diagnosis of PDH is made frequently with blood or tissue cultures or with urine *Histoplasma* antigen testing, which has a sensitivity of 92% in patients with disseminated disease.^{87–89}

EMPIRIC ANTIFUNGAL THERAPY FOR SUSPECTED INVASIVE FUNGAL INFECTIONS

For suspected IFI in the SOT recipient, empiric antifungal therapy should be considered, especially in patients who have potentially life-threatening conditions (pneumonia, meningitis, or a sepsis syndrome). It is important to evaluate risk factors for IFI and the likelihood of the specific fungal pathogen based on clinical signs and symptoms, radiography, and site of infection. Important considerations when deciding to administer antifungal therapy include current antifungal prophylaxis, institutional resistance patterns, and potential drug interactions and adverse effects.

In the SOT recipient who presents with respiratory symptoms and nodular opacities on chest imaging, it is reasonable to empirically start antifungal therapy after bronchoscopy and cultures have been performed. A third-generation triazole such as voriconazole is reasonable, because *Aspergillus* is the most common fungal cause. An amphotericin B preparation may also be considered, based on the patient's history and risk factors, especially if agents of mucormycosis or endemic fungi are likely. For the SOT patient with respiratory symptoms and GGOs on chest imaging, empiric therapy for PJP with trimethoprim-sulfamethoxazole should be considered if the patient is severely ill. Supportive

risk factors would include chronic high-dose corticosteroids, lack of PJP prophylaxis, and recent rejection.

For patients presenting with meningitis but without mass lesions on brain imaging, empiric therapy for cryptococcosis is not often warranted, as CSF cryptococcal antigen testing can be rapidly performed and definitive diagnosis made quickly. However, if empiric therapy is needed, current treatment guidelines recommend amphotericin B preparations plus flucytosine.⁶⁴ If there are numerous microabscesses suggestive of a disseminated *Candida* infection, then an azole or amphotericin B preparation could be used empirically.¹⁴⁴ Of note, echinocandins do not have adequate CNS penetration and should be avoided when there is CNS IFI.^{145–148} If there is a single large abscess or solid nodules, then amphotericin B would be a reasonable choice until the specific cause is identified.

For patients who present with a sepsis syndrome and no localizing symptoms, candidiasis is the most common IFI, so therapy recommended for candidiasis, such as an echinocandin, may be administered, especially in the critically ill.¹⁴⁴ For suspected PDH, empiric therapy with a lipid amphotericin B preparation may be necessary.¹⁴⁴

SUMMARY

In SOT recipients, IFIs are associated with significant morbidity and mortality, and consequently, are important to identify and treat as early as possible to minimize poor outcomes. Detection of IFIs can be difficult, because presenting symptoms are similar to those of other infections, and available fungal diagnostic techniques are limited. Clinicians often must rely on the patient's risk factors and clinical presentation to aid in diagnosis and management of infection. Knowledge of the epidemiology of IFIs in SOT recipients and clinical presentation patterns may enable clinicians to suspect fungal infections earlier and lead to more rapid diagnosis and appropriate therapy.

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KEY POINTS

- Identification of invasive fungal infections (IFIs) can be challenging, because the signs and symptoms are similar to other infections and diagnostic techniques are limited.
- *Aspergillus* and *Candida* species are the most frequent causes of IFIs in solid organ transplant (SOT) recipients.
- When an SOT recipient presents with pulmonary symptoms, chest imaging should be performed to evaluate for a fungal cause, which typically presents with nodular opacities.
- Because of immunosuppression, typical morphology of fungal skin lesions may be altered in SOT recipients, making skin biopsy an essential step for diagnosis.

Fig. 1.
Timing of IFIs following SOT.

Table 1

Epidemiology of invasive fungal infection in solid organ transplant recipients

Organ Transplanted	IFIs in Order of Decreasing Frequency
Kidney	<i>Candida</i> > <i>Crypto</i> > <i>Aspergillus</i> > Endemic mycoses > Molds > PJP
Liver	<i>Candida</i> > <i>Aspergillus</i> > <i>Crypto</i> > Endemic mycoses > Molds > PJP
Pancreas	<i>Candida</i> > Endemic mycoses > <i>Aspergillus</i> ≈ <i>Crypto</i> > Molds > PJP
Lung	<i>Aspergillus</i> > <i>Candida</i> > Molds > <i>Crypto</i> > PJP > Endemic mycoses
Heart	<i>Candida</i> > <i>Aspergillus</i> > Molds > <i>Crypto</i> > Endemic mycoses > PJP
Small bowel	<i>Candida</i> > <i>Crypto</i> > <i>Aspergillus</i> > Endemic mycoses > Molds > PJP

Abbreviation: *Crypto*, *Cryptococcus*.

Adapted from 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; 50:1101–11; and Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. Transpl Infect Dis 2010;12:220–9.

Table 2

Risk factors for invasive fungal infections by organ type

Organ Transplanted	Risk Factors
Liver ^{15–23}	Increased technical complexity of surgery Prolonged operation time Greater transfusion requirements Roux-en-Y biliary anastomosis Retransplantation Bleeding complications requiring reoperation Hepatic dysfunction Renal dysfunction, especially requiring HD CMV infection HHV6 infection
Lung ^{19,24–28}	Airway colonization with <i>Aspergillus</i> CMV infection Ischemia of the anastomosis Receipt of a single lung transplant Hypogammaglobulinemia Augmented immunosuppression
Kidney ^{29–31}	Diabetes mellitus Prolonged pretransplant dialysis Allograft rejection Tacrolimus Graft failure requiring reinitiation of HD Corticosteroids
Heart ^{1,8,32–34}	Broad-spectrum antibiotics Prolonged duration of antibiotics Central venous catheters ECMO Hemodialysis <i>Aspergillus</i> on BAL Reoperation CMV infection
Pancreas ³⁶	Increased donor age Enteric drainage (rather than bladder drainage) Transplantation after kidney transplantation Preoperative peritoneal dialysis Retransplantation
Small bowel ³⁷	Graft rejection or dysfunction Enhanced immunosuppression Anastomotic disruption Abdominal reoperation Multivisceral transplant

Abbreviation: HD, hemodialysis.

Table 3

Pulmonary invasive fungal infections based on radiographic findings

Radiographic Findings	Causative Fungi
Pulmonary nodules or masses	<i>Aspergillus</i> <i>Histoplasma</i> <i>Blastomyces</i> <i>Coccidioides</i> <i>Cryptococcus</i> Agents of mucormycosis <i>Fusarium</i> Phaeohyphomycosis
Pulmonary GGOs	PJP <i>Histoplasma</i>

Data from Refs. 44–47

Table 4

Central nervous system invasive fungal infections based on presenting signs and symptoms

Presenting Symptoms	Differential of IFIs
Meningitis	<i>Cryptococcus</i> <i>Histoplasma</i> <i>Coccidioides</i>
CNS abscess	<i>Candida</i> <i>Aspergillus</i> Agents of mucormycosis Dematiaceous fungi <i>Coccidioides</i> <i>Blastomyces</i> <i>Histoplasma</i>
Frontal lobe lesions ± sinus disease	<i>Aspergillus</i> Agents of mucormycosis <i>Fusarium</i> <i>Scedosporium</i>

Data from Refs. ^{94,98,100}

Table 5

Cutaneous presentations of invasive fungal infections in solid organ transplant recipients

IFI Cause	Cutaneous Presentations
Aspergillosis	Erythematous papules and plaques Necrotic or hemorrhagic eschar Cellulitis Pustules and subcutaneous abscesses Nodules Ulcers Hemorrhagic bullae
Cryptococcosis	Abscesses Pustules Papules Plaques Purpura Ulcers Cellulitis Sinus tracts
Mucormycosis	Necrotic eschar with surrounding erythema Cellulitis with necrosis Erythematous macules, nodules, or plaques
Phaeohyphomycosis	Nodules Cysts Cellulitis Plaques Eschars Ulcerations

Adapted from Virgili A, Zampino MR, Mantovani L. Fungal skin infections in organ transplant recipients. *Am J Clin Dermatol* 2002;3:19–35, with permission; and Lima AM, Rocha SP, Reis Filho EG, et al. Study of dermatoses in kidney transplant patients. *An Bras Dermatol* 2013;88:361–7.