“Invasive fungal infection” (IFI) is a catch-all term to describe a variety of serious infections caused by diverse fungal organisms including yeasts and molds. These infections affect a broad range of critically ill and immunosuppressed patients.1-3 IFI does not represent a homogenous group of infections; important differences between these infections exist with respect to prevalence, risk factors, presentation, and management strategies. This newsletter will review key points and differences regarding IFI due to some of the more common pathogenic yeasts (e.g., Candida) and molds (e.g., Aspergillus, Mucormycetes). Additionally, an illustrative hypothetical case study will be presented to demonstrate an approach to the diagnosis and management of one type of patient at risk for IFI—namely, a patient who has undergone lung transplant.

IFI Due to Candida Species (Invasive Yeasts)

The most common type of IFI caused by yeast is invasive candidiasis (IC). Candidemia— infection of the blood by the yeast Candida—has been estimated to be the most common cause of health care-associated bloodstream infection.4,5 Candidemia is responsible for substantial mortality, morbidity, and economic impact. It has been associated with an attributable mortality rate of up to 47%,1 and the costs of the infection in the United States have been estimated at upwards of $2 billion annually.6

Epidemiology

Infections caused by Candida species have a wide range of clinical manifestations, ranging from superficial infections to life-threatening invasive diseases.1 Of the many Candida species that cause invasive disease, C. albicans is most common overall, followed by C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei.1 These non-albicans species combined now account for about 50% of all cases.1 It’s important to note the prevalence of non-albicans species because strategies for managing IFI due to Candida may vary by species,1 and there is evidence to suggest that several non-albicans species are associated with poorer outcomes.7,8 A photomicrograph of C. albicans is shown in Figure 1.

Risk Factors

The increasing incidence of IC is largely a consequence of modern advances in medical therapeutics, and many of the risk factors that predispose patients to IFI due to Candida are due to these advances.1-6 These risk factors include exposure to broad-spectrum antibiotics, use of central venous catheters (CVCs), parenteral nutrition, dialysis, corticosteroid use, Candida colonization, severity of illness, recent major surgery (particularly abdominal), and necrotizing pancreatitis.1
Diagnosis
Timely diagnosis is often difficult due to the nonspecific nature of the signs and symptoms of the disease. Traditionally, culture of blood or other specimens collected from the body under sterile conditions has been considered the “gold standard” for diagnosis of IC. However, for many patients, blood cultures are negative due to the lack of culture sensitivity for Candida. Blood, fluid, and tissue cultures are also limited by slow turnaround times (as Candida grows relatively slowly compared with bacteria), and collecting tissue and fluid cultures often requires invasive procedures that could be dangerous or contraindicated for certain patients. To complicate matters further, Candida may colonize body fluids and tissues in large numbers without causing infection. Nonculture assays are emerging and can be used adjunctively with cultures to better diagnose IC and direct antifungal therapy. (These assays are discussed elsewhere in the myc/IFI program.)

Management
The Infectious Diseases Society of America (IDSA) provides clinical practice guidelines for the management of candidemia and other forms of IC. The most recent iteration of these guidelines was published in 2016. Management of candidemia is complicated by the diagnostic challenges alluded to above, the potential for Candida dissemination to other body sites, and the variety of possible treatment approaches.

IFI Due to Aspergillus or Mucorales (Invasive Molds)
IFI due to molds is distinct from that caused by yeasts in many ways—including which patients are at greatest risk as well as appropriate diagnostic approaches and management. These invasive mold infections can have a substantial impact on the patient populations at greatest risk. In a single-center retrospective study, 13% of patients who underwent allogeneic stem cell transplant developed an invasive mold infection within 12 months post-transplant. In a study of stem cell transplant recipients, the 12-month survival rate for patients who developed invasive aspergillosis (IA) was 25%. Another study indicated that the 12-month survival rate was higher for solid organ transplant (SOT) recipients, at 59%. This section outlines key information related to IFI due to molds, with a focus on Aspergillus.

Epidemiology
Increased use of prophylaxis against Candida has also contributed to an increased incidence of invasive molds (primarily Aspergillus) as the leading cause of IFI in many patient populations. In the same manner, prophylaxis against Aspergillus has reduced the incidence of Aspergillus infections but has led to an increased incidence of rare molds such as Mucorales.

Aspergillus is the most commonly identified pathogenic mold, and Aspergillus fumigatus is the most common species. Aspergillus can be found in soil, water, food, and air, but individuals with normal immune systems rarely develop disease from these exposures. However, when Aspergillus spores are inhaled by patients with weakened immune systems, the mold can invade the lungs or sinuses and cause invasive aspergillosis. Aspergillus also can be acquired through the skin by trauma or surgery. From these sites, the infection may spread to the brain or other organs. As with IA, invasive mucormycosis also occurs primarily via inhalation of fungal spores present in the environment, but also can result from trauma to the skin. Photomicrographs of A fumigatus and a member of the Mucorales order of rare molds are shown in Figure 2.

Risk Factors
Individuals at risk for developing IA include patients with prolonged neutropenia, allogeneic stem cell and SOT recipients, those receiving corticosteroid therapy, patients with advanced acquired immunodeficiency syndrome (AIDS), and patients with chronic granulomatous disease. The most common risk factors for invasive mucormycosis overlap somewhat and include prolonged neutropenia, corticosteroid therapy, uncontrolled diabetes, metabolic acidosis, and penetrating trauma or burns.

Diagnosis
As with IFI due to Candida, most signs and symptoms of invasive mold infection are nonspecific, and collecting cultures often requires invasive procedures that could be challenging for critically ill patients. Diagnosis has traditionally been based on cultures, histology, and imaging, but rapid nonculture diagnostic tests are increasingly being used.

Management
The IDSA provides clinical practice guidelines for the management of IA. Guidelines for the management of invasive mucormycosis have been put forward jointly by the European Society for Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology. Both guidelines highlight the fact that management strategies are highly dependent on patient type, individual patient characteristics, and history of antifungal treatment.
Hypothetical Case Study: Brandon
A Patient Who Develops IFI Following Lung Transplant

Introduction
IFI is one of many risks that SOT recipients face post transplant. IFI is a major cause of morbidity and mortality in this patient population.\textsuperscript{11} The incidence and type of IFI vary by the type of organ transplant and by transplant center. A 5-year prospective multicenter study showed that IC and IA were the most common types of IFI in SOT patients.\textsuperscript{11} The same study found a 12-month survival rate of 59\% for SOT recipients who developed IA.\textsuperscript{11}

Among lung transplant recipients, IA is the most prevalent IFI.\textsuperscript{11,17} In fact, in the multicenter study mentioned above, IA represented 44\% of all IFI cases in lung transplant recipients,\textsuperscript{11} and 78\% of IA cases were limited to the lungs.\textsuperscript{11} The following hypothetical patient case illustrates one approach to the diagnosis and management of a patient who has received a lung transplant and develops an IFI.

Patient Profile and Medical History
Brandon is a 45-year-old man who received a bilateral lung transplant. He experienced no complications during his transplant surgery and was discharged from the hospital 11 days after the procedure. Due to his immunosuppressed state, Brandon was placed on an oral antifungal as well as antiviral prophylaxis, in addition to an antibiotic. His outpatient immunosuppressant regimen included 2 immunosuppressant agents and an oral steroid.

Six months after his transplant, Brandon began experiencing steroid-resistant rejection, so his doctor prescribed additional immunosuppressive therapy to treat and prevent further graft rejection. However, the patient continued rejection (refractory acute rejection).

Because his acute rejection continued despite additional immunosuppressive therapy, Brandon’s doctor prescribed a monoclonal antibody to bolster his immunosuppressive regimen. Fifteen days after receiving the monoclonal antibody, Brandon began experiencing shortness of breath, nausea, and vomiting while at home. His wife brought him to the emergency department (ED) when he began to experience chest pain on deep inhalation. In the ED, he presented with a fever of 101.3°F, and serum chemistry revealed acute kidney injury. He was then admitted to the hospital for additional testing.

Assessment and Diagnosis
In the hospital, Brandon received an extensive workup that included a chest x-ray, computerized tomography (CT) scan, bronchoscopy with bronchoalveolar lavage (BAL) fluid collection, and a lung tissue biopsy. The chest x-ray revealed an irregular opacity in the right upper lung (Figure 3). The CT scan clearly confirmed the lesion, including evidence of cavitation (Figure 4). Due to these results, the infectious disease (ID) physician was concerned about possible breakthrough IFI despite Brandon’s antifungal therapy, as well as infections due to other possible nonfungal pathogens. The ID physician started broad-spectrum antimicrobial therapy, which included a switch from the oral prophylactic antifungal that Brandon was previously taking to an intravenous (IV) broad-spectrum antifungal agent.

A potassium hydroxide (KOH) test of the biopsied lung tissue was performed on the same day and produced a positive result, confirming that mold was present in the lungs. The microbiology lab cultured the tissue and, after 2 days, the culture grew a mold. Based on the appearance of the mold under the microscope, the care team made a diagnosis of IFI due to \textit{A fumigatus}.

(continued on page 4)
Hypothetical Case Study: Brandon
A Patient Who Develops IFI Following Lung Transplant (cont’d)

Management and Patient Response

After the diagnosis of IA was confirmed, the ID physician worked with the rest of the care team to assess the treatment plan. The broad-spectrum IV antifungal agent was continued, and, in conjunction with the transplant surgeon, the care team decided to reduce Brandon’s immunosuppressive regimen. After a week of IV mold-active antifungal therapy, Brandon began to show signs of clinical improvement, and his fever resolved. He experienced nausea during this time, which was treated with an antiemetic agent. He also experienced headaches, which prompted additional radiographic imaging of his head to ensure the infection did not involve the sinuses and that it had not spread to the brain. The imaging showed no evidence of sinus or brain involvement.

Outcome

After several more days of IV antifungal therapy, Brandon’s kidney function and breathing improved enough for him to be discharged from the hospital. His antifungal medication was switched to an oral formulation to facilitate continued treatment on an outpatient basis. The pharmacy department and the case manager worked with the ID physician to ensure that Brandon would be able to access and afford the oral antifungal medication as an outpatient. Additionally, the health care team provided Brandon with education about his disease prior to his discharge. He continued to follow up regularly with both the transplant and ID teams to ensure the health of his transplant and the continued improvement of his fungal infection.

After 3 months of oral antifungal therapy, improvement in Brandon’s symptoms and follow-up chest imaging was evident (Figure 5). However, because of concern about the potential for relapse of infection given his overall highly immunosuppressed state, he was continued on oral antifungal therapy for 12 months.

Conclusion

IFI comprises a diverse group of fungal pathogens affecting a diverse patient population. The hypothetical patient case presented here represents just one possible presentation of IFI and one patient type at risk for infection. Awareness of IFI in its many forms, presentations, and risk factors is important for the entire team that cares for critically ill and immunosuppressed patients. In Brandon’s case, many different health care providers were involved in identifying his infection and coordinating his care. The transplant team, pulmonary service, ID physician, pharmacists, and case managers all collaborated to foster a successful recovery.

Figure 5. Follow-up CT scan after 3 months of treatment, showing marked improvement.

References


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