Diagnosing Fungal Infections in Neutropenic Patients

Alison Gardner, RN, CNS, PhD

Fungal infections are among the most serious complications in neutropenic patients. A major problem that has compromised management of fungal infections is healthcare professionals’ inability to recognize the infections when they occur. No adequate diagnostic tools exist to detect many of the fungal infections. Early diagnosis of disseminated candidiasis is a challenge because only 35%–50% of neutropenic patients have positive blood cultures (Bodey, 1997), and radiologic tests have low specificity in that patient population. For example, a routine chest x-ray can be negative, yet a computed tomography (CT) scan of the chest can be positive for pneumonia the next day. Therefore, fungal infections often are advanced before diagnostic confirmation; thus, overall outcomes are poor. A great effort has been invested in developing serologic tests to detect circulating antigens of fungi.

A study of the epidemiology of sepsis revealed that the annual number of cases of sepsis caused by fungal organisms increased 207% between 1979 and 2000 (Zaoutis et al., 2005). The increase in invasive fungal infections is related to more people receiving immunosuppressive therapy for hematologic malignancies, allogeneic hematopoietic stem cell transplantation, and broad-spectrum antibiotics. Invasive therapies such as central venous catheterization, mechanical ventilation, parenteral nutrition, and gastrointestinal procedures also have contributed to an increase in fungal infections.

Candidiasis

Candida species are the leading cause of invasive fungal infections in hospitalized patients and the fourth most common isolate recovered from cases of nosocomial blood stream infections in the United States. Recent data from the Surveillance and Control of Pathogens Epidemiologic System regarding nosocomial bloodstream infections in U.S. hospitals identified a crude mortality rate of 40% for nosocomial candidemia, with 38% of the deaths directly attributable to the underlying disease (Wenzel & Edmond, 2001). Most bloodstream infections with Candida species are caused by Candida albicans, Candida glabrata, Candida tropicalis, or Candida parapsilosis (Fridkin, 2005). The remaining infections tend to be caused by Candida krusei, Candida lusitaniae, or Candida guilliermondii. All four of the major species produce biofilms that can form on central venous catheters. Antifungal drugs have a reduced ability to penetrate the biofilms and eradicate the organisms. Candida parapsilosis also can colonize skin, leading to nosocomial spread by the hands and persistence in hospital environments. Candida infections often involve disease outside the bloodstream. For example, disease may spread from the gastrointestinal tract to catheters and then to other organs. Patients with hepatosplenic candidiasis will be febrile and have abdominal pain and hepatosplenomegaly. Serum alkaline phosphatase levels usually are elevated greatly, disproportionately to other liver function tests. Hepatosplenic candidiasis can be diagnosed by CT scan or magnetic resonance imaging of the abdomen, which reveals multiple lesions in the liver or spleen. Treatment for the infection requires two to three weeks of therapy before patients show any response. The use of prophylactic fluconazole has greatly reduced the incidence of hepatosplenic candidiasis. Pulmonary nodules also can be detected by CT scan, and fungal skin lesions can be diagnosed by skin biopsy. Candida albicans accounts for approximately 50% of the cases of hematogenously disseminated candidiasis.
followed by Candida glabrata, Candida parapsilosis, and Candida tropicalis, each of which accounts for approximately 10%–25% of cases (Spellberg, Filler, & Edwards, 2006). In summary, candidiasis will remain prevalent in immunosuppressed patients because of more intensive chemotherapy regimens. It continues to be a cause of iatrogenic and nosocomial infections because of prolonged stays in intensive care units, parenteral nutrition, burns, gastrointestinal and cardiac surgery, treatment with broad-spectrum antibiotics, and central venous catheters.

Mold Infections

Two other types of fungal infections are from the molds Aspergillus and Fusarium. They are not as prevalent as Candida infections, but mortality rates can be as high as 80% (Fridkin, 2005). The infections are found predominantly in neutropenic patients.

The most common species of Aspergillus that cause infections are fumigatus, flavus, and terreus. The gold standards for the diagnosis of invasive aspergillosis are either positive results of a blood culture (rare) or positive biopsy specimens.

Sequential thoracic CT scanning is a standard method used in the diagnosis of invasive aspergillosis. Aspergillus infections have a propensity to invade blood vessels, causing hemorrhage and necrosis. Early lesions appear as small, round, dense areas located in the lung periphery. The CT scan halo sign (see Figure 1), described as a halo surrounding a fungal nodular infiltrate, occurs early in the course of invasive aspergillosis. The halo sign has been reported to be the first reliable sign of fungal infection with a high specificity (93%) but a low sensitivity (Weisser et al., 2005). The halo sign signifies edema or hemorrhage, but absence of the halo sign does not mean that a patient does not have a fungal infection. In a study of 25 neutropenic patients, Caillot et al. (2001) found that the CT scan halo sign occurred early in the diagnosis of invasive pulmonary aspergillosis but in most cases had a duration of less than five days. Seventy-five percent of initial CT scan halo signs disappeared within a week after diagnosis of invasive pulmonary aspergillosis, and 70% of patients had negative cultures from bronchoscopy (Caillot et al.).

Cavitation or necrosis is demonstrated by an air-crescent sign (see Figure 2), which occurs later in the course of the disease and usually is noted after bone marrow recovery. Fever, chest pain with deep inspiration, and hemoptysis are common clinical symptoms of pulmonary aspergillosis, and antifungal therapy should be initiated immediately.

Serologic tests for detecting aspergillosis have been investigated. The cell wall antigen that has been studied most intensively to date is galactomannan, a polysaccharide that encases cells and is secreted by growing hyphae. Galactomannan test results are interpreted as positive when an optical density index of equal to or greater than 0.5 is reached during two consecutive measurements (Marr & Leisenring, 2005). The test accurately detects galactomannan in the blood, and the results are used to estimate the probability that aspergillosis infection is present. Additional diagnostic testing, such as CT scanning, may be performed for patients who test positively for galactomannan to determine the presence of active infection. However, the galactomannan test may be positive five to eight days before chest CT scanning shows any evidence of infection. Patients who are neutropenic or have received antifungal prophylaxis can have false-negative galactomannan levels, and the use of the antibiotic piperacillin-tazobactam can result in false-positive levels (Weisser et al., 2005).

Another serologic test, β-D-glucan, is useful in detecting aspergillosis, as well as candidiasis, fusariosis, and trichosporonosis, another type of fungal infection. Absence of a positive β-D-glucan finding had a 100% negative predictive value, and the specificity of the test was 90% for a single positive test result and greater than 96% for more than two sequential positive results (Odabasi et al., 2004). The test recently was approved for use in the United States but is not available in all institutions.

Fusarium species are another type of mold whose infection has a rapid clinical course and high mortality rate of approximately 80%. The infections occur predominantly in immunocompromised patients such as bone marrow transplant recipients and those with acute leukemia. The organisms are found in the air and soil and are common plant pathogens. The predominant site of origin is the respiratory tract, although skin and nails can be portals of entry (Bodey, 2000). Some infections originate in the sinuses, producing circumoral erythema and retro-orbital pain, and may progress to endophthalmitis.

Like Aspergillus, Fusarium species have a propensity for invading blood vessels, causing thrombosis and infarction. Fusarium tends to disseminate more frequently than Aspergillus. Dissemination following sinus or pulmonary aspergillosis occurs in about 30% of cases, whereas Fusarium infection dissemination occurs in about 75% of cases (Bodey, 1997). Unlike Aspergillus, Fusarium can be cultured in the blood in about 70% of patients. Skin lesions are uncommon with Aspergillus but occur in about 75% of patients with disseminated Fusarium infection. Most patients develop multiple painful skin lesions. The most common lesion is a sharply demarcated black eschar surrounded by a grayish halo (see Figure 3). Organs involved in disseminated fusariosis include the lungs, liver, kidney, spleen, and brain (Fridkin, 2005). Surgical debridement or excision of infected tissue may be necessary. In
neutropenic patients, recovery of neutrophils is the critical factor for recovery. Figure 4 provides a summary of the most important criteria for detecting fungal infections. The figure is not meant to be a comprehensive list but serves as a guideline to assist in the early detection of fungal infections.

Management of Fungal Infections

Because fungal infections are so difficult to diagnose and because outcomes for invasive disease are poor, management is difficult. Many patients are treated preemptively when there is persistent fever and/or signs and symptoms of possible fungal infection. The expense and toxicity of antifungal therapy make that approach controversial.

The Infectious Diseases Society of America recommends that neutropenic patients with cancer who have persistent fever longer than three to five days while on broad-spectrum antibiotics should initiate antifungal therapy (Hughes et al., 2002). Amphotericin B is the drug of choice. Lipid formulations of amphotericin B (AmBisome®, Astellas Pharma US, Inc., Deerfield, IL) and amphotericin B lipid complex (Abelcet®, Enzon Pharmaceuticals, Inc., Bridgewater, NJ) allow higher doses of amphotericin to be administered with less drug-related toxicity. Abelcet has been associated with more infusion-related reactions and increases in serum creatinine, whereas AmBisome has been associated with more liver toxicity as demonstrated by elevation of liver enzymes (Fleming et al., 2001). Not all Candida species are sensitive to amphotericin. Candida lusitaniae has been found to be resistant to the drug, and Candida krusei often demonstrates decreased susceptibility to amphotericin. The drugs also are useful in treating the mold infections aspergillosis and fusariosis.

The azoles have improved the prognosis of fungal infections. Fluconazole and itraconazole are used frequently for prophylaxis of Candida infections, but Candida krusei and many Candida glabrata isolates are resistant to the drugs (Spellberg et al., 2006). Voriconazole is more effective than fluconazole for all Candida species and also is used for aspergillosis infection. Voriconazole has been associated with visual hallucinations in approximately 30% of patients. Posaconazole is a new azole recently approved by the U.S. Food and Drug Administration for prophylaxis of invasive Aspergillus and Candida infections for immunocompromised patients older than 13. Caspofungin and micafungin are in a class of drugs called echinocandins and are excellent for disseminated candidiasis, esophageal candidiasis, and aspergillosis. In addition, caspofungin has a low toxicity profile.

Antifungal drug combinations have been studied in recent trials. Caspofungin plus amphotericin B lipid complex (Kontoyiannis et al., 2003) and caspofungin plus voriconazole (Marr, Boeckh, Carter, Kim, & Corey, 2004) have shown modest improvement in fungal infections as compared to single-drug therapy. Treatment for fungal infections should be continued for at least 14 days (Spellberg et al., 2006). Colony-stimulating factors along with white blood cell transfusions have been beneficial in treating fungal infections. Granulocyte macrophage–colony-stimulating factor seems to have more benefit in candidiasis than aspergillosis. Despite advances in antifungal therapy, patients who remain neutropenic fail to respond to therapy. This is true not only for disseminated candidiasis but also for mold infections. Success is not related to dose or duration of antifungal therapy but rather whether the neutrophils recover.

Fungal infections are a major threat to immunocompromised patients. Many inpatient settings now have high-efficiency particle filters in all rooms for severely immunosuppressed patients, particularly hematology and blood and bone marrow transplant patients. The filters reduce aspergillosis infections in that patient population (Hahn et al., 2002).

Some progress has been made in developing reliable diagnostic tests, but the inability to diagnose fungal infections quickly and definitively remains a major obstacle to successful management. Also, the number of resistant fungal organisms is growing. Patients are receiving more intensive chemotherapy regimens with the hope of cure. Unfortunately, some

Figure 3. Black Eschar Lesions of Fusarium Infection

Figure 4. Diagnostic Criteria for Fungal Infections

Note. Based on information from Bodey, 1997, 2000; Caillot et al., 2001.
regimens cause prolonged neutropenia, which places patients at higher risk for developing fungal infections. In addition, more patients are treated in outpatient settings, and fungal spores are greater in the natural environment than in most hospital environments. For all of these reasons, an increase has occurred in patients developing these serious fungal infections.

**Author Contact:** Alison Gardner, RN, CNS, PhD, can be reached at agardner@mdanderson.org, with copy to editor at CJONEditor@ons.org.

**References**


