Aspergillus Pneumonia in Adult Patients With Acute Leukemia

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**Aspergillus** pneumonia often is a fatal consequence of prolonged neutropenia in patients with acute leukemia. Despite prompt diagnosis and adequate antifungal therapy, mortality remains high among these patients. Recognizing early signs and symptoms, as well as risk factors, is the key to reducing morbidity and mortality.

Most people are commonly exposed to Aspergillus, a fungal organism that is present in the soil; however, disseminated and invasive forms occur most often in those who are immunocompromised (Franquet, Giménez, & Hidalgo, 2004). Aspergillus pneumonia is a potentially fatal consequence of prolonged neutropenia caused by acute leukemia and can be difficult to treat despite prompt diagnosis and adequate antibiotic therapy (Reichenberger, Habicht, Gratwohl, & Tamm, 2002). Although increasing supportive care has successfully extended life during prolonged neutropenia because of myelosuppressive drugs, this also has led to greater susceptibility to infections in patients, with an associated rise in morbidity and mortality.

**Aspergillus**

Aspergillus survives well in air, dust, and moisture within healthcare facilities. Any disruption of dust or air within a hospital or healthcare facility can cause a release of airborne fungal spores. Absorbent building materials, such as wallboards, function as an ideal area for fungal spores to accumulate (Centers for Disease Control and Prevention, 2003). Therefore, the occurrence of Aspergillus has been directly related to building hygiene and construction work. Construction increases the concentration of Aspergillus conidia in the air, and inhaled spores can lead to colonization and subsequent infection, otherwise known as invasive aspergillosis (IA) (Reichenberger et al., 2002).

**Invasive Aspergillosis**

Aspergillus fumigatus is the most commonly found species in Aspergillus pneumonia (Latge, 1999). In a study of more than 4,000 patients with acute leukemia, the incidence of Aspergillus pneumonia was 6%, of whom 39% died (Pagano et al., 2010). An intact immune system is essential to successfully combat a fungal infection. Several factors adversely affect immune defenses in patients with hematologic disease and IA, including hematologic malignancy and neutropenia associated with chemotherapy agents used in induction, consolidation, and conditioning regimens (Safdar, 2008). Prolonged neutropenia remains the greatest risk factor in developing Aspergillus pneumonia. An absolute neutrophil count (ANC) of less than 500 (neutropenia) for greater than 20 days is the strongest predictive factor in diagnosing Aspergillus pneumonia (Reichenberger et al., 2002).

In patients with leukemia, damaged white blood cells impair immune response, allowing for fungal colonization (Pagano et al., 2010). Tumor necrosis factor (TNF) and macrophage inflammatory protein (MIP) are important in the defense against fungal infections (Reichenberger et al., 2002). TNF is a cytokine that is naturally present in the body and causes cell death by apoptosis. MIP facilitates neutrophil and macrophage chemotaxis, as well as neutrophil and macrophage activation against invading organisms (Gao et al., 1993). In patients with neutropenia, TNF and MIP are reduced, lowering the body’s natural defenses (Reichenberger et al., 2002).

**Diagnosis of Invasive Aspergillosis**

The signs and symptoms of Aspergillus pneumonia often are hard to distinguish from those of bacterial infections. Patients on adequate antibacterial therapy who remain persistently febrile should be evaluated for fungal pneumonia. Aspergillus infections tend to occur in the third week of neutropenia or later (Ferrara, MacDougall, & Gallagher, 2011).

Despite severe fungal infections, patients often remain afebrile with normal radiographic testing (Safdar, 2008). Therefore, radiologic imaging is of utmost importance in the diagnosis of Aspergillus.
pneumonia. Plain chest radiography is too insensitive for diagnosis of IA. Computed tomography (CT) is the cornerstone of testing for detecting aspergillus pneumonia. CT findings for aspergillus pneumonia generally include a macronodule or the “halo sign,” in which the nodule-like center is the dense fungal ball and is surrounded by a “ground glass attenuation,” consistent with necrosis and hemorrhagic infarction (Saftdar, 2008). A CT scan with pulmonary nodules or areas of consolidations is suspicious for IA, and the patient should be treated with antifungal therapy until proven otherwise (Reichenberger et al., 2002).

Serologic testing for IA is based on the detection of fungal-specific antigens, such as galactomannans and β-glucans. Sensitivity of antigen testing is dependent on the spread of disease; sensitivity of circulating antigens is significantly lower in IA than in disseminated disease. Sensitivity also is significantly compromised in patients being treated for fungal infections and in patients receiving antifungal prophylaxis. False positive tests also have been associated with the use of piperacillin and tazobactam combination (Saftdar, 2008). In addition, antibody testing is not useful in neutropenic patients because of an impaired antigen presentation and lymphocyte dysfunction (Reichenberger et al., 2002).

Polymerase chain reaction (PCR) is becoming a promising diagnostic test when used in conjunction with enzyme-linked immunosorbent assay and CT findings. In PCR testing, IA is diagnosed by the detection of aspergillus DNA. PCR targets several regions of the aspergillus fumigatus genome. PCR also may be more sensitive than cultures (blood or bronchoscopy) when testing for aspergillus (Fletcher, Barton, Verweij, & Evans, 1998).

Bronchoscopy with bronchoalveolar lavage (BAL) is an established tool for the diagnosis of aspergillus pneumonia. By using BAL or bronchial washings by culture, a diagnosis can be made with the detection of mold hyphae (Reichenberger et al., 2002). Microbiologic evidence should be used when available, and includes culture or microscopic evaluation (cytology or histopathology) of sputum specimens, BAL washings, transbronchial biopsies, fine-needle pulmonary aspirations, and open lung biopsies (Aliff et al., 2003). Tissue examination must be performed for definite diagnosis or exclusion of IA, which enables the distinction between colonization and invasive infection to be made (Reichenberger et al., 2002).

Treatment for Invasive Aspergillosis

Although various treatment options exist (see Table 1), the response rate to most first-line antifungal drugs is less than 50% (Kontoyiannis et al., 2003). Even when patients are treated adequately with pharmaceutical therapy, morbidity and mortality remain high (Reichenberger et al., 2002). The most important factor in improving patient outcomes is shortening the length of neutropenia so that the body’s defenses can adequately attack these organisms. However, clinical and radiographic signs of pulmonary infection may worsen in the immediate period of count recovery because of the increased inflammation associated with granulocyte recovery (Aliff et al., 2003).

Amphotericin

The gold standard of treatment in aspergillus pneumonia has been amphotericin B (AMB). AMB is an ergosterol-binding polypeptide that leads to the disintegration of the fungal membranes (Reichenberger et al., 2002). However, its clinical use has been associated with suboptimal benefit, and administration-related fever and chills can occur (Saftdar, 2008). Despite adequate prophylaxis, some common side effects of AMB include electrolyte imbalance and progressive renal failure (Reichenberger et al., 2002).

Lipid-bound formulations of amphotericin show the same microbiologic activity and are fairly well tolerated. These agents are less nephrotoxic and can be given at higher doses. Lipid-bound formulations are recommended in patients with IA who have severe side effects or fail to respond to traditional amphotericin therapy (Reichenberger et al., 2002). However, studies have revealed that previous azole therapy may induce resistance to amphotericin by reducing the amount of ergosterol in the fungus membrane (Reichenberger et al., 2002). The amphotericin is unable to adequately remove the outer layer of the fungal ball and, therefore, unable to disintegrate the fungus.

Other Antifungals

Although azoles have a small role in clinical care, they inhibit a late step in the ergosterol synthesis leading to the disintegration of the fungal cell membrane (Reichenberger et al., 2002). Itraconazole has been shown to be as effective as amphotericin in patients with IA; however, a poor side-effect profile leads to limited adherence in patients (Reichenberger et al., 2002). Voriconazole is a recently developed triazole that has high activity against aspergillus (Reichenberger et al., 2002). This drug is well tolerated; however, side effects can include visual disturbance, hepatoxicity, and a dermal rash (Reichenberger et al., 2002). When compared to amphotericin, voriconazole has been associated with better clinical outcomes for patients with IA (Saftdar, 2008). Caspofungin, an echinocandin, inhibits cell wall biosynthesis (Kontoyiannis et al., 2003). It has been used in combination with other antifungal agents as salvage therapy for patients with hematologic malignancies (Saftdar, 2008).

Implications for Practice

IA has a mortality rate of 60%-80% among patients with acute leukemia who have undergone bone marrow transplantation (Kontoyiannis et al., 2003). The presence of pleural effusions, use of high-dose steroids at the time of diagnosis, and prolonged administration of steroids also are poor prognostic factors (Saftdar, 2008).

Patients who are at high risk for developing IA should be identified prior to myeloablative therapy. These patients should be placed in isolation and have high-efficiency particulate air filtration during neutropenia. By creating laminar air flow, the amount of contamination with aspergillus conidia leading to the development of IA could markedly decrease (Reichenberger et al., 2002). Patients also should be on prophylactic antifungal therapy prior to initiating treatment or when the patients become neutropenic. Hematopoietic growth factors were not found to decrease the occurrence of IA in patients with acute leukemia (Gurion et al., 2012).

Assessment is key when detecting fungal pneumonia. Vital signs should be monitored frequently, and nurses should look for a fever greater than 38.3°C, a
TABLE 1. Antifungal Treatment Options for *Aspergillus* Pneumonia

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Action</th>
<th>Dosage</th>
<th>Side Effects</th>
<th>Interactions</th>
<th>Effectiveness</th>
<th>Nursing</th>
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| Amphotericin B (AMB) | AMB desoxycholate | Ergosterol-binding polyene that disintegrates the fungal membrane | 0.3–1.5 mg/kg/day; 1–1.5 mg/kg over 4–6 hours every other day once therapy is established; no more than 1.5 mg/kg/day | Fever and chills during infusion, hypokalemia, hypomagnesemia, progressive renal failure, and phlebitis at peripheral IV site | Aspergillus resistance results from altered ergosterol content of fungus membrane. Azole therapy may induce AMB resistance by reducing ergosterol in the fungal membrane. | 33%–54% | • Premedicate patient with 650 mg of acetaminophen and 25 mg of diphenhydramine.  
  • Administer through a central line (ideal).  
  • Educate patient on potential signs and symptoms.  
  • Encourage patient to drink plenty of fluids or use IVF.  
  • Use caution when giving with blood products (if reaction occurs, cannot rule out what caused reaction); confirmed compatibility only with 5% dextrose in water (DSW) IV solution. |
| AMB          | Liposomal AMB             | Ergosterol-binding polyene that disintegrates the fungal membrane | 1–3 mg/kg, can increase to 3–5 mg/kg | Nephrotoxicity and breakthrough fungal infections | Aspergillus resistance results from altered ergosterol content of fungus membrane. Azole therapy may induce AMB resistance by reducing ergosterol in the fungal membrane | 30%–60% | • Premedicate patient with 650 mg of acetaminophen and 25 mg of diphenhydramine.  
  • Administer through a central line (ideal).  
  • Educate patient on potential signs and symptoms.  
  • Encourage patient to drink plenty of fluids or use IVF.  
  • Use caution when giving with blood products (if reaction occurs, cannot rule out what caused reaction); confirmed compatibility only with DSW IV solution. |
| AMB          | AMB lipid complex         | Ergosterol-binding polyene that disintegrates the fungal membrane | 5 mg/kg/day | Nephrotoxicity and breakthrough fungal infections | Aspergillus resistance results from altered ergosterol content of fungus membrane. Azole therapy may induce AMB resistance by reducing ergosterol in the fungal membrane | 42% of patients intolerant or refractory | • Premedicate patient with 650 mg of acetaminophen and 25 mg of diphenhydramine.  
  • Administer through a central line (ideal).  
  • Educate patient on potential signs and symptoms.  
  • Encourage patient to drink plenty of fluids or use IVF.  
  • Use caution when giving with blood products (if reaction occurs, cannot rule out what caused reaction); confirmed compatibility only with DSW IV solution. |
| Azoles       | Itraconazole              | Inhibits lanosterol 14 \(\alpha\)-demethylase, which disintegrates the fungal cell membrane | PO: 400–600 mg daily, with a loading dose of 200 mg TID for 3 days, then 200 mg BID | Poor taste in mouth, nausea, vomiting, diarrhea, heart failure, hepatotoxicity | – | 39%–66% | • Do not administer with antacids.  
  • Administer capsules with meal.  
  • Administer oral solution on an empty stomach.  
  • Divide doses greater than 200 mg/day for BID dosing. |
| Azoles       | Voriconazole              | Inhibits lanosterol 14 \(\alpha\)-demethylase, which disintegrates the fungal cell membrane | PO: 200 mg every 12 hours; no more than 600 mg daily IV: 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours | Visual disturbance, hepatotoxicity, dermal rash, QT prolongation, renal toxicity | Give 1 hour before or after meals | 50%–75% | • Administer 1 hour before or 2 hours after meals.  
  • Watch for renal impairment if given IV. |
| Echinocandins | Caspofungin               | Inhibits the \(\beta\)-d-glucan synthetase, an enzyme that forms glucan polymers of the fungus wall | IV: 70 mg on day 1, then 50 mg/day after; no more than 70 mg/day | Fever, hypotension, diarrhea, infusion reactions, elevated liver enzymes | Use with concurrent cyclosporin may increase caspofungin levels and liver enzymes | 41%–45% | • Check to see if patient is on concurrent cyclosporin.  
  • Watch IV site for thrombophlebitis.  
  • Monitor patient for histamine reaction. |

*Note.* Based on information from Lexi-Comp Online™, 2013; Reichenberger et al., 2002.
heart rate greater than 100 beats per minute, and a new or increasing oxygen requirement. A physical examination should be done every 12 hours minimum for inpatients and at each outpatient contact to assess lung sounds. A meaningful review of systems should inquire about chills, chest pain, dyspnea on exertion, cough, as well as overall weakness and fatigue. These findings will help support the need for additional testing.

Conclusion

Despite adequate diagnostic evaluation, identifying aspergillus pneumonia often is difficult. Unfortunately, even after a definitive diagnosis is made and treatment has begun, the prognosis remains poor. Although several antifungal agents exist, their efficacy alone or in combination is suboptimal (Safdar, 2008), and more than 50% of patients will fail first-line therapy (Kontoyiannis et al., 2003). Patients at risk of developing IA should be identified early in treatment, and preventive actions should be taken prior to initiating myelosuppressive agents in patients with acute leukemia. Persistent and diligent nursing care can save patients’ lives by aiding in early detection and treatment of IA.

References


