Treatment of Aspergillosis in an Immunocompetent Patient: A Multidisciplinary Approach

Tuong-Vi Ho, RN, FNP, PhD, Ali Zalpour, PharmD, BCPS, Carmen D’Amico, RN, MSN, Maria Luzalie Niangar, RN, MSN, Bonnie Gentle, RN, MSN, Menchu Mante, RN, MSN, Rosalie Valdres, RN, MSN, Ashley Watson, RN, MSN, and Tejpal Grover, MD, MBA

Case Study: P.J. was a 69-year-old woman who was referred to a large cancer center for an evaluation of brain and lung masses presumed to be cancerous lesions. During the three months before the referral, P.J. had experienced a gradual 40 lb weight loss, shortness of breath with exertion, chest pain, lip tremor, edema and progressive weakening of lower extremities, overall fatigue, and increasing balance and gait disturbances. Her diagnostic workup revealed aspergillosis in her lungs and brain. This case study reports the process of differentiating between cancer and fungal disease, antifungal treatment modalities used, and the multidisciplinary management approach used in the care of P.J.

P.J. had lived an outdoor lifestyle in a mobile home on a ranch in Texas. She had a history of atrial fibrillation, uncontrolled type 2 diabetes mellitus, hypertension, thrombocytopenia, possible cirrhosis of the liver, and hypothyroidism. She had a brother with a history of renal cancer, a sister with gastric cancer, and another brother with a history of intracranial aneurysm. Her mother had had a benign brain tumor and diabetes mellitus and had died of congestive heart failure. P.J. reportedly had been in good health until three months before she was referred to the cancer center, and she knew of no family history of aspergillosis.

After P.J. experienced an episode of nausea, chills, and chest pain, she was taken to the local emergency department and underwent a complete cardiac workup; myocardial infarction was ruled out. Computed tomography (CT) of the brain revealed a lesion in the left cerebellum. Chest x-ray and CT of the lungs showed cavitated masses. P.J. was believed to have lung cancer with brain metastasis.

She was transferred to the cancer center for further workup of the findings and for treatment of her symptoms. No outside medical records were available during the initial evaluation, and P.J.’s entire medical history was obtained from her and her husband. Her laboratory test values, radiologic studies, and clinical findings on admission are listed Figure 1. After P.J. was stabilized for hyperglycemia, biopsies were done for tissue diagnosis of cancer versus other pathology. Findings from biopsies of her lungs were consistent with those of invasive pulmonary aspergillosis (IPA). Thus, P.J. was transferred to the cancer center with a presumed cancer diagnosis; however, biopsy results confirmed an IPA diagnosis. Her treatment of IPA, including multiple antifungal medications, are discussed later.

A multidisciplinary approach to P.J.’s treatment involved consultations with pulmonary medicine, infectious disease, nephrology, dermatology, neurology, physical medicine and rehabilitation, and nutrition services.
Pathophysiologic Features

The incidence of fungal infection has risen during the past decade with the increased use of antimicrobial agents. Some endemic fungi such as *Aspergillus fumigatus* can cause serious health problems in immunocompromised patients. This fungus commonly is found in soil, plant debris, and the indoor air environment. It releases airborne spores that may become toxigenic if contracted by immunocompromised patients. *Aspergillus* colonizes in the mucus of the bronchus. Multiple tests often are needed before the diagnosis can be confirmed because the infection has nonspecific signs and symptoms, the sputum and blood cultures have very low yield, and serologic tests have a low sensitivity for invasive disease. In addition, patients are often too ill to undergo invasive diagnostic tests or procedures.

*A. fumigatus* has become the most prevalent airborne fungal pathogen, causing severe and usually fatal infections in immunocompromised patients (Latge, 1999). Prolonged neutropenia, extensive corticosteroid therapy, and graft-versus-host disease are important risk factors for the development of IPA. Inhalation is the most common mode of entry for *Aspergillus* spores (conidia). Normally, pulmonary macrophages block the germination of the inhaled spores, preventing the endobronchial proliferation of hyphae that is essential to tissue invasion. If hyphae are allowed to develop, functioning neutrophils usually remove them (Morrison & Lew, 2001). However, if those host defenses are not intact, such as in patients with damaged respiratory epithelium related to radiotherapy, chemotherapy, graft-versus-host disease, or stem-cell transplantation, infection may develop. The inhaled spores attach to the damaged epithelium in the distal alveolar spaces and begin to germinate into angioinvasive filamentous hyphae that produce local tissue damage, hemorrhage, infarction, and coagulative necrosis (Latge). The viable hyphal fragments disseminate to distal sites, leading to hematogenously disseminated aspergillosis.

The central nervous system is the most common target of hematogenously disseminated aspergillosis (Morrison & Lew, 2001), but other sites include cutaneous and naso-orbital regions and blood vessels. Virtually any organ can become infected. The principal pathogenic species, *A. fumigatus* is involved in as many as 80% of all clinical cases (Morrison & Lew).

IPA entered P.J.’s lungs via inhaled spores, which likely had been present in the soil on her ranch and then disseminated to her brain, mimicking cancerous lesions in both locations. Although P.J. did not have cancer, her multiple comorbidities placed her at risk for the disseminated fungal infection.

Clinical Features

Symptoms of IPA include nonproductive cough, pleuritic pain, low-grade fever, hemoptysis, and dyspnea. Dissemination of hyphal fragments of *Aspergillus* to the brain also can cause neurologic symptoms (Denning, 1998), as experienced by P.J.. Those symptoms include weakening of the extremities and balance and gait disturbances.

### Strategies for Diagnosis

Early diagnosis of IPA is important for appropriate and prompt treatment (Raad et al., 2002). Although *A. fumigatus* has become the most prevalent airborne fungal pathogen over the past decade and causes severe and often fatal invasive infections in immunocompromised patients, it remains difficult to diagnose (Hizel et al. 2004). The lack of reliable and rapid diagnostic procedures is a major obstacle in the management of any fungal infection. Histologic and standard microbiologic techniques are important diagnostic tools. Still, the occurrence of false-negative and false-positive results is a persistent problem (Pfaller, Richter, & Diekema, 2005).

### Diagnostic Methods

#### Direct Diagnosis

A definitive diagnosis of IPA must be based on biopsy findings of *Aspergillus* hyphae in lung tissue (Hizel et al., 2004). Direct microscopic examination, perhaps the most successful and cost-effective means of diagnosing fungal infections, provides rapid diagnosis but unfortunately is often difficult and hazardous for patients with neutropenia and thrombocytopenia (Raad et al., 2002). After P.J.’s pulmonary consultation, she underwent bronchoscopy with transbronchial lung biopsy to confirm the diagnosis. P.J. was thrombocytopenic with a platelet count of 67,000; therefore, she received a platelet transfusion prior to the procedure.

#### Culturing

Culturing still is considered the gold standard and frequently is the most sensitive means of diagnosing fungal infections. A culture usually will identify the organism and determine its susceptibility to various antifungal agents. (Pfaller et al., 2005). Unfortunately, culturing can take up to several weeks, and results may not be available to help clinicians choose the appropriate antifungal treatment at the time of initial treatment or admission (Pfaller et al.) At the beginning of P.J.’s treatment, a sputum sample was obtained for bacterial and fungal culturing.

#### Other Methods

Because of the importance of early diagnosis of IPA, which may lead to higher

---

**Clinical Findings**
- 12-lead electrocardiogram: atrial fibrillation, rate 110 beats per minute
- Lung biopsy findings: *Aspergillus fumigatus*

**Laboratory Findings**
- White blood cell count: 15 k/ul
- Absolute neutrophil count: 13.9 k/ul
- Platelets: 67 k/ul
- Serum creatinine: 1 mg/dl
- Blood urea nitrogen: 39 mg/dl
- Bicarbonate: 27 meq/l
- Chloride: 97 meq/l
- Potassium: 4.9 meq/l
- Sodium: 133 meq/l
- Glucose: 502 mg/dl
- Blood and sputum cultures: negative for *Aspergillus fumigatus*
- Glycosylated hemoglobin A1C: 11.2%
- Bicarbonate: 27 meq/l
- Sodium: 23 meq/l
- Chloride: 97 meq/l
- Serum creatinine: 1 mg/dl
- Blood urea nitrogen: 39 mg/dl
- Absolute neutrophil count: 13.9 k/ul
- Platelets: 67 k/ul
- Bicarbonate: 27 meq/l
- Chloride: 97 meq/l
- Potassium: 4.9 meq/l
- Sodium: 133 meq/l
- Glucose: 502 mg/dl
- Blood and sputum cultures: negative for *Aspergillus fumigatus*

**Radionic Findings**
- Chest x-ray: left lower lung mass with hilar adenopathy
- Computed tomography of the lung: left lower lung mass
- Magnetic resonance imaging of the brain: mass, metastatic in nature

---

**Figure 1. Laboratory Values and Radiologic Findings on P.J.’s Admission**
cure rates, newer diagnostic methods are being investigated. The immunogenic properties of fungal organisms have been examined for the presence of fungal antigens and antibodies in biologic fluids (Pfaller et al., 2005). The U.S. Food and Drug Administration has approved the galactomannan assay as an adjunctive test for IPA diagnosis when applied to serum (Hizel et al., 2004). Diagnostic assays that detect fungal nucleic acids by polymerase chain reaction also have been investigated (Musher et al., 2004).

Radiographic Findings

Characteristic findings of IPA on chest CT scanning include a pulmonary nodule of 1 cm or larger in diameter and its associated halo sign. Because the halo sign is short lived, CT must be performed within five days of onset of disease for it to be useful in diagnosis. The halo sign is followed by the "air crescent" sign during the third week of the disease; however, this is considered a late sign and is not useful for providing a prompt diagnosis (Gaillot et al., 2001).

Pharmacologic Treatment

Pharmacologic treatment of aspergillosis includes the selection of an antifungal agent(s) that is capable of penetrating the body organ(s) involved, has the most favorable toxicity profile, has low rates of drug-drug interactions, and has been proven safe and effective in randomized clinical trials. Classic antifungal agents for the treatment of IPA are polyenes, azoles, and echinocandins (see Table 1).

Amphotericin B deoxycholate and its analogs, introduced in the mid-1960s, belong to a group of antifungal agents called polyenes. The fungicidal activity of these agents is achieved by their combining with ergosterol, a steroid present in the cell wall of fungi, thereby increasing the permeability of the fungi to oxidative injury. Amphotericin B has great activity against *A. fumigatus*, even though it has variable activity against other fungal species (Gallis, Drew, & Pickard, 1990). Amphotericin B reaches vital organs such as the liver, spleen, lungs, and kidneys (Christiansen, Bernard, Gold, & Armstrong, 1985) and can produce drug- and infusion-related toxicity. The common dose-related toxic effects of amphotericin B are nephrotoxicity and anemia. Immediate infusion-related reactions are common because of the release of interleukins and can result in hypotension, chills, and tachycardia (Pathak, Pien, & Carvalho, 1998). Several formulations of amphotericin B have been introduced in an attempt to reduce toxic effects. Those modified formulations include amphotericin B colloidal dispersion (Amphotec®, Ben Venue Laboratories, Inc.), amphotericin B lipid complex ( Abelcet®, Enzon Pharmaceuticals, Inc.), and liposomal-amphotericin B (AmBisome®, Gilead Sciences, Inc.), which all show different pharmacokinetics.

The paradigm of IPA treatment shifted with the introduction of azole antifungal agents. Azole agents exert their fungistatic effect by interfering with the enzyme activity of cytochrome P-450, decreasing ergosterol synthesis and thus altering the viability of the fungi.

Voriconazole (Vfend®, Pfizer Inc.), posaconazole (Noxafil®, Schering Corporation), and ravuconazole (investigational agent) are considered second-generation azole agents because they were designed by modification of the chemical structure of itraconazole (Sporanox®, Jansen-Ortho Inc.). These agents have a broad spectrum of activity and long serum half-lives.

Except for oral itraconazole, the absorption of which is pH dependent, the azole agents have good bioavailability and reach effective concentrations in various fluids such as cerebrospinal fluid. One of the major adverse effects of azole agents is hepatotoxicity because their primary metabolism occurs in the liver (Martinez, 2006).

Finally, within the past decade, the echinocandin fungicidal agents such as caspofungin acetate (Cancidas®, Merck & Co., Inc.), micafungin (Mycamine®, Astellas Pharma US, Inc.), and anidulafungin (Eraxis®, Pfizer Inc.) were introduced. Those semisynthetic lipopeptides target the cell wall of fungi by inhibiting the synthesis of beta-1, 3-D-glucan, hence causing osmotic imbalance and damaging the viability of fungi. Echinocandins are active against *Candida* and *Aspergillus* species and have become attractive agents because of their infrequent drug interactions, lower toxicity levels, and less need for monitoring (Martinez, 2006).

In a case report series (Nivoix et al., 2006), the efficacy and safety of a combination of caspofungin plus an azole or amphotericin B were assessed in 17 patients with invasive fungal infections. All of the patients were immunocompromised except one who had documented *A. fumigatus* with probable lung dissemination and acute pancreatitis and was undergoing hemodialysis. When the patient was given a combination of caspofungin and liposomal-amphotericin B, a partial response was achieved, which was defined as a substantial improvement in clinical

Treatment

IPA most frequently is seen in patients with hematologic malignancies who receive high doses of myelosuppressive chemotherapy in preparation for bone marrow transplantation, in patients taking immunosuppressive agents, and in those receiving long-term treatment with glucocorticoids. Mortality from IPA ranges from 30%–80% (Lin, Schranz, & Teutsch, 2001). Surgical debridement and prophylactic medical therapy are possible options to treat and prevent IPA. In 2000, the Infectious Diseases Society of America guidelines recommended specific treatment strategies for IPA. Surgical debridement and drainage were recommended for immunocompetent patients with acute invasive infection. The treatment was deemed sufficient in most patients, with antifungal therapy as a secondary consideration (Stevens et al., 2000). Surgical debridement was beyond the scope of care for P.J. because the infection was walled off in the lung field and therefore not accessible to surgical intervention. Surgery to remove the lesion in P.J.'s brain also was contraindicated. In this setting, surgical intervention is a last resort, reserved for symptomatic patients with mid-line shift or severe edema with increased intracranial pressure.

The use of antifungal medications as secondary prophylaxis for aspergillosis also has been considered. No conclusive data support the use of those agents in immunocompetent patients. However, promising preliminary data support the use of primary and secondary antifungal prophylaxis in patients with hematologic malignancy, especially in bone marrow transplant settings (De Pauw & Donnelly, 2007).
<table>
<thead>
<tr>
<th>AGENT</th>
<th>INDICATION</th>
<th>DOSAGE AND ROUTE</th>
<th>ADVERSE EFFECTS</th>
<th>MONITORING PARAMETERS</th>
<th>DRUG INTERACTIONS</th>
<th>CONTRAINDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoles</td>
<td>Aspergillosis, pulmonary and extrapulmonary, in patients who cannot tolerate amphotericin B or in whom aspergillosis is refractory to amphotericin B therapy</td>
<td>200–400 mg per day. Treatment for life-threatening situations is a loading dose (oral capsules or IV) of 200 mg twice daily for four consecutive doses, followed by 200 mg once daily.</td>
<td>Cardiovascular: congestive heart failure, hypertension, and peripheral and pulmonary edema Hepatic: increased liver enzymes, hepatitis, hepatic necrosis, and cholestasis Dermatologic and hypersensitivity: rash and pruritus Other: gynecomastia</td>
<td>Liver function tests (LFTs), basic metabolic panel (BMP), and signs and symptoms of heart failure</td>
<td><strong>Plasma concentrations of the following are increased by itraconazole:</strong> alfenilin, alprazolam, atorvastatin, budesonide, buspirone, busulfan, carbamazepine, cerivastatin, clofazimine, cisapride, cyclosporine, dexamethasone, diazepam, digoxin, disopyramide, doxetaxel, dofetilide, eletriptan, ergot alkaloids, fentanyl, halofantrine, indinavir, levomethadyl, lovastatin, methylprednisolone, midazolam, nisoldipine, pimozide, quinidine, rifabutin, ritonavir, saquinavir, simvastatin, sirolimus, tacrolimus, triazolam, trimetrexate, verapamil, vinca alkaloids, and warfarin Drugs that increase the plasma concentration of itraconazole: clarithromycin, erythromycin, indinavir, and ritonavir</td>
<td>• Congestive heart failure • Sensitivity to any component of itraconazole • No information is available on the cross-sensitivity of itraconazole with other azoles; it should be used with caution. • Concomitant administration of cisapride, dofetilide, ergot alkaloids, levomethadyl, lovastatin, midazolam, nisoldipine, quinidine, simvastatin, or triazolam</td>
</tr>
<tr>
<td>Itraconazole (Sporanox®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole (Vfend®)</td>
<td>Invasive aspergillosis</td>
<td>6 mg/kg via IV every 12 hours for the first 24 hours, then maintenance dose of 4 mg/kg every 12 hours or 200 mg orally every 12 hours</td>
<td>Visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, respiratory disorders, and elevated LFTs</td>
<td>LFTs and BMP</td>
<td>Drugs that decrease the plasma concentration of voriconazole: carbamazepine, long-acting barbiturates, rifabutin, and ritonavir</td>
<td>• Hypersensitivity to formulation of voriconazole • Concomitant use of astemizole, carbamazepine, cisapride, ergot alkaloids, efavirenz, long-acting barbiturates, pimozide, quinidine, rifabutin, rifampin, ritonavir, and terfenadine</td>
</tr>
<tr>
<td>Voriconazole (Vfend®)</td>
<td>Prophylaxis against invasive Aspergillosis and Candida infections because of hematopoietic stem cell transplantation or hematologic malignancies with prolonged neutropenia</td>
<td>200 mg orally three times a day</td>
<td>Heart rate and rhythm disorders: QT interval prolongation Hepatic and biliary: bilirubinemia and hepatic enzymes increased Body as a whole: general disorders, fever, headache, nausea and vomiting Neutropenia and anemia</td>
<td>LFTs and BMP</td>
<td>Coadministration with the following lowers concentration of posaconazole (avoid use if possible): cimetidine, phenytoin, and rifabutin Coadministration with the following increases plasma concentrations of the following: benzodiazepines, cyclosporine, diltiazem, statins, and tacrolimus</td>
<td>• Hypersensitivity to posaconazole • Coadministration of terfenadine, astemizole, pimozide, cisapride, and halofantrine may result in QT interval prolongation and torsades de pointes. • Coadministration with ergot alkaloids</td>
</tr>
</tbody>
</table>

*Continued on next page*
Table 1. Agents Commonly Indicated for Treatment of Aspergillosis (Continued)

<table>
<thead>
<tr>
<th>AGENT</th>
<th>INDICATION</th>
<th>DOSAGE AND ROUTE</th>
<th>ADVERSE EFFECTS</th>
<th>MONITORING PARAMETERS</th>
<th>DRUG INTERACTIONS</th>
<th>CONTRAINDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echinocandins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin acetate</td>
<td>Treatment of invasive aspergillosis in patients who cannot tolerate other therapies or in whom aspergillosis is refractory to other therapies. Caspofungin acetate has not been studied as initial therapy for invasive aspergillosis.</td>
<td>Loading dose of 70 mg via IV on day 1 followed by 50 mg IV daily</td>
<td>Body as a whole: fever, chills, and rash. Digestive system and liver: hypokalemia and increased liver enzymes Cardiovascular: hypotension or hypertension and tachycardia</td>
<td>LFTs</td>
<td>• Increase the dose of caspofungin to 70 mg daily if patients are taking rifampin. • Caspofungin acetate reduces the plasma concentration of tacrolimus. • Cyclosporine increases the plasma concentration of caspofungin acetate by approximately 35%.</td>
<td>Hypersensitivity to any component of this product</td>
</tr>
<tr>
<td><strong>Polyenes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>Serious systemic fungal infections: aspergillosis, blastomycosis, candidemia, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis</td>
<td>0.3–1.5 mg/kg via IV daily</td>
<td>Infusion related: headache, shaking, chills, fever, rigors, flushing, and nausea and vomiting Cardiopulmonary: arrhythmia, dyspnea, hypotension, peripheral and pulmonary edema, and tachypnea Renal: renal tubular acidosis, azotemia, increased serum creatinine and BUN levels, and nephrolithiasis Electrolyte imbalances: hypokalemia, hypomagnesemia, hypocalcemia, and hypostenuria Hematologic: anemia</td>
<td>Serum creatinine, blood urea nitrogen, BMP; complete blood cell count with differential, and LFTs</td>
<td>Antineoplastic agents: enhance the potential for renal toxicity, bronchospasm, and hypotension Corticosteroids and corticotropin (adrenocorticotropic hormone): potentiate amphotericin B–induced hypokalemia Digital glycosides: amphotericin B–induced hypokalemia may potentiate digitalis toxicity Flucytosine: increases the toxicity of flucytosine Aminoglycosides, clotrimazole, cyclosporin, fluconazole, ketoconazole, miconazole, and pentamidine: may enhance the potential for renal toxicity Skeletal muscle relaxants: amphotericin B–induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants Diuretics: predisposes patients to several toxic effects by depleting electrolytes</td>
<td>Hypersensitivity to amphotericin products</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion (Amphotec®)</td>
<td>Invasive aspergillosis when renal impairment or unacceptability to therapy precludes the use of amphotericin B deoxycholate in effective doses or when prior amphotericin B deoxycholate therapy has failed</td>
<td>3–4 mg/kg via IV daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B lipid complex (Abelcet®)</td>
<td>Invasive fungal infections that are refractory to conventional amphotericin B therapy. The indication is based on open-label treatment of patients who are intolerant to therapy or in whom conventional amphotericin B therapy fails.</td>
<td>5 mg/kg via IV daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B (Ambisome®)</td>
<td>Empirical therapy for presumed fungal infection in febrile, neutropenic patients. Treatment of patients with Aspergillus, Candida, or Cryptococcus infections refractory to amphotericin B deoxycholate or in patients in whom renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate</td>
<td>3–5 mg/kg via IV daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Anidulafungin and micafungin are not approved by the U.S. Food and Drug Administration for treatment of aspergillosis.

Note. IV amphotericin B products are not interchangeable. Conventional amphotericin B dosing is substantially different from that for lipid formulations.


a Rates of infusion-related and cardiopulmonary adverse events are increased, but electrolyte imbalances are similar compared with amphotericin B deoxycholate.
b Rates of infusion-related and cardiopulmonary adverse events are increased, but electrolyte imbalances are reduced compared with amphotericin B deoxycholate.
c Rates of all adverse events are lower than with amphotericin B deoxycholate.

Note. Anidulafungin and micafungin are not approved by the U.S. Food and Drug Administration for treatment of aspergillosis.

Note. IV amphotericin B products are not interchangeable. Conventional amphotericin B dosing is substantially different from that for lipid formulations.

signs, negative fungal cultures, and more than 50% reduction in lesion size as determined radiologically (Nivoix et al.).

A few case reports of IPA in immunocompetent patients have been published; in one, voriconazole was used successfully as monotherapy (Garcia, Troya, & Edwards, 2006). In a trial of immunocompromised patients, voriconazole provided partial or complete responses in 53% of patients with IPA, compared with 31.6% in those treated with amphotericin B deoxycholate. The survival rate at 12 weeks was 70.8% in the voriconazole group compared with 57.9% in the amphotericin B group (p = 0.02). Renal impairment was significantly higher in the amphotericin group (p = 0.001). Elevated liver enzymes and visual disturbances were higher in the voriconazole group; however, these differences were not statistically significant (p = 0.54) (Herbrecht et al., 2002).

In an in vitro study, reversible antagonism was noted between amphotericin B and itraconazole in A. fumigatus. Stronger antagonism was seen in isolates that were exposed to itraconazole first. Antagonism may be because of up-regulation of a gene that uses itraconazole as a substrate (Kontoyiannis et al., 2000).

A combination of voriconazole plus caspofungin was associated with a better three-month survival rate than with voriconazole alone (p = 0.05) in 47 patients with hematologic malignancies after hematopoietic stem-cell transplantation and in whom initial therapy with amphotericin B had failed (Marr, Boeckh, Carter, Kim, & Corey, 2004).

P.J. was treated with a combination of caspofungin and voriconazole to provide a synergistic effect with no antagonism between the two agents. Amphotericin B was avoided because of the potential for nephrotoxicity.

Pharmacologic therapy for IPA remains challenging, and until results of randomized clinical trials that specifically address the issue of IPA in immunocompetent patients like P.J. are available, caution must be exercised in (a) translating efficacy data from studies that enrolled immunosuppressed patients, (b) interpreting and closely monitoring institutional resistance patterns of Aspergillus species to antifungal agents, and (c) using combination therapy in individual cases, which requires close attention to toxicity profiles of antifungal agents.

The Infectious Diseases Society of America guidelines in 2000 recommended specific treatment strategies for IPA (Stevens et al., 2000). Since the publication of those guidelines, a few azole and echinocandin agents have been added, and new recommendations, scheduled for publication in 2008, will reflect the role of these new agents in the treatment of IPA.

**Multidisciplinary Approach to Treatment**

Some patients are prone to respiratory infection as a result of immune system dysregulation caused by cancer or other comorbidities. P.J. developed superimposed cytomegalovirus antigenemia, methicillin-resistant staphylococcal pneumonia, and systemic *Staphylococcus aureus*; in addition, she had positive biopsy findings for *A. fumigatus* in the lung with the same characteristic lesion in the brain.

A multidisciplinary approach was vital in the management of this complicated infection to decrease mortality. Consultation with pulmonary and infectious disease specialists was critical in the success of P.J.’s treatment. The pulmonologist initiated bronchoscopic techniques such as bronchial washings and biopsy to identify specific microorganisms. In addition, neurology and neurosurgical services assisted the primary team in managing P.J.’s mental status change (i.e., lethargy and confusion) that resulted from the medications and location of the Aspergillus lesions as well as other neurologic changes, including tremor and progressive weakness in the lower extremities. Short-term symptomatic management was recommended until the underlying infection could be treated adequately. Nephrologists also were consulted to provide specific treatment and close monitoring to preserve kidney function; this is important because patients such as P.J. require antimicrobial and antifungal agents, resulting in metabolic acidosis and other chemical abnormalities affecting the renal system.

Because of P.J.’s multiple antibiotic regimens, prolonged debilitation, and worsening infection, she developed painful weeping ulcers and multiple sites of skin breakdown. Therefore, a dermatologic evaluation was obtained early in the treatment plan, and a wound care nurse specialist provided optimal skin care. A dietary specialist also participated in P.J.’s care by providing specific recommendations to support her nutritional status during her ongoing treatment. Because of P.J.’s worsening condition and change in dietary habits, she had been experiencing poor nutritional intake. Maintaining good caloric intake and making appropriate diet modifications, however, would expedite such patients’ recovery.

IPA usually requires several weeks of treatment; therefore, physical therapy and rehabilitation are important to recovery, improving physical and emotional function and thus quality of life. Physical and occupational therapists also were consulted to help improve P.J.’s mobility, conditioning, and muscle strength. Aspergillosis can be quite debilitating; thus, recognition of the need to collaborate with multiple healthcare providers and specialists is very important to patients’ prognosis and survival.

**Case Study Follow-Up**

P.J. was discharged home after being in the hospital for almost a month. Home health service nurses assessed P.J.’s condition daily, and antifungal medication was to be administered via IV daily for an additional three weeks. Home physical and occupational therapists also monitored P.J.’s condition. About eight days following her discharge from the hospital, P.J. was readmitted because of failure to thrive, dehydration, and increased weakness. All of her home medications and her previous antifungal and antibacterial medications were reinstated. About one week later, P.J. developed acute renal failure and pneumonia and was admitted to the intensive care unit with respiratory distress and hypoxemia. P.J.’s condition continued to deteriorate despite aggressive treatment, and she died about two weeks after her second admission. An autopsy showed multiorgan failure, disseminated *Aspergillus* in the lungs and brain, fungal and pseudomonas pneumonias, and kidney and respiratory failure.

**Conclusion**

IPA can be deadly. In the beginning, patients may exhibit no symptoms, and usually the infection does not seriously damage any body organs. However,
Aspergillus can become invasive and disseminate to various organs, causing serious damage and death as in the case of P.J. Early recognition of the disease and timely diagnostic testing and treatment are important for curing the infection. In the case of complex disseminated aspergillosis, collaboration of multiple specialists is needed for optimal care of patients. Research about the treatment of the infection in immunocompetent patients is needed.

The authors gratefully acknowledge Carmelita Escalante, MD, for her expert review of this manuscript.

**Author Contact:** Tuong-Vi Ho, RN, FNP, PhD, can be reached at vho03@yahoo.com, with copy to editor at CJONEditor@ons.org.

**References**


