

Pulmonary Aspergillosis

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ABSTRACT

As the population of patients with prolonged neutropenia, those receiving hematopoietic stem cell transplantation or lung transplantation, or those with human immunodeficiency virus or acquired immunodeficiency syndrome continues to increase, the rising incidence of pulmonary aspergillosis is unlikely to diminish. *Aspergillus* species are ubiquitous in nature, have no geographic predilection, and the spectrum of disease they cause is myriad, ranging from noninvasive disease with colonization to disseminated disease with an associated high mortality rate. The extent of disease is thus largely responsible for both the choice and the duration of antifungal therapy. Recent years have seen an expansion of antifungal agents, with efficacy against *Aspergillus* requiring an understanding of the full spectrum of disease for them to be used appropriately. Diagnosis is often difficult because existing tests lack desired sensitivity or specificity.

KEYWORDS: Pulmonary aspergillosis, voriconazole, *Aspergillus fumigatus*

Aspergillosis refers to the spectrum of disease caused by *Aspergillus* species. The clinical manifestations of aspergillosis vary. The spectrum of pulmonary disease ranges from noninvasive disease, such as with colonization of the organism or the presence of a fungus ball (aspergilloma), or an allergic response responsible for the syndrome of allergic bronchopulmonary aspergillosis (ABPA), to semi-invasive or invasive infections such as chronic necrotizing pneumonia and invasive pulmonary aspergillosis.^{1,2}

Aspergillus species enter the host most commonly through the lungs by the inhalation of conidia. However, infection has also been reported by exposure and inhalation of water aerosols contaminated with *Aspergillus* conidia.^{3,4} Invasive aspergillosis is thus a major cause of morbidity and mortality in immunosuppressed patients. Without effective host defenses following pulmonary exposure, the conidia resting in alveoli begin to enlarge and germinate. Hyphal transformation with vascular invasion and dissemination of infection are potential sequela.

The incidence of infection with *Aspergillus* has increased in recent years, primarily due to the increasing number of immunosuppressed patients encountered in clinical practice with the advent of solid organ and bone marrow transplantation, the increased use of corticosteroids and other immune-modulating drugs, and the epidemic of infection with the human immunodeficiency virus (HIV). Established infection in these patient groups has proven difficult to eradicate, and despite significant advances in antifungal therapy in recent years, overall mortality with invasive disease remains high.

MYCOLOGY AND ETIOLOGIC AGENTS

Aspergillus was first described in 1729 and receives its name due to its resemblance to an aspergillum used to sprinkle holy water. A member of the family Trichocomaceae, *Aspergillus* species are closely related to another mold, *Penicillium*. However, identification of the causative organism responsible for most infections is usually not difficult, with four species

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Table 1 Frequency of *Aspergillus* Species in Invasive Aspergillosis

Species	Frequency (%)
<i>A. fumigatus</i>	66
<i>A. flavus</i>	14
<i>A. niger</i>	7
<i>A. terreus</i>	4
Other	9

Data from Patterson et al.²

responsible for the majority of illnesses. *A. fumigatus* is responsible for more than 90% of invasive disease in some reviews, with *A. flavus*, *A. terreus*, and *A. niger* responsible for the majority of remaining invasive aspergillosis cases (Table 1).² Other, less pathogenic, species may also cause invasive infection in those with more profound immunosuppression, including *A. amstelodami*, *A. avenaceus*, *A. caesiellus*, *A. candidus*, *A. carneus*, *A. chevalieri*, *A. clavatus*, *A. flavipes*, *A. glaucus*, *A. granulosis*, *A. lentulus*, *A. nidulans*, *A. ochraceus*, *A. oryzae*, *A. restrictus*, *A. sydowii*, *A. tetrazonus*, *A. ustus*, *A. versicolor*, and *A. wentii*. Isolation of these species should be considered significant only when the probability of invasive disease is compatible with the host and an appropriate clinical setting.⁵

EPIDEMIOLOGY

The increasing incidence of invasive aspergillosis is likely a result of the increasing number of patients at highest risk for this infection, and the increase in recognition as a result of improved noninvasive diagnostic testing.

Ubiquitous in nature and without geographic predilection, *Aspergillus* is found in water, food, air, soil, and decomposing vegetation. Traditionally, patients at highest risk for infection and invasive disease were those with either profound or prolonged neutropenia. Changing practices in oncology and stem cell transplantation have decreased both the duration and the frequency of neutropenia, and this may be further reduced with protocols for the use of granulocyte colony-stimulating factors (G-CSF). The temporal association of invasive disease has thus shifted to a bimodal distribution, with the highest risk seen early after transplantation (< 20 days), and a second peak in incidence occurring more than 100 days posttransplantation. This later peak in incidence is due primarily to the use of high-dose corticosteroid therapy in the treatment of acute or chronic graft versus host disease.

Patients undergoing solid organ transplantation are also at greater risk for invasive aspergillosis, particularly those undergoing lung transplantation, with an incidence of 10 to 15% in one analysis.⁶ The reasons for this include previous colonization with *Aspergillus* in the native or transplanted lung, a reduction in ciliary clear-

ance capability, and the continued exposure to the environment of the transplanted tissue.⁷

Invasive aspergillosis has also been described in other immunosuppressed populations. Infection with HIV, hereditary immunodeficiency states such as chronic granulomatous disease, the use of oral corticosteroids or tumor necrosis factor- α inhibitors such as infliximab all appear to predispose to invasive disease.^{2,8,9}

Recent data also suggest the incidence of invasive aspergillosis is increasing in nonimmunosuppressed patients in the intensive care setting.¹⁰

CLINICAL MANIFESTATIONS

The manifestations of aspergillosis are myriad and dependent upon both the site and the severity of involvement and host immune status. Although infection with *Aspergillus* has been reported involving virtually all organ sites, the upper airways, lungs, and surrounding structures are those most frequently involved. It is additionally important to recognize the spectrum of disease attributed to aspergillosis, ranging from invasive diseases such as invasive pulmonary aspergillosis, tracheobronchial aspergillosis, chronic necrotizing pulmonary aspergillosis, and invasive sinonasal aspergillosis, to noninvasive diseases such as aspergillus fungus ball, chronic pulmonary aspergillosis, allergic bronchopulmonary aspergillosis (ABPA), and allergic fungal sinusitis.

Invasive Disease

INVASIVE PULMONARY ASPERGILLOSIS

Invasive pulmonary aspergillosis (IPA) is the most common form of invasive disease. Traditionally, IPA was seen 10 to 14 days after hematopoietic stem cell transplantation and was associated with profound granulocytopenia.¹¹ Recent reports, however, document the shifting epidemiology of this infection, with less than one-third of all patients diagnosed with IPA being neutropenic at the time of diagnosis, which impacts clinical presentation and the period of high risk for infection.¹²

Clinical presentation of IPA includes pleuritic chest pain, dyspnea, hemoptysis, dry cough, and fever. A careful history should be taken in those at risk for IPA given their frequent inability to mount an immunologic response and thus lack of a febrile response. The symptoms of hemoptysis and pleuritic chest pain serve as a reminder to the angioinvasive nature of aspergillosis.

Radiographic imaging can be suggestive of IPA yet remains nonspecific. Diffuse nodular infiltrates, pleural-based wedge-shaped densities or cavitary lesions and pleural effusions are all commonly seen.¹³ Invasive

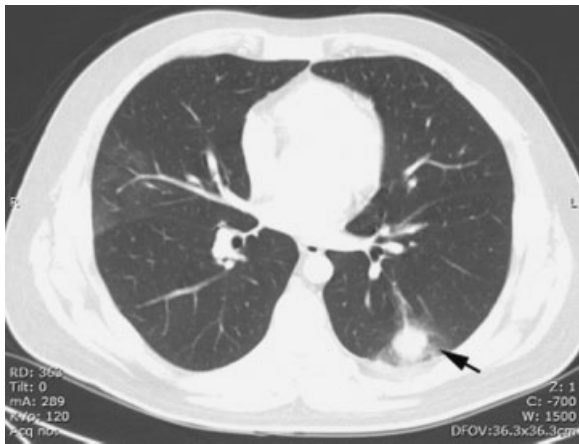


Figure 1 Computed tomography of the chest showing a "halo" sign of low attenuation surrounding a nodular lung lesion in early invasive pulmonary aspergillosis.

disease may also reveal a "halo" sign, an area of low attenuation surrounding a pulmonary nodule (Fig. 1). These areas may later cavitate and give rise to the "air-crescent" sign (Fig. 2).¹⁴ Although these radiographic findings are not specific for diagnosis and can be seen in a variety of other fungal and bacterial infections, they may be of assistance in the evaluation of high-risk patients.

Histopathological features of aspergillosis are useful to document tissue invasion and can show angioinvasion typical of invasive infection. *Aspergillus* is suggested by hyphae which are narrow and dichotomously branched at acute angles that can be demonstrated on a variety of stains such as hematoxylin and eosin (H&E) and Grocott-Gomori methenamine silver (GMS) stain (Fig. 3). However, the histological appearance is not specific for *Aspergillus* because similar histopathological features are found with other molds (including *Fusarium*, *Scedosporium*, and others), so cul-



Figure 2 Computed tomography of the chest showing an "air crescent" sign of invasive aspergillosis.

tures should be used to confirm identification of the organism.

TRACHEOBRONCHIAL ASPERGILLOSIS

The presence of *Aspergillus* in the large airways may represent colonization or, rarely, tracheobronchitis typical of infection in patients with acquired immunodeficiency syndrome (AIDS) or who have received lung transplants.^{15,16} Bronchoscopic findings include pseudo-membranous and ulcerative lesions. Infection of the anastomotic site in lung transplant patients causing dehiscence of the suture line has been reported.¹⁶ Non-specific symptoms predominate, with cough, chest pain, fever, and hemoptysis being most commonly reported.

CHRONIC FORMS OF PULMONARY ASPERGILLOSIS

The spectrum of aspergillosis of the lower respiratory tract includes other forms formerly referred to as

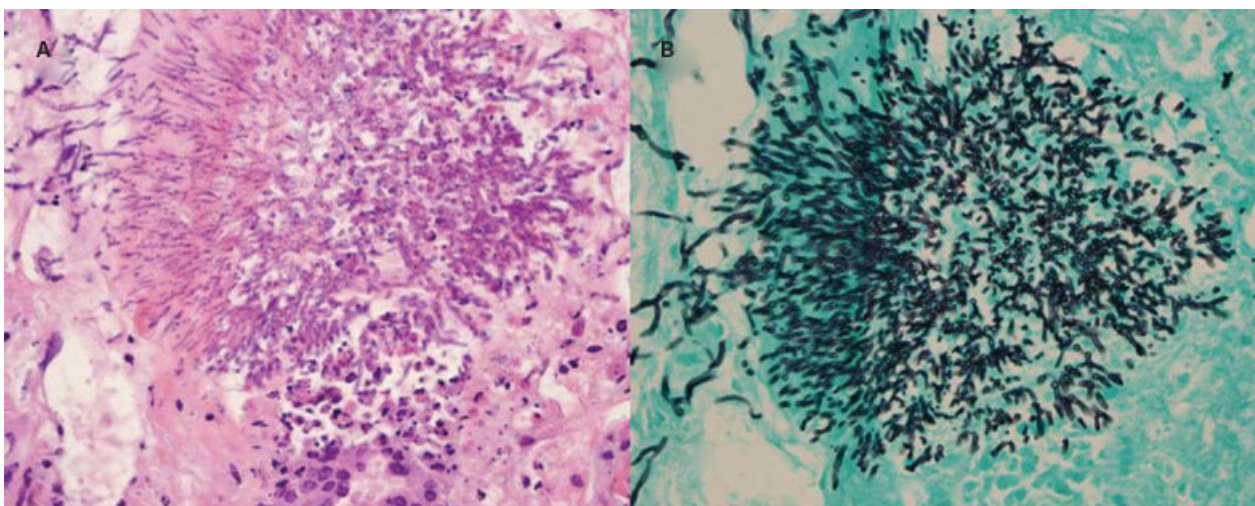


Figure 3 Lung tissue section showing thin, acutely branching hyphae on hematoxylin and eosin stain (A) and (B) Grocott-Gomori methenamine silver (GMS) stain invading pulmonary tissues.

Table 2 Spectrum of *Aspergillosis* of the Lower Respiratory Tract

Disease	Risk Factors	Treatment
Allergic bronchopulmonary aspergillosis (ABPA)	Asthma, cystic fibrosis	Corticosteroids, itraconazole
Chronic aspergillosis, including <i>Aspergillus</i> fungus ball	Preexisting structural lung disease (i.e., cavitation)	No therapy, itraconazole/voriconazole
Chronic cavitary or necrotizing aspergillosis	Structural lung disease, HIV/AIDS	Voriconazole
Tracheobronchial aspergillosis	Lung transplantation, HIV/AIDS	Voriconazole
Invasive aspergillosis	Prolonged or profound neutropenia, other immunosuppression	Voriconazole, alternates include amphotericin B, caspofungin, itraconazole, or posaconazole after stabilization of disease

Data from Hope et al.¹⁹

semi-invasive pulmonary aspergillosis and chronic necrotizing pulmonary aspergillosis.^{17,18} Recent insight into the chronic and progressive nature of infection with *Aspergillus* spp. has led some authors to define pulmonary aspergillosis along a continuum (Table 2).¹⁹ Chronic necrotizing pulmonary aspergillosis (CNPA) is the descriptive term applied to cavitary lung disease, chronic respiratory symptoms, and serum precipitating antibodies to *Aspergillus* spp. Several reports depict direct invasion of *Aspergillus* into the lung parenchyma, with CNPA thus described as a subacute or nonangioinvasive form.¹⁹ Several of these cases, however, report progressive damage to the lung parenchyma without clear evidence of tissue invasion. The term *chronic cavitary pulmonary aspergillosis (CCPA)* has been applied to the formation and expansion of multiple pulmonary cavities.²⁰ It is currently unclear if these distinctions of chronic pulmonary aspergillosis are academic in nature or will provide assistance in guiding antifungal therapy.

DISSEMINATED DISEASE

Unhindered, IPA often results in disseminated infection by hematogenous or contiguous spread. It is important to note that multifocal disease within one organ (i.e., IPA and tracheobronchial aspergillosis) is distinctly different from that of disseminated infection. Even with appropriate antifungal therapy at this stage, mortality rates are upward of 90%.^{2,21}

Noninvasive Disease

ASPERGILLOMA

An *Aspergillus* fungus ball, also known as an aspergilloma, grows in an existing pulmonary cavity, typically caused by emphysematous changes, carcinoma, or old tuberculosis. Although frequently asymptomatic, the presence of a fungus ball due to *Aspergillus* may cause hemoptysis and in rare cases can be fatal. The typical radiographic finding of a fungus ball due to *Aspergillus* is

a solid round mass within a cavitary lung lesion (Fig. 4). Surgical resection is the only proven therapy for these cases; however, the poor pulmonary reserve of most patients with this diagnosis precludes this invasive, although often definitive, therapy. When surgical treatment cannot be offered, long-term antifungal therapy has been shown to cause stabilization or improvement of pulmonary symptoms.²⁰

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction occurring after bronchi become colonized with *Aspergillus*. It is estimated that ABPA affects 1 to 2% of patients with asthma and 7% of all patients with cystic fibrosis.²² Central bronchiectasis on radiographic imaging can be diagnostic in the asthmatic patient. Other criteria for diagnosis include (1) asthma, (2) immediate cutaneous reactivity to *Aspergillus fumigatus*, (3) total serum immunoglobulin (Ig)E concentration > 500 IU/mL, (4) elevated serum IgE antibody levels to *Aspergillus*, (5) infiltrates on chest x-ray, (6) peripheral blood eosinophilia, and (7) serum-precipitating antibodies to *Aspergillus*. Patients with ABPA typically have a relapsing and remitting course. Corticosteroids are commonly used in the treatment of the asthmatic symptoms manifest during exacerbations. The benefits of antifungal

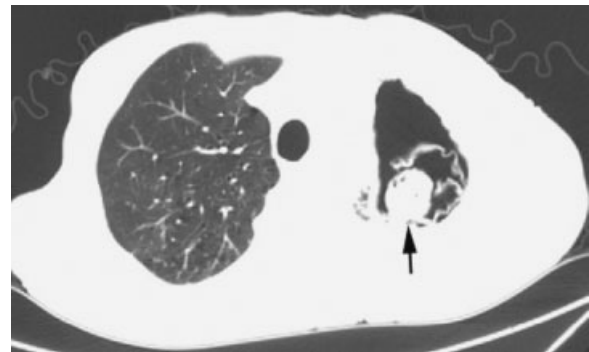


Figure 4 Computed tomography of the chest showing an *Aspergillus* fungal ball (aspergilloma) in a pulmonary cavity.

treatment in those who have steroid-dependent ABPA have been reported in a randomized, double-blind, placebo-controlled trial.²³

DIAGNOSIS

Definitive diagnosis of invasive aspergillosis necessitates visualization of the characteristic branching septate hyphae on microscopic examination of tissue (Fig. 3). Percutaneous needle aspiration, bronchoscopy, or video-assisted thoracoscopic biopsy are procedures most commonly used to obtain tissue. *Aspergillus* species grow well on standard media; however, specimens should be plated on fungal media to allow for optimal growth. False-negative results do occur, typically as a consequence of previous or concurrent antifungal therapy.^{24,25}

The poor candidacy of many patients with suspected invasive aspergillosis for surgical or other diagnostic procedures has prompted interest in noninvasive means for diagnosis. Serum antibody testing is often unhelpful for invasive infection because the majority of those afflicted with invasive aspergillosis (e.g., patients with severe immunodeficiency) often fail to mount an antibody response to infection. The galactomannan enzyme immunoassay (EIA) demonstrates proven reliability in patients with hematologic malignancy; however, the reported sensitivity varies from 44 to 90%.^{26,27} False-positive results have been reported in patients receiving piperacillin-tazobactam or amoxicillin-clavulanate or in those infected with the dimorphic fungi *H. capsulatum* or *B. dermatitidis*.²⁸ EIA testing is of highest value in the serial screening of high-risk patients. Its role in providing direction for the duration of antifungal therapy, however, is less clear; and other criteria, including the resolution of clinical and radiographic findings, should be used for this decision.

Other serum tests available for diagnosis include the fungal marker (1→3)- β -D-glucan. Unfortunately, the presence of (1→3)- β -D-glucan is not specific for *Aspergillus* but is indicative of invasive fungal infection with several possible fungal pathogens.²⁹ Polymerase chain reaction (PCR) has also been evaluated and appears promising as a potential diagnostic modality, but PCR is not yet commercially available for the diagnosis of *Aspergillus*.³⁰ The use of multiple concurrent, nonculture-based modalities has not been prospectively evaluated but may be a significant advance in noninvasive diagnostic testing for aspergillosis.

TREATMENT

Amphotericin B

Until recently, amphotericin B (AMB) deoxycholate was the antifungal of choice for invasive aspergillosis. AMB is a fungicidal polyene agent that binds to ergosterol, the

primary sterol present in the fungal cell membrane. This causes the formation of ion channels with ensuing fungal cell death. AMB has demonstrated activity against most *Aspergillus* isolates with the exception of *A. terreus*, which is inherently resistant. Significant side effects of therapy with AMB deoxycholate have been well described. Infusion-related reactions, including fever, chills, rigors, myalgias, arthralgias, bronchospasm, nausea, and vomiting, have been observed. The nephrotoxic side effects of AMB include azotemia, renal tubular acidosis, hypokalemia, and hypomagnesemia, with an incidence of renal toxicity approaching 30% of patients in one report.³¹ The morbidity and mortality associated with the use of AMB have prompted the search for improved antifungal agents with activity against *Aspergillus*. Over the past 10 years researchers have met this challenge with the development of several new antifungal medications with favorable efficacy and improved toxicity profiles compared with AMB. These include lipid formulations of AMB, the new azoles (voriconazole, posaconazole, and ravuconazole), and the echinocandins (caspofungin, micafungin, and anidulafungin).

The lipid formulations of AMB, such as AMB colloidal dispersion (ABCD), AMB lipid complex (ABLC), and the small unilamellar vesicle liposomal formulation [liposomal amphotericin (L-AMB)], have shown reduced nephrotoxicity in comparison with traditional AMB deoxycholate. In these formulations, amphotericin must be released from the synthetic phospholipids, necessitating higher doses of the lipid formulations for antifungal efficacy equivalent to that of AMB deoxycholate. Infusion-related side effects with the lipid formulations of AMB are less frequent than are those of AMB deoxycholate, but chest discomfort, respiratory distress, and hypoxia (particularly with the ABCD formulation) can be seen; therefore, the ABCD formulation is seldom recommended for clinical use.

When used for the treatment of invasive aspergillosis, ABLC is given in doses of 5 mg/kg/d. L-AMB has been used for salvage therapy of invasive aspergillosis at doses of 3 to 5 mg/kg/d, or 3 mg/kg/d when empirical antifungal therapy is required in febrile neutropenic patients. A recent study of primary therapy for invasive aspergillosis compared an initial dose of L-AMB at 10 mg/kg/d for 2 weeks to an initial dose of 3 mg/kg/d, with each followed by 3 mg/kg/d. Results showed similar efficacy and greater toxicity in the group of patients receiving higher initial L-AMB doses, suggesting that in this specific population of patients with early pulmonary aspergillosis higher doses are not beneficial.³²

Triazoles

The antifungal triazoles inhibit ergosterol synthesis through their inhibition of the fungal cytochrome P450 enzyme. This results in fungal cell membrane

dysfunction with inhibition of cell growth and ultimately fungal cell death. Side effects of the triazoles are predominantly hepatic, related to their inhibition of human P450 enzymes, and caution is required when prescribing other medications that also share the P450 system for their respective metabolism. Resistance of *Aspergillus* to the triazoles has been reported, but no species has predictable antifungal resistance to these agents, and clinical validation to determine breakpoints has not been established.

VORICONAZOLE

Voriconazole is available in both oral and intravenous (IV) formulations. The IV formulation is provided in a cyclodextrin vehicle that may accumulate in patients with renal impairment. The effect of cyclodextrin accumulation is uncertain at this time, but caution is advised in using the IV formulation in patients with renal insufficiency. Other side effects of voriconazole include liver dysfunction, skin rashes, hematologic disorders, headache, nausea, vomiting, and diarrhea. Visual disturbance is unique to voriconazole among the triazole antifungal drugs, with patients reporting photopsia (flashing lights), a transient and self-limited side effect.³³ A loading dose of 6 mg/kg intravenously every 12 hours for two doses, followed by 4 mg/kg every 12 hours, is recommended for the treatment of invasive aspergillosis. Oral therapy consists of 200 mg every 12 hours, but therapy can be maximized by the use of 4 mg/kg/dose; measurement of serum levels has been recommended in those receiving oral voriconazole. Pediatric patients clear voriconazole more rapidly than adults, and a maintenance dosage of 7 mg/kg is therefore recommended.

Voriconazole has become the recommended primary therapy for most patients with invasive pulmonary aspergillosis.³⁴ In a global clinical trial, voriconazole was compared with AMB deoxycholate with either study arm drug allowed to be followed by other licensed therapy.³⁵ Voriconazole was significantly more effective than AMB with improved clinical responses and improved survival. Thus AMB deoxycholate can no longer be recommended as primary therapy for invasive aspergillosis in most patients.

ITRACONAZOLE

Itraconazole is available in capsules, an oral solution, and an IV formulation. Absorption of the capsules is variable and affected by gastric acidity. Food or an acidic beverage is recommended when the capsules are prescribed, and the capsular formulation is not recommended in patients with severe/life-threatening infections despite the availability of serum drug levels. Side effects of itraconazole are elevation of the hepatic transaminases, hypertriglyceridemia, hypokalemia, nausea, and vomiting.³⁶ Oral doses of 400 mg/d (capsules) or 2.5 mg/kg twice daily (solution) are currently recommended for

invasive aspergillosis. When the intravenous formulation is preferred, doses of 200 mg twice daily for 2 days followed by 200 mg daily for 12 days are advocated. The erratic bioavailability and potential toxicities of itraconazole limit its use in patients with invasive disease, and the IV formulation has only limited data to support its use. For allergic syndromes and in less invasive disease, itraconazole remains a useful alternative.

POSACONAZOLE

One of the newest triazoles, posaconazole, is similar in structure to itraconazole. It is well tolerated, but steady-state levels are not obtained for up to 7 days, potentially decreasing its efficacy as primary therapy. Most frequently reported side effects are diarrhea, nausea, and dyspepsia, with the possibility for hepatic transaminase elevation similar to the other antifungal azoles. It is not metabolized by the liver so that hepatic toxicity may be less than seen with other azoles. However, posaconazole is an inhibitor of cytochrome P450 enzyme 3A4, and clinically significant drug interactions occur with agents that share this pathway, such as cyclosporine and tacrolimus. An IV formulation is not yet clinically available. Concurrent intake of food has been found to boost serum posaconazole levels fourfold.³⁷ The oral suspension preparation should be given as 200 mg three times daily when used for prophylaxis and as 800 mg in two to four divided doses when used as salvage therapy.³⁴

Posaconazole was evaluated in two studies of prophylaxis in high-risk patients undergoing hematopoietic stem cell transplantation with graft versus host disease and in patients with acute myelogenous leukemia or myelodysplastic syndrome.^{38,39} In these studies posaconazole reduced breakthrough aspergillosis, and in the study involving patients with acute myelogenous leukemia or myelodysplastic syndrome it improved survival compared with that of standard prophylaxis regimens.³⁹

Echinocandins

The echinocandins (caspofungin, micafungin, and anidulafungin) are a novel class of antifungal agents with a unique mechanism of action. These drugs inhibit synthesis of 1,3- β -glucan, a polysaccharide present in the cell wall of many pathogenic molds. Side effects of the echinocandins include increased hepatic transaminases, dyspepsia, headache, and the potential for histamine-like symptoms if rapid infusion is given.⁴⁰ Although all three of the currently available echinocandins have demonstrated activity against *Aspergillus*, caspofungin is the only one currently approved by the US Food and Drug Administration as second-line treatment for invasive aspergillosis. Current dosing recommendations include caspofungin given as 70 mg IV loading dose for one dose, followed by 50 mg daily for the duration of therapy. With significant impairment in hepatic function, a dose

reduction to 35 mg daily should be used. The optimal doses for micafungin and anidulafungin have yet to be established. Although the echinocandins have largely been used for salvage therapy of invasive aspergillosis, their distinctive mechanism of action has prompted interest in their potential for combination therapy with other antifungal agents; controlled trials in this area are lacking. Combinations of voriconazole and caspofungin have demonstrated improved efficacy in preclinical models, a finding supported by anecdotal clinical evidence and case series. Randomized clinical trials are urgently needed to establish the utility of these approaches.⁴¹

CONCLUSIONS

The incidence of infection with *Aspergillus* species continues to rise with the increasing immunosuppressed patient population. Thus, by necessity, the astute clinician will increasingly be required to both diagnose and treat the spectrum of pulmonary disease caused by *Aspergillus*. The recently expanded antifungal armamentarium offers the potential for more effective and less toxic therapy for this often lethal infection, but these agents offer distinct pharmacological profiles and indications for use. Early therapy is critical for a successful outcome, but the diagnosis remains difficult and knowledge of the clinical presentation and risk factors can lead to a heightened suspicion enabling earlier diagnosis. Finally, prevention of invasive pulmonary aspergillosis may be possible in high-risk patients.

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