**Educational Objectives**

- Describe the symptoms and manifestations of invasive aspergillosis
- Examine the efficacy and safety of conventional treatment options
- Explore investigational agents for the treatment of invasive aspergillosis

**Aspergillus** is a fungus with spore heads that radiate from a central structure. The genus was named because of its similarity in appearance to a brush or perforated globe used for sprinkling holy water (an aspergillum). One hundred and fifty species have been identified. *A. fumigatus* accounts for approximately 90% of cases of invasive aspergillosis (IA). The characteristics of *A. fumigatus* that might contribute to its pathogenicity include: the rapid growth within the genus; a very small spore size that enables the spores to penetrate deeply into the lung; a hydrophobic protein layer that covers and protects it from host defenses; and the ability to bind to laminin and fibrinogen, allowing greater adhesion in the airways. The first cases of invasive pulmonary aspergillosis as an opportunistic infection occurred in 1953 following the introduction of corticosteroids and cytotoxic chemotherapy.

Although IA can be disseminated, manifestations of the disease can also be found in the pulmonary, sinus, cutaneous, and alimentary tract. The majority of patients have pulmonary disease, but IA can enter through damaged skin or operative wounds, the cornea, or the ear, and infection can occur at the site of entry. The presentation of pulmonary disease differs based on the degree of immunosuppression of the patient affected. The most immunocompromised patients have the fewest symptoms and the disease progresses rapidly (e.g., one to two weeks from onset to death). The least immunocompromised patients have an indolent onset and progress slowly (e.g., several months from onset to diagnosis). Early symptoms can include dry cough, fever, and dull chest pain.

There has been a significant increase in the number of documented cases of IA over the last 25 years. A probable explanation stems from the increased use of immunosuppressive medications for conditions including: 1) new intensive cancer chemotherapy regimens for solid tumors; 2) solid organ transplantation; and 3) autoimmune diseases such as systemic lupus erythematosus. Likewise, a significant proportion of aspergillosis cases occur in AIDS patients. The associated mortality of aspergillosis ranges from 50% to 100% despite therapy. Therefore, it is important to treat early and aggressively. This article will review the therapeutic drug options including conventional amphotericin B, lipid-based formulations of amphotericin B, itraconazole, and caspofungin, as well as some investigational agents.

**Conventional Amphotericin B**

For over 40 years, amphotericin B has been the standard treatment for IA, particularly for severe and life-threatening infections. Although amphotericin B is associated with a number of adverse reactions, in many cases, the efficacy of the drug outweighs the risks. Because amphotericin B is the gold standard therapy for IA, according to the Infectious Diseases Society of America (IDSA) practice guidelines, and because of the lower cost associated with its use as compared to other agents, it is encouraged as first-line therapy. The other agents are reserved as second-line therapy for patients who either do not tolerate amphotericin B or who fail therapy. To reduce the number of patients who do not tolerate the nephrotoxicity of amphotericin B therapy, the methods of minimizing its nephrotoxic potential are discussed below.

**Mechanism of Action**

Amphotericin B exerts its antifungal effect by binding to ergosterol (a sterol similar to cholesterol) in the fungal cell wall, disrupting cell wall integrity, and thus increasing the membrane permeability. This process leads to cell lysis and the loss of intracellular contents necessary for cell survival.

**Efficacy**

The overall response rate for IA reported with amphotericin B has been 37% (range: 14%–83%). The wide response range can be accounted for by wide variation in the reported patient populations with respect to underlying diseases, extent of infection, resolution of neutropenia or other immunodeficiency, and duration of follow-up.

**Adverse Effects**

Amphotericin B use, however, is complicated by infusion-related reactions, renal toxicity, and related electrolyte disturbances. The infusion-related reactions include fever, chills, rigors, nausea, and vomiting, which can be reduced through the use of premedications or by slowing the infusion rate.

Although an increase in serum creatinine (SCr) is common, drug administration can be maintained as long as the degree of nephrotoxicity remains moderate (SCr <2.5 mg/dL or the glomerular filtration rate falls no more than 40% from baseline). If renal dysfunction becomes more severe, the dose may be reduced by administering the drug every other day or in an interrupted fashion (e.g., every two to five days), if the clinical condition will allow. The mechanism of

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renal toxicity is not entirely clear. Unfortunately, amphotericin B does have a weak affinity for the cholesterol molecules found in mammalian cell membranes. This results in the formation of intramembranous pores that alter the cell membrane permeability. In the kidney, this might cause direct renal tubular damage. Another hypothesis is that amphotericin B might affect tubuloglomerular feedback, resulting in a functional reduction in glomerular filtration that is unrelated to structural damage to the renal tubule cells. This can lead to increased serum creatinine and urea concentrations, a lessened ability to concentrate urine, hypokalemia, magnesium-wasting, or renal tubular acidosis.

The increased membrane permeability and other lesser defined mechanisms also lead to the wasting of other electrolytes. Hypokalemia and hypomagnesemia are common during amphotericin B therapy. These abnormalities might contribute to a lessened ability to concentrate the urine. If deficits in both electrolytes occur, the hypokalemia might be resistant to potassium replacement therapy unless the hypomagnesemia is corrected first. Amiloride 5 mg twice daily has been used to prevent the development of hypokalemia and might also reduce the urinary magnesium losses.

There are a variety of strategies to minimize nephrotoxicity, including sodium loading, discontinuing diuretic therapy, avoiding concomitant nephrotoxic drugs, limiting total doses to less than 4 grams (because renal impairment following cumulative doses <4 grams is usually reversible), and administering amphotericin B via continuous infusion.

A recently published study demonstrated that administering amphotericin B as a continuous infusion (along with the saline load) reduces nephrotoxicity and lowers infusion-related adverse effects (e.g., fever, chills, rigors). In this unblinded study, the amphotericin B was given in 500 ml of 5% glucose without any additives and administered through a separate line, either over 24 hours as a continuous infusion (n=40) or over four hours as a rapid infusion (n=40). The continuous-infusion arm trended toward higher daily and cumulative doses. There were significantly more dose reductions and infusion-related reactions (fever, chills, vomiting) in the arm receiving the rapid infusion as compared to the continuous-infusion arm. The ratio of peak serum creatinine to baseline creatinine concentrations was also significantly higher in the rapid-infusion group as compared to the continuous-infusion group, but returned to normal in all except two patients within three months after completion of therapy. The continuous infusion was found to be as least as effective as rapid infusion as it related to mortality; more deaths occurred in the rapid-infusion arm than in the continuous-infusion arm (3 vs. 0, respectively).

### Dosing

Because of the associated high mortality of this condition, IA should be treated with the highest recommended dose (1–1.5 mg/kg/day).

### Limitations

The primary drawback associated with the use of amphotericin B is the toxicity profile, especially nephrotoxicity. Elaboration on methods to minimize or control amphotericin B toxicity can be found in the literature. Drug interactions with amphotericin B primarily involve additive nephrotoxicity.

### Lipid-Based Formulations of Amphotericin B

The lipid-based formulations [i.e., amphotericin B lipid complex (ABLC; Abelcet, Liposome Company), amphotericin B colloidal dispersion (ABCD, Amphotec, Sequus Pharmaceuticals), and liposomal amphotericin B (LAMB, Ambisome, Fujisawa)] have not demonstrated superiority in the treatment of IA. The main advantage to their use is related to an attenuation of nephrotoxicity. They are currently indicated for patients who are refractory to or intolerant of conventional amphotericin B.

Although these formulations are not free of nephrotoxicity, the lipid-based formulation allows a larger dose to be administered over a longer period of time with relatively less renal toxicity. The lipid-based formulations differ in the type of phospholipid adjunct, as well as the phospholipid to amphotericin B ratio. There has been one head-to-head comparison of the lipid-based formulations, but it focused only on neutropenic fever and not specifically on aspergillosis. Therefore, it is unknown whether one agent offers any significant therapeutic advantage over another for this indication.

ABLC was the first lipid formulation to be marketed; it has the most information available on pediatric use; and it is the least expensive. Criteria for its use are listed in the current guidelines from the IDSA. The guidelines discuss the appropriate use for patients who have a documented or highly suspected systemic fungal infection and who have demonstrated either refractoriness to or intolerance of amphotericin B and are not candidates to receive other appropriate antifungals. The remainder of the discussion for this section will focus on the available literature for ABLC.

### Mechanism of Action

ABLC consists of lipid bilayers, called ribbons, carrying 33 mol% concentration of amphotericin B. It is thought that the lipid complex releases the active amphotericin at the site of the fungal infection through the action of phospholipases (released from the vascular smooth muscle, macrophages, and the infecting fungi). The active amphotericin then binds to the ergosterol in the fungal cell wall. This target-specific action is thought to reduce the risk of nephrotoxicity through reduced uptake into human cells.

### Efficacy

Most of the studies of ABLC have been compassionate-use or case-series studies in which small numbers of patients received the drug as second-line therapy after either becoming intolerant of or failing therapy with conventional amphotericin B. A summary of the studies evaluating the use of ABLC in the setting of IA is presented in Table 1.

### Adverse Effects

The most common adverse effects with ABLC are infusion-related reactions (e.g., chills, fever, nausea, vomiting, and hypotension). The incidence is similar to that seen with conventional amphotericin B. The same pre-medications described above for conventional amphotericin B are used for ABLC infusion-related reactions. Although the incidence of nephrotoxicity is lower than that seen with conventional amphotericin B,
an 11% incidence of increased serum creatinine is reported in the package insert and higher rates have been described in the individual studies (see Table 1). To prevent possible nephrotoxicity, it is prudent to minimize risks in ways similar to the methods listed above for conventional amphotericin B. It is common practice to provide sodium loading for patients receiving ABLC, if the patient’s fluid status allows. However, none of the current literature addresses this practice. Electrolyte wasting can also occur with ABLC. When Sharkey et al. compared conventional amphotericin B to ABLC, they found a similar incidence of hypokalemia and hypomagnesemia between the two treatments.

Dose/Administration

The recommended dose of ABLC is 5 mg/kg/day administered at a rate of 2.5 mg/kg/hour. If the infusion time exceeds two hours, the infusion bag must be shaken every two hours to mix the contents.

Limitations

The primary drawback associated with the use of lipid-based formulations of amphotericin B is drug toxicity. Although not as common as with conventional amphotericin B, toxicity can still be a dose-limiting factor.

Itraconazole

Because of the high incidence of intolerance of amphotericin B and the lack of alternative therapies for IA, the introduction of itraconazole in 1992 sparked much interest. Itraconazole, a synthetic broad-spectrum triazole, is currently available as an injection, oral solution, and capsule. The IV and capsule formulations are indicated for the treatment of aspergillosis in patients who are intolerant of or refractory to amphotericin B therapy. Itraconazole inhibits the cytochrome P-450 (CYP-450)-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. This inhibition is also partially responsible for the drug interactions encountered with itraconazole.

Mechanism of Action

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Efficacy

A multicenter open study was conducted by the Mycoses Study Group to determine the efficacy of oral itraconazole for IA. Patients were given 200 mg three times daily for four days, then 200 mg twice daily. The overall response rate at the end of treatment was 39%
This response rate appears relatively low. However, the authors commented that many of the patients were very ill, including patients who were neutropenic or had bone marrow transplants. They noted that 22% of patients in this study failed therapy, compared with 45% of similar patients treated with amphotericin B. Unfortunately, there have been no studies directly comparing itraconazole to amphotericin B for the treatment of aspergillosis to date, so the comparison is based only on historical data.

Based on this study, a comparative trial was attempted by the Mycoses Study Group and the manufacturer of itraconazole; however, it could not be completed because of enrollment reasons. Therefore, an analysis was conducted of the data from the remaining 125 patients who had received oral itraconazole through the compassionate-use studies and who met the criteria for IA.24 The overall response rate was 63% (79/125). One possible explanation for the better response rate in this analysis over the previous study is that fewer of the patients had extrapulmonary disease.

There have been no published trials that study the use of IV itraconazole for the treatment of disseminated aspergillosis in humans. The only published clinical trial using IV itraconazole for the treatment of aspergillosis is limited to pulmonary aspergillosis.25 This small study’s objective was to evaluate the effects of itraconazole as first-line therapy for pulmonary aspergillosis in heart transplant recipients. All four patients who initially received IV itraconazole were switched to amphotericin B because of radiographic and/or clinical worsening of the infection. All three patients who initially received amphotericin B had improvement of infection. The authors concluded that in heart transplant recipients, amphotericin B was superior to itraconazole in the treatment of invasive pulmonary aspergillosis.25

**Adverse Effects**

Common adverse effects observed with itraconazole include nausea, vomiting, hypokalemia, elevated liver-function tests, and rash. Liver-function tests should be monitored in patients with pre-existing hepatic function abnormalities and assessed for the development of any sign or symptom suggestive of liver dysfunction. Safety with the use of itraconazole beyond 14 days has not yet been established.26

In May, 2001, the FDA issued a health advisory and a black box warning was added to the package insert for all three formulations of itraconazole regarding potential cardiac effects.20,21,27 This was done in response to study findings and the analysis of post-marketing adverse event reports. The FDA stated a “small but real risk of developing congestive heart failure” associated with the use of any formulation of itraconazole.28 If signs or symptoms of congestive heart failure occur during itraconazole administration, its continued use should be reassessed.

**Dose/Administration**

The dose for the oral formulations is 200 mg three times daily for four days, then 200 mg twice daily when used for aspergillosis.1,23 The intravenous formulation is dosed twice daily for the first two days of therapy and once daily thereafter.29 It should be infused over one hour.

Dosage adjustments of the oral formulations (capsules and solution) of itraconazole are not needed in patients with renal impairment. However, the intravenous formulation is solubilized by the addition of hydroxypropyl-

**CE: Treatment of Invasive Aspergillosis**

Caspofungin, the first approved drug in a new class of antifungal agents called echinocandins, is currently available as an injection. It is indicated for the treatment of IA in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole).35 It has not been studied as initial therapy for IA.

**Mechanism of Action**

Caspofungin inhibits the activity of the enzyme glucan synthase, which leads to an inhibition of the synthesis of beta-(1,3)-D glucan, which is important for cell wall integrity.36 The echinocandins are unique among the other antifungal agents as they target the fungal cell wall, rather than the fungal cell membrane. Because the glucan is not present in mammalian cells, caspofungin might have less toxicity than other antifungal agents.36

**Efficacy**

The FDA based its approval decision for caspofungin on very limited clinical data. They also considered the efficacy and safety of alternative thera-

(30/76). This response rate appears relatively low. However, the authors commented that many of the patients were very ill, including patients who were neutropenic or had bone marrow transplants. They noted that 22% of patients in this study failed therapy, compared with 45% of similar patients treated with amphotericin B. Unfortunately, there have been no studies directly comparing itraconazole to amphotericin B for the treatment of aspergillosis to date, so the comparison is based only on historical data.

Based on this study, a comparative trial was attempted by the Mycoses Study Group and the manufacturer of itraconazole; however, it could not be completed because of enrollment reasons. Therefore, an analysis was conducted of the data from the remaining 125 patients who had received oral itraconazole through the compassionate-use studies and who met the criteria for IA.24 The overall response rate was 63% (79/125). One possible explanation for the better response rate in this analysis over the previous study is that fewer of the patients had extrapulmonary disease.

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**Adverse Effects**

Common adverse effects observed with itraconazole include nausea, vomiting, hypokalemia, elevated liver-function tests, and rash. Liver-function tests should be monitored in patients with pre-existing hepatic function abnormalities and assessed for the development of any sign or symptom suggestive of liver dysfunction. Safety with the use of itraconazole beyond 14 days has not yet been established.26

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**Dose/Administration**

The dose for the oral formulations is 200 mg three times daily for four days, then 200 mg twice daily when used for aspergillosis.1,23 The intravenous formulation is dosed twice daily for the first two days of therapy and once daily thereafter.29 It should be infused over one hour.

Dosage adjustments of the oral formulations (capsules and solution) of itraconazole are not needed in patients with renal impairment. However, the intravenous formulation is solubilized by the addition of hydroxypropyl-b-cyclodextrin, which is excreted unchanged in the urine. A six-fold reduction in the clearance of hydroxypropyl-b-cyclodextrin has been observed in patients with severely impaired renal function.26 As a result, the manufacturer does not recommend IV itraconazole in patients with severe renal dysfunction (CrCl <30 ml/min).20 There are currently no recommendations regarding dose adjustments in patients with hepatic impairment. A small study using the capsule formulation did not show significant alterations in the area under the time-concentration curve (AUC) of itraconazole in patients with cirrhosis, but the peak concentration was reduced by 47% and the elimination half-life had a two-fold increase.21

Itraconazole is a water-insoluble antifungal. To produce the solution formulation, cyclodextrin is used as a delivery system. Cyclodextrin is a ring of glucose molecules that can accept the lipophilic itraconazole molecule within the ring. This enables solubilization and delivery of the itraconazole to the gut lumen, resulting in absorption of the drug without absorption of the cyclodextrin.29 This increased solubility lends the oral solution a higher bioavailability than the capsule. The capsule is to be taken with food in order for the acid production to increase its solubility and absorption while the solution has the best bioavailability on an empty stomach.20,23 The absorption of capsules can also be enhanced by administering them with an acidic beverage such as cola.34

**Limitations**

There are several drawbacks to therapy with itraconazole, including drug interactions and issues surrounding the absorption of oral itraconazole.

Drug interactions with itraconazole occur by two major mechanisms. All formulations of itraconazole inhibit CYP3A4, an isoenzyme involved in the metabolism of many other medications. Because of this, itraconazole is contraindicated with the concomitant administration of astemizole, triazolam, and HMG-CoAs (statins). Concomitant administration of medications that can decrease the acidity of the stomach, such as antacids, proton pump inhibitors, and H2RAs, interact with the capsule formulation of itraconazole by decreasing its absorption.34

Another issue of concern results from frequent concomitant conditions: many patients who have aspergillosis also have hypochlorhydria and/or enteropathy, which might decrease the absorption of oral itraconazole.2 There might be a need to monitor itraconazole levels if a lack of absorption is suspected.20,34

**Caspofungin**

Caspofungin, the first approved drug in a new class of antifungal agents called echinocandins, is currently available as an injection. It is indicated for the treatment of IA in patients who are refractory to or intolerant of other therapies (i.e., amphotericin B, lipid formulations of amphotericin B, and/or itraconazole).35 It has not been studied as initial therapy for IA.

**Mechanism of Action**

Caspofungin inhibits the activity of the enzyme glucan synthase, which leads to an inhibition of the synthesis of beta-(1,3)-D glucan, which is important for cell wall integrity.36 The echinocandins are unique among the other antifungal agents as they target the fungal cell wall, rather than the fungal cell membrane. Because the glucan is not present in mammalian cells, caspofungin might have less toxicity than other antifungal agents.36

**Efficacy**

The FDA based its approval decision for caspofungin on very limited clinical data. They also considered the efficacy and safety of alternative thera-

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pies and the risk–benefit analysis when making the decision.\textsuperscript{36} One reason it was approved with such limited data is that it is used in a patient population that is critically ill and has few therapeutic options for the treatment of IA.\textsuperscript{27} The efficacy of caspofungin from a non-comparative open-label study of patients (n=63) with documented IA who were either unresponsive to or intolerant of previous therapies was compared to historical controls.\textsuperscript{35} According to the expert panel, 41\% (26/63) of patients who received at least one dose had a favorable response, compared with 38.5\% (25/65) in the intent-to-treat analysis or 44.8\% (25/56) in the clinically evaluable analysis. These data were compared to the results in the patients from the historical control group who were either refractory to or intolerant of other antifungal therapies, in which 19.8\% (19/96) responded.\textsuperscript{30}

### Adverse Effects

Adverse drug effects reported in patients treated with caspofungin include fever, phlebitis/thrombophlebitis, headache, nausea, vomiting, rash, skin flushing, mild liver-function test elevations, and a case of anaphylaxis.\textsuperscript{36} Overall, caspofungin was generally well-tolerated in the limited patient population that received it prior to approval (297 patients).

### Dose/Administration

The dose for caspofungin is a 70-mg loading dose on day one, then 50 mg daily thereafter.\textsuperscript{35} The dose may be increased to 70 mg daily if the clinical response is poor. The dose needs to be decreased in patients with hepatic dysfunction. The dose reduction is based on the patient’s Child-Pugh score; mild hepatic insufficiency (Child-Pugh score: 5–6) requires no dose adjustment, moderate hepatic insufficiency (Child-Pugh score: 7–9) requires that the daily dose be reduced from 50 to 35 mg. No data are available for severe hepatic insufficiency (Child-Pugh score >9) and caspofungin is not recommended in these patients.\textsuperscript{35} Caspofungin is administered by the intravenous route and should be given slowly over an hour.

### Limitations

One major drawback to therapy with caspofungin is the lack of information on drug interactions. Although the package insert states that it is not an inhibitor of any enzyme in the CYP-450 system, it is not a substrate for P-glycoprotein, and is a poor substrate for CYP-450 enzymes, it has several drug interactions with medications that are known to interact with the CYP-450 system.\textsuperscript{36} There are no data from formal drug interaction studies. However, it is thought that co-administration of inducers of drug clearance and/or mixed inducer-inhibitors might result in clinically significant reductions in caspofungin concentrations. Based on results from a small number of patients who received caspofungin with efavirenz, nelnavir, nevirapine, phenytoin, rifampin, dexamethasone, or carbamazepine, clinically significant reductions in caspofungin serum concentrations were observed.\textsuperscript{35} The mechanism of these interactions is not stated. In clinical studies, caspofungin did not induce the CYP3A4 metabolism of other medications. The package insert suggests considering an increase in the caspofungin dose to 70 mg daily when co-administered with these interacting agents if the patient is not clinically responding.\textsuperscript{35}

Co-administration of caspofungin and tacrolimus resulted in reduced tacrolimus levels, so standard monitoring of tacrolimus blood concentrations with appropriate dosage adjustments is recommended.\textsuperscript{35}

Of the four healthy subjects who received caspofungin with cyclosporine, three developed transient elevations of alanine transaminase (ALT) that were two to three times the upper limit of normal.\textsuperscript{35} Two of eight patients in another group who received the two drugs concomitantly also had elevations of ALT, slightly above the upper limit of normal. In addition, cyclosporine increases the AUC of caspofungin by approximately 35\%. Co-administration of caspofungin and cyclosporine is not recommended until further information on the interaction is available.\textsuperscript{35}

### Investigational Agents

Other drugs currently being studied for the treatment of aspergillosis include voriconazole (Viend, Pfizer), posaconazole, micafungin, liposomal nystatin (Nyotran, Aronex Pharmaceuticals), ravuconazole (an oral triazole), and anidulafungin (an echinocandin).\textsuperscript{30} The agents discussed in the literature most frequently are included below.

### Voriconazole (UK-109,496)

Voriconazole, a new extended-spectrum triazole antifungal agent, has been developed and might soon be available in both intravenous and oral formulations. On October 4, 2001, the Antiviral Drugs Advisory Committee to the FDA recommended that it be approved for the treatment of IA.\textsuperscript{30}

### Mechanism of Action

Like other azoles, voriconazole inhibits the CYP-450-dependent synthesis of ergosterol, a major component of the fungal cell wall.\textsuperscript{40} The theory has been stated that it might have a different activity profile and cross-resistance pattern than other azoles because the composition and content of the different sterols in the cell walls of fungi can vary. Another thought is that voriconazole might exhibit the same mechanisms of resistance as fluconazole and itraconazole, so cross-resistance should be expected, but the extent has not yet been determined.\textsuperscript{40} Ultimately, there is not a predictable pattern of cross-resistance for the azoles among Aspergillus species.

### Efficacy

There are limited published clinical data on the efficacy of voriconazole for the treatment of aspergillosis. An open-label, phase III comparative study was conducted that compared voriconazole with amphotericin B, followed by other antifungals, for the primary treatment of IA.\textsuperscript{41} Two hundred twenty-seven patients with confirmed IA were randomized to receive either voriconazole IV 6 mg/kg for two doses, followed by 4 mg/kg every 12 hours, or amphotericin B 1 mg/kg every day. Patients in the voriconazole group could be switched to oral medication, and patients in either group could be switched to other antifungals after the initial randomized therapy. The study was analyzed by an independent group in a blinded fashion as a modified intent-to-treat (at least one dose of the randomized drug and confirmed aspergillosis were required for inclusion in this analysis). Combining two studies was allowed by the FDA in order to get enough patients for significant analysis. A complete or partial response at week 12 was seen in 52.8\% of the voriconazole group compared to 31.6\% of the amphotericin B group, and the survival rate of patients was 70.8\% in the voriconazole group, versus 57.9\% in the amphotericin B group. A change was made to other antifungals in 37\% of the voriconazole patients and 88\% of the amphotericin B patients. Voriconazole was found to be superior to the amphotericin B regimen, and to have a significant survival advantage compared to the amphotericin B regimen.\textsuperscript{41}

A multicenter uncontrolled study was also conducted in which voriconazole was assessed as primary or salvage treatment of IA.\textsuperscript{40, 42} The
evaluable population included 58 patients who received voriconazole as primary therapy (patients received five days or less of prior therapy) and 54 who received it as salvage therapy. The primary-therapy patients had a 60.3% satisfactory response rate; the salvage therapy patients had a 37% satisfactory response rate. A historical control group was matched 2:1 to compare with similar patients from the voriconazole group. The voriconazole patients had a 52% satisfactory response rate as compared to the control group rate of 25%. Survival at day 90 was 55.4% in the voriconazole group and 41.7% in the control group. However, there were several factors in the study that could have contributed to the poorer results in the case control group. Patients in the voriconazole group were all in Europe, whereas patients in the historical control group were in both Europe and the U.S. There is a chance that patient care and support might be different between the countries. When the U.S. patients were removed from the historical control group, the global response rate for the historical control group increased to 29.3% and survival at day 90 increased to 57.3%. Other potential contributors were total days of treatment and differing inclusion and exclusion criteria that allowed for sicker patients in the historical control group, both of which could have biased the results in favor of the voriconazole group.

**Adverse Effects**

There is limited experience with the use of voriconazole in humans. More than one-third of those who received voriconazole experienced some type of abnormal vision, such as photophobia, altered color perception, ocular discomfort, and decreased vision. Most of the symptoms seemed to resolve with discontinuation of voriconazole, but, follow-up information was not available for all patients who discontinued the drug. It is not known whether restarting voriconazole could further compromise the vision, or whether it is safe to use voriconazole in patients with underlying vision problems.

Like other azoles, voriconazole can cause clinically significant liver-function test abnormalities. In the phase I studies, any hepatic function abnormalities were reversible when voriconazole was discontinued. In the phase III clinical studies, the manufacturer stated that the abnormalities in liver-function tests were associated with the concentration of voriconazole. Liver-function tests should be monitored in patients who receive voriconazole.

There was one death because of ventricular fibrillation in a phase III study, and this patient had underlying left ventricular dilatation and electrolyte abnormalities at the time of the event, but voriconazole could not be excluded as part of the cause. A difference in the incidence of arrhythmias in the voriconazole arm was not noted in the phase III controlled trials, but these studies were not set up to determine such a difference either. It should be used with caution in patients with underlying heart disease and on anti-arrhythmic drugs, and cardiac monitoring during the use of IV voriconazole should be considered. Patients should have electrolyte abnormalities corrected before receiving voriconazole.

A rash occurred in 18.6% of patients in a group of studies, but many of these patients had graft vs. host disease or were also on antihistamines, steroids, and immunosuppressants. The determination was made by the manufacturer and the FDA Advisory Committee that skin rash, including Stevens-Johnson syndrome, can occur with voriconazole administration. Clinical judgment should be used to determine whether to continue voriconazole in a patient with a rash.

**Dose/Administration**

Voriconazole has high oral bioavailability (98%), a large volume of distribution, and is eliminated by hepatic metabolism through the CYP-450 system. In patients with normal hepatic function, the recommended IV dose for treatment of IA is a load of 6 mg/kg every 12 hours for two doses, then 4 mg/kg every 12 hours. The recommended oral dose is a load of 400 mg every 12 hours for two doses, then 200 mg every 12 hours. In patients who weigh less than 40 kg, the recommendation is to give half the usual oral dose.

In patients with mild-to-moderate hepatic failure (Child-Pugh class A or B) the recommended dose for the load is the same, but the maintenance dose is halved. Voriconazole has not been studied in patients with severe hepatic failure (Child-Pugh class C), but the recommendation is to only use it if the benefit outweighs the potential risk, as it has been associated with elevations in liver-function tests and is primarily eliminated heptatically. Voriconazole has not been studied in patients with hepatitis B or C, so caution should be advised in those conditions.

**Limitations**

Other than the adverse effects discussed above, drug interactions are a potential limitation. Because voriconazole is both a substrate and an inhibitor for CYP2C19, CYP2C9, and CYP3A4, there is a potential for drug interactions.

Significant drug interactions were found to exist with the CYP-450 inducers rifampin, rifabutin, and phenytoin. They all decrease the C_{max} and AUC of voriconazole. The manufacturer has recommended that rifampin not be co-administered with voriconazole, and increasing the maintenance dose to 5 mg/kg IV or 400 mg twice daily orally when co-administered with rifabutin or phenytoin. Voriconazole was found to increase the C_{max} and AUC of warfarin, phenytoin, omeprazole, rifabutin, tacrolimus, sirolimus, and cyclosporine because of its effects on inhibition of the CYP2C9 and CYP3A4 isoenzymes. The manufacturer’s recommendations when co-administering voriconazole with certain drugs are listed in Table 2.

Some medications were not studied for interactions, but would be predicted to have interactions with voriconazole. It is recommended that carbamazepine and long-acting barbiturates be avoided with voriconazole; they are likely to significantly decrease voriconazole concentrations because of their induction of CYP-450 metabolism. It is recommended that ergot alkaloids be avoided because voriconazole can inhibit their metabolism and lead to increased ergot alkaloid concentrations.

There are also possible drug interactions with sulfonylureas, HMG CoA reductase inhibitors, benzodiazepines, and vinca alkaloids— as CYP-450 substrates, increased concentrations are likely because of their induction of metabolism. It is recommended that ergot alkaloids be avoided because voriconazole can inhibit their metabolism and lead to increased ergot alkaloid concentrations.

**Posaconazole (SCH-56592)**

Posaconazole is a second-generation triazole and structural analogue of itraconazole that exhibits excellent in vitro activity against *Aspergillus*. CE: Treatment of Invasive Aspergillosis
Its mechanism is selective potent inhibition of CYP-450-dependent demethylase, which is involved in ergosterol synthesis. It has fungicidal activity against Aspergillus spp. It is currently only available in an oral formulation and has high bioavailability. Because not all patients can take oral medications, a more water-soluble prodrug, to be given IV, is being developed (SCH-59884).38

An open-label, non-comparative study was conducted to evaluate posaconazole’s efficacy and safety for the treatment of invasive fungal infections refractory to or intolerant of standard therapy.43 Fifty-one patients (25 with aspergillosis) were given posaconazole 200 mg orally four times daily in the hospital and 400 mg orally twice daily after discharge. Of the 15 evaluable aspergillosis patients at week four, 53% had a clinical response. Of the seven patients evaluable at week eight, 85% had a clinical response. The most frequent side effects seen were diarrhea (8% of total patients), asthenia (4%), flatulence (4%), and eye pain (4%).43

**Micafungin (FK-463)**

Micafungin is a new echinocandin currently under development. Like the other echinocandin, caspofungin, it inhibits fungal cell wall synthesis by inhibiting the activity of the enzyme glucan synthase, which leads to an inhibition of the synthesis of beta-(1,3)-D glucan.38 It is only available for parenteral administration. It has potent in vitro activity against Aspergillus spp., but unlike amphotericin B and itraconazole, it is not fungicidal against them. When tested with amphotericin B, the combination was neither antagonistic nor synergistic against Aspergillus organisms in vitro.36

An open-label, multicenter study was conducted in 70 patients with deep mycosis definitely or presumably caused by Aspergillus or Candida spp.44 Patients received micafungin 12.5 to 150 mg/day. Of the patients with aspergillosis, 24/41 (59%) had clinical response and mycological response was seen in 12/19 (63%). Adverse effects were seen in 21 patients (30%).44

**Liposomal nystatin**

Nystatin, a polyene antibiotic closely related in structure to amphotericin B, has a broad antifungal spectrum including activity against Aspergillus. It has been used for over 30 years, but primarily as a topical agent because of its toxicity and insolubility. However, a liposomal formulation has been created, which might give new promise to IV use of this agent.30

A phase II study was conducted in which liposomal nystatin 4 mg/kg/day IV was administered to 24 patients with definite or probable IA who were refractory to or intolerant of amphotericin B.45 A complete response was seen in 5% of evaluable patients, and a partial response was seen in 26%. Dosage reduction was required for nephrotoxicity in 13% of the patients, and 92% were premedicated for chills or respiratory distress after the first infusion. Discontinuation occurred for severe rigors, chills, and hypotension in 8% of the patients enrolled in the study.45

**Combination Therapy With the Currently Available Antifungal Agents**

Little information is available regarding the use of azoles, flucytosine, or rifampin in combination with amphotericin B, itraconazole, or caspofungin. The role and efficacy of such combinations is not established in the treatment of IA. Potential problems might actually occur with the concurrent use of these drugs. The use of rifampin and itraconazole is limited by drug–drug interactions and the use of flucytosine might exacerbate myelosuppression in neutropenic patients. It might also be difficult to maintain nontoxic blood levels of flucytosine should the amphotericin B cause nephrotoxicity that might impair the excretion of flucytosine. The data regarding whether the combination of amphotericin B with itraconazole is antagonistic or synergistic are conflicting, clinical studies are needed.46-48 Studies of caspofungin in combination with amphotericin B suggest no antagonism; however, the clinical significance is unknown because it has not yet been studied in humans.35

**Cost of Therapy**

Along with efficacy and adverse effects, the cost of therapy must also be considered. Table 3 lists the weekly cost of therapy for each agent. In addition to the purchase price, the cost of administration and toxicity must also be considered. When it is well-tolerated, the conventional amphotericin B product remains the least expensive choice. However, when the infection is refractory to amphotericin therapy or when the patient cannot tolerate conventional amphotericin B because of nephrotoxicity, consideration must be given to the other agents.

**Duration of Therapy**

There are no guidelines regarding the duration of therapy for the treatment of IA. Clinical judgment should be used when determining the duration, and should include consideration of factors such as response to therapy, the extent of infection, and the patient’s underlying disease or immune status. In general, the treatment should be continued until clinical and radiographic abnormalities are resolved.

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**Table 2 Recommendations For Drugs Co-administered with Voriconazole**

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Manufacturer’s Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>monitor PT/other suitable anticoagulation tests; adjust warfarin dosage if warranted</td>
</tr>
<tr>
<td>phenytoin</td>
<td>monitor phenytoin concentrations and monitor for phenytoin-related adverse effects</td>
</tr>
<tr>
<td>omeprazole</td>
<td>reduce omeprazole dose by one-half</td>
</tr>
<tr>
<td>rifabutin</td>
<td>monitor CBC and adverse effects associated with rifabutin</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>reduce tacrolimus dose by one-third; monitor tacrolimus concentrations frequently</td>
</tr>
<tr>
<td>sirolimus</td>
<td>sirolimus is contraindicated with voriconazole</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>reduce cyclosporine dose by one-half; monitor cyclosporine concentrations frequently</td>
</tr>
</tbody>
</table>

**Table 3 Comparative Costs of Treatment for Invasive Aspergillosis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>AWP Cost&lt;sup&gt;47&lt;/sup&gt; Per 7 Days of Therapy for a 70-kg Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>1 to 1.5 mg/kg QD or continuous infusion</td>
<td>$114 to $171</td>
</tr>
<tr>
<td>Lipid Complex</td>
<td>5 mg/kg QD</td>
<td>$5,635</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70 mg load, then 50 mg QD</td>
<td>$2,624</td>
</tr>
<tr>
<td>Itraconazole capsule</td>
<td>200 mg tid x 4 days, then 200 mg bid</td>
<td>$280</td>
</tr>
<tr>
<td>Itraconazole solution</td>
<td>200 mg tid x 4 days, then 200 mg bid</td>
<td>$294</td>
</tr>
<tr>
<td>Itraconazole IV</td>
<td>200 mg bid x 2 days, then 200 mg QD</td>
<td>$1,386</td>
</tr>
</tbody>
</table>

<sup>AWP = average wholesale price; QD = daily; bid = twice daily; tid = three times daily.</sup>


