New Advances in Fungal Pharmacotherapy: Voriconazole and Caspofungin

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LEARNING OBJECTIVES

1. Describe the emerging fungal pathogens in immunocompromised patients.
2. Describe the 2 newest agents available for the treatment of fungal infections.
3. Compare the new agents with traditional agents for fungal infections.
4. Choose the appropriate therapy of both the new agents and older agents for fungal infections.

ABSTRACT: Fungal pathogens are quickly becoming a major cause for concern in hospitalized patients. Particular concern has developed over the rate and severity of systemic mycosis in immunocompromised patients. Until recently, treatment of these severe infections relied on first-generation azole antifungals or amphotericin B. The approval and availability of voriconazole, a second-generation triazole with activity against *Candida* and *Aspergillus* species, and the first echinocandin, caspofungin, have expanded the clinician's armamentarium against fungal infections. This review will help clarify the role in therapy of these 2 new agents. Increased clinical experience with the new agents may reduce the role of amphotericin B in the fight against system mycoses.

Introduction

Antifungal agents, particularly the azole antifungals, developed in the 1980s and 1990s, offered breakthroughs in toxicity reduction, but were severely limited by pharmacokinetic concerns such as poor bioavailability and spectrum of activity deficiencies. The human immunodeficiency virus (HIV) epidemic, coupled with advances in chemotherapy and bone marrow transplantation, resulted in the proliferation of more resistant fungal species, including *Candida albicans* and non-albicans *Candida* species. These infections are associated with significant

morbidity and mortality, and highlighted the need for new antifungal antibiotics.

Two new antifungal agents were recently approved to better manage aspergillosis and candidiasis. Voriconazole (Vfend®, Pfizer) and Caspofungin (Cancidas®, Merck) offer a broad spectrum of activity and minimal severe adverse effects. This continuing pharmacy education article will help the practitioner better understand these agents and their role in therapy.

This review will focus on the 2 newest systemic antifungals, but to gain perspective of the topic we first need to understand the fungal pathogens and currently available antifungal antibiotics.

Fungal Pathogens

Invasive fungal infections are becoming more prevalent because of the increasing population of immunosuppressed patients. Diseases such as HIV, cancer (and subsequent chemotherapy), solid organ or bone marrow transplantation coupled with increased intensive care unit (ICU) stays, broad-spectrum antibacterial therapy, and surgical interventions leave the clinician facing an ever-growing threat of fungal infection.

Antifungal therapy over the past 50 years has focused on *Candida albicans*, *Aspergillus fumigatus*, and mucormycoses. The past 2 decades have seen a shift in this spectrum with the emergence of non-albicans *Candida* species and other *Aspergillus* species as formidable pathogens.

The most distinct epidemiologic change in fungal infections has been the emergence of non-albicans *Candida* species. These species are less responsive to fluconazole therapy and may require the use of other antifungal agents for therapy. Table 1 summarizes the *Candida* species that cause human disease.

Table 1. Pathogenic *Candida* species

C. albicans	*C. parapsilosis*
C. glabrata (torulopsis)	*C. pseudotropicalis*
C. guilliermondii	*C. rugosa*
C. krusei	*C. stellatoidea*
C. lusitaniae	*C. tropicalis*

Superficial or localized candida infections are rarely life threatening, nor do these infections typically progress to hematogenous dissemination.[1] Typically, there must be the presence of a pathogenic organism and a compromised host to progress to a potentially lethal infection. Further confounding the treatment of fungal infections is the difficulty of diagnosing true infection. Blood culture is the absolute diagnostic standard for *Candida* species; however, it is rarely positive.[2]

Paralleling the emergence of other candidal species is the proliferation of *Aspergillus* infections, particularly in solid organ or bone marrow transplantation and leukemia patients. Aspergillosis is considered an opportunistic infection caused most commonly by *A. fumigatus* and *A. flavus*.[3]

Aspergillus species are ubiquitous in the environment and enter the patient most commonly via the respiratory tract. They thrive in well-vascularized areas and may invade blood vessels. Aspergillosis may also manifest as a localized infection affecting the skin,

sinus, or bronchi. Blood cultures are of little value in disseminated disease, leaving biopsy and tissue culture as the best diagnostic technique. Unlike candidal infections, superficial aspergillosis may invade local vessels and lead to necrosis and infarction.

Emerging fungal pathogens other than *candida* and *aspergillus* species are also a major concern in the immunocompromised. Zygomycoses (mucormycoses), *Fusarium*, and *Penicillium* are significant pathogens and must be considered in severely ill patients.

Fungi represent a significant proportion of pathogens in immunocompromised patients and must be considered early on when a patient appears to be infected.[4] The costs of not considering fungal pathogens can be significant. Neutropenic patients with *Aspergillus,* both localized and disseminated infection, have an expected mortality in excess of 80%, and patients with disseminated *Fusarium* may have a mortality rate approaching 100%.[3,5] Remaining of significant concern, the mortality rate in patients with candidemia may exceed 50%.[6] The need to effectively treat these patients is clearly apparent.

The following review will help the clinician decide which antifungal is the appropriate choice for his or her patient and illustrate the revealing role of the 2 newest agents, voriconazole and caspofungin, in the treatment of systemic fungal infections.

Currently Available Systemic Antifungals

There are 4 distinct classes of antifungal antibiotics: azole, polyene, pyrimidine, and echinocandin. Some of these classes have expanded in recent years and reflect well over 50 years of antifungal research.

Azoles

The azole class of antifungal antibiotics represented the newest class of agent until the advent of the echinocandins. The azole class is composed of triazole (fluconazole, voriconazole, itraconazole) and imidazole (ketoconazole) agents. Voriconazole represents the first of a new generation of azoles with enhanced activity versus *Aspergillus* and *Candida* species. The azoles are fungistatic and inhibit cytochrome P-450-dependent 14α-lanosterol demethylation in the fungal cell. This interference results in a defective cell wall and altered permeability.

The spectrum of activity of the azoles includes *Candida* species (*C. albicans* ≥ *C. tropicalis* = *C. parapsilosis* > others), *Cryptococcus neoformans*, and the dimorphic fungi such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum.* The only agents with reliable activity against *Aspergillus* species are itraconazole and voriconazole. Fluconazole is considered the drug of choice for *C. albicans* and cryptococcal disease.

The azoles are generally safe and well tolerated. They all have significant drug interactions with agents that are substrates or inducers/inhibitors of human CYP-450 isoenzymes. The older agent ketoconazole has fallen out of favor attributable to variable

bioavailability and drug interactions; however, the other agents in the class have good bioavailability and ease of dosing. These safety and oral dosing formulation advantages have resulted in the widespread use of the azoles for a variety of fungal infections.

Polyenes

There are 2 currently available polyene antifungals: amphotericin B (including lipid derivatives) and nystatin. Owing to significant toxicities, nystatin is reserved for topical administration only. Amphotericin B is considered the "gold standard" for most refractory or non-albicans (i.e., *C. krusei* and *C. glabrata*) fungal infections. The polyenes act by binding to ergosterol in the fungal cell membrane, altering permeability and causing fungal cell wall lysis. These agents are considered fungicidal for most fungal species. They demonstrate good activity against a wide variety of fungal pathogens, including most *Candida* species, *Cryptococcus neoformans*, *Aspergillus* species, and dimorphic fungi such as *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum.* The polyenes have few drug interactions; however, they have an unfavorable adverse effect profile. Amphotericin B has significant infusion-related and dose-dependent toxicities. Nephrotoxicity, fever, chills, rigors, hypokalemia, hypomagnesemia, and anemia have garnered this agent the widely known moniker of "Ampho-terrible."

The lipid-based amphotericin B products have been developed in response to the unacceptable toxicities of the conventional agent. The newer formulations (Amphotericin B Lipid Complex [Abelcet®] and Liposomal Amphotericin B [AmBisome®]) have demonstrated less nephrotoxicity when compared with the conventional product. Another lipid formulation, Amphotericin B Colloidal dispersion (ABCD), compares favorably with regard to efficacy with conventional amphotericin B, but had a higher rate of infusion-related toxicities, thus limiting widespread utility.[7] Liposomal amphotericin B (AmBisome®) has significantly fewer infusion-related toxicities, and may not require premedication (APAP + diphenhydramine +/- meperidine).

The currently available lipid products are U.S. Food and Drug Administration (FDA) indicated for patients intolerant of or refractory to conventional therapy; however, many experts feel that the lipid formulations have replaced conventional amphotericin B as the standard of care for serious fungal infections. Liposomal amphotericin B (AmBisome®) is also indicated for the empiric treatment of febrile, neutropenic patients; cryptococcal meningitis in HIV-infected patients; and visceral leishmaniasis. Amphotericin B lipid complex (Abelcet®) is indicated for cryptococcal meningitis in HIV patients.

The lipid formulations are associated with significant acquisition cost (AmBisome® > Abelcet® > conventional Amphotericin B); therefore, there has been a great deal of controversy over their routine use and formulary debate regarding selection of lipid formulation. A head-to-head, randomized, controlled clinical trial to evaluate safety and efficacy differences between the 2 most common lipid-based agents is yet to be conducted.

Pyrimidines

The pyrimidine class of antifungals contains the agent flucytosine (5-FC). This agent possesses a narrow spectrum of activity by inhibiting pyrimidine metabolism, RNA, and protein synthesis. The spectrum includes *Candida* species and *Cryptococcus neoformans*, and utility is limited to combination therapy for infections caused by these organisms. Resistance may be intrinsic or develop during therapy; therefore, combination therapy is necessary. Microbiologic synergy and improved clinical outcomes have been demonstrated with flucytosine and amphotericin B for cryptococcal meningitis.[8] Flucytosine is only available as an oral formulation and, therefore, is not be used in patients that cannot tolerate or take medications by mouth.

Flucytosine was initially developed as an antitumor agent but lacked significant activity in this area. It shares anti-pyrimidine (cytosine) properties of the anticancer agent fluorouracil (5-FU) and is converted to 5-FU in an intermediary step of activation within the fungal cell. This conversion may explain the major adverse events associated with flucytosine: myelosuppression, gastrointestinal distress, and hepatotoxicity. These effects are more common when serum concentrations are > 100 mcg/ml. Target concentrations are 50-100 mcg/ml to help avoid these adverse events.[9]

Echinocandins

Caspofungin is the prototype of the echinocandins, which represents a new class of antifungal agents. This class and agent will be reviewed in another section of this paper. There are several echinocandins under development, including anidulafungin and micafungin, which may reach approvable status in the near future.

Voriconazole

Voriconazole is a second-generation azole antifungal approved by the FDA in 2002. The second-generation azoles have been in development for nearly 10 years. Voriconazole (Vfend®, Pfizer) is a triazole, synthetic derivative of fluconazole (Diflucan®, Pfizer). The addition of an α-methyl group and the replacement of a triazole ring with a fluorinated pyrimidine increases activity over the parent compound fluconazole.

Activity

The mechanism of action of voriconazole is the same as all other azole antifungals (itraconazole, fluconazole, ketoconazole), which is inhibition of cytochrome P-450-dependent 14α-lanosterol demethylation.[10-11] This is the critical step in fungal membrane ergosterol synthesis.

Voriconazole has demonstrated in vitro activity against *Aspergillus fumigatus*, flavus, niger, and terreus species. *Aspergillus terreus* often expresses amphotericin B resistance. The majority of isolates studied in vivo and in vitro studies were *A. fumigatus* but several other *Aspergillus* isolates were noted in clinical trials. The agent also demonstrated variable in vitro activity against *Scedosporium apiospermum* and *Fusarium* species.

Voriconazole is fungistatic for most yeasts, but for *Aspergillus* species, it is fungicidal.[12] This increased activity against molds may be attributable to increased activity at the site of action

and a more complete inhibition of ergosterol synthesis.

Voriconazole is active against all *Candida* species including those resistant to fluconazole.[13] There is generally a 1-2 log reduction in minimum inhibitory concentrations (MICs) compared with fluconazole, although there have been isolates resistant to all azole antifungal antibiotics. Voriconazole also demonstrates in vitro activity against other yeasts including *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasma capsulatum*.

Resistance

There are several mechanisms of fungal resistance to azole antibiotics. These include overexpression of the target enzyme, point mutations in fungal enzymes, or the appearance of efflux pumps.[14] Resistance to one or more of the other azole antifungal agents may confer resistance to voriconazole and may require treatment with another class of antifungal.[11]

Pharmacology

Voriconazole is available for oral administration (film-coated tablets) or for intravenous infusion (lyophilized powder for solution). The powder for injection also contains sulfobutyl ether beta-cyclodextrin sodium (SEBCD).

The pharmacokinetics of voriconazole are nonlinear owing to saturation of its metabolism. Increases in dose by 50% result in an estimated 2.5-fold increase in total drug exposure.[11] Steady-state trough plasma concentrations are reached in 5 days without a loading dose and 1 day if a loading dose is administered. This underscores the critical need for appropriate dosing of this agent.

Oral absorption for voriconazole is excellent with an average bioavailability of 96%. Mean maximum plasma concentrations and area under the curve (AUC) are reduced when given with high-fat meals. Voriconazole is 58% protein-bound with extensive tissue distribution.

Voriconazole is metabolized by the human hepatic cytochrome P-450 isoenzymes, 2C19 (major), 2C9, and 3A4. Drug interactions with inducers/inhibitors and substrates of these enzymes are expected and described later. The drug is eliminated via hepatic metabolism with less than 2% excreted in the urine. Owing to non-linear kinetics, the half-life is dose dependent and not useful in the prediction of accumulation or toxicity.

No dose adjustments are required for differences in sex or elderly patients, and safety and effectiveness in pediatric patients below the age of 12 years have not been established.

In patients with moderate or severe renal failure (creatinine clearance < 50 ml/min), voriconazole IV should be avoided because of the accumulation of the SEBCD vehicle.

Voriconazole is typically given as a loading dose of 6 mg/kg (actual body weight) intravenous (IV) every 12 hours for 2 doses, followed by a maintenance dose of 4 mg/kg IV every 12 hours. Upon clinical improvement and toleration of either oral medication or diet or both the provider should consider

converting to the oral formulation in the following conversion: patients > 40 kg should receive 200 mg orally twice daily and patients < 40 kg should receive 100 mg orally twice daily.

Dosages may be adjusted higher if there is an inadequate response during oral therapy (up to 300 mg po q12h). If the patient cannot tolerate voriconazole, the IV maintenance dose may be reduced to 3 mg/kg twice daily.

Drug Interactions

The potential for significant drug interactions with voriconazole is high because of its metabolism by and inhibition of CYP-450 isoenzymes. Table 2 summarizes the key drug interactions for voriconazole. If doses of target agents (or voriconazole) are adjusted during voriconazole therapy, the clinician must remember to re-adjust after discontinuation of voriconazole (or target agent) therapy.

Table 2. Drug Interactions with Voriconazole

Target Drug	Effect	Recommendation
Carbamazepine	↓ Voriconazole levels	Contraindicated
Long-acting barbiturates	↓ Voriconazole levels	Contraindicated
Rifampin	↓ Voriconazole levels	Contraindicated
Cyclosporine	↑ Cyclosporine levels	Reduce dose by ½ and monitor plasma CSA levels
Quinidine	↑ Quinidine levels	Contraindicated
Sirolimus	↑ Sirolimus levels	Contraindicated
Tacrolimus	↑ Tacrolimus levels	Reduce dose by 1/3 and monitor plasma tacrolimus levels
Cisapride, Astemazole, Terfenadine	↑ Levels of target drug	Contraindicated (agents removed from U.S. market)
Warfarin	↑ Prothrombin time	Monitor PT/INR
Ergot alkaloids	↑ Ergot levels	Contraindicated
Omeprazole	↑ Omeprazole levels	Reduce dose by ½
Rifabutin	↓ Voriconazole levels & ↑ rifabutin levels	Contraindicated
Phenytoin	↓ Voriconazole levels & ↑ phenytoin levels	Double voriconazole dose & monitor phenytoin level
Sulfonylurea, statins, vinca alkaloids, calcium channel blockers, benzodiazepines	Proposed ↑ levels of target drug	Monitor serum concentrations or drug effect and consider dosage decrease of target drug

Adverse Events

The most frequent unique adverse event reported for voriconazole is visual disturbance. This effect was reported in ~ 30% of patients, and is reversible within 14 days of discontinuation. The effects were noted early in therapy, and may continue through the course of dosing. The visual disturbances include either altered or enhanced or both altered

and enhanced visual perception and blurred vision, and either color vision changes or photophobia or both. The disturbances are generally mild and rarely result in discontinuation of voriconazole therapy. The cause of the disturbances is unknown; however, decreases in the electroretinogram waveform amplitude, a decrease in the visual field, and an alteration of color perception were noted in healthy volunteers treated for 28 days.

In the cohort of all therapeutic studies (1493 patients) the incidence of other adverse drug reactions (ADRs) was mild and infrequent. Those reactions above 2% are listed in Table 3.

Table 3. Adverse Events of Voriconazole

ADR	Percentage
Fever	6.2
Chills	4.1
Headache	3.2
Tachycardia	2.5
Nausea	5.9
Vomiting	4.8
Liver function tests abnormal	2.7
Alkaline phosphatase increased	3.6
Hallucinations	2.5
Rash	5.8

Acquisition Costs

The acquisition costs for common doses of antifungals are summarized in Table 4.

Table 4. Acquisition Costs of Common Antifungals

Agent	Dose (70 kg patient)	Daily Acquisition Cost Average Wholesale Price (AWP)
Voriconazole (Vfend®)	420 mg IV BID (ld) 280 mg IV BID (md) 200 mg po BID	$ 354 $ 236 $ 50
Caspofungin (Cancidas®)	70 mg IV (ld) 50 mg IV (md)	$ 356 $ 277
Amphotericin B Lipid complex (Abelcet®)	350 mg IV daily (5 mg/kg)	$ 447
Liposomal Amphotericin B (AmBisome®)	210 mg IV daily (3 mg/kg) 350 mg IV daily (5 mg/kg)	$ 653 $1088
Fluconazole (Diflucan®)	400 mg IV daily 200 mg IV daily 200 mg po daily 100 mg po daily	$ 113 $ 77 $ 11 $ 7
Amphotericin B conventional	70 mg IV daily (1 mg/kg)	$ 8

Clinical Use of Aspergillosis

Voriconazole is indicated for the treatment of invasive aspergillosis based upon 2 published, large, randomized clinical trials.[15-16]

Denning and colleagues conducted an open, non-comparative, multicenter study evaluating the safety and efficacy of voriconazole in acute invasive aspergillosis.[15] This trial enrolled 140 patients, of which 116 were evaluable. Invasive aspergillosis was proven in 48 (41%) and probable in 68 (59%). The patients in the study were immunocompromised and treated with intravenous voriconazole 6 mg/kg twice daily for the first day and then 3 mg/kg twice daily for 6-27 days, followed by 200 mg orally for up to 24 weeks. Response rates for the population were 48% good response (14% complete, 34% partial), 21% stable response, and 31% failed to respond to therapy. A good response was determined to be resolution of all clinical signs and symptoms attributable to invasive aspergillosis and complete- or near-complete radiographic resolution. A partial response was defined as a major improvement or resolution of signs and symptoms attributable to invasive aspergillosis and at least a 50% improvement in radiologic findings. Failure encompassed progression and death owing to invasive aspergillosis. When compared with historical controls, the authors concluded that voriconazole demonstrated comparable efficacy with amphotericin B and itraconazole.

The larger, randomized trial enrolled 277 patients to compare voriconazole with standard amphotericin B therapy for primary treatment of aspergillosis.[16] Patients in this trial received 2 doses of voriconazole 6 mg/kg and subsequent doses of 4 mg/kg twice daily for at least 7 days followed by 200 mg orally twice daily or intravenous amphotericin B deoxycholate (1-1.5 mg/kg per day). There were 144 patients in the voriconazole group and 133 in the amphotericin B group with definitive or probable aspergillosis who received at least 1 dose of drug. Patients were evaluated at 12 weeks for response. Successful outcomes (complete or partial response) were recorded for 52.8% of those treated with voriconazole and 31.6% (CI 10.4-32.9%) for those treated with amphotericin B. Voriconazole also demonstrated a survival benefit (P = 0.02) compared with amphotericin B at 12 weeks. The overall incidence of drug toxicity was significantly lower in the voriconazole (P = 0.02) group; however, the incidence of transient visual disturbances (P = < 0.001) and skin reactions (P = 0.05) was higher in the voriconazole arm. This trial concluded that in patients with invasive aspergillosis, initial therapy with voriconazole, compared with amphotericin B, resulted in better responses, improved survival, and fewer side effects.

Other Serious Fungal Pathogens

Voriconazole is approved for the salvage treatment of infections caused by *Pseudallescharia boydii*, *Scedosporium apiospermum* (asexual form of *P. boydii*), and *Fusarium species*.[11]

Because the incidence of these serious fungal infections is low, case report data were pooled to analyze the utility of voriconazole. In 24 patients with *S. apiospermum* there was a 63% successful response with 3 patients relapsing within 4 weeks. Patients with

cerebral disease had a success rate of 60%. Nine of 21 patients (43%) with *Fusarium* species were treated successfully with voriconazole.

Febrile Neutropenia

Walsh and colleagues completed a randomized, international, multicenter trial of voriconazole compared with liposomal amphotericin B in patients with neutropenia and persistent fever.[17] The authors reported the response rates from 837 neutropenic patients (415 assigned to voriconazole and 422 to liposomal amphotericin B). The liposomal amphotericin B group had a successful response in 30.6% of patients while voriconazole had a success rate of 26%. The difference did not reach statistical difference. The voriconazole group had significantly fewer infusion-related toxicities and nephrotoxicity; however, they had a higher rate of visual disturbances. This study concluded that voriconazole is a suitable alternative to liposomal amphotericin B preparations for empiric antifungal therapy in patients with neutropenia and persistent fever. This study has generated controversy because, despite the authors' conclusions, the FDA did not extend approval to voriconazole for this indication. The study has been criticized because voriconazole did not reach noninferiority compared with liposomal amphotericin B. Voriconazole was statistically superior in one of the 5 subgroups (breakthrough fungal infections), while data favored liposomal amphotericin B in the other 4 categories (overall success rate, mortality, withdrawal attributable to perceived lack of efficacy), although not statistically significant.[18-20]

Candida Esophagitis

Voriconazole demonstrates in vitro activity against a variety of *Candida* species. It has enhanced activity compared with fluconazole against fluconazole-resistant *C. krusei*, *C. glabrata*, and *C. guilliermondii*.[21-22] This in vitro activity was clinically tested in a multicenter, double-blind, double-dummy study comparing voriconazole with fluconazole for the treatment of esophageal candidiasis.[23] This trial enrolled 391 patients, most with AIDS. The patients were given voriconazole 200 mg po daily or fluconazole 200 mg po daily for at least 7 days after clinical resolution. There was no statistical difference in cure rates between the 2 groups. A second trial conducted in AIDS patients with fluconazole-refractory esophagitis demonstrated clinical cure or significant response in 10 out of 12 patients.[24]

Other Systemic Mycoses

Voriconazole demonstrates good in vitro activity against a variety of other problematic fungal pathogens such as *C. neoformans*, *C. immitis*, and *H. capsulatum*.[25-28] To date, there have been no clinical trials published regarding the efficacy and safety of voriconazole for conditions caused by these organisms. Case reports suggest effectiveness; however, there is insufficient data to recommend voriconazole for treatment of these pathogens.[29]

Voriconazole was studied in a broad, open-label trial for the treatment of a variety of refractory fungal infections. The researchers reported the results of 372 patients treated with voriconazole for refractory, systemic *Candida* infection; aspergillosis; cryptococcosis;

fusariosis; penicilliosis; scedoporiosis; and mixed infections.

Table 5 summarizes the outcomes of each group.

Table 5. Outcomes from "Voriconazole Treatment for Less Common, Emerging, or Refractory Fungal Infections"[29]

Infection	Success (%)	
Aspergillosis	62/142	(43.7)
Candidiasis	50/87	(57.5)
Cryptococcosis	7/18	(38.9)
Fusariosis	5/11	(45.5)
Penicilliosis	9/10	(90)
Scedoporiosis	3/10	(30)
Mixed infections	2/4	(50)

The isolates came from a variety of sources including the blood and sterile body sites. The most frequent sites from which the organisms were isolated were aspergillosis, lung (61%) and candidiasis, esophagus 47%. The authors concluded that the outcomes for these refractory infections were comparable to other published reports using amphotericin B lipid complex, conventional amphotericin B, and fluconazole, and lead them to conclude that voriconazole is a good alternative for these difficult infections.[29]

Coccidioidal Meningitis: Case Report

Voriconazole demonstrates in vitro activity against *C. immitis*, the causative agent in Valley Fever (coccidioidomycosis), but has not been formally studied or given an FDA indication for the treatment of infection caused by this pathogen. A recently published case report discussed a patient with coccidioidal meningitis refractory to fluconazole therapy treated successfully with voriconazole. The patient tolerated intravenous therapy followed by oral voriconazole therapy and remained asymptomatic with magnetic resonance imaging- (MRI)-confirmed disappearance of brain lesions during and after > 2 years of therapy. The patient did experience transient photopsia and continual photosensitivity that lessened when the dose was reduced.[30] Voriconazole penetration into the cerebral spinal fluid (CSF) ranges from 22% to 100% of serum concentrations in a small group of immunocompromised patients.[31] The place in therapy of voriconazole for coccidioidomycosis remains to be determined, but results of in vitro work and case reports are promising for this potentially life-threatening disease.[26-28, 30]

Summary

Voriconazole is a promising triazole compound derived from fluconazole with enhanced activity against a variety of fungal species. Voriconazole is available as an oral and intravenous product, and may become the drug of choice for *Scedosporium* and *Fusarium* infections; however, because of adverse events, drug interactions, and evolving efficacy literature, it should not supplant fluconazole as first-line therapy for most candidal infections. The data for the use of voriconazole as a first-line agent in aspergillosis are strong and favor use

over all amphotericin B formulations. The oral formulation offers a potent, consistently bioavailable product for the management of aspergillosis for patients with a functional gastrointestinal tract. The clinician must consider the multiple, potential drug interactions and adverse events when considering voriconazole. Despite these limitations, voriconazole offers a significant advance in azole antifungals and a welcomed addition to the antifungal armamentarium.

Caspofungin

Caspofungin represents the first of the echinocandin antifungal antibiotics. Agents in this class target glucan synthesis in the fungal cell wall. Caspofungin is a pneumocandin B_0, a semisynthetic product fermented from the fungus *Glarea lozoyensis*, and is licensed in the United States as Cancidas® (Merck).[32]

Activity

Caspofungin selectively blocks the synthesis of β(1,3) - D - glucan of the fungal cell wall by non-competitive inhibition of the enzyme β(1,3) - D - glucan synthase, an essential component in the cell wall of many fungal species.

Caspofungin demonstrates in vitro activity against *Aspergillus* species (*A. fumigatus*, *A. flavus*, and *A. terreus*), and *Candida* species (*C. albicans*, *C. glabrata*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*). There is no reported activity against *Cryptococcus neoformans* as reported in a murine model; therefore, use for this infection is not recommended.[33]

Limited data regarding the development of resistance to caspofungin are available. In vitro resistance has been documented in experimental models; however, clinical relevance has not been correlated.[34]

The disruption of glucan synthesis results in both fungistatic (inhibition of cell growth) and fungicidal (lysis of cell) activity for a variety of fungal species. Caspofungin, in vitro, appears to be fungicidal against *Candida* species and both fungicidal and fungistatic against *Aspergillus* species.[35-36]

In vitro research is ongoing regarding the combination of caspofungin with other antifungal agents for candidal and aspergillus infections. Combinations with fluconazole provided indifferent activity against a variety of candidal isolates.[37] In another in vitro/in vivo (murine model) study, researchers concluded that combinations of caspofungin and amphotericin B or fluconazole were additive or synergistic for azole-resistant *Candida* isolates. They also concluded that mice treated with the combination therapy demonstrated a prolonged survival and reduced organism tissue burden.[38] Combinations of caspofungin with amphotericin B are promising and yield additive or synergistic results for *Aspergillus* species.[39-40]

Resistance

The echinocandin are new to clinical practice, and little is known regarding the frequency, distribution, and mechanisms of resistance. In vitro data suggest a mutation of the FKS1 gene, which functions as the target for the echinocandins.[34,41]

Pharmacology

Caspofungin is available as the diacetate form in a water-soluble, lyophilized powder for intravenous infusion.

Caspofungin is administered by IV infusion as a 70-mg dose on day one followed by a 50-mg IV daily maintenance dose.

Caspofungin demonstrated polyphasic distribution with a short α phase, a long (9- to 11-hour half-life) linear β phase, and a prolonged (40- to 50-hour half-life) γ phase. The compound is extensively bound to plasma albumin (97%). Caspofungin is eliminated through the kidneys as a metabolite of hydrolysis or n-acetylation. There is no cytochrome P-450 metabolism demonstrated with the compound. Less than 2% of caspofungin is excreted unchanged in the urine.

Drug-drug interactions with caspofungin are infrequent; however, increased monitoring of tacrolimus is suggested. When caspofungin is administered with known metabolism inducers such as efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine, the loading dose (70 mg) should be continued throughout concomitant therapy.

No dose adjustments are needed in renal insufficiency, and caspofungin is not dialyzable; therefore, no supplemental doses postdialysis are necessary. Accumulation may occur in patients with hepatic insufficiency; therefore, dosage reduction is suggested for patients with moderate hepatic insufficiency. Studies in patients with severe hepatic insufficiency have not been completed.

There were no pharmacokinetic differences noted between males and females or races when given a single dose of caspofungin. It is not necessary to adjust doses based on sex or race. Despite increased area under curve (AUC) exposures in elderly patients, no dose adjustments are needed based on age, but especially careful monitoring for adverse events may be warranted in this population.

Adverse events for caspofungin are summarized in Table 6. There have been cases of possible histamine-related symptoms, including rash, facial swelling, pruritus, sensation of warmth, and bronchospasm. Anaphylaxis has been reported with the administration of caspofungin. In a randomized, double-blinded, invasive candidiasis study, the incidence of overall adverse events was lower in the caspofungin (29%) group compared with those treated with amphotericin B (58%).[42]

Table 6. Adverse Drug Reactions of Caspofungin

ADR	Percentage
Chills	5.3
Fever	7.0
Phlebitis	3.5
Diarrhea	2.6
Vomiting	3.5
Increased ALT	3.7
Increased bilirubin	3.8
Increased alkaline phosphatase	8.3
Increased serum creatinine	3.7
Decreased potassium	9.9

Acquisition Costs

The acquisition costs for common doses of antifungals are summarized in Table 4.

Clinical Use

Caspofungin is FDA approved for the treatment of candidemia (intra-abdominal, peritonitis, pleural space), esophageal candidiasis, and invasive aspergillosis in patients who are refractory to or intolerant of other therapies.

Candidemia

One randomized clinical trial evaluated the use of caspofungin for systemic candidiasis.[43] The researchers randomized patients with systemic candidiasis to receive either caspofungin or conventional amphotericin B for 14 days. They used a modified intent-to-treat analysis and defined success as both microbiologic eradication and symptom resolution. Success was observed in 73% of the caspofungin-treated patients and 62% of the amphotericin B–treated patients. There was no statistical difference between the 2 groups. As mentioned previously, the incidence of adverse reactions was more frequent in the amphotericin B group.

Candida Esophagitis and Mucositis

Three published trials examined the effectiveness of caspofungin for the management of mucosal candidiasis.[43-45]

The first trial randomized 175 patients with candidal esophagitis to receive intravenous caspofungin (50 mg daily) or fluconazole (200 mg daily). Patients received therapy for an average of 9 days. The primary endpoint was favorable response overall at 5-7 days posttherapy. A favorable response was considered if there were both significant endoscopic improvement and complete resolution of symptoms. Results were comparable for the 2 groups and showed no statistical difference. There was no statistically significant difference in relapse rates between the groups; however, there was a trend toward fewer relapses in the fluconazole group at 28 days posttreatment.[43]

The second trial randomized 122 patients to receive either intravenous caspofungin (50 or 70 mg daily) or amphotericin B (0.5 mg/kg body weight daily). The primary endpoints were identical to the previous trial. Success rates for those treated with amphotericin B were 63%, 74%, and 88% in the amphotericin B, caspofungin 50 mg, and

caspofungin 70 mg groups, respectively. The differences did not achieve statistical significance for either caspofungin group. The rate of discontinuation for the amphotericin B arm was 24%, while only 4% and 7%, respectively, discontinued treatment in the 2 caspofungin groups.[44]

The third trial enrolled 140 patients with a variety of mucosal candidal infections. Nearly all of the patients had the diagnosis of AIDS and 63% had esophageal candidiasis. Patients received either amphotericin B (0.5 mg/kg body weight daily) or caspofungin (35, 50, or 70 mg daily) for 7-14 days. There was no statistically significant difference between the groups with regard to favorable clinical and endoscopic response. Drug-related adverse effects were significantly less in the caspofungin arms compared with the amphotericin B group.[45]

Invasive Aspergillosis

The results of a non-comparative, open-label trial involving 63 patients with invasive aspergillosis demonstrated a favorable response in patients treated with at least 1 dose of caspofungin. There was no comparator agent in this trial; however, an expert panel reviewing the data concluded that caspofungin was well tolerated and effective for invasive aspergillosis in patients who are refractory to or intolerant of itraconazole, conventional amphotericin B, or lipid formulations of amphotericin B.[32]

Combination Therapy Case Report

Although not FDA approved for use in combination therapy, there has been a 2-patient case series presented regarding the clinical use of combination therapy.[46] The authors concluded that the 2 patients with candidemia failed liposomal amphotericin B +/- flucytosine but responded rapidly to the combination of caspofungin and liposomal amphotericin B. The cases underscore the in vitro data that support synergistic or additive effects discussed previously.

Conclusions

The availability of caspofungin for *Candida* and *Aspergillus* infections represents a major step forward in the treatment of systemic fungal infections. Demonstrated activity against potentially azole-resistant *Candida* species and significantly fewer adverse events compared with conventional amphotericin B makes caspofungin an attractive agent for the treatment of these problematic infections. Issues regarding the significant acquisition costs and the lack of an oral formulation and the acquisition of more clinical experience will better define the role of caspofungin in the fight against fungal infections.

A Place in the Therapy of Voriconazole and Caspofungin

The clinical utility of voriconazole and caspofungin is still in development. The FDA has licensed the 2 products for indications previously discussed. As reviewed, there are excellent, well-controlled studies to suggest a place in the therapy of many significant fungal infections, including aspergillosis and candidiasis.

In the treatment of aspergillosis, voriconazole offers an effective, less toxic alternative to all forms of amphotericin B. Specific questions regarding visual disturbances, drug-drug interactions, and acquisition costs may limit the immediate adoption of

voriconazole as first-line therapy. Patients who are failing or who are intolerant to lipid formulations of amphotericin B will benefit from the availability of voriconazole. Owing to the limitations discussed previously, fluconazole should remain the drug of choice to treat most infections caused by *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*. Voriconazole may be used in treatment failures of these organisms or in the treatment of other *Candida* species; however, cross-resistance may occur. In a peer-reviewed summary of voriconazole, Johnson and Kaufmann concluded that voriconazole will likely become the drug of choice for invasive aspergillosis and *Scedosporium* infections; however, it should not replace fluconazole or other agents for most *Candida* infections.[47]

Three review articles regarding caspofungin conclude that there is insufficient information to fully recommend the routine use of caspofungin.[48-50] These articles were written prior to the expanded indication of candidal infections for caspofungin. This indication further defines the role of caspofungin for severe systemic infections. These data support the first-line use of caspofungin for infections caused by most non-albicans *Candida* species.

In the treatment of aspergillosis, caspofungin is FDA approved for refractory disease or previous therapy intolerance; newer data support the use of caspofungin first line for aspergillosis over conventional amphotericin B. The excellent safety profile and limited number of drug interactions for caspofungin make it an attractive replacement for amphotericin B for candidal infections; however, data to date do not support the replacement of fluconazole for most *Candida albicans, Candida tropicalis*, *and Candida parapsilosis* infections.

Conclusions

The development of voriconazole and caspofungin represents true advances in fungal pharmacotherapy. As fungal infections become more common, especially in those with compromised immune systems, the roles of voriconazole and caspofungin will be better defined. The evolving body of literature regarding voriconazole, caspofungin, and the lipid formulations of amphotericin B will eventually displace conventional amphotericin B as the "gold standard" for severe systemic infections. The end of the routine use of conventional amphotericin B is in sight.

References

1. Sobel JD, McKinsey D, Kaufman C, et al. Asymptomatic candiduria: a randomized, double blind study of treatment with fluconazole and placebo. *Clin Infect Dis*. 1999;30:19-24.

2. Berenguer J, Buck M, Witebsky F, et al. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis. Disseminated versus single-organ infection. *Diagn Microbiol Infect Dis*. 1993;17:103-109.

3. Abbasi S, Shenep JL, Hughes WT, et al. Aspergillosis in children with cancer; A 34-year experience. *Clin Infect Dis*. 1999;29:1210-1219.

4. Rex J. Managing Fungal Infections in the New Millennium, Medscape.com, April 7, 2000.

5. Bushelman SJ, Callen JP, Roth DN, et al. Disseminated *Fusarium solani* infection. *J Am Acad Dermatol*. 1995;32(2pt2):223-228.

6. Pagano L, Antinori A, Ammassari A, et al. Retrospective study of candidemia in patients with hematological malignancies. Clinical features, risk factors, and outcome of 76 episodes. *Eur J Haematol*. 1999;63:77-85.

7. Bowden R, Chandrasekar P, White MH, et al. A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. *Clin Infect Dis*. 2002;35(4);359-366.

8. Bennett JT, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med*. 1979;301:126-131.

9. Kauffman C, Frame PT. Bone marrow toxicity associated with 5-fluorocytosine therapy. *Antimicrob Agents Chemother*. 1977;11:244.

10. Sanati H, Belanger P, Fratti B, Ghannoum M. A new triazole, voriconazole (UK-109, 496), blocks sterol biosynthesis In *Candida albicans* and *Candida krusei*. *Antimicrob Agents Chemother*. 1997;41:2492-2496.

11. Vfend [package insert], New York: Pfizer, 2003.

12. Manavathu EK, Cutright JL, Chandrasekar PH. Organism-dependent fungicidal activities of azoles. *Antimicrob Agents Chemother*. 1998;42:3018-3021.

13. Marco F, Pfaller MA, Messer S, Jones RN. In vitro activities of voriconazole, and four other antifungal agents against 394 clinical isolates of *Candida*

species. *Antimicrob Agents Chemother*. 1998;42(1):161-3.

14. White TC, Marr KA, Bowden RA. Clinical, cellular, molecular factors that contribute to antifungal drug resistance. *Clin Microbiol Rev*. 1998;11:382-402.

15. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis*. 2002;34:563-571.

16. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408-415.

17. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med*. 2002;346(4):225-234.

18. Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy [letter]. *N Engl J Med*. 2002;346:1745-1747.

19. Ulman AJ, Heussel CP, Cornely OA. Voriconazole versus liposomal amphotericin B for empirical antifungal therapy [letter]. *N Engl J Med*. 2002;346:1745-1747.

20. Walsh TJ, Lee J, Dismukes WE. Decisions about voriconazole versus liposomal amphotericin B [letter]. *N Engl J Med*. 2002;346;1499.

21. Lozano-Chui M, Arikan S, Paetznick VL, et al. Optimizing voriconazole susceptibility testing of *Candida*: effects of incubation time, endpoint rule, species of *Candida*, and level of fluconazole susceptibility. *J Clin Microbiol*. 1999;37:2755-2759.

22. Nguyen MH, Yu CY. Voriconazole against fluconazole-susceptible and resistant *Candida* isolates: in-vitro efficacy compared with that of itraconazole and ketoconazole. *J Antimicrob Chemother*. 1998;42:253-256.

23. Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis*. 2001;33:1447-54.

24. Hegener P, Troke P, Fatkenheuer G, et al. Treatment of fluconazole-resistant candidiasis with voriconazole in patients with AIDS. *AIDS*. 1998;12:2227-2228.

25. Hoban DJ, Zahnel GC, Karlowsky JA. In vitro susceptibilities of *Candida* and *Cryptococcus neoformans* isolates from blood cultures of neutropenic patients. *Antimicrob*

Agents Chemother. 1999;43:1463-1464

26. Pfaller MA, Zhang J, Messer SA, et al. In vitro activities of voriconazole, fluconazole and itraconazole against 566 clinical isolates of *Cryptococcus neoformans* from the United States and Africa. *Antimicrob Agents Chemother*. 1999;43:169-171.

27. Espinel-Ingroff A. In vitro activity of the new triazole voriconazole (UK-109, 496) against opportunistic filamentous and dimorphic fungi and common and emerging yeast pathogens. *J Clin Microbiol*. 1998;36:198-202.

28. Li RK, Ciblak MA, Nordoff N, et al. In vitro activities of voriconazole, itraconazole and amphotericin B against *Blastomyces dermatitidis*, *Coccidioides immitis* and *Histoplasma capsulatum*. *Antimicrob Agents Chemother*. 2000;44:1734-1736.

29. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. 2003;36:1122-1131.

30. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. *Clin Infect Dis*. 2003;36:1619-1622.

31. Lustar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. *Clin Infect Dis*. 2003;37:728-32.

32. Cancidas [package insert], Rahway, NJ: Merck, 2003.

33. Abruzzo GK, Flattery AM, Gill CJ, et al. Evaluation of the echinocandin antifungal MK-0991 (L-743,872): efficacies in mouse models of disseminated aspergillosis, candidiasis and cryptococcosis. *Antimicrob Agents Chemother*. 1997;41:2333-2338.

34. Kurtz M, Abruzzo G, Flattery A, et al. Characterization of echinocandin-resistant mutants of *Candida albicans*; genetic, biochemical, and virulence studies. *Infection and Immunity*. 1996;64:3244-3251.

35. Ernst EJ, Klepser ME Messer SA, Pfaller MA. In vitro pharmacodynamic properties of MK-0991 determined by time-kill methods. *Diag Microbiol Infect Dis*. 1999;33:75-80.

36. Kurtz MB, Heath IB, Marrinan J, et al. Morphological effects of lipopeptids against *Aspergillus fumigatus* correlate with activities against (1,3)-beta-D-glucan synthase. *Antimicrob Agents Chemother*. 1994;38:1480-1489.

37. Roling EE, Klepser ME, Wasson A, et al. Antifungal activities of fluconazole, caspofungin (MK-0991), and anidulafungin

(LY303366) alone and in combination against *Candida spp*. and *Cryptococcus neoformans* via time-kill methods. *Diag Microbiol Infect Dis*. 2002;43:13-17.

38. Hossain MA, Reyes GH, Long LA, Ghannoum MA. Efficacy of caspofungin combined with amphotericin B or fluconazole against azole-resistant *Candida albicans* [abstract]]. In: Program and abstracts of the Focus on Fungal meeting 12 (Phoenix). Alpharetta, GA: Imedex, 2002. Available at www.doctorfungus.com.

39. Arikan S, Lozano-Chui M, Paetznick V, Rex JH. In vitro synergy of caspofungin and amphotericin B against *Aspergillus* and *Fusarium spp*. Antimicrob Agents Chemother 2002;46:245-247

40. Chandraskar PH, Cutright JL, Manavathu EK. In vitro activity of amphotericin B lipid complex in 2-drug combination with caspofungin against *Aspergillus fumigatus* [abstract]. In: Program and abstracts of the Focus on Fungal meeting 12 (Phoenix). Alpharetta, GA: Imedex, 2002. Available at www.doctorfungus.com.

41. Douglas CM, D'Ippolito JA, Shei GJ, et al. Identification of the *FKS1* gene of *Candida albicans* as the essential target of 1,2-beta-D-glucan synthase inhibitors. *Antimicro Agents Chemother*. 1997;41:2471-9.

42. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*. 2002;347:2020-2029.

43. Villaneuva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med*. 2002;113:294-299.

44. Villaneuva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin B for the treatment of *Candida* esophagitis. *Clin Infect Dis*. 2001;33:1529-1535.

45. Arathoon EG, Gotuzzo E, Noriega, et al. Randomized double-blind study of caspofungin versus amphotericin B for the treatment oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother*. 2002;46:451-457.

46. Nguyen HH, Avante CJ, Siddiqui J, King J, Cohen SH. Successful treatment of candidemia with caspofungin and liposomal amphotericin B after failure of monotherapy. In: Program and abstracts of the Focus on Fungal meeting 13 (Maui). Alpharetta, GA: Imedex, 2003. Available at www.doctorfungus.com.

47. Johnson LB, Kauffman CA. Voriconazole: A new triazole

antifungal agent. *Clin Infect Dis*. 2003;36:630-637.

48. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. *J Antimicrob Chemother*. 2003;51:513-521.

49. Deresinski SC, Stevens DA. Caspofungin. *Clin Infect Dis*. 2003;36:1445-1457.

50. Pacetti SA, Gelone SPECIES Caspofungin acetate for the treatment of invasive fungal infections. *Ann Pharmacother*. 2003;37:90-98.