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Use of Antifungal Combination Therapy: Agents, Order, and Timing

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Abstract Given the substantial morbidity and mortality related to invasive fungal infections, treatment with a combination of antifungal agents is often considered. A growing body of literature from in vitro studies, animal models, and clinical experience provides data evaluating this approach. This review describes combination antifungal strategies for the management of cryptococcal meningitis, invasive candidiasis, invasive aspergillosis, and rare mold infections. The potential effects that sequencing and timing have on the efficacy of such approaches are discussed, with a focus on recent clinical data in this arena.

Keywords Antifungal agents · Mycoses · Drug therapy, combination · Candidiasis · Amphotericin B · Flucytosine · Hematopoietic stem cell transplantation · Aspergillosis · Triazoles · Flucytosine · Imidazoles · Fluconazole · Zygomycosis · Mucormycosis · Fungi · Echinocandins · Aspergillus · Meningitis, cryptococcal · Cryptococcosis · Cryptococcus · Candida

Introduction

During the past decade, there has been a dramatic increase in the number of antifungal agents available to treat invasive fungal infections. Despite a relative lack of clinical data from randomized, controlled trials, the use of antifungal agents in combination is often considered, given the substantial morbidity and mortality related to these infections. This strategy is supported by examples of improved efficacy when using combination antifungal therapy in infections such as cryptococcal meningitis, as well as by supporting data from animal models, in vitro investigations, retrospective studies, and anecdotal case reports [1].

The rationale for combination antifungal therapy and the challenges in interpreting studies in this area have been extensively discussed in the literature [1–4]. Briefly, combination antifungal therapy approaches may be used to broaden the spectrum of activity, enhance the rate or extent of killing (eg, through synergy), minimize development of resistance, or reduce toxicities [2]. Both pharmacokinetic and pharmacodynamic interactions are evident for antifungals, but the most common reason for using or investigating combinations of these agents is the hope of achieving synergy. Of course, detrimental effects, including attenuation of activity, increased resistance or toxicity, increased cost, and drug interactions, are hazards of combination therapy and must be carefully considered, along with the difficulty of interpreting much of the in vitro, animal, and clinical data in this arena. These studies often use varying experimental methods that lack standardization, and there is a lack of correlation between findings from in vitro or animal models and results in the clinical setting. A lack of standardized end points and variations in the dose and duration of drug exposure in such studies can further complicate interpretation of these data.

Clinical trials have been attempted to establish the efficacy of combination antifungal therapy relative to single-agent therapy, but such studies have been limited by factors such as expense, challenges in enrollment, time

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to conduct such a study, and the difficulty in conducting such a trial in a setting where caregivers, patients, or families may consider monotherapy unappealing [5]. Thus, clinical decisions regarding the role of combination therapy for invasive fungal infections must balance the potential benefit of this approach with the known risks of mortality, expense, and adverse effects of a particular combination.

This paper describes antifungal agents commonly used in combination therapy and the potential effects of sequencing and timing on the efficacy of such approaches, with a focus on recent clinical data in this arena.

Cell Membrane Agents

Polyenes

Polyenes and azoles have pharmacologic targets within the fungal cell membrane. Polyenes approved by the US Food and Drug Administration (FDA) include amphotericin B and its lipid formulations (LFAB): amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD), and liposomal amphotericin B (LAmB) [6]. More than 200 polyene macrolide antibiotics have been identified, but polyenes other than amphotericin B have lacked formulations for systemic administration, have been less effective, or have been rather toxic when administered systemically [7].

Polyenes bind to sterol moieties, primarily ergosterol, in the fungal and mammalian cell membrane. This interaction results in formation of pores or channels in the membrane and subsequent leakage of small molecules. Also, the possibility of oxidative damage to fungal cells is evidenced by in vitro studies. Direct resistance to polyenes is rare, but resistance may arise when the fungus replaces membrane ergosterol with other sterols. Several fungi are primarily resistant to amphotericin B, including *Scedosporium* spp., *Aspergillus terreus*, and *Candida lusitaniae* [7].

Amphotericin B has been associated with infusion-related reactions and nephrotoxicity, although this may be reduced with use of the lipid formulations. Thus, LFAB are often favored in the clinical setting because they allow higher doses of amphotericin B (which are often necessary when treating invasive fungal infections) to be tolerated for extended periods [6, 8]. Use of the presently available polyenes in the clinical setting is also limited by their lack of oral bioavailability; these agents are available for administration only in injectable forms.

Azoles

Like polyenes, azoles also exert antifungal activity by targeting ergosterol in the fungal cell membrane. They impair ergosterol biosynthesis by inhibiting sterol 14-alpha-demethylase, a microsomal cytochrome P450–dependent enzyme system. The result is the accumulation of 14-alpha-methylsterols, which may disrupt close packing of acyl chains of phospholipids and impair the function of cell membrane-bound enzyme subsystems such as ATPase and enzymes of the electron transport system. Fungal cell growth is thus inhibited. In addition, some azoles directly increase permeability of the fungal cytoplasmic membrane, but only in concentrations achievable with topical use. Azoles available for systemic administration since the 1990s have included ketoconazole (1981), itraconazole (1992), and fluconazole (1990). A newer generation of triazoles have been developed, including voriconazole (approved for use by the FDA in 2002) and posaconazole (approved in 2006) [9•].

Although they are members of the same antifungal class, azoles have vastly different chemical properties, which impart differing pharmacokinetics and spectrum of activities. Ketoconazole is an imidazole characterized by five-membered ring structures containing two nitrogens, whereas triazoles such as fluconazole, itraconazole, voriconazole, and posaconazole are characterized by five-membered rings containing three nitrogens. The pharmacokinetics and antifungal activity of these agents are further affected by the presence of a long hydrophobic side chain in ketoconazole, itraconazole, and posaconazole, which makes these azoles more lipophilic than other azoles such as fluconazole and voriconazole [10].

Fluconazole lacks activity against *Aspergillus* spp. and many other molds, but other azoles (eg, itraconazole, voriconazole, and posaconazole) have demonstrated in vitro activity against *Aspergillus* spp. Use of itraconazole is complicated by its erratic drug absorption, drug-drug interactions, and lack of robust comparative studies for invasive mold infections. On the other hand, voriconazole demonstrated efficacy in a large randomized trial comparing it to amphotericin B followed by other licensed antifungal therapy, and it is recommended by the Infectious Diseases Society of America (IDSA) for invasive aspergillosis [8, 11]. These newer triazoles also have some advantages compared with older azoles against less common molds. For example, voriconazole has an FDA indication for treatment of invasive fungal infections due to *Fusarium* spp. and *Scedosporium apiospermum*. Unfortunately, voriconazole does not have activity against Zygomycetes, but posaconazole appears to have activity against *Rhizopus* spp. in vitro [12]. Both of these newer triazoles appear to have in vitro activity against *Alternaria* spp. and some other black fungi [13]. Additional clinical data are needed to support their use for these rare and emerging infections.

Itraconazole and the newer triazoles are more active than fluconazole against many of the dimorphic fungi [14•]. Fluconazole has lower response rates in clinical trials of histoplasmosis and sporotrichosis than newer azoles, but it has been used successfully in clinical cases of coccidioidomycosis [15]. Itraconazole has excellent activity against most dimorphic pathogens in vitro, and the most recent IDSA guidelines recommend it as a treatment option for management of histoplasmosis, sporotrichosis, coccidioidomycosis, and blastomycosis [16–19]. All of the second-generation triazoles have demonstrated activity against dimorphic yeasts in vitro, but clinical experience with these agents is evolving [17, 20]. More recently, a small clinical trial demonstrated efficacy of posaconazole in patients with coccidioidomycosis [21].

Use of the azole agents in the clinical setting is influenced by numerous factors, including spectrum of activity, pharmacokinetic profile, availability of intravenous and/or oral formulations, drug-drug interactions, and concern for azole resistance [8].

Cell Membrane Agents in Combination

Considerable concern has arisen regarding use of azoles in combination with amphotericin B, because these agents have the same target. Most in vitro studies have demonstrated mixed results of antagonism or indifference, whereas variable results for survival and tissue burden have been demonstrated in animal models of fungal infection [4]. Sequential exposure has also been problematic for this interaction: previous exposure to an azole seemed to reduce subsequent activity of amphotericin B [4, 22]. This effect is particularly concerning, as azole prophylaxis has become routine in high-risk immunocompromised patients. However, evidence of antagonism has generally not been apparent in the clinical setting. This difference may be related to pharmacokinetic clearance of the azole and reversibility of the antagonistic effects that the azole may have on polyene activity once azole exposure is eliminated [23].

Fluconazole and amphotericin B have produced efficacy rates comparable to those of fluconazole alone (12 mg/kg per day) for candidemia in one large randomized trial [24]. The combination of fluconazole and amphotericin B did not appear antagonistic in this study, and it resulted in faster sterilization of the bloodstream than fluconazole alone among these nonneutropenic patients with candidemia.

Two studies have also investigated combinations of fluconazole and amphotericin B as treatment for HIV-associated cryptococcal meningitis. In a small study, the combination of amphotericin B plus fluconazole did not sterilize cerebrospinal fluid (CSF) better than amphotericin B alone or a triple combination of amphotericin B, fluconazole, and flucytosine. Amphotericin B plus flucytosine resulted in sterilization of the CSF faster than any of the other treatments [25]. More patients (n=7) died in the amphotericin B plus fluconazole arm than in any other treatment group, but these patients may have had more severe disease at baseline. In another recent study, high-dose fluconazole (800 mg) plus amphotericin B (0.7 mg/kg per day) was associated with a trend towards more successful outcomes after 14 days than the same dose of amphotericin B alone (53.7% vs 41.3%) or with low-dose fluconazole (400 mg) (53.7% vs 27.1%), but this difference was not statistically significant [26•]. Taken together, these data suggest that the polyene-azole combination regimen did not demonstrate any clinical antagonism with fungal organism–based end points, compared with amphotericin B alone. In addition, the combination of amphotericin B plus fluconazole does not have significant advantages over the standard of amphotericin B plus flucytosine for cryptococcal meningitis, but it could be an alternative regimen for resource-limited settings.

Combination therapy is particularly appealing for mold infections because of their high associated mortality. Numerous case reports have suggested efficacy of polyene-azole combinations for mold infections [27••]. However, no prospective multicenter studies have evaluated second-generation triazoles in combination with polyenes in managing invasive mold infections, so improved efficacy of such a combination cannot be assumed. There is also some evidence from numerous series for the use of sequential therapy with azoles and polyenes. These studies have suggested the efficacy of polyenes as salvage therapy for mold infections in patients who had previously received azoles [28, 29••]. In one recent post hoc analysis of data from a double-blind study, subjects who received LAmB as primary therapy for invasive mold infections following azole prophylaxis responded similarly to those who had not previously received azoles. Favorable responses were observed in 49.1% (57/116) of patients who had previously received azoles and 45.9% (39/85) of those who had no prior azole exposure. Survival at 12 weeks was also similar among those who had azole exposure (63.8%) and those who had not received azoles (65.9%) [29••]. Additional studies may help to identify the best treatment approaches for salvage therapy of mold infections.

Other Agents That Affect Ergosterol Pathways

Allylamines

Terbinafine is a synthetic allylamine derivative that inhibits squalene epoxidase, an enzyme involved in ergosterol

synthesis. Terbinafine has generally been reserved for treatment of dermatophyte infections and onychomycosis, but it has shown synergistic potential in vitro when combined with some other antifungals. For example, synergy has been reported with combinations of terbinafine and fluconazole or voriconazole against *Candida* spp. in several in vitro studies [30]. Few studies have investigated combinations of echinocandins and terbinafine, but one in vitro study of caspofungin plus terbinafine observed synergy, additivity, or indifference, depending on the isolate and *Candida* spp. tested. True synergy was observed most frequently against terbinafine-resistant strains of *C. albicans* [31]. These effects may be influenced by in vitro testing methodology, especially if agents with differential killing rates are used. This adds to the complexity of interpreting these somewhat inconsistent results.

Terbinafine has relatively poor in vitro activity against *Aspergillus* spp. and other nondermatophyte filamentous fungi [32]. When used in combination with amphotericin B or flucytosine in vitro against *Aspergillus* spp., variable effects including indifference, antagonism, and synergy have been reported [33]. In an animal model of invasive aspergillosis, synergy was not apparent, but on the other hand, terbinafine did not appear to diminish the effects of amphotericin B [34]. Effects ranging from indifferent to synergistic have been reported in vitro against *Aspergillus* spp. for combinations of terbinafine and the azoles fluconazole, itraconazole, and voriconazole [33].

Clinically, there are isolated case reports summarizing the use of terbinafine in combination with other antifungals for the management of invasive fungal infections. Fluconazole-resistant and terbinafine-resistant oropharyngeal candidiasis responded to a combination of fluconazole and terbinafine [35]. Disseminated *Fusarium oxysporum* responded to the addition of terbinafine to amphotericin B [36]. A few cases of *Scedosporium prolificans* infections have responded to combinations of voriconazole and terbinafine, and scedosporiosis has been a particular area of interest for this combination [37–40].

Cell Wall–Active Agents

Fungal cell walls are an attractive and novel target for newer antifungal agents. Development of compounds targeting the cell wall is challenging because of the differential cell-wall composition among different fungi, as well as morphologic forms of the same species. These differences may explain some of the differential activity observed with cell wall–active agents. However, the mammalian system does not share this target, so toxicities should be low with compounds targeting the fungal cell wall.

Echinocandins

The first class of compounds for systemic antifungal therapy that target the cell wall entered routine clinical use with FDA approval of the echinocandins. These agents, which include caspofungin, micafungin, and anidulafungin, destabilize the fungal cell wall by depleting glucans, which are necessary to maintain its stability [8, 41]. The echinocandins primarily target the 1,3-beta-D-glucan synthase of susceptible fungi. 1,3-beta D glucan is a primary component of cell walls of *Candida* and *Aspergillus* spp. These agents have fungicidal activity against *Candida* spp. both in vitro and in vivo, and large clinical trials have demonstrated efficacy of caspofungin, micafungin, and anidulafungin for invasive candidiasis [41]. When combined with fluconazole, they have demonstrated only indifference in vitro against *Candida* spp.; murine models of candidiasis have demonstrated improved or similar tissue burden with this combination, compared with either agent alone [4, 42]. Echinocandins are fungistatic against *Aspergillus* spp., but because of their excellent safety profile, they are often considered for combination therapy in cases of invasive aspergillosis or as broad-spectrum empiric antifungal therapy in immunocompromised patients. Indifference or synergy has generally been reported from in vitro studies of echinocandins in combination with amphotericin B or triazoles [4]. Improvements in survival and tissue burden have also been reported in some animal models of invasive aspergillosis. Probably the most compelling data are in support of the combination of caspofungin and voriconazole for *Aspergillus* infection, as demonstrated in several animal models. This combination was associated with improved rates of sterilization of tissues compared with caspofungin alone, although survival was not better than with voriconazole monotherapy [43, 44]. In a recent animal model of invasive pulmonary aspergillosis, the combination of anidulafungin (5 mg/kg per day) plus voriconazole was associated with reduced pulmonary injury compared with either agent alone. At higher anidulafungin doses (10 mg/kg per day), this effect was attenuated, leading to concerns about dose escalation of echinocandins in combination [45]. The clinical significance of these findings remains to be demonstrated.

For reasons yet to be fully explained, echinocandins lack clinical activity against *Cryptococcus* spp. [4]. This class of agents has in vitro and in vivo activity against other fungal pathogens, including the cyst form of *Pneumocystis jiroveci*, dimorphic yeasts such as *Histoplasma capsulatum* and *Blastomyces dermatitidis*, some of the black molds, and *Scedosporium prolificans*. There is some evidence for combination antifungal therapy including echinocandins for zygomycosis [46]. They have even been suggested to display synergy when used in combination against molds such as *Fusarium* spp. [4].

In the clinical setting, echinocandins have been combined with polyenes or azoles for more difficult-to-treat infections [47–49•]. A small, prospective open-label trial compared LAmB (3 mg/kg per day) plus standard-dose caspofungin to high-dose LAmB monotherapy (10 mg/kg per day) for treatment of proven or probable invasive aspergillosis among patients with hematologic malignancies. Ten (67%) of 15 patients receiving the combination therapy responded, versus 4 (27%) of 15 receiving monotherapy. No clinical trials have been completed to prospectively evaluate echinocandin-azole combinations for mold infections, although a trial of anidulafungin versus the combination of anidulafungin plus voriconazole for the treatment of invasive aspergillosis is currently ongoing and should be finished in the near future (NCT00531479). However, numerous retrospective analyses have reported experience with such combinations.

The combination of caspofungin and voriconazole was used as initial therapy for invasive aspergillosis in a prospective, multicenter cohort of 40 solid-organ transplant recipients compared with a historical cohort of 47 patients who had received LFAB as primary therapy [50]. Treatment success was 70% among those receiving the combination regimen versus 51% among those who received LFAB, but this difference was not statistically significant (P=0.08). Survival at 90 days was better only for those with renal failure (adjusted HR, 0.32; 95% CI, 0.12–0.85; P=0.022), or infection with *A. fumigatus* (adjusted HR, 0.37; 95% CI, 0.16–0.84; P=0.019). The combination of voriconazole plus caspofungin was also compared with a historical cohort who received voriconazole as salvage therapy for invasive aspergillosis in hematopoietic stem cell transplant recipients [51]. In this retrospective cohort study, 3-month survival was better among those who received combination therapy (HR, 0.42; P=0.048).

Micafungin has been investigated as a single agent or in combination with other antifungal agents as primary or salvage regimens in two recent studies [52, 53•]. The first study described 225 evaluable adults and children who received micafungin for proven or probable invasive aspergillosis and who had refractory disease or were intolerant of initial antifungal therapy [52]. Micafungin was added to a failing antifungal regimen in 85% of these patients. Complete or partial responses were experienced by 35.6% (8% complete, 27.6% partial) of patients at the end of antifungal therapy, whereas 53.5% of patients experienced progression of infection. This small study showed no advantage of combination antifungal therapy compared with micafungin alone as either primary therapy (29.4% vs 50%) or salvage therapy (34.5% vs 40.9%).

In a second multicenter retrospective open-label study, 98 adult and pediatric stem cell transplant recipients with invasive aspergillosis (primarily pulmonary disease) received micafungin as a single agent (8%) or in combination with other antifungals (92%) as primary (15%) or salvage (85%) therapy [53•]. Amphotericin B or LFAB were most commonly used in conjunction with micafungin. Treatment success was experienced by 26% of patients, who had either complete (5%) or partial (20%) responses. Success rates were 24% among those receiving micafungin in combination with other antifungals and 38% among the eight patients receiving micafungin alone.

Smaller studies and case series suggest that echinocandin combinations may be promising, but conclusive evidence of synergistic effects in combination with other agents for invasive aspergillosis remains to be fully established in prospective, randomized, controlled clinical trials [54, 55•]. Clearly, these retrospective studies suffer from potential selection bias, which makes the true impact of combination antifungal therapy impossible to accurately determine.

Clinical data for management of zygomycosis and other rare mold infections with combination antifungal therapy is limited to case reports. In one recent review of 41 cases of rhinocerebral zygomycosis, a combination that included an amphotericin B preparation and caspofungin showed improved outcomes, including survival, compared with patients receiving monotherapy regimens [56]. There has also been interest in combination antifungal therapy in which an iron chelator, deferasirox, would add to the efficacy of antifungal agents for zygomycosis [57]. Additional data are needed to optimize antifungal therapy for these less common but serious fungal infections.

Antimetabolites

Flucytosine (5FC) is an antifungal agent that has been in use since its FDA approval in 1971. 5FC is deaminated to 5-fluorouracil (5FU), an antimetabolite in fungi but not in mammalian cells. Fluorouracil is metabolized to 5-fluorouridylic acid, which is then either incorporated into RNA or metabolized to a thymidylate synthase inhibitor, 5-fluorodeoxyuridylic acid, which hampers DNA synthesis in fungal cells. Use of flucytosine has been complicated by bone marrow suppression and nephrotoxicity, and use as monotherapy has been associated with rapid development of flucytosine resistance. Thus, flucytosine is typically used only in combination with other antifungals. The combination of flucytosine and amphotericin B remains the gold standard treatment for cryptococcal meningitis, well established on the basis of data from animal models and controlled clinical trials [58]. Flucytosine has also been added to azoles, including the second-generation triazole posaconazole, in vitro and in animal models of cryptococcosis [4].

Polyene-flucytosine and azole-flucytosine combinations for HIV-associated cryptococcal meningitis have recently

been explored in clinical trials [25, 59•]. In each of these studies, combination therapy was more fungicidal than flucytosine alone, as evidenced by measurements of *C. neoformans* colony-forming units (CFUs) in CSF. Together, these data suggest that flucytosine is a useful addition to these agents for the management of cryptococcal meningitis.

Against *Candida* spp., flucytosine has been added to both amphotericin B and azoles with variable results in vitro but generally improved survival or reduced tissue burden in animal models [4]. Among humans with invasive candidiasis, adding flucytosine to amphotericin B has been associated with good clinical success and faster clearance of peritonitis compared with fluconazole [4]. Flucytosine has also been used successfully in combination with the echinocandin caspofungin, amphotericin B, or both to clear refractory cases of candidemia, as detailed in published reports [60, 61].

Flucytosine has also demonstrated differential effects of synergy, antagonism, or indifference in combination with amphotericin B against *Aspergillus* spp. in vitro. In animal models of aspergillosis, the addition of flucytosine to amphotericin B was associated with improved survival relative to amphotericin B alone, but this effect was not robust in an immunocompromised host model of infection [4]. There are a few reports of successful combinations of flucytosine and amphotericin B or LFAB for cases of cerebral or sinus aspergillosis or spinal osteomyelitis due to *Aspergillus* in humans, but these are relatively rare [4]. Flucytosine has also been added to itraconazole in some cases of aspergillosis, including spondylodiscitis [4]. However, no clinical trials have explored the use of flucytosine in combination with other antifungals for the management of mold infections.

Current Recommendations for the Use of Combination Antifungal Therapy

On the basis of in vitro data, animal models, and clinical experience, recommendations regarding the role of combination antifungal therapy have been made in published practice guidelines of the IDSA (Table 1) [8, 16–19, 58, 62].

For HIV-associated cryptococcal meningitis in developed nations, the combination of amphotericin B plus flucytosine is preferred as initial (induction) therapy [58]. Other combinations are considered alternatives to first-line therapy; these include amphotericin B plus fluconazole

Table 1 Role of combination antifungal therapy in recent guidelines of the Infectious Diseases Society of America

Infection	Role of combination antifungal therapy	Strength of recommendation
Cryptococcosis [58]		
HIV-associated cryptococcal meningitis	*Preferred as induction therapy:*	
	Amphotericin B + flucytosine	A-I
	Alternative for induction therapy:	
	(LAmB or ABLC) + flucytosine	B-II
	Mentioned as alternatives, for induction and consolidation therapy along with other regimens:	
	Amphotericin B + fluconazole	B-I
	Fluconazole + flucytosine	B-II
Cryptococcal meningitis in transplant recipients	*Induction therapy:* (LAmB or ABLC) + flucytosine	B-III
Cryptococcal meningitis in patients without HIV or transplant	*Induction therapy:* amphotericin B + flucytosine	B-II
Candidiasis [62]		
Candidemia, osteoarticular infections, esophagitis	Not recommended for routine management	
CNS candidiasis	LFAB ± flucytosine	B-III
Candida endophthalmitis	Amphotericin B + flucytosine	A-III
Candida endocarditis or infected VAD, ICD, or pacemaker	(LFAB or amphotericin B) ± flucytosine	B-III
Aspergillosis [8]		
Invasive pulmonary aspergillosis	*Primary therapy:* not recommended for routine management	
	Salvage therapy: could be considered	B-II

ABLC amphotericin B lipid complex; *CNS* central nervous system; *ICD* implantable cardioverter defibrillator; *LAmB* liposomal amphotericin B; *LFAB* lipid formulations of amphotericin B; *VAD* ventricular assist device.

(800 mg/day), or fluconazole (≥ 800 mg daily, with 1,200 mg daily preferred) plus flucytosine.

For *Candida* spp. bloodstream infections, several agents are effective and well tolerated for most cases of disease. Therefore, the routine use of combination therapy for candidemia is not recommended [62]. Combination antifungal therapy can be considered for management of other forms of invasive candidiasis, which may be particularly difficult to treat and have not been studied in large clinical trials. Specifically, a combination of amphotericin B and flucytosine is recommended for at least the first several weeks of treatment of candidal infections of the central nervous system (CNS). This recommendation is based on available in vitro data and the pharmacokinetic profile of flucytosine, which may optimize concentrations within the CNS.

Similarly, flucytosine can be added to amphotericin B when managing serious cases of *Candida* endophthalmitis. In addition, combination therapy is often considered in initial management of *Candida* endocarditis, and flucytosine can be added to amphotericin B or a lipid formulation for this indication. In a meta-analysis that considered other factors such as surgical intervention, higher mortality was observed among patients who received antifungal monotherapy [63]. A more recent trend has been to add an azole, flucytosine, or even a polyene to echinocandin therapy for *Candida* endocarditis, and some success has been reported with these strategies. However, additional data are needed to establish the role of such combinations in the management of this serious *Candida* infection.

For initial therapy of invasive pulmonary aspergillosis, combination therapy is not endorsed as a first-line treatment option but may be considered in salvage situations [8]. Caspofungin plus voriconazole is mentioned as an option for CNS aspergillosis, but few clinical data are available to support this strategy and we await new studies in this area.

For the endemic mycoses, there are no recommendations to routinely use combination antifungal therapy [16–19]. However, a combination of amphotericin B plus an azole (typically fluconazole or itraconazole) may be considered for severe cases of coccidioidomycosis [19].

There are no published consensus guidelines for the management of rare mold infections, including zygomycosis. Thus the use of combination antifungal therapy for these infections should be determined on a case-by-case basis, considering all available in vitro data, animal models, and clinical experience.

Conclusions

In vitro data, animal models, and some clinical data are available to support the use of combination antifungal agents for some refractory and most difficult fungal infections. These strategies are sometimes used without robust data in the direst clinical situations, but that is no excuse for not pushing forward with robust, evidence-based studies to evaluate these treatments. Practice guidelines and reviews such as this can help practitioners to evaluate available data and can support clinical decision making at the bedside.

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