Recent Advances in the Management of Mucormycosis: From Bench to Bedside

Brad Spellberg,[1,2] Thomas J. Walsh,[3] Dimitrios P. Kontoyiannis,[4] John Edwards, Jr.,[1,2] and Ashraf S. Ibrahim[1,2]

[1]Division of Infectious Diseases, Los Angeles Biomedical Research Institute at Harbor–University of California at Los Angeles (UCLA) Medical Center, Torrance, and [2]The David Geffen School of Medicine at UCLA, Los Angeles, California; [3]National Cancer Institute, Bethesda, Maryland; and [4]The University of Texas M. D. Anderson Cancer Center, Houston

Recent therapeutic advances have the potential to improve outcomes of mucormycosis. Lipid formulations of amphotericin B (LFAB) have evolved as the cornerstone of primary therapy for mucormycosis. Posaconazole may be useful as salvage therapy, but it cannot be recommended as primary therapy for mucormycosis on the basis of available data. Preclinical and limited retrospective clinical data suggest that combination LFAB-echinocandin therapy may improve survival during mucormycosis. A definitive trial is needed to confirm these results. Combination therapy with LFAB and the iron chelator, deferasirox, also improved outcomes in animal models of mucormycosis. In contrast, combination polyene-posaconazole therapy was of no benefit in preclinical studies. Adjunctive therapy with recombinant cytokines, hyperbaric oxygen, and/or granulocyte transfusions can be considered for selected patients. Early initiation of therapy is critical to maximizing outcomes; recent developments in polymerase chain reaction technology are advancing early diagnostic strategies. Prospective, randomized clinical trials are needed to define optimal management strategies for mucormycosis.

Mucormycosis is a life-threatening infection caused by fungi of the order Mucorales. Recent reclassification has abolished the order Zygomycetes and placed the order Mucorales in the subphylum Mucormycotina [1]. Therefore, we refer to infection caused by Mucorales as mucormycosis, rather than zygomycosis.

Mucormycosis typically occurs in patients with diabetes mellitus, patients who have received organ or hematopoietic stem cell transplant (HSCT), patients with neutropenia, or patients with malignancy [2, 3]. The incidence of mucormycosis appears to be increasing [4], particularly in certain oncology centers [2, 5–7]. For decades, the mortality rate of mucormycosis has remained ⩾40% despite aggressive surgical and polyene antifungal therapy [2, 3, 8]. In particular, patients with hematologic malignancy or HSCT recipients have mortality rates in excess of 65% and 90%, respectively [2, 4, 6, 7]. However, as a result of recent translational research, funded by the US National Institutes of Health and industry, agents are now available to attack the Mucorales at multiple biochemical targets (figure 1). Here, we review treatment and diagnostic strategies for mucormycosis in the 21st century. We emphasize that these evolving management strategies are based on recent preclinical and limited, uncontrolled clinical data and that their validation requires definitive, prospective, controlled clinical trials.

Received 18 December 2008; accepted 16 February 2009; electronically published 12 May 2009.

Reprints or correspondence: Dr. Brad Spellberg, Harbor-UCLA Medical Center, 1124 West Carson St., RB2, Torrance, CA 90502 (bspellberg@labiomed.org).

Clinical Infectious Diseases 2009; 48:1743–51

1058-4838/2009/4812-0019$15.00
DOI: 10.1086/599105

ANTIFUNGAL AGENTS FOR MUCORMYCOSIS

Polyenes. Amphotericin B deoxycholate (AmB) remains the only licensed antifungal agent for the treatment of mucormycosis. However, lipid formulations of AmB (LFABs) are significantly less nephrotoxic and can be safely administered at higher doses for a longer period of time than AmB [9, 10]. In one study, amphotericin B lipid complex (ABLC) resulted in a 71% success rate as salvage therapy for mucormycosis [11]. Furthermore, treatment with liposomal amphotericin B (LAmB) was associated with a 67% survival rate (16 of 24 patients), compared with 39% survival (24 of 62 patients) with AmB ($P = .02$) among patients with cancer who experienced mucormycosis [4]. Thus, LFABs appear to be safer, efficacious alternatives to AmB for the treatment of mucormycosis (table 1).

Limited data suggest advantages of LAmB over ABLC for

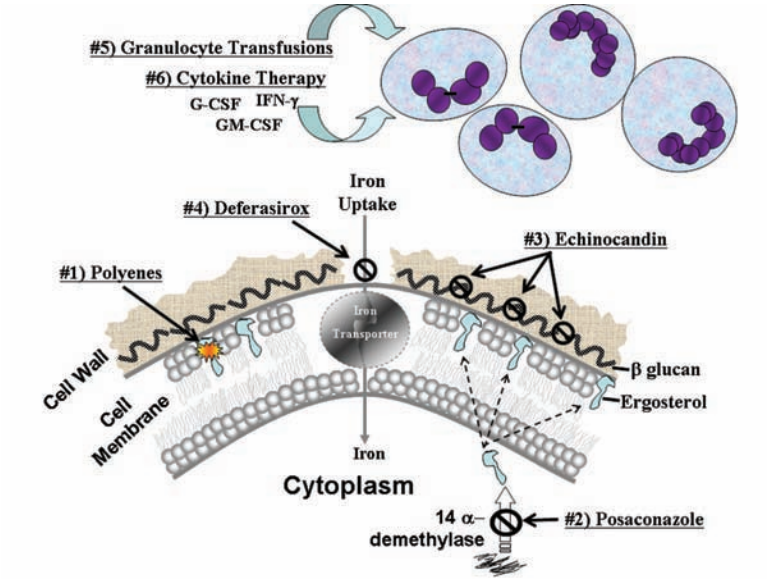

Figure 1. Current targets of therapy for mucormycosis. As a result of recent translational research, strategies are available to attack 4 biochemical targets in Mucorales. These targets include (1) polyene binding to ergosterol in the cell membrane, resulting in creation of pores in the membrane; (2) posaconazole inhibition of cytochrome p450 14-α-demethylase, blocking synthesis of cell membrane-stabilizing ergosterol; (3) echinocandin inhibition of cross-linking of β-glucan in the fungal cell wall; and (4) deferasirox iron chelation therapy, blocking uptake of iron, which is essential for fungal growth. In addition, adjunctive therapy with host immune enhancing strategies, such as (5) granulocyte transfusions and (6) cytokine therapy, are possible. Granulocytes can damage the fungal cell and can be activated by recombinant cytokines, including granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), and interferon-γ (IFN-γ). Polymorphonuclear leukocytes also can be delivered to the site of infection in neutropenic hosts by granulocyte transfusions. Polymorphonuclear leukocytes and lipid formulations of amphotericin B act synergistically to damage hyphae of *Rhizopus* species.

treating central nervous system mucormycosis. Specifically, LAmB levels in rabbit brain were ~5-fold above ABLC levels [12]. Furthermore, although LAmB and ABLC were similarly effective among neutropenic mice, LAmB was superior to ABLC when administered in identical dosages to diabetic ketoacidotic (DKA) mice infected with *Rhizopus oryzae,* primarily because of superior clearance of fungus from the brain [22]. These animal studies are complemented by a recent, retrospective series in which the outcomes of patients with rhino-orbital-cerebral mucormycosis were inferior when ABLC was used as primary therapy, compared with either AmB or LAmB [9].

The response of mucormycosis to antifungal agents is host and site dependent and is particularly problematic in patients with hematological disorders and HSCT recipients [2]. For example, Shoham et al. [23] recently reported a 32% response rate to LAmB as primary therapy for mucormycosis in 32 patients with hematological malignancies and pulmonary infections. Thus, host-dependent variation in response should be considered in prognosis and management of patients with mucormycosis and in designing clinical trials for the disease.

Azoles. Fluconazole and voriconazole do not have reliable activity against the agents of mucormycosis, and the activity of itraconazole is primarily limited to *Absidia* species [24–34]. In contrast, posaconazole has enhanced in vitro activity against the Mucorales, with reported 90% minimum inhibitory concentrations (MIC_{90}) of 1 to $\geq$ 4 μg/mL [24, 35–38]. However, among febrile patients with neutropenia or those with invasive fungal infection, posaconazole administered at a dosage of 400 mg orally twice daily resulted in serum levels <1 μg/mL, with considerable variability [39–41]. Although such levels may result in favorable outcome in the treatment of invasive aspergillosis [42], the MICs of *Aspergillus fumigatus* are consistently $\leq$0.5 μg/mL [43]. Therefore, pharmacokinetic and pharmacodynamic data raise concerns about the reliability of achieving adequate in vivo levels of oral posaconazole to treat mucormycosis, in contrast to aspergillosis. As a result, therapeutic drug monitoring may be warranted during treatment of mucormycosis with posaconazole, particularly among patients at high risk for malabsorption (e.g., patients with mucositis and patients with gasterointestinal graft-versus-host disease) [44].

Furthermore, data from murine models of mucormycosis (in which serum posaconazole levels are >5 μg/mL [45]) raise further concerns about the efficacy of posaconazole for mucormycosis. In neutropenic mice infected with *Mucor* species, Sun et al. [46] found that posaconazole was statistically significantly less effective than was AmB. Similarly, Dannaoui et al. [32] found that posaconazole was less effective than AmB in treating mice infected with *Rhizopus microsporus* or *Absidia*

Table 1. First-line antifungal options for mucormycosis.

Drug	Recommended dosage	Advantages and supporting studies	Disadvantages
Primary antifungal therapy			
AmB	1.0–1.5 mg/kg/day	>5 Decades clinical experience; inexpensive; only licensed agent for the treatment of mucormycosis	Highly toxic; poor CNS penetration
LAmB	5–10 mg/kg/day	Less nephrotoxic than AmB; better CNS penetration than AmB and ABLC [12]; improved outcomes vs. AmB in murine models and a retrospective clinical review [4, 13]	Expensive
ABLC	5–7.5 mg/kg/d	Less nephrotoxic than AmB; murine and retrospective clinical data suggest benefit of combination therapy with echinocandins [9, 14]	More nephrotoxic than LAmB [15]; possibly less efficacious than other options as monotherapy, particularly for CNS infection [9]
Primary combination therapy[a]			
Caspofungin plus lipid polyene	70 mg iv load, then 50 mg/day for ⩾2 weeks; 50 mg/m^2 iv for children [16]	Favorable toxicity profile; synergistic in murine disseminated mucormycosis [14]; retrospective clinical data suggested superior outcomes with combination caspofungin-lipid polyene therapy for rhino-orbital-cerebral mucormycosis [9]	Clinical data of combination therapy are very limited
Micafungin OR anidulafungin plus lipid polyene	100 mg/day for ⩾2 weeks; micafungin 4 mg/kg/day for children [17]; micafungin 10 mg/kg/day for low-birth weight infants [18]; anidulafungin 1.5 mg/kg/day for children [19]	Favorable toxicity profile; synergistic with LAmB in murine model of disseminated mucormycosis [20]	No clinical data
Deferasirox plus lipid polyene	20 mg/kg po qd for 2–4 weeks	Highly fungicidal for Mucorales in vitro [21]; synergistic with LAmB in murine model of disseminated mucormycosis [21]	Only available for enteral administration; no clinical data, although a phase II clinical trial is ongoing

NOTE. Primary therapy should generally include a polyene. Non–polyene-based regimens may be appropriate for patients who refuse polyene therapy or for patients with mild disease in relatively immunocompetent hosts that can be surgically eradicated (e.g., isolated suprafascial cutaneous infection). ABLC, amphotericin B lipid complex; AmB, amphotericin B deoxycholate; CNS, central nervous system; iv, intravenous; LAmB, liposomal amphotericin B; po, oral; qd, once per day.

[a] Prospective, randomized trials are necessary to confirm the suggestion of benefit of combination therapy from animal and small, retrospective human studies of mucormycosis. Also, increasing the dosage of any of the echinocandins is not recommended based on paradoxical loss of benefit of combination therapy at echinocandin dosages of ⩾3 mg/kg/d.

species. In addition, they found that posaconazole was no better than placebo for treating *R. oryzae,* which causes >70% of clinical cases of mucormycosis [2, 3, 9]. Finally, in 2 more-recent studies, posaconazole monotherapy was also no better than placebo for the treatment of *R. oryzae* infection in neutropenic or DKA mice [47, 48]. Thus, data from 4 groups of investigators indicated that posaconazole was inferior in efficacy to AmB for the treatment of murine mucormycosis, and 3 groups found that it was not superior to placebo for treating mice infected with *R. oryzae.*

On the basis of the available animal data and the absence of clinical data, posaconazole monotherapy cannot be recommended as primary treatment of mucormycosis. In contrast, available clinical data from open-label salvage studies suggest that posaconazole is a reasonable option for patients with mucormycosis who are refractory to or intolerant of polyenes [49, 50].

COMBINATION ANTIFUNGAL THERAPY FOR MUCORMYCOSIS

Echinocandins. *R. oryzae* expresses the target enzyme for echinocandins [51], and in DKA mice infected with *R. oryzae,* combination caspofungin plus ABLC therapy markedly improved survival, compared with monotherapy or placebo [14]. Combination therapy with LAmB plus either micafungin or anidulafungin also improved outcome in neutropenic and DKA mice with disseminated mucormycosis [20]. Enhanced exposure of β-glucan on the fungal surface, which results in immune stimulation, may be one of the mechanisms by which echinocandins improve outcomes in mucormycosis [52].

In a recent, small, retrospective study, combination LFAB-caspofungin therapy was associated with significantly improved outcomes for rhino-orbital-cerebral mucormycosis among patients with diabetes, compared with polyene monotherapy [9]. By multivariate analysis, only combination therapy was significantly associated with superior outcomes (odds ratio, 10.9 for success vs. monotherapy; $P = .02$). We emphasize that these data require confirmation in a prospective, randomized trial. In the meantime, if combination LFAB-echinocandin therapy is considered for mucormycosis, echinocandins should be administered at US Food and Drug Administration–approved dosages (table 1). Increasing the dosage of the echinocandins is not advisable because of a paradoxical loss of efficacy against murine mucormycosis at dosages $\geq$3 mg/kg/day [51, 20].

Iron chelation therapy. Deferoxamine iron chelation therapy predisposes to mucormycosis [53], because deferoxamine actually enhances delivery of iron to Mucorales [54, 55]. Indeed, animals infected with *R. oryzae* that are treated with iron or deferoxamine have markedly worse survival than do animals treated with placebo [54–56]. However, other iron chelators cannot be used by Mucorales to acquire iron [53, 54, 56]. In 2005, a new orally available iron chelator, deferasirox, was approved by the US Food and Drug Administration for the treatment of iron overload among patients with transfusion-dependent anemia [57]. Deferasirox was fungicidal for clinical isolates of Mucorales in vitro, with an MIC_{90} of 6.25 μg/mL [21]. The drug exhibited time-dependent killing, with cidality occurring at 12–24 h of drug exposure. Based on trough serum levels >15 μg/mL in patients who are treated with deferasirox at 20 mg/kg/day [58, 59], it should be feasible to maintain deferasirox serum levels in excess of the MICs of Mucorales.

In DKA mice with disseminated mucormycosis, deferasirox was as effective as LAmB therapy, and combination deferasirox-LAmB therapy synergistically improved survival (80% survival for combination vs. 40% for monotherapy vs. 0% for placebo) [21]. In particular, combination therapy resulted in a 100-fold decrease in brain fungal burden, compared with monotherapy. On the basis of these animal data, we successfully used deferasirox as salvage therapy for a patient with advanced rhino-cerebral mucormycosis who had progressive brainstem disease despite having received LAmB therapy [60]. Currently, a double-blinded, randomized, placebo-controlled, phase II safety/exploratory efficacy study of adjunctive deferasirox therapy (20 mg/kg/day for 14 days) for mucormycosis is ongoing (the Deferasirox-AmBisome Therapy for Mucormycosis—or DEFEAT Mucor—study [NCT00419770]).

Soummer et al. [61] recently reported the failure of salvage deferasirox for a patient who had undergone partial colectomy to resect mucormycosis. Although its intravenous formulation is under active clinical development [62], deferasirox, like posaconazole, is currently only available in oral formulation. Therefore, patients who are not likely to adequately absorb enteral medications (e.g., patients who have undergone intestinal surgery) should not be treated with deferasirox.

The toxicities of deferasirox therapy in nonhuman primates and in clinical trials have been extensively reviewed [57, 63, 64] and are beyond the scope of this article. Gastrointestinal symptoms (e.g., nausea and diarrhea) are the most common adverse effects of deferasirox therapy. However, the primary toxicity of concern is renal. Elevations in creatinine occurred in up to one-third of patients in deferasirox clinical trials [63, 65], but they were usually mild and reversible upon cessation of drug use. There have been rare postmarketing reports of severe acute renal failure resulting in hemodialysis for or death of iron-overloaded patients receiving deferasirox [66]. However, these patients typically had other underlying risk factors for renal failure. Therefore, the contribution of deferasirox to the renal failure in these cases is unclear.

Posaconazole combination therapy. Two recent preclinical studies evaluated the efficacy of posaconazole combination therapy for murine mucormycosis. In the first study, Rodriguez et al. [47] found that combining posaconazole with AmB en-

hanced the survival of neutropenic mice infected with *R. oryzae* only when compared to a subtherapeutic dosage (0.3 mg/kg/day) of AmB monotherapy. In contrast, combination therapy was of no advantage, compared with a standard dosage of AmB monotherapy (0.8 mg/kg/d). Similarly, we recently reported that combination posaconazole plus LAmB did not improve survival, compared with LAmB monotherapy, in either neutropenic or DKA mice with mucormycosis [48]. No clinical studies have evaluated combination posaconazole-polyene therapy for mucormycosis.

Other adjunctive therapies. Proinflammatory cytokines, such as interferon-γ and granulocyte macrophage colony-stimulating factor, enhance the ability of granulocytes to damage the agents of mucormycosis [67]. Case reports have described survival of patients with mucormycosis treated with adjunctive immune therapy with recombinant granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor, or with recombinant interferon-γ, in conjunction with LFAB [68–72]. The role of recombinant cytokines in the primary treatment of mucormycosis is not defined.

Granulocyte colony-stimulating factor–mobilized granulocyte transfusions have been increasingly used for refractory mycoses, including mucormycosis [73, 74]. Although the reported experience with granulocyte transfusions is limited, such transfusions may be life-saving for persistently neutropenic patients with mucormycosis. Finally, limited data indicate that hyperbaric oxygen may also be useful in health care centers with the appropriate technical expertise and facilities [75].

SUGGESTED TREATMENT STRATEGIES FOR MUCORMYCOSIS

General principles. The successful treatment of mucormycosis requires 4 steps: (1) early diagnosis; (2) reversal of underlying predisposing risk factors, if possible; (3) surgical debridement where applicable; and (4) prompt antifungal therapy [3]. We will review each of these principles in the context of recent advances in the treatment of mucormycosis.

Early diagnosis of mucormycosis. Initiation of polyene therapy within 5 days after diagnosis of mucormycosis was associated with improvement in survival, compared with initiation of polyene therapy at $\geq$6 days after diagnosis (83% vs. 49% survival) [76]. Therefore, establishing an early diagnosis of mucormycosis is critical to enable early initiation of active antifungal therapy.

Although some progress has been made in improving the laboratory yield of cultures for mucormycosis [77], the development of other diagnostic methods is a major unmet need for this infection. Development of quantitative polymerase chain reaction systems is a promising area of ongoing research to enable more-rapid diagnosis [78, 79]. For example, Kasai et al. [80] developed 2 real-time quantitative polymerase chain reaction assays that targeted the 28S rRNA gene for the diagnosis of mucormycosis caused by *Rhizopus, Mucor,* and *Cunninghamella* species. These polymerase chain reaction assays successfully detected circulating DNA in rabbits with experimental pulmonary mucormycosis. A prospective clinical study of molecular detection of pulmonary mucormycosis is currently being developed.

Among patients with rhino-orbital-cerebral disease, computed tomography typically reveals only sinusitis, so computed tomography that indicates the absence of deeper infection does not rule out mucormycosis [9]. Magnetic resonance imaging is more sensitive than computed tomography for detecting orbital and central nervous system involvement [9]. Computed tomography is useful for early detection of pulmonary mucormycosis, particularly in patients with cancer. By logistic regression, pulmonary mucormycosis in patients with cancer could be distinguished from aspergillosis on the basis of sinusitis, presence of multiple ($\geq$10) nodules on computed tomography, and pleural effusion [81]. Also, a recent retrospective study reported that 7 of 8 immunocompromised patients treated at a cancer center who had a reverse halo sign (focal area of ground-glass attenuation surrounded by a ring of consolidation) on chest computed tomography had mucormycosis, rather than other molds [82]. The reverse halo sign was seen early in the disease course of these patients. Further refinement of radiographic techniques for distinguishing mucormycosis from other infectious and noninfectious diseases is an important area of future research.

Reversal of underlying disease. It is critical to reverse or prevent underlying defects in host defense when treating patients with mucormycosis. Immunosuppressive medications, particularly corticosteroids, should be administered at reduced dosages or stopped if at all possible. Aggressive treatment to rapidly restore euglycemia and normal acid-base status is critical in diabetics in ketoacidosis.

Surgical management. Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of necrotic tissues may be critical for complete eradication of mucormycosis. In a logistic regression model, surgery was found to be an independent variable for favorable outcome among patients with mucormycosis [2]. Furthermore, in multiple case series, patients who did not undergo surgical debridement of mucormycosis had a far higher mortality rate than did patients who underwent surgery [6, 83–90]. Although there is potential selection bias in these case series, because patients who did not undergo surgery likely differed in disease severity or comorbidities from those who did, these data support the concept that surgical debridement is necessary to optimize cure rates.

The extent and timing of surgical debridement necessary to

Table 2. Salvage therapy for mucormycosis.

Drug	Recommended dosage	Advantages and supporting studies	Disadvantages
Posaconazole with or without lipid polyenes	200 mg po qid or 400 mg po bid	Convenient oral dosing of posaconazole; retrospective case series demonstrated 60%–70% "success" rates (complete plus partial response) [49, 50]	Monotherapy posaconazole efficacy less than polyenes in murine studies [32, 46, 47, 93]; combination posaconazole plus LFAB no better than LFAB alone in murine studies
Deferasirox plus lipid polyenes	20 mg/kg po qd for 2–4 weeks	Convenient oral dosing of deferasirox[a]; success in case report [60]	Limited published data
Granulocyte transfusions (for persistently neutropenic patients)	~10^9 cells/kg	Neutrophils and ABLC interact synergistically against Mucorales in vitro [95]; case reports of patients supported with granulocyte transfusions [73, 74]	Limited clinical data; infusion related toxicity and alloimmunization
Recombinant cytokines G-CSF, GM-CSF, or IFN-γ	Dose G-CSF at 5 μg/kg/day; GM-CSF at 100–250 $\mu g/m^2$; IFN-γ at 50 $\mu g/m^2$ for those with body surface area $\geq$0.5 m^2 and 1.5 μg/kg for those with body surface area <0.5 m^2	In vitro studies demonstrate augmented host response of PMNs to hyphal elements of *Rhizopus* species [67]; individual case reports [68–72]	Limited clinical data

NOTE. ABLC, amphotericin B lipid complex; bid, twice per day; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; PMN, polymorphonuclear leukocyte; po, oral; qd, once per day.

[a] Outpatient deferasirox therapy currently requires enrollment in the Exjade Patient Assistance and Support Services (EPASS) system [94]. Inpatient therapy does not require EPASS enrollment.

maximize outcomes of mucormycosis has never been defined. Limited data from a retrospective review of patients with rhino-orbital-cerebral mucormycosis [9] support the concept of an "aggressive-conservative" approach, in which intraoperative frozen sections are used to delineate the margins of infected tissues, and uninvolved tissues are spared from debridement when possible.

Primary antifungal therapy. Primary antifungal therapy for mucormycosis should be based on a polyene in most cases, unless patients refuse polyene therapy or, possibly, in cases of milder infection in relatively immunocompetent hosts for whom surgical eradication of disease has been accomplished (e.g., cases of isolated, suprafascial cutaneous infection) (table 1). The optimal dosages for treatment of mucormycosis are not known for any antifungal agent. Starting dosages of 1 mg/kg/day for AmB and 5–7.5 mg/kg/day for LAMB and ABLC are commonly used for adults and children. Whether higher dosages provide any additional benefit is uncertain. However, increasing the dosage of LAmB to 10 mg/kg/day for central nervous system mucormycosis may be considered on the basis of the limited polyene penetration into the brain. Higher dosages of LAmB do not result in pharmacokinetic advantage compared with a dosage of 10 mg/kg/day [91].

The role of combination therapy as primary treatment for mucormycosis has been the subject of a recent review, which concluded that the available data are insufficient to support a general recommendation [92]. As described above, limited data from mice [14, 20] and diabetic patients [9] suggest that combination echinocandin-LFAB therapy may be a reasonable strategy for treating mucormycosis, but these results require a confirmatory, prospective, randomized study.

Based on the lack of efficacy in animal models and the lack of available clinical data, primary combination therapy with LFAB plus posaconazole cannot currently be recommended. In contrast, preclinical data support the addition of deferasirox to initial LFAB therapy, particularly for central nervous system infection in diabetic patients. The ongoing phase II, DEFEAT Mucor clinical trial should clarify the safety profile of initial LFAB-deferasirox combination therapy. Ultimately, prospective, randomized phase III clinical trials will be required to determine whether any combination therapeutic regimen is superior to monotherapy with an LFAB.

Salvage therapy. Deferasirox or posaconazole are reasonable salvage options for patients with mucormycosis refractory to or intolerant of polyene therapy (table 2). Substantially more clinical data are available for posaconazole in this setting [49, 50]. If deferasirox is used, it should be administered for 2–4 weeks during salvage therapy, because in preclinical studies of non–iron-overloaded primates, deferasirox toxicity increased beyond 4 weeks of therapy [64]. In contrast, posaconazole appears to be quite safe, despite dosing for months to years [49, 50].

Granulocyte colony-stimulating factor–mobilized granulocyte transfusions may provide additional support for persistently neutropenic patients until recovery from neutropenia. Administration of granulocyte macrophage colony-stimulating factor or interferon-γ may further augment host response and antifungal effect in nonneutropenic patients with refractory infection.

Total duration of therapy. In the absence of comparative data, the total duration of therapy for mucormycosis should be individualized for each patient. In general, antifungal therapy for mucormycosis should be continued until all of the following objectives are attained: (1) there is resolution of clinical signs and symptoms of infection, (2) there is resolution or stabilization of residual radiographic signs of disease on serial im-

aging, and (3) there is resolution of underlying immunosuppression. Such a case is illustrated in a patient with lymphoma and renal mucormycosis [96].

For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is continued. Posaconazole may be an option if polyenes cannot be used for prolonged periods. For patients with intermittent immunosuppression, such as those receiving intermittent cycles of chemotherapy who have adequate leukocyte counts between cycles, secondary prophylaxis should be reinitiated during neutropenia and should continue until the recovery from neutropenia.

FUTURE DIRECTIONS

Unmet needs for improved diagnosis, treatment, and prevention of mucormycosis remain formidable. New radiographic, molecular, and antigenic tools are required to improve early detection and therapeutic monitoring. New antifungal agents and combinations of existing agents should be further explored in the laboratory and in clinical trials. Designing informative clinical trials to address this uncommon but frequently lethal infection is a challenge that will require innovative strategies. Definitive clinical data from prospective randomized studies are required to allow refinement and a stronger basis for therapeutic recommendations. Finally, an understanding of the basic molecular, metabolic, and immunological properties of these organisms is paramount to advancing our understanding of mucormycosis.

Acknowledgments

We thank Dr. Scott Filler for helpful comments.

Financial support. Public Health Service (K08 to B.J.S. and R01 AI063503 and R21 AI064716 to A.S.I.) and the intramural research program of the National Cancer Institute (to T.J.W.).

Potential conflicts of interest. B.S. has received consulting fees from Pfizer, Astellas, Basilea, Arpida, and Advanced Life Sciences; research support from Astellas, Gilead, Elan, Enzon, Novartis, Merck, and Pfizer; and speaker's honoraria from Merck, Pfizer, and Astellas. D.P.K. has received research support and honoraria from Schering-Plough, Pfizer, Astellas Pharma, Enzon Pharmaceuticals, and Merck. J.E. serves on the scientific advisory boards of Pfizer, Merck, and Gilead; has participated in educational programs regarding fungal infections funded by Pfizer, Merck, and Astellas; has received research laboratory support from Pfizer, Merck, and Gilead; and has participated in the Bristol-Myers Squibb Freedom to Discovery research program. A.S.I. has received research funding from Astellas, Enzon, Gilead, Merck, Elan, Novartis, and Pfizer and speaker's honoraria from Astellas. T.J.W.: no conflicts.

References

1. Hibbett DS, Binder M, Bischoff JF, et al. A higher-level phylogenetic classification of the fungi. Mycol Res **2007**; 111:509–47.
2. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis **2005**; 41:634–53.
3. Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev **2005**; 18:556–69.
4. Gleissner B, Schilling A, Anagnostopolous I, Siehl I, Thiel E. Improved outcome of zygomycosis in patients with hematological diseases? Leuk Lymphoma **2004**; 45:1351–60.
5. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis **2005**; 191:1350–60.
6. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis **2000**; 30: 851–6.
7. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
8. Ribes JA, Vanover-Sams CL, Baker DJ. Zygomycetes in human disease. Clin Microbiol Rev **2000**; 13:236–301.
9. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis **2008**; 47:364–71.
10. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. N Engl J Med **1999**; 340:764–71.
11. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis **1998**; 26:1383–96.
12. Groll AH, Giri N, Petraitis V, et al. Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental *Candida albicans* infection of the central nervous system. J Infect Dis **2000**; 182:274–82.
13. Ibrahim AS, Avanessian V, Spellberg B, Edwards JE Jr. Liposomal amphotericin B, and not amphotericin B deoxycholate, improves survival of diabetic mice infected with *Rhizopus oryzae.* Antimicrob Agents Chemother **2003**; 47:3343–4.
14. Spellberg B, Fu Y, Edwards JE Jr, Ibrahim AS. Combination therapy with amphotericin B lipid complex and caspofungin acetate of disseminated zygomycosis in diabetic ketoacidotic mice. Antimicrob Agents Chemother **2005**; 49:830–2.
15. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. Clin Infect Dis **2000**; 31:1155–63.
16. Walsh TJ, Adamson PC, Seibel NL, et al. Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. Antimicrob Agents Chemother **2005**; 49:4536–45.
17. Seibel NL, Schwartz C, Arrieta A, et al. Safety, tolerability, and pharmacokinetics of Micafungin (FK463) in febrile neutropenic pediatric patients. Antimicrob Agents Chemother **2005**; 49:3317–24.
18. Benjamin DK, Smith PB, Arrieta A, et al. Safety and pharmacokinetics of repeat-dose micafungin in neonates [abstract A-012]. In: Program and abstracts of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2008**.
19. Benjamin DK Jr, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. Antimicrob Agents Chemother **2006**; 50:632–8.
20. Ibrahim AS, Gebremariam T, Fu Y, Edwards JE Jr, Spellberg B. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother **2008**; 52:1556–8.
21. Ibrahim AS, Gebermariam T, Fu Y, et al. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest **2007**; 117:2649–57.
22. Ibrahim AS, Gebremariam T, Husseiny MI, et al. Comparison of lipid

amphotericin B preparations in treating murine zygomycosis. Antimicrob Agents Chemother **2008**; 52:1573–6.
23. Shoham S, Magill S, Merz WG, et al. Primary treatment of invasive zygomycosis in immunocompromised patients [abstract M-2174]. In: Program and abstracts of the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2008**.
24. Sun QN, Fothergill AW, McCarthy DI, Rinaldi MG, Graybill JR. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother **2002**; 46:1581–2.
25. Trifilio SM, Bennett CL, Yarnold PR, et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transplant **2007**; 39:425–9.
26. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med **2004**; 350:950–2.
27. Kauffman CA. Zygomycosis: reemergence of an old pathogen. Clin Infect Dis **2004**; 39:588–90.
28. Imhof A, Balajee SA, Fredricks DN, Englund JA, Marr KA. Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. Clin Infect Dis **2004**; 39:743–6.
29. Ide L, Buysschaert I, Demuynck H, et al. Zygomycosis in neutropenic patients with past *Aspergillus* infection: a role for posaconazole? Clin Microbiol Infect **2004**; 10:862–3.
30. Vigouroux S, Morin O, Moreau P, et al. Zygomycosis after prolonged use of voriconazole in immunocompromised patients with hematologic disease: attention required. Clin Infect Dis **2005**; 40:e35–7.
31. Rickerts V, Bohme A, Just-Nubling G. Risk factor for invasive zygomycosis in patients with hematologic malignancies. Mycoses **2002**; 45(Suppl 1):27–30.
32. Dannaoui E, Meis JF, Loebenberg D, Verweij PE. Activity of posaconazole in treatment of experimental disseminated zygomycosis. Antimicrob Agents Chemother **2003**; 47:3647–50.
33. Dannaoui E, Meletiadis J, Mouton JW, Meis JF, Verweij PE. In vitro susceptibilities of zygomycetes to conventional and new antifungals. J Antimicrob Chemother **2003**; 51:45–52.
34. Van Cutsem J, Van Gerven F, Fransen J, Janssen PA. Treatment of experimental zygomycosis in guinea pigs with azoles and with amphotericin B. Chemotherapy **1989**; 35:267–72.
35. Pfaller MA, Messer SA, Hollis RJ, Jones RN. Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. Antimicrob Agents Chemother **2002**; 46:1032–7.
36. Almyroudis NG, Sutton DA, Fothergill AW, Rinaldi MG, Kusne S. In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother **2007**; 51:2587–90.
37. Lass-Florl C, Mayr A, Perkhofer S, et al. The activities of antifungal agents against yeasts and filamentous fungi: assessment according to EUCAST methodology. Antimicrob Agents Chemother **2008**; 52: 3637–41.
38. Arikan S, Sancak B, Alp S, Hascelik G, McNicholas P. Comparative in vitro activities of posaconazole, voriconazole, itraconazole, and amphotericin B against *Aspergillus* and *Rhizopus,* and synergy testing for *Rhizopus.* Med Mycol **2008**; 46:567–73.
39. Ullmann AJ, Cornely OA, Burchardt A, et al. Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother **2006**; 50:658–66.
40. Krishna G, Sansone-Parsons A, Martinho M, Kantesaria B, Pedicone L. Posaconazole plasma concentrations in juvenile patients with invasive fungal infection. Antimicrob Agents Chemother **2007**; 51:812–8.
41. Krishna G, Martinho M, Chandrasekar P, Ullmann AJ, Patino H. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy **2007**; 27:1627–36.
42. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis **2007**; 44:2–12.
43. Pfaller MA, Messer SA, Boyken L, Hollis RJ, Diekema DJ. In vitro susceptibility testing of filamentous fungi: comparison of Etest and reference M38-A microdilution methods for determining posaconazole MICs. Diagn Microbiol Infect Dis **2003**; 45:241–4.
44. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother **2008**; 53:24–34.
45. Andes D, Marchillo K, Conklin R, et al. Pharmacodynamics of a new triazole, posaconazole, in a murine model of disseminated candidiasis. Antimicrob Agents Chemother **2004**; 48:137–42.
46. Sun QN, Najvar LK, Bocanegra R, Loebenberg D, Graybill JR. In vivo activity of posaconazole against Mucor spp. in an immunosuppressed-mouse model. Antimicrob Agents Chemother **2002**; 46:2310–2.
47. Rodriguez MM, Serena C, Marine M, Pastor FJ, Guarro J. Posaconazole combined with amphotericin B, an effective therapy for a murine-disseminated infection caused by *Rhizopus oryzae.* Antimicrob Agents Chemother **2008**; 52:3786–8.
48. Ibrahim AS, Gebermariam T, Schwartz JA, Edwards JE Jr, Spellberg B. Posaconazole mono- or combination therapy for the treatment of murine zygomycosis. Antimicrob Agents Chemother **2009**; 53:772–5.
49. van Burik JA, Hare RS, Solomon HF, Corrado ML, Kontoyiannis DP. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis **2006**; 42:e61–5.
50. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother **2006**; 50:126–33.
51. Ibrahim AS, Bowman JC, Avanessian V, et al. Caspofungin inhibits *Rhizopus oryzae* 1,3-β-D-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis. Antimicrob Agents Chemother **2005**; 49:721–7.
52. Lamaris GA, Lewis RE, Chamilos G, et al. Caspofungin-mediated β-glucan unmasking and enhancement of human polymorphonuclear neutrophil activity against *Aspergillus* and non-*Aspergillus* hyphae. J Infect Dis **2008**; 198:186–92.
53. Boelaert JR, Van Cutsem J, de Locht M, Schneider YJ, Crichton RR. Deferoxamine augments growth and pathogenicity of *Rhizopus,* while hydroxypyridinone chelators have no effect. Kidney Int **1994**; 45: 667–71.
54. Boelaert JR, de Locht M, Van Cutsem J, et al. Mucormycosis during deferoxamine therapy is a siderophore-mediated infection: in vitro and in vivo animal studies. J Clin Invest **1993**; 91:1979–86.
55. de Locht M, Boelaert JR, Schneider YJ. Iron uptake from ferrioxamine and from ferrirhizoferrin by germinating spores of *Rhizopus microsporus.* Biochem Pharmacol **1994**; 47:1843–50.
56. Ibrahim AS, Edwards JE Jr, Fu Y, Spellberg B. Deferiprone iron chelation as a novel therapy for experimental mucormycosis. J Antimicrob Chemother **2006**; 58:1070–3.
57. Cappellini MD. Iron-chelating therapy with the new oral agent ICL670 (Exjade). Best Pract Res Clin Haematol **2005**; 18:289–98.
58. Piga A, Galanello R, Forni GL, et al. Randomized phase II trial of deferasirox (Exjade, ICL670), a once-daily, orally-administered iron chelator, in comparison to deferoxamine in thalassemia patients with transfusional iron overload. Haematologica **2006**; 91:873–80.
59. Miyazawa K, Ohyashiki K, Urabe A, et al. A safety, pharmacokinetic and pharmacodynamic investigation of deferasirox (Exjade, ICL670) in patients with transfusion-dependent anemias and iron-overload: a phase I study in Japan. Int J Hematol **2008**; 88:73–81.

60. Reed C, Ibrahim A, Edwards JE Jr, Walot I, Spellberg B. Deferasirox, an iron-chelating agent, as salvage therapy for rhinocerebral mucormycosis. Antimicrob Agents Chemother **2006**; 50:3968–9.
61. Soummer A, Mathonnet A, Scatton O, et al. Failure of deferasirox, an iron chelator agent, combined with antifungals in a case of severe zygomycosis. Antimicrob Agents Chemother **2008**; 52:1585–6.
62. Sechaud R, Robeva A, Belleli R, Balez S. Absolute oral bioavailability and disposition of deferasirox in healthy human subjects. J Clin Pharmacol **2008**; 48:919–25.
63. Vichinsky E. Clinical application of deferasirox: practical patient management. Am J Hematol **2008**; 83:398–402.
64. Nick H, Wong A, Acklin P, et al. ICL670A: preclinical profile. Adv Exp Med Biol **2002**; 509:185–203.
65. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with β-thalassemia. Blood **2006**; 107:3455–62.
66. Important information about exjade (deferasirox) tablets for oral suspension. Novartis, **2007**. Available at: http://www.fda.gov/MEDwatch/safety/2007/Exjade_DHCPL_May2007.pdf. Accessed 22 April 2009.
67. Gil-Lamaignere C, Simitsopoulou M, Roilides E, Maloukou A, Winn RM, Walsh TJ. Interferon-γ and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. J Infect Dis **2005**; 191: 1180–7.
68. Abzug MJ, Walsh TJ. Interferon-γ and colony-stimulating factors as adjuvant therapy for refractory fungal infections in children. Pediatr Infect Dis J **2004**; 23:769–73.
69. Gonzalez CE, Couriel DR, Walsh TJ. Disseminated zygomycosis in a neutropenic patient: successful treatment with amphotericin B lipid complex and granulocyte colony-stimulating factor. Clin Infect Dis **1997**; 24:192–6.
70. Kullberg BJ, Anaissie EJ. Cytokines as therapy for opportunistic fungal infections. Res Immunol **1998**; 149:478–88; discussion 515.
71. Ma B, Seymour JF, Januszewicz H, Slavin MA. Cure of pulmonary *Rhizomucor pusillus* infection in a patient with hairy-cell leukemia: role of liposomal amphotericin B and GM-CSF. Leuk Lymphoma **2001**; 42: 1393–9.
72. Mastroianni A. Paranasal sinus mucormycosis in an immunocompetent host: efficacy and safety of combination therapy with liposomal amphotericin B and adjuvant rHuGM-CSF. Infez Med **2004**; 12:278–83.
73. Grigull L, Beilken A, Schmid H, et al. Secondary prophylaxis of invasive fungal infections with combination antifungal therapy and G-CSF–mobilized granulocyte transfusions in three children with hematological malignancies. Support Care Cancer **2006**; 14:783–6.
74. Slavin MA, Kannan K, Buchanan MR, Sasadeusz J, Roberts AW. Successful allogeneic stem cell transplant after invasive pulmonary zygomycosis. Leuk Lymphoma **2002**; 43:437–9.
75. John BV, Chamilos G, Kontoyiannis DP. Hyperbaric oxygen as an adjunctive treatment for zygomycosis. Clin Microbiol Infect **2005**; 11: 515–7.
76. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B–based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis **2008**; 47:503–9.
77. Kontoyiannis DP, Chamilos G, Hassan SA, Lewis RE, Albert ND, Tarrand JJ. Increased culture recovery of zygomycetes under physiologic temperature conditions. Am J Clin Pathol **2007**; 127:208–12.
78. Francesconi A, Kasai M, Harrington SM, et al. Automated and manual methods of DNA extraction for *Aspergillus fumigatus* and *Rhizopus oryzae* analyzed by quantitative real-time PCR. J Clin Microbiol **2008**; 46:1978–84.
79. Hata DJ, Buckwalter SP, Pritt BS, Roberts GD, Wengenack NL. Real-time PCR method for detection of zygomycetes. J Clin Microbiol **2008**; 46:2353–8.
80. Kasai M, Harrington SM, Francesconi A, et al. Detection of a molecular biomarker for zygomycetes by quantitative PCR assays of plasma, bronchoalveolar lavage, and lung tissue in a rabbit model of experimental pulmonary zygomycosis. J Clin Microbiol **2008**; 46:3690–702.
81. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis **2005**; 41:60–6.
82. Wahba H, Truong MT, Lei X, Kontoyiannis DP, Marom EM. Reversed halo sign in invasive pulmonary fungal infections. Clin Infect Dis **2008**; 46:1733–7.
83. Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis: a retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol **2003**; 51:231–6.
84. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral mucormycosis: evolution of the disease and treatment options. Laryngoscope **1997**; 107:855–62.
85. Khor BS, Lee MH, Leu HS, Liu JW. Rhinocerebral mucormycosis in Taiwan. J Microbiol Immunol Infect **2003**; 36:266–9.
86. Petrikkos G, Skiada A, Sambatakou H, et al. Mucormycosis: ten-year experience at a tertiary-care center in Greece. Eur J Clin Microbiol Infect Dis **2003**; 22:753–6.
87. Tedder M, Spratt JA, Anstadt MP, Hegde SS, Tedder SD, Lowe JE. Pulmonary mucormycosis: results of medical and surgical therapy. Ann Thorac Surg **1994**; 57:1044–50.
88. Pavie J, Lafaurie M, Lacroix C, et al. Successful treatment of pulmonary mucormycosis in an allogenic bone-marrow transplant recipient with combined medical and surgical therapy. Scand J Infect Dis **2004**; 36: 767–9.
89. Reid VJ, Solnik DL, Daskalakis T, Sheka KP. Management of bronchovascular mucormycosis in a diabetic: a surgical success. Ann Thorac Surg **2004**; 78:1449–51.
90. Asai K, Suzuki K, Takahashi T, Ito Y, Kazui T, Kita Y. Pulmonary resection with chest wall removal and reconstruction for invasive pulmonary mucormycosis during antileukemia chemotherapy. Jpn J Thorac Cardiovasc Surg **2003**; 51:163–6.
91. Walsh TJ, Goodman JL, Pappas P, et al. Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with *Aspergillus* species and other filamentous fungi: maximum tolerated dose study. Antimicrob Agents Chemother **2001**; 45:3487–96.
92. Walsh TJ, Kontoyiannis DP. Editorial commentary: what is the role of combination therapy in management of zygomycosis? Clin Infect Dis **2008**; 47:372–4.
93. Spellberg BJ, Gebremariam T, Edwards JE, Ibrahim AS. Posaconazole mono- or combination therapy for murine mucormycosis [abstract M3762]. In: Program and abstracts of the Interscience Convention on Antimicrobial Agents and Chemotherapy (ICAAC)–Infectious Diseases Society of America (IDSA). Washington, DC: IDSA, **2008**.
94. Novartis. Exjade patient assistance and support services. Available at: http://www.us.exjade.com/info/getting-exjade/home.jsp. Accessed 11 May 2009.
95. Simitsopoulou M, Roilides E, Maloukou A, Gil-Lamaignere C, Walsh TJ. Interaction of amphotericin B lipid formulations and triazoles with human polymorphonuclear leucocytes for antifungal activity against zygomycetes. Mycoses **2008**; 51:147–54.
96. Weng DE, Wilson WH, Little R, Walsh TJ. Successful medical management of isolated renal zygomycosis: case report and review. Clin Infect Dis **1998**; 26:601–5.