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Risk factors for mortality in patients with mucormycosis

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Optimal clinical care and clinical investigation of patients with mucormycosis are limited by absence of controlled trials, and absence of well-defined predictors of mortality or clinical response. The Deferasirox-AmBisome Therapy for mucormycosis (DEFEAT Mucor) study was the first randomized clinical trial conducted on patients with mucormycosis, and demonstrated that adjunctive deferasirox therapy did not improve outcomes of the disease. The current study describes clinical factors from the 20 patients enrolled to identify those associated with 90-day mortality of the 11 (55%) patients who died by day 90. Age, diabetes mellitus, transplant status, or antifungal therapy were not associated with mortality. However, active malignancy or neutropenia at enrollment were associated with increased mortality. Pulmonary infection was linked with lower Kaplan-Meier survival compared to non-pulmonary infection. Higher baseline serum concentrations of iron and ferritin were also associated with mortality. No patient who progressed clinically during the first 14 days of study therapy survived; however, many patients who clinically improved during that time did not survive to 90 days. In contrast, day 30 clinical response was predictive of 90-day survival. These factors may be useful in defining enrollment randomization stratification critieria for future clinical trials, and in supporting clinical care of patients with mucormycosis.

Keywords mucormycosis, randomized controlled trial, mortality, risk factors

Introduction

Until recently, only retrospective studies were available to define risk factors for patients with mucormycosis [1–9]. Features associated with increased mortality in those studies included prolonged neutropenia, underlying leukemia or hematopoeitic stem cell transplantation, delayed initiation of polyene therapy, and use of antifungal therapy other than lipid formulations of amphotericin. More recently, the results of the first randomized, controlled trial on patients with mucormycosis were reported [10]. The Deferasirox-AmBisome Therapy for Mucormycosis, (DEFEAT Mucor; NCT00419770) study was a randomized, double-blinded, placebo-controlled, phase II efficacy study of adjunctive deferasirox therapy for mucormycosis. The purpose of the DEFEAT Mucor study was to define the safety, and exploratory efficacy of short-term deferasirox therapy to provide a foundation for potential future studies. The study was designed based on the importance of iron availability for the causal agents growth and pathogenesis [11–13]. The trial results showed high mortality in patients treated with deferasirox [10]. A variety of imbalances among the study arms confounded conclusions regarding the effect of study therapy.

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The current analyses were conducted to define factors aside from the treatment intervention, which were associated with mortality in patients with mucormycosis, both to inform optimal clinical care and future clinical trials on patients with mucormycosis.

Methods

Study design

The study design, and results, of the DEFEAT Mucor study (NCT00419770) have been reported previously [10]. In brief, this was a phase II randomized, double-blinded (i.e., blinding of patients, investigators, and endpoint adjudication committee), placebo-controlled trial of adjunctive deferasirox therapy, in addition to liposomal amphotericin B (LAmB) therapy for the treatment of mucormycosis. Patients 2 years of age or older were eligible for the study if they had proven or probable mucormycosis, as determined by modified European Organization for the Research and Treatment of Cancer (EORTC)/Mycoses Study Group (MSG) criteria [14].

Subjects were excluded if they: had a high likelihood of death within 48 h, or had a high likelihood of death due to underlying disease within 30 days, as assessed by the site investigator; had infection limited to supra-fascial skin; or had received more than 14 days of polyene antifungal therapy. Enrollment was discouraged for patients with serum creatinine levels of ≥ 3 mg/dL or a creatinine clearance of < 30 ml/min by the Cockroft-Gault formula, and those with both an AST or ALT more than 10-times the upper limit of normal and a direct bilirubin more than 5-times normal. Twenty patients were randomized in the DEFEAT Mucor Study, and form the population for the current analyses. Details on these 20 patients can be found in reference [10].

A blinded, independent Endpoint Adjudication Committee determined whether clinical signs, symptoms and radiographic images were improved, stable, or worse at each follow-up visit. Judgments were based on data provided by site investigators, and adjudicated global success or failure for each patient based on protocol-specified criteria. The study was conducted in accordance with the Declaration of Helsinki, and guidelines for studies involving human subjects. The protocol was approved by the institutional review board at each study site, as well as by the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, which was the sponsor of the study.

Study assessments and endpoint definitions

Clinical signs and symptoms were evaluated prior to enrollment, at days 7 and 14 of study medication administration, and after 30 or 90 days of follow-up. Per the protocol, computerized tomography (CT) or magnetic resonance imaging (MRI) scans of the affected areas were obtained 4 days before or after enrollment, and again within 4 days after the ending of administration of the blinded study medication; other CT or MRIs obtained for clinical care were also obtained. Blood, for safety parameters, was obtained every other day during the period of administration of the blinded study medication.

The clinical assessment was performed by the Efficacy Adjudication Committee using pre-specified criteria by comparing sequential clinical status assessments done for the baseline, at day 7, and at the end of blinded study medication using case report forms. Development of a new sign or symptom, not previously recorded, or worsening of the quantitative estimate of the severity of signs or symptoms previously recorded, indicated clinical progression. Stability was indicated by no changed in signs or symptoms, and improvement was indicated by resolution of previously recorded signs or symptoms, or overall improvement in the quantitative estimate of the severity of signs or symptoms.

Global response for the primary efficacy endpoint was dichotomized as success (i.e., patient was alive and had stable or improved clinical assessment and improved radiographic assessment) or failure (i.e., patient had died, or progressed clinically, or stable or progressed radiographic assessment).

Statistical analysis

A variety of demographic, disease, and laboratory factors were evaluated to determine if any were associated with a higher risk of mortality through the last observation (i.e., 90 days for 19 patients, 100 days for one patient who had a serious adverse event before day 90 and was followed to resolution). For the purpose of determining impact on survival or death, continuous variables were dichotomized based on their median values. Proportions were compared by Fisher's Exact or Chi-squared test as appropriate. Kaplan-Meier curves were analyzed by log rank test. All analyses are provided for descriptive purposes.

Results

Demographic and disease characteristics

Older and younger patients had similar mortality rates (Table 1); the median [range] age was similar among patients who survived or died (i.e., 52 [range 38–75] years vs. 53 [range 30–68] years). Mortality rates were not significantly different for patients with or without a history of diabetes mellitus (DM), corticosteroid use, transplantation, or with pulmonary, rhino-orbital, or gastrointestinal infections

Table 1 90-day mortality rates by demographics, risk factors, and laboratory values.

Variable	Stratification of variable	90-day mortality no. dead/no. total (percent mortality)	*P* value
Age (years)*	≥53	6/10 (60%)	0.5
	<53	5/10 (50%)	
Infection site	Pulmonary	6/8 (75%)	0.2
	Rhino-orbital	5/11 (45%)	
	Gastrointestinal	0/1 (0%)	
Diabetes mellitus (DM)	Yes	6/13 (27%)	0.3
	No	5/7 (71%)	
DM with no other risk factor	Yes	1/5 (20%)	0.1
	No	10/15 (67%)	
Malignancy†	Yes	8/10 (80%)	0.03
	No	3/10 (30%)	
Neutropenia‡	Yes	5/5 (100%)	0.03
	No	6/15 (40%)	
Corticosteroid use	Yes	7/11 (64%)	0.3
	No	4/9 (44%)	
Transplant	Yes	5/9 (56%)	0.7
	No	6/11 (55%)	
Solid organ	Yes	1/4 (25%)	0.2
	No	10/16 (63%)	
Hematopoeitic	Yes	4/5 (80%)	0.2
	No	7/15 (47%)	
Baseline (at enrollment) laboratory values*			
Creatinine	≥1 mg/dL	4/10 (40%)	0.2
	<1 mg/Dl	7/10 (70%)	
Absolute neutrophil count	≥3,600 cells/μl	4/10 (40%)	0.2
	<3,600 cells/μl	7/10 (70%)	
Serum iron	≥72 mg/dL	8/10 (80%)	0.03
	<72 mg/dL	3/10 (30%)	
Ferritin	≥2,700 mg/dL	8/10 (80%)	0.03
	<2,700 mg/dL	3/10 (30%)	
Glucose	≥146 mg/dL	5/10 (50%)	0.5
		6/10 (60%)	

*Continuous variables were dichotomized at their median values across all 20 patients. †All malignancies were hematologic (including myelodysplastic syndrome, leukemia, and lymphoma). ‡Neutropenia defined as an absolute neutrophil count ≤500 cells/μl at enrollment.

(Table 1). However, Kaplan-Meier analysis showed that survival was worse for patients with pulmonary compared to those with non-pulmonary sites of infection (Fig. 1A). Patients with active malignancy had higher mortality rates (80% vs. 30%, $P = 0.03$) and worse Kaplan-Meier survival than those who did not (Table 1, Fig. 1B). Furthermore, patients with neutropenia at baseline, defined as an absolute neutrophil count of <500 cells/μl, had higher mortality rates than those who did not (100% vs. 40%, $P = 0.03$, Table 1). The increased mortality of those with active malignancy could not be attributed solely to concomitant neutropenia, as three of five patients (60%) with cancer but without neutropenia died.

Baseline laboratory values

Patients with higher or lower serum creatinine, absolute neutrophil counts, or serum glucose had similar mortality rates (Table 1). However, higher serum iron or ferritin concentrations were both associated with 80% mortality rates compared to 30% mortality for patients with lower levels ($P = 0.03$ for each, Table 1). Serum concentrations of iron and ferritin were concordant with malignancy status; all patients with malignancy had serum concentrations of iron above the median, and 9 of 10 of these patients had serum concentrations of ferritin above the median. All eight patients with malignancy that died had serum concentrations of iron and ferritin above the median.

Antifungal therapy

Sixteen patients received antifungal therapy before enrolling in the study. Mortality rates for these patients were similar irrespective of the type of specific antifungal therapy administered prior to enrollment (Table 2).

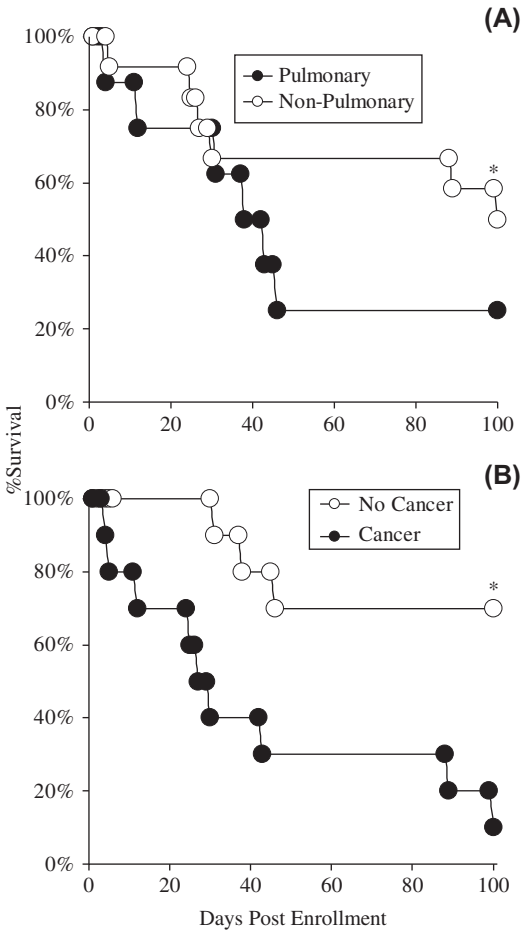

Fig. 1 Survival times stratified by exploratory variables. (A) Patients with pulmonary ($n = 8$) versus non-pulmonary sites of infection ($n = 11$ rhino-orbital infection and 1 gastrointestinal infection). (B) Patients with or without cancer ($n = 10$ for each). *$P < 0.05$ by log rank test.

Per the protocol, all patients received LAmB therapy during the study period. The median daily dose delivered during the study period was 7.5 mg/kg. Patients receiving at least 7.5 mg/kg/day had similar mortality rates to patients who received lower dosages (Table 2). Similarly, patients who received 5 mg/kg/day LAmB, including one patient who received 4 mg/kg/day despite the minimum dose specified in the protocol, had similar mortality rates to those who received higher doses.

There were no significant differences in the mortality rates between patients who were treated with adjunctive echinocandin, posaconazole, or either of the two drugs during the study period (Table 2). There was a trend toward higher mortality in patients who received blood transfusions versus those who did not (73% vs. 33%, $P = 0.09$). There was no significant difference between the proportion of patients with or without cancer who were transfused (70% with cancer, 40% without cancer, $P = 0.2$). Of the 11 patients who were transfused with ≥ 4 red blood cell units, 7 (64%) had underlying malignancy. In an additional analysis, patients ($n = 7$) who were transfused with ≥ 8 red blood cell units trended toward a higher mortality rate than patients ($n = 13$) who had received fewer red blood cell units or were not transfused (86% vs. 38%, $P = 0.06$).

Clinical and radiographic predictors of survival

Clinical response, defined as improved or stable, at day 7 was sensitive but not specific, and overall had poor accuracy for predicting survival of patients with mucormycosis infection (Table 3). Clinical response at the end-of-therapy evaluation (EOT; i.e., within the first 14 days of therapy) was 100% sensitive for predicting survival, since no patients who ultimately survived had worsened clinically before EOT. However, clinical response at EOT was nonspecific, since numerous patients who eventually died were clinically stable or improved by EOT. Clinical response at day 30 was both sensitive and specific for predicting survival, with a fair positive predictive value (75%) and excellent negative predictive value (100%) for predicting survival. Requiring that patients be clinically improved (i.e., adjudicating patients who were clinically stable as clinical failures) enhanced specificity, but variably affected the overall accuracy of clinical response in predicting survival depending on the timing of the evaluation (Table 3).

Radiographic response (i.e., required improvement in CT or MRI versus baseline) was inaccurate for predicting survival at all time points (Table 3). The accuracy of CT or MRI response for predicting survival was better at EOT than day 7, but even at EOT one-half of patients who survived did not have an improved CT or MRI. Allowing stable radiographs to be adjudicated as radiographic success marginally affected accuracy for predicting survival. Insufficient CT or MRI results were available after EOT to determine accuracy of subsequent scans for predicting survival.

Global success (i.e., clinically stable or better, and radiographic improvement) at EOT was inaccurate, but improved considerably by day 30 and day 90 (Table 3) for predicting survival. However, because two patients who survived had progression on CT or MRI scans completed between day 30 and 90, global success was less accurate than clinical response for predicting three-month survival.

Discussion

It is important to understand factors associated with survival of patients with mucormycosis, both to improve clinical practice and to refine protocols for future clinical trials on patients with the disease. The DEFEAT Mucor study

Table 2 90-day mortality rates by treatment characteristics.

Variable	Stratification of variable	90-day mortality No. dead/no. total (percent mortality)	*P* value
Pre-study antifungal therapy			
LAmB	Yes	6/9 (67%)	0.3
	No	5/11 (45%)	
ABLC*	Yes	3/5 (60%)	0.6
	No	8/15 (53%)	
AmB*	Yes	0/1 (0%)	0.5
	No	11/19 (58%)	
Posaconazole	Yes	2/3 (67%)	0.6
	No	9/17 (53%)	
Therapy during study period			
LAmB dose*			
≥7.5 mg/kg/d	Yes	6/10 (60%)	0.5
	No	5/10 (50%)	
≤5 mg/kg/d	Yes	4/9 (44%)	0.2
	No	7/11 (64%)	
Receipt of other antifungal therapy			
Echinocandin	Yes	4/8 (50%)	0.8
	No	7/12 (58%)	
Posaconazole	Yes	3/6 (50%)	0.8
	No	8/14 (57%)	
Either†	Yes	6/12 (50%)	0.5
	No	5/8 (63%)	
Receipt of red blood cell (RBC) transfusion	Yes	8/11 (73%)	0.09
	No	3/9 (33%)	
RBC units transfused‡	≥4 units	8/11 (73%)	0.09
	<4 units	3/9 (33%)	
	≥8 units	6/7 (86%)	0.06
	<8 units	5/13 (38%)	

*ABLC, amphotericin B lipid complex; AmB, amphotericin B deoxycholate; †one patient who survived and one patient who died each were treated simultaneously with an echinocandin and posaconazole. ‡Median number of RBC units transfused for all 20 patients was 4, and all patients who were transfused received at least 4 units of RBCs; as a post-hoc analysis, 8 was chosen as a cut-off, since it was the median value of units transfused in patients who died.

was small, but afforded the first prospective, randomized opportunity to evaluate patient risk factors, and endpoints as predictors of survival in patients with mucormycosis. The current prospective data from a randomized trial are important to confirm findings from larger retrospective, observational studies. As has been suggested by previous retrospective data [1,5,9], malignancy or neutropenia were associated with increased mortality rates. Patients with higher concentrations of iron or ferritin at baseline also had increased mortality; however, most patients with higher concentrations of iron or ferritin also had cancer. Thus, the relationship between concentrations of iron and ferritin, and mortality, may reflect increased baseline iron stores in patients resulting in more severe infection [8,11–13,15], more severe underlying disease, or both.

Receipt of a blood transfusion during the study period was not associated with higher mortality. Nevertheless, there were trends toward higher mortality of patients who received more transfusions. This association could have been driven by the fact that patients with malignancies were more likely to require multiple transfusions, but patients with or without a cancer did not have significantly different rates of high volume red cell transfusions. Thus, the potential for multiple transfusions to exacerbate the severity of infection by providing free iron to the fungus remains of theoretical concern.

A wide range of daily LAmB doses was used, including dosages as high as 20 mg/kg/day. Although the number of subjects in DEFEAT was low, patients who received higher daily dosages did not have improved survival. This finding is consistent with the pharmacokinetics of LAmB, since there is no advantage of dosages greater than 10 mg/kg/day, because serum concentrations do not increase, and may decrease, at dosages above 10 mg/kg/day [16]. A dosage of 5 mg/kg/day is likely adequate for treating most patients with mucormycosis, although it is reasonable to consider dose-escalation to 7.5 or 10 mg/kg/day in patients with CNS infection [15,17].

Table 3 Clinical, radiographic, and global responses as predictors of 90-day survival.

Time point	Sensitivity*	Specificity*	PPV*	NPV*	Accuracy*
Clinical response (stable or improved)					
Day 7	89%	64%	67%	88%	75%
EOT†	100%	36%	56%	100%	65%
Day 30	100%	73%	75%	100%	85%
Day 90	100%	100%	100%	100%	100%
Modified clinical response (improved)					
Day 7	56%	82%	71%	69%	70%
EOT	89%	73%	73%	89%	80%
Day 30	89%	73%	73%	89%	80%
Day 90	100%	100%	100%	100%	100%
Radiographic response (improved)‡					
Day 7	14%	33%	33%	14%	20%
EOT	50%	67%	67%	50%	57%
Global response (alive, clinically stable or improved, and radiographically improved)					
EOT	44%	82%	67%	64%	65%
Day 30	78%	91%	88%	83%	85%
Day 90	78%	100%	100%	85%	90%

*Sensitivity = the percentage of surviving patients with response divided by the number of all surviving patients; Specificity = the percentage of patients without response who died divided by the number of all patients who died; PPV = positive predictive value, which is the percentage of patients with response and who survived divided by all of the patients with response; NPV = negative predictive value, which is the percentage of patients without response and who died divided by all of the patients with lack of response; Accuracy = [(number of patients with response who survived) + (number of patients with lack of response who died) / (all patients)]. †EOT = end-of-therapy. ‡10 CT or MRIs available at day 7 and 14 available at EOT.

Of significance for selecting endpoints for future studies is the need to understand the relationship between early endpoints and longer term survival. Based on anecdotal experience [18,19], it was hoped that inclusion of a radiographic endpoint would enable superior power to detect an effect of deferasirox in the DEFEAT Mucor study. However, radiographic results were highly inaccurate for predicting outcomes in the DEFEAT Mucor study. Patients who survived often had early progression based on CT or MRI scans, whereas patients who died by 90 days often had no evidence of progression in early scans. Thus, caution should be used in incorporating radiographic results into future study endpoints. Furthermore, these results suggest that following serial CT or MRI scans at early timepoints may not be helpful in determining who will, or will not, survive the infection in clinical practice.

In contrast with radiologic assessments, clinical stability was a better early predictor of future survival. Indeed, progression of disease within the first 7 days of therapy had an 88% negative predictive value (NPV) for determining who would survive the infection. Furthermore, no patients who had progressed clinically at EOT (i.e., within the first 14 days of therapy) survived to 90 days. However, early improvement did not necessarily predict survival. Even by day 30 after enrollment, clinical stability or improvement only had a 75% positive predictive value (PPV) for survival. Creation of a global response assessment did not add to the accuracy using of clinical improvement alone. Mortality occurred steadily with time, even between the 30 and 90 day follow-up times. These data indicate that 90 day all-cause mortality is the most appropriate endpoint for a future superiority study of novel treatments for mucormycosis.

The primary limitations of this study are its small size and the heterogeneity of the population enrolled in the DEFEAT Mucor study. Patients enrolled in the study had a variety of risk factors, ranging from active malignancy to diabetes mellitus to solid organ transplantation. The heterogeneity of this patient population could have obscured risk factors for long-term mortality that differ among patients with varying underlying risk factors for infection. Given the small number of patients, no effort was made to conduct a multifactorial analysis, and interactions amongst the variables examined cannot be excluded. Similarly, the effect of study treatment, which influenced survival [10], might also influence the analysis given the imbalances in the initial randomization. Like any correlative analysis, any of the variables examined may be a surrogate for a relevant patho-physiologic factor and must be interpreted with caution. Also, it was not possible to distinguish mortality attributable to mucormycosis from that due to progression of an underlying disease. Thus, the current conclusions concerning mortality risk must be viewed in the context of the patient population studied.

In the DEFEAT Mucor study, patients were allowed to have received up to 14 days of antifungal therapy prior to enrollment. The current analysis considers time to death

starting from the time patients were enrolled in the clinical trial, rather than from the time of symptom onset or time of first antifungal therapy prior to enrollment in the study. Thus, it is possible that the timing of response rates, and death, are somewhat different in clinical practice, during which timing is measured typically from symptom onset and/or initiation of antifungal therapy. However, only two deaths occurred past day 50 of follow-up, and patients generally had received less than 14 days of therapy prior to enrollment, per the design of the protocol. Thus it is unlikely that the conclusions would be substantially altered by timing from initiation of antifungal therapy.

In summary, patients with mucormycosis were more likely to survive if they were not neutropenic, had lower baseline serum concentrations of iron or ferritin, or if their infection was not associated with malignancy. Radiographic results through day 30 were not predictive of survival by day 90, suggesting that serial CT or MRI scans are over utilized clinically, and should not be relied upon to determine efficacy of new treatments in future clinical trials. Clinical response was highly sensitive at detecting those unlikely to survive (i.e., those who had clinical progression during the first 1–2 weeks of therapy after enrollment were very unlikely to survive), but not specific at predicting who would survive (i.e., many of those who were clinically improved during the first 1–2 weeks of therapy, or even out to 30 days, died by day 90). Hence, all-cause mortality at day 90 appears to be the most relevant endpoint for future interventional studies of mucormycosis.

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References

1 Roden MM, Zaoutis TE, Buchanan WL, *et al*. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis* 2005; **41**: 634–653.
2 Singh N, Aguado JM, Bonatti H, *et al*. Zygomycosis in solid organ transplant recipients: a prospective, matched case-control study to assess risks for disease and outcome. *J Infect Dis* 2009; **200**: 1002–1011.
3 Reed C, Bryant R, Ibrahim AS, *et al*. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. *Clin Infect Dis* 2008; **47**: 364–371.
4 Gleissner B, Schilling A, Anagnostopolous I, Siehl I, Thiel E. Improved outcome of zygomycosis in patients with hematological diseases? *Leuk Lymphoma* 2004; **45**: 1351–1360.
5 Shoham S, Magill SS, Merz WG, *et al*. Primary treatment of zygomycosis with liposomal amphotericin B: analysis of 28 cases. *Med Mycol* 2009; **48**: 511–517.
6 Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis* 2000; **30**: 851–856.
7 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**: 1350–1360.
8 Chamilos G, Lewis RE, Hu J, *et al*. *Drosophila melanogaster* as a model host to dissect the immunopathogenesis of zygomycosis. *Proc Natl Acad Sci USA* 2008; **105**: 9367–9372.
9 Skiada A, Pagano L, Groll A, *et al*. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. *Clin Microbiol Infect* 2011; **17**: 1859–1867.
10 Spellberg B, Ibrahim AS, Chin-Hong PV, *et al*. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded placebo controlled trial. *J Antimicrob Chemother* 2011; **67**: 715–722.
11 Ibrahim AS, Gebermariam T, Fu Y, *et al*. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. *J Clin Invest* 2007; **117**: 2649–2657.
12 Ibrahim AS, Gebremariam T, Lin L, *et al*. The high affinity iron permease is a key virulence factor required for *Rhizopus oryzae* pathogenesis. *Mol Microbiol* 2010; **77**: 587–604.
13 Spellberg B, Edwards J Jr, Ibrahim A. Novel perspectives on mucormycosis: pathophysiology, presentation, and management. *Clin Microbiol Rev* 2005; **18**: 556–569.

14 Ascioglu S, Rex JH, de Pauw B, *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.
15 Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr, Ibrahim AS. Recent advances in the management of mucormycosis: from bench to bedside. *Clin Infect Dis* 2009; **48**: 1743–1751.
16 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**: 3487–3496.
17 Kontoyiannis DP, Lewis RE. How I treat mucormycosis. *Blood* 2011; **118**: 1216–1224.
18 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**: 3968–3869.
19 Spellberg B, Andes D, Perez M, *et al*. Safety and outcomes of open-label deferasirox iron chelation therapy for mucormycosis. *Antimicrob Agents Chemother* 2009; **53**: 3122–3125.

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