SUPPLEMENT ARTICLE

A Global Analysis of Mucormycosis in France: The RetroZygo Study (2005–2007)

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Background. Mucormycosis is a deadly invasive fungal infection whose characteristics are only partially understood.

Methods. Data on mucormycosis obtained in France between 2005 and 2007 from 2 notification systems were merged. The 2008 European Organisation for Research and Treatment of Cancer/Mycoses Study Group definition criteria were applied and risk factors for death were analyzed by hazard ratios (HRs) calculated from the Cox proportional hazards regression model.

Results. A total of 101 cases (60 proven, 41 probable), mostly in men (58%) >50 years (mean age, 50.7 ± 19.9) were recorded. Hematological malignancies represented 50% (median time for occurrence, 8.8 months after disease onset), diabetes 23%, and trauma 18% of cases. Sites of infection were lungs (28%; 79% in hematology patients), rhinocerebral (25%; 64% in diabetic patients), skin (20%), and disseminated (18%). Median time between first symptoms and diagnosis was 2 weeks. The main fungal species were *Rhizopus oryzae* (32%) and *Lichtheimia* species (29%). In cases where the causative species was identified, *R. oryzae* was present in 85% of rhinocerebral forms compared with only 17% of nonrhinocerebral forms ($P < .001$). Treatment consisted of surgery in 59% and antifungals in 87% of cases (liposomal amphotericin B in 61%). Ninety-day survival was 56%; it was reduced in cases of dissemination compared with rhinocerebral (HR, 5.38 [2.0–14.1]; $P < .001$), pulmonary (HR, 2.2 [1.0–4.7]; $P = .04$), or skin localization (HR, 5.73 [1.9–17.5]; $P = .002$); survival was reduced in cases of hematological malignancies compared with diabetes mellitus (HR, 2.3 [1.0–5.2]; $P < .05$) or trauma (HR, 6.9 [1.6–28.6], $P = .008$) and if ≥2 underlying conditions (HR, 5.9 [1.8–19.0]; $P = .004$). Mucormycosis localization remained the only independent factor associated with survival.

Conclusions. This 3-year study performed in one country shows the diverse clinical presentation of mucormycosis with a high prevalence of primary skin infection following trauma and a prognosis significantly influenced by localization.

Mucormycosis is a devastating acute invasive filamentous fungal infection occurring mostly in patients with uncontrolled diabetes mellitus [1] and in patients who are severely immunocompromised, such as those with hematological malignancy [2] or those who have undergone solid organ transplantaion or hematopoietic stem cell transplantation (HSCT) [3]. Of note, several cases also occurred following trauma with contaminated soil [4]. Numerous cases have now been recognized as an additional complication of healthcare procedures. Mucormycosis incidence has recently increased, not only in patients with hematological malignancies, but also in those with diabetes mellitus [1]. The recommended first-line therapeutic strategy includes the use of a lipid formulation of amphotericin B in addition to

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Clinical Infectious Diseases 2012;54(S1):S35–43

DOI: 10.1093/cid/cir880

radical surgery [5]. The prognosis of mucormycosis remains poor, with recently reported mortality rates varying between 45% and 64%, depending on underlying disease [6–10].

Data concerning the global epidemiology of mucormycosis are scarce and have been mostly obtained from reviews of case reports or small series, or from original studies usually focused on specific populations (patients with diabetes or hematological conditions or allogeneic stem cell transplantation). In addition, most of the data regarding the causative species come from the United States, which excludes other geographical areas that could influence the proportion of major *Mucorales* genera and species, and even the occurrence of rare species. Finally, information on outcome is limited and risk factors for death have not been precisely defined.

We therefore conducted a retrospective study (RetroZygo Study) on proven and probable mucormycosis cases in France from 1 January 2005 to 31 December 2007. To improve the comprehensiveness of this study, we combined 2 independent sources of information. Our objective was to describe the current underlying diseases associated with mucormycosis, their relationship with clinical presentation, and within the order Mucorales, as well as the outcome and risk factors for death.

METHODS

Sources of Data

Mucormycosis cases diagnosed in France between 1 January 2005 and 31 December 2007 were identified through 2 independent sources of recording [11]: the French hospital information system (Programme de Médicalisation des Systèmes d'Information [PMSI]) and the National Reference Center for Mycoses and Antifungals (NRCMA). The NRCMA surveillance is based on volunteer participation from French microbiologists/mycologists and clinicians and on information collected upon experts' requests. All records with mucormycosis diagnosis during the study period were extracted from both databases and a few additional cases were recorded through other sources (microbiologists, clinicians, and/or pathologists aware of the RetroZygo Study).

Database Management and Validation of Cases

For each case, the referring physician, who was contacted, provided the age, sex, birth date, and name. After exclusion of duplicates and of cases diagnosed outside the study period, the clinician in charge was requested to complete a questionnaire upon receipt of the patient's consent with epidemiological, clinical, biological, and treatment data. All data were recorded anonymously through a secured database. After review by a dedicated medical monitor (G. M.), each case was then validated by 3 of the authors (F. L., E. D., and O. L.), according to the criteria described in the following section. The study was approved by the Institut Pasteur Internal Review Board (2009-34/IRB) and by the Commission Nationale de l'Informatique et des Libertés according to French law.

Mucormycosis Diagnostic Criteria

The 2008 European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria were used and only modified by the inclusion of diabetes mellitus and trauma in case of temporal relationship with mucormycosis [12]. Only proven and probable infections were retained. In the absence of a positive culture when histopathology was suggestive of mucormycosis, the diagnosis was confirmed by an experienced histopathologist. The date of diagnosis corresponded to the first mycological or histological evidence of mucormycosis.

Because members of the Mucorales family are difficult to identify based only on phenotypic observation, the analysis exclusively took into account the sequence-based species identification of isolates or tissue samples performed in the laboratory of origin or at the NCRMA [13, 14].

Definitions (Underlying Diseases, Clinical Presentation)

Five main underlying diseases were considered but only 1 was assigned to each patient in the following order: (1) hematological malignancy whenever present; (2) diabetes mellitus in the absence of hematological malignancy; (3) trauma in the absence of diabetes mellitus or hematological malignancy; (4) solid organ transplantation in the absence of diabetes mellitus, hematological malignancy, and trauma; and (5) "others" in the absence of all the previous diseases. For each patient, we then determined the number of associated underlying conditions such as neutropenia or steroid administration [12].

Clinical forms of mucormycosis were defined as pulmonary, rhinocerebral, cutaneous, or disseminated ($\geq$2 noncontiguous sites involved). Rhinocerebral localizations were individualized as sino-orbital, with cerebral involvement and isolated sinusitis [15].

Statistical Analysis

Relationships between categorical variables were tested using the χ^2 test or Fisher exact test, and relationships between continuous variables were tested using the Student *t* test or the Wilcoxon signed-rank test, when appropriate.

Survival at 90 days was calculated from the date of diagnosis. Patients were censored at 90 days if still alive and before if lost to follow-up. Survival curves were derived from Kaplan-Meier estimates. The log-rank test was used to compare survival distributions between subgroups. If significant, pairwise tests were then performed.

The prognostic effect of surgery was analyzed in 2 ways: comparing patients with or without surgery, (1) whenever the date, and (2) with surgery as a time-dependent variable (ie, only taken into account after mucormycosis diagnosis).

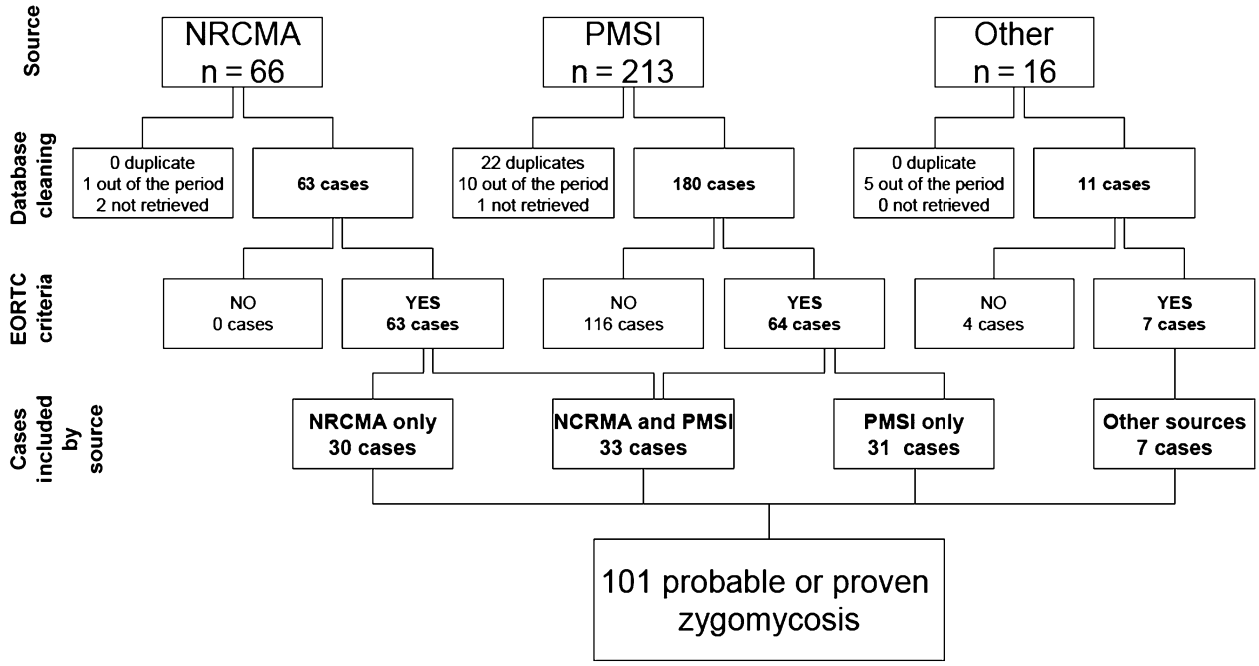

Figure 1. Sources of 101 proven or probable cases of mucormycosis in France (2005–2007). Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NRCMA, National Reference Center for Mycoses and Antifungals; PMSI, Programme de Médicalisation des Systèmes d'Information.

All statistical analyses were performed using the R software package (http://cran.r-project.org). Statistical significance was considered for P values $<.05$, and all tests were 2-sided.

RESULTS

Collection of Data

Data were collected for 262 cases (PMSI [n = 213], NRCMA [n = 66], and other sources [n = 16] 33 cases were retrieved by CNRMA and PMSI). After exclusion of duplicates, cases outside the study period, and cases for which data were unavailable, 101 cases of proven or probable mucormycosis were included (31 cases reported by PMSI alone, 30 by NRCMA alone, 33 by both sources, and 7 by other sources) (Figure 1).

Classification of Cases

Mucormycosis was proven for 60 patients. Diagnosis was obtained by positive histology (n = 58) including 32 of 58 (55%) with a positive fungal culture, or only by positive culture of *Mucorales* species from a sterile site (n = 2). Histological material from 10 of 26 patients with a negative culture was retrospectively analyzed and the diagnosis of mucormycosis was confirmed for all 10 (Figure 2).

Mucormycosis was probable for 41 patients. Diagnosis was based on the presence of hyphae that are suggestive of *Mucorales* species in tissue, but a negative culture in a compatible clinical and radiological context was found for 7 patients. For the remaining 34 patients presenting with host and clinical criteria, diagnosis was based on a positive culture from a nonsterile site either alone (n = 21) or associated with positive direct examination (n = 13).

Patient Characteristics

The mean age of the patients was 50.7 (SD, 19.9) years (range, 9–87 years), with men representing the majority (58%). Five cases were considered related to healthcare. The 2 most common underlying diseases were hematological malignancies (50%) and diabetes mellitus (23%). Hematological malignancies included 27 acute leukemia (17 myeloid, 10 lymphoid), 15 lymphoma, and 8 other malignancies. The median time between the diagnosis of malignancy and mucormycosis was 8.8 months (up to 290 months). Twelve patients had HSCT: allogeneic stem cell transplantation (6 familial, 3 nonfamilial), or auto-HSCT (n = 3). The median time between HSCT and mucormycosis was 6.8 months (range, 1.8–98 months). Recent trauma (traffic or farm accidents [n = 7], leisure or gardening trauma [n = 4], and other trauma [n = 5]) or severe burns (n = 2) were present in 18 (18%) patients. The median number of underlying diseases or associated underlying medical conditions per patient was 2 (range, 0–6) (Table 1).

Of note, the majority of patients received antifungal(s) in the 3 months prior to the diagnosis of mucormycosis (polyenes [n = 18], voriconazole [n = 26], caspofungin [n = 17], posaconazole [n = 6], or fluconazole [n = 16]).

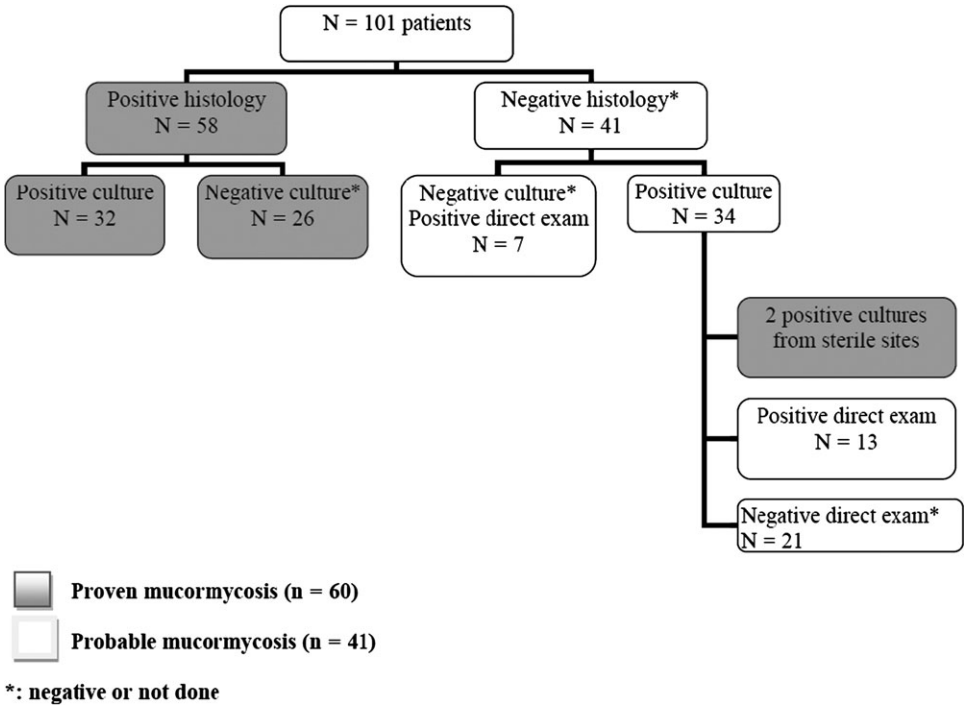

Figure 2. Histological and mycological results obtained in 101 proven or probable cases of mucormycosis.

Sites of Infections According to Underlying Diseases

The most frequent localizations were isolated pulmonary (n = 28), rhinocerebral (n = 25; 10 sinusitis, 5 sino-orbital, and 10 with cerebral involvement), or cutaneous (n = 20). The remaining cases were 18 dissemination, 4 gastrointestinal and one liver mucormycosis, 3 brain lesions without sinus involvement, 1 keratitis, and 1 mandibular osteitis. The median time between the first symptoms and diagnosis was 2 weeks (range, 0–30 weeks), significantly shorter for patients with HSCT compared with those with diabetes mellitus (1 week [range, 1–30] vs 3 weeks [range, 1–18]; $P = .009$) and for patients with trauma (1 week [range, 0–16]) compared with those with diabetes mellitus (3 weeks [range, 1–18]; $P < .001$), hematological malignancy (2 weeks [range, 0–25]; $P = .0497$), or solid organ transplantation (6 weeks [range, 3–20]; $P = .016$) (Figure 3). The time between first symptoms and diagnosis was significantly shorter in patients with cutaneous mucormycosis (1 week [range, 0–3]) than in those presenting with rhinocerebral localization (3 weeks [range, 1–18]; $P = .0021$), pulmonary (2 weeks [range, 0–20]; $P = .0113$), or disseminated disease (2.5 weeks [range, 1–25]; $P = .002$).

Localization of Mucormycosis According to the 3 Main Underlying Diseases

Isolated pulmonary (22 of 50 [44%]) and disseminated (13 of 50 [26%]) infections were the most frequent presentations in patients with hematological malignancies, whereas rhinocerebral (16 of 23 [70%]) and pulmonary (3 of 23 [13%]) infections were most frequent in patients with diabetes mellitus. Hematological malignancy was more frequent in patients with pulmonary lesions than in those with no lung involvement (79% [22 of 28] vs 38% [28 of 73]; $P < .001$), and in patients with disseminated rather than nondisseminated disease (72% [13 of 18] vs 44% [37 of 83]; $P = .003$). Likewise, diabetes mellitus was present for 16 of 25 (64%) of patients with rhinocerebral localization compared with those without (7 of 76 [9%]; $P < .001$) (Table 2).

Mucormycosis in Children

Eight cases were reported in children (<18 years; median age, 13.4 years [range, 9–17 years]). The underlying conditions were trauma (n = 4) and hematological malignancy (n = 4, including 1 with HSCT). Localizations were skin (n = 4), lungs (n = 2), liver (n = 1), and disseminated (n = 1). Four children died within 90 days of diagnosis.

Mucorales Species Involved

The proportion of patients for whom the culture was positive was 48%, 68%, and 95% for rhinocerebral, pulmonary, and cutaneous localization, respectively. Molecular identification to the species level was obtained from culture for 54 of 68 (79%) patients with a positive culture, and from tissue for 5 of 33 (15%) patients with a negative culture. The 3 main fungal species identified were *Rhizopus oryzae*, *Lichtheimia* species, and *Rhizopus microsporus* (Table 1). In cases where the causative

Table 1. Characteristics of 101 Patients With Proven or Probable Mucormycosis in France, 2005–2007

	No (%) of Patients
Mean (SD) age, years	50.7 (±19.9)
Male sex	59/101 (58)
Main risk factor	
Hematological malignancy[a]	50/101 (50)
+ HSCT	12/50 (24)
+ GVHD	5/50 (10)
+ Diabetes mellitus	9/50 (18)
+ Corticosteroids	13/50 (26)
+ Neutropenia	41/50 (80)
Diabetes mellitus[b]	23/101 (23)
Type 1	10/23 (43)
Ketoacidosis	8/23 (35)
Solid organ transplantation	3/101 (3)
Trauma	18/101 (18)
Other[c]	7/101 (7)
No. of main underlying diseases/ associated medical condition	
≤1	26/101 (26)
2	46/101 (45)
≥ 3	29/101 (29)
Fungal species	
Rhizopus oryzae	(32%)
Lichtheimia spp	(29%)
Rhizopus microsporus	(17%)
Rhizomucor pusillus	(7%)
Cunninghamella spp	(7%)
Saksenaea vasiformis	(3%)
Mucor circillenoides	(3%)
Apophysomyces elegans	(2%)
First-line therapy	
L-AmB	(n = 53)
Amphotericin B deoxycholate	(n = 6)
Amphotericin B lipid complex posaconazole	(n = 1) (n = 12)
Amphotericin B lipid complex or L-AmB and posaconazole	(n = 11)
L-AmB and caspofungin	(n = 3)
L-AmB, posaconazole and caspofungin	(n = 1)

Abbreviations: GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; SD, standard deviation.

Underlying associated medical conditions were:

[a] For patients with hematological malignancy: immunosuppressive therapy (n = 11), systemic inflammatory disease (n = 2), chronic obstructive pulmonary disease, human immunodeficiency virus infection (n = 1), and solid organ transplantation (n = 1).

[b] For diabetic patients: systemic inflammatory disease (n = 7), immunosuppressive therapy and chronic renal failure (n = 3, respectively) and chronic obstructive pulmonary disease (n = 2).

[c] Other main underlying diseases were: 2 solid tumors, neutropenia due to marrow necrosis, intravenous drug use, chronic alcoholism, vascular surgery in a case of surgical site mucormycosis, and no factor in 1 case.

species was identified, *R. oryzae* was present in 85% (11 of 13) of rhinocerebral forms, compared with only 17% (8 of 46) of nonrhinocerebral forms ($P < .001$).

Treatment

Among the 101 patients, a first-line antifungal treatment was prescribed for mucormycosis to 87 patients (Table 1). No treatment was recorded for 14 patients (14%) because of postmortem diagnosis (n = 1), ocular localized infection, or immediate premortem diagnosis. Local antifungal therapy was used for ocular localized infection.

In 99 of 101 patients, the median follow-up time was 36 months (0–67). Overall, 62 deaths (including the 14% postmortem) were observed, and the global survival rate was 30% (95% confidence interval [CI], 21%–43%). At day 90, 8 patients were lost to follow-up and 43 deaths were recorded, leading to a survival rate of 56% (95% CI, 46%–66%).

The mortality rate at day 90 differed significantly according to localization ($P < .001$) (Figure 4*A*); it was 25%, 79%, 48%, and 22% in rhinocerebral, disseminated, pulmonary, and cutaneous infections, respectively. Mortality was higher for disseminated forms compared with rhinocerebral (hazard ratio [HR], 5.38 [2.0–14.1]; $P < .001$), pulmonary (HR, 2.2 [1.0–4.7]; $P = .04$), or skin localization (HR, 5.73 [1.9–17.5]; $P = .002$). Among patients with rhinocerebral localizations, the 90-day mortality was 56% in cases of cerebral involvement and 20% for sino-orbital forms, and no death was observed for isolated sinusitis.

Mortality also significantly differed as a function of the underlying disease ($P = .008$) (Figure 4*B*). The mortality rate was 60%, 32%, and 11% in patients with hematological malignancies, diabetes mellitus, and after trauma, respectively. It was higher for patients with hematological malignancies compared with diabetes mellitus (HR, 2.3 [1.0–5.2]; $P = .0495$) or with trauma (HR, 6.9 [1.6–28.6]; $P = .008$). Patients with 2 underlying diseases/underlying associated medical conditions or more had a higher mortality than those with 1 or no risk factor (HR, 5.9 [1.8–19.0]; $P = .004$) (Figure 5).

Surgery was performed in 59% of cases. Whenever performed (before or after the diagnosis), it was associated with a higher survival (HR, 3.26 [1.73–6.13]; $P < .001$). When considering only patients who did not undergo surgery before diagnosis and taking into account surgery as a time-dependent covariate in the model, surgery had no prognostic effect (HR, 0.8 [0.4–1.6]; $P = .6$).

The type of first-line antifungal treatment was not associated with survival ($P = .25$). The 15 patients treated with combination therapy were mostly patients with hematological malignancies (11 patients, including 7 with disseminated disease). Among the 12 patients treated with posaconazole first-line therapy, 6 had diabetes mellitus, and 7 had rhinocerebral localization. Finally, patients with proven or probable mucormycosis

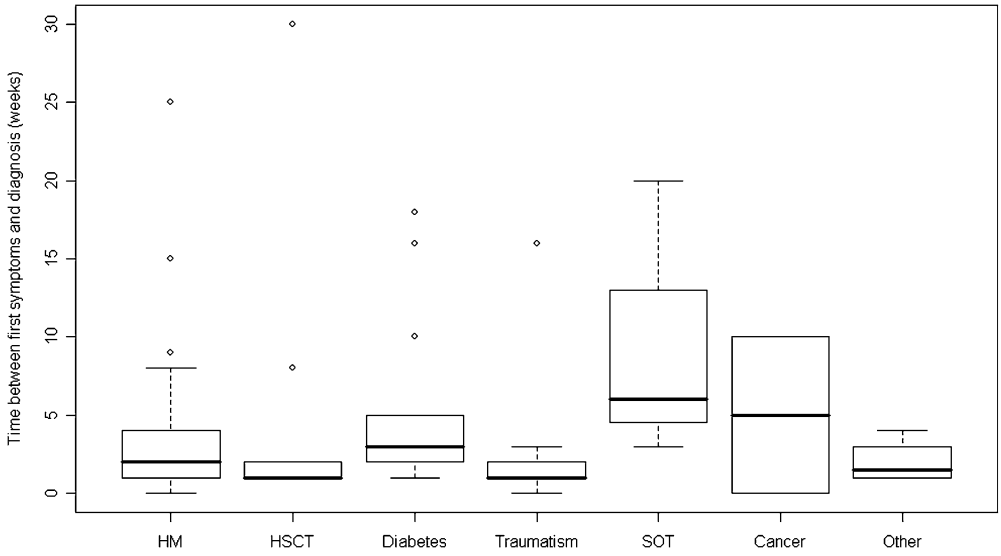

Figure 3. Distribution of time between first symptoms attributable to mucormycosis and diagnosis according to underlying diseases. $P < .001$ for HSCT versus diabetes mellitus; $P < .0001$, $P < .05$, $P < .02$ for trauma versus diabetes mellitus, hematological malignancy, or solid organ transplantation, respectively. Abbreviations: HM, hematological malignancy; HSCT, hematopoietic stem cell transplantation; SOT, solid organ transplant.

had a similar survival rate (odds ratio, 1.6; $P = .142$). Multivariate analysis including only main underlying diseases and mucormycosis localization showed that dissemination was the only independent factor associated with 90-day survival.

DISCUSSION

This nationwide retrospective study over a period of 3 years allowed the analysis of 101 proven or probable mucormycosis cases, mainly identified through a combination of 2 independent sources of data. Based on a capture-recapture assessment [11], these cases are estimated to be representative of all cases of mucormycosis occurring in the country, regardless of their underlying diseases. In addition, all cases were validated by experts and classified according to the current EORTC/MSG criteria, and identification of *Mucorales* genus and species within the order Mucorales was based on nucleotide sequence analysis. However, this study is limited by the retrospective design, which reduces information exhaustivity.

Patients with hematological malignancies represented here were in the group with the highest prevalence in accordance with the results of 2 recent multicenter studies performed in the same period, where 62% and 44% of patients had hematological malignancies [2, 16]. Among the hematology patients, the proportion of patients with allogeneic stem cell transplantations was 18% here and 9% in Italy [2]. These findings are consistent with the comprehensive literature review by Roden et al, who demonstrated that patients with hematological malignancies and HSCT were the 2 most rapidly increasing populations developing mucormycosis [15]. Diabetic patients represented the second largest underlying disease group here, whereas they represented the largest group in the literature review by Roden et al [15], thereby indirectly emphasizing the major role of hematological malignancies in the occurrence of mucormycosis

Table 2. Clinical Localization of the Infection According to the Main Underlying Disease in 101 Cases of Mucormycosis

	No.(%) of Patients With Each Underlying Factor				
	Hematological Malignancy (n = 50)	Diabetes Mellitus (n = 23)	Trauma (n = 18)	SOT (n = 3)	Other (n = 7)
Lung	22 (44)	3 (13)	0	1	2
Rhinocerebral	6 (12)	16 (70)	1 (6)	0	2
Cutaneous	4 (8)	0	15 (83)	0	1
Disseminated	13 (26)	2 (9)	1 (6)	1	1
Other	5 (10)	2 (9)	1 (6)	1	1

Abbreviation: SOT, solid organ transplant.

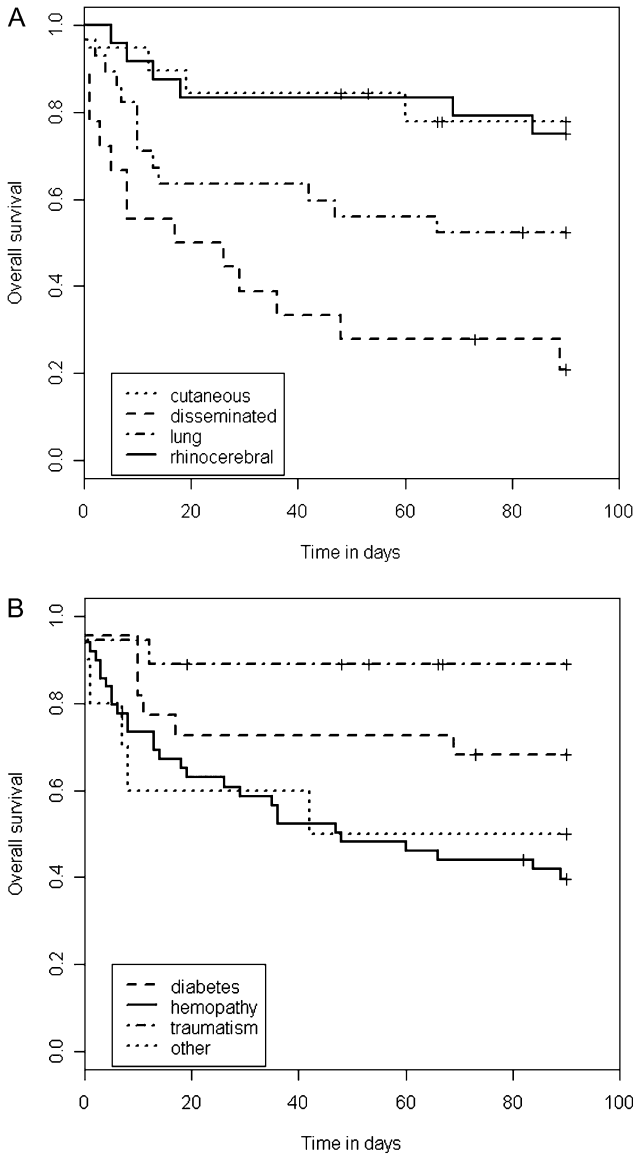

Figure 4. *A,* Ninety-day survival according to mucormycosis localization (Kaplan–Meier plots). *B,* Ninety-day survival of mucormycosis according to the main underlying disease (Kaplan–Meier plots).

today. Our study showed that trauma represented the third most frequent underlying condition (18%), more than previously reported in recent series (ie, 2%, 3%, and 12%, respectively) [2, 8, 15]. Such differences are probably due to the different populations studied, since hematology centers represented the largest source of patients in previous studies.

Another interesting result is the presence of at least 2 predisposing conditions for mucormycosis in 50% of patients. This is reminiscent of recent data from a prospective international study conducted in solid organ transplant recipients showing that diabetes mellitus and renal failure posed additional risk for mucormycosis occurrence [9].

Of note, the main underlying disease significantly influenced not only the time to diagnosis, but also the localization of infection. Indeed, we found a significant association between hematological malignancy and lung involvement or disseminated infection and between diabetes mellitus and rhinocerebral infection. Such associations were previously demonstrated in 1 study that found rhinocerebral localizations in 66% of the diabetic patients and lung localizations in 60% of the hematology patients [15]. Similar data were reported through passive notification in a recent European registry and in an Indian study in hematology and diabetic populations, respectively [8, 9]. Although we cannot specifically comment here due to the small number of patients who received a solid organ transplant, the proportion of those with lung or rhinocerebral involvement was 39% and 26%, respectively, in a recent international study [9]. These differences in clinical presentation according to the underlying disease are not currently explained. Pathogenic abnormalities predisposing to mucormycosis are neutrophil dysfunction, decreased macrophage phagocytosis of *Mucorales* species due to low serum pH, and hyperglycemia and elevation of unbound iron acting as a growth factor for *Mucorales* species, but they do not explain the predominance of rhinocerebral lesions in diabetic patients or the lung involvement in hematology patients. We found also an association between rhinocerebral lesions and infection by *R. oryzae*. Interestingly, a recent study found that the glucose-related protein GRP78 that mediates invasion by *R. oryzae* was overexpressed in diabetic mice compared with controls [17].

Although the most frequent species found here and in previously published studies from the United States is *R. oryzae*, we also documented a high prevalence of *Lichtheimia* species. Such high *Lichtheimia* species prevalence was also reported in recent studies from Europe (24%, 18%, and 19%, respectively, in [2, 8, 16]). By contrast, *Lichtheimia* species was reported in 5% and 3% of cases from an international review and in India, respectively [9, 15]. These contrasted results are probably related to different ecological environments and emphasize the need for local epidemiological studies.

Therapeutic trials in mucormycosis are scarce and explain why recommendations like those from ECIL3 are only based on data from retrospective studies. The study of Roden et al demonstrated that surgery was an independent variable predicting improved outcome [15]. Surgery is believed to improve the prognosis of mucormycosis based on several retrospective studies [16], and a recent study in solid organ transplant recipients demonstrating that surgery independently influenced the outcome [9]. It should be stressed that we cannot ascertain whether surgery was used for all site locations, no matter how severe the infection, and therefore, this has hampered a definite conclusion on its efficacy for the most severely infected patients.

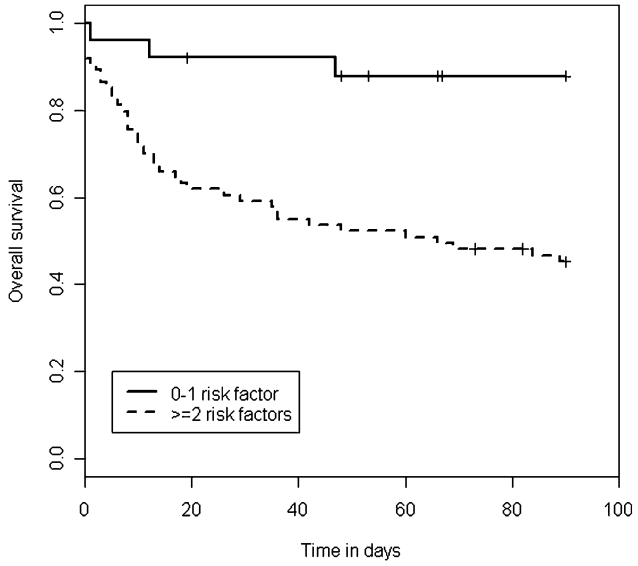

Figure 5. Impact of the number of underlying diseases/associated medical conditions on 90-day survival (Kaplan–Meier plots).

Regarding the first-line antifungal strategy, several limited retrospective clinical trials have shown that liposomal amphotericin B gave response rates of 23%–58% [18] and in a recent study performed in solid organ transplant recipients with rhinocerebral lesions, liposomal amphotericin B treatment was an independent factor for survival [19]. The first retrospective multicenter report dedicated to understanding the role of liposomal amphotericin B in the primary treatment of mucormycosis found a complete or partial response in 32% of patients and an overall survival of 39% [10]. Whether or not higher doses of liposomal amphotericin B will be associated with better results with acceptable tolerance is currently being investigated in the pilot AmbiZygo Study in France involving a total of 40 patients (http://clinicaltrials.gov/ct2/search). Finally, posaconazole has not yet been studied as a first-line therapy [20].

We decided to report global mortality data at 90 days, considering that mucormycosis-related mortality usually occurs early in the course of the disease. The 44% overall mortality rate reported here is similar to other rates recently determined [2, 10, 16]. Of major importance, the presence of >1 underlying condition significantly increased the risk of death compared with 1 or no risk factor for mucormycosis, and dissemination was an independent factor for death. The latter result was also recently reported in solid organ transplant recipients [9]. Of note, the mortality of patients with rhinocerebral lesions varied according to orbital and/or cerebral involvement, in accordance with recently published data specifically from the transplant population [19].

In conclusion, this 3-year study performed in France provides new insights into the current presentation and prognosis of mucormycosis. The clinical presentation was more diverse than expected, with a high prevalence of primary cutaneous mucormycosis due to a large number of patients with trauma and a prognosis significantly influenced by the localization.

Notes

Acknowledgments. We thank the following principal investigators of the French Mycosis Study Group (France), who contributed to the current database. Those outside Paris (in alphabetical order by city) are as follows:

Agen (C. Freimann, P. Rispal), Amiens (E. Lewandowski, T. Chouaki, H. Dupont, G. Damaj, P. Mertl), Angers (P. Six, J. P. Bouchara, H. Hitoto, N. Ifrah, T. Urban), Apt (T. Carrelet), Arles (J. P. Pellegrini), Aurillac (A. Mosser), Auxerre (A. Calmelet), Bagnères de Bigorre (F. Braman), Bain de Bretagne (D. Bordes), Belfort (D. Pobel), Besançon (A. Dussaucy, J. ;F. Viel, F. Grenouillet, G. Blasco, F. Legrand, J. C. Navellou, E. Plouvier, L. Tavernier, B. Kantelip), Bordeaux (A. Kostrzewa, B. Couprie, J. P. Bebear, E. Blanchart, L. De Gabory, M. Dupon, C. Deminière), Boulogne Billancourt (L. Comar), Bourg en Bresse (N. Peslin), Brest (J. M. Cauvin), Bry sur Marne (G. B. Ibara), Caen (M. J. D'Alche-Gautier, C. Duhamel, R. Verdon), Cahors (A. Simons), Chalons en Champagne (F. Canas, P. Berger), Charleville (I. Frangi), Chartres (P. Denier), Cherbourg (G. Acher, M. Barre), Clamart (C. Soler, L. Bargues, D. Brousse, J. P. Perez), Clermont Ferrand (J. Afonso, D. Pons, J. O. Bay, C. Jacomet, P. Dechelotte), Créteil (S. Bretagne, K. Belhadj), Dijon (C. Quantin, D. Caillot), Doullens (M. Derancourt), Dreux (J. M. Vogt), Echirolles (J. F. Peresse), Foix (E. Hornus), Frejus (Y. Pinier, J. Gutnecht), Grande Synthe (F. Pierchon), Garches (S. Baron), Grenoble (J. Fauconnier, B. Lebeau), Ispoure (J. Sahuc), Lens (C. Courouble, P. Morel), Libourne (D. Crenn), Lievin (B. Duquesne), Lille (B. Sendid, C. Berthon, V. Coiteux), Limoges (A. Vergnenègre, D. Ajzenberg, I. Pommepuy), Lorient (J. B. Boubier), Lyon (P. Messy, A. L. Bienvenu, Y. François, M. Michallet, J. L. Peix), Mainvilliers (T. Al Jijakli), Mantes la Jolie (M. Meyer), Marseille (M. Bertrand, V. J. Bardou, M. H. Giovannini, B. Beylot, S. Ranque, A. Stein, S. Masson, P. Metellus, A. M. Stoppa), Meaux (A. Fiacre, G. Kassab), Melun (G. Amghar), Montpellier (C. Michelon-Meslé, P. Rispail, L. Durand), Nancy (K. Alzahouri, M. Machouart, A. Debourgogne, Dr Witz, J. F. Chassagne, A. Gerard, E. Simon), Nanterre (D. Carradot), Nantes (D. Antonioli, F. Gay-Andrieu, N. Corradini), Nice (G. Daideri, M. Gari-Toussaint, H. Hyvernat, M. Poiree, P. M. Roger), Nimes (C. Lechiche, .L Lachaud), Niort (A. Garcia, S. Labbe), Peronne (P. Decroix), Perpignan (M. Saada, C. Billotet), Poitiers (C. Kauffman-Lacroix, C. Godet), Pontoise (D. Decup), Reims (D. Blanc, H. Daragon, D. Toubas, C. Nérot), Rennes (A. Fresnel, X. Carsin, J. P. Gangneux, C. Arvieux, T. Lamy de la Chapelle, N. Rioux), Ruffec (E. P. Satre), Salons de Provence (G. Gineyt), Sens (M. Fourre), Saint-Etienne (J. M. Rodrigues, B. Trombert, P. Vercherin, H. Raberin, J. Cornillon, F. Lucht), Saint Julien en Genevois (D. Pietri), Sainte Catherine (P. H. Miquel), Strasbourg (F. Binder, N. Roeslin, V. Letscher-Bru, J. P. Dupeyron, R. Herbrecht), Suresnes (C. Leclerc), Toulon (C. Michel, H. Redier), Toulouse (L. Molinier, S. Cassaing, M. Alvarez, L. Esposito, B. Marchou, X. Brousset, E. Uro-Coste), Tourcoing (I. Vérin, P. Patoz, S. Alfandari, X. Lemaire, Y. Yazdanpanah, X. Froment), Tours (S. Sunder, J. Chandenier, E. Gyan), Troyes (F. Benaoudia), Valence (D. Le Magny), Valenciennes (J. Kohler), Vannes (H. Journel), Verdun (J. Deleau), Vesoul (P. Selles), Villiers Semeurs (F. Sini).

Those in Paris are as follows:

Antoine Beclère (F. Doucet-Populaire, L. Savale), Avicenne (C. Bouges-Michel), Bichat (C. Chochillon, O. Brugière, M. Wolff, V. Joly, H. Adle-Biassette), Cochin (M. T. Baixench), HEGP (G. Chatellier), Hôtel Dieu (M. Cornet), Institut Montsouris (Y. Péan), Lariboisière (T. Meas, R. Kania), Necker (C. Lebihan, M. E. Bougnoux), Pitié Salpétrière (A. Fekkar, A. Datry, L. Bodin, Y. Samson), Robert Debré (B. Brethon), Saint-Antoine (M. Develoux, F. Isnard), Saint-Joseph (H. Pons-Pouchelle), Saint-Louis (C. Lacroix, P. Ribaud, A. Xhaard, A. Bergeron-Lafaurie, O. Marie, J. Pavie,

E. Raffoux), Tenon (A. Parrot).

We also thank D. Van Cauteren (Institut de Veille Sanitaire) and all the medical officers in charge of the French hospital information system in the selected hospitals, who helped to identify the patients from the PMSI database.

Financial support. This work was supported by a specific grant from the Institut de Veille Sanitaire.

Supplement sponsorship. This article was published as part of a supplement entitled "Advances Against Mucormycosis: A Tribute to the Memory and Courage of Hank Schueler," sponsored by the Henry Schueler 41&9 Foundation.

Potential conflicts of interest. E. D. is a member of the boards of Merck Sharpe & Dohme (MSD) and Astellas and has received speaker's fees from Gilead and MSD; O. L. is a member of the MSD board, is a consultant for Astellas and Gilead Sciences, and received grants or speaker's fees from MSD and Pfizer. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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