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REVIEW

The burden of mucormycosis in HIV-infected patients: A systematic review

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Summary *Objectives:* Mucormycosis is an invasive fungal infection afflicting immunocompromised patients, causing a significant degree of morbidity and mortality. The purpose of the study was to provide a comprehensive analysis describing the epidemiology and outcome of mucormycosis in the scenario of HIV infection.
Methods: We systematically searched PubMed for reports about mucormycosis associated with HIV. Eligible studies describe the predisposing factor, clinical form, treatment, and survival outcome.
Results: We included 61 articles from 212 reviewed abstracts, corresponding to 67 cases. Patients were mostly men (68.2%) with a median $CD4^+$ count of 47 [IQR 17—100] cells/mm^3. Intravenous drug use (50%), neutropenia (29.7%) and corticosteroid use (25%) were the predominant associated factors. The main clinical forms were disseminated (20.9%), renal (19.4%), and rhino-cerebral (17.9%). *Rhizopus* (45.5%) and *Lichtheimia* spp (30.3%) were the main fungal isolates. Treatment consisted of antifungal therapy and surgery in 38.8%. Overall mortality rate was 52.2%, and varied with the site of infection: 92.9% for disseminated disease, 62.5% for cerebral disease, 60% for pulmonary infection, and 36.4% for cutaneous infection. Survival was worse for those who did not initiate antifungals ($p = .04$), who were antiretroviral naïve

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($p = .01$), who were admitted to ICU ($p = .003$) or had disseminated disease ($p = .007$).
Conclusions: Mucormycosis is a life-threatening infection in HIV patients and clinician should be aware of this co-infection in the differential diagnosis of HIV opportunistic infections.

Introduction

Mucormycosis is an emerging invasive fungal infection caused predominantly by the order — Mucorales — which encompasses the genera *Rhizopus*, *Mucor*, *Litcheimia*, *Cunninghamella*, *Rhizomucor*, *Apophysomyces*, and *Saksenaea*.[1] The disease accounts for extreme morbidity and mortality in adult and pediatric immunocompromised patients. The traditional predisposing conditions for mucormycosis include hematological malignancies, severe neutropenia, uncontrolled diabetes mellitus, trauma, prolonged use of corticosteroids and malnutrition.[2] However, infection with the human immunodeficiency virus (HIV) has not been considered a significant risk factor for mucormycosis. Furthermore, it has been postulated that in this scenario, mucormycosis assumes a peculiar clinical profile contrasting with what is observed in other high-risk populations.[3] Not infrequently, dissemination occurs and is almost always fatal.[4,5]

To date, there has been no comprehensive review of mucormycosis in HIV infection to guide our understanding of the epidemiology of this condition. Thus, we performed a systematic review of the literature to better understand the current epidemiology, predisposing factors and outcomes of mucormycosis in HIV positive patients.

Methods

Search strategy and selection criteria

We performed an automated search on PubMed database for studies reporting mucormycosis in the context of HIV infection. Our search was not restricted neither by time nor language. Manual search methods included footnote chasing and searching the reference list of relevant articles, for the ascertainment of additional case reports. The PRISMA guideline was followed.[6] Three authors independently (JM, MG, AV) assessed articles for eligibility and extracted the data, with a fourth reviewer (CL) consulted when there was a disagreement. The following search strategy was used in PubMed: "Mucormycosis" OR "Zygomycosis" AND "HIV" OR "AIDS". Our search ended on January 31, 2016. To be eligible for inclusion in the analysis, studies should have met the following criteria: (I) be case reports or case series, (II) enrolled HIV-infected individuals, irrespective of age, co-infected with mucormycosis, and (III) provide sufficient details on the diagnostics tools (i.e.; histopathology, culture, PCR); clinical category; underlying risk factor; treatment modality, and outcome. We excluded studies that were pure reviews, those that reported only on HIV-uninfected subjects or cohorts. The initial search consisted of a title and abstract revision, and those articles deemed ineligible were excluded.

Definitions

The diagnosis of mucormycosis had to be confirmed by histopathology of specimens, by growth on culture medium or by amplification of DNA sequences from tissue biopsy or other samples. Those cases with probable or suspected mucormycosis without mycology or histopathology confirmation were not included. The identification of broad aseptate or pauci-septate, ribbon-like hyphae with right-angled branching in a tissue specimen was considered highly suggestive of mucormycosis infection.

Clinical forms were in accordance with ECMM/ISHAM Working Group on Zygomycosis.[7] Predisposing factors or comorbidities that triggered the development of mucormycosis were assessed. Treatment was documented in a prespecified manner: description of amphotericin B treatment (either alone or in combination with other antifungals); duration of amphotericin B treatment, cumulative dose of amphotericin B, type of amphotericin B formulation, presence of surgery and type of surgery intervention (i.e.; debridement, organ resection, local excision, etc.). When not specified in the publication, we estimated the approximate duration of amphotericin B therapy for adult patients by dividing the total dose by 70 kg and assuming a dosage of 1 mg/kg/day.

Highly active antiretroviral therapy (HAART) was defined as a combination of three or more antiretrovirals, which generally included a backbone of two nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) plus a third anchor drug (i.e.; ritonavir-boosted protease inhibitor, integrase inhibitor or a non-nucleoside reverse transcriptase inhibitor).

Post-HAART era is the period where a combination containing a boosted—protease inhibitor antiretroviral drug was available. This period starts after 1996.

Outcome

The primary outcome was in-hospital mortality. To facilitate comparisons with published studies, we compute all-cause 30-day mortality, extracting from each publication the time from admission to death.

Data extraction

The final clinical model was constructed in an Excel datasheet, combining categorical and numerical variables. Categorical variables include country of publication, gender, HAART experience at the time of mucormycosis diagnosis, risk factors, clinical categories, diagnostic procedures, diagnostic means, outcome, infecting organism, the presence of concurrent opportunistic diseases, time of diagnosis (alive or postmortem) and intensive care unit (ICU) admission. Numerical variables included the year of publication, age, $CD4^+$ cell count, time from admission to death, duration of polyene therapy, cumulative dose of

amphotericin B and number of concurrent opportunistic diseases.

Statistical analysis

Categorical variables were compared using chi-square or Fisher's exact test (two-sided), whereas continuous variables were compared by the Mann—Whitney *U* test. Determinants of in-hospital mortality were examined by univariate analysis. Kaplan—Meier survival analysis was performed for 30-day mortality and assessed by the log-rank test. All statistical analyzes were considered significant if p values were $<.05$. Calculations were performed with the SPSS version 23.0 (SPSS, Chicago, IL, USA).

Results

The initial database search identified 212 records, of which 47 were excluded based on title and abstract review. Additional 6 publications were identified by manual search. After exclusion of 102 articles (i.e.; review articles [$n = 54$]; non-relevant articles [$n = 34$]; HIV-negative mucormycosis cases [$n = 14$]), 63 articles were assessed for eligibility through full-text review. Supplementary Fig. 1 depicts the PRISMA flow diagram.

A total of 61 studies met the inclusion criteria for abstraction. These studies corresponded to 67 individual cases of mucormycosis published between 1988 and 2016. Supplementary Table 1 shows the demographic and clinic data of those cases, in order of date of publication.

Geographic distribution

Fungi causing mucormycosis are distributed worldwide and are ubiquitously found in the environment. However, the majority of cases were from Europe (most of them from Spain) (28 cases), followed by North America (27 cases). Asia and the Middle East, Latin America and the Caribbean, and Africa sub-regions contributed to 7,3 and 2 cases, respectively. The cases were reported from different medical institutions, and during different time points.

Demographics

The mean patient age was 35 years (SD $\pm$ 10.5), with a predominance of men (68.2%; male to female ratio 2.1:1). Four cases occurred in $\leq$18 years old (6%; pediatric cases). Mucormycosis prompted the diagnosis of HIV infection in nineteen patients (31.1%). At the time of the initial mucormycosis diagnosis, twenty patients (29.9%) were on HAART. The median $CD4^+$ cell count at hospital admission was 47 [IQR 17—100] cells/mm^3.

Diagnosis and etiology

Sixty patients (89.6%) were diagnosed by histopathology, whereas only 33 (49.2%) were positive by culture. In twenty-five cases (37.3%), the diagnosis was positive in both histopathology and culture. Molecular methods provided fungal identification in just one patient.[8] Those methods provided identification of the fungus by genus ($n = 6$) and species level ($n = 5$). Table 2 shows the etiological agents isolated. *Rhizopus* spp accounted for almost half of the isolates (45.5%). There was no infection with multiples species. Autopsy (19.4%), skin (18%), kidney (18%), brain and sinus biopsy (9.7%) were the most common methods used for recovery of the infecting organism. Eighteen patients (26.8%) were diagnosed with other diagnostic procedures (i.e.; bronchoalveolar lavage, direct sputum smear, palate biopsy). Interestingly, no case of mucormycosis was diagnosed based on positive blood culture. Eleven cases (16.4%) were diagnosed post-mortem. Almost half (42.9%) of the patients diagnosed at autopsy presented with disseminated disease.

Clinical forms and predisposing factors

Table 1 shows the clinical characteristics of patients with HIV-associated mucormycosis. The commonest comorbidities were a history of intravenous drugs use (IVDU) (50%), neutropenia (29.7%) and corticosteroid use (25%). Patients who were IVDU were more likely to have renal mucormycosis compared with patients without IVDU (34.4% vs 6.3%, $p = .005$, respectively). Similarly, IVDU subjects were more likely to develop isolated cerebral mucormycosis compared with non-IVDU (22.6% vs 3.1%, $p = .02$, respectively).

Diabetes mellitus (DM) was present in ten patients (15.6%); the majority were type 2 (8 cases, 88.9%). Three cases of acute ketoacidosis were reported.[9—11] Of note, we observed interesting cases of DM in the HIV scenario: DM secondary to long-term steroids use; protease inhibitor-induced DM and DM associated with pentamidine-induced pancreatitis, used for secondary *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.[10—12] Individuals with DM had a higher risk of developing the rhino-cerebral form compared to non-diabetics (50% vs 11.1%, $p = .003$, respectively).

Conversely, patients who sustained trauma (either major or minor) were more likely to have cutaneous infections compared with patients without trauma (55.6% vs 10.9%, $p = .001$, respectively). Four cases (5.9%) presented no underlying risk factors.[13—16]

Ten out of sixteen patients (23.8%) who reported use of corticosteroid therapy had data with regard to time of corticosteroid use during hospitalization. The median number of days was 19.5 (IQR 8.75—21). The main reasons for administration of steroids were PJP (31.25%) and non-Hodgkin lymphoma (18.75%).

Clinical categories

Disseminated disease represented the most common clinical form of mucormycosis. Of the 14 disseminated cases, the infection was generalized disseminated in seven [i.e.; the primary site of infection was impossible to identify]. The mean number of regions affected was 3 (range; 2—7). Individual sites affected were represented in various combinations; including gastrointestinal ($n = 12$), lung ($n = 7$), kidney ($n = 6$) and spleen ($n = 5$). There was no case of secondary skin dissemination. There were 2 solid

Table 1 Characteristics of the patients with HIV-associated mucormycosis [**1988—2016**].

	N (n = 67)	Frequency (%)
Clinical categories		
Disseminated	14	20.9
Renal	13	19.4
Rhino-cerebral[a]	12	17.9
Cutaneous	11	16.4
Isolated cerebral	8	11.9
Pulmonary	5	7.5
Others[b]	4	6
Co-morbidity or underlying predisposing factors		
History of IDU	32	50
Neutropenia	19	29.7
Corticosteroid use	16	25
Diabetes mellitus	10	15.6
Major or minor trauma	9	14.1
Cancer chemotherapy	6	9.4
Other[c]	15	23.3

[a] Include rhino-orbital, rhino-orbital-cerebral, nasal, and rhino-cerebral forms, with 4,4,2 and 2 cases, respectively.
[b] Refers to gastrointestinal, isolated ocular, articular and splenic forms, with 1 for each form.
[c] Refers to solid organ transplantation, malnutrition, occupational exposure, radiotherapy, metabolic acidosis, hematologic malignancies, iron overload and no underlying factor besides HIV infection.

Table 2 Pathogens causing HIV-associated mucormycosis **[1988—2016]**.

Genus	Species	No. isolates (%)
Rhizopus spp		15 (45.5)
	R. arrizus	5
	R. microsporus	1
	R. stolonifer	1
Lichtheimia spp		10 (30.3)
	L. corymbifera	7
Mucor spp		5 (15.2)
Rhizomucor spp		1 (3.0)
Cunninhamella		1 (3.0)
	C. *bertholletiae*	1
Conidiobolus spp		1 (3.0)

organ transplant recipients (one each for liver and kidney), and both evolved with a fatal disseminated disease.[4,17] Four out of 6 patients who were admitted to ICU presented disseminated disease.

All cases of renal mucormycosis, except one, were unilateral (i.e.; isolated renal mucormycosis). Six involved the right-side and 7 the left-side. The most common findings were flank pain (92.3%), enlarged kidney (84.6%), fever (76.9%), and abnormalities in renal blood flow (46.2%). Other less frequent findings included loss of cortico-medullary differentiation, urologic complaints, dyspnea and renal infarction.

Cutaneous involvement was predominantly of the superficial form, apart from two cases that were nodular and gangrenous.[14,18] In three cases where the source of infection was the skin, dissemination occurred subsequently. Necrotic ulcers, black eschars, and painful skin lesions were the most common findings in this category in 64.3%, 50%, and 28.6%, respectively. Other less reported findings were alopecia, cellulitis, hyperkeratotic plaque and pruritus.[14,19,20]

Of the 8 cases presenting with isolated cerebral mucormycosis, 7 were in association with IVDU. Three cases were known to have injected an illegal drug (i.e.; heroin; heroin and cocaine; and cocaine). In all cases the lesions were located in the basal ganglia; they were unilateral lesions in three, bilateral in three and unknown in 2 cases. The most common clinical findings included altered mental status (83.3%), hemiplegia (66.7%), fever (50%), and cranial nerve palsies (33.3%). No evidence of meningeal involvement was present in any of the patients.

Atypical manifestations of mucormycosis did occur (i.e.; isolated panendophthalmitis; knee septic arthritis and isolated spleen abscess).[16,21,22]

Other opportunistic diseases associated with mucormycosis infection

During hospitalization, thirty-two cases (57.1%) were also diagnosed and treated for other opportunistic diseases. The mean number of opportunistic diseases were 1 (range, 1—3). The most prevalent opportunistic agents were *Pneumocystis jirovecii* ($n = 8$), cytomegalovirus ($n = 4$), and *Mycobacterium tuberculosis* ($n = 4$). Aspergillus — another filamentous invasive fungus - was reported concomitantly in 3 cases.[23—25]

Management

Fifty-two (77.6%) patients initiated some form of antifungal regimen during hospitalization. In contrast, fifteen patients (22.4%) did not receive antifungal therapy either due to initially disease severity or because they died prior to diagnosis.

Deoxycholate amphotericin B (74%) was the amphotericin formulation of choice, compared with liposomal (18%) and lipid complex (4%). Combinations of amphotericin B formulations were administered in 2 instances (i.e.; switching from deoxycholate to liposomal amphotericin B due to renal toxicity and switching to deoxycholate formulation for maintenance therapy after an intensive phase with liposomal amphotericin B).

Amphotericin B alone (i.e.; without another antifungal agent) was the mainstay of therapy in 84.6%. In addition, in 7 cases amphotericin was administered in combination with other agents (flucytosine, $n = 1$; itraconazole, $n = 1$; fluconazole, $n = 1$, posaconazole, $n = 4$). The median cumulative dosage of amphotericin B was 2.2 g (IQR; 0.9—4.4). Moreover, the median number of days with amphotericin was 25 days (IQR 13.2—78.2). There was a difference between the median duration of amphotericin B according to the outcome, although the difference was not statistically significant. (21 *vs* 30 days, for survivors and non-survivors, respectively, $p = .96$).

Adjunctive granulocyte-macrophage colony stimulating factor was administered in three patients. One had AIDS-related lymphoma and was on chemotherapy.[26] The other was a recent hepatic transplant recipient on use of immunosuppressive drugs to avoid organ rejection.[4] Finally, one patient presented with multiples episodes of moderate to severe neutropenia before and during hospital admission.[19]

Surgery, alone or as part of antifungal therapy, was performed in 27 cases (40.3%). The most common surgical procedures performed were elective nephrectomy ($n = 8$, 29.6%), sinus surgery ($n = 6$, 22.2%) and skin debridement consisting of local excision of necrotic areas ($n = 5$, 18.5%). There was just one case in which treatment consisted of surgery without other intervention.[16] That was a case of a young male who developed unilateral panophthalmitis and sudden loss of vision. Evisceration was done and the patient responded well after surgery. The combination of surgery and antifungal regimens was performed in 26 (38.8%) cases.

Outcomes

Overall mortality was higher in the 1990s compared to other decades (Fig. 1). The mortality did not change within the 2 HAART periods (pre vs post-HAART era). Thirty-five patients (52.2%) died during hospital admission. Data with respect to the outcome was unknown in one case.[27]

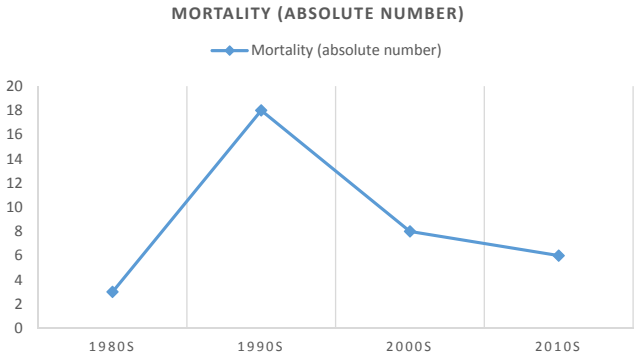

Figure 1 Mortality due to HIV-associated mucormycosis since the 1980s, by decade.

The choice of therapy was an important determinant of prognosis. Mortality of invasive mucormycosis in patients with no antifungal therapy was 93%, in those with no surgery, 75%; and in those with combined antifungal and surgery therapy, 20%.

Mortality varied with the site of infection: death occurred in 92.9% in disseminated disease, 62.5% with isolated cerebral, 60% with pulmonary infection, and 36.4% with cutaneous disease. No difference in mortality was observed between fungal species. Similarly, there was no association between HAART administration and hospital-mortality.

Independent positive predictors of mortality by univariate analysis were the presence of disseminated disease ($p = .001$) and ICU admission ($p = .008$). Conversely, surgery ($p < .001$), and use of antifungal therapy ($p < .001$) were independent negative predictors.

Twenty-nine patients had complete data regarding time to death. In this group, the median number of days from admission to death was 21 days (IQR 10—90, range 1—365 days). The 30-day all-cause mortality was 55% ($n = 16$).

The Kaplan—Meier curves showed that survival diverged between patients who use any type of antifungal therapy vs patients who had not initiated specific therapy; HAART naïve vs HAART experienced patients; ICU vs non-ICU admitted patients; and disseminated vs non-disseminated disease (Table 3). Fig. 2 shows the Kaplan-Meir survival curves for the whole patient cohort and stratified by the presence of disseminated disease.

Discussion

Mucormycosis is the third most relevant invasive fungal infection (IFI) following candidiasis and aspergillosis in immunocompromised subjects leading to a significant degree of morbidity and mortality.[1] Globally, the incidence of mucormycosis is on the rise as a result of the expansion of the population at risk, but also because of the optimization of microbiology techniques for *Mucor* isolation. A population-based survey of IFI conducted in metropolitan France during 2001—2010 showed that the incidence of mucormycosis increased by 7.3% per year.[28] Similarly, a single center retrospective analysis done in India showed that the incidence of mucormycosis increased from 12.9 cases/year

Table 3 Survival following hospitalization for HIV-associated mucormycosis **[1988—2016]**.

Variables	Survival (median days)	95% confidence interval		p value[a]
		Lower bound	Upper bound	
Antifungal not initiated	13	5.4	20.5	**.04**
Any antifungal initiated	40	0.5	79.4	
HAART naive	14	7.0	20.9	**.01**
HAART experienced	49	20.1	77.8	
ICU admission	10	3.5	16.4	**.003**
Non-ICU admission	40	11.5	68.4	
Disseminated disease	15	12.9	17.0	**.007**
Non-disseminated disease	57	29.2	84.7	

p values $<.05$ were highlighted in bold.
[a] p values were calculated with Log Rank (Mantel—Cox) test.

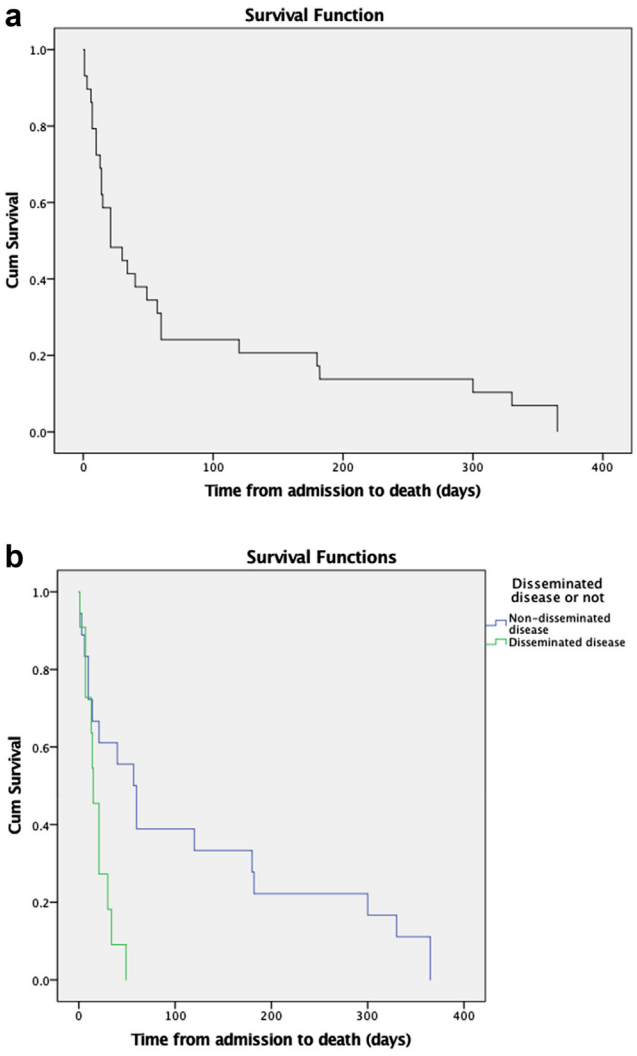

Figure 2 (a) Kaplan Meier survival curve of all patients with HIV-associated mucormycosis. (b) Kaplan Meier survival curve stratified by the disseminated disease presence. Patients with disseminated disease ($n = 14$) *versus* non-disseminated disease ($n = 52$). Log Rank test equals 7.156; $p < .007$.

(1990–1999) to 35.6 cases/year (2000–2004).[29] In addition, a study conducted over a 9-year time period in Belgium found that the annual incidence rate increment from 0.0019 cases/10.000 patient-days in 2000 to 0.148 cases/10.000 patient-days in 2009 ($p = .01$).[30] Finally, in the largest review of mucormycosis cases in the English-language literature, Roden and colleagues compiled 929 cases of mucormycosis from 1885 to 2004, and concluded that there was a substantial increase in the reporting during the study period.[31]

In this systematic review, unlike the traditional risk factors commonly associated with mucormycosis at high-risk populations, we found that in the HIV scenario, parental drug use, neutropenia, and corticosteroid use were the most significant predisposing factors to mucormycosis.

We found a distinct epidemiology profile of mucormycosis in this study compared to other global reports. The disseminated form is a rare manifestation of mucormycosis in the general population, however, in our review, the disseminated disease was the most common presentation, seen in 14 patients (20.9%), and associated with poor outcome.[30,32–34] Notably, we did not find a case of secondary skin involvement in disseminated disease; contrasting with other endemic and opportunistic fungal infections (i.e.; in sporotrichosis where the skin may be the site of inoculation and the dissemination of the fungus and in cryptococcosis and histoplasmosis, where the skin involvement may be present in 10% of the cases).[35] Moreover, we found that renal mucormycosis was the second leading manifestation in this scenario, which is in contrast to previous data which showed that renal infection occurred in 2%.[31] The higher proportion of renal disease observed in our study might be attributed to a substantially higher number of patients who were intravenous drug users (50%), especially of heroin, cocaine, and amphetamines. As proof of principle, animal data showed that mice developed both central nervous system and renal infection after intravenous inoculation of Phycomycetes and inorganic matter (such as colloidal carbon and iron).[36,37] Besides, intravenous drugs might act as vasoconstrictors and sensitizes the vasculature to further damage.[38]

Another key epidemiological feature observed in our study was the younger age of the subjects. Previous data showed that the median age of patients with mucormycosis varied from 50 to 54 years, differing from the mean age of 35 observed in our cohort.[30,32–34,39] Difference in patient's population analyzed (i.e.; HIV *versus* non-HIV-infected) might partly explain this phenomenon.

The above characteristics emphasize that mucormycosis in HIV-infected hosts behave differently compared to other host populations. For instance, in patients with bone marrow and solid organ transplants as well as in those with malignancies, the pulmonary form represents the main clinical manifestation of mucormycosis, in contrast to the 7.5% found in HIV patients.[29] Moreover, we found that the gastrointestinal form is an extremely rare manifestation in HIV patients, contrasting to 7% and 6% in solid-organ transplants and desferoxamine therapy subjects, respectively.[29]

HIV/AIDS *per se* does not seem to be a significant risk factor for mucormycosis, justifying the paucity of AIDS reports in this scenario. First, neutrophils, but not necessarily T-cell lymphocytes, are critical for inhibiting fungal spore proliferation *in vitro*.[40] Second, in both clinical and autopsy series, the frequency of mucormycosis in infected patients varied from 0.12 to 4.9%.[29–33,41,42] Third, the rarity of HIV-mucormycosis co-infection is reflected by the number of cases whose predisposing factors were HIV only. In our study, just 4 out of 67 cases had no other underlying factor. Finally, we believe that mucormycosis should only be considered in the differential diagnosis of fungal opportunistic infections when subjects present with an advanced level of immunosuppression (i.e. $CD4^{+} < 50$ cells/mm^3) and harbor additional risk factors such as IVDU and neutropenia. Early consideration of disseminated disease should be actively pursued, since dissemination is frequently encountered in HIV patients.

As expected, most of the patients in our study were infected with *Rhizopus* spp., which accounts for most cases of mucormycosis, with *R. arrhizus (formerly known as R.*

oryzae) being the predominant species.[2] Conversely, we found a higher proportion of *Lichtheimia* spp (formerly known as *Absidia*) in our cohort (30%). The difference may be due to predominance of European cases (41.7%) in this literature review, where *Lichtheimia* is known to predominate.[32,33]

The fact that the majority of patients were diagnosed by histopathology and later in the disease course (i.e.; post-mortem diagnosis in 16.4%) underscore the eminent need to validate rapid serological and molecular diagnostics tests for mucormycosis. Increased awareness of this fungal disease amongst clinicians is critical to establish a timely diagnosis and to reduce fatal disease-related outcomes. Thus, HIV physicians should be aware that mucormycosis, albeit rare, may occur in those patients, and that in 31% it was the initial manifestation of the AIDS syndrome.

Interestingly, we found that in more than half of the cases co-infection with other opportunistic pathogens occurred. This fact was unsurprising considering the severe immunologic impairment observed in our population (median $CD4^+$ 47 cells/mm^3). Twenty-five patients (37.3%) were HAART-naïve at hospital admission. Here, we reinforce the well-known concept that HAART is the cornerstone of the contemporary HIV therapy, increasing survival rates similar to what is seen in uninfected populations. Recent HIV treatment guidelines recommend on universal initiation of HAART for all HIV-infected patients, regardless of $CD4^+$ count.[43]

Despite the availability of amphotericin B — which is the mainstay of invasive mucormycosis therapy —, there has been no significant improvement in mucormycosis-associated mortality over time. The 30-day mortality remains high (55%) and comparable to that reported elsewhere.[39] In our study, the poorest outcomes were identified in patients with disseminated disease and in those that were admitted to ICU. Conversely, surgery and administration of antifungal treatment increased survival. In fact, in our analysis, the group with better outcomes (survival rate of 80%) were those that had a combination of surgical debridement plus antifungal treatment corroborating with current treatment recommendations.[44]

Our study has limitations. First, as with any systematic review, there was a bias in case ascertainment, because studies that are not indexed in electronic databases tend to be excluded (reporting bias). Second, our reported confidence intervals are somewhat larger, due to our limited sample size. Third, we were unable to provide a clear picture of HIV-associated mucormycosis in pediatric populations, due to our limited sample size (i.e.; four). However, 2 out of 4 children with mucormycosis presented with the generalized disseminated infection at admission and both died during hospitalization. Four, our review's findings were predominantly case reports from Europe and the United Sates. However, those cases were reported from different institutions, partly eliminating the bias. Finally, our review encompasses the burden of mucormycosis in HIV-infected patients, specifically the strains belonging to the order Mucorales.

In summary, our study represents the first attempt to describe the burden of mucormycosis in HIV-infected patients. We found that HIV-associated mucormycosis is frequently fatal and associated with severe immunosuppression, IVDU, neutropenia, and corticosteroid use. The mortality is high, particularly in those with disseminated disease and ICU admission. This review means to raise awareness among HIV physicians, that mucormycosis should be included in the differential diagnosis of opportunistic fungal infection in late stage HIV patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2016.06.013.

Conflicts of interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest relevant to this manuscript.

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