SUPPLEMENT ARTICLE

Healthcare-Associated Mucormycosis

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Mucormycosis is a severe emerging invasive fungal infection that occurs as a consequence of environmental exposure. We exhaustively reviewed all the cases of mucormycosis (European Organisation for Research and Treatment of Cancer/Mycoses Study Group 2008 criteria) attributed to healthcare procedures that occurred between 1970 and 2008. A total of 169 cases were studied (29% children, 61% male). Major underlying diseases were solid organ transplantation (24%), diabetes mellitus (22%), and severe prematurity (21%). Skin was the most common localization (57%), followed by gastrointestinal tract (15%). Culture results were available in 75% (92% positive), and results of histological examination were positive in 95%. *Rhizopus* was the most frequent genus (43%). Infection portal of entry included surgery and presence of medical devices such as catheters or adhesive tape. Outbreaks and clusters were related to adhesive bandages (19 cases), wooden tongue depressors (n = 5), ostomy bags (n = 2), water circuitry damage (n = 2), and adjacent building construction (n = 5). Thorough investigations are mandatory to identify healthcare-associated mucormycosis, notably in neonatology, hematological, and transplantation units.

Rapid diagnosis and treatment of mucormycosis are urgent in clinical mycology. Indeed, the environmental filamentous fungi of the order Mucorales are able to quickly disseminate because of their vascular tropism [1] following trauma in contact with soil or decaying matter [2]. Mucormycosis is also one of the most severe opportunistic infections in patients who have received a transplant, those with diabetes, and those with hematological malignancies [3–7]. Overall, mucormycosis represents 7.2%–8% of invasive fungal infections in recipients of stem cell transplant and 2% in solid organ transplantation (SOT) recipients [3, 8–10].

The incidence of mucormycosis has increased in the past 20 years, in part due to the increasing use of immunosuppressive drugs or to prolonged antifungal treatments lacking activity against Mucorales [7, 11], such as caspofungin or voriconazole, the latter enhancing *Rhizopus oryzae* virulence [12]. Accordingly, the first-line therapy for most experts is a lipid formulation of amphotericin B in association with aggressive surgery [13]. The diagnosis remains challenging. For any other pathogen, culture is the preferred method for identifying genus and species, but histopathological examination remains essential. Molecular tools have been recently developed to identify different Mucorales directly from tissue samples [14]. Nevertheless, as a consequence of delayed diagnosis and lack of optimal treatment, the mortality remains very high and risk factors for death, such as therapeutic delay, have recently been individualized [6, 7, 10, 15].

Hospitalization and ambulatory care represent risk factors that are well known for infection caused by bacteria, yeasts, or *Aspergillus* species. However, the occurrence of mucormycosis during healthcare procedures is not well documented and is probably underestimated. Moreover, the epidemiological and clinical

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features, including the outcome of healthcare-associated mucormycosis (HCM), are not known. We have thus reviewed extensively the medical literature to gain a better insight into HCM.

METHODS

Search Strategy and Selection Criteria

The PubMed database was used to search for publications of studies restricted to humans with "zygomycosis," "mucormycosis," and "phycomycosis" as keywords, plus additional terms, including "*Rhizopus,*" "*Cunninghamella,*" "*Apophysomyces,*" "*Mucor,*" "*Rhizomucor,*" "*Absidia*" (now classified as "*Lichtheimia*"), "*Saksenaea,*" "hospital-acquired," "nosocomial," "healthcare," "ocular," "endophthalmitis," "cornea," "osteomyelitis," "graft," "cutaneous," "pulmonary," "cardiac," "injection," "thermal," "water," "postoperative," "filamentous fungi," "prevention," "preservation fluid," "air," "ventilation," "air conditioner," "neonates," "transplant," "solid organ transplantation," "bone marrow transplantation," and "intensive care unit." After reviewing this initial series of reports, the individual references listed in each publication were again reviewed for identification of additional case reports. All zygomycosis and mucormycosis cases published from January 1970 through December 2008 were recorded for the analysis. To update, recent publications were collected until January 2010.

Definitions

We qualified cases as HCM when they were associated with any healthcare procedure (medical devices and surgery, including SOT or diagnostic or therapeutic invasive procedures) with an identified or suspected source of infection. We excluded those with unclear infection source, because the mucormycosis incubation period is unknown and numbers of mucormycosis labeled as "nosocomial" were, in fact, probably community acquired. When only immunosuppression or a known trauma was recorded, the case was not retained here [16].

Throughout the manuscript, we will refer to the cases not associated with healthcare as common mucormycosis (CM), except for the cases diagnosed in neonatology units. To compare CM with HCM, we used only data currently available for CM, including, potentially, some HCM cases [7].

The definition of invasive fungal disease has been recently revised [17]. The diagnosis of proven mucormycosis required histological examination of tissue samples. However, in case histopathological examination was not performed, recovery of a Mucorales by culture of a clinical specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site was considered to be consistent with proven mucormycosis. Because Mucorales members are environmental fungi, samples from nonsterile sites were excluded, unless a precise microbiological documentation of an environmental contamination was mentioned [18–22]. This last criterion was added to the definition of probable mucormycosis cases in a predisposed patient [17].

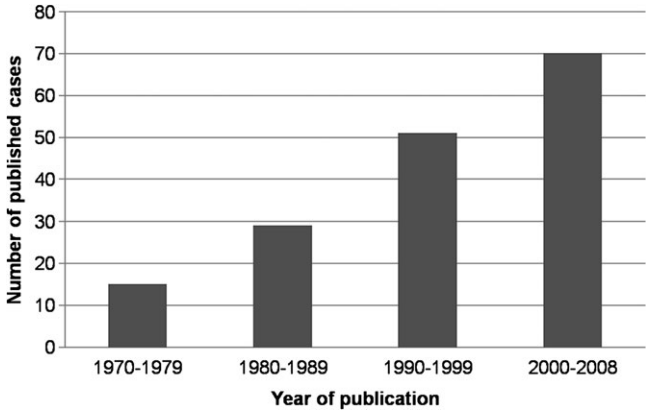

Figure 1. Distribution of 169 published cases of healthcare-associated mucormycosis, 1970–2008.

All patients >15 years of age were considered adults. Prematurity was defined by a gestational age at birth of <37 weeks, and severe prematurity was defined as birth at <32 weeks' gestation. Documentation of the primary underlying condition was required for each reported case. Any corticosteroid treatment administered at the time of diagnosis was recorded. As described by Roden et al., documentation of the primary site of infection and the localized or disseminated status of the infection (≥2 noncontiguous body sites infected) was required [7]. Infections in which acquisition occurred after invasive procedures outside the hospital were retained here but were identified as ambulatory care infections. Reported outbreaks were considered as such when the same fungal species was identified from clinical samples and recently evidenced environmental source. Antifungal and surgical treatments and mortality related to mucormycosis were recorded. Recent modifications in Mucorales classification were taken into account [23, 24].

Statistical Methods

Ordinal data were presented as mean ± standard error of the mean (SEM). Categorical variables were compared using χ^2 test. A P value <.05 by univariate analysis was considered to be statistically significant.

RESULTS

Demographic Characteristics

A total of 169 individual cases of HCM were identified between 1970 and 2008, of which 121 (72%) were recorded after 1990 (Figure 1). Of these cases, 163 were defined as proven and 6 as

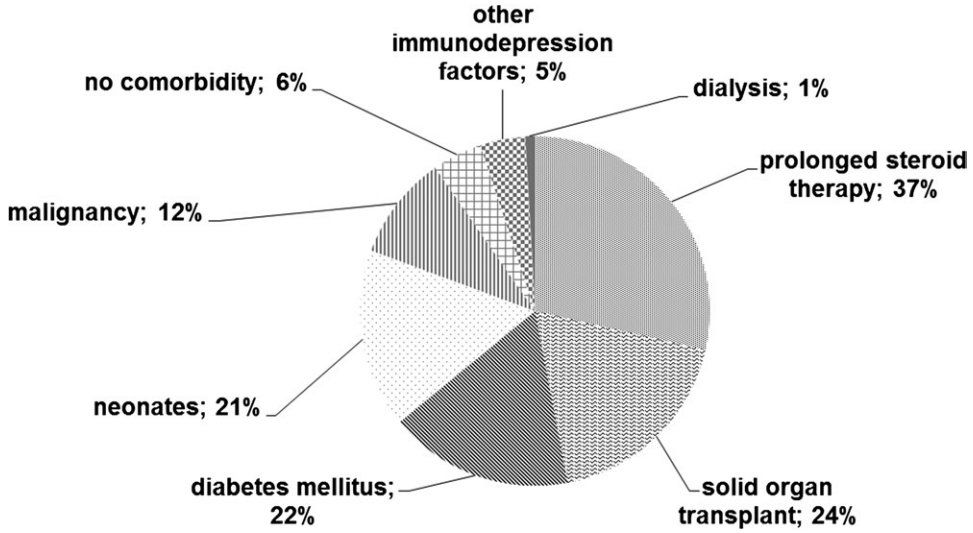

Figure 2. Distribution (%) of healthcare-associated mucormycosis risk factors recorded in 169 cases. Malignancies include 20 cases of hematological diseases and 1 solid tumor. Among the former 20 cases, only 2 were marrow allografted. Other immunodepression causes included HIV infection, systemic lupus erythematosus, rheumatoid arthritis, dilated cardiomyopathy, malnutrition, burn, and admission to intensive care unit.

probable mucormycosis. Mean age (± SEM) of patients was 42 ± 16 years. The studied population included 49 children (29%) and 61% male individuals. One hundred forty-eight of 166 patients (89%) underwent treatment: medical alone (n = 40), surgical alone (n = 18), or both (n = 90). Overall mortality rate was 50% (84 of 169 patients died), but was higher when treatment did not combine antifungal drugs and surgery (50% [29 of 58] vs 38% [34 of 90]; $P = .142$) and in neonates (64% [23 of 36] vs 46% [61 of 133]; $P = .055$).

Underlying Diseases

Five groups of underlying diseases were individualized: SOT (n = 40), malignancy including 2 hematological stem cell transplantations (n = 21), neonates (n = 36), underlying disorders or treatments leading to immunosuppression (n = 46), and absence of identified risk factors (n = 26) (Figure 2).

Recent (<3 months) or current immunosuppressive regimens including corticosteroids were prescribed to 62 of 169 (37%) patients. Corticosteroids were prescribed for systemic diseases in 4 of 62 (6%) patients [25–28]. Diabetes mellitus was reported in 37 (22%) of 169 patients and was the only underlying disease in 16 of 169 (9%) patients. More than 1 risk factor was detected in 21 of 169 patients (12%); among them, diabetes mellitus was associated in 12 of 21 (57%) cases with SOT but not with hematological malignancies.

Most of the 169 patients (n = 89 [53%]) were admitted to the surgery unit or intensive care unit. Twenty patients (20%) received ambulatory care. Overall, 69 of 169 (41%) cases of HCM were considered surgical site infections. Cardiovascular surgery ranked first in procedures associated with HCM [25, 29–41], followed by digestive [25, 42–47], ophthalmologic, urologic, and orthopedic surgery [48–52].

Primary Localizations of Infection

Skin Localizations

HCM involved skin in 96 of 196 (57%) cases. Premature infants (19 of 33 [58%]) and surgical patients (39 of 69 [56%]) were the predominant populations in which cutaneous mucormycosis was observed (Figure 3) [53–57]. Of the 96 patients with skin localization, 22 (23%) underwent SOT and 25 (26%) developed surgical site infection within 19 days (range, 4–60 days) after surgery. Secondary dissemination was reported during 7 of 25 (28%) surgical site infections up to 3 months after contamination [54, 56–61].

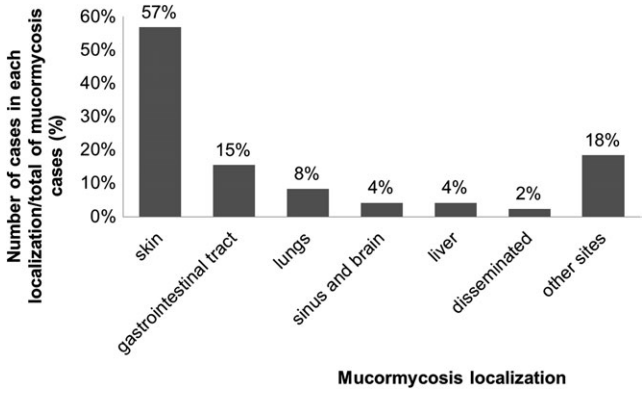

Figure 3. Body-site localization in 169 cases of healthcare-associated mucormycosis (%). Other sites (n = 31) include heart, kidney, bone, joint, eye, vessels, peritoneum, and bladder.

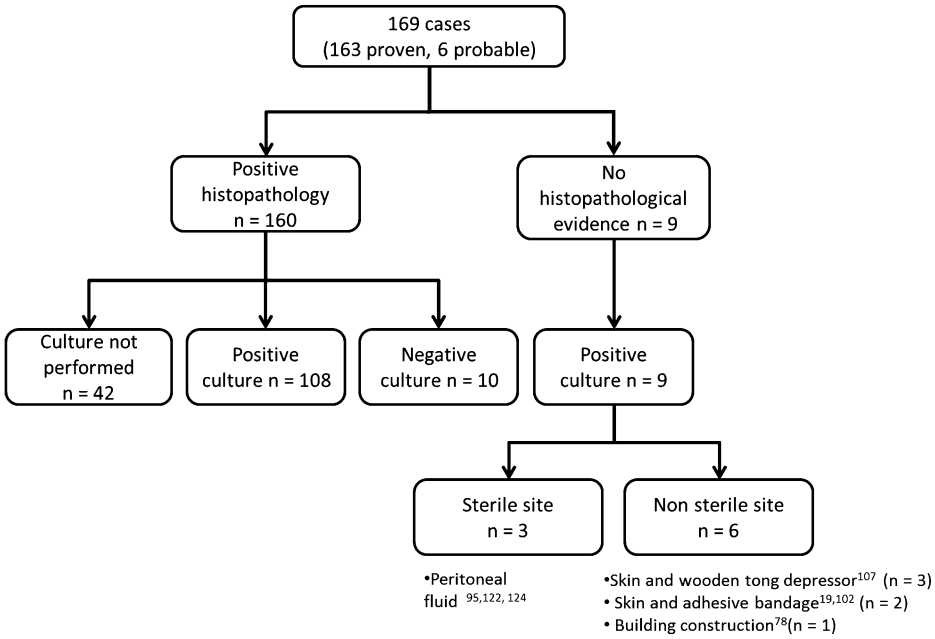

Figure 4. Diagnostic strategy performed in 163 proven and 6 probable cases of healthcare-associated mucormycosis.

Intra-abdominal Localizations

Two different populations were prone to primary gastrointestinal tract infection (n = 21): (1) neonates (12 of 49 [24%] were premature [62–70] and 2 of 49 [4%] were full-term [70, 71]) and (2) nonimmunocompromised adults admitted to the intensive care unit (6 of 21 [29%]) [72, 73] or who underwent digestive surgery (n = 1) [46]. Gut localization was secondary in 5 cases [74–76].

Pulmonary Localizations

Primary lung involvement was rare (10 of 169 [6%] cases) [77–82] In contrast, lungs were a secondary localization of hepatic (n = 3) or cutaneous mucormycosis (n = 1) [38, 75]. Lung transplantation was a risk factor, and infection involved bronchial anastomosis [80, 81]. Presence of Mucorales in the donor's respiratory tract should prompt early therapeutic intervention in the recipient.

Others

Infection of prosthetic valves or cardiac graft causes endocarditis or endovascular infection leading to embolism, aneurysm, graft loss, or aortic rupture [29, 31–33, 35, 36, 39, 40, 61, 83–85]. Endophtalmitis occurring 4–8 weeks after cataract surgery was observed [48–50]. Rhinocerebral involvement and sinusitis were reported in 5 (3%) and 2 (1%) of the 169 cases, respectively [86–89], including some that occurred after dental extraction or airborne contamination. The 4 cases of disseminated mucormycosis occurred after surgery [51, 75] and during extensive renovation [90]. Bone localizations consisted of osteomyelitis, including spondylodiscitis and a tibial abscess [91–93]. Finally, a permanent catheter was responsible for bladder mucormycosis [94].

Histological/Microbiological Findings

Histological examination was performed in 160 of 169 (95%) cases and always revealed typical hyphae [2]. The 9 remaining cases are described in Figure 4. A culture was performed in 127 of 169 cases (75%), and results were positive in 117 (92%) of these cases, leading to the identification of *Rhizopus* species as the most frequent pathogen (43%). However, a large number of the isolates remained unidentified (Figure 5*A*). The main localizations according to the Mucorales genera are presented in Figure 5*B*. *Rhizopus* species were predominantly found in cutaneous mucormycosis (60 of 73 cases [82%]). *Cunninghamella bertholletiae* was responsible for pulmonary (n = 4), cutaneous (n = 2), disseminated (n = 1), or peritoneal (n = 1) mucormycosis [82, 95]. Of note, the use of molecular diagnostic tools was reported in only 2 recent publications [40, 96].

Outbreaks

Adhesive Bandages

The first outbreak was reported in the late 1970s at 10 American hospitals and implicated elasticized bandages contaminated with *Rhizopus* species [19, 97–103] (Table 1). After the manufacturer took preventive measures, the association between mucormycosis and adhesive bandages decreased markedly after 1980. Nevertheless, isolated cases or clusters have occurred in the context of surgical procedures, in premature infants, and more recently, in a burn unit [99, 104, 106].

Ostomy Bags and Other Adhesive Devices

A cluster of 2 cases occurred in 2005 in a North American hospital. Ostomy bags that have adhesive containing karaya

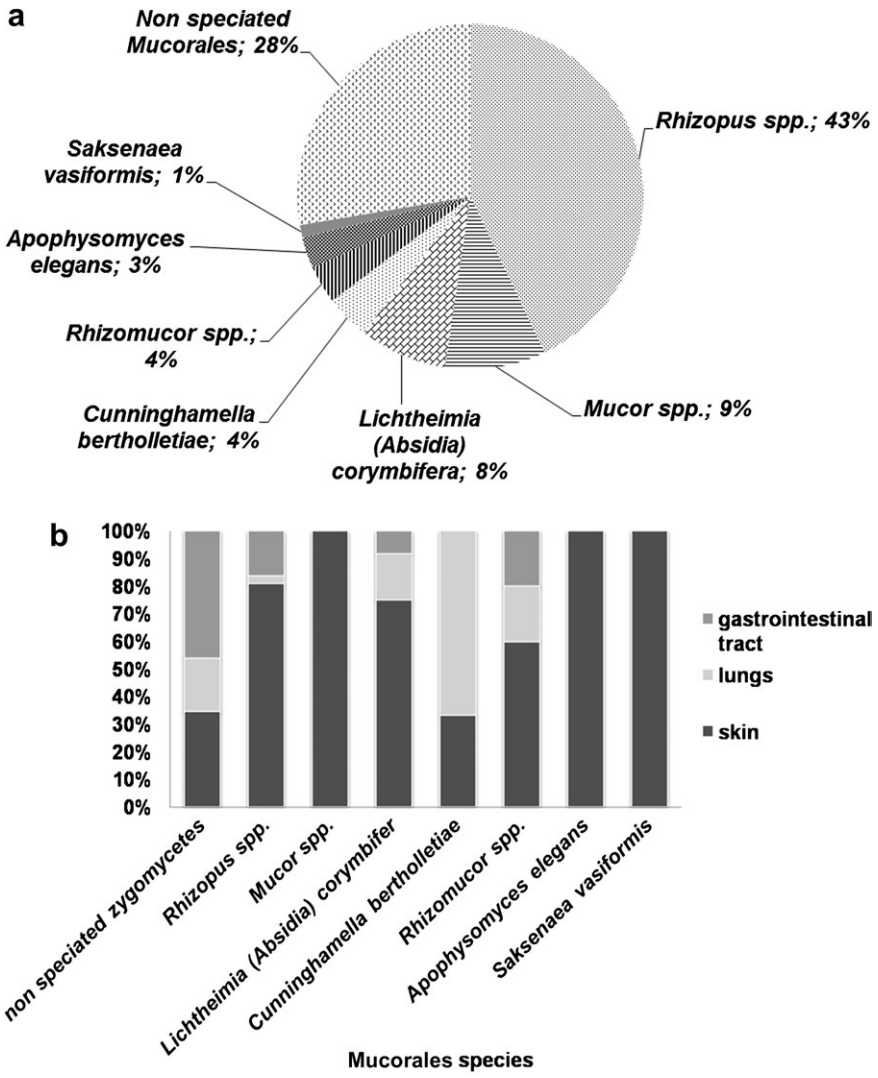

Figure 5. *A*, Distribution of Mucorales species responsible for healthcare-associated mucormycosis. *Rhizopus* species included *R. oryzae* (21 of 73 [29%]), *R. microsporus* (12 of 73 [16%]), and nonspeciated *Rhizopus* species (40 of 73 [55%]). *B*, Distribution of Mucorales species according to the 3 major body site localizations; skin, gastrointestinal tract, and lungs represented 69% of the localizations.

gum, a product derived from the sap of an exotic tree, were identified as the source of *R. oryzae* [96]. Isolated cases related to the use of ostomy bags have also been reported in a premature infant [76] and in an adult with renal insufficiency [107].

Wooden Tongue Depressors

An outbreak in 4 premature infants was reported in 1996 in England [105]. Wooden tongue depressors inserted into a piece of foam tubing were used as splints for intravenous and arterial cannulation sites. Five other clustered cases occurred in 2004 in Spain [72], related to wooden tongue depressors used to prepare oral treatments given through a nasogastric catheter.

Environmental Contamination

HCM was documented with environmental samples only in 34 of 169 (20%) cases. All the clusters investigated occurred in hematology (n = 9) or neonatology units (n = 2) [60, 78, 79, 87, 90]. Building construction was implicated in 5 cases and was associated only with pulmonary mucormycosis [78, 79]. Other environmental sources were difficult to investigate. A nasal packing had probably promoted the occurrence of rhinocerebral mucormycosis in 3 patients with acute leukemia [87], and 2 cases were associated with water damage in a room [60].

Graft-Transmitted Mucormycosis

Graft may be directly responsible for mucormycosis (24 of 169 cases [14%]), corresponding to 60% of SOT recipients. Clinical features did not differ from the other HCM. Primary hepatic mucormycosis occurred only in liver transplant recipients (n = 6) [5, 74, 75, 108]. Major secondary localizations were lungs and gastrointestinal tract [74, 75]. Renal mucormycosis presented as acute rejection in 4 kidney transplant recipients [109–111]. Time from kidney transplantation to diagnosis of mucormycosis

Table 1. Published Outbreaks of Healthcare-Associated Mucormycosis

Reference	No. of Cases	Origin of Contamination	Microorganism	Localization	Underlying Condition	Death Attributable to Mucormycosis
[103]	17	Elastoplast	*Rhizopus microsporus* (8 of 17)	Skin	Surgery, corticosteroids, cancer, diabetes mellitus	Not available
[104]	5	Elastoplast	*Lichtheimia corymbifera*	Skin	Burn unit	3 (60%)
[72]	5	Wooden tongue depressors	*R. microsporus*	Digestive tract	ICU, steroids	3 (60%)
[105]	4	Wooden tongue depressors	*R. microsporus*	Skin	Premature infant	2 (50%)
[79]	2	Building construction	*Mucor indicus* (1 of 2)	Lungs	Premature infant	2 (100%)
[78]	3	Building construction	*Cunninghamella bertholletiae*	Lungs	Hematological malignancies	2 (66%)
[96]	2	Ostomy bags	*Rhizopus* species	Skin	Surgery, corticosteroids	1 (50%)
[60]	2	Water circuitry damage	*Rhizomucor pusillus* (1 of 2)	Rhinocerebral, disseminated	Hematological malignancies	0/2

Abbreviation: ICU, intensive care unit.

was 19 days, 43 days, 2 months, and 9 months. Graft artery mucormycosis was described in 3 cases, and all patients died [84, 85, 108].

Other Procedures

Catheters and Drains

Intravenous or intra-arterial catheters (n = 26), a permanent bladder catheter (n = 1) [94], and thoracic drains (n = 2) were incriminated in several cases [30, 57]. Only 3 studies have investigated the patient's environment and revealed positive Mucorales culture results [60, 66, 112]. In one of the cases, the authors explored the causative link with adhesive bands and ambient air [112]. The sources of contamination have been either the catheter itself or any device in contact with the patient's skin.

Adhesive Tapes and Bandages

Cutaneous mucormycosis (n =11) was associated with the use of adhesive tape [26, 27, 53, 113], adhesive urine bag [59], temperature probe of a radiant heater in a premature infant [53], electrodes for vital-sign monitoring [54, 58], and a skin patch to test for hypersensitivity [114, 115]. The nonsterilized cotton stockingette from a plaster was identified as the source of cutaneous mucormycosis after a pathological arm fracture [116].

Dental Extractions

Dental extraction (n = 5) [86, 88, 89, 91, 117] and local anesthesia may cause mucormycosis during the procedure (n = 1) [118]. It was associated with rhinocerebral involvement [86, 88, 89] and osteomyelitis of the maxilla [91, 117]. Two patients had diabetes mellitus [88, 89], and 5 were outpatients. In 5 of 6 cases, the species was not determined.

Devices for Diabetic Patients

Patients with type 1 or 2 diabetes are prone to develop mucormycosis [119]. Insulin injections were implicated in 2 cases leading to infection with *C. bertholletiae* or *Rhizomucor pusillus* [28, 120]. Cases linked to the use of blood glucose self-monitoring equipment [121] or with the use of subcutaneous insulin infusion pump [28] have also been described.

Intravascular Devices

Intravascular devices, such as artery stent [83], implantable left ventricular assist device [40], and prosthetic valve (n = 4) [31, 33, 35, 39], were incriminated. The isolates involved were either unspeciated (n = 2) or belonged to the *Mucor* genus (n = 4).

Peritoneal Dialysis

Two of the 4 cases of mucormycosis linked to peritoneal dialysis were caused by *Rhizopus* species [122, 123]. Two cases were caused by *C. bertholletiae* and *Mucor ramosissimus*, respectively, and the species responsible for the last case was not identified [25, 95, 124]. Peritoneal dialysis was performed in each case during ambulatory care.

Various Procedures

Anecdotal cases of HCM were identified after intramuscular injection of corticosteroids, vitamins and anticoagulant [125–128], and even nasal packing [87].

DISCUSSION

HCM and CM share common species distribution, diagnostic difficulties, and poor prognosis, whereas body site, distribution of underlying diseases, and sources of contamination differ. Cases of CM are in large part caused by *Rhizopus* species (47%), as are cases of HCM (43%) [7]. When comparing our study with a recently performed European study including 230 patients, *Mucor* species and *Lichtheimia* (*Absidia*) species were ranked second and third, respectively [129]. It must be kept in mind that almost one-third of the isolates of HCM were not identified. Only 2 publications

noted the contribution of molecular tools for Mucorales identification [40, 96]. Of note, *Saksenaea vasiformis* and *Apophysomyces. elegans* were always associated with cutaneous HCM, whereas *C. bertholletiae* was the most frequent Mucorales found in pulmonary HCM.

False positivity is also a common problem because of contamination at the time of sampling or in the laboratory by ubiquitous environmental spores [18]. An example of this disadvantage was the pseudo-outbreak of mucormycosis due to the contamination of wooden tongue depressors with *Rhizopus* species [130–132]. Furthermore, 2 patients who had fever of unknown origin and a history of parenteral nutrition developed Mucorales fungemia [133, 134]. We cannot exclude that those 2 cases were in fact attributable to laboratory fungal contamination. Despite the major role of medical and surgical treatments in mucormycosis, the mortality associated with HCM remains high, in fact as high as in CM. In contrast with what is observed during CM, sinus and rhinocerebral involvements were not the main localizations during HCM. Indeed, the rupture of the skin barrier was associated with the majority of HCM, especially after surgical procedures [135]. Of interest, 21 of 26 (81%) immunocompetent patients who developed HCM underwent a surgical procedure, compared with 18% of patients who had CM ($P < .01$) [7, 136]. Patients suffering from hematological malignancy, SOT recipients, and severely premature infants were the most exposed populations to HCM. In the literature, 5%–7% of cases of CM were diagnosed in SOT recipients, whereas this population represented 24% of HCM, mostly because of the high number of graft-transmitted mucormycosis (Table 2) [7, 136]. Thus, cutaneous mucormycosis in those patients should prompt further investigations, especially when the infection site is located under adhesive devices or in contact with catheters or drains. For a long time, air has been suspected as the major source for nosocomial fungal infections [137, 138]. Correlations between the presence of filamentous fungi in the immunocompromised patient's environment and the risk of invasive fungal disease have been reported [139–142]. Investigations about increased airborne fungal load should be conducted especially during hospital renovation and construction activities in the vicinity of the care units [143]. In emerging countries, some operating theaters are equipped with air conditioners but inefficient air filters, which may lead to a significant increased fungal risk [144]. Hospital water is also a potential reservoir for fungi [145]. Nevertheless, this risk seems low, but there is no consensual threshold for water contamination correlated with a risk of developing invasive fungal infections [146].

Various food items contain Mucorales (Table 3) [2]. Even if the food eaten by strongly immunosuppressed patients is controlled [148], Mucorales sporangiospores have been found in food items intended for hematological unit patients [147]. Feeding solutions prepared from commercial solutions [133] and drug preparation may also be implicated, as in a recent alert concerning contaminated allopurinol as a source of gastrointestinal mucormycosis in Hong Kong [149]. Thus, any confirmed primary gastrointestinal mucormycosis should

Table 2. Comparisons Between Common and Healthcare–Associated Mucormycosis

Characteristic	Common Mucormycosis[a]	HCM	*P* Value
Age	38.8	42	
Male sex	605/929 (65)	103/169 (61)	.30
Outcome			
Mortality	504/929 (54)	84/169 (50)	.28
Risk factors			
No underlying condition	176/929 (19)	26/169 (15)	.27
Surgery	32/176 (18)	21/26 (81)	<.01
Underlying condition			
Diabetes mellitus	337/929 (36)	37/169 (22)	<.01
Malignancy	154/929 (17)	21/169 (12)	.18
SOT	61/929 (7)	40/169 (24)	<.01
HSCT	44/929 (5)	2/169 (1)	.04
Neonates[b]	27/929 (3)	36/169 (21)	<.01
Main body site localizations			
Skin	176/929 (19)	96/169 (57)	<.01
Gastrointestinal tract	66/929 (7)	21/169 (12)	.02
Lungs	224/929 (24)	10/169 (6)	<.01
Sinus	359/929 (39)	7/169 (4)	<.01

Abbreviations: HCM, healthcare-associated mucormycosis; HSCT, hematological stem cell transplantation; SOT, solid organ transplantation.

[a] Common mucormycosis includes the cases described by Roden et al during 1940–1999 [7].

[b] Neonates include premature infants, low-birth-weight infants, and full-term neonates hospitalized in a neonatology unit since birth.

Table 3. Various Food Items Contaminated With Mucorales

Foodstuffs Known to Contain Mucorales [2]	Foodstuffs Containing Mucorales Found in Hematological Unit [147]
Barley	
Sorghum	
Wheat	
Corn	
Oat	
Rice	Regular tea
Onions	Biscuits
Cotton	Freeze-dried soup
Groundnuts	Pepper
Sweet potatoes	
Pecans	
Brazil nuts	
Oranges	
Honey	
Tomatoes	

prompt microbiological investigations of the drugs administered to the patient.

In conclusion, HCM has become a matter of concern, mostly in heavily immunocompromised patients, such as severely premature neonates, SOT recipients, and those with hematological malignancies. Although it shares common features with CM, the former differs by the frequency of skin involvement, the number of immunocompetent patients who underwent surgery, and clustered cases with a suspected or proven common source of infection. Clusters of mucormycosis deserve careful investigations, particularly regarding biomaterials used for the treatment of severe premature infants, during surgery, and in any immunocompromised patients. Molecular diagnostic tools now more commonly used should help assess the precise environmental fungal source of contamination.

Notes

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