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Bone and joint infections caused by mucormycetes: A challenging osteoarticular mycosis of the twenty-first century

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Abstract

Osteomyelitis and arthritis caused by mucormycetes are rare diseases that rank among the most challenging complications in orthopedic and trauma surgery. The aim of this work is to review the epidemiological, clinical, diagnostic, and therapeutic aspects of the osteoarticular mucormycosis with particular emphasis on high-risk patients. A systematic review of osteoarticular mucormycosis was performed using PUBMED and EMBASE

databases from 1978 to 2014. Among 34 patients with median age 41 (0.5–73 years), 24 (71%) were males. While 12 (35%) were immunocompromised patients, 14 (41%) had prior surgery, and seven (21%) suffered trauma. Other underlying conditions included diabetes mellitus, hematological malignancies, transplantation, and corticosteroid therapy. The median diagnostic delay from onset of symptoms and signs was 60 (10–180) days. The principal mechanism of the infection was direct inoculation (n = 19; 56%), and in immunocompromised patients was usually hematogenous disseminated. The long bones were infected by trauma or surgery, while a wide variety of bones were involved by hematogenous dissemination. Combined surgery and amphotericin B treatment were implemented in 28 (82%) and eight (23%) had an unfavorable outcome. Osteoarticular mucormycosis occurs most frequently after trauma or surgical procedures. These infections are progressively destructive and more virulent in individuals with impaired immune systems. Early diagnosis, timely administration of amphotericin B, control of underlying conditions, and surgical debridement of infected tissue are critical for successful management of osteoarticular mucormycosis.

Key words: Mucormycosis, osteomyelitis, arthritis, bone infections, amphotericin B, treatment.

Introduction

Fungi that belong to the order Mucorales comprise predominantly naturally occurring saprotrophs that inhabit soil and decomposing matter.[1] While most of the fungi within the order Mucorales are seldom involved in human infections, the incidence of life-threatening disease caused by several species is increasing in hosts with severe immune or metabolic impairment, hematological malignancy, hematopoietic stem cell transplantation, and uncontrolled ketoacidosis diabetes mellitus.[2–5] Infections often take a dramatic course with unfavorable prognosis and mortality due to deeply invasive, and disseminated disease in patients with immunodeficiencies.[6]

Osteoarticular mycoses are uncommon diseases. During the past several years, several major systematic reviews have elucidated the key demographic, diagnostic, therapeutic, and outcome variables of many of the osteoarticular mycoses.[7–17] However, there remains to be completed a comprehensive analysis focused exclusively on osteoarticular mucormycosis. We therefore undertook a systematic review of the epidemiological, clinical, diagnostic, and therapeutic aspects of these serious infections with particular emphasis on the net state of immunosuppression, the effect of age, different routes of infection, anatomical distribution, and outcome.

Methods

Search criteria

In order to identify fungal osteomyelitis and arthritis caused by Mucormycetes, we used the OvidSP search platform in MEDLINE and EMBASE databases from 1978 to 2014, using the following keywords: fungi, *Rhizopus*, *Apophysomyces*, *Mucor*, *Cunninghamella*, *Lichtheimia* (formerly *Absidia*), *Saksenaea*, Zygomycetes, zygomycosis, mucormycosis, systemic mycosis, bone diseases, bone infection, osteitis, osteomyelitis, periostitis, spondylitis, discitis, osteochondritis, osteomyelitis, periostitis, infectious arthritis, bone and joint infections, and reactive arthritis

We included cases in the final analysis for the years 1978–2014 with data on osteomyelitis and or arthritis, site of infection, underlying disease, antifungal therapy, and surgical intervention. Among other parameters considered in the case analysis were diagnostic images, inflammatory markers, and disease manifestations. We excluded cases with bone extension from rhinosinusitis, cases with missing full texts, and cases of non-English literature.

Data extraction

The following parameters were extracted from each study when present: age, sex, risk factors, prior surgery, treatment, antifungal agent, duration of treatment, time to diagnosis, fever, inflammatory markers, neutropenia, radiological features, type of bone infection, surgical intervention, histopathology, microscopy, culture, fungal species, and outcomes.

Terminology and definitions

There are different classification systems by which to classify osteomyelitis.[18] Descriptive terms were applied to mechanisms of bone infection, criteria for diagnostic

probability, onset of disease, and histopathologic characteristics of osteomyelitis. All definitions used throughout this study were utilized in previous studies of osteoarticular mycoses:[10–17]

Direct inoculation: local bone or joint infection following a breach of cutaneous integrity;

Hematogenous: seeding of bone or joint by dissemination from a distant site of inoculation and/or infection;

Contiguous: describes the seeding of bone or joint from an adjacent site of infection; Proven fungal osteomyelitis: evidence of a positive culture and/or histology from bone tissue, joint fluid, or metal hardware;

Probable fungal osteomyelitis: compatible clinical and radiological features of osteomyelitis with evidence of positive histology and/or fungal culture from an extra-osteoarticular site;

Complete response: resolution of clinical and radiological findings of osteomyelitis; Partial response: incomplete resolution of clinical, and/or radiological findings of osteomyelitis, or incomplete clinical improvement without the availability of radiological data;

Overall response: complete or partial response of clinical and radiological findings of osteomyelitis;

Pediatric patients: patients who were ≤15 years;

Elevated white blood cell (WBC) count: >10,000/μl.

Data analysis and statistical methods

Descriptive statistics were used to summarize all demographic and clinical characteristics of the patients. The quality of data (review of completeness, data verification, validation) was assured by the lead investigator (SJT). All statistical analyses were performed using statistical packages SPSS 19.0 (SPSS Inc. Chicago, IL).

Results

Identification of cases

A total of 34 individual cases from 30 publications (Table 1) of osteoarticular infections fulfilled the prespecified definition criteria. Cases were classified as proven in 82% (n = 28) with positive hyphae in histopathology sections, and probable in 18% (n = 6) in which histopathology was not performed.

Etiology

The most common pathogens of the Mucorales that caused bone and joint infections were *Rhizopus* species (15 cases)[19–29] followed by *Apophysomyces elegans* (four cases)[30–33], *Mucor* species (three cases),[34–36] *Cunninghamella bertholletiae* (two cases),[37,38] and one case for each *Lichtheimia* (formerly *Absidia*) *corymbifera*[39] and *Saksenaea vasiformis*.[40] A genus was not specified in eight cases of histologically documented mucormycosis.[41–48] All patients were infected with one fungal species.

Patient population and comorbidities

The demographic characteristics of the 34 patients are described in Table 2. Among the 34 patients with bone and joint infection, male subjects predominated (71%). The disease was more responsible for osteomyelitis in adults (≥15 years). Among the underlying conditions in immunocompetent patients were trauma, vehicular accidents with fracture, and puncture of the knee or penetrating wounds. The underlying conditions identified for the majority of patients included prior surgery (41%), trauma (21%), corticosteroids (21%), and diabetes mellitus (18%). Severely immunocompromised patients including those with hematological malignancies, bone marrow/stem cell transplantation, solid organ transplantation, and HIV/AIDS, accounted for 35% of cases.

Clinical manifestation and mechanisms of infection

The most frequently reported clinical manifestations were restricted movements (62%), local pain, tenderness, and/or swelling (59%), and cellulitis/abscess (24%) (Table 3). Fever was seldom reported. Elevated inflammatory markers were detected for ESR and WBC; data for C-reactive protein was not available.

Direct inoculation was the main mechanism of infection in 56% of cases, especially in patients subjected to prior trauma, accident, or previous surgery. Hematogenous dissemination occurred in 24% of cases, particularly in patients with hematological malignancy and other immune impairments. Contiguous spread was observed in the remaining 21%.

Diagnostic procedures

Open surgical wounds were the main biopsy procedure of most (87.5%) reported cases. The median diagnostic delay from onset of symptoms and signs in all cases of mucormycetes bone and joint infections was 60 (10–180) days (Table 3).

Table 1. Cases of mucormycetes bone and joint infection (1978–2014).

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
1	Moore PH et al. 1978	18/M	*Rhizopus* species	Fanconi anemia, neutropenia, Steroid injection	Hip	Not done	None	Unknown	Died
2	Echols RM et al. 1979	18/F	*Rhizopus* species	Anemia and thyroid hypoplasia	Hip, right femoral neck	+	Debridement	AmB/ unspecified	Survived
3	Buruma OJ et al. 1979	60/M	Not identified	Prior operation	Osteomyelitis of vertebral bodies C1-C5	Autopsy (+)	None	None	Died
4	Maliwan N et al. 1984	58/M	Mucor species	Road accident, Diabetes	Ankle septic arthritis	+	Curettage of the bones swelling/ drainage	AmB/ unspecified	Survived
5	Pierce PF et al. 1987	24/M	*Saksenaea vasiformis*	Road accident, open fracture	Tibia	+	Amputation	AmB/45	Survived
6	Moztaza JM, 1989	27/M	*Cunninghamella bertholletiae*	HIV	Knee joints arthritis	Not done	None	AmB/ unspecified	Died
7	Huffnagle KE et al. 1992	30/M	*Apophysomyces elegans*	Fell from 55 ft high with multiple bone fractures	Limb osteomyelitis (Humerus, femur, tibia, fibula)	+	Amputation of both right leg and hand	AmB/35	Died
8	Buhl MR et al. 1992	38/F	Not identified	None	Temporal bone osteomyelitis	+	None	AmB/21	Survived
9	Chaudhuri R et al. 1992	63/M	*Rhizopus rhizopodIformis*	Prior bowel perforation due to CMV infection, renal transplant	Osteomyelitis of the cuboid bone	+	Debridement and excision of cuboid bone	AmB/28	Survived

Table 1 –*Continued.*

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
10	Weinberg W G et al. 1993	59/M	*Apophysomyces elegans*	Penetrating injection from door/Right prescapular area infection	Osteitis of the scapula	+	Extensive debridement, removal of infected parts from the scapula	AmB/100	Survived
11	Eaton ME et al. 1994	70/M	*Apophysomyces elegans*	None	Osteomyelitis of the sternum	+	Debridement, sternectomy and removal of lower ribs bilaterally	AmB/90	Survived
12	Meis JF et al. 1994	69/M	*Apophysomyces elegans*	None	Osteomyelitis of the humerus	+	Debridement, amputation	AmB/60	Survived
13	Shaw CJ et al. 1994	54/M	*Rhizopus rhizopodiformis*	Renal transplant, Resection of ileum for perforation secondary to CMV infection	Cuboid bone	+	Draining of abscess, and the cuboid was excised	AmB/ unspecified	Survived
14	Fortun J et al. 1995	32/M	Not identified	Traffic accident, Open wounds, fractures	Facial and orbital bones	+	Debridement	AmB/75	Survived
15	Oo MM et al. 1998	28/M	Rhizopus species	AML with GVHD bone marrow transplant, steroids	Petrous bone	+	Debridement	AmB/ unspecified	Died
16	Stevanovic MV et al. 1999	52/F	Not identified	Diabetes, infection developed by intravenous line on the right forearm	Osteomyelitis of the right hand	+	Above elbow amputation	AmB/ unspecified (AmB not tolerated)	Survived
17	Holtom PD et al. 2000	60/M	Mucor species	Diabetes, Liver disease, bleeding gastric ulcer, acetabular fracture left hip, wrist in a fall at work	Tibia	+	Above knee amputation	AmB/ unspecified	Survived

Table 1 –*Continued.*

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
18	Burke WV et al. 2002	34/F	Not identified	Arthroscopic ACL reconstruction	Tibia	+	Debridement, open arthrotomy with a medial parapatellar approach, synovectomy, allograft prosthesis, massive bone resection	AmB/30	Survived
19	Chen F et al. 2006	75/F	*Rhizopus rhizopodiformis*	Pain, weakness, numb and lower back pain (L4-L5) after limb disc puncture	Spondylodiscitis after lumbar disc puncture and vertebral osteomyelitis	+	Surgical debridement several times and autologous bone graft transplantation	AmB, flucytosine, itraconazole/ 490	Died
20	Adler N et al. 2008	41/M	*Rhizopus* species	Fall on his head directly, scalp wound and laceration	Osteomyelitis of the scalp bone	+	Resection of the infected scalp and cranial bone and cranioplasty	AmB/180	Survived
21	Parra-Ruiz J et al. 2008	28/M	*Lichtheimia corymbifera* (*Absidia corymbifera*)	HIV	Knee Septic arthritis	Not done	Arthrotomy and synovectomy	AmB/90	Survived
22	Jones NF et al. 2008	0.5/M	Not identified	Liver transplant, with history of neonatal hepatitis	Ulna	+	Debridement, skin allograft	AmB, VCZ/75	Survived

Table 1 –*Continued.*

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
23	Wilkins RM et al. 2009	51/M	*Rhizopus* species	Arthroscopic ACL reconstruction	Femur	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, removal of implants and grafts, massive bone resection	AmB/45 Posaconazole/ 90	Survived
24	Muscolo DL et al. 2009	26/M	*Rhizopus microsporus*	ACL reconstruction	Femur	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, removal of implants and grafts, massive bone resection	AmB/45	Survived
25	Muscolo DL et al. 2009	29/M	*Rhizopus microsporus*	ACL reconstruction	Tibia	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, removal of implants and grafts, massive bone resection	AmB/45	Survived

Table 1 –*Continued.*

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
26	Muscolo DL et al. 2009	27/F	*Rhizopus microsporus*	ACL reconstruction	Femur	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, removal of implants and grafts, massive bone resection	AmB/45	Survived
27	Muscolo DL et al. 2009	52/M	*Rhizopus microsporus*	ACL reconstruction	Tibia	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, removal of implants and grafts, massive bone resection	AmB/45	Survived
28	Muscolo DL et al. 2009	35/F	*Rhizopus microsporus*	ACL reconstruction	Tibia	+	Debridement consisting of open arthrotomy with a medial parapatellar approach, synovectomy, allograft prosthesis, massive bone resection	AmB/45	Survived

Table 1 –*Continued.*

No.	Ref	Age/ sex	Culture results	Predisposing factors	Site of infection	Hyphae in Histopathology	Surgical treatment	antifungal treatment/ duration (days)	Outcome
29	Oswal NP et al. 2012	68/F	Not identified	Diabetes,	Osteomyelitis of the mandible	+	Debridement, removal of left third molar	AmB, 1 day	Died
30	Arockiaraj J et al. 2012	41/M	Not identified	AML, Autologous bone marrow transplant, Diabetes	Femur	+	Debridement and internal fixation, bone grafting	AmB/90	Survived
31	Dinasarapu CR et al. 2010	59/M	*Mucor* species	Diabetes, Necrotizing fasciitis and left foot ul-cer/Hypertension, nephropathy presented with swollen leg and left foot	Osteomyelitis extended to calcaneus	+	Debridement with amputation of forth and fifth digit	AmB, posaconazole/ 55	Survived
32	Vashi N et al. 2012	33/F	*Rhizopus* species	Pre-B cell ALL, Hematopoietic cell transplantation, Chronically ingrown nail on her right great toe	Tibia	Note done	Debridement lavage and drainage, irrigation, removal of ingrown toe nail	Caspofungin, AmB, Posaconazole/ 573	Survived
33	Navanukroh O et al. 2014	42/F	*Cunninghamella bertholletiae*	Renal transplant on corticosteroids	Osteomyelitis of the sacral spine + epidural abscess	Not done	Decompressive laminectomy	AmB/90	Survived
34	Harrasser N et al. 2014	73/M	*Rhizopus microsporus*	Hematological disease with allogeneic bone marrow transplantation	Osteomyelitis of both femurs and hip + both tibiae	Not done	Debridement, proximal femoral resection	AmB, posaconazole/ 45	Died

ACL, Anterior cruciate ligament reconstruction.

Table 2. Demographic characteristic and underlying conditions of Mucorales bone and joint infections reported between 1978 and 2014.

Demographic characteristic Total (n = 34)	Number of cases (%)
Age (years)	
Median (min–max)	41 (0.5–73)
Mean ± SD	42.8 ± 17.9
Adults	33 (97)
Pediatrics	1 (3)
Sex	
Male	24 (71)
Female	10 (29)
Underlying conditions*	
Diabetes	6 (18)
Trauma	7 (21)
Prior surgery	14 (41)
Drug user	2 (6)
Alcohol abuse	1 (3)
Chemotherapy	3 (9)
Steroids	7 (21)
Neutropenia	2 (6)
Prosthesis	1 (3)
Immumocompromised	12 (35)
Hematological malignancy	4 (12)
Liver transplant	1 (3)
Renal transplant	3 (9)
BMT	2 (6)
HIV/AIDS (CD4 $\leq$200/μl)	2 (6)

*Some cases have more than one underlying condition.

Diagnostic imaging

Osteoarticular abnormalities detected by different diagnostic imaging modalities included osteolytic lesions, bone destruction/erosion, lucencies, and increase of radionuclide uptake (Table 3). Magnetic resonance imaging demonstrated low signal intensity on T1 weighted and patches of high signal intensity on T2 weighted images.

Treatment and outcome

Patients with osteoarticular mucormycosis were usually managed with combined medical and surgical intervention. Surgical intervention and/or medical therapy was reported in 33 (97%) of 34 patients (Table 3).

Among the 33 patients who received treatment, most patients 28 (85%) were managed with a combination of antifungal therapy and surgery, four (12%) with antifungal agents, and one (3%) with surgical treatment only. One patient died before initiation of any therapeutic intervention. All cases were treated with amphotericin B. Posaconazole was used as maintenance therapy after amphotericin B treatment in 4 cases. The median duration of medical

Table 3. Clinical characteristics and anatomical distribution of osteoarticular infections due to mucormycetes fungi reported in the literature from 1978 to 2014.

Diagnostic approach	Total N = 34 (%)
Clinical manifestation*	
Pain/tenderness/swelling	20 (59)
Cellulitis/ulcer/abscess	8 (24)
Neurological deficit	4 (12)
Movement painfully restricted	21 (62)
Fever	8 (24)
Types of infection	
Direct inoculation	19 (56)
Hematogenous	8 (24)
Contiguous	7 (21)
Initial presentation of osteoarticular infections	
One bone infected	28 (82)
Two bones infected	4 (12)
$\geq$3 bones infected	2 (6)
Bone involvement	
Skull and facial bones	6 (18)
Upper limb	2 (6)
Scapula	1 (3)
Sternum	1 (3)
Vertebra	3 (9)
Femur	4 (12)
Hip osteomyelitis/multiple sites	4 (12)
Tibia	7 (21)
Knee arthritis	2 (6)
Foot	4 (12)
Radiological features*	
Osteolytic lesion	14 (41)
Increase of nuclear scan uptake TC^{99} m/Ga^{67}	8 (23)
Bone destruction/erosion	3 (9)
Lucency	3 (9)
Necrosis	2 (6)
Not specified	7 (21)
Inflammatory markers	
ESR	
Mean ± SD	74 ± 27
Median (Range)	69 (40–107)
WBC	
Mean ± SD	16,891 ± 8,265
Median (Range)	16,150 (7,000–29,400)
Types of biopsy	N = 32
Open surgical wound	28 (87)
Percutaneous needle biopsy	3 (9)
Arthroscopy	1 (3)
Diagnostic delay (days)	
Mean ± SD	73 ± 47
Median (Range)	60 (10–180)

Table 3 –*Continued.*

Diagnostic approach	Total N = 34 (%)
Treatment	N = 33 (one died before treatment)
Only Amphotericin B	4 (12)
Only Surgery	1 (3)
Amphotericin B + surgery	28 (85)
Duration of medical treatment, median (range) d	45 (5–573)
Type of surgical intervention (n = 29)	
Debridement	11 (38)
Amputation	5 (17)
Bone grafting/multiple procedures/ Autotransplantation/Fixation	7 (24)
Decompressive laminectomy	1 (3.5)
Excision	5 (17)
Outcome	
Complete response	14 (41)
Partial response	12 (35)
Crude mortality	8 (24)
Attributable death	6 (18)

*Some cases demonstrate more than one symptom.

treatment was 45 (5–573) days. Debridement was the most frequent surgical intervention (38%) followed by bone grafting/fixation procedures (21%), amputation (15%), and full excision (15%) (Table 3).

An overall response rate of 76% was achieved in the treatment of 34 mucormycetes bone and joint infection with complete response in 41% and partial response in 35%. One patient died before treatment could be initiated. Overall mortality rate was 24% with 6 (75%) of these deaths attributable to advanced bone infection and treatment failure with amphotericin B, while two were related to progressive risk factors and infection (Table 3).

Discussion

The majority of cases of osteoarticular mycoses are caused by *Aspergillus*[11,14,16] and *Candida* species.[8,10,13] Other osteoarticular mycoses are caused by dimorphic fungi, which demonstrate distinctive clinical presentations, emerge in endemic areas, occur predominantly in immunocompetent patients, and develop from hematogenous dissemination.[12] Most of these infections present with an indolent clinical course.

Osteoarticular mucormycosis, by comparison, is relentlessly progressive with soft tissue compromise and bone destruction that may necessitate extremity amputation.[19,34] While mucormycosis is highly aggressive and destructive in lung, sinuses, and brain, it is more indolent in bone with average time to diagnosis of 73 days,

The destructive nature of Mucormycetes as causative pathogens of osteomyelitis, in addition to specific risk factors and underlying conditions associated with these pathogens, represent a formidable challenge to clinicians due to limited treatment options, and comparatively high directly related mortality compared to that of osteoarticular infections caused by other fungi. An important characteristic of these polymorphic infections is the fact that mucormycosis can infect a wide variety of bones and joints with no real predilection of the site of infection. The site depends on the mechanism of infection, affecting the long bones after trauma or surgery, or a wide variety of bones after hematogenous dissemination. That 56% of cases were caused by direct inoculation rather than involving the respiratory tract or causing disseminated disease likely accounts for the lower mortality in osteoarticular mucormycosis when compared to those in more lethal pulmonary, sino-orbital, and rhinocerebral forms of these infections, which approach 80%, depending upon species.[6]

As with *Aspergillus*,[11,14,16] *Candida*,[10,13] and other non-*Aspergillus* moulds,[17] osteoarticular infections, there is a high male predominance with >2:1 male-to-female ratio in cases of mucormycosis of the bones and joints. Two main pathogenic mechanisms of infection were observed in immunocompetent patients. The first one was a community-acquired infection by direct inoculation during trauma, and the second one was a healthcare-associated infection after surgical procedures. Hematogenous dissemination was especially observed in patients with hematological malignancy or who were otherwise immunocompromised. Unlike *Candida* osteoarticular infections, which were reported as a result of hematogenous spread,[10] direct inoculation is the cause of infection for the majority (56%) of mucormycosis reported herein.

A definitive diagnosis of osteoarticular mucormycosis was delayed by a median of 60 days from the onset of symptoms and signs. Contributing to this delay is the paucity of fever in most cases, while elevated inflammatory markers (ESR, WBC) were nonspecifically elevated. Localized pain, tenderness, and swelling should prompt diagnostic imaging, which then lead to biopsy if imaging is compatible with osteoarticular infection.

The diagnostic imaging features of the osteolytic lesion, bone destruction/erosion, and MRI T_2 weighted signal intensity are compatible with infection process but not characteristic for mucormycetes. Thus, evaluation of suspected mucormycetes infection of bone and joint should include biopsy for culture and histopathology, as well as visualization of the distinct ribbon-like hyphae in the clinical specimen using fluorescent dye.

Osteoarticular mucormycosis constitutes a serious diagnostic and therapeutic challenge. Despite antifungal treatment and surgical intervention, mortality was 24%, which is higher than the values previously reported to other fungal osteoarticular infections[12,17] but less than percentage mortality for *Aspergillus* osteomyelitis.[11]

As reflected in the 85% of patients in this report, surgical intervention combined with antifungal therapy is widely considered an important treatment option of mucormycetes osteomyelitis and joint infections. Debridement of the infected tissues and bone excision were the primary surgical strategies applied for local control in mucormycete osteomyelitis. Some patients had bone reconstruction with allograft.[20] Synovectomy and prosthetic joint replacement were used in the surgical management of septic arthritis. These bone reconstructions were performed during a second operation, several weeks or months after debridement.

Bone grafting and autotransplantation, were the leading interventional procedures used for reconstruction mucormycetes osteoarticular infections. The delay between radical debridement and reconstruction was at least six months and 9.6 months at median[20] in order to avoid secondary infection of the graft. This delayed bone repair and reconstruction may be essential to control the relapse of the disease in the transplanted reconstruction material.

Similarly, within other mould osteoarticular infections, the majority of patients with *Aspergillus* (67%) and *non-Aspergillus* (69%) osteoarticular infections received antifungal therapy plus surgery.[11,17] By comparison, 48% of patients with *Candida* osteoarticular infections were treated with combined antifungal and surgical intervention.[10]

Therapeutic success in osteoarticular mucormycosis depends on early diagnosis, the etiologic agent, severity of infection, underlying host factors, comorbidities, as well as type and location of infected bone. For example, the osteoarticular infection caused by *A. elegans* with ≥3 types of bones led to unfavorable prognosis[30] or amputation.[33] Among 34 cases of bone and joint infections due to mucormycosis, medical therapy in all cases consisted of an AmB formulation with eight having an unfavorable outcome. Amphotericin B is the primary agent for treatment of mucromycetous infections of bone and joint tissue. There are no controlled studies to support combinations of antifungal therapy of osteoarticular mucormycosis.

Guidelines for the treatment of osteoarticular mucormycosis require antifungal therapy with amphotericin B and surgical intervention in most cases. In ESCMID and ECCM joint guidelines,[49] liposomal amphotericin B is recommended as the principal first-line agent for treatment of mucormycosis. Although salvage therapy with posaconazole for the treatment of mucormycosis has been reported,[50,51] it is not recommended as primary therapy. In this study, posaconazole was used as a maintenance therapy in the treatment of four patients, one of who died. Whether isavuconazole, which was recently introduced for the primary treatment of mucormycosis,[52] has a role in the management of osteoarticular mucormycosis warrants further study. Reversal of primary immune impairments, including recovery from neutropenia, withdrawal of corticosteroids, and reversal of metabolic derangements in diabetes mellitus are essential to successful management of osteoarticular mucormycosis.

In summary, the standards of current management of this debilitating and potentially lethal infection remain early diagnosis, liposomal amphotericin B, surgical resection, and reversal of host defects.

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Declaration of interest

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