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Aspergillus Osteomyelitis: Epidemiology, Clinical Manifestations, Management, and Outcome

Maria N. Gamaletsou[1,2,3,4], **Blandine Rammaert**[3,4,5,6], **Marimelle A. Bueno**[1], **Brad Moriyama**[7], **Nikolaos V. Sipsas**[2,3,4], **Dimitrios P. Kontoyiannis**[8], **Emmanuel Roilides**[3,4,9], **Valerie Zeller**[10], **Roberta Prinapori**[11], **Saad Jaber Tajaldeen**[12], **Barry Brause**[1,3,4], **Olivier Lortholary**[3,4,5,6], and **Thomas J. Walsh**[1,3,4]

[1]Weill Cornell Medical Center of Cornell University, New York, NY, USA

[2]National and Kapodistrian University of Athens, Athens, Greece

[3]Center for Osteoarticular Mycoses, Hospital for Special Surgery, New York, NY, USA

[4]International Osteoarticular Mycoses Study Consortium

[5]Université Paris-Descartes, Sorbonne Paris Cité, APHP, Service des Maladies Infectieuses et Tropicales, Hôpital Necker-Enfants Malades, Centre d'Infectiologie Necker-Pasteur, Institut Imagine, Paris, France

[6]Unité de Mycologie Moléculaire, Institut Pasteur, Paris, France

[7]Department of Pharmacy, NIH Clinical Center, Bethesda, MD, USA

[8]MD Anderson Cancer Center, Houston, TX, USA

[9]Aristotle University, Thessaloniki, Greece

[10]Osteoarticular Reference Center, Groupe Hospitalier Diaconesses-Croix Saint-Simon, Paris, France

[11]Infectious Disease Department, San Martino di Genoa Hospital, University of Genoa, Genoa, Italy

[12]Mycology Laboratory, University of Doha, Qatar

Abstract

Background—The epidemiology, pathogenesis, diagnosis, and management of *Aspergillus* osteomyelitis are not well understood.

Correspondence: Dr. Thomas J. Walsh, Transplantation-Oncology Infectious Diseases Program, Weill Cornell Medical Center and Cornell University, 1300 York Ave, Rm A421, New York City, NY 10065, thw2003@med.cornell.edu, 212-746-6320 (main office).

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Methods—Protocol-defined cases of *Aspergillus* osteomyelitis published in the English literature were reviewed for comorbidities, microbiology, mechanisms of infection, clinical manifestations, radiological findings, inflammatory biomarkers, antifungal therapy, and outcome.

Results—Among 180 evaluable patients, 127 (71%) were males. Possible predisposing medical conditions in 103 (57%) included pharmacological immunosuppression, primary immunodeficiency, and neutropenia. Seventy-three others (41%) had prior open fracture, trauma or surgery. Eighty (44%) followed a hematogenous mechanism, 58 (32%) contiguous infections, and 42 (23%) direct inoculation. *Aspergillus* osteomyelitis was the first manifestation of aspergillosis in 77%. Pain and tenderness were present in 80%. The most frequently infected sites were vertebrae (46%), cranium (23%), ribs (16%), and long bones (13%). Patients with vertebral *Aspergillus* osteomyelitis had more previous orthopedic surgery (19% vs 0%; P=0.02), while those with cranial osteomyelitis had more diabetes mellitus (32% vs 8%; P=0.002) and prior head/neck surgery (12% vs 0%; P=0.02). Radiologic findings included osteolysis, soft-tissue extension, and uptake on T2-weighted images. Vertebral body *Aspergillus* osteomyelitis was complicated by spinal-cord compression in 47% and neurological deficits in 41%. Forty-four patients (24%) received only antifungal therapy, while 121(67%) were managed with surgery and antifungal therapy. Overall mortality was 25%. Median duration of therapy was 90 days (range, 10–772 days). There were fewer relapses in patients managed with surgery plus antifungal therapy in comparison to those managed with antifungal therapy alone (8% vs 30%; P=0.006).

Conclusions—*Aspergillus* osteomyelitis is a debilitating infection affecting both immunocompromised and immunocompetent patients. The most common sites are vertebrae, ribs, and cranium. Based upon this comprehensive review, management of *Aspergillus* osteomyelitis optimally includes antifungal therapy and selective surgery to avoid relapse and to achieve a complete response.

INTRODUCTION

Aspergillus osteomyelitis is a debilitating and severe form of invasive aspergillosis [1–4]. Patients suffering from *Aspergillus* osteomyelitis may suffer protracted pain, immobilization and loss of function. As the population of immunocompromised patients continues to expand, *Aspergillus* osteomyelitis will likely increase in direct relation. There have been various case series, which review a selected aspect of *Aspergillus* osteomyelitis, a specific host population, a single institutional experience, or multicenter case registry [1–165]. While these reports have contributed to our knowledge of *Aspergillus* osteomyelitis, there is no contemporary comprehensive review of literature by which to understand the epidemiology, clinical manifestations, diagnosis, management, and outcome of *Aspergillus* osteomyelitis using a large and highly detailed case analysis. We therefore conducted an extensive literature review of *Aspergillus* osteomyelitis using high stringency detailed case criteria to provide such a resource for the diagnosis and treatment of this serious infection.

METHODS

Study Design

This is a comprehensive review of reported cases of *Aspergillus* osteomyelitis as published in the English literature. We initiated our search by reviewing all English references as

published in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) using the key words: *Aspergillus*, aspergillosis, osteomyelitis, arthritis, and bone. We then carefully included only well-described references for single case reports or case series that provided sufficient data. After this initial series of reports was reviewed, individual references listed in each publication were again reviewed for ascertainment of additional case reports.

Criteria for inclusion and exclusion of cases of *Aspergillus* osteomyelitis

Cases selected in the initial screen were then included in the final analysis if the following data were available: documentation of *Aspergillus* osteomyelitis, anatomical location of infection, underlying condition, therapeutic intervention, and outcome. Cases not including this essential information, or if after being reviewed, did not contain sufficient data by which to draw definitive conclusions, were excluded. Among other parameters sought, but not obligatory for inclusion of a case in the analysis, were comorbidities, clinical manifestations, radiological features, and inflammatory markers. Cases of aspergillosis complicating arthroplasty and prosthetic joints were considered to be septic arthritis and excluded unless there was clear documentation of osteomyelitis. Cases consisting only of *Aspergllus* sinusitis were excluded due to lack of consistent criteria used in defining concomitant osteomyelitis.

Definitions

The following definitions were used throughout the study.

Mechanisms of bone infection—

Direct inoculation	Seeding of bone tissue by trauma or surgical manipulation.
Hematogenous	Seeding of bone tissue by bloodborne route.
Contiguous	Seeding of bone tissue from an adjacent focus of *Aspergillus* infection.

Criteria for diagnostic probability, onset of infection, and therapeutic response—

Proven *Aspergillus* osteomyelitis	evidence of a positive culture, and/ or histology from bone tissue or metal hardware.
Probable *Aspergillus* osteomyelitis	compatible clinical and radiological features of osteomyelitis with evidence of a positive culture of *Aspergillus* and/ or histology from a site other than bone tissue or metal hardware.
Breakthrough *Aspergillus* osteomyelitis	development of *Aspergillus* osteomyelitis in a patient who is already receiving one or more mould-active antifungal agents at the clinically apparent onset of *Aspergillus* osteomyelitis.

De novo Aspergillus osteomyelitis	development of *Aspergillus* osteomyelitis in a patient who is not receiving a mould-active antifungal agent at the clinically apparent onset of *Aspergillus* osteomyelitis or during the previous three days.
Complete response (CR)	Complete resolution of clinical and radiological findings of osteomyelitis.
Partial response (PR)	Partial resolution of clinical, and/or radiological findings of osteomyelitis, or partial clinical improvement without availability of radiological data.

Data Collection and Analysis

Among the variables studied were *Aspergillus* spp., primary underlying condition, comorbidities, clinical manifestations, radiological features, treatment, and outcome. Data were collected and presented with descriptive statistics to determine the possible risk factors for development of *Aspergillus* osteomyelitis. Differences in proportions were analyzed by chi-square or Fisher's exact test. A *P*-value of <0.05 was considered to be significant.

RESULTS

Study population

Among 339 screened cases, there were 180 well-described cases of *Aspergillus* osteomyelitis in the English literature that fulfilled criteria for inclusion in the database over a study period from 1947 to 2013 [1–160].

Demographic characteristics and underlying conditions

Table 1 depicts the demographic features and possible risk factors for *Aspergillus* osteomyelitis according to site. *Aspergillus* osteomyelitis occurred predominantly in males. Pediatric patients constituted 21% of the population. All but four patients had at least one possible predisposing factor, including corticosteroids (29%), primary immunodeficiency (15%), and neutropenia (7%). Chronic granulomatous disease (CGD) was the most common primary immunodeficiency associated with *Aspergillus* osteomyelitis. Constituting 15% of all cases, CGD caused 73% of pediatric cases of *Aspergillus* osteomyelitis. Patients with vertebral *Aspergillus* osteomyelitis compared to those with cranial *Aspergillus* osteomyelitis had significantly more previous orthopedic surgery (19% vs 0%; $P=0.02$), while those with cranial osteomyelitis had more diabetes mellitus (32% vs 8%; $P=0.002$) and prior head/neck surgery (12% vs 0%; $P=0.02$).

Classification of *Aspergillus* osteomyelitis and Mechanisms of Osteoarticular Infection

Cases were distributed as proven in 53% and probable in 47% (Table 2). The majority of cases of *Aspergillus* osteomyelitis (44%) were hematogenously infected, followed by contiguous involvement (32%), and direct inoculation (23%).

Osteoarticular distribution

Aspergillus osteomyelitis presented as two or more non-contiguously infected bones infected in 56% of cases (Table 2). The vertebral bodies, cranial bones, and ribs were the most frequently infected bones. Although long bones were infrequently infected, the tibia was the most commonly infected site. Osteomyelitis plus arthritis was observed in synovial joints in 15 cases (8.3%). Spondylodiscitis occurred in 72 (40%). There was a 47% frequency of spinal cord compression among 83 patients with vertebral *Aspergillus* osteomyelitis. Among 28 cases of aspergillosis of the ribs, 16 (57%) had primary immunodeficiency in comparisons to 12 (8.6%) of 151 without a primary immunodeficiency ($p<0.0001$). The preponderance of cases of costal aspergillosis complicating primary immunodeficiency developed through direct extension from a contiguous pulmonary focus.

Diagnostic procedures

The diagnosis of *Aspergillus* osteomyelitis was established most frequently by open biopsy (55%) and by percutaneous biopsy (36%) (Table 3). From these specimens, *Aspergillus* spp. were recovered and detected by direct culture and/or histology.

Clinical Microbiology

The most common species recovered was *Aspergillus fumigatus* followed by *Aspergillus flavus* (Table 3). Most cases had one species of *Aspergillus*. Among the five cases in which serum galactomannan index (GMI) data were reported, one had an elevated GMI of 5.6 to 6.3, while the GMI values were negative in the remaining cases. Bacteria were co-cultured from the same lesion in 19 cases; these consisted most frequently of *Staphylococcus* species followed by Gram-negative bacilli, including *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

Clinical manifestations

Pain and tenderness were the most common manifestations of *Aspergillus* osteomyelitis in 80% of cases, while fever was infrequent (22%) (Table 4). Sinus tract formation and draining purulence was present in 27% of cases. Thirty-four patients (19%) had neurological deficits in relation to spinal cord compression and cranial aspergillosis. *Aspergillus* osteomyelitis developed *de novo* before the initiation of antifungal agents in most cases (77%).

Markers of inflammation

Median erythrocyte sediment rate (ESR) and C-reactive protein (CRP) levels were elevated at 86 mm/h (10–148) and 51 mg/dl (1.5–151)(Table 4). Although the median WBC and % neutrophil differential count were not increased, the upper limits of the ranges of these values were markedly elevated.

Diagnostic imaging

Among the radiologic patterns observed for *Aspergillus* osteomyelitis, osteolysis, bone destruction, and bone erosion were the most common findings (65%), followed by extension of the infection into soft tissues (26%) (Table 4). Less common changes (<5%) included

periosteal reaction, abscess, and sequestrum. Spinal cord compression, decreased intervertebral space, paraspinal abscess, epidural abscess, subdural abscess, and spondylolisthesis were the most common changes in diagnostic imaging of the spinal column. The most common features of magnetic resonance imaging (MRI) of *Aspergillus* osteomyelitis included decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted images, and increased gadolinium contrast enhancement of T1-weighted images.

Effect of age

As the localization of osteomyelitis to bony sites may vary as a function of age for bacteria and *Candida* spp., we also addressed this question for *Aspergillus* (Table 5). Infection of the ribs occurred significantly more frequent in infants, toddlers, and children (12/37 (32%)) in comparison to that of adults (15/141 (11%)) (P=0.003). This relation is driven by the significant relationship between primary immunodeficiency, particularly CGD, and *Aspergillus* osteomyelitis (P<0.0001). Direct inoculation as a mechanism of infection was present more frequently in adults (35/141 (25%)) than in infants, toddlers, and children (3/37 (8%)) (P=0.05). This mechanism was associated with a higher frequency of surgically and traumatically related infections in adults.

Vertebral Aspergillosis

The vertebral bodies were the most commonly infected sites of osteomyelitis caused by *Aspergillus*. Among the 83 cases, the most commonly infected hosts were those with primary immunodeficiency, solid organ transplant, IV drug use, COPD, and diabetes mellitus. Sixteen patients (19%) underwent prior orthopedic surgery and 27 (33%) received corticosteroid therapy. Thirty-nine (47%) had spinal cord compression and associated neurological deficits. Sixteen (19%) of cases were associated with *Aspergillus* paraspinal abscess. Special surgical approaches to vertebral aspergillosis in these patients included bone grafting, spinal stabilization, decompression, and intervertebral body fusion.

Cranial Aspergillosis

Among the 41 cases of cranial *Aspergillus* osteomyelitis, 28 (68%) had contiguous infection, including 15 patients with *Aspergillus* malignant externa otitis, middle ear infection, and mastoiditis. Eight other patients had prior surgery or previous trauma, which served as the focus of infection, while the remaining patients had systemic immunological impairments, including diabetes mellitus, neutropenia, corticosteroids, HIV infection, primary immunodeficiency, and transplantation.

Aspergillosis of the Ribs and/or Sternum

Aspergillosis of the ribs and sternum tended to occur in a younger population with 36% of patients being ≤18 years of age (Table 1). Among those with *Aspergillus* osteomyelitis of the ribs, 16 (57%) had primary immunodeficiency, most commonly CGD. Among those with rib and/or sternal infection, 48% had primary immunodeficiency. Ten (30%) of patients had prior thoracic surgery, which was associated especially with sternal osteomyelitis. The

combination of ribs and sternum as well as that of vertebrae and ribs were the most common combinations of bone infections.

Aspergillosis of the Femurs and/or Tibias

Femoral and/or tibial aspergillosis also tended to occur in a younger population with 41% of patients being ≤18 years (Table 1). Six (27%) of these patients also had a primary immunodeficiency. The highest proportion (23%) of solid organ transplantation among the different sites was associated with femoral and tibial aspergillosis. Prior orthopedic surgery constituted the third most risk group in 18%.

Treatment and Outcome

The majority (67%) of patients were managed with both antifungal therapy and surgery versus 24% who received antifungal therapy only and 7% who received only surgery (Table 6). Median duration of therapy was 90 days (range, 10–772 days). Fourteen patients (8%) ceased antifungal therapy due to toxicity. Surgical intervention most frequently was required for debridement, amputation, or drainage. Vertebral infections were further managed by bone grafting, stabilization, fusion, and spinal cord decompression.

The therapeutic effect of antifungal therapy with or without surgery and the effect of single agent versus combination antifungal therapy are presented in Table 7. The %CR in the medical-surgical group (57%) was similar to that of the medical group (52%) (P=0.22). However, the relapse rate of 8% for 121 patients managed with surgery plus antifungal therapy was significantly lower in comparison to a relapse rate of 30% among the 44 patients treated with antifungal therapy only (P=0.006). When evaluating overall responses of antifungal therapy alone as monotherapy (40%) versus combination therapy (63%), there was a non-significant trend favoring two antifungal agents. By comparison, among those patients receiving surgery plus antifungal therapy, there was no benefit of monotherapy (59%) versus combination therapy (58%). Overall mortality was 25%. Survival was similar regardless of *Aspergillus* species.

When analyzed according to different antifungal agents, the overall response rate was similar for amphotericin B, itraconazole, and voriconazole (Table 7). There were inadequate data for posaconazole. Moreover, there was no apparent advantage to combination antifungal therapy versus single agent.

DISCUSSION

This comprehensive review and analysis of cases of *Aspergillus* osteomyelitis identified key features of this infection that have not been heretofore well understood in previous small case series or individual case reports. The pathogenesis of vertebral and costal *Aspergillus* osteomyelitis arose commonly from direct invasion from contiguous pulmonary foci, as well as from hematogenous dissemination. Most cases (nearly 80%) of *Aspergillus* osteomyelitis presented as the first manifestation of invasive aspergillosis. Unlike bacterial and *Candida* osteomyelitides [167], there was no age-dependent effect on site of infection. Vertebral *Aspergillus* osteomyelitis presented predominantly as spondylodiscitis with a nearly one-half of cases progressing to spinal cord compression associated with neurological deficits.

Cranial aspergillosis occurred in a widely divergent population at risk for localized infections. Favorable outcome for *Aspergillus* osteomyelitis consisted of antifungal therapy and individualized surgery based upon site and local complications.

The immunocompetent population had preceding thoracic and abdominal surgery or open fractures, as well as no prior surgical procedure or trauma. Vertebral and costal *Aspergillus* osteomyelitis arose from contiguous pulmonary aspergillosis, by hematogenous dissemination, and occasionally by traumatic inoculation. Cranial aspergillosis arose most commonly from a contiguous focus.

The methodology of this study assessed individual cases with a high degree of detail to permit analysis of a robust data set. While case series from single sites or literature reviews of specific aspects are informative, they may lack numerical power for detailed comparison. For instance, a study reported by Kirby et al [153] reviews therapeutic outcome of patients with *Aspergillus* osteomyelitis before 2006 but without considering location, surgery, host, epidemiological, clinical, radiographic, or laboratory features that are important to understanding this crippling infection. Among patients within the case series, many did not fulfill evaluability criteria for inclusion in this study [153–162]. The overall demographics of these case series, however, were similar to those reported within this study.

Patients with CGD in this study comprised 73% of all pediatric cases of *Aspergillus* osteomyelitis. CGD constituted the highest risk underlying condition for development of *Aspergillus* osteomyelitis of the long bones, most commonly tibia and femur. Infections of long bones in children with CGD developed most frequently via hematogenous dissemination from a pulmonary focus. Our findings of incidence and pathogen distribution in CGD-affected patients with *Aspergillus* osteomyelitis are in accordance with other published reports [157, 154, 152, 160]. Our findings also are consistent with the case series by Dotis and Roilides who reported 46 cases of *Aspergillus* osteomyelitis complicating CGD, where the median age was 8 years and overall mortality was 37% [152]. Young males with CGD were predominantly infected. *A. fumigatus* was the most frequent mould causing about 80% of fungal infections in CGD patients [152, 160]. The most frequently affected bones in CGD patients were vertebrae followed by ribs, femur, and skull. There were cases where lungs were not involved. Thus, although the extension of lung aspergillosis to the adjacent chest wall is a main mechanism of *Aspergillus* osteomyelitis, our study showed that hematogenous dissemination constitutes a basic pathogenic factor. Patients with CGD have a distinctively high risk for infections caused by *Aspergillus nidulans*, where mortality is significantly greater compared to that of *A. fumigatus* [154, 157]. In most CGD patients, osteomyelitis can be controlled by prompt medical treatment, immunotherapy, and surgical intervention.

Early recognition of *Aspergillus* osteomyelitis depends upon recognizing vulnerable populations with symptoms of osseous tenderness, pain, sinus tracts and/or drainage. The symptoms of pain and tenderness over a bony area in an immunocompromised patient should prompt further evaluation for osteomyelitis, especially that of *Aspergillus* osteomyelitis. This study, however, demonstrates that non-immunocompromised patients are also an important population at risk. Prior surgical procedures, especially orthopedic and

thoracic surgery, which may have served as a source of direct inoculation, were documented in 40% of cases.

Among more than 500 reported cases of postoperative aspergillosis, Pasqualotto and Denning found that orthopedic surgery accounted for 42 and mediastinitis for 11 [166]. Postoperative orthopedic aspergillosis was characterized by a delay in onset of infection-related symptoms measured in terms of months to years [99,113,138]. Most cases were treated successfully with debridement and antifungal chemotherapy. Sternal wound infection with or with out mediastinitis was an uncommon form of postoperative osteomyelitis. Among reported cases of sternal osteomyelitis [16,162–164], some have been described in the setting of two nosocomial outbreaks [163–164]. Those 10 cases within the outbreaks were caused by *A. flavus* following coronary artery bypass graft surgery. The median postoperative interval of onset was 14 days but with a wide range from 5 to 147 days. Three patients had 7 episodes requiring repeated debridement. Eight of ten patients were ultimately were treated successfully with removal of sternal wires, curettage, and, with one exception, antifungal therapy. Thus, postoperative *Aspergillus* osteomyelitis should be considered in the differential diagnosis of delayed onset bone infection, especially when bacterial cultures are negative. Cultures positive postoperatively from clinically infected bone should not be considered to be contaminants.

The vertebrae were the most commonly infected sites in *Aspergillus* osteomyelitis. The literature and our own clinical experience reveal that the route of infection of the vertebral bodies with *Aspergillus* osteomyelitis occurs via contiguous transpleural extension into adjacent vertebral bodies or by hematogenous dissemination to these bones. Among patients with *Aspergillus* vertebral osteomyelitis, 41% had contiguous extension from a pulmonary source. Similarly the ribs were also frequently infected from contiguous pulmonary infection in 25% of cases. Moreover, among the 26 patients with pulmonary aspergillosis prior to *Aspergillus* osteomyelitis, 7 patients suffered from rib *Aspergillus* osteomyelitis and 19 patients from vertebral *Aspergillus* osteomyelitis. These findings suggest that patients with known invasive pulmonary aspergillosis who complain of persistent pain pleuritic or back pain may also have contiguous vertebral and rib infection. Evaluation of the chest CT scan in patients with invasive pulmonary aspergillosis and complaints of thoracic or back pain would then include an assessment using both lung windows and bone windows for evaluation of concomitant osteomyelitis.

Aspergillus vertebral osteomyelitis and spondylodiscitis were frequently complicated by spinal cord compression and epidural abscess [1,3,4,51,53,54]. Our study documented a 47% frequency of spinal cord compression among 86 patients with vertebral body *Aspergillus* osteomyelitis. The most debilitating cases arose from the thoracic and cervical levels. Vertebral aspergillosis developed in those who were immunocompromised as well as in apparently immunocompetent patients. The extent of immunosuppression for development of vertebral aspergillosis may be relatively minimal, as in the case of two patients with chronic obstructive pulmonary disease treated with brief courses of systemic corticosteroids and inhaled steroids who developed *Aspergillus* spondylodiscitis [46]. The routes of infection of the vertebral bodies and epidural space appear to be contiguous involvement from lung, hematogenous distribution, and direct inoculation. The features of

Aspergillus vertebral osteomyelitis in immunocompetent patients, as described Studemeister and Stevens, underscore that hematogenous dissemination may occur even in a seemingly normal host [53]. In the absence of an adjacent pulmonary focus for diagnosis, percutaneous needle aspirate and diagnostic cytology of the vertebral lesion may yield the organism [14, 58]. The clinical manifestations of vertebral *Aspergillus* osteomyelitis constitute lower motor neuron findings, including weakness of extremities, diminished reflexes and incontinence in the setting of suspected or documented warrant neurosurgical intervention. Management consists of surgical decompression, debridement of vertebral and epidural infected tissue, and treatment with voriconazole.

After vertebral and costal aspergillosis, cranial aspergillosis was the most frequent from of *Aspergillus* osteoarticular infection [26,44,47–50,52,56,57,60]. This form of *Aspergillus* osteomyelitis has not been well described beyond individual case reports and may be underdiagnosed. In addition to the cranial vault, petrous bone, and the base of the skull, especially the clivus, are common locations for this serious form of *Aspergillus* osteomyelitis [48]. A common setting for cranial *Aspergillus* osteomyelitis included otalgia and otorrhoea in the context of progressive middle ear infection, broad spectrum antibiotics, and diabetes mellitus. Management of cranial *Aspergillus* osteomyelitis usually consisted of a combination of medical and surgical interventions. The overall response rate (91%), including complete (59%) and partial responses (32%), was similar to that of all patients with *Aspergillus* osteomyelitis (84%).

Microbiological or histological documentation of *Aspergillus* osteomyelitis is important for management. The diagnostic imaging features of osteolysis, bone destruction, and increased MRI T2-weighted signal intensity are compatible with an infectious process but not for aspergillosis. While vertebral or rib *Aspergillus* osteomyelitis could be reasonably inferred from a microbiologically documented pulmonary aspergillosis, non-contiguous infections necessitate a definitive diagnosis. Moreover, only 40 (22%) of all patients with *Aspergillus* osteomyelitis had a previous diagnosis of invasive aspergillosis. As only five patients with *Aspergillus* osteomyelitis had data on serum galactomannan, no conclusions can be drawn concerning the utility of this biomarker in diagnosis of osteoarticular aspergillosis. Thus, biopsy with culture and histology is important for prognosis, management, and diagnostic exclusion of the other processes, including bacterial pathogens, malignancy, and other mycoses.

Within the differential diagnosis of osteoarticular mycoses, *Aspergillus* osteomyelitis differs from *Candida* osteomyelitis, the most common form of fungal infection of bone [166], in several ways. *Aspergillus* osteomyelitis is approximately four times more likely to arise from contiguous infection than is *Candida* osteomyelitis. This difference is related to the relationship between invasive pulmonary aspergillosis extending contiguously into adjacent ribs and vertebrae. *Candida* osteomyelitis is more frequently associated with concomitant septic arthritis with the knee joint being more than ten times more likely to be infected than in *Aspergillus* osteomyelitis. Among patients with *Candida* osteomyelitis, there were significant differences in the distribution of bony involvement between pediatric patients and adult patients; i.e., femoral and tibial bones were significantly more involved in infants, toddlers, and children, while the vertebrae were infected more commonly in adults. By

comparison, such differences between pediatric patients and adult patients with *Aspergillus* osteomyelitis were not observed. The age-dependent differences in *Candida* osteomyelitis may be related to the greater propensity for hematogenous dissemination of small yeast forms in a pattern similar to that of bacterial osteomyelitis. By comparison, *Aspergillus* does not disseminate as yeast forms and is more likely to cause osteomyelitis by contiguous infection. Finally, while *Candida* osteomyelitis was relatively common in neonates and infants, *Aspergillus* osteomyelitis was not found in neonates and seldom in infants. Primary immunodeficiencies, particularly chronic granulomatous disease, were present in 15% of cases of *Aspergillus* osteomyelitis, but not found in *Candida* osteomyelitis.

Inflammatory biomarkers were highly variable in their expression in *Aspergillus* osteomyelitis. When biomarkers are elevated, they suggest osteomyelitis in the appropriate clinical setting of pain and radiological lesions. As *Aspergillus* osteomyelitis and *Candida* osteomyelitis are both associated with elevated inflammatory biomarkers [166], biopsy and culture of lesions are required for definitive diagnosis and pathogen-directed therapy.

Management of *Aspergillus* osteomyelitis included antifungal therapy and surgical debridement in most cases. For patients undergoing surgery, there was a significant reduction from 30% to 8% in the frequency of relapsed osteoarticular aspergillosis. In the absence of surgical resection, recurrence of *Aspergillus* osteomyelitis was relatively common after discontinuation of therapy. Antifungal therapy was then resumed and continued for a more extended course for a complete or partial response. Surgery appeared to have the effect of debulking or eliminating a sufficient amount of infected bone to significantly reduce the probability of recurrent infection when antifungal therapy was discontinued.

The optimal duration of therapy of *Aspergillus* osteomyelitis is not known. While the median duration of therapy was 90 days, the range is extensive from 10 to 772 days. Although the guidelines of the Infectious Diseases Society of America for treatment of *Aspergillus* infections recommend a minimum of 6 to 8 weeks of therapy [167], this range is based upon expert opinion and no systematic literature review or prospective study. Moreover, these recommendations do not address the impact on duration of treatment by surgery, which can reduce the rate of relapse.

Among the options for antifungal agents, amphotericin B, itraconazole, and voriconazole had similar response rates. As the median duration of therapy was 90 days, administration of an amphotericin B formulation for that length of time may be associated with cumulative nephrotoxicity and the morbidity of prolonged venous access. Itraconazole is a viable option for extended therapy of *Aspergillus* osteomyelitis [59]; however, for some patients, bioavailability remains challenging for the capsular form and gastrointestinal intolerance for the oral solution. Voriconazole, which also has been used successfully for treatment of *Aspergillus* osteomyelitis [1, 48, 55], has the flexibility of parenteral and oral formulations, as well as acceptable bioavailability; however, the limitations of protracted voriconazole therapy include solar hypersensitivity and autoinduction with progressively declining levels [168, 169]. Voriconazole also has been used as salvage therapy for refractory *Aspergillus* osteomyelitis [41]. Although the number of treated cases is sparse, posaconazole also has

been used successfully in management of *Aspergillus* osteomyelitis [42,45]. The challenges of oral bioavailability are similar to those of itraconazole.

This study has several potential intrinsic limitations. Review of published cases may be affected by publication biases with description of unusual organisms, or a tendency to report successfully treated cases, as well as cases spanning several decades, when supportive care, antifungal agents, surgical techniques have evolved in the meantime. However, the large number of well defined cases in this report supplants these possible limitations with a consistency of definitions and detail of analysis. Exclusion of these cases with inadequate data does not affect the strength of conclusions drawn from the 180 analyzed cases to the general population suffered from *Aspergillus* osteomyelitis. Despite these limitations, this review is the most comprehensive and detailed analysis of *Aspergillus* osteomyelitis to provide a guide to clinicians of this serious infection.

In summary, *Aspergillus* osteomyelitis is a debilitating infection that may develop in both immunocompromised and immunocompetent patients. The vertebral bodies and ribs, which are the most frequently involved sites, are infected either via contiguous extension from a pleuropulmonary focus or via hematogenous dissemination. Cranial *Aspergillus* osteomyelitis is an anatomically and clinically distinctive infection, particularly in those with diabetes mellitus or prior head/neck surgery. Most patients are managed with combined medical and surgical therapy. Surgical intervention is especially important in vertebral involvement, where the risk of spinal cord compression is relatively high. Therapy with an amphotericin B formulation or the triazoles, itraconazole or voriconazole, is effective in the medical management of most cases of *Aspergillus* osteomyelitis. Thus, management of *Aspergillus* osteomyelitis optimally includes antifungal therapy and individualized surgery based upon site and local complications to achieve a favorable outcome.

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Table 1

Demographic Characteristics of *Aspergillus* Osteomyelitis

	Total (N=180)	Vertebral Osteomyelitis (N=83)	Cranial Osteomyelitis (N=41)	Rib and/or Sternal Osteomyelitis (N=33)	Femoral and/or Tibial Osteomyeltis* (N=22)	Other Sites (N=7)
Characteristics	***n* (%)**	***n* (%)**	***n* (%)**	***n (%)***	***n (%)***	***n (%)***
Median age [range][a]	48 y [1–87y]	49 y [1.5–78]	58 y [4–87]	31y [2–70]	29y [1–61]	32y [1–70]
Adults (>18 y)	141 (78)	71 (86)	33 (80)	20 (61)	13 (59)	7 (100)
Pediatric population (≤18 y)	37 (21)	11 (12)	8 (20)	12 (36)	9 (41)	0 (0)
Toddlers/Children (1y–≤18y)	35 (20)	11 (12)	8 (20)	12 (36)	7 (32)	0 (0)
Infants (<12 mo)	1 (1)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Gender[b]						
Females	52 (29)	24 (29)	24 (59)	7 (21)	5 (23)	0 (0)
Males	127 (71)	59 (71)	17 (41)	26 (79)	18 (82)	7 (100)
Underlying conditions						
Primary	27 (15)	9 (11)	2 (5)	16 (48)	6 (27)	0 (0)
Immunodeficiency[c]						
Hematologic malignancy	19 (11)	4 (5)	6 (15)	5 (15)	3 (14)	1 (14)
SOT	17 (9)	10 (12)	0 (0)	0 (0)	5 (23)	2 (28)
Solid tumors	7 (4)	3 (4)	2 (5)	2 (6)	0 (0)	0 (0)
HSCT	4 (2)	1 (1)	3 (7)	0 (0)	0 (0)	0 (0)
IV drug use	12 (7)	6 (7)	1 (2)	5 (15)	2 (9)	0 (0)
HIV/AIDS	9 (5)	0 (0)	7 (17)	1 (3)	0 (0)	1 (14)
COPD	19 (11)	13 (16)	0 (0)	4 (12)	2 (9)	0 (0)
Ethanol abuse	6 (3)	2 (2)	1 (2)	3 (9)	1 (5)	0 (0)
Diabetes mellitus	29 (16)	7 (8)[d]	13 (32)[d]	7 (21)	2 (9)	0 (0)
Prior Surgery:	57 (32)	33 (40)	8 (20)	10 (30)	5 (23)	5 (71)
Orthopedic	23 (13)	16 (19)[e]	0 (0)[e]	0 (0)	4 (18)	3 (43)
Thoracic	19 (11)	6 (7)	1 (2)	10 (30)	0 (0)	2 (28)
Abdominal	10 (6)	7 (8)	2 (5)	0 (0)	1 (5)	0 (0)

	Total (N=180)	Vertebral Osteomyelitis (N=83)	Cranial Osteomyelitis (N=41)	Rib and/or Sternal Osteomyelitis (N=33)	Femoral and/or Tibial Osteomyeltis* (N=22)	Other Sites (N=7)
Characteristics	***n* (%)**	***n* (%)**	***n* (%)**	***n (%)***	***n (%)***	***n (%)***
Head/Neck	5 (3)	0 (0)[f]	5 (12)[f]	0 (0)	0 (0)	0 (0)
Prior broad spectrum antibiotics	108 (60)	38 (46)	31 (76)	22 (67)	15 (68)	2 (28)
Prior antifungal agents	22 (12)	12 (14)	2 (5)	4 (12)	3 (14)	1 (14)
Open fracture	5 (3)	1 (1)	0 (0)	0 (0)	3 (14)	1 (14)
Trauma/open wound	13 (7)	1 (1)	3 (5)	0 (0)	7 (32)	2 (28)
Neutropenia	13 (7)	3 (4)	4 (10)	2 (6)	3 (14)	1 (14)
Corticosteroids	52 (29)	27 (33)	11 (27)	4 (12)	8 (36)	2 (28)
Pharmacological immunosuppresion other than corticosteroids	27 (15)	10 (12)	3 (7)	4 (12)	7 (32)	3 (43)

[a] For 2 cases age-variable was not available

[b] For 1 case gender-variable was not available

[c] Twenty-three (85%) had chronic granulomatous disease

SOT: solid organ transplantation

HSCT: hematopoietic stem cell transplantation

COPD: chronic obstructive pulmonary disease

[d] P=0.002

[e] P=0.02

[f] P=0.02

Table 2

Classification, Apparent Mechanisms and Anatomical Distribution of *Aspergillus* Osteomyelitis

Classification of *Aspergillus* osteomyelitis (N=180)	
	***n* (%)**
Proven	95 (53)
Probable	85 (47)
Apparent mechanisms of infection	
Hematogenous	80 (44)
Contiguous	58 (32)
Direct inoculation	42 (23)
Osteoarticular Involvement	
1 bone infected	79 (44)
2 bones infected	60 (33)
≥3 bones infected	41 (23)
Type of Bone Infected[a]	
Vertebra	83 (46)
Spondylodiscitis	72 (40)
Cranium	41 (23)
Ribs	28 (16)
Tibia	13 (7)
Sternum	10 (6)
Femur	11 (6)
Other[b]	14 (8)
Joint Involvement	
Synovial Joint	15 (8)
Hip	4 (2)
Ankle	3 (2)
Carpus	3 (2)
Knee	3 (2)
Other[c]	2 (1)
Costochondral Joint	10 (6)
Lumbosacral Joint	4 (2)

[a] More than one type of bone was infected in some patients

[b] Includes tarsus, pelvis, humerus, carpus, metacarpus, phalanx, fibula, ulna, and calcaneus bones at <1% each

[c] Includes sternoclavicular, and sacroiliac joint at 0.5% each

Table 3

Diagnostic Approaches and Microbiology of *Aspergillus* species Causing *Aspergillus* Osteomyelitis

Diagnostic Approach for Tissue Specimen Collection[a] (N=180)	
	***n* (%)**
Core biopsy	64 (36)
Open biopsy/ surgery	99 (55)
Swab	9 (5)
FNA[b]	16 (9)
Microbiology and Histopathology	
Direct Culture	156 (87)
Histology	116 (64)
Direct Culture and Histology	93 (52)
	*1 PCR
***Aspergillus* species**	
Aspergillus fumigatus	110 (61)
Aspergillus flavus	35 (20)
Aspergillus niger	6 (3)
Aspergillus terreus	5 (3)
Aspergillus nidulans	3 (2)
Aspergillus versicolor	2 (1)
Non specified	25 (14)
***Aspergillus* spp. recovered by culture per patient**	
1 *Aspergillus* spp.	175 (97)
≥ 1 *Aspergillus* spp.	5 (3)
Bacteria as recovered in cultures mixed with *Aspergillus* spp.[c]	
Staphylococcus aureus	9 (5)
Staphylococcus epidermidis	3 (2)
***Streptococcus* spp.**	2 (1)
Diptheroids	2 (1)
Pseudomonas aeruginosa	1 (0.5)
***Klebsiella* spp.**	1 (0.5)
Enterobacter cloacae	1 (0.5)
***Mycobacterium avium* complex**	1 (0.5)
Other[d]	2 (1)

[a] some patients had more than one diagnostic procedure

[b] FNA: fine needle aspirate

[c] 32 bacterial organisms were recovered from 19 (11%) patients

[d] Gram-negative bacteria

Table 4

Clinical Manifestations, Radiological Features, and Inflammatory Markers of *Aspergillus* Osteomyelitis

Clinical Manifestations[a] (N=180)	
	No (%)
Local symptoms	
Pain/ tenderness	145 (80)
Erythema	15 (8)
Edema	26 (14)
Fever	39 (22)
Limitation of function/ movement	18 (10)
Draining pus/ sinus	48 (27)
Neurological deficits related to vertebral aspergillosis	39 (22)
Fracture developing as a sequela of *Aspergillus* osteomyelitis	2 (1)
Initial Presentation of Aspergillosis	
De novo Aspergillus osteomyelitis	138 (77)
Breakthrough aspergillosis	42 (23)
Radiological Features[a]	
Osteolysis/ bone destruction/ bone erosion	117 (65)
Extension into soft tissues	47 (26)
Spinal cord compression	39 (22)
Increase of Nuclear Scan uptake (Tc^{99m}/ Ga^{67}) (n=41)	36/41 (87)
Increase of density in CT	27 (15)
MRI characteristics (n=51)	
Decrease of signal intensity on T1 (MRI)	23/51 (45)
Increase of signal intensity on T2 (MRI)	21/51 (41)
Increase of contrast-enhanced T1 (MRI)	19/51 (37)
Decrease of intervertebral space	16 (9)
Paraspinal abscess	16 (9)
Epidural abscess	14 (8)
Fracture	10 (6)
Necrotic bone	9 (5)
Periosteal reaction	6 (3)
Spondylolisthesis	5 (3)
Decreased articular space	5 (3)
Bone abscess	3 (2)
Subdural abscess	2 (1)
Sequestrum	2 (1)

Inflammatory markers		
	% elevated (n)	**Median (range)**
WBC (/mm3)	>10,000/mm3; 45% (n=53)	9,270 (100–37,000)
PMNs (%)	>80%; 30% (n=30)	79.3 (10.3–90)
ESR (mm/h)	>15 mm/hr; 96% (n=58)	86 (10–148)
CRP (mg/dl)	> 1 mg/dL; 100% (n=15)	51.5 (1.5–151)

[a]Clinical manifestations not reported in the case reports are assumed to be absent.

[b]Radiological methods included conventional radiographs (83), computed tomography (69), magnetic resonance (51), radionuclide scanning (41), and ultrasound (3)

Table 5

Effect of Age by Site of Infection, Clinical Manifestations, and Outcome in *Aspergillus* Osteomyelitis (N=180)

Age[a]	Mechanism (n)	Bone site by reported frequency of involvement (n)	Bone involvement/ Site of long bones infected (n)	Symptoms (n)	Outcome[b] (n)
Infants, Toddlers and Children (37)	Contiguous (11) Hematogenous (23) Direct inoculation (3)	Vertebra (11) Cranium (8) Femur (4) Ribs (12)[c] Sternum (0) Humerus (2) Tibia (5)	1 bone involved (20) 2 bones involved (5) ≥3 bone involved (12) Metaphysis (7) Epiphysis (0) Diaphysis (3)	Local pain (25) Fever (15) Limitation of function/movement (5) Draining pus (8)	Complete response (18) Partial response (10) Relapse (1) Death (12)
Adults (141)	Hematogenous (75) Direct inoculation (35) Contiguous (31)	Vertebra (71) Cranium (33) Femur (6) Ribs (15)[c] Sternum (10) Humerus (0) Tibia (8)	1 bone involved (58) 2 bones involved (55) ≥3 bone involved (28) Epiphysis (5) Metaphysis (4) Diaphysis (2)	Local pain (119) Fever (24) Limitation of function/movement (12) Draining pus (40)	Complete response (81) Partial response (40) Relapse (16) Death (32)

[a] The ages of two patients was not defined in the original reports

[b] Some patients had relapsed infection followed by subsequent partial or complete response

[c] P=0.003

Table 6

Treatment and Outcome According to Site of Infection

Intervention	All cases N (%)	Vertebral Aspergillosis *n* (%)	Cranial Aspergillosis *n* (%)	Rib and/or Sternal Osteomyelitis* *n* (%)	Femoral and/or Tibial Osteomyelitis* *n* (%)	Others *n* (%)
	180	83 (46)	41 (23)	33 (18)	22 (12)	7 (4)
MEDICAL THERAPY[a]						
Only Antifungal Agents	44 (24)	18 (22)	10 (24)	10 (30)	6 (27)	0 (0)
Only Surgery	12 (7)	6 (7)	2 (5)	2 (6)	1 (5)	1 (14)
Antifungal Agents and Surgery	121 (67)	58 (70)	28 (68)	19 (58)	15 (68)	1 (14)
Median	90 d	90 d	90 d	165 d	218 d	150 d
Duration of Medical Treatment [range]	[10-772]	[14-772]	[10-365]	[23-540]	[10-395]	[10-410]
SURGICAL INTERVENTION						
Debridement	124 (69)	60 (72)	29 (71)	16 (48)	16 (73)	3 (45)
Amputation	21 (12)	1 (1)*	0 (0)	13 (39)	1 (5)	6 (86)
Drainage	27 (15)	12 (14)	6 (15)	4 (12)	5 (23)	0 (0)
Bone grafting	18 (10)	16 (19)	0 (0)	0 (0)	0 (0)	2 (28)
Stabilization	14 (8)	13 (16)	0 (0)	0 (0)	0 (0)	1 (14)
Decompression	10 (6)	10 (12)	0 (0)	0 (0)	0 (0)	0 (0)
Fixation	9 (5)	6 (7)	0 (0)	1 (3)	2 (9)	0 (0)
Lavage	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)
Intervertebral body fusion	5 (3)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Removal of hardware	2 (1)	1 (1)	0 (0)	0 (0)	0 (0)	1 (14)
Insertion of prosthesis	2 (1)	1 (1)	0 (0)	0 (0)	0 (0)	1 (14)
OUTCOME						
Complete response	101 (56)	45 (54)	24 (58)	15 (45)	15 (68)	6 (86)
Partial response	51 (28)	22 (27)	13 (32)	12 (36)	4 (18)	0 (0)
Relapse	18 (10)	7 (8)	5 (12)	6 (18)	0 (0)	0 (0)
Death	45 (25)	19 (23) *6 *Aspergillus*-related-deaths	13 (32) *3 *Aspergillus*-related-deaths	7 (21) *2 *Aspergillus*-related-deaths	5 (23)	1 (14) *1 *Aspergillus*-related-deaths

[a] data were insufficient for 3 patients to define the type of medical or surgical management

[*] ribs alone (n=23)

[*] sternum alone (n=5)

[*] ribs and sternum (n=5)

Table 7

Outcome According to Treatment Strategy (N=180)

Antifungal Treatment Alone (N=44)					Antifungal Treatment + Surgery (N=121)*				
	CR (%)	PR (%)	R (%)	D (%)		CR (%)	PR (%)	R (%)	D (%)
Overall Response	52[a]	27	30[b]	30	**Overall Response**	57[a]	30	8[b]	20
Monotherapy (N=20)	40	35	15	45	**Monotherapy** (N=76)	59	28	8	22
Amphotericin B (N=16)	38	31	13	56[c]	**Amphotericin-B** (N=50)	64	20	10	26[d]
Itraconazole (N=1)	100	0	0	0	**Itraconazole** (N=14)	57	43	0	14
Voriconazole (N=2)	0	100	50	0	**Voriconazole** (N=10)	50	30	10	20
Others (N=1)	100	0	0	0	**Others** (N=2)	0	100	0	0
Combination Antifungal Therapy (N=24)	63	21	4	17[e]	**Combination Antifungal Therapy** (N=45)	58	31	9	20[f]

*12 patients underwent only surgery, and for 3 cases there were insufficient data on treatment

CR: complete response

PR: partial response

R: relapse

D: death

[a] *P*=0.22

[b] *P*=0.006

[c] Related-to-*Aspergillus*-death: 5 cases

[d] Related-to-*Aspergillus*-death: 2 cases

[e] Related-to-*Aspergillus*-death: 2 cases

[f] Related-to-*Aspergillus*-death: 1 case