

# ***Aspergillus* spp. osteoarticular infections: an updated systematic review on the diagnosis, treatment and outcomes of 186 confirmed cases**

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## **Abstract**

*Aspergillus* spp. osteoarticular infections are destructive opportunistic infections, while there is no clear consensus on their management. The purpose of this review is to investigate the current literature regarding *Aspergillus* spp. osteoarticular infections. An electronic search of the PubMed and Scopus databases was conducted considering studies that assessed osteoarticular infections from *Aspergillus* spp. We included only studies with biopsy proven documentation of positive cultures or histological findings for *Aspergillus* spp., and those with essential information for each case such as the anatomical location of the infection, the type of treatment (conservative, surgical, combination), the antifungal therapy, and the outcome. Overall, 148 studies from 1965 to 2021 including 186 patients were included in the review. One hundred and seven (57.5%) patients underwent surgical debridement in addition to antifungal therapy, while 79 (42.7%) patients were treated only conservatively. Complete infection resolution was reported in 107 (57.5%) patients, while partial resolution in 29 (15.5%) patients. Surgical debridement resulted in higher complete infection resolution rate compared to only antifungal therapy (70.0% vs. 40.5%;  $P < 0.001$ ), while complete resolution rate was similar for antifungal monotherapy and combination/sequential therapy (58.3% vs. 54.5%;  $P = 0.76$ ). Last, complete resolution rate was also similar for monotherapy with amphotericin B (58.1%) and voriconazole (58.6%;  $P = 0.95$ ). The results of this study indicate that antifungal monotherapy has similar efficacy with combination/sequential therapy, while voriconazole has similar efficacy with amphotericin B. Moreover, surgical debridement of the infected focus results in better outcomes in terms of infection eradication compared to conservative treatment.

## **Lay Summary**

Antifungal monotherapy has similar efficacy with combination/sequential therapy, and voriconazole has similar efficacy with amphotericin B for the treatment of *Aspergillus* spp. osteoarticular infections, while surgical debridement of the infected focus improves the infection eradication rate.

**Keywords:** *Aspergillus* spp., osteoarticular infection, diagnosis, management, antifungal agents

## **Introduction**

Although fungal osteoarticular infections are rare opportunistic infections, their incidence is higher in certain population groups, such as in immunocompromised hosts. These destructive infections pose a challenging surgical problem that requires prolonged antifungal treatment. *Candida* genus is the most common fungal group that causes osteoarticular infections, followed by *Aspergillus* spp.<sup>1</sup> Although *Aspergillus* spp. usually infect the lower respiratory tract system causing inva-

sive aspergillosis, they can also infect bones and joints with devastating sequelae.<sup>2</sup> These pathogens have certain characteristics such as small conidia size that allows enhanced tissue penetration, while due to the abundance of negatively charged sialic acid on their surface they can strongly adhere to the host proteins.<sup>3</sup> Their infectious potential is additionally increased by the presence of melanin in their surface that provides resistance to reactive oxygen species and phagocytosis. While there are several studies evaluating osteoarticular infections from

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*Candida* spp., there is only sparse information about osteoarticular infections from *Aspergillus* spp. Moreover, the available literature for osteoarticular infections from *Aspergillus* spp. is limited to small case series and case reports providing a lower quality level of evidence.<sup>4,5</sup>

The management of osteoarticular infections from *Aspergillus* spp. in terms of diagnosis and treatment requires a multidisciplinary approach and collaboration between infectious disease physicians, microbiologists, and orthopedic surgeons. The lack of sufficient data results in significant heterogeneity in the treatment of these infections in terms of the indicated antifungal agents, the antifungal regime (monotherapy vs. combination therapy/sequential therapy), the dose of the antifungal agents and the overall duration of the therapy. Moreover, the indication for surgical treatment is not as clear as in other bacterial osteoarticular infections.<sup>6,7</sup>

The purpose of this review is to investigate the current literature regarding the epidemiology, pathophysiology, diagnosis, and treatment of fungal osteoarticular infections from *Aspergillus* spp. We aimed to collect and report the available information only from studies with biopsy-proven osteoarticular aspergillosis that also provide sufficient information regarding the success or failure of well described treatment protocols in terms of eradicating these infections.

## Methods

### Search protocol/databases

A methodological protocol for systematic reviews based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was followed in order to identify and evaluate studies that were assessing the topic of interest of this review. The review of the literature was performed between December 2021 and February 2022.

An electronic search in PubMed and Scopus databases was conducted until February 10, 2022 to identify eligible studies using a combination of the following terms: 'aspergillus', 'aspergillosis', 'osseous', 'osteoarticular', 'musculoskeletal', 'bone', 'osteomyelitis', 'septic arthritis', 'orthopedic', 'spondylodiscitis', 'periprosthetic joint infections'. After an initial screening for eligibility by titles and abstracts of the retrieved articles, studies that were clearly irrelevant to our investigational target were excluded. The rest of the retrieved articles underwent full text review to evaluate whether they were meeting the inclusion criteria for this systematic review. The review process was independently performed by two investigators (EM and KZ), while any disagreement regarding the inclusion of the studies were resolved by a third author (AGT). Additionally, all the references cited in the articles that underwent full text review and all the references cited in previously published reviews were manually searched by two investigators (AGT and DVP) to identify any other studies, in order to minimize the possibility of missing out studies.

### Selection criteria

We considered studies assessing osteoarticular infections from *Aspergillus* spp. We evaluated randomized clinical trials, cohort studies (retrospective or prospective), and observational studies (case series or case reports) published in the English literature. Inclusion criteria included: (i) biopsy proven documentation of positive cultures or histological findings for *Aspergillus* spp. from a tissue sample taken from the infected

osteoarticular location, and (ii) detailed report of essential information for each case: essential information was considered the anatomical location of the infection, the type of treatment (conservative, surgical, combination), the antifungal therapy (agents, monotherapy vs. combination therapy), and the outcome (complete resolution [defined as complete clinical improvement without any clinical signs of infection], partial resolution [defined as incomplete clinical improvement with partial resolution of the clinical signs of infection, with or without radiological findings of partial resolution of the infection], recurrence [defined as recurrent development of clinical signs of infection], death). Review studies, studies not involving humans, studies with suspected cases without documentation of positive culture or histological findings, and studies with inadequate information such as missing information about the treatment or outcome were excluded.

### Data extraction and data analysis

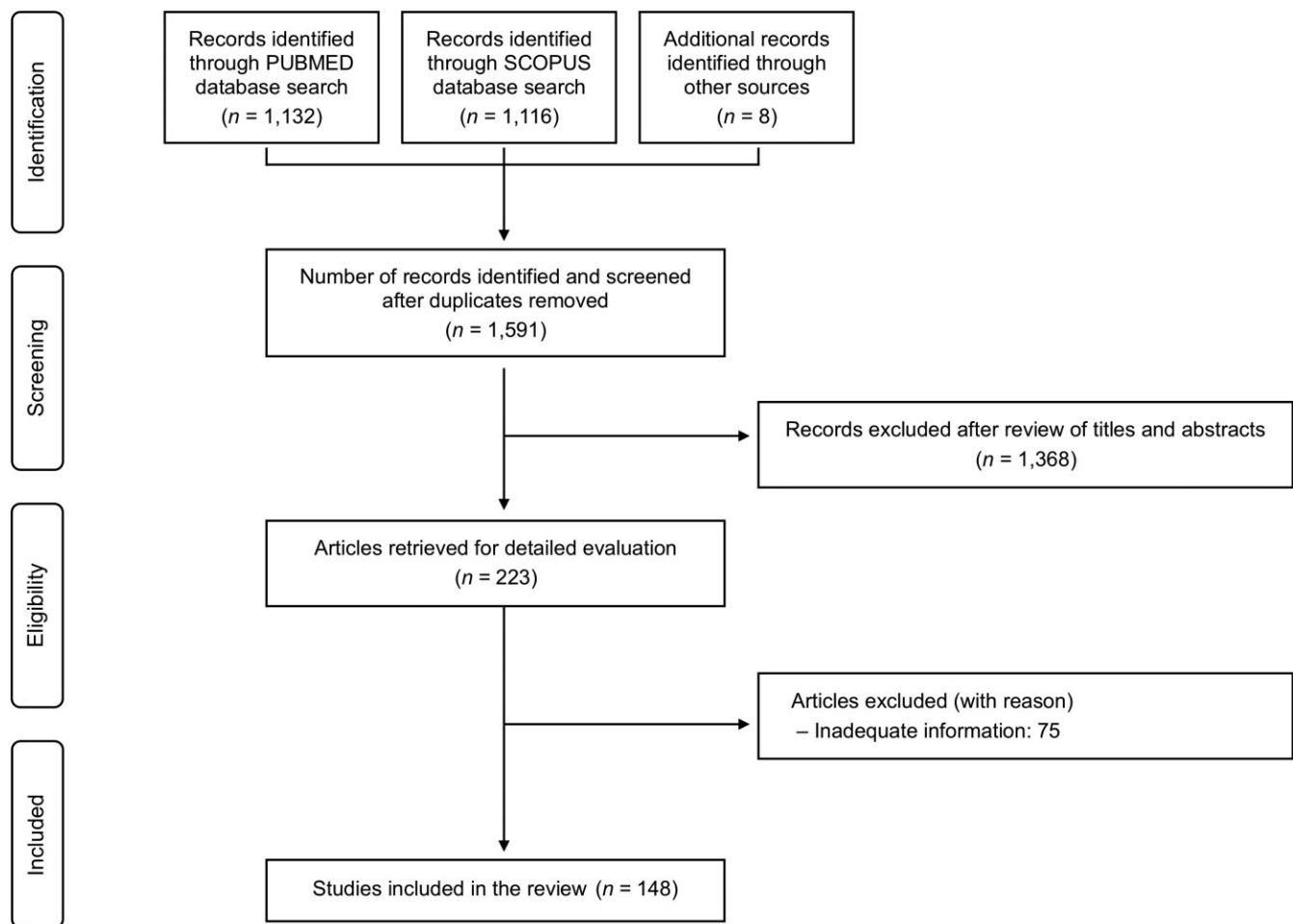
A standard excel sheet was used by two authors (EM and KZ) for an independent data extraction of the reported information from each included study. Data on patients' demographics (age, gender) and underlying condition (corticosteroids, immunodeficiency, malignancy, etc.), microbiological data (*Aspergillus* species, coexisting infection from another pathogen), location (spine, cranial bones, thoracic ribs, etc.), route of infection (hematogenous, contiguous, direct inoculation), and clinical manifestations were extracted. Moreover, the type of biopsy and method for diagnosis (direct culture, histology etc.), the imaging findings and inflammatory markers (white blood cell (WBC) count, erythrocyte sedimentation rate, C-reactive protein) were recorded. Last, data on the surgical treatment, antifungal therapy (monotherapy vs. combination therapy), antifungal regimen (agents, dose, duration), and outcome (complete resolution, partial resolution, recurrence, death from a non-infectious cause, death related to aspergillosis) were also extracted for each case.

Descriptive statistics were used to present the extracted data. Due to the high heterogeneity in extracted data, analysis of these data as a formal meta-analysis was not considered feasible, and only limited data analysis regarding the association between treatment and outcome was performed. Specifically, the infection resolution rate was compared between patients who received only antifungal therapy vs. patients who additionally underwent surgical debridement, between patients who received monotherapy vs. patients who received combination therapy, and between patients who received amphotericin B or voriconazole as monotherapy. Comparisons were performed using the chi square statistical test. Last, propensity score matching was performed using logistic regression models to reduce selection bias and adjust the comparison between patients who received amphotericin B and those who received voriconazole for certain confounding factors including age, gender, and underlying condition. The statistical analysis was performed using the Stata 15.0 software (Stata Corp., College Station, TX, USA), while a *P*-value lower than 0.05 indicated statistical significance.

## Results

### Study characteristics and patient demographics

Our search algorithm identified 1,132 records in PubMed database and 1,116 records in Scopus database, while 8



**Figure 1.** Flow diagram depicting the flow of information through the different phases of the systematic review.

records were also identified through manual search of the reference lists of the articles that underwent full text review (Fig. 1). Following removal of duplicates from the retrieved articles, our search resulted in 1,591 records. After reviewing the abstracts/titles of these articles, 1,368 articles were considered clearly irrelevant to the topic of interest and were excluded, mainly because they were evaluating different pathogens, or they were not on humans. In a following step, 223 articles underwent detailed evaluation through full text review, and 75 of these were excluded because they did not provide sufficient information based on the inclusion criteria of our review protocol. Therefore, 148 studies including 186 patients met the eligibility criteria of this review and were included.<sup>8–155</sup> The included studies were conducted over a period from 1965 to 2021. All included studies were case reports or small case series with up to 7 cases, while there were no cohort comparative studies. In particular, among the 148 studies, there were 130 studies reporting just one case, 11 studies reporting 2 cases, 2 studies reporting 3 cases, 2 studies reporting 4 cases, 1 study reporting 5 cases, 1 study reporting 6 cases, and 1 study reporting 7 cases.

The median age of the 186 patients was 44 (Interquartile Range [IQR]: 20–60) years, while osteoarticular aspergillosis was more common in men (125 males, 67.2%). There were 30 (16.1%) pediatric cases (<14 year-old) among the included cases. The most common underlying condition in these pa-

tients was chronic granulomatous disease ( $n = 35$ , 18.8%), a genetic disorder characterized by immunodeficiency, followed by hematologic neoplasia ( $n = 30$ , 16.1%), other causes of immunodeficiency (immunosuppression therapy or other immunodeficiency disorder;  $n = 23$ , 12.3%) and diabetes ( $n = 23$ , 12.3%). Moreover, 33 (17.7%) patients were on corticosteroids when they developed osteoarticular infection from *Aspergillus* spp., while 11 (5.9%) patients were IV drug users. For 21 patients (11.2%) relevant information about presence of any underlying condition was missing. The demographics and comorbidities of the study population are summarized in Table 1.

### Location and route of infection

Overall, 192 infected foci were identified in the 186 included patients. Osteoarticular aspergillosis in two different anatomic locations was evident in 6 (3.2%) patients. Aspergillosis was located in spine causing spondylodiscitis with or without abscesses in 100 out of the 192 infected locations (52.0%), while the second most common location included the osseous structures of the thoracic cavity including the ribs and the sternum (18.2%, **Supplementary Table 1**). Other common locations for these infections included the long bones of lower extremities ( $n = 9$ , 4.6%) and the bones of the foot ( $n = 6$ , 3.1%), while the cranial bones ( $n = 9$ , 4.6%) and the maxilla/mandible ( $n = 5$ , 2.6%) were also commonly

**Table 1.** Demographics of the study population.

Variables	Patients (n = 186)
Age (years)	40.9 ± 21.4, 44 (20–60)
Gender (male)	125 (67.2)
Comorbidities/Underlying condition	
Chronic granulomatous disease	35 (18.8)
Hematologic neoplasia	30 (16.1)
Immunodeficiency/immunosuppression	23 (12.3)
therapy	23 (12.3)
Diabetes	14 (7.5)
Tuberculosis	15 (8.0)
Other	11 (5.9)
IV drug users	14 (7.5)
None	21 (11.2)
Not mentioned	
Corticosteroids	33 (17.7)

Data are presented as means ± SD, medians and IQR, or as absolute frequencies (percentages) when appropriate.

infected. Last, septic arthritis due to aspergillosis was evident in 22 (11.3%) patients, with the knee being the most commonly infected joint ( $n = 10$ , 5.2%).

The route of infections varied based on the location of the infection. Overall, the most common route of infection overall was contiguous spread ( $n = 72$ , 37.5%) followed by direct inoculation after surgery or trauma in 64 cases (33.3%; 25 cases following surgery and 39 cases following trauma) and hematogenous spread in 56 cases (29.1%, **Supplementary Table 1**). Hematogenous spread was the most common route for spinal ( $n = 42$ , 42.0%) and cranial infections ( $n = 4$ , 44.3%), while for infections in the osseous structures of the thoracic cavity the most common route was contiguous spread ( $n = 25$ , 71.4%). Conversely, direct inoculation was the most common cause for aspergillosis in joints ( $n = 14$ , 63.6%).

Pulmonary involvement was evident in 41 patients (22.0%) with osteoarticular infection from *Aspergillus* spp. Among these 41 patients, the osteoarticular infection was located in

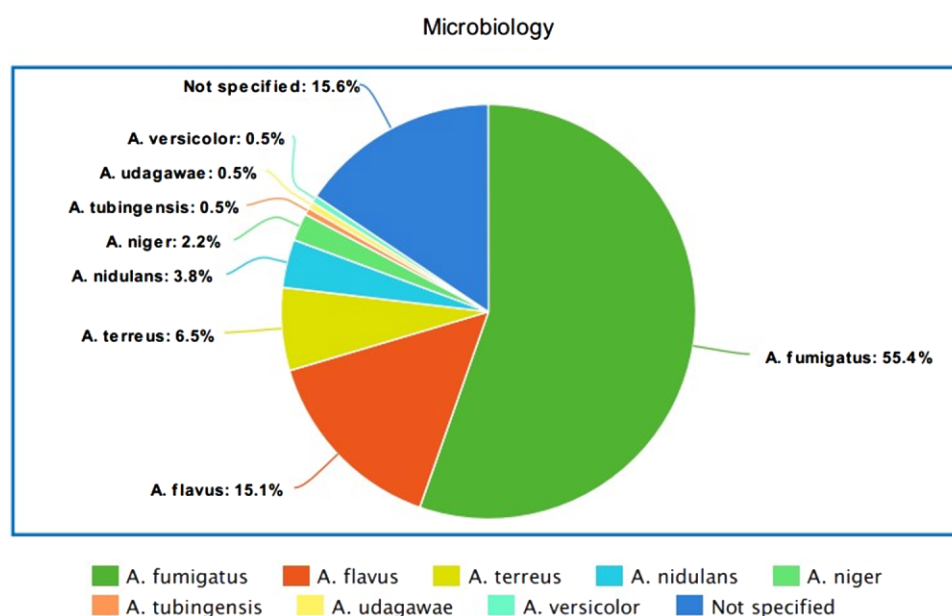
the osseous structures of the thoracic cavity in 25 patients, in the spine in 13 patients, and in the cranial bones in 3 patients.

### Microbiology and markers of inflammation

In the majority of patients the fungal infections were caused by *A. fumigatus* ( $n = 103$ , 55.3%), while other common *Aspergillus* spp. causing bone and joint infections included *A. flavus* in 28 patients (15%), *A. terreus* in 12 patients (6.4%), and *A. nidulans* in 7 patients (3.7%, Fig. 2). In 29 cases (15.6%) the pathogen was not specified. Interestingly, concomitant bacterial infections were reported in 13 patients (6.9%), with the most common co-cultured pathogens being *Staphylococcus* spp. ( $n = 7$ , 3.7%) followed by *Enterobacteriaceae* ( $n = 4$ , 2.1%) and *Pseudomonas aeruginosa* ( $n = 2$ , 1.0%).

In 92 (49.4%) patients *Aspergillus* osteomyelitis was diagnosed by positive cultures, while in 84 (45.1%) *Aspergillus* spp. were detected by both cultures and histological examination. In 5 (2.6%) patients the diagnosis was established by positive cultures and positive Polymerase Chain Reaction (PCR), and in 4 (2.1%) patients aspergillosis was confirmed by positive cultures and elevated serum galactomannan index, a fungal cell wall component. Regarding the 6 patients with positive PCR for *Aspergillus* spp., PCR analysis was performed on tissue sample in 4 patients, while in 2 patients the source of the specimen for the PCR analysis was not reported. Moreover, in 1 (0.5%) patient aspergillosis was diagnosed by positive cultures, histology examination, and positive serological findings (elevated serum galactomannan index, Table 2).

Regarding the markers of inflammation, the median WBC count was 8.700 (IQR: 6.000–12.500)/ml, while the median C Reactive Protein (CRP) was 52 (IQR: 24–105) mg/L. Interestingly, WBC count was elevated ( $> 12.000$ /ml) only in 61 (32.7%) patients with osteoarticular aspergillosis, as opposed to CRP levels which were abnormal in 168 patients (90.3%; Table 2). Information about WBC count and CRP levels were missing for 25 patients (13.4%) and 18 patients

**Figure 2.** Microbiology of *Aspergillus* species. Mycological identification was performed through direct culture, histologic examination, and PCR analysis.



**Table 2.** Diagnostic studies and markers of inflammation.

Studies	Patients ( <i>n</i> = 186)
Direct culture	92 (49.4)
Histology and direct culture	84 (45.1)
Direct culture and PCR	5 (2.6)
Direct cultures and serology	4 (2.1)
Direct cultures, histology and PCR	1 (0.5)
WBC count ( $\times 10^3/\text{ml}$ )	$9.3 \pm 4.5, 8.7 (6.0\text{--}12.5)$
*Abnormal WBC count ( $>12 \times 10^3/\text{ml}$ )	61 (32.7)
CRP (mg/L)	$78.4 \pm 69.8, 52.0 (24.0\text{--}105.0)$
*Abnormal CRP ( $>10 \text{ mg/L}$ )	168 (90.3)

Data are presented as means  $\pm$  SD, medians and IQR, or as absolute frequencies (percentages) when appropriate.

Abbreviations: PCR, Polymerase Chain Reaction; WBC, White Blood Cell; ESR, Erythrocyte Sedimentation Rate; CRP, C Reactive Protein.

\*WBC count and CRP levels were missing for 25 and 18 patients, respectively.

(9.6%), respectively. In 2 immunocompromised patients (1.0%) severe neutropenia ( $<500 \text{ cells/ml}$ ) was also reported.

### Antifungal agents, protocols, and treatment outcomes

The antifungal regimens, the duration of treatment, and the rates of complete resolution are summarized in Table 3. Overall, 107 (57.5%) patients underwent surgical debridement in addition to antifungal therapy, while 79 (42.5%) patients were treated conservatively and received antifungal therapy. Although in most studies the indications for surgical treatment were not reported, the authors of some studies reported failed conservative treatment and clinical deterioration as surgical indications. Moreover, the location of the infection was associated with the decision for surgical treatment since all patients with septic arthritis (22 patients) and most patients with infection in lower/upper extremities (16 patients) underwent surgical treatment, as opposed to patients with infections in other locations such as in spine, who were mostly treated

conservatively. The duration of antifungal treatment was similar between patients who were treated surgically and those who were treated conservatively (medians: 145 days vs. 120 days,  $P = 0.79$ ).

Regarding the antifungal treatment, 120 (64.5%) patients received antifungal monotherapy while the rest 66 (34.5%) received a combination/sequential therapy. Fifty-five (29.5%) patients received amphotericin B (either liposomal or deoxycholate) as monotherapy, 46 (24.7%) patients received voriconazole as monotherapy, and 16 (8.6%) patients received itraconazole as monotherapy. Moreover, 28 (15.0%) patients received a combination/sequential therapy with amphotericin B and itraconazole, 15 (8.0%) patients received a combination/sequential therapy with amphotericin B and 5-Fluorocytosine, and 8 (4.3%) received a combination/sequential therapy with amphotericin B and voriconazole. Overall, amphotericin B was administered in 114 (61.2%) patients (amphotericin B deoxycholate in 28 patients, liposomal amphotericin B in 56 patients, and not defined in 30 patients). Voriconazole was the second most common antifungal agent administered in 61 (32.7%) patients with a median daily dose of 400 (380–460) mg, and itraconazole was the third most commonly used antifungal agent, administered in 48 (25.8%) patients with median daily dose of 400 (IQR: 400–400) mg (Supplementary Table 2).

Regarding the outcome, complete resolution of the infection was reported in 107 (57.5%) patients, while partial resolution was reported in 29 (15.5%) patients and recurrence of the infection in 17 (9.1%) patients (Table 4). The median time of recurrence after the end of the antifungal treatment was 4.2 (IQR: 2.1–6.9) months. The overall mortality rate was 16.1% ( $n = 30$ ). In most deceased patients ( $n = 27, 14.5\%$ ) their death was not related to aspergillosis, while death related to aspergillosis was reported in 3 (1.6%) patients. Complete resolution of the infection was more common in patients who were treated surgically ( $n = 75, 70.0\%$ ) in addition to antifungal therapy, compared to those who received only antifungal therapy ( $n = 32, 40.5\%$ ,  $P < 0.001$ ). Conversely, patients who received antifungal monotherapy and patients who

**Table 3.** Treatment protocols and rates of complete infection resolution.

Treatment modalities	Patients ( <i>n</i> = 186)	Duration (days)	Complete resolution
Total	186 (100)	$155.5 \pm 110.9,$ 126 (63–190)	107 (57.5)
Amphotericin B monotherapy	55 (29.5)	$62.1 \pm 40.1,$ 56 (30–70)	32 (58.1)
Voriconazole monotherapy	46 (24.7)	$158.2 \pm 94.2,$ 140 (97–180)	27 (58.6)
Amphotericin B + Itraconazole	28 (15.0)	$164.9 \pm 143.0,$ 112 (70–201)	16 (57.1)
Itraconazole monotherapy	16 (8.6)	$204.0 \pm 125.2,$ 180 (90–328)	8 (50.0)
Amphotericin B + 5-Fluorocytosine	15 (8.0)	$66.0 \pm 22.6,$ 63 (45–90)	6 (40.0)
Amphotericin B + Voriconazole	8 (4.3)	$158.4 \pm 90.4,$ 144 (105–204)	3 (37.5)
Other antifungal regimes	34 (18.2)	$120.9 \pm 50.4,$ 110 (80–150)	15 (44.1)
Surgical debridement	107 (57.5)	$155.3 \pm 104.6,$ 145 (60–194)	75 (70.0)
Conservative treatment	79 (42.5)	$155.9 \pm 80.1,$ 120 (20–180)	32 (40.5)

Data are presented as means  $\pm$  SD, medians and IQR, or as absolute frequencies (percentages) when appropriate.

**Table 4.** Outcome and survival rates.

Outcome	Patients ( <i>n</i> = 186)	Duration of treatment (days)
Complete resolution	107 (57.5)	167.2 ± 114.9, 144 (70–201)
Partial resolution	29 (15.5)	168.0 ± 59.8, 160 (119–217)
Recurrence	17 (9.1)	186.7 ± 111.1, 202.5 (103.5–270)
Death due to fungal sepsis	3 (1.6)	60.6 ± 42.6, 40 (36–124)
Death due to other reasons	30 (16.1)	64.6 ± 49.6, 45 (30–112)

Data are presented as means ± SD, medians and IQR, or as absolute frequencies (percentages) when appropriate.

received combination/sequential antifungal therapy had similar rate of complete infection resolution (*n* = 70, 58.3% vs. *n* = 36, 54.5%; *P* = 0.76). Last, the rate of complete infection resolution was also similar between patients who received amphotericin B as monotherapy (*n* = 32, 58.1%) and patients who received voriconazole as monotherapy (*n* = 27, 58.6%; *P* = 0.95). The rate of complete infection resolution was also similar for amphotericin B and voriconazole after propensity score matching adjusted for age, gender, and underlying condition (Odds Ratio: 1.14, 95% Confidence Interval: 0.92–1.41, *P* = 0.22).

## Discussion

Although osteoarticular infections due to *Aspergillus* spp. are relatively uncommon, they can present with increased frequency in patients with certain comorbidities such as immunodeficiency disorders. However, there are only small studies with proven osteoarticular aspergillosis that provide sufficient data regarding the diagnosis, treatment, and outcome of these infections. These small studies lack numerical power for any comparative outcomes. This is also reflected by the results of our systematic review, since 87% of the included studies were case reports, while only 2 studies included more than 5 patients. This systematic review reported on the outcomes of 186 patients with proven osteoarticular aspergillosis who received several different antifungal regimes with or without surgical treatment. Our results indicate that monotherapy is as effective as combination or sequential therapy, while voriconazole has similar efficacy with amphotericin B as monotherapy. Moreover, the better outcomes that were seen in surgically treated patients highlight the importance of surgical debridement of the infected focus for the successful treatment of osteoarticular aspergillosis.

The higher incidence of osteoarticular aspergillosis in immunocompromised patients was also confirmed by the results of our study. Specifically, 18.8% of the patients had chronic granulomatous disease, a genetic disorder that results in immunodeficiency, while 12.3% of them suffered from another immunodeficiency disorder or they were receiving immunosuppression therapy. In addition, hematologic neoplasia was reported in 16.1% of the included patients and corticosteroids in 17.7% of the patients. All these conditions are associated with immunodeficiency and susceptibility to fungal infections. Chronic granulomatous disease has been also identified by other studies as a predominant immunodeficiency disorder in patients with osteoarticular aspergillosis. Gamaletsou et al. conducted a systematic review evaluating 180 patients with proven or suspected osteoarticular aspergillosis and reported that chronic granulomatous disease was evident in 12.7% of all cases and in 73% of pediatric cases, while in our study chronic granulomatous disease was

evident in even more patients (18.8% of all cases and 85% of pediatric cases [*<*16 years]).<sup>156</sup>

The most commonly isolated pathogen in our study was *A. fumigatus* (55.3%), followed by *A. flavus* (15.0%). Although this is similar to other studies in which *A. fumigatus* and *A. flavus* were also identified as the most common *Aspergillus* species, microbiology varied based on the age and the comorbidities of our population. *A. nidulans* was more frequently reported in younger patients, probably due to the higher incidence of primary immunodeficiency in this age group, while it was the most common pathogen in patients with chronic granulomatous disease (45%). This finding is consistent with the review study of Dotis et al. who reported on 46 cases of osteoarticular aspergillosis in patients with chronic granulomatous disease.<sup>157</sup> Dotis et al. revealed that infections from *A. nidulans* were more common in these patients and were associated with higher mortality compared to other *Aspergillus* species.

Our results indicate that the route of infection varies depending on the location of the infection. Specifically, hematogenous spread was the most common route for spinal infection, while costal aspergillosis was associated with contiguous spread, and aspergillosis in lower and upper extremities was associated with direct inoculation following surgery or trauma. Hematogenous spread is the most common mechanism for both bacterial and fungal spondylodiscitis, while contiguous transpleural dissemination from a pulmonary focus is also commonly involved in spinal infections. Clinicians should consider the possibility of spinal aspergillosis in patients with pulmonary aspergillosis who complain of back pain, and should have a low threshold for ordering imaging studies to diagnose or rule out vertebral involvement. The predominance of contiguous spread in cases of costal aspergillosis also indicates direct extension from pulmonary foci due to the close proximity with these foci. Similar to spinal infections, further imaging evaluation with a CT scan (using bone window) or MRI is necessary in patients with pulmonary aspergillosis and persistent pleuritic pain, since these patients may also need surgical debridement in addition to the antifungal therapy for the successful eradication of the costal foci. As opposed to spinal and costal aspergillosis, direct inoculation was reported as the most common route in cases of infections in the upper and lower extremities, as well as in case of sternal aspergillosis. This highlights the importance of perioperative preventive measures in immunocompromised patients, while clinicians should consider these pathogens in case of posttraumatic or postoperative signs of infections in this population.

The high heterogeneity in the antifungal therapy for the treatment of osteoarticular aspergillosis was also reflected by the results of our study. Our results indicate that antifungal monotherapy has similar outcomes with antifungal combination/sequential therapy, while also amphotericin B

monotherapy has similar outcomes with voriconazole monotherapy. The overall safety profile and pharmacokinetics of voriconazole are preferable than that of amphotericin B. This is also reflected by the Infectious Diseases Society of America (IDSA) guidelines which recommend voriconazole as the primary antifungal agent and liposomal amphotericin B as an alternative option for the treatment of osteoarticular aspergillosis.<sup>158</sup> Amphotericin B is associated with significant nephrotoxicity, while the prolonged venous access for its administration is another significant disadvantage associated with certain complications such as thrombophlebitis and systemic infections. On the other hand, voriconazole has the flexibility of both parenteral and oral administration, and although it is also associated with certain adverse events such as solar hypersensitivity, it has minor nephrotoxicity and is considered a safer option compared to amphotericin B. Voriconazole has acceptable oral bioavailability (45–75% in children and 90% in adults), however, prolonged therapy can result in autoinduction of metabolism with decreasing levels.<sup>159</sup> Therefore, monitoring of trough levels after establishment of initial therapeutic levels is recommended in patients who receive voriconazole to detect off-target trough levels due to autoinduction, which will require subsequent dose adjustments.<sup>160</sup>

The median duration of antifungal treatment was 5 months (155 days). Based on the IDSA guidelines, the recommended duration of therapy is at least 8 weeks–6 months.<sup>158</sup> However, this recommendation is based upon small case series and expert opinion, while the wide range of the recommended duration also reflects the lack of high-quality evidence for the treatment of these infections. The minimum recommended duration of 60 days is in line only with the amphotericin B treatment as monotherapy (median duration 56 days in our study), while the median duration of all other antifungal regimes was significantly longer. The median duration of antifungal treatment in our study was also longer than the respective duration of medical treatment that was reported in the systematic review by Gamaletsou et al. (90 days), despite the fact that number of patients who received amphotericin B as monotherapy was comparable between the two studies.<sup>156</sup> Prospective studies are needed to evaluate whether shorter antifungal therapies have comparable results with prolonged treatments. Last, we found that surgical debridement of the infected focus results in better outcomes in terms of infection eradication and is associated with lower relapse rate, which is consistent with the IDSA guidelines and the results of other studies that also highlight the importance of surgical treatment.<sup>161</sup> However, the decision for surgical treatment should be based on several factors, such as patient's comorbidities and the location of the infection. The risk/benefit ratio of surgical treatment widely varies based on the location of the infection. The results of surgical treatment in terms of infection eradication are not the same for all locations. Moreover, surgery in certain locations is associated with higher morbidity than in other locations, since, for example, the risk of spine surgery is significantly higher than the risk of a surgical debridement of a toe infection.

Our systematic review is the largest review with biopsy proven *Aspergillus* spp. osteoarticular infection and extensive comparison of different treatment strategies. In our review, we identified 186 patients, while another systematic review by Gamaletsou et al. included a similar number of cases (180 patients).<sup>156</sup> However, almost half of the patients in the re-

view by Gamaletsou et al. were 'probable' cases and not confirmed cases by biopsy. Probable cases were patients with clinical and radiological signs indicative of osteomyelitis with positive culture of *Aspergillus* spp. from another location other than the bone, such as patients with pulmonary aspergillosis. However, the possibility of a bacterial and not *Aspergillus* spp. osteomyelitis in these cases cannot be excluded, therefore, the true number of *Aspergillus* spp. osteoarticular infections in that review may be significantly lower. Moreover, our review is the first systematic review including only cases with full available data regarding significant parameters such as the treatment strategy (antifungal agents, surgical treatment) and the final outcome (complete vs. partial resolution, recurrence, death) of these infections, therefore, we eliminated any bias resulting from missing data. Last, we conducted a more comprehensive analysis of the collected data than any other systematic review, comparing surgical vs. conservative treatment, antifungal monotherapy vs. combination/sequential therapy, and amphotericin B vs. voriconazole in terms of infection resolution.

There are some limitations of this systematic review that must be also addressed. Due to publication bias, our results may reveal better treatment outcomes than the real success rate, since studies with positive results are more likely to be published. However, our strict inclusion criteria for studies with only detailed report of their outcomes minimize this risk, which is also shown by the fact that the rate of complete resolution of the infection in our study was lower than that reported in other recent systematic reviews. Moreover, the data that were analyzed for the comparisons of the different treatment approaches (antifungal agents, surgical treatment, monotherapy vs. combination therapy) are from small studies rather than high level large studies, therefore, the results of these comparisons should be interpreted with caution. However, the large number of included cases provides valuable information regarding the management of these infections. Another limitation is that the comparison of resolution rates between groups of patients receiving different therapeutic interventions is of observational nature and, thus, may have been affected by bias (confounding by indication). The treatment allocation was not randomized, and the indication of treatment might be related to the risk of outcomes; thus, the resulting imbalance in the underlying profiles between groups of patients receiving different treatments might generate biased results. Several factors such as the age and the underlying condition of the patients may affect the success rate of any treatment intervention. These confounding factors were not taken into consideration, and the comparison between the different treatment groups was not adjusted for these confounding factors. The comparison of the resolution rates between the different treatment modalities should be also interpreted with caution because the total follow up is not reported in many cases, therefore, estimations about the recurrence rate and the rate of complete/incomplete resolution can be biased by the heterogeneity in the duration of the follow up of the included patients. Last, the different time periods of the included studies is another potential bias, since different time periods are related to different diagnostic/treatment approaches and different antifungal agents.

In conclusion, osteoarticular aspergillosis should be considered in cases of immunocompromised patients with signs of infection and musculoskeletal symptoms such as low back pain or pleuritic pain. Prompt diagnosis of osteoarticular

aspergillosis is essential since surgical debridement is crucial for its successful treatment as shown by the results of this review, whereas in bacterial infections the indications for surgical treatment can be more conservative. Moreover, the results of this study indicate that antifungal monotherapy is as effective as combination/sequential therapy, minimizing the risk of adverse events from antifungal agents. Last, voriconazole monotherapy have comparable results with amphotericin B monotherapy, and its favorable characteristics in terms of safety and route of administration makes voriconazole the recommended antifungal agent for the treatment of *Aspergillus* spp. osteoarticular infections. The duration of antifungal therapy highly varies in the literature, therefore, large prospective, carefully designed and adequately powered studies are warranted in order to identify the optimal duration of antifungal therapy.

## Supplementary material

Supplementary material is available at [Medical Mycology](#) online.

## Declaration of interest

The authors have no financial, consultant, institutional, and other relationships that might lead to bias or conflict of interest.

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