Fungal Infections of the Bones and Joints

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Osteoarticular complications may occur with a variety of invasive fungal infections, and seem to be increasing with growing use of prosthetic joints and as the immuno-suppressed patient population increases. Epidemiology, pathogenesis, presentation, and management strategies differ somewhat among the different fungal species. This review focuses on recent developments in diagnostic and management approaches for patients with osteoarticular mycoses, and outlines specific treatment strategies for the different species.

Introduction

Osteomyelitis and arthritis can be serious complications of fungal infection and require long courses of therapy. Osteoarticular involvement has been reported among adults, children, and neonates with invasive infections due to a number of fungal pathogens, including Candida species, Aspergillus species, Sporothrix schenckii, Coccioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Histoplasma capsulatum and Histoplasma duboisi, Cryptococcus neoforms, and other more rare fungi such as Pseudallescheria boydii, Curvularia species, Fusarium species, Exophiala jeanselmei, and Penicillium marneffei. In the past several years, incidence of these infections appears to be increasing, paralleling the overall increase in incidence of fungal infections. New diagnostic techniques may enable improved diagnosis of these infections, enabling earlier and more effective management of these serious infections. In general, the risk factors for development of mycotic osteoarthritis have not been well defined, but appear to be similar to those identified for invasive fungal infection. The epidemiology, pathogenesis, clinical presentation, and management strategy vary somewhat among the different fungal pathogens. In this paper, we will discuss the most common of these infections in more detail, with a focus on developments in the past few years.

Candida species

Candida organisms are commensal yeasts that cause invasive, mucosal, and superficial infections in humans. Although over 200 Candida species have been identified, nine species cause the majority of human candidal infections. Candida albicans has been the most common Candida species described in invasive fungal infections, although in recent years the nonalbicans Candida species have been reported with increasing frequency. Nonalbicans Candida species are the predominant pathogens among patients with nosocomial candidemia in some centers in the northeastern and southeastern United States [1]. Similarly, at Duke University Medical Center, Candida tropicalis has become the predominant pathogen isolated among neutropenic patients while Candida glabrata has been isolated with increasing frequency among surgical patients with candidemia. Since these species are often resistant to conventional antifungal therapies and have been associated with higher mortality than C. albicans, management of systemic nonalbicans candidal infections requires special consideration. Candidal arthritis and osteomyelitis have been most frequently reported in the context of C. albicans, although infections due to C. glabrata, C. tropicalis, Candida parapsilosis, Candida lusitaniae, Candida guillermondii, Candida zeylanoides, and others have also occurred [2]. In prosthetic joints, less pathogenic fungi such as C. parapsilosis may cause infection. In a recent review of candidal vertebral osteomyelitis, Miller and Mejicano [3•] found C. albicans in 57%, C. tropicalis in 17%, C. glabrata in 12%, C. parapsilosis in 3%, Candida kefyr in 2%, and C. guilliermondii in 2% of 57 culture-confirmed cases. In addition, mixed infection with C. tropicalis and C. glabrata was observed in one case.

Despite the emergence of candidemia as the fourth most common cause of bloodstream infections in hospitalized patients, Candida osteomyelitis and arthritis remain relatively rare [4]. The mechanism of infection in most cases of candidal arthritis is due to hematogenous spread, occurring in 1% to 2% of patients with systemic candidiasis [5]. Dissemination of Candida after injection of heroin intravenously has also been reported, often with skin, ocular, as well as osteoarticular involvement [6]. Direct inoculation of the joint space via intra-articular injection may also occur, such as after intra-articular corticosteroid injections or arthrocentesis. Direct inoculation of Candida species may also occur through surgical procedures or
trauma, and is aided by selective pressure of antibacterials, resulting in development of sternal osteomyelitis such as the occasional case of sternal osteomyelitis after median sternotomy for heart surgery.

No prospective studies have specifically evaluated risk factors for development of osteoarticular *Candida* infection, but they are presumed to be similar to risk factors for candidal bloodstream infections. In adults, risk factors for candidemia have been identified in several series and include indwelling intravascular catheters; prior surgery; malignancy; intensive care unit hospitalization; and receipt of antibiotics, chemotherapy, steroids, and parenteral nutrition. Cases of candidal osteomyelitis have recently been reported among liver transplant recipients, patients receiving hyperalimentation, those with HIV infection, patients undergoing bone marrow transplantation, and those with other underlying immunosuppression [7–10]. Intravenous heroin injection, in particular brown heroin with lemon juice, has been associated with candidal infection that includes characteristic skin and osteoarticular involvement [11]. In cases of vertebral osteomyelitis, risk factors such as presence of a central venous catheter (53%), prior antibiotic therapy (50%), immunosuppression (37%), and intravenous drug abuse (22%) have been present in a significant number of cases [3•].

*Candida* arthritis has also been reported among patients with prosthetic joints, in the absence of previously documented candidemia [12]. In these cases, classic risk factors for invasive fungal infection are often absent. These cases may represent contamination or direct implantation of fungus at the time of surgery or soon afterwards in the setting of antibacterial prophylaxis or treatment. These reports are rare, with less than 25 cases in the literature. Cases in clinical practice are probably increasing as a result of increasing use of joint prostheses. For instance, in 1995 Hansen and Andersen [13] reviewed 45 cases of candidal arthritis, and a prosthetic joint was the predisposing factor in 17 of these cases. Intraarticular glucocorticoid injection was the predisposing factor in six cases, all of which involved the knee. Five patients had received organ transplantation and subsequent immunosuppressive therapy, and one of these patients also had a prothetic joint and another had received an intra-articular glucocorticoid injection.

In adult patients, bones of the axial skeleton are primarily involved in candidal osteomyelitis, while in neonates, involvement of the long bones and extremities is more common. In reported cases of candidal osteomyelitis in adults, the vertebral and intervertebral disks are the most commonly affected sites and most often arise from seeding during hematogenous spread. In a recent review, 95% of vertebral osteomyelitis cases involved the lower thoracic or lumbosacral spine [3•]. Other sites include long bones such as the femur or fibula, the sternum, and costochondral junction of the ribs, scapula, and proximal humerus (especially among intravenous heroin users). Candidal mediastinitis with yeast involvement of sternum and costochondral junctions has become an increasingly recognized entity [14].

*Candida* arthritis can occur in any joint, and has been reported to occur in multiple joints in up to 37% of cases. The knee is the most commonly affected site for all fungal arthritis including *Candida*, but infection of hips, shoulders, and ankles occasionally occurs.

In adults, candidal osteomyelitis frequently presents as a late complication of candidemia, and has generally been reported to occur 2 to 15 months after the initial *Candida* bloodstream infection [15]. Patients usually present with clinical signs or symptoms that are classical for osteomyelitis, including localized bone or joint pain, swelling, or drainage from soft tissues. Fever characterizes less than half of reported cases, and a contiguous palpable abscess may be present in some cases [15]. Among patients with vertebral osteomyelitis, elevated erythrocyte sedimentation rate was the most remarkable clinical laboratory abnormality noted, and was present in 87% of 59 cases. Elevated leukocyte count was only noted in 17% of cases [3•].

Two types of presentations have been described among patients with candidal arthritis: 1) those with acute onset with obvious synovial and systemic symptoms, and 2) those with a milder or more chronic clinical course with little pain and few synovial or systemic symptoms. The former cases may be diagnosed early in the course of disseminated infection, while those with the more insidious onset may experience diagnostic delay of several months to years, and are more common in the presence of prosthetic material.

Isolation of *Candida* species from bone biopsy, curettage, or synovial fluid from joints is important for accurate diagnosis of osteomyelitis or arthritis. Histopathologic confirmation of infection is extremely helpful. As with bacteria, cultures from superficial wounds, overlying ulcers, and fistulae are not reliable.

In the most recent review of *Candida* osteomyelitis cases in the literature, Gathe et al. [15] reported a delay of more than 1 month from the onset of symptoms to diagnosis of osteomyelitis in 83% of cases. Miller and Mejican [3•] reported a similar rate for cases of vertebral osteomyelitis, with 83% having symptoms for at least 1 month and 29% having symptoms for more than 3 months prior to the diagnosis. Thus, new diagnostic strategies or more aggressive collection of specimens from bones and joints are critical for earlier detection and diagnosis. Laboratory assays under investigation include measurement of glucan in body fluids and urinary D-arabinitol/L-arabinitol ratio. Recently, Eisen et al. [16] reported a case of vertebral osteomyelitis due to *C. tropicalis* in which elevated urinary ratios of D-arabinitol/L-arabinitol indicated ongoing deep-seated infection after the initial episode of candidemia. However, this strategy has yet to be evaluated in clinical trials.

**Management**

As recently outlined by the Infectious Diseases Society of America (IDSA), appropriate management of candidal
osteomyelitis involves two principles: surgical intervention and systemic antifungal therapy [17••]. In the case of candidal arthritis, systemic antifungal therapy plus joint drainage, joint lavage, or removal of infected prosthetic material may be necessary to achieve a consistent cure. Open drainage is particularly critical in the case of candidal arthritis of the native hip [17••]. In almost all cases of prosthetic joint arthritis, removal of the prosthesis is necessary for cure, and suppressive antifungal regimens alone are recommended only for cases in which cure is not the primary endpoint. In 1998, Brooks and Pupparo [18] reported the first case of candidal prosthetic joint infection in which the primary prosthesis was salvaged, but this is probably a rare occurrence. A new prosthesis may be replaced after initial antifungal therapy is completed and when there are no signs of infection. In most cases of successfully treated candidal osteomyelitis and arthritis, long-term antifungal therapy (up to 1 year) was administered as a regimen of choice. This prolonged course is usually followed with the use of azoles.

The gold standard for treatment of candidal osteomyelitis and arthritis is intravenous amphotericin B. There is no consensus regarding duration of therapy or total amphotericin B dose, but treatment has been recommended to continue for at least 2 to 4 weeks after resolution of clinical signs or symptoms of infection resolve and/or there is microbiologic evidence of eradication of infection [19]. Usual daily doses range from 0.5 to 0.6 mg/kg/d and are typically administered for 6 to 10 weeks [6,17••]. Intra-articular injections of amphotericin B have also been successfully used in addition to systemic amphotericin B in some cases of candidal arthritis [2,20]. However, amphotericin B could irritate the joint surfaces and cause more inflammation when injected locally. Substantial synovial fluid levels are achieved with intravenous administration of amphotericin B (20%–100% of serum level), so intra-articular antifungal injections are discouraged [17••].

Lipid formulations of amphotericin B have been used to treat candidal osteomyelitis and arthritis in situations where nephrotoxicity limited the use of amphotericin B deoxycholate. Both liposomal amphotericin B (AmBisome, Fujisawa Healthcare, Inc., Deerfield, IL) and amphotericin B colloidal dispersion have been used in this context [19]. No comparative trials have proposed dosing or demonstrated efficacy of lipid amphotericin B preparations in the treatment of candidal osteoarticular infections, so these agents should be reserved for those who are intolerant or refractory to other therapies.

Amphotericin B deoxycholate and lipid preparations have also been used in concert with fluconazole, with variable clinical success. Fluconazole may be synergistic in some cases of candidal infection, but combination therapy has not been demonstrated to improve clinical outcomes when compared with amphotericin B alone and should be left to the experience of the treating clinician. Fluconazole monotherapy is not recommended for bone and joint infections due to rapid development of drug resistance in these infections, which have the potential for a large burden of yeasts.

Fluconazole is a triazole antifungal that is available both in intravenous and oral preparations, and has been shown to be equally efficacious as amphotericin B deoxycholate in treating candidemia among non-neutropenic patients. Bone penetration of fluconazole is reportedly poor, and in a study using positron emission tomographic scanning for radiolabeled drug after a 400-mg dose, penetration of fluconazole into bone approximated 30% of corresponding blood levels [22]. Mean plateau concentrations in bone were 1.29 ± 0.29 μg/g, which are well below the 6 μg/g that is suggested for most strains of Candida. In contrast, synovial fluid concentrations have been estimated to reach 90% to 100% that of plasma [22–24]. The role of azoles to treat fungal osteoarticular infections was reviewed by Perez-Gomez et al. [6] in 1998. In all cases of candidal osteomyelitis and arthritis, fluconazole was the azole employed. In several cases, fluconazole was successfully used as first-line therapy, but therapeutic failures that later responded to amphotericin B have also been reported [25–28]. Of 17 cases reviewed in one series, 81% were successfully treated. Doses ranged from 100 mg to 400 mg fluconazole per day, with a duration of therapy of 4 weeks to 10 months. We recommend the higher dose in patients with normal renal function [6]. Inadequate doses of fluconazole have been associated with therapeutic failure. Thus, appropriate dosing is especially important among patients with altered clearance, such as those undergoing continuous arteriovenous hemodiafiltration (CAVHD) or continuous venovenous hemodialysis (CVVHD). Clearance of fluconazole among patients undergoing CAVHD has been reported to be similar to that of patients with normal renal function, so similar daily doses should be used. Dose reduction of fluconazole is only recommended for those with creatinine clearances less than 50 mL/min or those undergoing continuous ambulatory peritoneal dialysis or intermittent hemodialysis.

Direct azole resistance among Candida species may be associated with therapeutic failure, although no such cases among patients with osteoarticular complications have been reported. Incidence of fluconazole resistance may be increased among those who have received the drug previously, so azole resistance should be considered among patients who develop osteoarticular complications after receiving fluconazole or those who relapse after initial azole therapy. In vitro testing may help identify these strains.

As outlined by the recent guidelines published by the IDSA, an appropriate management strategy for candidal osteomyelitis includes intravenous amphotericin B for 2 to 3 weeks and then fluconazole for a total of 6 to 12 months. Prolonged courses of antifungal therapy for 2 to 6 weeks (in concert with appropriate joint drainage) are also recommended for candidal arthritis [17••]. Since some C. albicans and nonalbicans Candida species are primarily
resistant to fluconazole, it seems prudent to obtain results of in vitro susceptibility testing before using this agent, particularly if the patient has received fluconazole previously or has infection due to nonalbicans *Candida*.

Newer antifungal agents such as caspofungin and voriconazole are under study for the treatment of invasive candidiasis, but data regarding their efficacy and safety in treating candida osteomyelitis and/or arthritis are not yet available. The promise of these and other new agents will add significantly to our clinical armamentarium in the coming years for these *Candida* infections.

Among neonates, factors such as broad-spectrum antimicrobial use, prolonged catheterization, parenteral nutrition, and acidosis have been associated with increased risk of candidemia. In contrast to adults, osteoarticular involvement appears to be a more frequent complication of candidemia in infants, and while often associated with the initial presentation, may also occur long after the initial bloodstream infection [29,30]. The largest review of infantile candidal arthritis to date involved 21 cases that were reported between 1960 and 1980 [30]. *C. albicans* was the most frequent species in this series, isolated in 19 of 21 patients. In 17 cases, osteoarticular involvement accompanied multisystemic candidiasis. Polytarticular involvement among infants appeared to be somewhat higher than that reported with bacterial septic arthritis, with 33% of candidal cases compared with 10% to 15% of bacterial septic arthritis cases reported in the literature. Similar to bacterial septic arthritis, the knee was the site most commonly involved (42%), followed by the hip, shoulder, ankle, elbow, and wrist. Among neonates, indolent presentations of candidal arthritis are common, which is in contrast to the more dramatic presentation of bacterial septic arthritis among infants and adults. Among infants, the most common clinical sign of osteoarticular infection is abnormal positioning of the affected limb. In this series, the time lag between diagnosis of candidiasis (including systemic, candidemia, and/or candiduria) and osteoarticular disease was approximately 3 weeks (range, 1–5 weeks). Candidal arthritis was commonly accompanied by osteomyelitis of the adjacent bone (66% of cases). This is much more common than that reported for bacterial septic arthritis in the literature (10%–25%).

Recently, *Candida* arthritis in infants has been reported to occur long after an initial episode of candidemia [29,31]. Swanson *et al.* [29] reported three infantile cases that were preceded by initial episodes of candidemia a mean of 108 days after the initial positive blood culture for *C. albicans* and 11 weeks after completion of the initial systemic antifungal regimen. Presentation at the time of diagnosis included subtle clinical symptoms. Bone scan in one of three patients revealed adjacent osteomyelitis. During the initial candidemia episode, disseminated disease was ruled out in two patients and the third patient was treated presumptively for candidal meningitis. All three infants received systemic antifungal therapy with amphotericin B for the initial episode of candidemia, with apparent clinical success. One patient had received a 10-day course while the other two patients received 4 weeks of treatment. All three patients responded well to treatment for *Candida* arthritis, with a second course of amphotericin B. One patient was treated with 3 weeks of amphotericin B intravenously, one patient with adjacent osteomyelitis received 6 weeks of intravenous amphotericin B and 12 weeks of flucytosine, and one patient underwent open lavage of the affected joint and intravenous amphotericin B for 6 weeks. Long-term follow-up was available in two patients, and both had no long-term sequelae.

Because of the frequency of disseminated disease among neonates with candidemia, all neonates with candidal bloodstream infections should be carefully monitored for development of infectious complications, including osteomyelitis and arthritis, with close follow-up during their early outpatient visits.

Once diagnosed, management of neonatal osteoarticular candidiasis should follow similar principles as in neonatal systemic candidiasis, including intravenous administration of amphotericin B. There are no definitive recommendations for length of therapy, but 20 to 30 mg/kg total dose has been recommended and toxicity of amphotericin B in this patient population is less common than in adults. [31,32].

**Cryptococcus neoformans**

*Cryptococcus neoformans* is an encapsulated yeast that is ubiquitous in the environment and most commonly causes central nervous system or pulmonary disease. Osteoarticular complications of *C. neoformans* infection are an uncommon phenomenon in the setting of AIDS, but have been reported in up to 5% of cases in immunocompetent hosts. Underlying conditions that result in immunocompromise seem to predispose to cryptococcal disease. However, the rapidity of infection among AIDS patients may contribute to the lack of osteoarticular features observed during the acute presentation of these patients. In severely immunosuppressed patients with high burden of organisms, *Cryptococcus* may be cultured and/or seen in bone marrow biopsies. Sarcoidosis has been particularly associated with development of clinical cryptococcal osteomyelitis, and was present in 26% of skeletal cryptococcosis cases reviewed in 1990 by Behrman *et al.* [33]. Development of osteomyelitis is most commonly due to hematogenous dissemination, but can also occur after direct inoculation. Arthritis is a rare complication, and usually occurs secondary to extension of adjacent osteomyelitis or seeding of a joint during a cryptococcemia related to recent immunosuppression.

Clinically, patients with cryptococcal osteomyelitis present with tenderness and swelling of the site, and fever may or may not be present. Most often osteomyelitis involves a single skeletal area. When multiple sites are
involved, contiguous spread should be suspected. Cryptococcal osteomyelitis most often involves the vertebrae, although cases involving bones of the skull, hands, and hips have been reported [34].

In non-AIDS patients, cryptococcal arthritis most often presents subacutely and involves a mild synovitis. In AIDS or other immunosuppressed patients, development of arthritis can occur quite rapidly, and may present with acute pain in the affected joint [34].

The knee joint is most commonly affected in cryptococcal arthritis, and examination of joint fluid reveals cell counts that may have a wide range of numbers but can reach as high as 15,000 cells/μL. Diagnosis of osteomyelitis is best made by biopsy, and histopathology generally reveals acute and chronic inflammation with circumscribed areas of bony destruction and perhaps abscesses with mucoid, gelatinous pus. Sometimes stains of the specimen reveal yeasts. If C. neoformans is isolated from another site, and a biopsy specimen is not available, radiologic findings in the absence of other causes may help make the diagnosis. Serum cryptococcal antigen among patients with osteomyelitis is positive in less than half of cases, so a negative antigen test does not rule out bone or joint infection [34]. A positive test, however, could be a helpful clue to the presence of Cryptococcus in an abnormal bone or joint.

Cryptococcal osteomyelitis should be managed with systemic antifungal therapy. Surgical removal of infected bone (sequestrum) and surrounding soft tissue may improve recovery time in some cases, but surgery alone is not recommended and is only adjunctive. In the case of cryptococcal arthritis, there have been no reports documenting the additional benefit of joint lavage or drainage in addition to systemic antifungal therapy, and cryptococcal arthritis doesn’t need as much attention to drainage as a bacterial septic joint. In all cases of osteoarticular cryptococcosis, patients should be considered to have disseminated disease and receive treatment. If there is concomitant central nervous system (CNS) involvement and osteoarticular cryptococcosis, then intravenous amphotericin B 0.7 mg/kg/d plus flucytosine 100 mg/kg/d orally should be used for induction therapy for 2 weeks. Induction is then followed by fluconazole 400 to 800 mg daily for 10 weeks, and then fluconazole 200 mg per day for 1 year. These recommendations are consistent with recent IDSA treatment guidelines [35]. If CNS cultures are negative, then we recommend managing osteoarticular cryptococcosis with fluconazole 200 to 400 mg daily for 6 months to 1 year.

**Aspergillus species**

Aspergillus species are molds known to cause invasive disease, aspergillosis, and allergic bronchopulmonary disease. Although the lungs are primarily involved in invasive aspergillosis, other sites such as the sinuses, central nervous system, eyes, skin, heart, and bones are affected. Osteomyelitis associated with Aspergillus species most often involves the vertebrae or sinuses, but has also been reported to infect the sternum, ribs, and skull. In children, the mechanism of infection is predominantly contiguous spread from pulmonary or cutaneous foci, but in adults hematogenous dissemination is more common. Direct inoculation via a surgical procedure or trauma may also predispose a patient for osteomyelitis due to *Aspergillus* species. Most patients who develop osteomyelitis have some degree of underlying immunocompromise, chronic granulomatous disease, or intravenous drug abuse. Arthritis is a rare complication of aspergillosis, and has been observed in the setting of immunosuppression and following surgical procedures [36].

**Management**

The IDSA recently published treatment guidelines for aspergillosis, and recommends surgical debridement and systemic antifungal therapy for those with osteomyelitis. Since amphotericin B does not achieve high levels in bone, IDSA suggests that the addition of other agents such as flucytosine or rifampin be considered. Use of alternative agents, such as itraconazole, should be reserved for those with visceral dissemination, non-neutropenic patients, and those with only mild-to-moderate immunosuppression. Fluconazole has no clinical activity against *Aspergillus* species, so it should not be used to treat these infections. Perez-Gomez et al. [36] summarized 21 cases of osteoarticular aspergillosis that were treated with itraconazole. Eighteen cases were caused by *Aspergillus fumigatus* and three were due to *Aspergillus flavus*. Successful outcomes were achieved in eighteen cases. Surgical procedures accompanied systemic antifungal therapy in six cases. Itraconazole therapy was administered at doses of 200 to 600 mg/d for a duration ranging from 3 to 55 months. For infections involving vertebral disk spaces, itraconazole doses of 3 to 5 mg/kg/d have been recommended. When itraconazole is employed for systemic antifungal infections such as osteomyelitis, serum concentration monitoring should be performed to document adequate levels.

Newer agents such as caspofungin, voriconazole, and posaconazole are highly active against *Aspergillus* species, but to date, no reports have documented use of these agents in the treatment of osteoarticular aspergillosis. Penetration of these agents into bone or joint fluid has also not been well-documented. Therefore, additional study and clinical experience is necessary before these agents can be recommended for use in managing osteoarticular aspergillosis.

**Coccidioides immitis**

*Coccidioides immitis* is a dimorphic fungus that most often causes subclinical infection in endemic areas. Acute, subacute, and chronic pneumonic coccidioidomycosis occur less commonly, and extrapulmonary disseminated disease is even more rare [37–38]. Self-limited arthralgias
commonly occur in the acute phase of coccidioidomycosis, but osteoarticular complications are less frequent, occurring in less than 0.5% of the total infected population [38]. This more serious chronic granulomatous arthritis can be hematogenous to the synovia or spread contiguously from adjacent osteomyelitis, and may occur in 10% to 50% of individuals with disseminated coccidioidomycosis [36]. Schwarz [39] briefly reviewed the epidemiology, diagnosis, and management of osteoarticular complications of coccidiomycosis in 1984, and since that time little new data have been published.

Management

Poor results in terms of function have been previously reported with the combination of amphotericin B and surgical management. However, amphotericin B therapy has been associated with a decrease in mortality from 37% to 9% among those with bone lesions in the setting of disseminated coccidioidomycosis, and has historically been the treatment of choice [39,40]. Demonstrated efficacy, improved tolerability, and oral dosage forms have made azoles attractive agents for management of patients with coccidioidomycosis. This is reflected in recent guidelines published by the IDSA, which recommend azoles as first-line therapy for extrapulmonary manifestations of disseminated coccidioidomycosis [41••]. Ketoconazole, itraconazole, and fluconazole at doses of 400 mg/d are suggested. Higher fluconazole doses may be used, up to 800 mg/d, but may be associated with increased toxicity.

Several studies have compared oral fluconazole and itraconazole in the treatment of disseminated coccidioidomycosis. Most recently, Galgiani et al. [37•] compared fluconazole (400 mg tablets every day) and itraconazole (200 mg capsules twice a day) among 198 patients with non–life-threatening, nonmeningeal coccidioidomycosis. Treatment was continued for 1 year, and response was assessed at 8 and 12 months. Overall, there was a trend toward higher efficacy with itraconazole, with 72% of patients responding at 12 months versus 57% in the fluconazole arm, but this result was not statistically significant ($P = 0.05$). Fifty patients with skeletal disease were included in this study, of whom 10 had joint involvement and 14 had vertebral involvement. Among patients with skeletal disease, response at 8 and 12 months again trended in favor of itraconazole with 70% response versus 37% for fluconazole ($P = 0.03$). Long-term follow-up of these patients was not included in this investigation, so thorough assessment of relapse rates is not possible. In an earlier nonrandomized open-label study conducted by the National Institutes of Allergy and Infectious Diseases Study Group, a response rate of 86% was found among 14 patients with skeletal involvement receiving fluconazole for coccidioidomycosis [42]. Six of 14 responded to fluconazole at a dose of 200 mg daily after approximately 5 months. Seven patients had their fluconazole dose escalated to 400 mg daily, and six responded after approximately 7 months. Overall, fluconazole treatment was continued for almost 2 years in these patients, and despite this, relapse occurred in 50% of patients after fluconazole was discontinued.

Voriconazole has demonstrated potent activity against *C. immitis* in vitro, but clinical utility is limited by lack of availability in vivo experience at this time, and early experience in humans has been favorable with posaconazole. Based on these data and IDSA guidelines, we would recommend itraconazole as initial therapy for limited osteoarticular coccidioidomycosis for at least 1 year, although fluconazole would also be a reasonable choice.

*Blastomyces dermatitidis*

*Blastomyces dermatitidis* is a dimorphic fungus that causes asymptomatic infection, acute or chronic pneumonia, and disseminated infection in endemic regions. Skin, bones, and genitourinary tract are the most common sites of extrapulmonary blastomycosis. Reports of skeletal involvement vary among series of blastomycosis with 5.5% to 48% noted in series published from 1956 to 1992 [43•]. Bone and/or joint infection has been reported in up to 60% of those with extrapulmonary disease. The vertebrae, ribs, skull, and long bones are most commonly affected [39]. Vertebral blastomycosis has been reviewed in detail, and most often involves the lower thoracic and lumbar spine. Development of contiguous abscess (paravertebral or psoas abscess) is common [43•]. Joint infection is somewhat less common, and usually occurs secondary to contiguous spread from adjacent osteomyelitis or hematogenous dissemination. If untreated, polyarticular extension may occur [44]. Schwarz [39] reviewed developments in osteoarticular blastomycosis in 1984, and since that time, the most important advance has involved new therapeutic strategies with the availability of azole compounds. According to recommendations published by the IDSA in 2000, all patients with extrapulmonary blastomycosis should be treated with systemic antifungal therapy [45••]. Surgery has only a limited role in managing this disease. In those with mild to moderate osteomyelitis without central nervous system disease or immunocompromised states, itraconazole (200–400 mg/d) is recommended for at least 12 months. Amphotericin B is also a reasonable alternative for those who cannot tolerate azoles, or those in whom disease progressed during azole therapy. In these cases, amphotericin B 0.5 to 0.7 mg/kg/d for a total dose of 1.5 to 2.5 g is recommended. Treatment should begin with intravenous amphotericin B at a dose of 0.7 to 1 mg/kg/d if CNS or life-threatening disease is present, or the patient has serious underlying conditions such as AIDS, immunodeficiency disorders, or is receiving medications that result in an immunocompromised state (steroids, cytotoxic chemotherapy, immunosuppressants). Amphotericin B may be continued for a total dose of 1.5 to 2.5 g, or in the case of CNS infection, a total dose of 2 g.
Since no information has been published regarding the use of lipid amphotericin B formulations for CNS blastomycosis, the IDSA reserves these agents for those who cannot tolerate amphotericin B deoxycholate [45••].

In immunocompromised hosts without CNS disease, the IDSA suggests a strategy of induction with at least 1 g of intravenous amphotericin B (0.7–1 mg/kg/d) and continuation with itraconazole 200 to 400 mg daily for 1 year. Intravenous amphotericin B is also the treatment of choice for children with life-threatening or CNS disease and pregnant women. Chronic suppressive therapy with itraconazole should be considered for immunocompromised patients. Fluconazole is a reasonable alternative for those who cannot tolerate itraconazole or among those who have had CNS involvement. A prospective, randomized, multicenter pilot study by the NIAID Mycoses Study Group (MSG) evaluated doses of 400 and 800 mg of fluconazole per day for at least 6 months in the treatment of non–life-threatening blastomycosis. Results were similar between the two groups, with an overall response of 87%. Follow-up information was available for 25 of 40 patients, and in this population no relapse was documented. Unfortunately, only four patients in this series had skeletal involvement, so data are inadequate to accurately assess performance of fluconazole in skeletal blastomycosis in this particular trial [46]. Ketoconazole is generally not tolerated as well as fluconazole or itraconazole, and it has been associated with higher relapse rates when used as secondary prophylaxis, so it is not recommended [45••]. Voriconazole and posaconazole have good activity in vitro, but published clinical data are lacking to support their use in treating blastomycosis [47].

Histoplasma capsulatum

Histoplasma duboisii, the cause of African histoplasmosis, and H. capsulatum are common causes of systemic fungal infections worldwide. H. duboisii has been more frequently associated with osteoarticular complications, but in the United States, H. capsulatum is the predominant species associated with clinical disease. H. capsulatum is a dimorphic fungus that is endemic in certain areas of Latin America and North America, such as the areas surrounding the Ohio and Mississippi River valleys. Recent reports have highlighted this disease, such as the acute presentation among US college students after exposure while on spring break in Acapulco, Mexico, and transmission from donor to recipients in kidney transplantation [48,49]. Histoplasmosis is the most common systemic fungal infection in the United States, but despite this, the incidence of osteoarticular infection is disproportionately low (less than 0.1%) [39]. The most common form of rheumatic involvement with histoplasmosis occurs during acute infection, when a migratory polyarthritis syndrome commonly occurs. This is often associated with skin lesions such as erythema nodosum or erythema multiforme, and is probably due to the reactive host inflammatory response to infection, without evidence of yeast in the joint spaces [50••]. Antifungal therapy is not generally required for the polyarticular arthritis that often occurs with acute histoplasmosis. In these cases, the IDSA recommends management with a nonsteroidal anti-inflammatory agent for 2 to 12 weeks. However, in the more rare cases of osteomyelitis, arthritis, or tenosynovitis that complicate disseminated histoplasmosis with yeast in tissue and fluid, systemic antifungal therapy is recommended. Septic arthritis caused by H. capsulatum is a rare occurrence, with less 10 cases reported in the literature. The first case of prosthetic joint infection caused by H. capsulatum was reported a few years ago [51]. In this case, the patient presented with sinus tracts in the thigh, overlying a total hip arthroplasty, which had been placed 8 years earlier. The etiology of the infection was not determined until 5 years later, when the patient presented once again with hip pain and swelling. Comorbidities precluded removal of the joint, so the patient was managed with oral itraconazole (200 mg daily) as suppressive therapy for life. In four of six other published cases prosthetic joint removal was necessary [51].

Management

In hospitalized non-AIDS patients with osteoarticular H. capsulatum infection, we recommend initial therapy with intravenous amphotericin B 0.7 mg/kg/d for approximately 2 weeks followed by itraconazole (200 mg every day [qd] or twice a day [bid]) for 6 to 18 months, and at least until H. capsulatum antigen concentrations in serum and urine are less than four units. This is in agreement with IDSA guidelines [50••]. In less severe cases, itraconazole therapy (200 mg qd or bid) for 6 to 18 months is probably sufficient. Among patients with AIDS, induction therapy with amphotericin B and/or itraconazole for a total of 12 weeks, followed by lifelong suppression with itraconazole, is considered, depending on the patient’s response to highly active antiretroviral therapy. In AIDS patients who are hospitalized with severe disease, treatment should be initiated with amphotericin B and then switched to itraconazole (200 mg bid) when hospitalization is no longer necessary or when the patient becomes afebrile, is able to take oral medications, and does not require blood pressure or ventilatory support, intravenous fluids, or hyperalimentation [50••]. In milder cases not requiring hospitalization in AIDS patients, therapy can be initiated with itraconazole 200 mg three times a day (tid) for 3 days, and then continued bid for a total of 12 weeks. Lifelong suppressive therapy with itraconazole 200 mg once or twice daily is recommended by the IDSA, with serum and urine antigen concentration determinations every 3 months to assess for relapse.

Limited reports to date have documented the efficacy of lipid formulations of amphotericin B in the treatment of osteoarticular or disseminated histoplasmosis, so in general these agents should be reserved for those who...
cannot tolerate first-line therapies. Results from a comparative trial in AIDS patients with disseminated disease was recently presented [52]. Subjects were randomized to receive either liposomal amphotericin B or amphotericin B deoxycholate induction therapy for 2 weeks, then followed by itraconazole for 10 weeks. In this study higher clinical success rates were achieved with liposomal amphotericin B versus amphotericin B deoxycholate (86% vs 59%, \( P = 0.01 \)), and patients receiving the liposomal formulation experienced fewer infusion-related side effects and less nephrotoxicity. Time to defervescence, mortality, and microbiologic response rates were similar between the two treatment groups.

There is limited experience with use of fluconazole in the management of histoplasmosis, and this agent has poor in vitro activity against \( H. \) capsulatum [6]. In addition, development of resistance to fluconazole may occur during therapy, resulting in relapse of infection [50••]. Thus, fluconazole should be used only when patients cannot tolerate first-line regimens. The usual dose in nonimmunocompromised patients is 400 mg daily, but should be increased to 800 mg daily when used in immunocompromised patients. Careful follow-up, including urine and blood histoplasma antigen concentrations, is necessary in patients receiving fluconazole to assess for treatment failure and relapse.

Ketoconazole is another alternative for treatment of disseminated histoplasmosis, as recently outlined by the IDSA [50••]. However, since itraconazole and fluconazole are better tolerated than ketoconazole, they are preferred. Ketoconazole has demonstrated efficacy and may be employed when use of first-line agents is not possible [50••]. Although voriconazole and posaconazole have activity against \( H. \) capsulatum in vitro, there is limited clinical experience to date with these agents [47].

For maintenance therapy in AIDS patients, amphotericin B 50 mg intravenously weekly is an alternative among patients who cannot tolerate itraconazole therapy and has been very effective (81%–97%) [50••]. This regimen is generally not well tolerated, requires ongoing intravenous access, and has low patient acceptance, so maintenance therapy with itraconazole is preferred [50••].

**Sporothrix schenckii**

*Sporothrix schenckii* is a dimorphic fungus that is ubiquitous in the environment and most commonly found in soil and plants. The most common type of infection caused by *S. schenckii* involves cutaneous tissue. Systemic sporotrichosis is rare, and occurs most often among those with outdoor occupations or hobbies, alcohol abuse, or some form of immunocompromised state. Systemic disease, when present, can manifest in both unifocal or multifocal forms. The unifocal form of sporotrichosis usually involves cutaneous disease of the lungs or arthritis, such as chronic granulomatous arthritis or oligoarthritis. The multifocal disease often involves joints and bones as well as skin. Osteoarticular disease is the most common form of extracutaneous sporotrichosis. The mechanism of infection involves contiguous spread from a cutaneous focus, direct inoculation of the tissue by the organism, or hematogenous dissemination. Those with osteoarticular findings often present with a single “hot” joint that is swollen and tender, and may have an effusion. The knee is the most common joint affected, but hand, elbow, and ankle joints may also be involved. These patients generally have limited systemic symptoms, but may have an elevated erythrocyte sedimentation rate. Diagnosis is often delayed, and best made by arthrocentesis of the affected joint. Histologic examination of biopsy specimens from the affected tissue may also be helpful in making the diagnosis. In cases of osteomyelitis, the radiologic signs are often slow to develop and may involve a periosteal reaction and periaricular osteopenia, loss of articular cartilage, and cystic changes.

**Management**

Perez-Gomez et al. [6] reviewed the features of eight cases of osteoarticular sporotrichosis, of which five had successful outcomes after surgical intervention and amphotericin B followed by itraconazole for 1 to 30 months. It has been suggested that at least 200 mg/d of itraconazole is necessary for lasting clinical success. The IDSA recently published recommendations for management of these infections, and recommends itraconazole 200 mg bid as initial therapy in most patients [53••]. Intravenous amphotericin B and surgical debridement of the infected joints has been reported with clinical success in the literature. However, relapses are not uncommon, and occur in up to 35% to 40% of cases. Because of systemic toxicity associated with amphotericin B and the availability of alternatives that are as effective and better tolerated, we agree with IDSA recommendations that intravenous amphotericin B be administered only for patients with extensive involvement or among those in whom itraconazole fails [53••]. Intra-articular amphotericin B has also been successfully employed in some cases of articular sporotrichosis, but the IDSA does not routinely recommend this approach [53••,54]. Other alternatives include fluconazole, for which there is only one case report of successful treatment of systemic sporotrichosis in the literature [55]. The IDSA recommends fluconazole only for patients who cannot receive itraconazole or amphotericin B [53]. In this case, fluconazole should be dosed at a minimum of 800 mg/d in those with normal renal function. Dose adjustment may be necessary for those with renal impairment.

The newer triazoles such as voriconazole, posaconazole, and ravuconazole await clinical experience. Terbinafine has some successful experience in cutaneous sporotrichosis but its success in bone and joint infections awaits further experience before any recommendation can be made.
Other fungi

Other fungi such as *P. marneffei*, *Paecilomyces varioti*, *Phialophora parasitica*, *Curvularia* species, *Exophiala jeanselmei*, *Fusarium* species, and *Scedosporium* species are rarer causes of invasive fungal infection in humans, but cases of osteoarticular infection have been increasingly reported in the past 15 years [56–63]. The most recent of these was reported by Pun and Fang in 2000, which involved a case of multiple sites of *P. marneffei* osteomyelitis and abscesses in a 30-year-old Filipino woman with a history of mixed connective tissue disease [57]. She was managed with a combination of surgical debridement, amphotericin B, and fluconazole. Additional abscesses initially developed while receiving systemic antifungals, but the woman eventually responded to treatment over 3 to 4 weeks.

We anticipate increased incidence of these fungal infections in the coming years, as medical interventions increase the population of immunocompromised hosts. Although no case reports are published to date with newer agents to treat these entities, voriconazole in particular has excellent activity in vitro and in vivo against *Scedosporium apiospermum*. Voriconazole has been used on a compassionate-use basis and in clinical trials to treat such infections, and we await its potential approval by the Food and Drug Administration. For the rare and unusual fungi, no single recommendation can be made. It is important to make a correct identification with histopathology and culture, then ask for expert infectious diseases opinion to plan a specific treatment strategy.

Conclusions

Although fungal arthritis and osteomyelitis are not common clinical problems, they do occur and are actually increasing as the immunocompromised patient population rises. In this review, we have attempted to collate the clinical experience in management to help clinicians devise guidelines for treatment (Table 1). Some of the infections can be difficult to manage, but most can be cured.

### Table 1. Treatment recommendations for most common osteoarticular fungal infections

<table>
<thead>
<tr>
<th>Candidiasis</th>
<th>Arthritis</th>
<th>Surgical debridement plus amphotericin B IV for 2–3 weeks, followed by fluconazole for a total of 6–12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td></td>
<td>Surgical debridement plus amphotericin B IV for 2–3 weeks, followed by fluconazole</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>CNS and osteoarticular involvement</td>
<td>Amphotericin B 0.7 mg/kg/d plus flucytosine 100 mg/kg/d for 2 weeks, then fluconazole 400–800 mg/d for 10 weeks, then fluconazole 200 mg/d for 1 year</td>
</tr>
<tr>
<td></td>
<td>Osteoarticular, no CNS involvement</td>
<td>Amphotericin B 0.7 mg/kg/d plus flucytosine 100 mg/kg/d for 2 weeks, then fluconazole 400–800 mg/d for 10 weeks, then fluconazole 200 mg/d for 1 year</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>Osteomyelitis</td>
<td>Surgical debridement plus amphotericin B with or without flucytosine or rifampin; alternative (visceral dissemination, non-neutropenics, and those with only mild-to-moderate immunosuppression): surgical debridement plus itraconazole</td>
</tr>
<tr>
<td>Coccidioidomycosis</td>
<td>Disseminated, extrapulmonary</td>
<td>Flucytosine, itraconazole, or ketoconazole 400 mg orally qd for at least 12 months, longer if severe immunodeficiency; alternative: amphotericin B IV induction followed by azole for at least 12 months, longer if severe immunodeficiency</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>Osteoarticular</td>
<td>Itraconazole 200 mg bid for 12 months; alternative: amphotericin B IV 1–2 g total dose; alternative: fluconazole 800 mg qd for 12 months</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td>Life threatening</td>
<td>Amphotericin B IV, 1.5–2.5 g total dose</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis, mild-to-moderate</td>
<td>Itraconazole 200–400 mg qd for at least 1 year; alternative: fluconazole or ketoconazole 400–800 mg qd for at least 1 year; alternative (if progressing on azole or azole toxicity): amphotericin B 0.5–0.7 mg/kg/d, total dose 1.5–2.5 g</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td></td>
<td>Amphotericin B IV, 1.5–2.5 g total dose, consider chronic suppressive therapy with itraconazole</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>Hospitalized, non-AIDS, osteoarticular</td>
<td>Amphotericin B IV 0.7 mg/kg/d for 2 weeks, then itraconazole 200 mg qd or bid for 6–18 months</td>
</tr>
<tr>
<td></td>
<td>Less severe osteoarticular, non-AIDS</td>
<td>Itraconazole 200 mg qd or bid for 6–18 months</td>
</tr>
<tr>
<td></td>
<td>AIDS patients, severe</td>
<td>Amphotericin B IV with or without itraconazole for 12 weeks, then itraconazole indefinitely</td>
</tr>
<tr>
<td></td>
<td>AIDS patients, severe</td>
<td>Itraconazole 200 mg bid, then itraconazole 200 mg qd or bid indefinitely</td>
</tr>
<tr>
<td></td>
<td>AIDS patients, less severe</td>
<td>Itraconazole 200 mg tid for 3 days, then itraconazole 200 mg bid for 12 weeks, then itraconazole 200 mg qd or bid indefinitely</td>
</tr>
</tbody>
</table>

bid—twice a day; CNS—central nervous system; IV—intravenous; qd—every day; tid—three times a day.
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance
•• Of major importance


Review of 59 published cases of candidal vertebral osteomyelitis including epidemiology, presentation, diagnosis, and management.


