Acta Orthop. Belg., 2017, **83**, 110-123

ORIGINAL STUDY

Difficult to treat osteoarticulars infections : Focus on Mycobacterial and Fungal infections

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Bone and joint infections are rare but often devastating. While bacteria are most commonly encountered organisms, mycobacteria and fungi are less frequent. Management of the latter is often more complex, especially in the presence of foreign material. We will increasingly be faced with mycobacterial and fungal bone infections, as medical conditions and newer therapeutics lead to more immunosuppression. In this article, we will review osteomyelitis, septic arthritis and peri-prosthetic joint infections related to mycobacteria and fungi.

Key words : osteomyelitis ; arthritis ; peri-prosthetic joint infection ; joint arthroplasty ; candida ; aspergillus ; mycobacteria tuberculosis ; non tuberculous mycobacteria (NTM).

INTRODUCTION

Bone and joint infections are rare but often devastating *(28,64)*. The main causative pathogens are bacteria : gram positive cocci, followed by gram negative bacilli and anaerobic bacteria. Other organisms such as mycobacteria and fungi are more rarely involved *(15,28,37,64,81)* but treatment of the latter is more complex, especially in the presence of foreign material. Orthopedic surgeons and infectious diseases specialists will be increasingly faced with mycobacterial and fungal bone infections, as medical conditions and newer therapeutics lead to more immunosuppression.

To guide clinical practice, we will review the existing literature on the topic, and discuss the epidemiology, clinical presentations and treatments of osteomyelitis, septic arthritis and prosthetic joint infections related to mycobacteria and fungi.

Mycobacterial Infections of Bones and Joints

Osteomyelitis and Septic arthritis

Mycobacterium tuberculosis (MTB) is by far the most common cause of mycobacterial osteomyelitis and arthritis worldwide *(28)*. The incidence of nontuberculous mycobacteria (NTM) disease has

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No benefits or funds were received in support of this study. The authors report no conflict of interests.

increased dramatically in the last few years, hand in hand with the AIDS epidemic. Bone destruction and a relatively slow onset of symptoms are common to MTB and NTM, but there are differences in the epidemiology and treatment of these conditions *(15,28,37,64,81)*.

Epidemiology

Bone and joint MTB currently accounts for 2.2-4.7 % of all TB cases and around 10–15 % of extrapulmonary MTB cases in Europe and the US. In high-resource settings, a bimodal age distribution is observed with natives being affected over 55 years of age while immigrants tend to be younger (20–35 years old) *(14,39, 62)*. The main risk factors for mycobacterium tuberculosis are : age > 65 years, country of origin, and female gender *(14,36,39)*.

Specific risk factors for NTM bone infection are a history of trauma or penetrating wounds ; osteomyelitis in a geographic setting where a particular NTM is known to be endemic ; and an immunocompromised status *(70)*.

Pathogenesis and clinical presentation

MTB osteomyelitis and arthritis generally arise from foci of bacilli lodged in bone during the mycobacteremia of the primary infection. Tuberculous bacilli may also travel from the lung to the spine by Batson's paravertebral venous plexus, or by lymphatic drainage to the para-aortic lymph nodes. Given its rich vascular supply, the growth plate of long bones is the most frequently infected site. Tuberculous arthritis is believed to result from an initial bone focus extending into the joint.

A large US–based study of bone and joint tuberculosis over a 4-year period revealed that the most common site of bony tuberculosis was the spine (40%) ; followed by weight-bearing joints (hip and knee) ; and lastly other sites *(22)*. The proportion of spinal disease was found to be greater than 50% in more recent studies *(36,39)*. The predilection for spinal disease may be explained by its rich vascular supply. Thoracic disease is more common in children and adolescents ; lumbar disease is commoner in adults *(58,64)*. Most cases of tuberculous bone and joint disease are isolated to one area, but multifocal disease has been described *(43)*.

The symptoms of tuberculous (MTB) bone and joint infections are nonspecific, often indolent, usually leading to significant delays in diagnosis, resulting in bone or joint destruction. Only about 50% of affected patients have chest radiographs suggestive of tuberculous infection, further obscuring the diagnosis. Pain or local swelling are the most frequent presenting complaints *(34)*, while fever and weight loss are present in only a minority of patients *(28,64)*. Cutaneous fistulae, abscesses, and obvious joint deformities can be present. Spinal disease may be associated with neurologic deficits and patients with thoracic spine disease are at particular risk of paraparesis or paraplegia.

Atypical mycobacterial osteomyelitis and arthritis in non-immunocompromised individuals is often secondary to direct inoculation from trauma or surgery *(17,28,46,55)*. However, hematogenous dissemination of NTM with multifocal disease, including bone and joint involvement, can occur in immunocompromised individuals, mainly in individuals with AIDS [1]. NTM have a predilection for foreign bodies, such as prosthetic joints *(28,37,64)*.

The clinical presentation of native bone and joint disease NTM is similar to that of MTB tuberculosis.

Diagnosis

Diagnosis of mycobacterial infection of native bone and joint requires a high suspicion index. Different diagnostic methods are available to help in or confirm the diagnosis : tuberculin skin tests, Interferon gamma release assays (IGRA), microscopy, mycobacterial cultures, histology and Polymerase chain reaction (PCR).Acid-fast smears are positive in only a minority of patients. Confirmation of a clinical diagnosis should be attempted by mycobacterial culture, also crucial for antimicrobial sensitivities. Culture of deeper structures is crucial, from bone, abscesses, or synovial tissue, to avoid growing colonising organisms. An older review of the use of synovial fluid culture for M. tuberculosis reported a sensitivity of 79%, whereas synovial tissue culture had a sensitivity of 94% *(77)*.

When mycobacterial cultures were ommitted, histology can be helpful. Histologic evidence of mycobacterial infection has been reported in 94% of

synovial biopsy specimens (Figure 1), but presence of granulomatous inflammation alone is not specific enough *(41)*.

The detection of mycobacterial genetic material may also aid in the diagnosis. Lawn et al. found that the use of Xpert® MTB/RIF had a sensitivity of 81.3% and specificity of 99.8% in nonrespiratory specimens for the diagnosis of extrapulmonary tuberculosis *(47)*. Also, PCR was found in one study to have a high sensitivity, specificity, and accuracy (95%, 83%, and 92%, respectively) in detecting M. tuberculosis from formaldehyde solution-fixed, paraffin-embedded tissue samples from histologically proven tuberculous spondylitis *(7)*.

Of note, cell count and biochemistry findings from tuberculous joint fluids, although typical of inflammatory arthritis, are not specific *(41)*.

Imaging is very useful in diagnosing such infections, particularly for spinal disease, where MRI is the gold standard (Figure 2).

Treatment

Treatment of native bone and joint mycobacterial infections is described in Tables 1 and 2.

Large clinical trials have confirmed that standard short-course therapy for drug-sensitive bone MTB consisting of 6 months of isoniazid and rifampin, with pyrazinamide during the first 2 months, is effective *(51-52)*. Prolonged therapy can be considered for slow-responders *(28,64)*.

The role of surgery for bone and joint tuberculosis is relatively straightforward for sites other than the spine : while not essential, it can play a role in draining abscesses and decompressing vital structures, such as nerves *(52,74-76)*. Joints that are significantly damaged may require debridement and possible fusion or replacement. On the other hand, patients with spinal tuberculosis tend to develop late neurologic and musculoskeletal complications (progressive kyphosis and spinal instability) if treated medically only. Given the close proximity of vital structures, it has been argued that aggressive surgical treatment should be used to stabilize the spine and prevent kyphosis, unless only very mild disease is present *(74)*. Some have had successes with medical therapy alone *(52)*. With adequate antituberculous chemotherapy, and surgery when required, relapses are uncommon (0-5 %). The reported mortality of spinal TB is usually low (0-6 %) *(61)*.

There are no large randomized trials on NTM infections, but a combination of surgery and antibiotics is usually advocated for the treatment of bone and joint NTM. Aggressive surgical intervention can be justified for abscesses. In general, NTM are more resistant to antituberculous drugs than M tuberculosis, and in vitro resistance testing may not correlate with clinical response *(76)*.

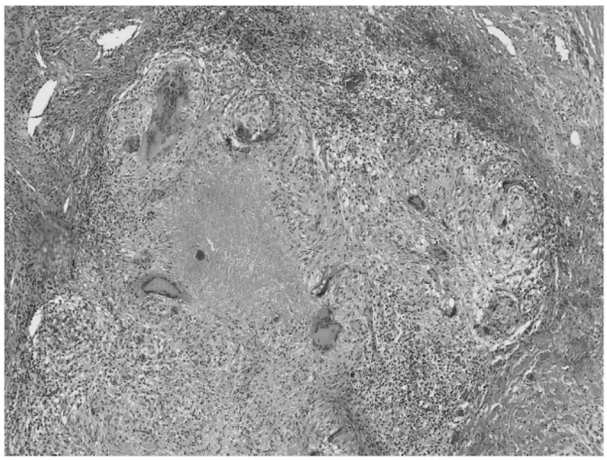

Fig. 1. — Histology of tuberculous osteomyelitis showing necrotising granuloma with giant cells surrounded by a lymphocytic infiltrate (H&E x 300)

Prosthetic joint infections

Prosthetic joint infections (PJI) due to MTB are rare *(6,65)*. They can occur in patients with no prior history of TB. The typical case is a misdiagnosed patient presenting with knee or hip osteoarthritis, treated with joint arthroplasty, who (sometimes much) later develops culture-negative chronic PJI *(6)*. Immunosuppressive therapy can be the precipitating event.

The diagnosis is often difficult and should be suspected in culture-negative PJI with histological features of granulomatous lesions with macrophages and multinucleate cells with or without caseum. The diagnosis is confirmed by isolation of the microorganism on Loëwenstein culture or by molecular techniques (PCR).

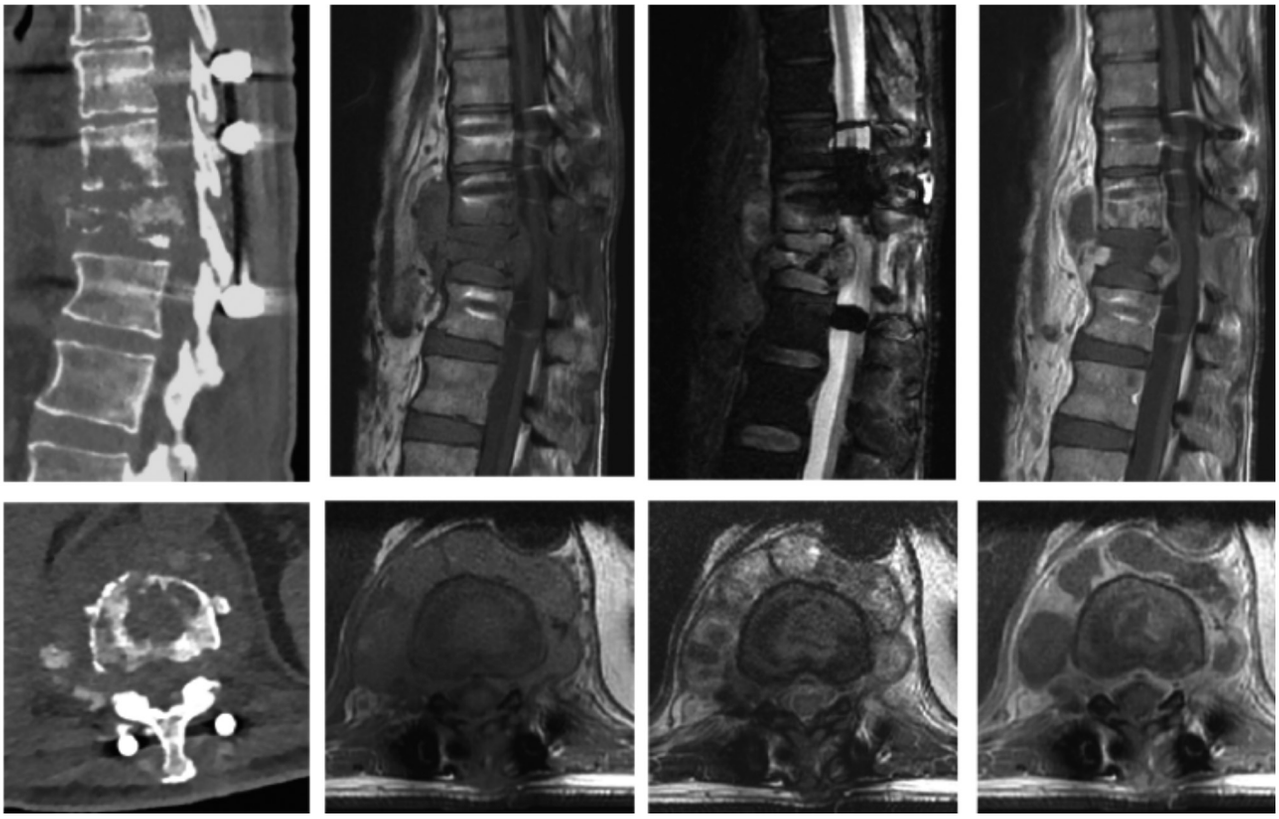

Fig. 2. — Left pannels : sagittal (top) and transverse (bottom) CT scan views of thoracic vertebrae following arthrodesis of T12 for a pathological fracture. Subsequent images : paired sagittal (top) and transverse (bottom) MRI views of the thoraco-lombar region in T1, T2 with suppression of the fat signals and T1 following injection, respectively. Osteolytic destruction of T12 can be observed, with extention of the infection to the surrounding soft tissues and a large epidural leak ; calcifications are best seen on the CT images. Such destruction of a vertebral body, with extention of collections to the surrounding soft tissues, particularly to the anterior paraspinal space, is very suggestive of a tuberculous spondylitis, especially when found in patients of Asian, Oriental or African origin.

Resection arthroplasty or arthrodesis has been used to treat this type of PJI, but when there is no loosening of the prosthesis, the patient may be cured with debridement, exchange of plastic components while retaining the prosthesis, and prolonged antituberculous therapy (9-12 months) (Table III).

NTM is also an infrequent cause of prosthetic joint infections. Early onset knee NTM PJI infection has been described after contamination with NTM from tap water-derived fluids peroperatively *(66)*. Recently, a similar cluster of *M. fortuitum* prosthetic joint infections was reported *(11,20)*. Empirical antibiotics should cover rapid growth mycobacteria, especially *M. fortuitum*, before identification results are known.

Combination of surgery and antimicrobial therapy is the preferred approach for NTM *(31,79)*. Prolonged antibiotics seem necessary before re-implantation ; the optimal duration of antibiotic therapy is unknown (Table III). Minimum 6 months targetted antimycobacterial is recommended, and the regimen can be extended to 12 months or more in patients with disseminated disease *(79)*.

Fungal Infections of Bones and Joints

Candida infections

Osteomyelitis

Candida osteomyelitis is associated with significant morbidity *(24)*.

Gamaletsou found that there was a strong male predominance with > 2:1 male :female ratio *(24)*.

Table I. — Osteomyelitis with rarer organisms

Charateristics	*Mycobacterium Tuberculosis(MTB)*	*Non-Tuberculous Mycobacteria (NTM)*	*Candida spp*	*Aspergillus spp*
Frequency	2.2-4.7 % of all cases of TB 10-15% of extrapulmonary TB	rare	rare	Very rare
Risk factors	Age> 65 yeras Female sex Foreign birth	History of trauma or wound puncture Osteomyelitis in endemic area Immunocompromised status	Candidaemia Risk factors for invasive candidiasis (abdominal surgery, parenteral nutrition, indwelling catheters…) Cutaneous candidiasis Invasive candidiasis	Immunocompromised status Prior open fracture, trauma or surgery
Mechanisms/ Pathogenesis	Hematogenous spread during primary infection From the lungs to the spine via Batson's paravertebral venous plexus Lymphatic spread to the para-aortic lymph nodes	Hematogenous spread in immunocompromised hosts Direct inoculation by trauma or surgery in immunocompetent hosts	Hematogenous dissemination Direct inoculation and/or contiguous spread	Hematogenous, Contiguous or Direct inoculation
Clinical presentation	Pain or local swelling Fever and weight loss Cutaneous fistulae or abscesses Joint deformity Paraparesis or paraplegia if spinal location	Pain or local swelling Fever and weight loss Cutaneous fistulae or abscesses Joint deformity Paraparesis or paraplegia if spinal location	Symptoms of insidious onset Subacute or chronic course: pain, swelling, sinus tract formation	Osseous tenderness, pain, sinus tract formation and/or spontaneous drainage
Microbiology	Mycobacterium tuberculosis	Often negative cultures	Candida albicans (65%) C. tropicalis (16%) C. glabrata(8%) C. parapsilosis (7%)	Aspergillus fumigatus (55%) Aspergillus flavus (12%) Aspergillus nidulans (7%)
Medical treatment	Classical antituberculosis treatment (rifampin, isoniazid, pyrazynamide, ethambutol) Duration: 6-9months	Depending on the microorganism involved and suceptibility results if available Duration: unknown	*Fluconazole, 400 mg (6 mg/kg) daily, for 6–12 months or *an echinocandin (caspofungin 50–70 mg daily, or anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole 400 mg (6 mg/kg) daily, for 6–12 months or *Lipid formulation AmB, 3–5 mg/kg daily, for at least 2 weeks followed by fluconazole 400 mg (6 mg/kg) daily, for 6–12 months (alternative)	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h Duration:3–6 months or longer
Surgical management	Abscess debridement: removing purulent necrotic tissues from normal tissue Spinal cord decompression Permanent spinal stabilization: preventing or correcting deformity	Surgical debridement Abscess drainage	Debridement in selected cases	Surgical debridement of infected and necrotic bone Case by case discussion

Table II. — Septic arthritis with rarer organisms

Charateristics	*Mycobacterium Tuberculosis(MT)*	*NTM*	*Candida spp*	*Aspergillus spp*
Frequency	2.2-4.7 % of all cases of TB 10-15% of extrapulmonary TB	rare	Rare but 80 % of fungal PJI	Uncommon
Risk factors	Age> 65 yeras Female sex Foreign birth	History of trauma or wound puncture History of osteomyelitis in endemic areas Immunocompromised status	Immunocompromised status Candidemia or other invasive candidiasis	Classically in immunocompromised hosts Possible in immunocompetent patients
Mechanisms/ Pathogenesis	Hematogenous spread Spread from a bone infectious focus extending into the joint	Hematogenous in immunocompromised hosts Direct inoculation by trauma or surgery in immunocompetent hosts	Hematogenous spread (80%)	Hematogenous spread in immunocompromised patients In immunocompetent patients: history of preceding surgery or open fractures
Clinical presentation	Local pain and tenderness Oedema and erythema Limitation of function and movements Sinus tracts (Fever and night sweats: uncommon)	Local pain and tenderness Oedema and erythema Limitation of function and movement Sinus tracts (Fever and night sweats: uncommon)	Local pain and tenderness Oedema and erythema Limitation of function and movement Sinus tracts (Fever: uncommon)	Local pain and tenderness Oedema and erythema Limitation of function and movement Sinus tracts
Microbiology	Mycobacterium tuberculosis	Variety of species	Candida albicans (63%) Candida tropicalis (14%) Candida parapsilosis (11%) Candida krusei (4%,) Candida glabrata (2%)-Candida lusitaniae	Apergillus fumigatus
Medical treatment	Classical antituberculosis treatment (rifampin, isoniazid, pyrazynamide, ethambutol) Duration: 6-9 months	Depending on the available microorganism and suceptibility test results Duration: unknown	*Fluconazole 400 mg (6 mg/kg) daily, for 6 weeks or *an echinocandin (caspofungin 50–70 mg daily, or anidulafungin 100 mg daily) for 2 weeks followed by fluconazole400 mg (6 mg/kg) daily, for at least 4 weeks or *Lipid formulation AmB, 3–5 mg/kg daily, for 2 weeks, followed by fluconazole 400 mg (6 mg/kg) daily, for at least 4 weeks (alternative)	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12h; oral dosage is 200 mg every 12 h Duration: minimum 6–8 weeks warranted in non immunocompromised patients; longer in immunocompromised patients
Surgical management	Drainage in all cases	Drainage in all cases	Drainage in all cases	Drainage in all cases

Candida osteomyelitis develops predominantly in patients who are not neutropenic or otherwise immunocompromised. A high index of suspicion is needed for all candidemic patients with subsequent localizing osteoarticular symptoms. Similarly, patients with localizing osteoarticular symptoms following surgery should be further evaluated for Candida osteomyelitis.

Hematogenous dissemination is commonest, but direct inoculation or contiguous spread of infection occur. Involvement of 2 or more bones is common, so when a single focus of infection is identified, other sites should be sought. The axial skeleton is the most commonly affected site in adults ; in children, it is the long bones (*12,24,32,56,68*). Most patients present with localizing symptoms of insidious onset with only moderate blood inflammatory markers *(24)*.

Non-albicans Candida species were found to be an increasingly frequent cause of Candida osteomyelitis with bacterial copathogens, including *S. aureus*. Some authors found Candida albicans in 65% of cases, C. tropicalis in 16%, C. glabrata in 8%, and C. parapsilosis in 7% *(24)*.

The evidence favors the use of fluconazole or an echinocandin rather than amphotericin B *(12-13,24,33,48,50,56,59-60,67-68,71,)*. Fluconazole has been used successfully as initial therapy for patients who have susceptible isolates, but treatment failures have also been reported *(13,33,50,71)*. The Infectious Diseases Society of America (IDSA) recommends fluconazole daily, for 6-12 months or an echinocandin for at least 2 weeks followed by fluconazole daily, for 6-12 months *(60)*. Lipid formulation AmB, daily, for at least 2 weeks followed by fluconazole daily, for 6-12 months is a less attractive alternative (Table I). Surgical debridement is recommended in selected cases *(60)*.

Septic arthritis

Fungal arthritis is infrequent ; a Candida species is most often involved *(4,26)*. Early reports suggested that Candida arthritis developed most commonly as a complication of disseminated candidiasis *(21,54)*. In the series by Gamaletsou et al, candida arthritis was associated with a wide range of underlying conditions : 34% were immunocompromised but the majority had no apparent underlying immune impairment ; most had had a candidemia or invasive candidiasis before or during the episode of arthritis, but 26% patients had no preexisting candidiasis *(26)*. *Candida albicans, C. tropicalis, and C. parapsilosis* were the most common *Candida spp* identified *(26)*.

Symptoms include local pain and tenderness, oedema, and localized erythema. Fever seems uncommon. Limitation of function and movement is seen in one third of patients. Sinus tracts and draining pus are rare (Table II). In the context of invasive candidiasis or candidemia, evaluation of musculoskeletal symptoms may reveal localization to 1 or more joints. However, because Candida arthritis also may arise de novo in more than 25% of patients, a high index of suspicion is warranted *(26)*.

Arthrocentesis or arthroscopy is essential for a definitive diagnosis to provide histological and bacterial specimens to confirmed the diagnosis (Figure 3 and 4).

Treatment of Candida arthritis should relieve symptoms, eradicate infection, prevent joint injury and restore function. Surgical drainage is indicated in all cases of septic arthritis *(60)*. There is no evidence-based standard treatment regimen for patients with fungal osteoarticular infections of native joints. The Infectious Diseases Society of America (IDSA) guidelines recommend fluconazole for 6 weeks or an echinocandin for 2 weeks followed by fluconazole for at least 4 weeks. Lipid formulation AmB, for 2 weeks, followed by fluconazole for at least 4 weeks, is a second choice alternative *(60)*. However, given the activity of echinocandins on Candida biofilms *(44,57,69)* initial therapy with an echinocandin seems a reasonable approach.

Prosthetic joint infection

Fungal PJI is uncommon, occurs in approximately 1% of all PJIs *(3,63),* and most are caused by *Candida albicans* and *Candida parapsilosis* *(3,38,40,63)*. Extensive comorbidities and decreased immunity are considered risk factors *(3,38,63)*. Host factors include an immunosuppressed state, diabetes mellitus, rheumatoid arthritis, malignancy, tuberculosis, and/or renal insufficiency *(1,40,44,)*. Other factors include drug abuse, prolonged antibiotic use, indwelling catheters, malnutrition, severe burns, and multiple abdominal surgeries *(1,3,40)* ; as well as previous

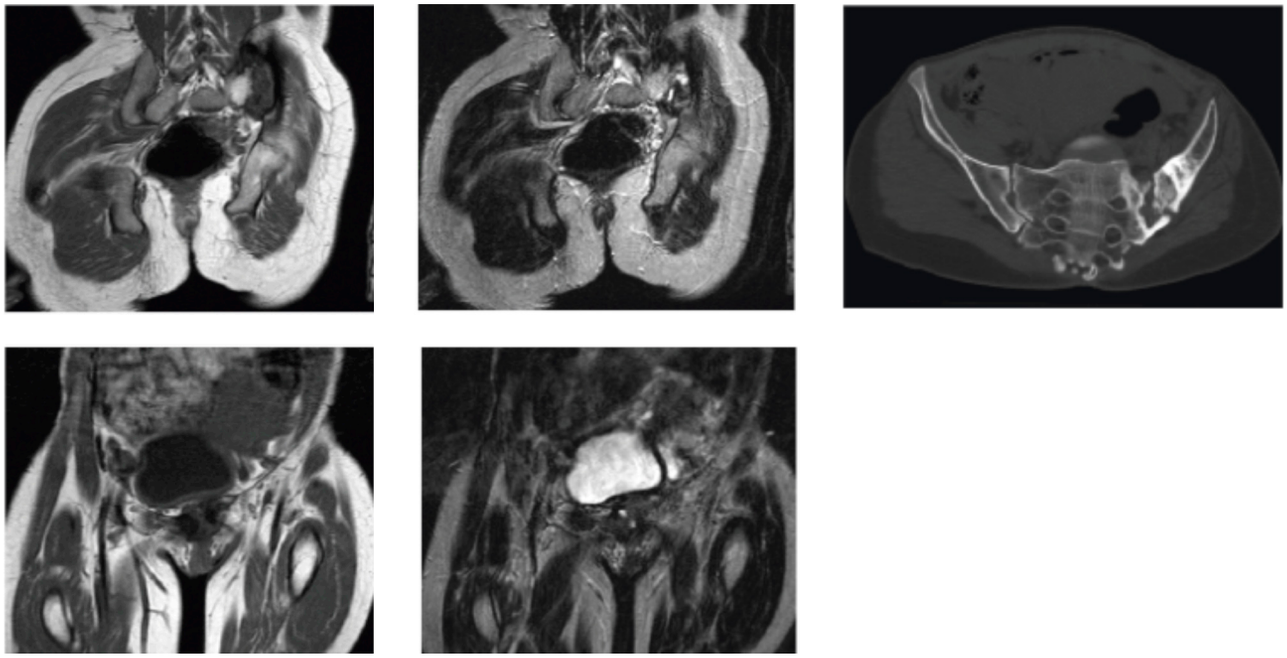

Fig. 3. — Candida arthritis. MRI images in T1 (left) and T2 (centre) showing bone marrow lesions around the left sacro-iliac joint and pubic symphysis (hyposignal in T1, intermediate signal in T2), suggesting 2 infectious foci. Right: transverse view showing destruction of the joint's edges, with thickening of the joint space and consolidation of surrounding tissues.

PJIs, revision surgery, and cutaneous candidiasis *(1,3,10,19,40,80)*.

In a series of 164 fungal PJIs, most patients presented with symptoms of chronic infection such as pain (78%) and swelling (65%). Other symptoms included warmth (18%), limited range of motion (10%), redness (8%), and fever (7%). Wound drainage and sinus tract were described in 4% and 9% of patients, respectively (42). The mean duration from last performed arthroplasty to diagnosis of fungal PJI was 27 months (range 2 weeks to 22 years).

Surgical options are similar to those for bacterial PJIs *(56)*. Kuiper et al. found no evidence that 1-stage revision or 'debridement, antibiotics, irrigation, and retention' (DAIR) or antifungal therapy alone adequately controlled fungal PJI *(42)*. A two-stage revision should therefore be the standard treatment for fungal PJI. After resection of the prosthesis, we recommend systemic antifungal treatment for at least 6 weeks, provided complete resolution of inflammatory parameters. Reimplantation can then be performed. This was confirmed in a recent systematic reviews of fungal PJI of the knee *(38)*. Most authors suggest a minimum duration of 6 weeks antifungals after reimplantation *(1,63)* but others suggest minimum 12 months *(2-3)*. Amphotericin B or fluconazole have been considered the drugs of choice *(2)*. The use of echocandins was only described in a few reports *(8,18,30,49)*, but it may be a good alternative (low toxicity, broad spectrum), especially for fluconazole-resistant fungal species, or if amphotericin B is not tolerated by the patient. If removal of the arthroplasty is not an option, chronic suppression with fluconazole is recommended. This is summarised in Table III.

Aspergillus infections

Osteomyelitis

Aspergillus osteomyelitis is a debilitating and severe form of invasive aspergillosis *(25,35,72)*. Nearly 80% of Aspergillus osteomyelitis in the literature were the first manifestations of invasive aspergillosis. The most common infecting species were *Aspergillus fumigatus* (55%), *Aspergillus*

flavus (12%), and *Aspergillus nidulans* (7%).

As the population of immunocompromised patients continues to expand, so will Aspergillus osteomyelitis. Gamaletsou (25) saw predisposing medical conditions present in 103 (57%) patients including pharmacological immunosuppression, primary immunodeficiency, and neutropenia. Seventy-three others (apparently immunocompetent) (41%) had prior open fracture, trauma or surgery. In his own review, Gabrielli et al (23) found that comorbidities included chronic granulomatous disease (19%), haematological malignancies (11%), transplantation (11%), diabetes (6%), pulmonary disease (4%), steroid therapy (4%), and human immunodeficiency virus infection (4%).

In the Gamaletsou et al. review *(25),* the most frequently infected sites were vertebrae (46%), cranium (23%), ribs (16%), and long bones (13%). Patients with vertebral Aspergillus osteomyelitis had had 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). Gabrielli et al (23) found that the sites of infection in their 310 cases included the spine (49%), the base of the skull, paranasal sinuses and jaw (18%), ribs (9%), long bones (9%), sternum (5%), and chest wall (4%). Vertebral disease was predominantly spondylodiscitis with nearly 50% of cases progressing to spinal cord compression associated with neurological deficits. Vertebral and costal disease arose from contiguous pulmonary aspergillosis, by hematogenous dissemination ; occasionally by traumatic inoculation *(25)*.

Early recognition of Aspergillus osteomyelitis depends upon recognizing vulnerable populations with symptoms of osseous tenderness, pain, sinus tracts and/or drainage. Histological and bacterial specimens are essential for the diagnosis.

The Infectious Diseases Society of America (IDSA) treatment guidelines state that voriconazole is recommended as 1st-line antifungal agent for IA,

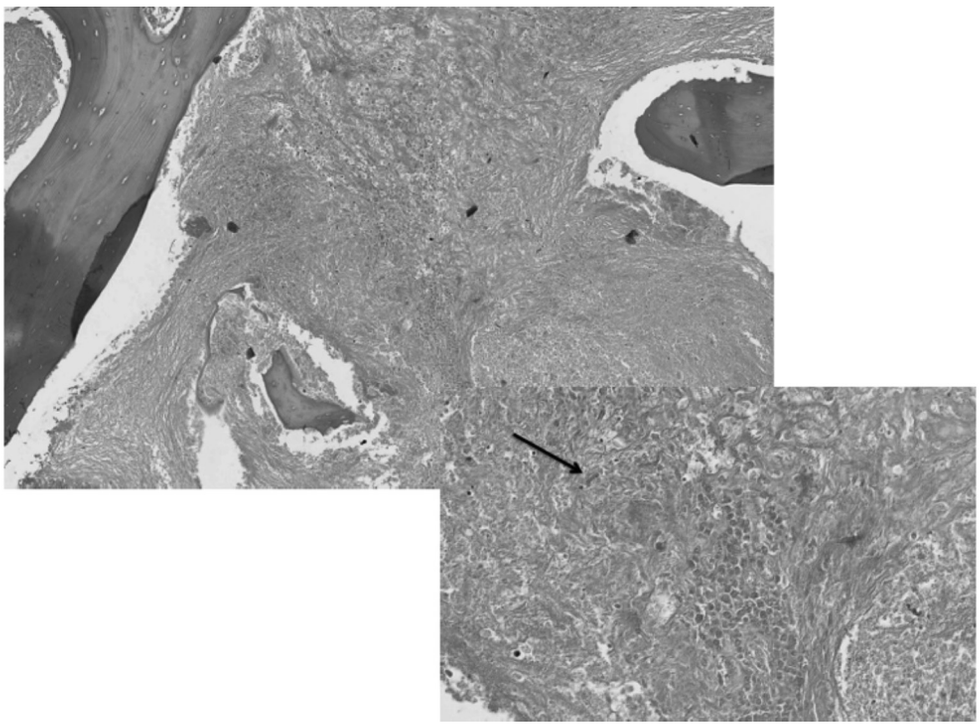

Fig. 4. — Histolopathology bone section using standard stain showing extensive necrosis within cancellous bone, and some lysed inflammatory cells (H&E x 200). At a larger magnification (H&E x 600), rare filaments can be detected (arrow), suggestive of fungal infection.

Table III. — Prosthetic joint infections with rarer organisms

Characteristics	*Mycobacterium tuberculosis (MTB)*	*Non-tuberculous mycobacteria (NTM)*	*Candida spp*	*Aspergillus spp*
Frequency	rare	Rare but more common than MTB	1% of all fungal PJI	Very rare But 8.8% of fungal PJI
Risk factors	History of arthroplasty History of MTB or not (Immunosuppresion is not a risk factor)	History of trauma or surgery, Immunosuppression	Extensive comorbidity and decreased immunity	Immunocompromised status
Mechanisms/ pathogenesis	Unknown	Intraoperative contamination in early PJI		-
Clinical presentation	PJI with negative cultures	PJI with negative cultures	Pain and swelling Calor and Erythema Fever Limited range of motion Wound drainage/ sinus tract	Local pain and tenderness Oedema and erythema Limitation of function and movement Sinus tracts
Microbiology	Mycobacterium tuberculosis	Variety of species particulary *Mycobacterium fortuitum*	Candida albicans and Candida parapsilosis	Aspergillus fumigatus Aspergillus niger (very rare)
Medical treatment	Classical antituberculosis treatment (rifampin, isoniazid, pyrazynamide, ethambutol) Duration: 6-9 months	Depending on the microorganism found and results of suceptibility tests Duration: unknown	*Fluconazole 400 mg (6 mg/kg) daily, for 6 weeks or *an echinocandin (caspofungin 50–70 mg daily, or anidulafungin 100 mg daily) for 2 weeks followed by fluconazole 400 mg (6 mg/kg) daily, for 6 weeks or longer (up to 12 months) *Lipid formulation AmB, 3–5 mg/kg daily, for 2 weeks, followed by fluconazole 400 mg (6 mg/kg) daily, for 6 weeks or longer (alternative)	Voriconazole (6 mg/kg IV every 12 h for 1 day, followed by 4 mg/kg IV every 12 h; oral dosage is 200 mg every 12 h Unknown duration; minimun 3 months
Surgical treatment	Arthrodesis 2-stage exchange arthroplasty Debridement and prothesis retention if no loosening of the implant	2-stage exchange arthroplasty	2-stage exchange arthroplasty (6weeks of antifungal between the two stages)	2-stage exchange arthroplasty combined with prolonged antifungal therapy is highly recommended.

including Aspergillus osteomyelitis *(78)*. Despite the paucity of prospective data, voriconazole appears to be the drug of choice for Aspergillus osteomyelitis, based on its activity against Aspergillus, the bioavailability of the oral formulation, and its acceptable side-effect profile. In addition, voriconazole is minimally protein bound and reaches high concentrations in difficult to penetrate compartments *(16)*.

The optimal duration of treatment for Aspergillus osteomyelitis is unknown (Table I). In the study of Horn et al *(35),* six of 8 patients who were alive at follow-up had been treated for a minimum of 12 weeks. Interestingly, the 2 patients with a complete response were treated for 16 and 26 days, each with surgical debridement, for a rib cartilage and

sternal infection, respectively. In the review of Gamaletsou et al *(25),* 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).

Guidelines still recommend treatments of 3-6 months, with individualized treatments *(78).*

Septic arthritis

Primary infection of a joint by an aspergillus species is uncommon but is associated with a high morbidity and mortality *(27,29).* In earlier reports immunocompromised patients were predominantly affected *(29).* More recent studies have shown that non immunocompromised patients are also at risk *(25).* The infection usually spreads to the joint through the haematogenous route from lungs. The immunocompetent population may have a history of preceding surgery or open fractures *(25).* The hip joint is the most commonly involved joint followed by the knee, the wrist and the ankle *(25). Aspergillus fumigatus* is the most common Aspergillus spp involved *(53).*

Diagnosis is diffucult and requires a high index of suspicion. Confirming the diagnosis requires joint puncture for microbiological and histopathological analyses. The organism can be isolated from the synovial fluid and the total leukocyte cell counts are generally above 5000/mm^3, associated with a relative neutrophilia. Aspergillus grows very fast and the cultures are usually visible within 2 to 4 days, although in some cases it may require a longer incubation period *(73).*

The treatment of Aspergillus arthritis includes surgical drainage along with administration of antifungal agents like amphotericin B or voriconazole (Table II), despite the lack of consensus *(78).* There is risk of nephrotoxicity with the use of amphotericin B so its maximum dose and duration should be stringently regulated. Voriconazole can be used both intravenous and oral dosage form with fewer side effects. The duration of treatment is unknown. In the IDSA guidelines, treatment for a minimum of 6–8 weeks is warranted in non-immunocompromised patients. For immunocompromised patients, considering long-term suppressive therapy or treatment throughout the duration of the immunosuppression is appropriate *(78).*

Prosthetic Joint Infection

Aspergillus PJI is rare. In a series of 45 fungal knee PJIs, Aspergillus *spp* were the causative agents in 4/45 (8.8%) : Aspergillus fumigatus in 3/4, Aspergillus niger in 1/4 *(27).* Most cases have been described in immunocompromised patients *(9)* ; one case report describes aspergillus in a knee PJI in a non-immunocompromised patient with a megaprothesis *(5).*

A two-stage exchange arthroplasty combined with prolonged antifungal therapy is highly recommended for the treatment of an Aspergillus PJIs *(5)* (Table III). The Infectious Diseases Society of America (IDSA) treatment guidelines state that voriconazole is recommended as 1st-line antifungal agent for an invasive aspergillosis, including Aspergillus osteorarticular infections *(78).* The optimal duration of antifungal therapy is unknown. For immunocompromised patients, consideration of long-term suppressive therapy or treatment

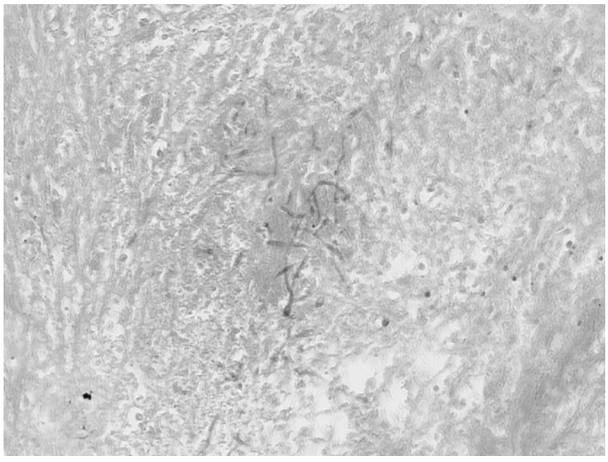

***Fig. 5.*.** — Histolopathology bone section using standard stain showing extensive necrosis within cancellous bone, and some lysed inflammatory cells (H&E x200). At a larger magnification (H&E x600), rare filaments can be detected (arrow), suggestive of fungal infection.

throughout the duration of immunosuppression is appropriate.

CONCLUSIONS

We have presented a review of the literature regarding the management of bone and joint infections due to mycobacterial and fungal infections. In this area of scarce evidence-based data, we think that this comprehensive review can be valuable to guide clinicians in the diagnosis and treatment of such difficult infections.

REFERENCES

1. **Anagnostakos K, Kelm J, Schmitt E, Jung J**. Fungal periprosthetic hip and knee joint infections clinical experience with a 2-stage treatment protocol. *J Arthroplasty* 2012 ; 27 : 293-8.
2. **Austen S, van der Weegen W, Verduin C M, et al.** Coccidioidomycosisinfection of a total knee arthroplasty in a nonendemic region. *J Arthroplasty* 2013 ; 28 : 375.
3. **Azzam K, Parvizi J, Jungkind D, et al**. Microbiological, clinical, and surgical featuresof fungal prosthetic joint infections : a multi-institutional experience. *J Bone Joint Surg (Am)* (Suppl 6) 2009 ; 91 : 142-9.
4. **Bariteau JT, Waryasz GR, McDonnell M et al**. Fungal osteomyelitis and septic arthritis. *J Am Acad Orthop Surg* 2014 ; 22 : 390-401.
5. **Baumann PA, Cunningham B, Patel NS, Finn HA**. Aspergillus fumigatus infection in a mega prosthetic total knee arthroplasty : salvage by staged reimplantation with 5-year follow-up. *J Arthroplasty*. 2001 ; 16 : 498-503.
6. **Berbari EF, Hanssen AD, Duffy MC, et al.** Prosthetic joint infection due to Mycobacterium tuberculosis : a case report and review of the literature. *Am J Orthop* 1998 ; 27 : 219-227
7. **Berk RH, Yazici M, Atabey N, et al.** .Detection of Mycobacterium tuberculosis in formaldehyde solutionfixed, paraffin-embedded tissue by polymerase chain reaction in Pott's disease. *Spine* 1996 ; 21 : 1991-5
8. **Bland C M, Thomas S.** Micafungin plus fluconazole in an infected knee with retained hardware due to Candida albicans. Ann Pharmacother 2009 ; 43 (3) : 528-31.
9. **Brooks DH, Pupparo F**. Successful salvage of a primary total knee arthroplasty infected with Candida parapsilosis. *J Arthroplasty* 1998 ; 13 : 707
10. **Chiu W-K, Chung K-Y, Cheung K-W, Chiu K-H.** Candida parapsilosis total hip arthroplasty infection : case report and literature review. *J Orthop Trauma* 2013 ; 17 : 33-6.
11. **Cornelius L, Reddix R, Burchett C, et al**. Cluster of Mycobacterium fortuitum prosthetic joint infections. *J Surg Orthop Adv* 2007 ; 16 : 196-198.
12. **Cornely OA, Lasso M, Betts R, et al**. Caspofungin for the treatment of less com- mon forms of invasive candidiasis. *J Antimicrob Chemother* 2007 ; 60 : 363-9.
13. **Dan M, Priel I**. Failure of fluconazole therapy for sternal osteomyelitis due to Candida albicans. *Clin Infect Dis* 1994 ; 18 : 126-7.
14. **Davies P, Humpries MJ, Byfield SP, et al**. Bone and Joint tuberculosis. A survey of notifications in England and Wales. *J Bone Joint Surg B*. 1984 ; 66 : 326-330.
15. **Del Puppo L, Janssens JP, Kherad O, et al** . Bone tuberculosis : when consider this diagnosis? *Rev Med Suisse*. 2016 ; 12 : 262-5.
16. **Denes E, Bournediere A,Durox H, et al** .Voriconazole concentrations in synovial fluid and bone tissues. *J Antimicrob Chemother* 2007 ; 59 : 818-819.
17. **Dubey M, Kalantri Y, Hemvani N, Chitnis DS**. Chronic knee monoarthritis caused by Mycobacterium chelonae. *Natl Med J India* 2007 ; 20 : 240-241.
18. **Dumaine V, Eyrolle L, Baixench M T, et al** . Successful treatment of prosthetic knee Candida glabrata infection with caspofungin combined with flucytosine. *Int J Antimicrob Agents* 2008 ; 31 : 398-9.
19. **Dutronc H, Dauchy F A, Cazanave C, et al** . Candida prosthetic infections : case series and literature review. *Scand J Infect Dis* 2010 ; 42 : 890-5.
20. **Eid AJ, Berbari EF, Sia IG, et al**. Prosthetic joint infection due to rapidly growing mycobacteria : report of 8 cases and review of the literature. *Clin Infect Dis* 2007, 45 : 687-694.
21. **Fainstein V, Gilmore C, Hopfer RL et al**. Septic arthritis due to Candida species on patients with cancer : report of five cases and review of the literature. *Rev Infect Dis* 1982 ; 4 : 78-85.
22. **Farer LS, Lowell AM, Meador MP**. Extrapulmonary tuberculosis in the United States.*Am J Epidemiol* 1979 ; 109 : 205-17.
23. **Gabrielli E, Fothergill AW, Brescini L,et al.** Osteomyelitis caused by Aspergillus species : a review of 310 reported cases. *Clin Microbiol Infect*. 2014 ; 20 : 559-65.
24. **Gamaletsou MN, Kontoyiannis DP, Sipsas NV, et al..** Candida osteomyelitis : analysis of 207 pediatric and adult cases (1970-2011). *Clin Infect Dis*. 2012 ; 55 : 1338-51
25. **Gamaletsou MN, Rammaert B, Bueno MA, et al**. Aspergillus osteomyelitis : epidemiology, clinical manifestations, management, and outcome. *J Infect*. 2014 ; 68 :478-93.
26. **Gamaletsou MN, Rammaert B, Bueno MA,et al**. Candida Arthritis : Analysis of 112 Pediatric and Adult Cases. *Open Forum Infect Dis*. 2015 ; 3 :ofv207.
27. **García-Arias M, Balsa A, Mola EM**. Septic arthritis. *Best Pract Res Clin Rheumatol*. 2011 ; 25 : 407-421.
28. **Gardam M, Lim S.** Mycobacterial osteomyelitis and arthritis. *Infect Dis Clin North Am*. 2005 ; 19 : 819-30.

29. **Golmia R, Bello I, Marra A, et al**. Aspergillus fumigatus joint infection : a review. *Semin Arthritis Rheum*. 2011 ; 40 : 580-584.
30. **Graw B, Woolson S, Huddleston J I**. Candida infection in total knee arthroplasty with successful reimplantation. *J Knee Surg* 2010 ; 23 : 169-74.
31. **Griffith DE, Aksamit T, Brown-Elliot BA, et al**. An official ATS/DSA statement : diagnosis,treatment and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007, 175 : 367-416
32. **Hendrickx L, Van Wijngaerden E, Samson I, Peetermans WE.** Candidal vertebral osteomyelitis : report of 6 patients, and a review. *Clin Infect Dis* 2001 ; 32 : 527-33
33. **Hennequin C, Bouree P, Hiesse C, et al.** Spondylodiskitis due to Candida albicans : report of two patients who were successfully treated with fluconazole and review of the literature. *Clin Infect Dis* 1996 ; 23 : 176-8.
34. **Hodgson SP, Ormerod LP**. Ten-year experience of bone and joint tuberculosis in Blackburn 1978–1987. *J R Coll Surg Edinb* 1990 ; 35 : 259-62.
35. **Horn D, Sae-Tia S, Neofytos D**. Aspergillus osteomyelitis : review of 12 cases identified by the Prospective Antifungal Therapy Alliance registry. *Diagn Microbiol Infect Dis*. 2009 ; 63 : 384-7
36. **Houshian S, Poulsen S, Riegels-Nielsen P.** Bone and joint tuberculosis in Denmark : increase due to immigration. *Acta Orthop Scand* 2000 ; 71 : 312-5.
37. **Izawa K, Kitada S.** clinical analysis of osteoarticular non tuberculous mycobacteria infection . *Kekkaku*. 2016 ; 91 : 1-8.
38. **Jakobs O, Schoof B, Klatte TO, et al**. Fungal Periprosthetic Joint Infection in Total Knee Arthroplasty : A Systematic Review. Orthop Rev (Pavia). 2015 ; 7 : 5623.
39. **Jutte PC, Louenhout-Royackers JH, Borgdorf MW, Horn JR**. Increase of bone and joint tuberculosis in the Netherlands. *J Bone Joint Surg*. 2004 ; 86 : 901-904.
40. **Kelesidis T, Tsiodras S**. Candida albicans prosthetic hip infection in elderly patients : is fluconazole monotherapy an option? *Scand J Infect Dis* 2010 ;4 2 : 12-21.
41. **Kostman JR, Rush P, Reginato AJ.** Granulomatous tophaceous gout mimickingtuberculous tenosynovitis : report of two cases. *Clin Infect Dis* 1995 ; 21 : 217-9.
42. **Kuiper JW, van den Bekerom MP, van der Stappen J, et al** 2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections. *Acta Orthop*. 2013 ; 84 : 517-23.
43. **Kumar K, Saxena MB.** Multifocal osteoarticular tuberculosis. *Int Orthop* 1988 ; 12 : 135-8.
44. **Kuhn DM, George T, Chandra J et al**. Antifungal susceptibility of Candida biofilms : unique efficacy of amphotericin B lipid formulations and echinocandins. *Antimicrob Agents Chemother* 2002 ; 46 : 1773-80.
45. **Kumar K, Saxena MB**. Multifocal osteoarticular tuberculosis. *Int Orthop* 1988 ; 12 : 135-8.
46. **Lam A, Toma W, Schlesinger N.** Mycobacterium marinum arthritis mimicking rheumatoid arthritis. *J Rheumatol* 2006 ; 33 : 817-819.
47. **Lawn SD , Zumla AI**. Diagnosis of extrapulmonary tuberculosis using the Xpert® MTB/RIF ass. *Expert Rev Anti Infect Ther*. 2012 ; 10 : 631-635.
48. **Legout L, Assal M, Rohner P, et al**. Successful treatment of Candida parapsilosis (fluconazole-resistant) osteomyelitis with caspo- fungin in a HIV patient. *Scand J Infect Dis* 2006 ; 38 : 728-30.
49. **Lejko-Zupanc T, Mozina E, Vrevc F**. Caspofungin as treatment for Candida glabrata hip infection. *Int J Antimicrob Agents* 2005 ; 25 : 273-4.
50. **Malani PN, McNeil SA, Bradley SF, Kauffman CA**. Candida albicans sternal wound infections : a chronic and recurrent complication of median sternotomy. *Clin Infect Dis* 2002 ; 35 : 1316-20.
51. **Medical Research Council Working Party on Tuberculosis of the Spine.** Five-yearassessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Fourteenth report of the Medical Research Council Working Party on Tuberculosis of the Spine. *Int Orthop* 1999 ; 23 : 73-81.
52. **Medical Research Council Working Party on Tuberculosis of the Spine.** Controlled trial of short-course regimens of chemotherapy in the ambulatory treatment of spinal tuberculosis : results at three years of a study in Korea. Twelfth report of the Medical Research CouncilWorking Party on Tuberculosis of the Spine. *J Bone Joint Surg Br* 1993 ; 75 : 240-8.
53. **Mekan SF, Saeed O, Khan JA**. Invasive aspergillosis with polyarthritis. *Mycoses* 2004 ; 47 : 518-520.
54. **Muñoz-Fernández S, Maciá MA, Pantoja L et al**. Osteoarticular infection in intravenous drug abusers : influence of HIV infection and differences with non drug abusers. *Ann Rheum Dis* 1993 ; 52 : 570-4.
55. **Murdoch DM, McDonald JR**. Mycobacterium avium-intracellulare cellulitis occurring with septic arthritis after joint injection : a case report. *BMC Infect Dis* 2007 ;7 : 9.
56. **Neofytos D, Huprikar S, Reboli A, et al**. Treatment and outcomes of Candida os- teomyelitis : review of 53 cases from the PATH Alliance(R) registry. *Eur J Clin Microbiol Infect Dis* 2014 ; 33 : 135-41.
57. **Nett JE, Crawford K, Marchillo K, Andes DR** Role of Fks1p and matrix glucan in Candida albicans biofilm resistance to an echinocandin, pyrimidine, and polyene. *Antimicrob Agents Chemother* 2010 ; 54 : 3505-8.
58. **Omari B, Robertson JM, Nelson RJ, et al**. Pott's disease : a resurgent challenge to the thoracic surgeon. *Chest* 1989 ;95 : 145-50.
59. **Ostrosky-Zeichner L, Oude Lashof AM, et al**. Voriconazole salvage treatment of invasive candidiasis. *Eur J Clin Microbiol Infect Dis* 2003 ; 22 : 651-5.
60. **Pappas PG, Kauffman CA, Andes DR, et al** . Clinical Practice Guideline for the Management of Candidiasis : 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016 15 ;62 : e1-50.

61. **Petitjean G, Fluckiger U, Scharen S, et al.** Vertebral osteomyelitis caused by nontuberculous mycobacteria. *Clin Microbiol Infect* 2004 ;10 : 951-3.
62. **Peto HM, Pratt RH, Harrington TA, et al.** Epidemiology of extrapulmonary tuberculosis in the United States, 1993-96. *Clin Infect Dis*. 2009 ;49 : 1350-1357.
63. **Phelan D M, Osmon D R, Keating M R, et al.** Delayed reimplantationarthroplasty for candidal prosthetic joint infection : a report of 4 cases and review of the literature. *Clin Infect Dis* 2002 ; 34 : 930-8.
64. **Pigrau-Serrallach C1, Rodríguez-Pardo D.** Bone and joint tuberculosis. *Eur Spine J*. 2013 ; 22 Suppl 4 : 556-66.
65. **Rezai A, Lee M, Cooper P, et al**. Modern management of spinal tuberculosis. *Neurosurgery* 36 : 87-97.
66. **Segal A, Krausse ES (2007)** Infected total hip arthroplasty after intravesical bacillus Calmette-Guerin therapy. *J Arthroplasty* 2006 ; 22 : 759-762.
67. **Schilling A, Seibold M, Mansmann V,** Gleissner B. Successfully treated Candida krusei infection of the lumbar spine with combined caspofungin/posaconazole therapy. *Med Mycol* 2008 ; 46 :7 9-83.
68. **Slenker AK, Keith SW, Horn DL.** Two hundred and eleven cases of Candida os- teomyelitis : 17 case reports and a review of the literature. Diagn Microbiol Infect Dis 2012 ; 73 : 89-93.
69. **Simitsopoulou M, Peshkova P, Tasina E et al**. Species-specific and drug-specific differences in susceptibility of Candida biofilms to echinocandins : characterization of less common bloodstream isolates. *Antimicrob Agents Chemother* 2013 ; 57 : 2562-70.
70. **Spinner RJ, Sexton DJ, Goldner RD, et al.** Periprosthetic infections due to Mycobacteriumtuberculosis in patients with no prior history of tuberculosis. *J Arthroplasty* 1996 ; 11 : 217-22.
71. **Sugar AM, Saunders C, Diamond RD.** Successful treatment of Candida osteomy-elitis with fluconazole. A noncomparative study of two patients. *Diagn Microbiol Infect Dis* 1990 ; 13 : 517-20.
72. **Tew CW, Han FC, Jureen R, Tey BH.** Aspergillus vertebral osteomyelitis and epidural abscess. *Singapore Med J*. 2009 ; 50 : e151-4.
73. **Tiwari V, Khatri K, Khan SA1, Nath D**. Disseminated Aspergillus flavus following septic arthritis in an immunocompetent patient : a case report. *BMC Res Notes* 2014 Oct 9 ; 7 : 709.
74. **Upadhyay SS, Saji MJ, Sell P, et al.** Longitudinal changes in spinal deformity after anterior spinal surgery for tuberculosis of the spine in adults : a comparative analysis between radical and debridement surgery. *Spine* 1994 ; 19 : 542-9.
75. **Upadhyay SS, Saji MJ, Sell P, et al**. Spinal deformity after childhood surgery for tuberculosis of the spine : a comparison of radical surgery and debridement. *J Bone Joint Surg Br* 1994 ; 76 : 91-8.
76. **Upadhyay SS, Sell P, Saji MJ, et al.** Surgical management of spinal tuberculosis in adults : Hong Kong operation compared with debridement surgery for short and long term outcome of deformity. *Clin Orthop* 1994 ; 302 : 173-82.
77. **Wallace R, Cohen AS.** Tuberculous arthritis : a report of two cases with review of biopsy and synovial fluid findings. *Am J Med* 1976 ; 61 : 277-82.
78. **Walsh TJ, Anaissie EJ, Denning DW, et al.** Treatment of aspergillosis :clinical practice guidelines of the Infectious Disease Society of America. *Clin Infect Dis* 2008 ; 46 : 327-360.
79. **Wang SX, Yang CJ, Chen YC, Lay CJ, Tsai CC.** Septic arthritis caused by Mycobacterium fortuitum and Mycobacterium abscessus in a prosthetic knee joint : case report and review of literature. *Intern Med*. 2011 ; 50 : 2227-32.
80. **Wu M H, Hsu K Y.** Candidal arthritis in revision knee arthroplasty successfully treated with sequential parenteral-oral fluconazole and amphotericin B-loaded cement spacer. *Knee Surg Sports Traumatol Arthrosc* 2011 ; 19 : 273-6.
81. **Yoon HJ, Song YG, Park WI, Chol JP, Chanh KH, Kim JM**. Clinical manifestations and diagnosis of extrapulmonary tuberculosis. *Yonsei Med J*. 2004 ; 45 : 453-461.