Review

# Osteoraticular Tuberculosis-Brief Review of Clinical Morphological and Therapeutic Profiles

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**ABSTRACT:** Osteoarticular tuberculosis (OATB) is a rare form of tuberculosis (TB) whose incidence rose significantly nowadays especially in the underdeveloped countries. The main risk factors predisposing to this new challenge for the medical system are the Human Immunodeficiency Virus (HIV) epidemic, the migration from TB endemic areas and the development of drug and multidrug-resistant strains of Mycobacterium tuberculosis (Mt). The disease affects both genders and any age group although the distribution depending on gender is controversial and that depending on age has a bimodal pattern. In most cases the initial focus is elsewhere in the organism and the most frequent pathway of dissemination is lympho-haematogenous. The clinical picture includes local symptoms as pain, tenderness and limitation of motion, with some particularities depending on the segment of the osteoarticular system involved, sometimes accompanying systemic symptoms specific for TB and other specific clinical signs as cold abscesses and sinuses. The radiographic features are not specific, CT demonstrates abnormalities earlier than plain radiography and MRI is superior to plain radiographs in showing the extent of extraskeletal involvement. Both CT and MRI can be used in patient follow-up to evaluate responses to therapy. TBhas been reported in all bones of the body, the various sites including the spine (most often involved) and extraspinal sites (arthritis, osteomyelitis and tenosynovitis and bursitis). Two basic types of disease patterns could be present: the granular type (most often in adults) and the caseous exudative type (most often in children) one of which being predominant. The algorithm of diagnosis includes several steps of which detection of Mt is the gold standard. The actual treatment is primarily medical, consisting of antituberculosis chemotherapy (ATT), surgical interventions being warranted only for selected cases. It is essential that clinicians know and refresh their knowledge about manifestations of OATB.

***KEYWORDS:*** *extrapulmonary tuberculosis, osteoarticular system, bones, joints*

## Introduction

Osteoarticular tuberculosis (OATB) defines any inflammatory process determined by Mycobacterium tuberculosis (Mt) localized in bones, joins or both structures. Tuberculosis (TB) still represents one of the major causes of skeletal infection in many parts of the world [1,2].

TB, and its bone and joint involvement too, is produced by members of a group of closely related bacterial species named the Mycobacterium tuberculosis complex (MTBC) all of them being obligate pathogens. Moreover, due to new molecular diagnostic markers identified using the complete genome sequencing of MTBC by polymerase chain reaction (PCR)-based typing methods, the Mt spinal involvement, better known also as Pott's spine, is one of the oldest diseases known to mankind [3-5].

There are several terms used in the literature to name the disease: TB of the osteoarticular system; bone and joints TB; skeletal TB; musculoskeletal TB. The last two terms are used by some authors [6] to name only the extra spinal TB lesions.

Most authors consider that bone and joint tuberculous disease is always secondary to a primary or reactivated focus of infection [7].

However, there are authors [8] that are reporting isolated patients with osteoarticular involvement, apparently healthy, without personal of family history of TB, cases that could be considered as primary skeletal involvement.

OATB is also a part who does not represent a large proportion of extra pulmonary involvement (EPTB) of Mt [9,10]. Many studies placed the bone and joint TB lesions on the third position in the frequency hierarchy of extra pulmonary sites of TB [11,12]. However, there are studies on restricted geographic areas [13] in which skeletal TB lesions were found as the most common site of extra pulmonary involvement.

The incidence of OATB among the extra pulmonary sites varied both in time and depending on the socioeconomic status of different geographic areas. Thus, whereas in the past skeletal involvement accounted for only 10-18% of all extra pulmonary cases, incidence that remained almost the same (10-15%) in the last years in developed countries, nowadays OATB incidence raised up to 20% and even to 35% of all extra pulmonary cases mainly in underdeveloped countries [9,11,13-26].

## Incidence. Predisposing factors

OATB is a rare form of TB. The limits of the incidence variation range among all TB cases are 1-6% [9,11,14,19-23,25-32].

This variation is observed both in time and in different geographical and social economic areas and is the consequence of a wide range of factors that predispose to or raise the risk of TB appearance in general and of osteoarticular involvement in particular.

These factors can be grouped depending on their area of intervention in three categories: general factors, factors encountered mostly in developed countries/areas and factors encountered mostly in underdeveloped countries/areas. They are summarized in Table 1 [1,2,8,18,24,33-38].

***Table 1. The predisposing/risk factors of TB and OATB***

| Predisposing/Risk Factor | Type of Risk Factor | Prevalence* | | |
|---|---|---|---|---|
| | | A | B | C |
| **Growing number of people with suppression of the immune system** | *- Immunosuppressive diseases* | Yes | | |
| | *- Immunosuppressive therapies* | Yes | | |
| | *- HIV positive patients/AIDS* | Yes | | |
| **Development of drug and multidrug-resistant strains of Mt** | | Yes | | |
| **Increasing exposure of healthcare workers** | | Yes | | |
| **Individual factors** | *- Women* | Yes | | |
| | *- Repeated pregnancies and Lactation* | Yes | | |
| | *- Blacks* | Yes | | |
| | *- Alcohol abuse* | Yes | | |
| | *- Drug abuse* | Yes | | |
| **Individual Diseases** | *- Diabetes mellitus* | Yes | | |
| | *- Chronic renal failure* | Yes | | |
| | *- Chronic obstructive disease* | Yes | | |
| | *- Liver cirrhosis* | Yes | | |
| | *- Lymphoproliferative disorders* | Yes | | |
| **Aging population** | *- Debilitated with other diseases* | Yes | | |
| | *- Growing number* | | Yes | |
| **Declining public health interest in TB control** | | | Yes | |
| **Immigration from countries/areas with high TB prevalence/TB endemic** | | | Yes | |
| **Socioeconomic factors** | *- Poverty* | | | Yes |
| | *- Homelessness* | | | Yes |
| | *- Malnutrition mainly of protein* | | | Yes |
| | *- Poor sanitation* | | | Yes |
| | *- Overcrowded housing* | | | Yes |

HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome;
* A = General factor; B = Specific mostly for Developed countries/areas; C = Specific mostly for Underdeveloped countries/areas

The appearance and permanent increase of HIV epidemic influenced significantly the incidence and the prevalence of all forms of TB irrespective of geographical area or socioeconomic status. Moreover, this influence was reciprocal. Thus, on one hand, in the USA for instance, 10% of EPTB cases occur in HIV-infected patients and in some regions of


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Africa, up to one-third of adults with osteoarticular infections are HIV positive. On the other hand, TB is often the first manifestation of HIV infection [2,24,33,36,37,39,40].

The development of drug and multidrug-resistant strains of Mt is another major factor that influenced the alarming resurgence of TB in general and OATB in particular in both developed and developing countries.

Apart from the two above mentioned factors, the distinctive risk factors for developed countries are the growing number of elderly segment of population and the migration from TB endemic areas whereas for the developing countries the socioeconomic factors are on the first place. However, an interesting aspect should be pointed out for the developed countries from Europe especially, namely a surprising declining public health interest in TB control [2].

## Gender and Age

Data in the literature concerning the relationship of TB osteoarticular involvement and the patients' gender are controversial: whereas some authors are reporting a predominance of bone and joint lesions in women [10,11,19,41] others found the balance tilted in favor of men [6,12,42,43]. However, the spinal involvement, which is by far the most commonly affected site of the musculoskeletal system is encountered with equal frequency in both genders [34].

Bone and joint TB is encountered in any age group [1,35]. However, the dispersion in relation to age groups of OATB has a bimodal pattern: whereas in developed countries/areas the bone and joint lesions are encountered in the elderly (people older than 55 years), in the under developed countries/areas the lesions are more common in children and younger adults (around 30 years of age) [5,19,40,44-48]. Though, it should be stressed that skeletal TB in children started to be significant in the developed world [6].

## Pathogenesis

The initial TB lesion is either primary or reactivated dormant visceral focus of infection. This could be a pulmonary lesion or an infection of the genitourinary (kidney) digestive (liver) or lymph nodes (mediastinal, mesenteric or cervical groups) systems [7,34,48,49-57].

The pathways through which TB spreads from the initial outbreak to osteoarticular structures are, in order of frequency, the following [7,15,43,45,54,58-63]:

- Blood vessels pathway-the most frequently encountered. It is paucibacillary.
- Lymphatic pathway-less commonly encountered.
- Direct spread from a contiguous lesion.
- Rare paths:
- Direct inoculation of the Mt into the site
- Bone and joints accidental or operative trauma

The routes and the frequency they are used in the dissemination of the TB infection to the musculoskeletal system structures is summarized in Table 2.

***Table 2. Pathways of Osteoarticular involvement by Mt***

| Site | Pathway | | | |
|---|---|---|---|---|
| | **Hematogenous** | **Lymphatic** | **Local spread** | **Direct inoculation** |
| **Spinal** | ***Yes*** | Less commonly | Rare | |
| **Joints (Arthritis)** | ***Yes*** | | Yes | |
| **Bone (Osteomyelitis)** | ***Yes*** | Less commonly | Yes | |
| **Tenosynovitis/Bursitis** | Yes | | ***Yes*** | |
| **Myositis** | Extremely rare | | ***Yes*** | Yes |

In the spine involvement, spread occurs either via the arterial or the venous route as a result of back flow. The most common route of spread to the vertebral body is the Batson's prevertebral venous plexus (a valve-less system that allows free flow of blood in both directions depending upon the pressure generated by the intraabdominal and intrathoracic cavities. The hematogenous route is represented by a rich vascular plexus consisting of an arterial arcade placed in the subchondral region of each vertebra that derives from anterior and posterior spinal arteries which facilitates Mt spread in the dense vasculature of cancellous bone of the vertebral bodies paradiskal regions [5,34].

The vascular pathway for the joints is represented by the subsynovial vessels [32].

Apart from the hematogenous pathway, the bones and joints could contaminate each other through bidirectional local spread. Usually the

process starts in the growth plates of bones which have a better blood supply, and then spreads transphyseally into the joint spaces either from epiphyseal (more common in adults) or metaphyseal (more common in children) lesions [32,64,65].

The synovial and muscular involvement is most often the result of local spread from adjacent lymph nodes, bone, or articular TB lesions, the hematogenous or lymphatic spread without a previous bone involvement being extremely rare [32]. However, myositis could be caused by the use of a contaminated syringe or medical device [61]. Primary bursitis due to hematogenous spread is rare [66].

## Clinical picture

TB infection of the bones and joints has some general features: it is chronic, slowly progressive and destructive, often resulting in walking difficulties and disability [10]. In joint involvement, the clinical picture is more flagrant and obvious in adults than in children [18].

The clinical manifestations are divided in two main groups: constitutional symptoms (accompanying systemic symptoms) and local symptoms.

### Accompanying systemic symptoms

Accompanying systemic symptoms are present in approximately 20-30% of cases of OATB. The classical constitutional features indicating the presence of an active TB process are: malaise, low-grade fevers, evening rise in temperature, night sweats, weight loss, anorexia, generalized body aches, and fatigue [5,59,67,68].

### Local symptoms

The most common local symptoms of OATB regardless the involved tissue/tissues are: pain, tenderness and limitation of motion [67]. However, there are some particularities of the local clinical manifestations depending on the segment of the osteoarticular system involved. These individual features are summarized in Table 3 [52,68].

***Table 3. The Side specific clinical complains***

| Clinical Manifestation | Osteoarticular System Segment | | | | | | |
|---|---|---|---|---|---|---|---|
| | Bones | Joints-Synovial and Articular Involvement (Stages*) | | | | | Muscles |
| | | I | II | III | IV | V | |
| **Insidious Onset** | ***Yes*** | ***Yes*** | | | | | ***Yes*** |
| **Local Tenderness/ Pain** | Yes | Yes | | | | | Yes** |
| **Local Warmth** | ***Yes*** | Yes | | | | | |
| **Swelling/ Effusion** | Yes | Yes | Yes | | | | Yes |
| **Stiffness** | | | | | | | ***Yes*** |
| **Limitation of motion** | | 25% | 25-50% | 75% | 75% Subluxation/ Dislocation | Ankylosis | |
| **Lesion associated (bones/joints)** | Yes | No | Erosion/Lysis (one/more) Diminution of Joint space | Subpericondral cyst Loss of Joint space | Joint Distruction | | ***Yes*** |

**Legend**: *= Tuli Classification [52] Stage I-Synovitis; Stage II-Early arthritis; Stages III and IV-Advanced Arthritis; Stage V-Ankylosis; **= "Night cries" that wake the patient from sleep

### Other specific clinical signs

Other specific clinical signs include: ***lymphadenopathy***, commonly encountered, formation of ***cold abscesses*** and ***sinus drainage***, the latter being present in one third of cases [5,67,68].

Cold abscesses are characterized by lack of pain and other signs of inflammation and sinuses could be sometimes the only presentation, being often misdiagnosed as pyogenic infection or diabetic foot [5,69].

Clinical expression of a tuberculous sinus include: soft tissue fluctuation, bluish discoloration at the periphery, undermined edges, sero-sanguinous discharge, matted draining lymph nodes, and fixation to bone [67].

Sinuses are common and abscess formation may occur in osteomyelitis. On the other hand, sinus formation is rare in tenosynovitis [32,68].
Particular features of spine TB

Pain is the most frequent symptom, its intensity varying from constant mild dull aching to severe disabling. Spasm of the surrounding muscles could be severe.

Progression of kyphosis is most common in children with multiple levels of involvement in the thoracic spine and the deformity of the spine


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is more severe with how the diagnosis is delayed in the younger age group [5,18,34,53,54,68,70,71].

Findings in patients with tuberculous spinal disease are summarized in Table 4.

***Table 4. The clinical complains in Spine TB***

| Clinical Manifestation | Spine Involvement | | | | |
|---|---|---|---|---|---|
| | General | Cervical | Thoracic / Lumbar / Thoracolumbar | | Sacral |
| **Involvement** | 50% of all OATB | Uncommon | Most frequently | Less frequently<br>Most frequently | Uncommon |
| **Pain typically localized to the site of involvement** | ***Yes*** | Yes | back pain | back pain | back pain |
| **Local tenderness** | ***Yes*** | Yes | Yes | Yes | Yes |
| **Weakness** | ***Yes*** | | Yes | Yes | Yes |
| **Truncal rigidity/stiffness due to spasm of the surrounding muscles** | ***Yes*** | Yes Torticolis | Yes | Yes | |
| **Painful restricted joint movements in all directions** | ***Yes*** | Yes | Yes | Yes | Yes |
| **Kyphotic deformity** | ***Gibbus*** | Gibbus | Gibbus | Sometimes | |
| **Neurologic signs/deficit** | ***Common*** | Numbness of the upper and lower extremities Progresses to Tetraplegia | Lower-extremity symptoms Progress to paraplegia | Uncommon Numbness | Numbness |
| **Cold abscess** | ***Yes*** | Hoarseness, Stridor, Dysphagia | Yes | Yes | |
| **Lymphadenopathy** | | | | | ***Common*** |
| **Sinuses** | | | | | ***Common*** |

Neurologic deterioration may occur in both the active and healed stages of the disease, the reported incidence of neurological deficits varying from 23 to 76%. The neurological symptoms are the consequence of the compression of the spinal cord or its roots, the level of spinal cord involvement determining the extent of neurological manifestations. For instance, patients with cauda equina compression due to lumbar and sacral vertebral damage could present cauda-equina syndrome, characterized by decreased or absent reflexes among the affected muscle groups (in contrast to the hyperreflexia seen with spinal cord compression) along with bladder involvement [5,54,72].

The causes of neurologic compromise during the active phase are inflammatory edema, extradural compression from posterior extension of an abscess (pus, caseous material, granulation tissue, sequestrae), or an internal gibbus following collapse or malalignment of the involved vertebrae [73]. Rarely, the neurologic compromise could be expressed as a "spinal tumor syndrome" without bony changes as a result of tubercular granulomas presence in extradural, intradural, or intramedullary locations [67].

Neurologic compromise in "healed disease" (meaning more than 2 years after disease onset) could be determined by: spinal stenosis, direct compression from an internal gibbus deformity, and constriction by peridural fibrosis [73].

Abscess formation is common. Abscesses may migrate posteriorly into the spinal canal, anterior underneath the anterior longitudinal ligament, as well as into neighboring visceral structures. In cervical region, large abscesses can determine hoarseness, stridor, and dysphagia. Abscesses appearing below the diaphragm, typically migrate along the psoas sheath and exit via sinuses in the groin or buttock region [53,54,68].

In most cases the spinal TB lesion is insidious in onset and slow in progression and only rarely there is an acute manifestation [5,53]

Clinical and radiographic presentation of skeletal TB in patients from endemic areas differs from that of individuals from non-endemic areas. Thus, in endemic areas patients present a higher incidence of multifocal skeletal involvement, periosteal reaction, bone sclerosis, and severe bone destruction. In turn, in non-endemic areas patients are older, with a debilitating underlying disease and usually present solitary, osteolytic lesions that involve

the axial skeleton, thoracolumbar vertebral bodies, and hips [74].

## Imaging investigation

### Plain Radiographs

There are no specific radiographic features that are pathognomonic of TB of bones or joints and, in the advanced stages, mimics other osteoarticular lesions.

The most common radiographic figures are summarized in Table 5 [18,32,52,54,75-77].

Tuberculous osteomyelitis may mimic a variety of conditions on plain radiographs. The most common presentation of osseous involvement is a solitary lytic lesion, usually with a sclerotic rim. Sometimes, lesions may cross the physis and new bone formation may be observed subperiosteally [52,54,68,78,79,80].

***Table 5. Main radiographic findings in OATB***

| Radiological Fetures | Osteoarticular System Segment | | | | | | |
|---|---|---|---|---|---|---|---|
| | Bones | Joints-Synovial and Articular Involvement (Stages*) | | | | | |
| | | I | II | III | IV | V | |
| **Soft tissue Swelling** | **Yes** | **Yes** | **Yes** | | | | |
| **Osteopenia/Osteoporosis** | Yes | Yes | Yes | | | | |
| **Periosteal reaction** | Minimal | | | | | | |
| **Osteolysis** | Yes | | | | | | |
| **Subchondral erosions** | | | Yes | | | | |
| **Diminution in joint space** | | | Yes | Yes | | | |
| **Cysts** | | | | Yes | | | |
| **Significant loss of joint space** | | | | Yes | | | |
| **Joint destruction** | | | | | Yes | | |
| **Sclerosis** | Less | | | | | | |
| **Sequestration** | Uncommon | | | | | | |
| **New bone formation** | Yes | | | | | | |
| **Calcifications** | | In the distended bursae | | | | | |
| **Ankylosis** | | | | | | Yes | |

Legend: *= Tuli Classification [52] Stage I-Synovitis; Stage II-Early arthritis; Stages III and IV-Advanced Arthritis; Stage V-Ankylosis

The classical triad of radiologic characteristics of TB tenosynovitis and arthritis, also known as the "Phemister triad", is: juxta-articular osteoporosis, peripheral osseous erosion and gradual narrowing of the intra-articular space though this can be mimicked in rheumatoid arthritis and fungal disease [81,82,83].

Radiographic changes in the joint are absent or non-specific in the early stages of disease. Subchondral erosions involve both sides of the joint and cross the epiphysis in more than one-third of affected children. Cysts in bones appear adjacent to a joint (Fig. 1a) [18,84,85].

Depending on the site of the vertebral lesion and the frequency of appearance, the spine lesions were systematized by Garg et al [5] as shown in Table 6.

***Table 6. Main radiographic findings in Spine TB (modified after Garg et al [5])***

| Type of involvement | | Radiological appearances | |
|---|---|---|---|
| | | Vertebra | Intervertebral disk/space |
| **Typical** | **Paradiskal** | Adjacent margins of two consecutive vertebrae involved. | The intervening disk space reduced |
| | **Central** | Central portion of a single vertebra involved | Proximal and distal disk spaces intact |
| | **Anterior marginal** | Destructive lesion in one of the anterior margins of the body of a vertebra | Minimally involving the disk space but sparing the vertebrae on either side |
| **Atypicsl** | **Skipped lesions** | Circumferentially involvement of two noncontiguous vertebral levels without destruction of the adjacent vertebral bodies | No destruction of intervertebral disks |
| | **Posterior** | Posterior arch involved without involvement of vertebral body | |
| | **Synovial** | Synovial membrane of atlanto-axial and atlanto-occipital joints | |

For the spine, radiographic features suggestive of TB are [18,54,68,86]:

- Multiple levels of involvement (more than two levels)
- Multicentric involvement
- Involvement of the vertebral body with rarefaction of the vertebral end plates
- Relative preservation of the intervertebral disc/disc space but with increasing loss of disc height
- Variable degrees of osseous destruction with late fusion or bone collapse
- New-bone formation
- Subligamentous spread


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- Larger sized paravertebral soft-tissue abscesses, often with calcifications and rim enhancement around

Chest radiographs may show evidence of pulmonary disease in half of patients with OATB, but active pulmonary disease is present in less than 20% of patients (6.9-29% of cases) [19,40,87,88].

## Computed tomography (CT)

CT demonstrates abnormalities earlier than plain radiography and is best because allows the evaluation of the osseous or joint involvement degree [5,54].

Thus, CT is useful for the detection, visualization and evaluation of:

- The degree of bone destruction
- Sequestrum formation (although rare)
- The presence or absence of periosteal reaction
- Epidural lesions containing bone fragments
- Extension in the surrounding soft tissue, calcifications, sclerosis
- Soft tissue abscesses
- Calcifications within the cold abscess [5,32,85, 89-92].

For the spine, CT is particularly of the greatest value because visualizes:

- The disko-vertebral lesions and paravertebral abscesses (Fig. 1b)
- The delineation of encroachment of the spinal canal by posterior extension of inflammatory tissue, bone or disk material [93,94].

Finally, CT is particularly useful for guiding fine needle aspiration or biopsy to provide material for histopathological examination, PCR-based assay for mycobacterial DNA, and culture [32].

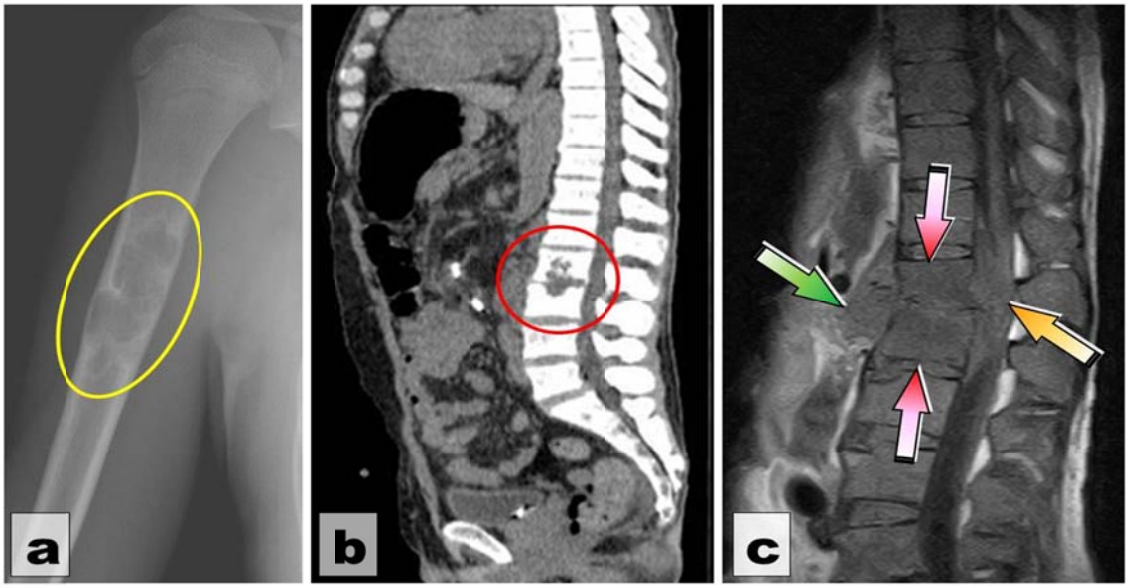


***Fig. 1 Imaging investigations.***
***(a) Arm radiography: Solitary multilocular lytic lesion with a sclerotic rim (yellow oval);***
***(b) Profile Spine CT-STIR1: L2-L3 "mirror" caries with intervertebral disk evanescence (red circle);***
***(c) MRI of the lumbar spine T1-w sagittal plane: Erosive changes involving the inferior aspect of L1 and superior part of L2 with collapse of the intervertebral space (red arrows) and paravertebral abscess involving the spinal canal (yellow arrow) and the prevertebral soft tissues (green arrow)***

## Magnetic resonance imaging (MRI)

Magnetic resonance imaging (with gadolinium enhancement) is the modality of choice for early detection of joint TB even its early findings are nonspecific and may demonstrate intraosseous involvement earlier than the other imaging modalities in osteomyelitis. MRI is also more sensitive than x-ray and more specific than CT in the diagnosis of spinal TB because it can differentiate between granulation tissue and abscess, identify soft-tissue masses and assess the degree of bone destruction. However, bone anatomy and abnormalities, including calcifications and sequestra, are better seen on CT scanning. [5,32,54,95,96]. For joint lesions, MRI can detect: joint effusion, marrow edema, and sometimes abnormalities within the articular cartilage and subchondral bone during the stage of arthritis [97,98].

In tenosynovitis, the investigation helps to delineate the precise extent of soft tissue

involvement and the associated lesions of neighboring bones and joints [32].

In bursitis, the examination reveals: bursal uniform distension, multiple small abscesses in the bursa or the presence of caseous necrosis and fibrotic material within the fluid-filled bursa (the latter on T2W images) [99,100].

For spinal TB, MRI offers more comprehensive information about:

- The extent of involvement/degree of destruction of the vertebral bodies and intervertebral disk (vertebral collapse, and spinal deformities)
- The location and size of paravertebral and/or epidural cold abscesses (Fig. 1c)
- Rapid determination of the mechanism for neurologic involvement
- The presence of spinal cord pathology (impingement or compression, intradural /intramedullary disease, myelomalacia) [5,54,85,89-92].

***Ultrasound examination (USG)***

USG is the primary investigation to confirm the diagnosis of tenosynovitis and to reveal the degree and extent of tendon and tendon sheath involvement. It is also helpful, as we already mentioned above, for guiding fine needle aspiration or biopsy to provide material for other types of biological examination, especially in myositis and bursitis [32,101].

## Morphology

### Location

Tuberculosis has been reported in all bones of the body [102,103].

The various sites of Osteoarticular system include [16,18,48,66,68,78,83,94,104]:

- ***Spine***-most often involved-50%
- ***Extraspinal sites***-represent together the rest of 50%, being individually less common:
- *Joints* (TB arthropathy)-60% of all extraspinal sites
- *Bones* (TB osteomyelitis including the unusual TB dactylitis-metacarpal or phalanx)-38% of all extraspinal sites
- *Tendon sheath* and *Bursae* (TB tenosynovitis and bursitis)-2% or less of all extraspinal sites

**In the spine**, the most affected segment is the thoracic region with less than 50%, followed by the lumbar region and cervical region, gathering together these three regions 80% of all cases. In the rest, the lesions involve more than one region, the combinations being (in the decreasing order of frequency) the thoraco-lumbar region, the cervico-dorsal region and the lumbo-sacral region (Fig. 2) [34].

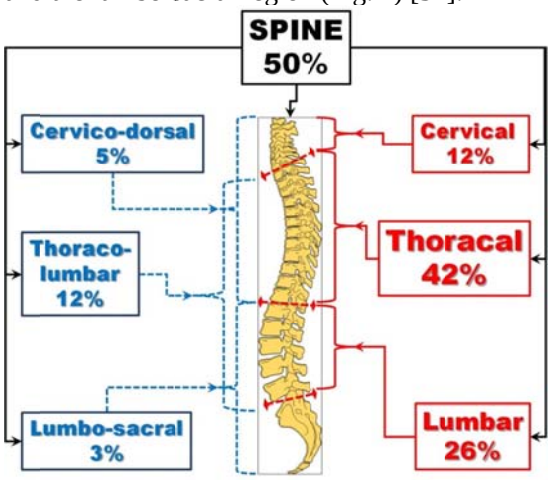


***Fig. 2. Spine Involvment***

**Arthritis.** TB arthritis occurs most frequently at weight bearing joints such as the hip (1 red) and knee (2 red) which account for 15% to 30% and 10% to 20% of non-spinal cases of skeletal TB, respectively. They are followed by, in order of frequency, the sacroiliac (3 red), shoulder (4 red), elbow (5 red), and ankle joints (6 red) (Fig. 3 red marks) [16,18,20,32,48,105,106].

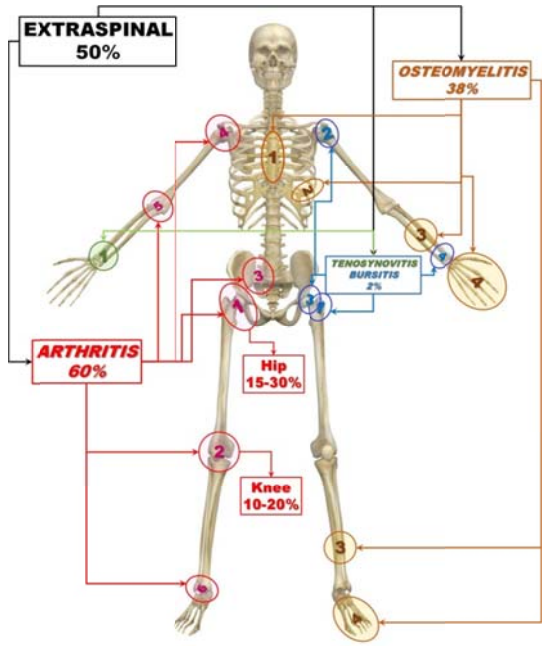


***Fig. 3. Extraspinal sites***

**Osteomyelitis.** Extraspinal bone lesions caused by TB represent according to some authors less than 5% of cases of OATB [54,68].

TB lesions could be found in manubrium sterni, sternum isolated (1 brown), spinous processes, odontoid process, spine of the


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scapula, skull, pelvis, long bones of the extremities (3 brown) and the small bones of the hands and feet (metacarpus, metatarsus, and phalanges-4 brown)). The bones of the hands are more affected than the bones of the feet. The ribs are also frequently involved (2 brown) (Fig. 3 brown marks) [32,34,107,108].

**Tenosynovitis and Bursitis.** The most frequently involved tendon sheaths are the flexor tendon sheaths of the dominant hand and the most affected bursae are the trochanteric, subacromial, subgluteal, and radioulnar wrist bursae (Fig. 3 green marks) [24,54,66,109]

**Myositis.** The cases of TB pyomyositis are rare. Any muscle may be involved but the reported cases were mentioning the muscles of the upper and lower extremities as well as of the chest and abdominal wall [110-113].

TB arthropathy is characteristically monoarticular. However, oligoarticular or polyarticular joint disease could be encountered in around 10% of patients (5-15%) only occasionally with small joint involvement, and more often in those who are immunosuppressed [7,8,20,65,114].

The bone lesions are also usually solitary but multifocal bone involvement may be rarely seen (accounting for 10% of patients with skeletal TB and 1%-3% of all TB cases), with the lesions at different stages of development due either to hematogenous spread, with bacilli being seeded at different times or to a patient with suppressed immune response [30,32,57,115]

During the time, unusual forms of skeletal TB were reported such as:

- Multiple cystic TB (one or more large, oval areas of rarefaction, children) [116,117,118].
- Disseminated skeletal TB (multiple osseous and/or articular sites, in compromised host) [100,119,120,121].
- Closed multiple diaphysitis (swelling in forearms and legs in compromised children) [100].
- Spina ventosa, a spindle shaped expansion with multiple layers of subperiostial new bone, occurring in the short tubular bones of the hands and feet [68].

## Morphological changes

The conflict between Mt and the hosting tissue (bone, synovial structures, cartilage, muscle, soft tissue) is evolving in several steps:

- Ingestion of Mt by mononuclear cells at the site of deposition
- Transformation of mononuclear cells into epithelioid cells and their coalescence into giant Langhans cells
- Tubercle formation by ring-shaped arrangement of lymphocytes around a group of epithelioid cells
- Caseation development within the center of the tubercle.
- Cold abscess formation by intensification of the host inflammatory response, resulting in exudation and liquefaction. The cold abscess is composed of serum, leukocytes, caseation, bone debris, and bacilli [68].

There could be several end results if this conflict such as:

- Resolution with minimal or no morbidity
- Healed disease with residual deformity
- Walled off lesions with calcification of caseous tissue
- A low-grade chronic granular lesion
- Local or miliary spread of the disease that may result in death [52].

Two basic types of disease patterns could be present:

- The ***granular type*** (Fig. 4 a and b)-occurs most often in adults. Is characterized by:
- More insidious and less destructive than the caseous exudative type
- Abscess formation less common.
- The ***caseous exudative type*** (Fig. 4 c and d)-occurs most often in children. Is characterized by:
- Bone destruction
- Local swelling
- Abscess formation
- Sinus formation
- Constitutional symptoms.

Because host-parasite interactions in TB are dynamic, with mixed patterns and transitions, one of the two patterns may predominate either in osseous or synovial involvement [62,122,123].

**Arthritis.** Articular disease often starts as a synovitis, with joint effusion, followed by formation of granulation tissue that typically accompanies synovial proliferation (pannus). Then the pannus begins to erode and destroy the cartilage, determines further demineralization and marginal erosions of the periarticular bones and eventually results in destruction of the articular surfaces of the joint [105,124-127]. If the disease has been inactive for a long time, new bone formation could be expected [128].

**Osteomyelitis.** Extraspinal TB osteomyelitis presents as a solitary cold abscess (lytic lesion with a sclerotic rim), with swelling and only mild erythema and pain, and may be misdiagnosed as a tumor [24,68].

In the long bones, the lesions begin and develop most often in the epiphysis, more precisely in the metaphysis and causes tubercle formation in the marrow, with secondary infection of the trabeculae. In rare cases, the diaphysis may also be affected. The lesion may also penetrate the physis or extend into an adjacent joint [32,59,68].

The active phase of tuberculous osteomyelitis is characterized by bone destruction without sequestra and with minimal new bone formation [129].

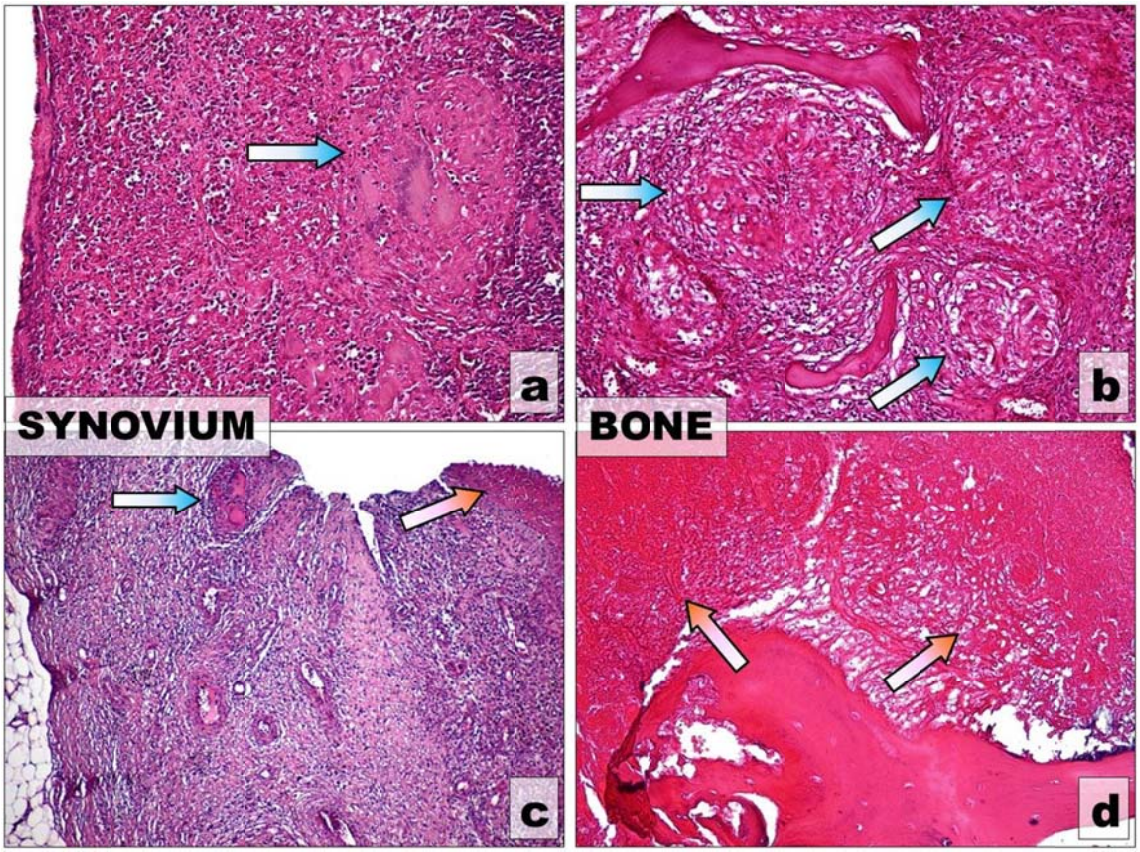


***Fig. 4. Main histological patterns of OATB. UP: Granular type-Giant Langhans cell granulomas (blue arrows) placed (a) in the synovium (b) in the cancellous bone, H-E stain, x10;***
***DOWN Caseous necrosis (red arrows) (a) in the synovium x4 (b) in the compact bone, x10, H-E stain***

**Tenosynovitis.** In general, the morphologic changes are nonspecific tendon and synovial thickening predominate, with relatively little synovial sheath effusion [32]. Jaovisidha et al [66] described three stages of TB tenosynovitis:

- The *hygromatous* stage-characterized by the presence of fluid inside the tendon sheath without associated sheath thickening.
- The *serofibrinous* stage-characterized by thickening of the flexor tendons and synovium, with multiple tiny nodules within the synovial fluid, corresponding to the rice bodies previously reported in the literature.
- The *fungoid* stage-characterized by a soft tissue mass involving the tendon and tendon sheath.

**Bursitis.** The bursa inflammation is expressing like a cold abscess or draining fistula that does not respond to conventional antibiotic therapy [24].

Bursa could be uniformly distended by caseous necrosis and fibrotic material, with calcifications in the wall or multiple small abscesses in the bursa could be seen [99,100].

**Myositis.** Abscess formation is the rule in all cases of pyomyositis. Associated cellulitis and osteoarticular involvement may also be present [110, 130].

**Spine.** Typical bone lesion for spine TB is destruction of the anterior region of vertebral bodies with subsequent collapse of the spine [105,126].

Two distinct patterns of vertebral TB are described [57]:

- The first is ***Spondylitis without disc involvement***, which is exceedingly more


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common. Multilevel vertebral body involvement could occur in this form as skip lesions.

- The second pattern is *Destruction of **two or more contiguous vertebrae associated with late-onset disc infection***, which results in intervertebral space narrowing due to disc herniation into the collapsed vertebral body; this is regarded as an atypical radiologic feature of vertebral TB.

In children, TB of the spine generally involves the osseous tissue of the vertebrae and not the cartilaginous growth plate [18].

## Diagnosis

The algorithm of diagnosis in OATB includes several steps [8,26,53,131-133].

1. ***Epidemiological background***-Pay attention to the patient's country of origin and his history of prior known or possible TB contact.

2. ***Clinical examination***-a high index of clinical suspicion given the indolent nature of tuberculous bone and joint disease and especially:

- In patients with no evidence of active chest disease (more than half of cases)

- In patients with HIV infection and relatively high CD4 counts and no other signs or symptoms of TB

3. ***Paraclinical examination***

- Tuberculin Skin Test (TST)

- Enzyme-Linked Immunosorbent Assays (ELISA)

- Interferon Gamma Release Assays (IGRAs)

4. ***Imagistic examination***

- Radiology

- Computed Tomography (CT) which can be helpful for:

- The detection of osseous or joint involvement/destruction, the presence or absence of periosteal reaction and soft tissue masses or calcifications, sclerosis, and soft tissue abscesses.

- Guidance of percutaneous biopsy or abscess drainage [32, 134].

- Magnetic Resonance Imaging (MRI)

- Useful in showing the extent of the disease, particularly in spinal lesions [135].

- The preferred technique to demonstrate early bone marrow changes in tuberculous osteomyelitis and arthritis, joint effusion, and cartilage destruction [32].

- Superior to plain radiographs in showing the extent of extraskeletal involvement, particularly in the case of compromise of the vertebral canal and the epidural space [74].

- Both CT and MRI can be used in patient follow-up to evaluate responses to therapy [135].

- USG-particularly useful for guiding fine needle aspiration or biopsy [32].

5. ***Detection of Mt*** by:

- Ziehl-Neelsen and immunohistochemistry stains on smears and histological slides

- Culture of Mt from bone/synovial/soft tissue/draining sinuses, synovial fluid although, in some cases, cultures may reveal colonizing bacteria or fungi that are erroneously assumed to be the causative pathogen.

- Polymerase Chain Reaction (PCR)

The material used for detection could be [132,133]:

- Synovial fluid or purulent infected material obtained by aspiration or fine needle aspiration biopsy

- Bone/synovial/soft tissue obtained by biopsy

The traditional criteria for diagnosing TB are:

- Chest radiology

- Detection of acid-fast bacilli by Ziehl-Neelsen stain on microscopy and culture [4,136-138].

Microscopy is the most rapid diagnostic tool but it is very insensitive, yielding only 10-30% of culture-positive samples [4].

Biopsy may be required to clear up diagnostic confusion, being the most definitive test for tuberculous arthritis. It must be performed in cases in which microbiologic tests give negative results, the demonstration of caseating granulomas on histological examination being of significant value [49,53,139].

Culture is the gold standard for the diagnosis of osseous TB is culture of mycobacteria from bone tissue or synovial fluid but may take four weeks to obtain conclusive results even with enhanced culture systems [4,53].

Newer methods of diagnosis, especially polymerase chain reaction (PCR) on obtained joint tissue biopsies, appears promising in the early diagnosis of tuberculous arthritis [140].

Drug susceptibility testing of isolates is essential. In this respect, the Xpert MTB/RIF assay is an automated nucleic acid amplification test that can simultaneously identify Mt and rifampin resistance; it has been shown to be fast and accurate in diagnosing musculoskeletal TB in children and adults [132,133,141].

### Tuberculosis of spine in childhood

A special mention about spine TB in children should be made because in this group of age the deformity is "dynamic in continuum" and could

lead either to correction or deterioration therefore needing active surveillance till the entire growth potential is completed [142].

The progression of the spine deformities implies three overlapping phases:

- **Phase I**-Active phase
- **Phase II**-Growth phase
- **Phase III**-Late phase

There is an increased collapse for each vertebral loss and may increase or decrease during the growth phase in children as opposed to the adults where the collapse is proportionate to the extent of destruction and stops with consolidation of the lesion [142].

Rajasekaran (1999) [143] defined a "Spine at risk" concept, described by four radiological signs which offer reliable prediction of progression of the deformity and are of inestimable assistance for identifying "children at risk" for severe deformity. These are:

- Facet joint dislocation which triggers disaster in childhood lesion
- Retropulsion sign
- Lateral translation
- Topplling Over sign.

***Table 7. Main types of Spine TB progression through Phase II (modified after Rajasekaran-2013)***

| Type | Subtype | Description | |
|---|---|---|---|
| **Type I** | **Type Ia** | Progression of the deformity throughout the growth phase continuously after Phase I | |
| | **Type Ib** | A spurt of progression after a delay period of 3–6 years<br>Progression showed the highest increase in deformity although the increase of deformity occurs | |
| **Type II** | **Type IIa** | Progression shows beneficial effects during growth phase with a decrease in the deformity after the healed stage. | Immediately after Phase1<br>Maximum decrease of the deformity |
| | **Type IIb** | | After a delay period of 3–6 years |
| **Type III** | | Progression with minimal destruction (No any major changes in the deformity during the active or the healed phases) | |

He identified also the risk factors for severe increase of deformity, namely:

- Patients less than 10 years of age at the onset of the disease
- An initial kyphosis angle of more than 30 degrees;
- Vertebral body loss of greater than 1.5
- Involvement of more than 3 vertebral bodies;
- Presence of "spine at risk" signs in radiographs;
- Global involvement of the vertebrae and
- Children who have partial or no fusion during adolescent growth spurt.

Based on these observations, five main types of progression were finally defined during the Growth phase (Table 7) [144].

## Differential diagnosis

The differential diagnosis of skeletal TB includes:

- Subacute or chronic infections due to pathogens or diseases such as (depending upon epidemiologic factors):
- Staphylococcus aureus osteomyelitis
- Brucellosis
- Melioidosis
- Actinomycosis
- Candidiasis
- Histoplasmosis
- Metastatic malignancy (especially multifocal bone involvement)

For spine TB, the following differential diagnosis should be considered:

- Degenerative disc and facet joint disease
- Vertebral body collapse due to osteopenia (due to a variety of causes such as osteoporosis and chronic corticosteroid therapy)
- Spondyloarthropathy, spondylitis
- Pyogenic spinal infection
- Brucellar spondylitis
- Sarcoidosis
- Malignancy-(metastases, multiple myeloma, lymphoma)

## Treatment

Before the advent of chemotherapy in 1940s, the only treatments available for TB were surgical interventions as well as a general improvement in an individual's immunity through empirical methods as rest, good nutrition, sunlight, fresh air and hygiene [106,128,142,145].

Nowadays, the treatment of OATB is primarily medical, consisting of antituberculosis chemotherapy (ATT). Surgical interventions are only an adjunct to appropriate ATT, being warranted only for selected cases [18]. Adequate nutritional support is however essential, as in all forms of TB [53].

The goals of treatment are:

- Infection containment and eradication
- Pain relief


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- Preservation and Restoration of bone and joint function [146].

## Antimicrobial therapy

The treatment is based on antituberculous therapy (ATT). The selection of drugs is generally the same as that for pulmonary TB (isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol). The drug regimen depends on whether or not the patient has HIV infection or drug-resistant TB [7,62,147].

Successful medical treatment of TB requires a minimum of three drugs to which the Mt is susceptible, and at least one of these drugs must be bactericidal [18]. The optimal duration of therapy for OATB treatment is uncertain however many authors recommend at least 9 to 12 months for bone and joint involvement, especially for patients on regimens that do not include rifampin and/or for patients with extensive or advanced disease, particularly if it is difficult to assess the response to therapy [147-151].

The duration of therapy has wide variations depending on the site of the oasteoarticular system involved, such as:

- 6 months in sacral TB,
- 12-18 months in various spinal sites,
- 12-18 months in TB of craniovertebral junction
- 14-18 months in sternoclavicular joint involvement
- 12-20 months in TB affecting the talus
- 12 months in TB of metacarpals and phalanges [71, 152-156].

Multi-drug-resistant TB should be suspected if osteoarticular disease activity shows no signs of improvement after 4-6 months of uninterrupted therapy [53].

ATT gives good results with low morbidity and mortality, approximately 90% to 95% of patients healing without sequelae if treated at an early stage [7,157]. However, even chemotherapy can effectively treat the disease at any stage, the ultimate functional result depends upon the degree of tissue damage at the start of the treatment [54].

## Auxiliary methods

In arthritis, Splints may be used for a short time to relieve acute symptoms and for a long time in specific cases of TB of the joints to prevent deformities of the infected extremities [158, 159]. In spine TB, various types of spinal support in the form of collars, braces and corsets, may need to be used [53].

## Surgery

## Extraspinal TB

The role of surgery in treatment of extraspinal TB is still somewhat controversial, varying throughout different regions of the world both in terms of indications for surgery and the specific procedures recommended.

As a general rule, surgery is reserved for specific indications, most often to establish the diagnosis or to treat complications of the disease process. Thus, surgery is recommended for approximately 5% of uncomplicated cases, and 60% of those with neurologic deficits [68,160].

Tuli [52] proposed a pattern of the natural history of TB arthritis progresses through five consecutive steps defining for each stage the therapeutic strategy too. This treatment algorithm is summarized in Table 8. ATT is mandatory for any of the five stages, surgery being reserved only for the advanced stages.

***Table 8. The therapeutic algorithm for TB joint involvement proposed by Tuli [52]***

| Arthritis Stage | ATT | Auxiliary Treatment | Surgical Treatment |
|---|---|---|---|
| **Stage I (Synovitis)** | YES | 1) Rest<br>2) ROM<br>3) Splinting | |
| **Stage II (early arthritis)** | YES | 1) Rest<br>2) ROM<br>3) Splinting | 1) Synovectomy |
| **Stage III (advanced arthritis)** | YES | | 2) Osteotomy<br>3) Arthrodesis<br>4) Arthroplasty |
| **Stage IV (advanced arthritis)** | YES | | 2) Osteotomy<br>3) Arthrodesis<br>4) Arthroplasty |
| **Stage V (Ankylosis)** | YES | | 2) Osteotomy<br>3) Arthrodesis<br>4) Arthroplasty |

Legend: ATT= Antituberculous treatment; ROM= Range of Motion exercises

The main indications for surgery are:
- Biopsy
- Patient unresponsive after 4 to 5 months of ATT
- Severe joint cartilage destruction
- Joint deformity
- Large abscesses
- Patients with neurological manifestations
- Patients where healing gave a painful joint ankylosis
- Multiple drug resistance [26,47].

The range of surgical procedures that could be carried out includes:
- Incision and drainage of abscesses
- Synovectomy
- Excisional arthroplasty for the hip or the elbow
- Arthrodesis for the ankle, the wrist, or the knee
- Joint replacement if the disease has remained inactive for more than 10 years [7,24,147,158,161].

## Spine TB

In spinal TB too, the treatment is primarily medical, with anti TB drug regimens. The surgical treatment is reserved for only two main situations:
- patients with neurological complication not responding to medical treatment
- some children with TB of the spine [34,142].

The major aim of treatment is to prevent paraplegia. Besides this, decompression, stabilization, and deformity correction are the main specific goals of the surgical interventions [34, 54].

Indications for surgery have to be individualized and are synthesized in Table 9.

***Table 9. Indications of surgery in spinal tuberculosis***

| Type of Patient | Indication | | Type of Indication |
|---|---|---|---|
| **Without neurological complications** | For biopsy, to establish a diagnosis in case of uncertainty (inability to obtain adequate material for culture by other means | | R "Middle path" |
| | Failure to respond to ATT | Evidence of ongoing infection | |
| | | Progressive bone destruction | |
| | Failure to respond to conservative therapy | | |
| | Prevention of severe kyphosis in young children with extensive dorsal lesions | | |
| | Mechanical reasons | Destruction of two or more vertebrae | A "Middle path" |
| | | Involvement of the Posterior elements/Circumferential disease | |
| | | Spinal instability caused by destruction or collapse | |
| | | Progression of spinal instability despite ATT | |
| | | Deformity is likely | |
| | | Kyphosis/deformity > $40^0$ at presentation | |
| | | Progression of kyphosis/ deformity despite ATT | |
| | Large Abscess Paraspinal/Paravertebral | Increasing in size despite medical treatment | A |
| | | Respiratory obstruction developed | |
| | Chest wall cold abscess | | A |
| **With neurological complications** | New, Worsening/Progressive and Severe/Advanced Neural complications/deficit | | "Middle path" |
| | Lack of improvement/recovery of Neural complications despite ATT | | |
| | Persistent Pain/Spasm | A demonstrable mechanical block | R |
| | Nerve root compression | Instability because the lack of fusion | "Middle path" |
| | Neurological deficits in patients for whom prolonged bed rest may lead to other problems | | R |
| | Paraplegia of rapid onset/severe paraplegia | | |
| | Late-onset paraplegia | | |
| | Painful paraplegia in elderly patients | | |
| | Neural arch disease | | |
| | Spinal tumor syndrome (epidural spinal tuberculoma without osseous involvement) | | |
| **Recurrence** | | | |

Legend: ATT = Antituberculous treatment; A=Absolute indication; R=Relative indication

For acute situations, some authors defined absolute and relative indications that are mentioned in the table [5,18,54,162-171]. The specific indications of the "middle path", popularized by Tuli in India in the 70s are also highlighted [148].The main strategies of approach in the surgical treatment of spinal TB are the following [54]:

- Chemotherapy alone (no capability for spinal surgery)


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- "Middle path" (surgery for specific indications) [148]

- Routine decompression/debridement and bone grafting

Recommendations for surgical treatment are based upon:

- The location of involvement (anterior, posterior, circumferential)

- The risk or presence of kyphotic deformity

- The neurologic status

- The status of the disease (active or healed)

- The experience of the surgeon

- The resources available locally [54].

The operative approach of the spine could be anterior or posterior. The ***anterior approach*** is usually recommended and used and can allow:

- Abscesses evacuation

- Excision of all avascular material

- Safe anterior decompression of the spinal cord

The ***posterior approach*** is rarely indicated, ie in two circumstances:

- When posterior spinal elements are more involved than the anterior ones

- When both the anterior and the posterior elements are involved and posterior stabilization is needed before anterior decompression and arthrodesis is performed [172].

## Outcome

The results of prolonged ATT treatment completed when necessary with surgery gives, in most patients, encouraging results. The few cases of osteoarticular multidrug-resistant TB have a good outcome too with second-line anti-TB drugs combined with surgery [24,172].

## Conclusions

It is essential that clinicians know and update their knowledge on the manifestations of OATB so they can recognize and diagnose this curable disease before definitive surgery is practiced. The surgery should be limited to the diagnosis or treatment of life threatening complications.

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