

Spinal Tuberculosis: Rethinking an Old Disease

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Abstract

Despite of the fact that the earliest cases of Spinal Tuberculosis date from 2400 BC, the first modern description was made in 1779 by Sir Percival Pott in the European population. The improvement of public health measures and the introduction of effective anti-tuberculosis drugs have made the infection virtually eradicated in developed countries. However, migration phenomena, the infection by human immunodeficiency virus (HIV) and other causes of immunodeficiency as diabetes and cancer chemotherapy have led to a resurgence of tuberculosis in parts of the world where the disease was sporadic or unknown. It is currently considered a public health problem, both in developed and developing countries.

Recently the clinical and radiological features of Spinal Tuberculosis have changed considerably. Atypical presentations are more common nowadays. The improvement of diagnosis and therapeutic management has lead to better clinical outcomes. However, early diagnosis and appropriate treatment remain the mainstay predictors of successful outcomes, preventing the most serious complications of Spinal Tuberculosis: neurological deficits and spinal deformities.

The main aim of this review is to discuss the historical aspects of the disease management as well as the most recent challenges. The authors included articles with acceptable design, clearly explained results and justified conclusions according to the data, regardless of their time of publication.

Keywords: Spinal tuberculosis; Pott disease; Tuberculous spondylodiscitis; *Mycobacterium tuberculosis*; Spinal tuberculosis management; Surgical treatment of spinal tuberculosis; Spinal deformities

Introduction

Spinal Tuberculosis (ST) is one of the oldest diseases known to mankind. Evidences of infection were found on vertebral remains dated from the Iron Age in Europe, and on mummies from South America and ancient Egypt. Despite of the fact the earliest cases of ST date from 2400 BC, the first modern description was made in 1779 by Sir Percival Pott in the European population. Thus, ST is also known as Pott's disease [1,2].

The infection is caused by a highly aerobic, alcohol-acid-resistant, non-proteolytic enzyme-producing *bacillus*, the *Mycobacterium tuberculosis*, also known as Koch's *bacillus* (BK) (In honor of its discoverer, the German bacteriologist Robert Koch) [3].

The improvement of public health measures and the introduction of effective anti-tuberculosis drugs have made the infection virtually eradicated in developed countries. However, migration phenomena and the infection by human immunodeficiency virus (HIV) have led to a resurgence of tuberculosis (TB) in parts of the world where the disease was sporadic or unknown [4,5]. It is currently considered a public health problem, both in developed and developing countries. Early diagnosis and appropriate treatment are essential to prevent the most serious complications of Pott's disease: neurological deficits and spinal deformities.

Objective and Methods

The reports about different aspects of ST included in this review, with acceptable design, clearly explained results and justified conclusions according to the data. Since, one of the aims of this review was to discuss the historical aspects of TB management; we included articles, regardless of their time of publication.

Epidemiology

According to data from the World Health Organization (WHO), in 2016 about one-third of the world's population is infected with

Mycobacterium tuberculosis, although only a small percentage of the infected develops the illness [6]. The exact incidence and prevalence of Pott's disease are not known for most countries. However, it is assumed to be proportional to pulmonary infection [7]. Approximately 10% of patients with extrapulmonary tuberculosis have skeletal involvement. The spine is the most frequently affected area [7,8].

Spinal Tuberculosis represents about 50% of all cases of skeletal tuberculosis. People with impaired immune systems due to chemotherapy for cancer, old age, *diabetes mellitus*, alcoholism, malnutrition and drug abuse, are at greater risk of developing the disease. In the case of Human Immunodeficiency Virus (HIV) co-infection the risk is 26 to 31 times higher, since *Mycobacterium tuberculosis* infection is the most common opportunistic infection associated with HIV [3,6].

The genetic susceptibility associated to ST was also demonstrated by Zhang et al. in 2010. This group investigated, in the Chinese population, the association between this infection and the Fok-I Polymorphism in the vitamin D receptor gene, demonstrating that this gene increases the susceptibility to ST [9,10].

In 2015, 10.4 million new cases of TB worldwide were detected. Sixty percent of the cases were diagnosed in 6 countries: India, Indonesia, China, Nigeria, Pakistan and South Africa. 400 000 had HIV infection [6]. The 2013 United Kingdom (UK) Public Health Agency report notified 7892 cases of TB in 2013; 73% of cases occurred in people not born in the UK, with 15% having arrived in the country less than 2 years ago; 4.5% (353 patients) had spinal cord injury [11].

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Ramos et al. published a study on the North American population in 2011. It reported 75 858 patients with tuberculosis and 3.7% (2789) of these presented vertebral complications [12]. In endemic countries, ST is more common in children and young adults, while the disease affects more the adult population in the developed eastern and western countries [7].

Pathophysiology

The *Mycobacterium tuberculosis* complex *bacillus* causes tuberculosis. There are 60 species described but only a minority cause disease in humans: the *Mycobacterium tuberculosis* (which is the most common), the *Mycobacterium bovis*, the *Mycobacterium microti* and the *Mycobacterium africanum* [3].

Tuberculosis of the spine is a local manifestation of a systemic disease. It is always secondary to a primary focus on another part of the body, often pulmonary or genito-urinary. In 80% of cases it is difficult to detect the primary focus [13]. Although it can also occur by direct dissemination from adjacent structures, vertebral infection occurs, in the majority of cases, by hematogenous dissemination of the *bacillus*, both via arterial and venous [7,14]. Each vertebra is nourished by a rich subchondral arterial plexus that derives from the anterior and posterior vertebral arteries, being associated with the dissemination of the *bacillus* to the paradiscal areas.

The infection of the vertebral body is associated with the intraosseous venous plexus derived from the Batson paravertebral venous plexus. The most common type of ST is the paradiscal that occurs in about 90 to 95% of cases, in which the *bacillus* infects the anterior part of the vertebral body, adjacent to the subchondral plaque. From this focus, the infection extends to the central part of the body and intervertebral disc, which is spared until late stages of the disease, due to the fact that the *Mycobacterium tuberculosis* lacks proteolytic enzymes.

The other types (representing 5% to 10%) include: central tuberculosis, in which the disc is not involved, being characterized by the destruction and collapse of the vertebral body with the appearance of *Vertebra plana*; the posterior type with involvement of the posterior elements; and the non-skeletal type, characterized by the formation of abscesses without complications at the bone level. Although in the adult the anterior part of the vertebral body is classically the first to be affected by the infection that extends secondarily to the disc, that in precariously vascularized in this age, in the child, the intervertebral disc may be primarily affected once is more vascularized [8,13,15-17].

Spinal Tuberculosis is characterized by kyphotic deformity due to progressive destruction of the intervertebral space and adjacent vertebral bodies, formation of cold abscesses by extension to adjacent ligaments and soft tissues, and neurological deficits due to mechanical compression or direct effect of infection under neural structures [18]. Any area of the spine can be affected, however, the lower thoracic region is most frequently affected (40% to 50% of the cases), followed by the lumbar spine (35% to 45%) and the cervical spine (10%) [19].

Clinical Features

Spinal tuberculosis is a chronic disease with slow and insidious progression. The total duration of the illness varies from few months to few years, with average disease duration ranging from 4 to 11 months. Usually, patients seek advice only when there is severe pain, marked deformity, or neurological symptoms [7,20].

Pain, neurological deficit, cold abscess, and kyphotic deformity are the characteristic features of ST [16,21]. Constitutional symptoms of malaise,

fatigue, loss of weight and appetite, evening rise in temperature and night sweats may also be present but are more typical of pulmonary TB.

Back pain is the most frequent symptom of ST and several studies report the presence of back pain in 90% to 100% of patients with this disease [22,23]. It can vary from a relatively weak but constant pain, to a severe and disabling pain. Typically, it is located in the affected area and may present mechanical or radicular characteristics. Chronic back pain was the only symptom observed in 61% of cases of ST [7,24].

Paravertebral cold abscesses develop slowly when the infection extends to adjacent ligaments and soft tissues. They are painless, have no other inflammatory signs and are very suggestive of ST, being observed in about 50% of the cases [7,21]. They can grow to a very large size and the presentation depends on the affected vertebral area. In the cervical region the pus accumulates behind the fascia, forming retropharyngeal abscesses that produce considerable mass effect, causing dysphagia, breathing difficulties and hoarseness. They may also progress and invade the mediastinum, trachea, esophagus and the pleural cavity. In the thoracic spine they appear as fusiform tumefactions or *bulbous paravertebral* abscesses. Abscesses developing within the lumbar area may manifest in the groin or thigh through extension via the sheath of the psoas muscle, or in the gluteal region, by progression along the gluteal vein [15,25].

The most serious and dreaded symptoms of ST are neurological complications, reported in 32% to 76% of cases, depending on the study [3,26,27]. The type of neurological deficit is determined by the vertebral level involved and any untreated deficit in time can progress to paraplegia or tetraplegia [7].

Neurological deficits can occur at any stage of the vertebral disease. In 1967, Hodgson classified neurological deficits into 2 groups, according to the activity of the infection: the early onset deficits, that occur in the active phase of the disease and the late onset deficits that appear up to 10 to 20 years after the vertebral infection, in the healed disease phase (Table 1) [28,29].

As the disease progresses, the collapse of one or more vertebral bodies determines a kyphotic deformity. The development of kyphotic deformity is the rule and not the exception in ST. The pattern of progression of deformity differs between adults and children. In the adult, kyphosis evolves during the active phase of the disease and the final deformity is related to the extent of vertebral damage, generally not exceeding 30°. In the child, considerable changes are expectable, even after healing the infection, due to injury of the vertebral growth plate, either triggered by the disease itself, either by surgical intervention or biomechanical factors [30-33].

Rajasekaran et al. demonstrated, at pediatric age, the occurrence of morphological changes during growth, both in kyphosis fusion

Early onset deficit	Late onset deficit
Mechanical pressure of the spinal cord by an abscess, granulation tissue, tubercular debris, caseous tissue or mechanical instability	Stretching of the cord due to severe kyphosis
Infective thrombosis or endarteritis of spinal vessels	Fibrotic tissue involving the dura
Tuberculous myelitis and tuberculous arachnoiditis by direct involvement of the the cord and meninges by tubercular infection	

Table 1: Causes of neurological involvement in spinal tuberculosis.

mass, and levels not involved, above and below. They also described 3 possible types of progression of the deformity. In type I, there is an increase in deformity with growth, in type II there is an improvement in deformity with growth and in type III there are no important changes in the deformity associated with growth. In addition, they described four radiographic signs of “spine at risk”: retropulsion, subluxation, lateral translation and toppling. Children with 2 spine at risk signs are at increased risk of severe worsening of the deformity. Thus, it is recommended to maintain periodic surveillance until the end of growth [32,34].

Vertebral destruction and kyphotic deformity may be associated with instability and three types of vertebral restabilization are described. When the contact area in the distal vertebra is wide, type A-restabilization occurs. In the case of severe vertebral destruction, with marked loss of vertebral height and severe kyphosis associated with subluxation or dislocation of one or both facets, restabilization occurs through bridges of contact between the proximal and distal vertebra, type B restabilization. When severe destruction of the anterior column happens, type C restabilization can occur, as the wedge of the remaining part of the vertebral body grows.

The dislocation of both facets is associated with buckling collapse, being possible the rotation of 90° of the proximal vertebral body. The buckling collapse is common in children under 7 years old, with affection of 3 or more vertebral bodies in the dorsal or dorsolumbar spine [32,35].

Diagnosis

The etiological diagnosis of TB requires the identification of BK in a biological sample or through molecular tests [17]. However, in the ST the strong correlation between the clinical and radiological findings can be sufficient in order to establish the diagnostic. Thereby it is crucial to understand the clinical behavior of the infection and the radiological findings that characterize this infection.

Imaging Studies

Radiography

Despite its simplicity, radiography frequently provides enough information for a diagnostic and treatment of ST. This imaging study



Figure 1: Lateral X-ray showing erosion of the upper L1 platform in a early stage of spinal tuberculosis.

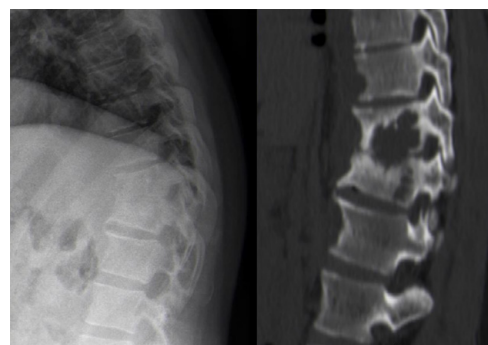


Figure 2: Lateral X-ray and sagittal CT scan showing destruction and collapse of two adjacent vertebral bodies.

is still very valuable in countries with less financial resources. It is important to highlight that a radiolucent lesion only appears on the X-ray where 30% of the mineral density of the bone has been lost, thus these alterations are never evident during the initial phase of the disease. According to Kumar, the radiographic aspects of the infection of the anterior spinal column are so characteristic that in most of the cases, it can be diagnosed only using this method of the image [7,17]. Spinal Tuberculosis usually presents with osteopenia of the vertebral platforms, narrowing of the pars articularis and loss of definition of the paradiscal margins of the vertebral bodies. The occurrence of a lytic lesion without the formation of new bone is common [3,36]. The progression of the infection leads to a hardly noticeable loss of the discal height and to bone destruction that is mostly anterior (Figure 1).

The central type lesions generally present with destruction, ballooning and concentric collapsing of the vertebral bodies. In the infection of the posterior elements, the destruction of the pedicles and lamina, the erosion of adjacent ribs and the posterior cortical of the vertebral body can occur.

The cold paravertebral abscesses are observed on simple X-rays as shades on the soft tissues adjacent to the column [7,36]. In the case of cervical involvement, the increase of pre-vertebral space is suggestive of the presence of an retro pharyngeal abscess. Abscesses with a longer duration can produce concave erosions in the anterior margin of the vertebral bodies, giving images of scalloped type, denominated aneurism phenomenon. The presence of calcifications in abscesses is uncommon but very suggestive of ST and is related with the fact that BK doesn't produce proteolytic enzymes [7,37-39].

The craniovertebral and cervicothoracic junctions are difficult to evaluate by this method of the image.

Computed tomography (CT)

Allows the diagnosis of the vertebral alterations earlier in time than X-ray, giving the characteristics in a more detailed way regarding the osseous lesions, from the involvement of the posterior elements, the involvement of the craniovertebral junction and the cervicothoracic junction and the sacroiliac articulations (Figure 2) [3,7,36]. According to Jain et al. 4 patterns of destruction can be observed in a CT: (1) fragmentary in 47% of the cases; (2) osteolytic in 34%; (3) sclerotic in 10% and (4) subperiosteally in 30% [27,36,40].

CT also allows to evaluate the involvement of the soft tissues and paravertebral abscesses, being an excellent method to detect abscess calcifications and is also useful in the evaluation of the medullar compression by the inflammatory tissue or sequestrum [7].

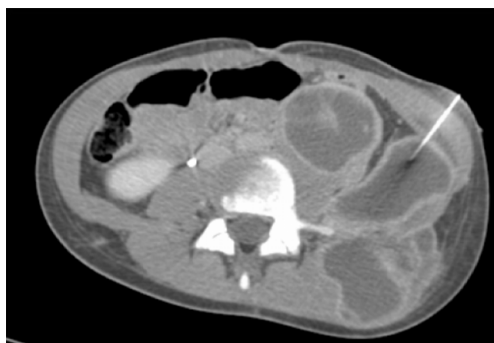


Figure 3: CT guided biopsy of a left flank abscess with origin in dorsolumbar spine.

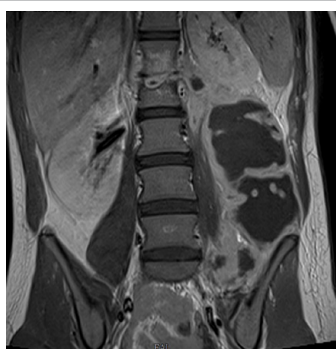


Figure 4: MRI coronal scan showing large paravertebral abscess with necrotic tissue.



Figure 5: Epidural abscess of the cervical spine without osseous involvement on sagittal MRI.

This method of the image is successfully used in the performance of guided biopsies (Figure 3).

Magnetic resonance image (MRI)

With a better sensitivity than simple radiography and more specificity than CT, MRI is the imaging method of choice for the diagnostic of spondylodiscitis. The sensitivity and the specificity described for this method of image are 96% and 93%, respectively [7,41].

It allows an earlier diagnosis than any other method of image. In the early stages the alterations are less specific and insufficient for the diagnostic of ST with the only features detectable, signs of discal degeneration associated with the alteration of the signal from the bone marrow of the vertebral body (that appears hypo intense in the T1-Weighted sequences and hyper intense T2 -Weighted sequences)

[3,36,41,42]. The use of contrast increases the precision of the MRI, particularly at early stages, also allowing the differential diagnosis with degenerative alterations (Modic 1 type) or metastatic disease.

Characteristic findings of ST include destruction of 2 adjacent vertebral bodies in opposing end-plates with the vertebral disc relatively well preserved or the reaching of multiple vertebral bodies, oedema of the vertebral body, extension of the infection beneath the longitudinal anterior ligament and the presence of pre-vertebral, para -vertebral, intraosseous or epidural abscesses that are generally smooth with thin walls [3,36,42]. The formation of this abscesses is most common with a TB infection than with a pyogenic one, due to its more insidious nature. In that case, they appear with a well-defined paraspinal abnormal signal that in association with a thin smooth abscess wall has a specificity of 90% for the infection due to BK (Figure 4) [3]. On the other hand, a thick abscess wall entailing irregular contrast enhancement is more suggestive of a pyogenic infection [7,36].

MRI also presents high precision to differentiate granular tissues from cold abscesses and allows assessing in a detailed way the involved tissues, the anatomical localisation of the abscesses, the involvement of the neurological structures and the vertebral non-continuous disease [7,36,37]. This imaging study also allows the evaluation of the craniovertebral junction and other rarer locations of the disease (Figure 5) [36,39].

Despite its usefulness and its precision, there are no pathognomonic MRI findings to distinguish a tuberculosis infection from other infections or neoplasia [7]. Recently, diffusion-weighted MRI (DW-MRI) and apparent diffusion coefficient (CAD) values are used in patients of ST and is useful in differentiating tuberculosis vertebral body involvement from metastatic lesions, but these values should always be interpreted in association with clinical history and conventional MRI findings [43]. An MRI has also its place in the follow up of the patient, allowing to evaluate the response to the treatment and the healing of the infection.

Scintigraphy

Despite being an old way of diagnostic, it still plays a role in the diagnosis of ST, allowing the early traceability of lesions and the detection of peripheral lesions, away from the primary vertebral outbreak [41]. It is particularly useful in the differential diagnostic with metastatic lesions.

According to the literature, it has a sensitivity of 65% to 97%, having overall a low specificity for the tuberculosis aetiology [7]. A scintigraphy using Gallium demonstrates positivity earlier than with Technetium 99 m [41,44,45].

Laboratorial Investigations

Tuberculin skin test (Mantoux)

Is recommended by WHO in countries with smaller economical means, being positive in 63% to 90% of the patients with TB [38]. It doesn't differentiate the active infections from the latent ones or induced reaction due to the vaccine BCG (*Bacillus Calmette-Guérin*) [3]. A positive Mantoux test will require a more detailed investigation and a negative test cannot rule out the TB diagnosis [38].

Hematological tests

The standard analytical study is part of the routine in ST. Anemia is a frequent finding and unspecific. Leucocytose is common in the acute phase of the response of the body to several diseases, including infections. In the spinal tuberculosis the leucocytic count is a parameter

less useful, being only raised in 30% to 50% of the affected patients, and according to Gouliouris immunocompromised patients or over 60 years will have a greater probability of having a normal count of normal cells [41]. Currently, the ratio lymphocytes/monocytes have promising results with a potential biomarker of the therapeutic response [46].

An Erythrocyte Sedimentation Rate will be high (>20 mm/h) in 60% to 83% of the patients, returning to closer to the normal when the active infection is under control [7]. It is sensitive tracer but nonspecific, that may be high in patients without infectious pathology [41]. The C-reactive Protein is also generally raised in most of the cases of acute infection [47].

Molecular and enzymatic diagnostic

A Polymerase Chain Reaction (PCR) is efficient in the fast and early diagnostic of the disease with sensitivity and specificity described from 61% to 90%, respectively. It is particularly useful in cases with low *bacilli* load being able to detect as few as 10-50 tubercle *bacilli*. Pandey et al. have described a strong concordance between the results of the PCR and the histological results [48]. Although, because of the possibility of false positives and negatives, PCR doesn't allow the definitive diagnosis [3,7].

ELISA test assess the response of the immunoglobulin M and G to diverse *Mycobacterium tuberculosis* antigens. Currently, its use is not recommended for the diagnostic of the active disease as it does not allow to differentiate between active disease, treated disease of induced response by the BCG vaccine [3].

The interferon-Gamma release assays (IGRA) are enzyme-linked immunosorbent assays that measure the levels of IFN-gamma in the blood in response to *Mycobacterium tuberculosis* antigens [49]. One of the IGRA with the best acuity for diagnostic is QuantiFERON-TB Gold, with a sensitivity and a specificity estimated at 84% and 95%, respectively [3,7]. The inability to distinguish the healed infection from the latent infection is the principal limitation for the use of this test.

Tissue Analysis

The sample analysis of a vertebral lesion represents the gold standard in the ST diagnosis. The etiological confirmation can lay on the demonstration of the fast-acid *bacilli* in the smear, in the characteristic histological findings or in the culture of the pathological agent.

Despite that, in the presence of a negative tissue analysis, the diagnosis of ST can be established based on the correlation between the clinical part and the radiological findings [7]. The samples are generally obtained from a guided biopsy, generally by TC, but can also be collected during a surgical intervention, when it is indicated.

In a group of 29 patients with ST, Francis et al. has reported positivity of the smear in 52% of the patients and 83% in the culture [50]. In another study from Mates et al., 75% of the performed cultures have established the diagnosis [51].

The histology is diagnostic in 60% of the cases, being the most common findings the inflammatory lymphocytic infiltrate (76%), epithelioid cell granulomas (70% to 90%) and granular necrotic background (83%). Scattered multinucleated and Langhans' giant cells can be present in up to 56% of the cases [3,52].

The performance of drug sensitivity tests (DST) is of primordial interest in the infectious pathology. Since the results are not immediate, the therapy should start before these results are available. The Agar environment (BACTEC®) is currently the gold standard, with positivity of cultures described in 83% to 87% and the DST results in around 11,3 days [3,53].

The Xpert® MYB/RIF, validated for the pulmonary TB and sponsored by WHO, also showed promising results for the vertebral infection in a 2014 study. In this study, the Xpert® MTB/RIF was positive in 97.2% of the analyzed samples, the DST results were available in 48 hours, the sensitivity was of 95,6% and the specificity of 96.2%, with a detection limit of 139 CFU/ml of *bacilli* [54].

All cases of multi-drug resistant TB (MDR-TB) were diagnosed accurately with the GeneXpert® test.

Management

Prophylaxis

Improving of living conditions and the nutritional status of the population are the most important method to reduce the prevalence of tuberculosis. The lack of access to basic health services, food, insecurity, and inadequate living conditions fuels TB transmission [55].

The BCG vaccine, introduced in 1950, provides protection in about 80% of cases and reduce the severity of the disease. In most developing countries it is given to all new-borns, whereas in countries with a lower prevalence of tuberculosis, selective immunization is performed in risk groups [56].

Nowadays, there are 15 vaccines candidates for clinical trials, including recombinant BCG vaccine, attenuated *Mycobacterium tuberculosis* strains, recombinant viral-vectored platforms, protein/adjuvant combinations and mycobacterial extracts [57].

Historical perspective

Before the introduction of anti-tubercular drugs, patients were submitted to orthodox treatments or random surgical procedures which resulted into a high mortality and morbidity rates [58].

In India, the Atharvans treated skeletal tuberculosis with "Sipudru", an herbal preparation, and sunlight. Hippocrates (450 BC) and Galen (131-201 AD) tried to correct kyphotic deformities with manual pressure, traction, and improvised orthoses, without success. 1-4 Most recently, since the 18th century, patients were admitted in sanatoriums for periods ranging from 1 to 5 years, where they were guaranteed rest and adequate nutrition [56].

Anti-tubercular chemotherapy emerged with the appearance of streptomycin in 1947, isoniazid and pyrazinamide in 1952, ethambutol in 1961 and rifampin in 1965. The idea that anti-tubercular drugs did not penetrate intraosseous lesions supported, for a long time, the surgical approach to manage this disease. The emergence of studies demonstrating the efficacy of pharmacological treatment, even in the presence of abscesses, cavities and caseous granulomas, has increasingly supported pharmacological treatment as the basis of the spinal tuberculosis approach.

Controversy over the approach in these patients was not easy to overcome. By 1960, Hodgson and Stock advocated routine surgical treatment and Konstam advocate routine conservative treatment.

Based on the results of several studies that demonstrated that there was no evidence to support the advantage of routine surgical treatment associated with pharmacological treatment compared to the pharmacological treatment alone, Tuly proposed a "middle path regimen" that advocates drugs as the basis of treatment and reserves surgery for specific indications [3,7,18].

Tuly's concept is still used today with good results and has made the surgical indications more selective, less for the control of the disease

General principles of pharmacological treatment of tuberculosis
<i>Mycobacterium tuberculosis</i> is a slow-growing bacillus and drugs that act on rapidly multiplying bacteria are less effective against this bacillus.
<i>Mycobacterium tuberculosis</i> has a cell wall that is poorly permeable to most antibiotics.
Multi-drug chemotherapy is essential since there are different types of bacilli in each colony with different growth kinetics and metabolic characteristics as below:
- Extracellular rapidly dividing bacilli.
- Extracellular slowly or intermittently dividing bacilli.
- Intracellular intermittently dividing bacilli.
- Dormant bacilli.
The performance of the drugs is variable as shown below:
- Rifampicin: bactericidal action on extracellular bacilli of slow multiplication.
- Isoniazid, streptomycin, and ethambutol: action on extracellular bacilli in rapid multiplication.
- Pyrazinamide: action on macrophages acting on intracellular bacilli.
- There are no effective drugs on dormant bacilli, which are the cause of relapse.
- Primary and acquired resistance to one of the drugs is common.
- The lag effect of antitubercular drugs allows for "intermittent therapy", thus improving compliance.

Table 2: General principles of pharmacological treatment of tuberculosis.

and more for the prevention and correction of spinal deformities and neural complications [3,56,59-61].

Medical Therapy

Anti-tubercular chemotherapy

The association of several antitubercular drugs it's the mainstay of the treatment of ST, with documented response rates of 82% to 95%. The results are excellent both in pain relief and in improving or controlling the progression of neurological deficits and kyphotic deformity [7,60]. Tuli et al. reported neurological recovery in 30% to 40% of patients with neurological deficits, submitted to conservative treatment [60]. Patients with neurological deficits caused by fluid collections in the extradural space are excellent candidates for pharmacological treatment, whoever, when MRI shows extradural compression by granulation or caseous tissue, a favourable response to pharmacological treatment is not likely to be expected and therefore, an early surgical approach should be considered [26].

Mycobacterium tuberculosis and associated species are strictly aerobic, with better replication in regions with high tissue oxygen tension, such as the lungs. In this way, pulmonary tuberculosis is generally multi-bacillary and bone tuberculosis is a paucibacillary infection. Thus, several studies documents that the pharmacological action on a paucibacillary infection is at least as effective as in multibacillary infection. However, Jain et al. demonstrated that antituberculosis drugs may not achieve minimum inhibitory concentrations in sclerotic bone lesions [15].

Rajasekaran et al. described six general principles on which rests the pharmacological treatment of tuberculosis (Table 2) [58].

Although some aspects of pharmacological treatment are consensual, there is still much controversy regarding the duration of treatment.

In the 2010 WHO guidelines, ST is included in category I of treatment and a regimen in 2 phases is recommended for this category. In the first 2 months (intensive phase) 4 first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin) should be administered, and in the following 4 months (continuation phase), isoniazid and rifampicin [3,7,62,63].

The WHO and the American Thoracic Society (ATS), attending to the difficulty of monitoring the therapeutic response in ST, recommend in this specific case, the prolongation of the continuation phase for a further 3 months, for a total of 9 months of treatment [63,64].

The recommendations of the British Thoracic Society are similar to the WHO's endorsements, but there is a reference to prolongation of the continuation phase, up to 12 or 24 months (or until there is a radiological or pathological evidence of disease regression) [7].

The regimen is the same for children, with dose adjustment to weight. The presence of comorbidities also does not justify any therapeutic change to this regimen, although potential drug interactions, particularly with antiretroviral, should be considered [65].

Second-line drugs have a higher cost, greater toxicity and are less effective in the treatment of *Mycobacterium tuberculosis* infection [3,58,63].

Directly observed therapy short course (DOTS)

Patients with TB, similarly with patients with other chronic diseases, have low compliance to the drugs intake, being this fact the most common cause of treatment failure and the emergence of acquired drug resistance. Direct observation of the drugs intake is the best method to ensure that the patients follow the regimen, being nowadays facilitated by the intermittent drugs regimens which permit the drugs intake for 2 or 3 times a week [7,58].

Multi drug resistant tuberculosis (MDR-TB)

Isoniazid and rifampicine resistance is termed MDR-TB and, if in addition, there is resistance to a fluoroquinolone or at least one second-line injectable drug, it is termed extensively multi drug resistant tuberculosis (XDR-TB) [3,66]. Increased incidence of MDR-TB, particularly in co-infection with HIV is, nowadays, one of the greatest threats to global health, with an estimated prevalence in pulmonary TB of 3.4%, for primary resistance, and 25% for acquired resistance. The prevalence of resistance in ST is still unknown [65].

As there are no specific guidelines for the treatment of MDR-TB in spinal infection, the treatment of this pathology should be followed by the WHO or ATS guidelines for the treatment of MDR pulmonary infection, which advocates a therapeutic regimen lasting no less than 18-24 months. Ideally treatment should be based on DST. The regimen should include at least 4 previously unused drugs. First-line drugs such as ethambutol and pyrazinamide may be used, although many laboratories are unable to rule out ethambutol resistance even after DST [67].

In patients with MDR-TB, a regimen with at least five effective tuberculous medicines during the intensive phase is recommended, including pyrazinamide and four core second-line tuberculous drugs-

Indications for surgical treatment
Sample collection if uncertain diagnosis
Failure of conservative treatment
Severe persistent pain
Prevention or correction of spinal instability
Prevention or correction of kyphotic deformity
Kyphosis with $\geq 60^\circ$ or if the kyphosis is likely to heal with this amount deformity
In children <7 years, with 3 or more affected vertebral bodies and/or two or more "signs of spine at risk"
Drainage of large cold abscesses
-Large paravertebral abscess showing marked increase despite 3 to 6 months chemotherapy
-Cervical abscess causing difficulty in deglutition and breathing
Decompression of spinal cord and neural structures
-Neurological deficits progressing or not improving despite chemotherapy
-MRI showing granulation/caseous tissue as the cause of compression
-Recurrence of neurological deficits

Table 3: Indications for surgical treatment.

one from Group A (levofloxacin, moxifloxacin, gatifloxacin), one from Group B (amikacin, capreomycin, kanamycin, streptomycin), and at least two from Group C (ethionamide or prothionamide; cycloserine or terizidone; linezolid; clofazimine). If the minimum number of effective medicines cannot be composed as given above, an agent like bedaquiline, imipenem–cilastatin, meropenem, amoxicillin clavulanate, among others, may be added to bring the total to five [68].

About 50% of patients experience adverse effects with these treatment regimens [3,67,68].

A study by Rajasekaran describes 5 factors predictive of success in the treatment of spinal MDR-TB, which include: progressive clinical improvement at 6 months, radiographic improvement during treatment, multi-resistant infection to less than 3 drugs, the need to use 4 or fewer second-line drugs and no need to change the regimen during treatment [3].

Despite the improvements in the treatment of these cases, it is agreed that there is an urgent need for shorter, easier treatment for all patients with drug-susceptible and drug-resistant tuberculosis, faster point-of-care diagnostics, and effective vaccines to prevent TB in all populations.

Surgical treatment

Despite the fact that the mainstay of treatment is medical management, antitubercular drugs alone may not solve all the complications of vertebral infection.

In general, indications for surgical treatment include decompression of the spinal cord and neural structures, prevention or correction of kyphotic deformity, prevention or correction of spinal instability, drainage of large cold abscesses, failure of conservative treatment, presence of severe persistent pain or need of sample collection for diagnosis (Table 3) [3,66,68-70].

Surgical techniques have evolved considerably from decompression and non-instrumented arthrodesis to the use of pedicle screws and anterior reconstruction implants. The work of Oga et al. played a preponderant role in this evolution by demonstrating that *Mycobacterium* spp. does not form extensive biofilms. Hence, the use of an implant is considered safe when anti-tubercular chemotherapy regimen is being used [69,71].

The development of posterior surgical techniques that allow transpedicular or transforaminal decompression and anterior reconstruction have changed the surgical approach of spinal tuberculosis.

Nowadays it is clear that it's sufficient to remove all pus, caseous tissue and sequestrum, in order to decompress the neurological structures. Thus, radical debridement of the lesion is no longer indicated and is associated with a higher rate of surgical failure by creating a larger bone gap that requires a larger graft, increasing the risk of slip or fracture [26,72].

The surgical approach aims at the debridement of tissues, decompression of neurological structures and stabilization of the spine. These goals can be achieved by:

1. Debridement and/or decompression and anterior fusion.
2. Debridement and/or decompression and posterior fusion.
3. Debridement and/or decompression and anterior fusion followed by instrumented simultaneous or sequential posterior arthrodesis.
4. Instrumented posterior arthrodesis followed by debridement and/or decompression and anterior fusion.

Anterior approach

In the great majority of cases, the posterior elements of the spine are not affected in this infection. Granulation tissue mainly causes the compression of neurological structures, caseous material and abscesses with anterior origin. It is within this concept's support that the anterior approach was popularized by Hodgson et al. [69]. The authors described 93% of fusion rate in the routinely use of debridement by anterior approach [69,72,73].

This approach allows direct debridement of the pre-vertebral intra-spinal focus of infection and correction of kyphosis by reconstruction of the anterior column with the use of graft [70,72,73]. For the same technique, several authors described a good neurological recovery, absence of recurrence of the infection at long-term follow-up, and corrections of the kyphotic angle between 18° and 20° [26,70,74,75].

However, there are other publications describing a loss of kyphosis in the long-term follow-up, especially in patients with affection of dorsal spine [3,35,76,77]. The success of anterior debridement followed by fusion has been shown to be inversely related with the length of the reconstruction [78].

At the cervical spine, abscess drainage, corporectomy and fixation, are performed by anterior approach. Posterior stabilization is only used when patients suffer an extensive bone destruction [72].

Dorsal spine can be approached by thoracotomy (transthoracic or transpleural) or by an anterolateral approach (extrapleural) [69].

Thoracotomy is a technique used in cases of extensive disease, requiring an experienced surgical team and access to an intensive care unit. Even with an excellent surgical framing, it has a peri-operative mortality of 6%, which is around 11% in cases of severe paraplegia [76].

In patients with extensive abscess but with no neurological deficit, the anterior approach remains standard reference [72].

The advantages of this approach are the optimal exposure to debridement, the defect correction with graft and instrumentation in a single surgical time and through the same incision, minimizing the surgical time, blood losses and the risk of graft injury during the patient's positioning for a second approach.

This approach also allows saving spinal segments, preventing the fusion of unnecessary levels. Anterior fixation can be used in short-segment disease because healthy vertebral bodies are necessary above and below the diseased segment to provide sustenance. So, this type of instrumentation can only be used in mild to moderate kyphosis [69].

An anterior approach should only be used when posterior elements are preserved, otherwise this technique does not provide mechanical stability. The same happens in pan vertebral disease [76,79].

In patients with compromised lung function, thoracotomy is not recommended, because of the risk of severe postoperative complications [69,70]. In these cases, the anterolateral (extrapleural) approach can be used.

This technique also allows better spinal cord exposure in patients with severe kyphotic deformity, comparing with the transthoracic approach [70]. According to Rasouli et al. this approach is safer than the transthoracic, by allowing a good exposure of the spine from the 2nd thoracic vertebra to the 5th lumbar vertebra [18]. Jain et al. reported for a single-stage anterior decompression, followed by Hartshill's posterior fixation by an anterolateral approach, an average correction of 49.08° to 25° of the kyphotic angle [3,80].

Posterior approach

The neurological structures can be decompressed by posterior, posterolateral or transpedicular approach along with posterior stabilization. It's being increasingly used in the last years with excellent results, mainly due to the advent of pedicular screws. Many surgeons prefer posterior-only surgery. Its great advantages are the familiarity of the approach and the lower morbidity, ensuring optimal exposure for circumferential decompression either by transforaminal or by transpedicular route. It also facilitates the extension of the instrumentation to multiple levels and provides a greater security for

the anterior reconstruction, avoiding the complications inherent to the opening of the thoracic and abdominal cavities (Figure 6) [3,69].

Posterior instrumentation also takes advantage of the fact that posterior elements are more spared by infection, compared to anterior elements, offering better conditions for instrumentation [56].

In patients with early disease and no severe deformity, transpedicular decompression and posterior instrumentation allow symptomatic relief and prevent the progression of deformity and the development of neurological deficits. In cases of advanced disease, a posterior approach allows the placement of bone grafts or cages for correction of deformity and reconstruction of the anterior column [55,75,76,80].

Several studies have demonstrated superiority of the posterior approach over the anterior one for the correction of kyphotic deformity [69,72,81].

Zhang et al. made a comparative study in elderly with thoracic spine tuberculosis, comparing the results between surgical management with posterior approach and combined anterior and posterior approaches, and described better clinical outcomes with the posterior approach alone [81].

Combined approaches

Several studies describe good to excellent results with anterior decompression followed by anterior or posterior instrumentation [78].

Posterior instrumentation after anterior decompression and reconstruction, in a simultaneous or sequential procedure, is indicated to prevent complications associated with the anterior graft, in patients with long segments affected (> 4 segments), in cases of pan vertebral disease or when significant kyphosis correction is necessary [3,76].

Several authors obtained good results with a sequential approach, with times between surgeries varying between 11 and 21 days. Moon et al. obtained a kyphosis correction from 37° to 15°, and Chen et al. from 34.6° to 17.3° [3,82,83]. Louw described a correction of the kyphotic angle from 56° to 27° through anterior transthoracic decompression, reconstruction with vascularized rib graft and posterior osteotomies, at the same surgical time or 2 weeks after the first intervention [84].

Osteotomies and vertebral resection

Angular kyphosis secondary to tuberculosis infection may progress after the healing of the disease and may lead to sagittal imbalance, cardiopulmonary compromise, and late onset neurological deficits.

Treatment of established kyphotic deformities can be difficult and requires osteotomies for adequate correction, which can be performed by anterior-only, posterior-only or combined procedures [78]. The pedicle subtraction osteotomy (PSO) allows the correction of 20-30° of the kyphotic angle in a single level.

In the presence of severe deformity, the three-column osteotomy may be necessary. Since the advent of posterior only vertebral column resection (PVCR) popularized by Suk et al. several authors have performed PCVR or similar osteotomies to correct severe deformities due to tuberculosis of the spine, with good results [33,69,85-87].

Rajasekaran describes a closing-opening wedge osteotomy that is effective for the correction of severe post tubercular kyphosis allowing deformity correction with minimal complications [87].

Osteotomies are technically demanding and have a complication rate that is as high as 40%, including dural tears, temporary or permanent neurological deficits, pulmonary complications, and blood



Figure 6: Post-operative lateral X-ray and CT scan after decompression, reconstruction with bone graft and fixation by a posterior-only approach.

Diagnosis	Clinical features	Typical anatomic location	Imagiological features	Characteristic features
Pyogenic spondylitis	Fever, marked back pain, myelopathy	Lumbar and cervical spine	Destruction of vertebral bodies and disc spaces, sclerosis, marked enhancement of the lesion, small para-vertebral lesion, and epidural extension	Rapid disc destruction Sparing of the osterior elements
Brucellar spondylitis	Fever, malaise, weight loss, back pain, myelopathy	Lumbar spine	Intact vertebral architecture despite diffuse vertebral osteomyelitis, lytic lesions in disco-vertebral junction, sclerosis, small Para spinal lesion anterior osteophytes	Anterior "parrot beak" Gas in discs Sparing of the osterior elements History of ingestion of unpasteurized Milk or contact with goats
Osteoporotic lesions	Back pain associated with minor trauma Presence of other osteoporotic fractures	Thoracic and thoraco-lumbar spine	Decreased bone density Vertebral body wedging that can be associated with posterior vertebral wall fracture with retro pulsion	Progressive kyphosis Pedicle usually spared
Metastatic disease	Bone pain at night, back pain, and/or radicular pain, myelopathy Presence of systemic malignancy	Thoracic spine	Lytic or sclerotic lesions, bony destruction with epidural mass	Vertebral body and posterior elements lesions Preserved discs Halo sign
Lymphoma	Malaise, backache Fever	Skip or contiguous multilevel involvement	Lytic lesions Paraspinal masses Epidural lesions	Paraspinal masses with vertebral lesion but no extensive cortical bone destruction

Table 4: Differential diagnosis.

loss. For this reason, this procedure is only recommended in the case of severe kyphosis, both in the active and healing disease [69,88].

Minimal invasive spine surgery

Minimally invasive techniques are routinely used in degenerative pathology and have been increasingly used in ST [89].

Video assisted thoracoscopy is performed to decrease the complications associated with thoracotomy, with comparable results to the open procedures in scoliosis. This minimal invasive technique is also being used in surgical management of spinal tuberculosis but few studies have addressed its role [69].

A study by Lü, in 50 patients with 5 years' follow-up concludes that anterior mini-open approach assisted by thoracoscopy can be a safe and effective technique for anterior debridement and reconstruction in thoracic spine. This technique is a feasible option for the treatment of thoracic tuberculosis while both minimizing the risk of complications and allowing easier intervention for potential intraoperative complications [90].

Percutaneous fixation and mini-invasive posterolateral decompression have also been used in this pathology. They allow the stabilization of the thoracic and lumbar spine as well as decompression and interbody fusion by lateral or transforaminal route [90]. Several studies report good fusion rates with encouraging functional outcomes after percutaneous fixation [89,91].

Atypical Forms of Spinal Tuberculosis

Any forms of ST that do not manifest with typical clinical and radiologic features of the disease are considered to be atypical spinal tuberculosis. An incidence of 2.1% has been reported for this kind of presentation [92]. This is best evaluated with MRI and its reported forms include: spondylitis without discitis, central single vertebral body lesion, skip lesions, isolated involvement of the posterior elements and isolated intraspinal lesions.

Multiple Vertebral Disease is an atypical form of presentation

whose incidence is described in 7% to 10%, but it is estimated that the incidence of this kind of presentation would be higher if whole spine MRI was performed [18]. The lesions may be in continuity or may affect different levels in different regions of the spine (skip lesions) [39].

An atypical presentation may pose a diagnostic and therapeutic dilemma for treating clinicians, resulting in a delay in diagnosis [13].

However, it has been suggested that these lesions can have the same outcome and prognosis as typical presentation if diagnosed and treated at the early stages, applying the same principles for patients with typical features [92].

Differential Diagnosis

Common differential diagnosis includes pyogenic spondylitis, brucellar spondylitis, osteoporotic lesions, sarcoidosis, metastasis, multiple myeloma, and lymphoma. Spinal tuberculosis should be considered in the differential diagnosis of chronic back pain, with or without constitutional, neurological, or other musculoskeletal manifestations [7,36,39].

In pyogenic spondylitis, lumbar and cervical segments are more often affected. The destruction of the intervertebral disk is more pronounced than the destruction of the bone elements and there is usually no kyphotic deformity. The onset of the disease is more acute with a marked systemic affectation.

In brucellar spondylitis the lumbar spine is more affected and the discal involvement is pronounced. This disease has little impact in the paravertebral soft-tissues. Osteoporotic lesions are more frequently found in thoracic spine and usually spare the pedicles. The mineral bone density is decreased in this disease.

Thoracic segment is also the most common location for metastatic lesions and must be considered in all old age patients with vertebral collapse. The involvement of the posterior vertebral body wall, pedicle and lamina is usually found. The discal height is preserved, however lymphoma and multiple myeloma may infiltrate the disk (Table 4) [7,36,37,41,42].

Conclusion

Spinal Tuberculosis is one of the oldest diseases known to mankind but remains an important public health problem nowadays. Migration phenomena and the infection by HIV have led to resurgence of this disease bringing new challenges such as atypical presentations, drug resistances and HIV co-infection.

It's of extreme importance to understand the infection and its behavior to provide an early diagnosis that remain the mainstay of good outcome when associated with adequate treatment.

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