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Review Article

Spinal tuberculosis: a comprehensive review for the modern spine surgeon

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Abstract Nearly one-third of the human population is infected with tuberculosis. Of those with active disease, approximately 10% are impacted by skeletal tuberculosis. Though, traditionally a disease of the developing world and susceptible populations, with the rise of immigration, patients may present in developed countries. The microbe responsible is the *mycobacterium tuberculosis* complex bacillus. The infection begins in the anterior vertebral bodies. The natural history and presentation are notable for cold abscesses causing mass effect, early or late neurological deficit, and kyphotic deformity of the spine caused by anterior vertebral body destruction. The disease can be diagnosed with laboratory studies and characteristic imaging findings, but tissue diagnosis with cultures, histology, and polymerase chain reaction is the gold standard. The cornerstone of medical management is multidrug chemotherapy to minimize relapse and drug resistance, and can be curative for spinal tuberculosis with minimal residual kyphosis. Surgical management is reserved for patients presenting with neurological deficits or severe kyphosis. The mainstays of surgical management are debridement, correction of spinal deformity and stable fusion. With appropriate and timely management, clinical outcomes of the treatment of spinal tuberculosis are overall excellent.

Keywords: Gibbus; Kyphosis; Medical management of tuberculosis; Pott's disease; Spinal tuberculosis; Surgical management of spinal tuberculosis; Tuberculosis

Introduction and Epidemiology

Tuberculosis is one of the oldest known infectious diseases of man, with evidence of spinal tuberculosis seen in the spinal deformities of mummies dating 9000 BC [1]. With its documentation in the texts of nearly every ancient civilization, tuberculosis has been widely recognized for millennia, however only in recent decades has an effective treatment for the disease come into commonplace [2].

Worldwide an estimated 2 billion people are infected with tuberculosis. Only 5% to 15% will become symptomatic. The remainder have latent infection [3]. The exact incidence of spinal tuberculosis is unknown but extra-pulmonary tuberculosis is found in 20% of infected individuals [4]. Skeletal tuberculosis is found in nearly 10% of patients with active pulmonary disease; the spine is most common skeletal site of involvement (~50% of patients with skeletal tuberculosis) [5]

Throughout history, tuberculosis has been seen as a disease of the disadvantaged population, including socioeconomic status and vulnerable health status. Patients who are immune-compromised [6], at the extremes of age, diabetics, smokers, cancer patients, and alcoholics are at an increased risk [7]. With outbreaks in the developed world occurring in prisons or homeless shelters, overcrowded living conditions is another risk factor. Tuberculosis disproportionately infects the poor in both developed and developing nations [8,9]. Currently, one of the most striking risk factors for tuberculosis infection is Human Immunodeficiency Virus (HIV) [7], which is associated with a 21- to 30-fold increased risk of developing the disease [5].

There are endemic regions of tuberculosis worldwide (Fig. 1). Sub-Saharan Africa is perhaps the most densely burdened, largely caused by the concentration of HIV

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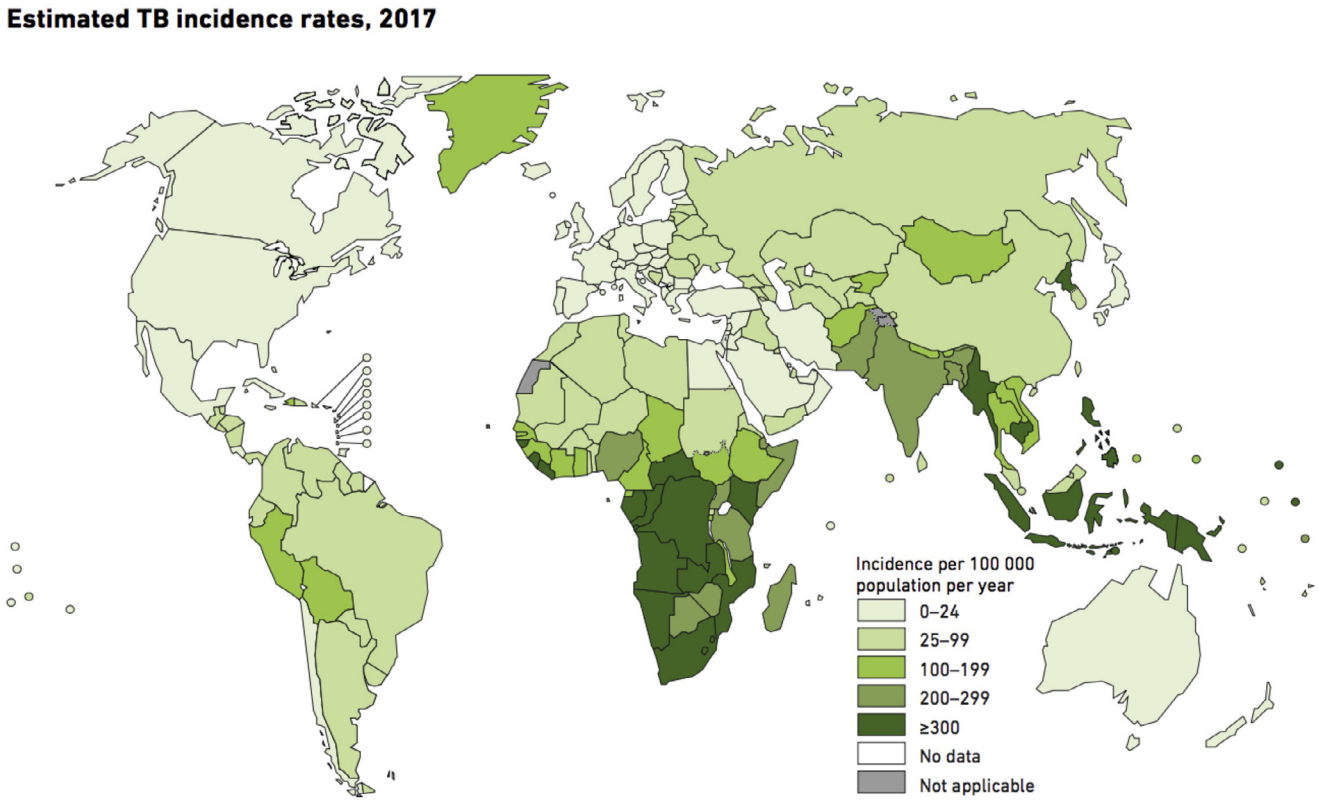

Fig. 1. This map from the World Health Organization's 2018 tuberculosis report shows the endemic regions of tuberculosis. Reprinted with permission from the World Health Organization [3].

infection and poverty in the region [7]. Of the 10.4 million new cases of tuberculosis worldwide in 2015, approximately 60% came from just 6 countries: India, Indonesia, China, Nigeria, Pakistan, and South Africa [7]. In the United States, the incidence of tuberculosis is four times higher in foreign-born persons compared with natives [10]. In 2006, approximately 60% of new cases of tuberculosis in the US were in foreign born persons [11]. Fifty-three percent of cases among foreign-born persons occurred in migrants from Sub-Saharan Africa and Southeast Asia [11].

Pathogenesis

The microbe responsible is *mycobacterium tuberculosis complex bacillus*. There are 60 species of this bacillus described, but only a select few are associated with clinical manifestations of the disease [5]. The primary route of infection is pulmonary or genitourinary and 50% of all tuberculosis patients have a primary lung foci or history of pulmonary tuberculosis [4]. Spinal tuberculosis is a secondary infection, which generally occurs via hematogenous spread [12]. However it is not clear whether spinal tuberculosis requires active disease elsewhere or whether spinal tuberculosis implies that the patient is contagious [4].

Unlike most infections of the spine, 95% of spinal tuberculosis begins in the anterior vertebral body. The infection spreads from either arterial spread in paradiscal region, or from the valveless venous plexus, Batson's paravertebral plexus, into the central vertebral body [12]. The infection tends to spread subligamentously under the anterior longitudinal ligament and into the posterior vertebral body. The intervertebral disc is often last to be affected caused by the lack of proteolytic enzymes inherent in the bacillus [5,12]. Though in adults, the vertebral body is nearly always involved, children with more vascular discs may have a discal focus of the disease [13]. If left untreated, the bony involvement in spinal tuberculosis eventually destroys the anterior vertebral bodies, leading to kyphosis. The bony destruction of the anterior elements is fragmentary in 47% of the cases; osteolytic in 34%, subperiosteal in 30% cases, and localized destruction with sclerotic margins in 10% (Fig. 2) [14].

Natural history

Spinal tuberculosis is a chronic manifestation of the infectious disease. Only 20% to 30% of the patients with spinal TB have constitutional symptoms [12]. It has an insidious progression with three major clinical features: (1) cold abscesses, (2) neurologic deficit, and (3) long-term kyphotic deformity of the spine.

Cold abscesses are collections of purulence originating from the infected vertebrae, without surrounding inflammatory response [5,12]. Seen in 70% of spinal tuberculosis [15], they are slow growing, without proteolytic enzymes, and spread subligamentously. They are often located in

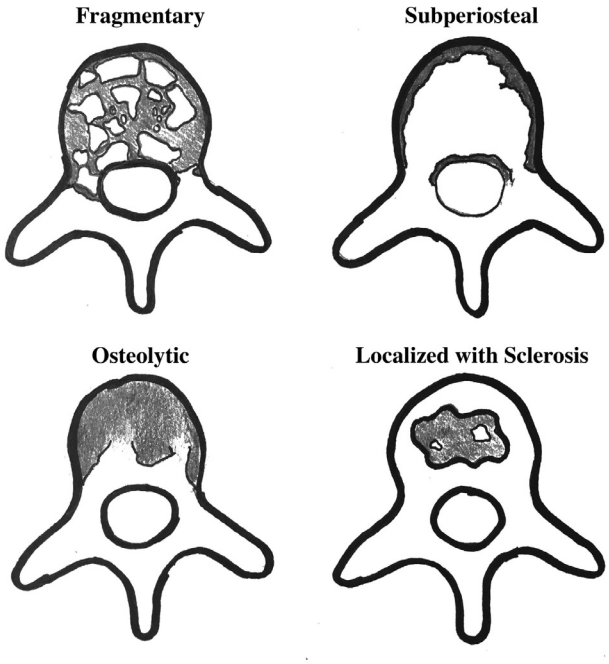

Fig. 2. The bony destruction of the anterior elements is fragmentary in 47% of the cases; osteolytic in 34%, subperiosteal in 30% cases, and localized destruction with sclerotic margins in 10%.

paravertebral tissue [16]. The effects of these cold abscesses are largely related to mass effect, not inflammation. The effects are variable depending on location (Table 1) [12,17].

Neurologic deficit occurs in approximately 10% to 20% of individuals with spinal tuberculosis in developed countries, and is twice as prevalent in developing nations [18]. This manifestation is more common in cervical and thoracic disease caused by the close proximity of the spinal cord, and more rare in the capacious lumbar spine. The early signs of compressive pathology are radicular pain, focal weakness, and sensory changes along affected nerve roots. Eventually the neurologic symptoms can progress to myelopathy and paraplegia, or even tetraplegia if cephalad enough [12].

Hodgson, one of the early surgical innovators in the study of spinal tuberculosis, classified neurologic changes into early onset or late onset [19]. Early onset neurologic deficits occur while the infection is active and untreated and are caused by cord compression by mass effect of a cold abscess, caseous tubercular debris, or granuloma. Mechanical instability of the spine caused by structural destruction of the vertebral column can also occur. Mechanical compression of the spinal cord makes it more susceptible to injury from a mechanical instability event. The cord itself can become infected, and cord edema can also be responsible for neurologic deficits. In rare instances, arteritis of the spinal artery can result in thrombosis and ischemia of the spinal cord [5,12,13,18,19].

Neurologic deficits can also occur after treatment and healing of the tubercular lesions. Such events can occur years to even decades after active disease. Fibrosis of the dura can cause compression of the cord and make it more susceptible to injury and paralysis. However, the more common cause of late neurologic changes are the severe kyphotic deformity that can result for spinal tuberculosis [5,18–20]. The deformity itself can result in spinal cord compression. It can also result in secondary bony bridging within the canal, which can lead to cord transection [12].

Kyphotic deformity as a late sequela of spinal tuberculosis is a critical component of the natural history of spinal tuberculosis [21–25]. The kyphosis is initially caused by the anterior structural destruction of the vertebral body. This destruction is halted by medical treatment of the disease. The magnitude and location of vertebral body collapse impacts the degree of sagittal plane deformity (Fig. 3). Type A reconstitution results from minimal vertebral body destruction and an intact posterior column. Type B reconstitution is a result of when the antero-inferior edge of superior body rests on the inferior vertebral body and causes a 40 to 60 degree kyphosis. Type C reconstitution occurs when the anterior edge of superior bodies rest on anterior edge of inferior body and typically causes a kyphosis greater than 100 degrees which grows [15].

The late behavior of the kyphotic deformity is determined by three factors: (1) kyphotic angulation, (2) growth remaining, and (3) spine-at-risk signs. In adults diagnosed with spinal tuberculosis, the kyphotic deformity is generally less than 30 degrees. After medical treatment, this deformity progresses an average of 15 degrees and then remains a fixed deformity. However a kyphosis greater than 60 will continue to progress [26]. In children, the destruction of the vertebral body and endplate, combined with the continuation of growth in the spine can cause deformity to progress. In 40% the kyphosis worsens, 40% improves, and in 20% it stays constant [21,22]. Early deformity can show predictive signs of worsening late deformity. These plain radiographic indicators were coined the “spine-at-risk signs” by Rajasekaran et al. [22,25]. The four signs are separation of the facet joints, retropulsion of the vertebral body, lateral translation (in the coronal plane), and toppling (the vertebrae just above the lesion tilts to a degree where its anterior surface comes into contact with the superior surface of the

Table 1
The location, incidence, and characteristics of cold abscesses

Location	Incidence	Characteristics
Cervical and upper thoracic spine	10%	Retropharyngeal abscesses can result in dysphagia, hoarseness and respiratory distress
Lower thoracic spine	40%–50%	Fusiform paravertebral swellings
Lumbar spine	35%–45%	Descends down beneath the inguinal ligament to appear in groin/thigh. It can also track into the gluteal region as it follows the iliac vessels

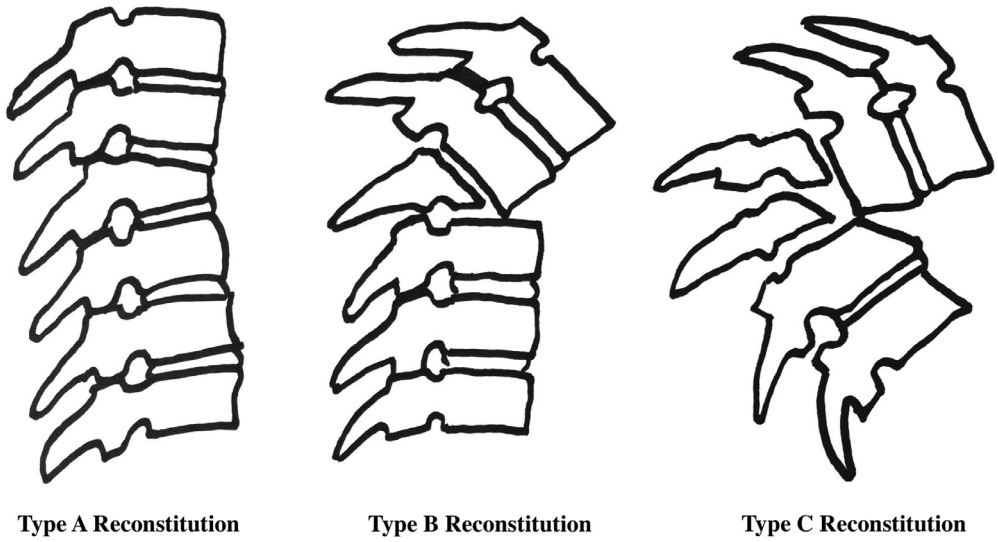

Fig. 3. Type A reconstitution results from minimal vertebral body destruction and an intact posterior column. Type B reconstitution is a result when the antero–inferior edge of superior body rests on the inferior vertebral body and causes a 40 to 60 degree kyphosis. Type C reconstitution occurs when the anterior edge of superior bodies rest on anterior edge of inferior body and typically causes a kyphosis greater than 100 degrees which grows.

vertebra below the lesion) (Fig. 4). Three or more of these signs are highly predictive of the development of severe late kyphosis [24].

History and physical exam

Spinal tuberculosis is an insidious disease. The time from symptoms to diagnosis used to be 12 months, however now it is closer to 3 to 6 months [15]. A high index of suspicion is essential for a timely diagnosis, which is why an understanding of the epidemiology and geography of the disease is essential. Chronically ill individuals, socioeconomically compromised, IV drug abusers, and patients on TNF-α inhibitors for autoimmune diseases are at the highest risk. However contact with family members from high-risk nations/immigrants must also be considered.

Constitutional symptoms including malaise, loss of weight and appetite, night sweats, evening rise in temperature, generalized body aches, and fatigue, are often considered good clues. However one or more of these symptoms are present in only 20% to 38% of patients with skeletal tuberculosis [12,27]. These symptoms are more indicative of active pulmonary tuberculosis [5]. It is not clear whether spinal tuberculosis requires active disease elsewhere or whether it implies contagiousness [4].

Cold abscesses and lymphadenopathy are another set of clues that can lead to the diagnosis. The mass effect from cold abscesses is more prominent than the inflammation

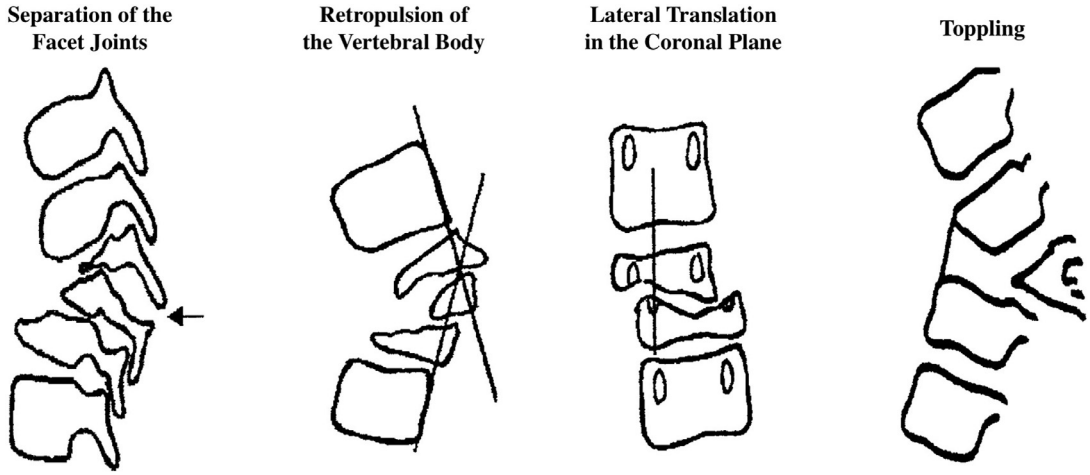

Fig. 4. Early deformity can show predictive signs of worsening late deformity. These plain radiographic indicators were coined the "Spine-at-Risk signs" by Rajasekaran et al. The four signs are separation of the facet joints, retropulsion of the vertebral body, lateral translation (in the coronal plane), and toppling (the vertebrae just above the lesion tilts to a degree where its anterior surface comes into contact with the superior surface of the vertebra below the lesion). [25].

that is more characteristic of other bacterial abscesses. In the cervical spine, cold abscesses can cause dysphagia, hoarseness, or even respiratory distress. Fusiform paravertebral swellings are characteristic of thoracic spine involvement and lumbar spine abscesses descend along the psoas sheath, traversing beneath the inguinal ligament to appear in the groin, thigh, or gluteal region [12].

Back pain is perhaps the most common complaint of spinal tuberculosis, found in 90% to 100% of all spinal tuberculosis, and being the sole symptom in 61% of cases [5,27]. Axial back pain is multifactorial and can be a symptom of tissue destruction of the anterior vertebral bodies, mass effect by cold abscess, or instability of the spine. Radicular pain, however, involves nerve root compression caused by mass effect or vertebral body collapse. Often in developing nations, the presence of weakness is what brings a patient to the healthcare provider. Neurologic deficit may be present in 23% to 76% of presenting patient depending on the study cited [28].

Neurologic deficits can be as subtle as a clumsy gait, or as severe as quadriparesis if the cervical cord is involved. Thoracic and lumbar involvement can produce paraparesis and may have sphincter involvement [15]. Upper motor neuron involvement can result in hyperreflexia and clonus which can be noticed by a physician before detected by patient [29]. In rare cases, the sole symptom a patient presents with is neurological symptoms from an intraspinal tuberculoma [30].

Spinal deformity may also clue a physician in to a disease process involving the spine. Spinal tuberculosis nearly always results in kyphosis. The degree of kyphosis is dependent on the number of vertebrae involved and type of vertebral reconstitution [15]. A knuckle deformity results from involvement of a single vertebra. A gibbous is seen with the involvement of 2 to 3 vertebrae (Fig. 5a). Occasionally a compensatory lordosis is seen adjacent to such kyphotic deformities and the presence of a global kyphosis suggests multiple vertebral involvement [15].

Diagnostic work-up

The diagnosis of spinal tuberculosis can be established from laboratory studies, imaging, and tissue diagnosis.

Laboratory tests

The first laboratory studies considered are a complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein, which are all nonspecific in showing

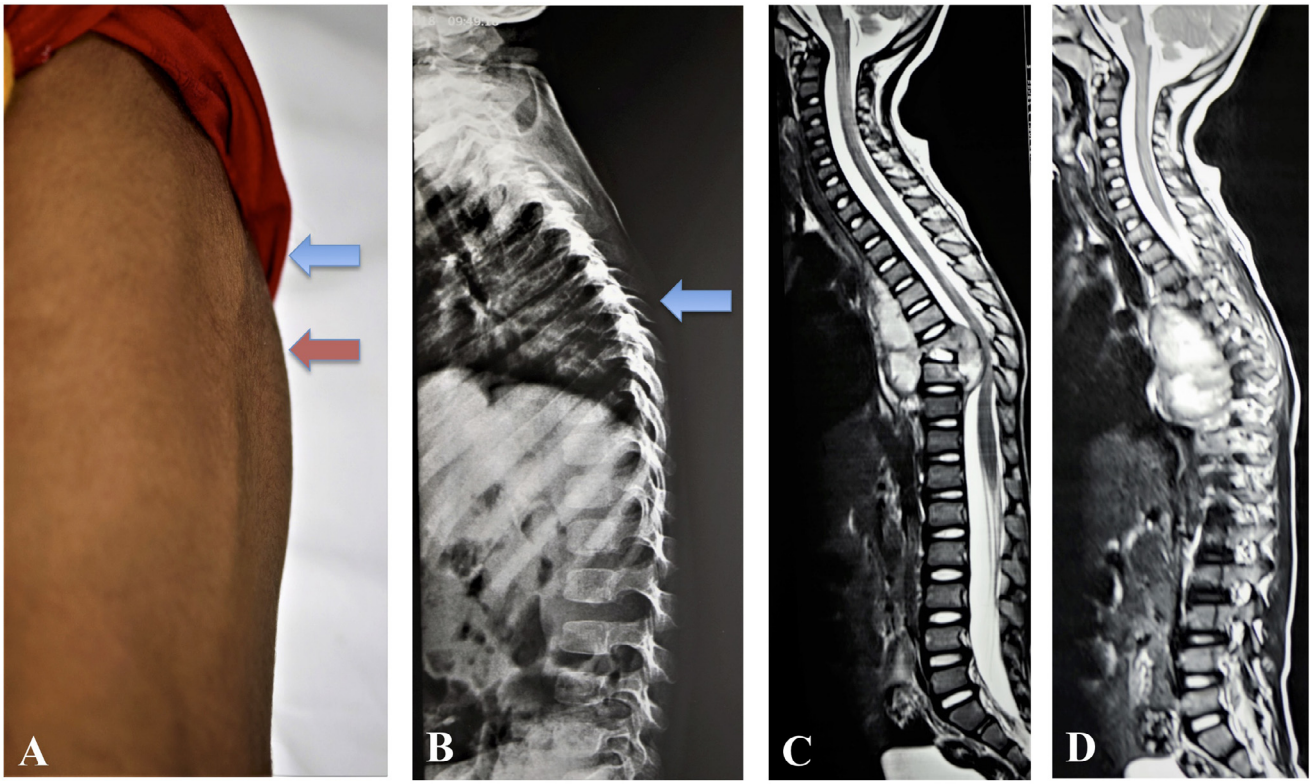

Fig. 5. (A) is a clinical image of a subtle gibbous deformity in the mid thoracic spine of a 5-year-old boy with back pain (blue arrow), with a concavity just caudal to the gibbous suggesting a compensatory lordosis (orange arrow). (B) is a lateral spine radiograph showing very large para-spinal shadow at the mid to lower thoracic spine (blue arrow). (C) is the central sagittal cut of the patient's full spine MRI. (D) is the para-central cut. There is destruction and collapse of the T8 vertebra, with some end plate destruction of the caudal end plate, intact intervertebral disc space and decreased T9 vertebral height. There is signal change in both of these vertebrae with a large prevertebral, subligamentous, epidural, and para-spinal collection. The epidural collection is indenting the cord. Clinical images courtesy of Dr. Mathew Varghese MS.

infectious processes [5,12,15,20]. Leukocytosis may be noted in cases of active disease, but is present in only 30% to 50% of cases with spinal tuberculosis [5]. Some level of anemia of chronic disease is also common. An ESR>20 mm/h has been noted in 60% to 83% of patients with tuberculosis [15]. Cell differential should also be obtained as a lymphocyte to monocyte ratio can be used to monitor response to therapy [31].

The Mantoux Test, the purified protein derivative or tuberculosis skin test, which most healthcare providers are familiar with, can be used as a screening tool. However this does not differentiate active from latent disease. It is positive in 63% to 90% of cases with spinal tuberculosis [5]. It also requires the use of clinical judgment, especially when evaluating immune-compromised hosts.

Interferon-γ release assays are another serologic option, which test for different *M. tuberculosis* antigens and are not affected by prior Bacille Calmette-Guerin vaccination [32]. The World Health Organization (WHO) does not recommend quantiferon for active disease and recommends that it should be used in conjunction with clinical history, imaging, cultures, and exam [15].

Imaging

Imaging of the back pain with a suspicion for tuberculosis should begin with standard AP and lateral spine radiographs with the use of advanced imaging modalities as clinically warranted. Spine radiographs, though rudimentary, are often enough to diagnose the disease, and form the cornerstone of diagnostics in resource poor, endemic regions. Spinal tuberculosis has a characteristic loss of bone density in the anterior spine. Lytic lesions involve the vertebral body and paradiscal margins (Fig. 5b) [5]. Radiographs can also show cold abscesses, with soft tissue shadows in the paraspinal region, and retropharangeal space in the case of cervical tuberculosis. The cold abscesses can scallop the lateral portion of vertebral bodies. The presence of calcifications in these soft tissue shadows is highly suggestive of spinal tuberculosis [12]. Radiographs can also reveal kyphotic deformities through a single or multiple contiguous or noncontiguous vertebrae [15]. However the disadvantage is that radiographs often reveal the classic findings only in later stages of the disease. One-third of calcium must be depleted from the bone before the lesion is apparent on radiographs [33]. Chest X-rays are also critical as concomitant pulmonary disease is present in over 50% of patients with spinal tuberculosis [4].

Computed tomography (CT) can detect bony destruction earlier than plain radiographs [20]. However these are rarely used unless there is a contraindication to Magnetic resonance imaging. Lesions smaller than 1.5 cm and soft tissue calcifications are also more accurately depicted [12]. Computed tomography can also better characterize the cause of canal encroachment, abscess, bone, or discal material [15]. Over 60% of spinal tuberculosis has canal encroachment.

Magnetic resonance imaging has increased sensitivity than radiographs (93%) and increased specificity than CT (96%) [34]. Contrast enhanced MRI increases the accuracy of diagnosis and improves the diagnostic accuracy for any patient with a suspicion of this disease process, or questionable diagnosis [5]. MRI is indispensable for the diagnosis in patients with neurologic deficit to assess cord compression [12,15]. Tuberculosis in the vertebral bodies appears hypointense on T1 and hyperintense on T2. Contrast can differentiate between Modic degenerative changes and infection. The characteristic finding is multiple effected vertebral bodies with well-preserved discs [5]. A full spine MRI is essential in order to identify noncontiguous lesions, which are present in 15% to 20% of patients [15].

Some centers are now recommending the use of full spine MRI as soon as spinal tuberculosis is diagnosed. This has two advantages. It allows for the diagnosis of disease before destruction on vertebra and subsequent kyphosis/scoliosis and associated disability from deformity. It also helps identify skip lesions. This is important as initially the plain radiographs only identify the worst affected area and the less involved segments are missed. These less involved segments may progress into collapse as part of natural progression of the disease, even while the patient is on treatment. On repeat plain X-rays, this progression of the initial less involved segment may be misinterpreted as a new lesion, leading to the misdiagnosis of multi-drug resistant (MDR) tuberculosis.

Tubercular cold abscesses have a characteristic appearance on MRI and are uniquely different from pyogenic abscesses. Cold abscesses travel subligamentously along contiguous vertebral bodies and have smooth thin walls as opposed to the thick walls with irregular contrast enhancement seen in pyogenic infections (Fig. 5c and d). Such appearance is 90% specific for tuberculosis [16]. Magnetic resonance imaging also allows for assessment of cord. Myelopathy, myelomalacia, and cord edema has been shown to be predictive of recovery in patients with neurological deficits [20]. Atrophy of the cord has worse outcomes whereas cord edema is associated with better prognosis of recovery [35].

Other imaging modalities also play a role in spinal tuberculosis. Bone scan may show other skeletal sites of involvement however there is limited evidence that it can accurately differentiate between infection and metastasis [5,12]. Positron emission tomography (PET) may have a role in identifying hypermetabolic abscesses to target for higher yield to obtain tissue biopsy specimens [36]. Recent reports on the use of PET/CT to assess activity of the disease are encouraging. The PET/CT technology allows detailed analysis of changes in individual tuberculous lesions over time, and monitoring of the response of these lesions to treatment [37].

Tissue diagnosis

Tissue diagnosis is the gold standard diagnostic test for spinal tuberculosis [5,12,15,16,20]. All tissue samples should be sent for culture, histopathology, and polymerase chain reaction [15]. Tissue can be obtained via CT guided needle biopsy or surgical biopsy if image guidance fails or surgical management is imminent [12]. The yield of cultures is highly dependent on the surgical/radiographic skill of the performer and the number of cultures sent and from which foci [15]. The success of image guidance can be quite high with CT guided fine needle aspiration, with one study finding 89% positive cultures and 100% positive histopathology [38].

Culture and smear are *not* the gold standard in spinal tuberculosis as tuberculosis is a paucibacillary disease. Often, the patients may have already started medical therapies, further lowering the bacterial yield [15]. The use of Ziehl–Neelsen Staining and culture using Lowenstein –Jensen culture media demonstrate positive results in 52% of smears and 83% of cultures [39]. The culture usually takes 4 to 6 weeks of incubation period [20]. Newer mediums such as BACTEC 12 B and GeneXpert MTB/RIF are allowing for point of care testing and may only require 1 to 2 weeks of incubation time, with sensitivities and specificities approaching 90% [5,15]. It is also critical to run antimicrobial sensitivities, to identify and appropriately treat MDR tuberculosis [15].

Histopathology has substantially higher diagnostic success rate as compared with cultures, with 100% confirmation in one report [38]. Cytology shows characteristic epithelioid cell granulomas, granular necrosis, lymphocytes, and Langerhans giant cells (Fig. 6) [40]. Polymerase chain reaction is a new promising technique for diagnosis. Recent studies show a test sensitivity of 90% in spinal tuberculosis samples [41,42] and a specificity of 83% to 90% [43]. The diagnosis can be obtained orders of magnitude faster, with results within 24 hours [41]. Polymerase chain reaction also overcomes the challenges of detecting a paucibacilar disease, and can detect as few as 10 to 50 tubercle bacilli [5].

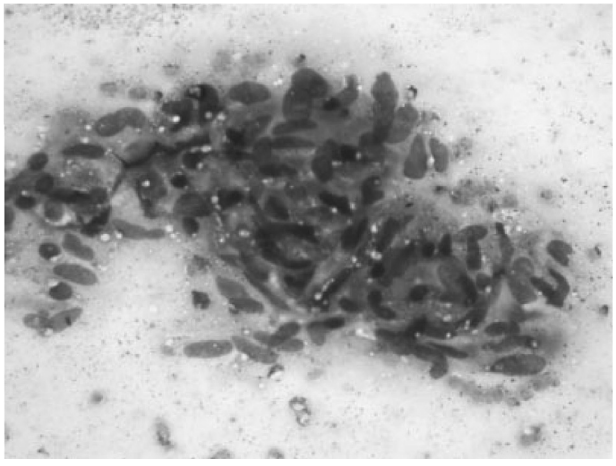

Fig. 6. This is a 400× magnified image of a Hematoxylin and eosin stained fine needle aspiration from a spinal tuberculosis patient's cold abscess. The cytology smear shows an epithelioid cell granuloma with background necrosis. [40].

Treatment algorithm

The treatment of tuberculosis has been documented for millennia. Herbal therapies have been described in texts from ancient India and Hippocrates described rudimentary spinal bracing for the disease. In the preantibiotic era, sanatoria were mainstay of treatment. Often located in resort-like settings, heliotherapy (phototherapy) and nutrition were the major interventions, treating the constitutional systemic symptoms rather than the underlying pathogen [44]. As a result, only 25% of these patients actually achieved healing [20].

Perhaps the most dramatic historic change in the treatment of spinal tuberculosis was the advent of antimicrobial therapies [44]. Streptomycin was the first antimicrobial therapy, which came about in 1943. The study of the efficacy of this drug in 1947 by the Medical Research Council (MRC) of the United Kingdom is often cited as the first randomized control trial and cemented the role of antimicrobial therapies for this disease. The next three decades produced numerous other antibiotics, including isoniazid (1952), rifampin (1966), pyrazinamide (1970) and ethambutol, which composed the pillars of the current chemotherapy regimens for the disease [45].

During this similar timeframe, surgical treatment of spinal tuberculosis was becoming more popular. Anterior surgical debridement and fusion was advocated by Hodgson and Stock who developed the Hong Kong technique [46], a transpleural anterolateral approach to the thoracic spine that was developed during their time treating spinal tuberculosis at Hong Kong University [47,48]. Arguing that the drainage of the abscess, best accessed anteriorly, was the critical component to successful cure, their first paper published in 1956 revolutionized the surgical treatment of the disease [49].

At the same time, Konstam was publishing reports on the medical ambulatory management of spinal tuberculosis based on his management of patients in Africa [50,51]. Later reports by Tuli and Kumar confirmed that antimicrobial concentrations in and around the abscesses and bony tissue exceeded minimum inhibitory concentrations [52,53]. In successful therapy, the abscesses were shown to resorb and the bony lesions filled in with new bone or sclerotic bone. Medical management alone also consistently yielded neurologic recovery, despite the time course of the paraplegia, as the slow growing compression was resolved.

The "Middle Path" approach was developed by Tuli in the 1960s [44]. Patients often presented as poor surgical candidates and his approach began with triple agent antituberculosis chemotherapy in all patients, regardless of neurologic deficit. The treatment also incorporated nutritional

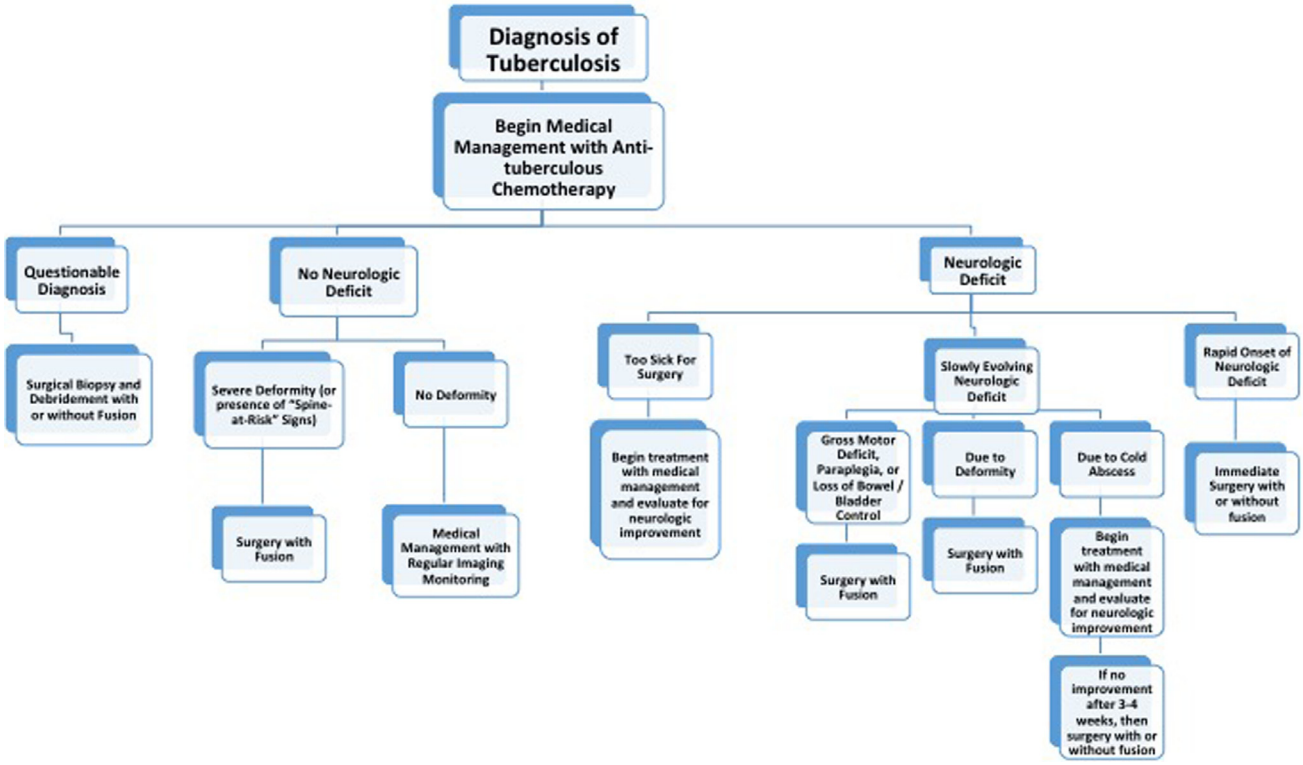

Fig. 7. An algorithm showing the modern surgical indications for spinal tuberculosis.

optimization with high protein diets and vitamins. Only those patients who showed no improvement or progression of neurologic symptoms approximately 1 month after therapy, had persistent abscesses, or recurrence at the 3 to 6 month surveillance radiographs underwent surgery. In 1975, he reported surgery was necessary in only 6% of patients without neurologic deficits and 60% of patients with neurologic deficits. Given that this treatment algorithm yielded favorable results compared with radical debridement, the authors recommended treating spinal tuberculosis with chemotherapy as the first line of treatment.

The comparison between operative and nonoperative spinal tuberculosis was expanded upon by randomized controlled trials conducted by the MRC, studying chemotherapy with and without surgical debridement [54]. The 2006 Cochrane review [54] included two well conducted randomized trials from the 1970s and 1980s, and did not find sufficient evidence to conclusively recommend routine surgical treatment for the treatment of spinal tuberculosis.

There is not complete consensus on the surgical indication for patient presenting with neurologic deficits. Much of the current debate centers on how to manage neurologic deficits in patients with spinal tuberculosis [18,55–58]. This ranges from recommending surgical management only for complete paraplegia [58], to recommending surgical management of all neurologic deficits [57]. Given the success of nonsurgical management of spinal tuberculosis [44,52,56,59], both in curing the disease, but also in resolving neurologic symptoms, the patient, surgery should be used judiciously.

Kyphotic deformity is gaining far more attention as a late sequela of spinal tuberculosis and a critical component of the natural history of spinal tuberculosis [21–25]. The neurologic complications can be slow evolving, caused by gradual spinal cord compression, or can be rapid, if the deformity leads to an instability episode. Surgical intervention is now performed on patients with a kyphosis greater than 60 degrees, and in pediatric patients with "spine-at-risk" signs. Current surgical indications have been shaped by the aforementioned studies to be restricted to cases with uncertain diagnosis requiring open surgical biopsy, gross motor deficits (less than two out of five muscle strength) [56] or rapidly evolving neurologic deficits at presentation, deformity concerning for progression or instability, or for deficits refractory to 3 to 4 weeks of antituberculous chemotherapy (Fig. 7).

Medical management

The goals of the medical management of spinal tuberculosis are: (1) cure the patient of infection, (2) prevent development of drug resistant tuberculosis, (3) prevent disability caused by neurologic deficits or kyphosis, and (4) prevent relapse.

Numerous drugs have been used to treat spinal tuberculosis. They can be classified as bacteriostatic, or bactericidal.

Table 2
World Health Organization's classification of antituberculous drugs

Group	Drugs
Group 1: First line oral agents	isoniazid, rifampin, ethambutol, pyrazinamide, rifabutin
Group 2: Injectable agents	kanamycin, amikacin, capreomycin, streptomycin
Group 3: Fluoroquinolones	moxifloxacin, levofloxacin, gatifloxacin, ofloxacin
Group 4: Oral bacteriostatic second-line agents	ethionamide, protionamide, cycloserine, terizidone, para-aminosalicylic acid
Group 5: Agents with unclear efficacy	clofazimine, linezolid, amoxicillin-clavulanate, thiacetazone, clarithromycin, carbapenems

Reprinted with permission from the World Health Organization [60].

They also differentially treat intracellular versus extracellular tuberculosis, and some (such as pyrazinamide) are more effective in rapidly multiplying active disease and others in slowly multiplying. The WHO has classified antitubercular drugs as shown in Table 2 [60].

The most critical factor in choosing a regimen is preventing the development of drug resistance. The creation of drug resistant strains with single agent therapy was understood even in the first trials of streptomycin. With the use of three or more agents, the risk of developing such a resistance is negligible [45]. All regimens have an intensive phase for the rapidly multiplying bacteria followed by a longer continuation phase for the intracellular bacteria. Though initial treatment protocols were 18 months long, trials by the MRC showed shorter courses were as effective [61], with more recent data confirming 0% relapse rates after just 6 months of rifampin, isoniazid, and pyrazinamide [62]. The most commonly prescribed regimen for sensitive tuberculosis does not differ for pulmonary and extrapulmonary disease. Both the WHO and Centers for Disease Control recommend 2 months of rifampin, isoniazid, pyrazinamide, and ethambutol followed by a 4 month continuation therapy of rifampin and isoniazid [60].

In the developing world, treatment adherence was difficult to maintain in the long term. Directly Observed Treatment – Short Course (DOTS) is defined by the WHO as patient taking medications under the observation of a health care worker, or layperson that functions as a treatment supporter [63] caused by the resource intensive nature of supervised therapy, DOTS therapy can be administered every 2 to 3 days. Studies show a lag phase for 1 to 2 days after the drug washes out before bacteria start multiplying again, supporting this type of intermittent therapy [64]. Daily administration is recommended in an adequately resourced healthcare setting.

The most critical principle when treating tuberculosis medically is obtaining cultures samples to determine the ideal regimen. Tissue diagnosis is essential if empiric treatment is not effective. Careless prescribing of incomplete drug regimens and noncompliance with treatment course has led to the development of resistant strains of tuberculosis. This ranges from MDR with bacteria resistant to isoniazid and Rifampin, to Extensively Drug Resistant tuberculosis with bacteria resistant to fluoroquinolones and at least one second-line injectable drugs, to Total Drug Resistant tuberculosis (TDR) [65].

Clinical suspicion is crucial to diagnosing MDR, however if medical treatment is not effective, DOTS must be halted at once [66] and the temptation to add a single agent to the current regimen (addition syndrome) must be resisted [67]. If a tissue diagnosis has not been obtained, this should become the priority, either with CT guidance or surgical biopsy. Infectious disease experts with an understanding of the MDR strains regionally can also be involved.

Determining the endpoint of medical management is challenging. In pulmonary tuberculosis, the sputum can sufficiently guide the physician. In spinal tuberculosis, radiographs may take months after successful therapy to show the reossification, sclerosis, and fusion of the spinal lytic changes [43]. MRI changes following medical therapy can also be vexing. With the constitutional improvement in a patient, an MRI done 2 to 3 months after initiation of therapy can show worsening of the abscesses caused by a rebound immune response known as immune reconstitution inflammatory syndrome [68]. The PET/CT may offer a more reliable option to monitor drug response [37].

The medical management of adults and children with spinal tuberculosis is nearly identical, with specific changes in the dosing of the medications. Special consideration should be given to the use of ethambutol in children, caused by the ocular toxicity associated with the drug. There is expert opinion that in children with osteoarticular and spinal tuberculosis, the continuation phase of therapy should be doubled, for a total of 10 to 12 months of therapy [69].

The medical management in the dual infected patient, tuberculosis and HIV, has separate considerations, which is especially important given the concomitant infection often encountered in endemic regions. The first is the interaction between antiretrovirals, specifically protease inhibitors, and rifamycins. As both drug types go through the CYP450 pathway, the blood plasma levels of rifampin may be significantly decreased. However combinations of certain drugs, such as ritonavir and rifampin, have been shown to adequately treat both HIV and tuberculosis [70]. A second consideration is paradoxical worsening of tuberculosis following the start of HIV treatment. The enhanced immune response may cause a worsening of the signs and symptoms of tuberculosis. Though a treating clinician must perform a thorough evaluation of other causes of worsening, this paradoxical reaction should be considered before diagnosing treatment failure and changing the chemotherapeutic regimen [71]. Despite these challenges, spinal tuberculosis has been successfully treated in patients with dual infection with HIV, even in the absence of treatment of the HIV using standardized antituberculous regimens [72,73].

Control of the spinal deformity during nonoperative management of tuberculosis was traditionally done through

prolonged bed rest. The middle path approach also used bracing during medical management to minimize progression of deformity [59]. However contemporary management of tuberculosis does not necessitate the use of bracing [12]. Modern literature on the treatment of spinal tuberculosis with nonoperative measures has shown successful treatment with patients ambulating without the use of bracing, caused by the topical climate in endemic regions which lowers bracing compliance [56]. Bracing is sometimes prescribed after operative management of tuberculosis, however there are no current evidence based guidelines and the use of postoperative bracing is often based on surgeon preference [74].

Surgical management

Before the antituberculous era, surgical debridement was considered the basis of the surgical treatment of tuberculosis. The decompression of the abscess, and removal of any material compressing the cord was essential, especially in cases of severe neurologic deficit caused by such cord compression. Neurologic recovery is regularly observed after cord decompression, despite lengthy periods of neurologic deficits, as the compression is slow growing unlike in acute cases of paraplegia via trauma.

Hodgson and Stock, in their early experience attempted posterior-only fusion of the spine. This approach could not access the anterior abscesses and they found that this anterior disease prevented posterior spinal fusion. This led to their development of the anterior approach. However even with the early experience by Hodgson and Stock, it became clear that debridement alone was not advisable. Debridement of the anterior infected tissue involved the radical excision of vertebral bone and discs, which removed the structural integrity of the anterior column of the spine and led to the creation of instability in the spine, progression of deformity and possibility of late onset paraplegia [47–49]. Like Percival Pott's initial reports, they recognized the importance of bone healing and fusion as crucial to the success of treatment.

To combat this anterior bony insufficiency, Hodgson and Stock inserted fibular allograft struts into the anterior defects, allowing for anterior fusion of the spine [47]. More modern studies examined the outcomes of such anterior arthrodesis. Without additional instrumentation, longer grafts had increased rates of graft slippage, subsidence, fracture, or absorption compared with short segment strut grafts spanning single destroyed vertebrae [75]. Anterior instrumentation with titanium cages, plates and screws allows for increased stability and ability to correct deformity. However it also comes with hardware complications such as displacement of the instrumentation and damage to the viscera and anterior vessels [15].

With the advent of segmental posterior instrumentation with pedicle screws, posterior approaches to correcting spinal deformity and achieving stable fusion have become more relevant. With antituberculous chemotherapy the anterior abscesses have been shown to resorb and fill in with new sclerotic or woven bone. Through the costotransversectomy approach, anterior access can also be reached through the posterior approach for further disease debridement and placement of anterior struts. This has allowed for powerful deformity correction with some studies showing improved correction with posterior compared with anterior instrumentation [15]. Rajasekaran has also described a single stage, all posterior closing and opening wedge osteotomy to correct post-tubercular deformity [76].

Combining anterior and posterior approaches allow for thorough debridement, decompression, and strut grafting anteriorly, followed by posterior stabilization and instrumentation [77–79]. This leads to improved biomechanics and decreased recurrence and revision surgeries. Minimally invasive surgery techniques using video assisted thoracoscopic decompression of the anterior tuberculous lesions and minimally invasive instrumentation have also recently been reported. Such techniques minimize surgical morbidity however indications are primarily for debridement, as these techniques only allow for minimal correction of deformity [80,81].

With the advent of antitubercular chemotherapy, surgical management is an adjunct to the principle treatment, which is medical. Neither the neurologic status of the patient, nor the urgency of surgical management of spinal tuberculosis, should delay the start of antituberculous medical therapy, which should be begun as soon as a patient presents with confirmed spinal tuberculosis. The duration of antituberculous chemotherapy should not be altered based on whether or not the patient underwent surgical debridement of spinal tuberculosis. Studies have shown cure with a 6-month course of antitubercular medications [82,83]. Determining the end point of medical management in a patient who underwent surgical management can be challenging as the normal radiographic markers of healing, such as reconstitution and sclerosis of the effected vertebrae may not be visible. The return of signs and symptoms, laboratory markers such as ESR, C-reactive protein, and radiographic progression of deformity can aid in determining recurrence or reactivation [82].

Perioperative care

Often the patients with spinal tuberculosis are not ideal surgical candidates. They are either compromised hosts to begin with, such as HIV infected individuals, which resulted in the tuberculosis infection, or the disease has begun to take a systemic toll. Pulmonary function is also decreased in severe kyphosis. The middle path approach was instituted specifically for this reason, treating patients medically until they were either optimized for surgical treatment or their indication necessitated surgery. Now perioperative management involves systemic, nutritional and pulmonary optimization for surgery.

Postoperative care of such patient includes not only continued antituberculous chemotherapy but also likely ICU care to allow for resuscitation after surgeries with significant blood loss, fluids shifts and to allow for persistent cord perfusion after correction of spinal cord deformity to prevent the development of postoperative cord ischemia. Though initial reports recommend the placement of plaster of paris casts [46], modern instrumentation rarely requires the use of orthotics postoperatively, and the use of bracing is generally based on surgeon preference [74].

Of note, those caring for the patients with spinal tuberculosis should follow tuberculosis prevention guidelines as outlined by the Centers for Disease Control. This includes the use of airborne precautions, respiratory protection with appropriately rated respirators, and regular screenings of health care providers for patients with transmittable tuberculosis. Those providers present in the operating theatre with spinal tuberculosis patients should wear appropriate respiratory protection for airborne particles. The operating theatre should not have pressurized airflow, which could spread airborne particles to other regions of the facility, and the patient should have a bacterial filter placed on their endotracheal tube. Though no antitubercular chemoprophylaxis is recommended for providers caring for patients with tuberculosis, those in low to medium risk environments should have annual tuberculosis skin test screening, and those in high risk facilities with potential ongoing transmission should have screens every 8 to 10 weeks. Treatment for tuberculosis should be started immediately upon a positive screening test [84].

Outcomes

In the modern era, spinal tuberculosis has generally good outcomes with all treatment modalities, with approximately 90% showing improved outcomes (pain, neurologic recovery, and deformity) after medical and/or surgical management [13,15]. This is a far improvement from the 25% positive outcomes in the preantituberculous drug era [44]. The cornerstone of treatment continues to be antituberculous medications. The consistent completion of antituberculous chemotherapy regimens yielded relapse rates of ~2% in one study of spinal tuberculosis [85].

Management of spinal deformity depends on the stage of disease at presentation. Modern surgical spine techniques have allowed for impressive correction of deformity and studies on the natural history of post-tuberculous kyphosis [16,24–26,75] have demonstrated the cases which require early surgical intervention.

Neurologic recovery is also consistently seen in medical and surgical management of spinal tuberculosis. In Tuli's middle path approach, 40% of patients treated with medical therapy alone grossly recovered their neurologic deficits [59]. More recent studies examining patients with neurologic deficits treated surgically found that 92% had marked improvement. Seventy-four percent went from nonambulatory to ambulatory [86]. Though MRI findings were not necessarily predictive of outcome in this study, another study showed that younger age, incomplete paraplegia, and surgical management were associated with improved neurologic recovery [87]. Late onset neurologic deficits, however, may have more challenging surgical treatments, as the deficit is from either chronic severe deformity or mechanical instability and trauma.

Summary

Though an ancient disease, the last 50 years have brought about remarkable advances in the diagnosis and treatment of spinal tuberculosis. The most impactful advance has been that of antituberculous chemotherapy which has allowed for the ambulatory treatment of this pathology, without the need for surgery in the majority of cases. Diagnostic advances in the availability of advanced imaging and polymerase chain reaction have allowed for the rapid initiation of therapies. However more work needs to be done in understanding the future of this disease. The prevalence of drug resistance has limited the efficacy of medical management in certain endemic regions. And despite the power corrections offered by modern spinal instrumentation, the kyphotic deformity associated with tuberculosis remains a challenge in poorly resourced regions of the world. It is critical, especially with the degree of globalization in our world today, for the contemporary surgeon to understand the comprehensive natural history, diagnostic and management strategies for spinal tuberculosis in order to adequately treat this challenging disease.

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Supplementary materials

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