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Tuberculous spondylodiscitis: epidemiology, clinical features, treatment, and outcome

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Abstract. – *Background:* Tuberculous spondylodiscitis (TS) is a rare but serious clinical condition which may lead to severe deformity and early or late neurological complications.

***Aim:* To discuss certain aspects of the approach to TSs, focusing upon epidemiology, diagnosis, and treatment outcome.**

***Materials and Methods:* For the purpose of this review, a literature search was performed using the Pubmed database through to 19th October 2011 to identify studies published in the last 20 years, concerned in epidemiological, clinical, diagnostic, and therapeutical aspects of TS in adults. Only studies drafted in English language and reporting case series of more than 20 patients have been included.**

***Results:* TS has been reported to accounts for 1-5% of all TB cases, and for about 50% of the cases of articulo-skeletal TB infections. Despite the actual availability of more effective diagnostic tools, early recognition of TS remains difficult and a high index of suspicion is needed due to the chronic nature of the disease and its insidious and variable clinical presentation. A prompt diagnosis is required to improve long term outcome, and a microbiological confirmation is recommended to enable appropriate choice of anti-mycobacterial agents. Surgery has an important role in alleviating pain, correcting deformities and neurological impairment, and restoring function.**

***Conclusions:* Further studies are required to assess the appropriate duration of anti-microbial treatment, also in regarding of a combined surgical approach.**

Key words:

Tuberculosis, Spondylodiscitis, Pott's disease, Epidemiology, Treatment, Outcome.

Introduction

Tuberculous spondylodiscitis (TS), known also as Pott's disease, was first described in 1779 by Percival Pott, one of the leading surgeons in London in the eighteenth century[1].

The spine is the most common site for osseous involvement by tuberculosis (TB). TS has been reported to accounts for 1-5% of all TB cases from many reports[2-8], and for about 50% of the cases of articulo-skeletal TB infections[2,9-11].

Comparative studies of spontaneous spinal infections performed in developed countries show that *Mycobacterium (M.) tuberculosis* is the causative agent of spinal infections with a frequency ranging from 17% to 39%, thus representing an important issue even in a contest of low endemicity for TB infection[2,12-15].

Many observational studies have been published in the last 20 years in order to identify the clinical, microbiological, and radiological features of patients with TS and to assess the correct management in terms of diagnosis and treatment[3,5,6,8,9,12-14,16-36]. Most of these studies have been conducted in developing nations, where the incidence of tuberculosis is higher and the average age of patients at presentation is lower[16,19,20,22,24,28,29,34]. Aim of this review is to discuss certain aspects of the approach to TSs, focusing upon epidemiology, diagnosis, and treatment outcome.

Epidemiology

Tuberculosis remains the most common cause of death due to an infectious disease worldwide: according to the World Health Organization's Global TB Report 2010, in 2009, there were 9.4 million estimated incident cases (range, 8.9 million-9.9 million) of TB globally (equivalent to 137 cases per 100 000 population); 1.3 million people died among Human Immunodeficiency Virus (HIV)-negative people (range, 1.2 million-1.5 million) and 0.38 million died among HIV-positive people (range, 0.32 million-0.45 million) because of tuberculosis[37].

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Most of the estimated number of cases of TB occurred in Asia (55%) and Africa (30%), and smaller proportions were registered in Eastern Mediterranean Region (7%), European Region (4%), and Region of the Americas (3%). Of the 9.4 million incident cases in 2009, about 1.0-1.2 million (11-13%) were HIV-positive[37].

Data suggest that tuberculosis is still a major problem of public health not only in developing countries but also in the western world[37], where the highest burden of disease involves immigrants and foreign-born patients.

In Europe, 329 391 new episodes of TB and 46 241 deaths due to TB have been reported in 2009; the estimated percentage of extra-pulmonary cases in European countries was about 14%[38].

In United States, even if the number of TB cases reported annually has decreased by approximately 57% since 1992, with a decline of 10.5% in 2009 compared to 2008, the proportion of total cases occurring in foreign-born persons has increased every year from 1993 to 2008, and in 2009 59% of TB cases occurred in foreign-born persons[39].

Large migratory movements from areas where TB is endemic, the accumulation in large cities of enormous pockets of poverty, unemployment, poor nutrition, and poor living facilities have been recognized as major elements that play a role in the resurgence in TB in developed countries. In addition, the HIV epidemic, the emergence of multidrug-resistant strains of *M. tuberculosis*, and the immunity deterioration due to aging, all contribute to made TB an increasingly common problem, especially among ethnic minorities[40-47], and extra-pulmonary forms of TB have been reported to be more frequent among immigrants in developed countries[48,49]. In most of the studies performed in western countries (United Kingdom, United States, France, Switzerland) immigrant patients represented more than 50% of patients diagnosed with TS[5,23,31-33].

Demographic characteristics and principal risk factors reported in 29 different observational studies are shown in Table I.

The mean age of presentation of TS is reported to range between 30 to 40 years[5,18,20,22,28,29,34,36]. In the retrospective review performed by Turgut et al[36] and including all cases of TS reported in Turkey from 1985 to 1996, the mean age was 32 years, whereas in a large French epidemiological study on spondylodiscitis, TS was significantly more common in patients aged under 40 compared to those over 40[50].

However, a recent Japanese epidemiological survey reported that the proportion of TB infection among patients aged more than 70 years was 31.2% of the total case of TSs in 1994, and by 2002 had increased to 41.5%; the same study reported a similar trend for spinal TB[26]. Increasing life expectancy deals with the occurrence of a series of concatenating events: malnutrition, underlying acute or chronic diseases, and the biological changes with aging, all contributing to the expected age-associated decline in cellular immune responses to infecting agents such as *M. tuberculosis*[51,52].

Risk factors for TS has been largely investigated in several studies: underling diseases such as diabetes mellitus and chronic renal failure have been found in 5% to 25% and 2% to 31% of patients, respectively[3,6,12,13,16,17,27,31,35], whereas prolonged corticosteroid therapy has been reported in 3% to 13% of patients[3,6,16,17,27,35]. TB is the most common and virulent opportunistic infection associated with HIV disease[53], and skeletal tuberculosis is more frequent in HIV-positive patients than in HIV-negative[54]. Godlwana et al[19], in their study performed in South Africa, reported a rate of HIV seropositive of 28% of total TS cases, and similar results were found by both Leibert and Rezai in USA (27% and 25% respectively)[25,33]. Finally, in a patient presenting with chronic back-pain, high suspicion of TS should be evocated by a previous history of TB, which is reported in a proportion ranging from 5% to 100% of patients diagnosed with TS[3,6,13,16,19,27,31,32,35].

Pathogenesis

In a significant percentage of TS cases there is no evidence of primary infection: concurrent localizations of TB in other sites are reported in 3% to 65% of cases, with a rate of pulmonary involvement that ranges from 1% to 67%, mostly accounting for more than 20%[3,5,6,8,12,13,16,18,24, 26,29,31,33-36] (Table II).

As for pyogenic spondylodiscitis, TSs can result from arterial haematogenous seeding of the *M. tuberculosis* starting from a quiescent or active pulmonary focus, or can be due to contiguous or lymphatic spread from pleural disease[55].

Table I. Country, number of patients, demographic characteristics, and risks factors in 29 different observational studies.

Author (reference)	Study period	Country	Patients (n°)	Male	Age (mean)	Foreign born	HIV	IDU	DM	CRF	Cortico-steroids	Previous TB
Alothman et al (3)	1985-1998	Saudi Arabia	69	53.6	53	-	-	-	10	-	3	7.2
Alavi et al (16)	1999-2008	Iran	69	60.8	44	-	17.4	17.4	8.7	14.5	13	28.9
Colmenero et al (12)	1983-1995	Spain	42	50	-	-	-	7.1	4.9	-	-	-
Colmenero et al [2] (17)	1983-2002	Spain	78	51.3	49	5.1	7.7	11.5	11.5	-	5.1	-
Cormican et al (5)	1999-2004	UK	21	61.9	35	90.5	4.8	4.8	-	-	-	-
Dharmalingam (18)	2000-2002	Malaysia	33	72.7	36	9	-	-	-	-	-	-
Goldwana et al (19)	2005-2006	South Africa	104	46	-	-	28	-	-	-	-	100
Hadadi et al (20)	2003-2005	Iran	22	56.5	40	43.5	-	-	-	-	-	-
Hayes et al (21)	1985-1992	UK	21	52.4	38	-	-	-	-	-	-	-
Jalle et al (22)	1985-1989	Malaysia	31	61.3	35.4	-	-	-	-	-	-	-
Janssens et al (23)	1976-1986	Switzerland	26	61.5	48	53.8	-	-	-	-	-	-
Khorvash et al (24)	-	Iran	100	58	-	-	-	-	-	-	-	-
Kim et al (13)	2003-2007	South Korea	47	36.2	55	-	-	-	17	0	-	12.8
Leibert et al (25)	1988-1995	USA	26	69.2	44	46.1	26.9	26.9	-	-	-	-
Luzzati et al (14)	1995-2005	Italy	27	-	-	-	-	-	-	-	-	-
Maeda et al (26)	1990-2002	Japan	23	43.5	76	-	-	-	-	-	-	-
Mulleman et al (27)	1986-2003	France	24	37	61	37.5	0	-	8.3	-	8.3	25
Mwachaka et al (28)	2004-2009	Kenia	129	52.7	33	-	0	-	-	-	-	-
Nene et al (29)	1998-2000	India	70	38.5	37	-	0	-	-	-	-	-
Nussbaum et al (8)	1973-1993	USA	29	41.4	-	58.6	-	-	-	-	-	-
Park et al (30)	1994-2003	South Korea	137	50.4	44	-	-	-	-	-	-	-
Pertuiset et al (31)	1980-1994	France	103	66	41	68	0	-	1	1.9	1	18
Ramachandran et al (32)	1998-2002	UK	34	54	47	86.2	-	-	-	-	-	18.4
Rezai et al (33)	1988-1993	USA	20	70	49	50	25	25	-	-	-	-
Solagberu et al (34)	1994-1999	Nigeria	27	50	27	-	-	-	-	-	-	-
Su et al (35)	2002-2008	Taiwan	48	50	64	-	2.1	6.3	25	31.3	4.2	12.5
Talbot et al (9)	1999-2004	UK	29	-	-	-	-	-	-	-	-	-
Turgut et al (36)	1985-1996	Turkey	694	50	32	-	-	-	-	-	-	-
Weng et al (6)	1998-2007	Taiwan	38	60.5	68	-	-	-	18.4	18.4	5.3	5.3

All values are presented as % of patients except as noted otherwise in line 1. Abbreviations: IDU: intravenous drug user; DM: diabetes mellituts; CRF: chronic renal failure; TB: tuberculosis. Where absent, data were not available.

Table II. Localization of TS lesions, disease extension, and presence of other foci of TB infection in 29 different observational studies.

Author (reference)	Involved vertebre (mean)	Cervical	Thoracic	Thoraco-lumbar localiza-tion	Lumbar locali-zation	Lumbo-sacral localization	Disc involv-ment	Paraspinal abscess	Epidural compres-sion	Posterior involve-ment	Other foci of TB	Pulmonary TB
Alothman et al (3)	-	-	55	-	36	-	-	80	33	-	2.9	1.4
Alavi et al (16)	-	-	14.5	-	-	-	-	47.8	-	-	44.9	17.4
Colmenero et al (12)	2.6	0	64.3	-	33.3	-	-	78.3	-	-	33.3	-
Colmenero et al[2](17)	2.6	3.9	41	14.1	32.1	6.4	97.4	73.1	65.4	76.9	19.2	11.5
Cormican et al (5)	2.6	-	-	-	-	-	95.3	-	65	-	33	19
Dharmalingam (18)	-	18.2	30.3	6.1	27.2	6.1	-	-	-	-	-	66.6
Goldwana et al (19)	-	11	42	10	30	5	-	-	-	-	-	-
Hadadi et al (20)	-	-	50	-	22.7	-	53.3	29.6	-	-	-	-
Hayes et al (21)	-	14.3	66.7	-	19	-	-	-	-	-	-	23.8
Jalle et al (22)	-	-	-	-	-	-	-	-	-	-	-	-
Janssens et al (23)	2.2	53.8	-	7.7	38.5	-	-	57	-	-	38.5	-
Khorvash et al (24)	-	5	11	29	-	-	-	20	-	-	-	18
Kim et al (13)	-	8.5	38.3	-	53.2	-	-	59.6	63.8	-	31.9	25.5
Leibert et al (25)	-	-	-	-	-	-	-	-	-	-	-	-
Luzzati et al (14)	-	7.4	37	44.4	11.1	0	-	-	-	-	-	-
Maeda et al (26)	2.3	4.3	47.8	30.4	21.7	-	73.9	86.9	-	17.4	4	4
Mulleman et al (27)	-	8.3	45.8	-	50	-	58.3	-	-	-	-	-
Mwachaka et al (28)	1.8	6.2	43.4	8.8	37.2	2.7	-	-	-	-	-	-
Nene et al (29)	2.5	-	84.3	15.7	-	-	71.4	32.8	30	2.8	-	2.8
Nussbaum et al (8)	-	3	55	10	28	-	-	45	31	-	52	10
Park et al (30)	2.2	-	31.3	9.7	44.8	-	-	58.6	28.6	-	15.5	-
Pertuiset et al (31)	-	12	47	-	66	-	49.5	-	-	5.8	27	15.5
Ramachandran et al (32)	-	13.1	39.5	-	26.3	-	-	-	-	-	31.6	-
Rezai et al (33)	2.5	10	65	10	20	-	85	90	65	-	65	65
Solagberu et al (34)	-	7.4	22.2	22.2	40.7	-	-	-	-	-	11.1	11.1
Su et al (35)	2.5	4.2	33.3	16.7	41.7	4.2	-	77.1	37.5	-	25	22.9
Talbot et al (9)	-	6.9	27.5	13.8	34.5	-	-	-	-	-	-	-
Turgut et al (36)	-	4.2	55.8	16.9	22.8	-	-	-	-	4.7	5	2.7
Weng et al (6)	3.5	2	37	8	39	11	84	50	71	-	42.1	39.5

All values are presented as % of patients except as noted otherwise in line 1. Abbreviations: TB, tuberculosis. Where absent, data were not available.

Since the intervertebral disc does not have a direct blood supply in adults, most haematogenous infections of the disc space are the result of dissemination from the adjacent bone. The natural evolution of the infection is the formation of a granuloma, whose centre tends to caseate and to become necrotic. The infection can then progress to destroy the bone, causing pain and leading to the collapse of the vertebral bodies producing the classic roentgenographic picture of anterior wedging of two adjacent vertebral bodies with destruction of the intervertebral disk. Physical findings of a tender spine, prominence or gibbus are common clinical presentation[55-57]. The vertebral body collapse has been reported with a frequency ranging from 13% to 87%[3,8,26,35].

The thoracic segment and the thoraco-lumbar hinge represent the most frequent localizations of TS, followed by lumbar and cervical segments (Table II). In the largest case series published by Turgut, the thoracic spine was involved in 55.8% of cases, the lumbar in 22.8%, and the cervical in 4.2%[36]. However, Park et al[30] reported a more frequent involvement of the lumbar segment (44.8%), followed by thoracic (31.3%), and thoraco-lumbar hinge (9.7%).

The predominant localization in the thoracic segment could be related to the frequent involvement of mediastinal lymph nodes and the pleura in pulmonary TB, from where microorganisms can reach the vertebral bone through the lymphatic route as mentioned above[55].

Tuberculous lesions are more likely to involve more than two vertebrae compared to pyogenic cases[13], ranging the mean number of vertebrae involved from 1.8 to 3.5[5,6,12,17,23,26,28-30,33,35] (Table II).

Compared to pyogenic haematogenous spondilodiscitis, in TSs the posterior elements of the vertebrae (pedicles, transverse processes, laminae, and posterior spinous processes) could be involved more frequently[58,59]. Maeda et al[26] reported a posterior involvement in 17% of TS cases; in these patients severe neurological deficits are generally present[60,61]. The involvement of the intervertebral disc space has been frequently reported, with a proportion that varies from 50% to 97.5%[5,6,17,20,26-30,33]. Pertuiset at al[31] identified two distinct patterns of TS: the classic form of spondylodiscitis, and an increasingly common atypical form characterized by spondylitis without disk involvement; their data suggest that the atypical form could now be the most common form of TS in foreign-born subjects in industrialized countries, although the reasons for this remain unclear.

TSs are frequently complicated by formation of large paravertebral abscesses, which have been reported in 20% to 90% of cases[3,6,8,12,13,16,17,20,23,24,26,29,30,33,35]. Anterior epidural abscesses in TSs have generally similar characteristics to those of pyogenic spondylodiscitis[55], and epidural compression occurs frequently in TSs, with percentages up to 50% of cases in some studies[5,6,13,17,33] (Table II). In addition, abscesses may be found in sites far from the infectious focus, particularly in the sheaths of the psoas muscles[55-57].

TSs have in general a more indolent and less painful clinical evolution than pyogenic infections, because of microbiological characteristics of *M. tuberculosis* consisting in slow growth, propensity for an oxygen rich environment, and absence of proteolytic enzymes. Consequently, neurological complications due to spinal cord compression are frequent. Nerve roots may be compressed with consequent pain or radiculopathy, but more commonly compression on spinal cord or cauda equina gives rise to myelopathy or paraplegia. These neurological complications can occur early in active disease due to inflammatory tissues, epidural abscess, protruded disc, pachymengitis, or spinal subluxation, but also after years from TS event due to severe kyphosis with chronic spinal cord compression and atrophy, with or without reactivation of the infection (late-onset paraplegia)[54-56,61].

Clinical presentation

Principal signs and symptoms reported in 29 different observational studies are shown in Table III. The clinical manifestations of TSs are related to both systemic illness and/or local infection. As stated above, evidence of other foci of tuberculosis and systemic symptoms have been reported with rates ranging from 3 to 65%[3,5,6,8,12,13,16,18,24,26,29,31,33-36] (Table II). However, Turgut[36] found that only 35 patients out of a total of 694 cases reviewed (5%) had evidence of other foci of infection and only 16 (2.7%) a pulmonary involvement.

Fever is often absent, reported in less than 40% of cases in most of the studies[3,5,6,8,12,16,17,26,27,31,35], whereas weight loss, night sweats, and malaise are manifestations that occur generally in less than 30% of patients[3,5,16,27,28,35,36].

Table III. Clinical characteristics of TS in 29 different observational studies.

Author (reference)	Back pain	LEW symptoms	Constitutional	Fever	Weight loss	Night sweats	Neurological symptoms	Diagnostic delay (months)
Alothman et al (3)	84	28	-	32	27.5	22	28	-
Alavi et al (16)	98.5	-	-	26.1	14.5	17.4	26.1	6.8
Colmenero et al (12)	90	-	45	32	-	-	76	5.7
Colmenero et al [2] (17)	83.3	-	35.9	34.6	-	-	44.9	6.1
Cormican et al (5)	100	9.5	47.6	24	24	29	29	11
Dharmalingam (18)	-	-	-	-	-	-	51	-
Goldwana et al (19)	-	-	-	-	-	-	56	-
Hadadi et al (20)	-	-	-	-	-	-	68	18
Hayes et al (21)	95.2	-	71.4	-	-	-	47	3.7
Jalle et al (22)	90.3	-	-	-	-	-	30.9	-
Janssens et al (23)	-	-	-	-	-	-	46	4
Khorvash et al (24)	99	-	80	-	-	-	34	2-3
Kim et al (13)	87.2	-	-	17	-	-	27.7	3
Leibert et al (25)	100	-	-	57.7	57.7	-	26.7	3
Luzzati et al (14)	96.3	-	-	14.8	-	-	63	4
Maeda et al (26)	82.6	-	-	30.4	-	-	56.5	4.9
Mulleman et al (27)	100	-	33.3	37.5	41.7	-	-	4.3
Mwachaka et al (28)	77.5	72.9	-	-	7	20.9	72.9	-
Nene et al (29)	-	-	-	-	-	-	15.7	-
Nussbaum et al (8)	79	-	-	45	-	-	76	-
Park et al (30)	-	-	-	-	-	-	-	-
Pertuiset et al (31)	97	-	56	31	48	18	50	4
Ramachandran et al (32)	-	-	-	-	-	-	36.8	-
Rezai et al (33)	100	40	-	-	35	-	50	3
Solagberu et al (34)	-	-	-	-	-	-	88.9	-
Su et al (35)	95.8	62.5	-	39.6	8.3	-	77.1	6.9
Talbot et al (9)	-	-	-	-	-	-	20.7	-
Turgut et al (36)	21.3	69.2	-	1.6	-	-	-	-
Weng et al (6)	100	53	8	16	-	-	26	2

All values are presented as % of patients except as noted otherwise in line 1. Abbreviations: LEW: lower extremities weakness. Where absent, data were not available

Back pain, often associated with spine stiffness and spasms of the paravertebral muscles, is the most common reported symptom, occurring in more than 80% of patients[3,5,6,12-14,16,17,21,22,24-27,33,35], followed by lower extremities weakness, found in up to 73% of patients[28,36]. Torticollis, neck pain, stiffness, dysphagia, and/or inspiratory stridor are the most frequent clinical manifestations in cervical TSs[63]. When diagnosis is made in advanced stages, soft tissue swelling, draining sinus, and spinal tenderness could be evident at physical examination[16]. Kyphotic deformity of the spine occurs as a consequence of collapse of the anterior spinal elements and is more frequent in thoracic TSs than in other spine localizations[64]; Colmenero et al[12] reported a rate of spinal deformity of 41%.

Neurological involvement has been reported in 16-89% of TS cases[3,5,6,8,12-14,16,17,19-22,24,26,28,29,31-35]. Neurological deficits occur because of kyphotic deformity, spinal abscess, and/or granulation tissue compressing the spinal cord or cauda equina[64]. In the study by Colmenero et al[17], neurological impairment has been reported in 45% of TS cases, and paraplegia was present in 6%; these patients were more likely to have epidural, paraspinal or psoas abscesses. The most common signs of neurological impairment are numbness, lower limb weakness, and urinary disorders[20,28,33,34].

Diagnosis

The large spread in symptoms duration before diagnosis reflects both the variable and chronic nature of the disease both the difficulty in recognising spinal TB. This can explain why the mean duration of symptoms before a correct diagnosis is formulated could be so long: it ranges from 2 months to 4 years[6,12-14,16,17,20,24,25,27,33,35]. In addition, in the elderly diagnosis of TSs could be more difficult, and delays may result: the common presentation with a persistent, localized pain in the back, in absence of other systemic symptoms (e.g. fever), is often misdiagnosed because the majority of elderly have some degree of backache due to degenerative changes or osteoporosis of the spine. Of note, spinal metastasis and other causes of pathological fractures should be considered in the differential diagnosis of TSs in elderly[26].

For these reasons physicians must exercise a high index of suspicion to achieve early diagnosis of TSs. Diagnostic tools for TSs can be divided into two major groups: invasive and non-invasive procedures. Diagnostic tools utilized and evidence of vertebral collapse on magnetic resonance imaging (MRI) in 29 different observational studies are reported in Table IV.

Among non-invasive diagnostic tools, laboratory studies can be suggestive of chronic infection (anaemia, hypoproteinemia), and an elevated erythrocyte sedimentation rate (ESR) is usually found[8,12,20,21,35,62]. Interestingly, the C reactive protein (CRP) has been usually found to be normal or slightly elevated, whereas white blood cells count is normal in most of cases[6,26].

Tuberculin skin test and interferon gamma-release assays (IGRA) are approved as indirect tests for diagnosis of *M. tuberculosis* infections. However, these tests do not allow to discriminate active from latent infections, but when integrated with clinical and radiological findings, they can give to clinicians an important diagnostic orientation[66]. The percentage of positive tuberculin skin test ranges from 10% to 83% of patients in the studies considered[8,17,20,22,24,25,27,28,31,33,34], whereas no data have been specifically reported to this date about the role of IGRA in TSs.

Imaging studies are essential for diagnosis and management of TSs, and could allow the differential diagnosis by assessing features that are characteristic of certain infectious etiologies, inflammatory lesions, and malignancies. Soft tissue mass with calcification or bony fragments, vertebral collapse with relative preservation of the intervertebral disc, gibbus deformity, and presence of large paravertebral mass or abscesses have been considered characteristics of TS[7,67].

Plain radiography, usually employed as a screening test, characteristically shows a destructive process of the thoracic or lumbar vertebrae with involvement of the adjacent disc space which is usually evident later in the course of the disease and is less pronounced than in pyogenic infections[68].

Computed tomography (CT) scanning in the axial plane with bone windows can be utilized to define the precise extent of bone involvement and to identify a calcified paraspinal mass, common in TSs[68,69] but rare in pyogenic abscesses[70].

MRI has become the method of choice for diagnosis of TS, due to its capability to provide information about the epidural space and spinal cord[71-73]. A proportion from 20% to 100% of patients underwent a MR in the studies analyzed[3,5,6,8,17,26-28,31,33,35]. The major MRI findings reported by Maeda et al[26] were osteolytic changes (86%), narrowing of disc space (73%), loss of vertebral body height (69%), erosion of the vertebral endplates (56%).

Table IV. Radiological and microbiological diagnostic tools and evidence of vertebral collapse on Magnetic Resonance Imaging in 29 different observational studies.

Author (reference)	TST°	Biopsy*	Surgical§	RGNA§	Smear+	Coltural+	Histology+	MRI^	Vertebral Collaps^
Alothman et al (3)	-	72.4	54	46	30	50	70	49.3	87
Alavi et al (16)	-	-	-	-	21.7	8.7	39.1	18.8	-
Colmenero et al (12)	-	80.9	-	-	-	47	-	-	-
Colmenero et al[2] (17)	83.1	79.4	60	40	-	56.4	-	56.4	-
Cormican et al (5)	-	90.5	21	79	75	76	-	95.2	-
Dharmalingam (18)	-	48.5	-	-	-	-	-	-	-
Goldwana et al (19)	-	-	-	-	-	-	-	-	-
Hadadi et al (20)	36.3	-	-	-	-	-	-	-	-
Hayes et al (21)	-	-	-	-	-	-	-	-	-
Jalle et al (22)	70.9	-	-	-	-	-	-	-	-
Janssens et al (23)	-	53.8	-	-	14	21	76	-	-
Khorvash et al (24)	68	40	-	-	25	62.5	92.5	100	-
Kim et al (13)	-	-	-	-	-	91.1	-	-	-
Leibert et al (25)	80.8	-	-	-	-	-	-	-	-
Luzzati et al (14)	-	-	-	-	-	81.5	18.5	-	-
Maeda et al (26)	-	100	-	-	-	-	91.3	100	13
Mulleman et al (27)	58.3	87.5	4.7	95.2	-	65	40	41.7	-
Mwachaka et al (28)	10	25.6	100	0	-	10	-	45	-
Nene et al (29)	-	15.7	-	100	-	27.3	45.5	-	-
Nussbaum et al (8)	62	100	59	41	-	-	-	28	31
Park et al (30)	-	-	-	-	-	-	-	-	-
Pertuiset et al (31)	64	90.2	17	83	32	83	70	42.7	-
Ramachandran et al (32)	-	-	-	-	-	-	-	-	-
Rezai et al (33)	95	90	-	89.9	-	-	-	60	-
Solagberu et al (34)	66.7	-	-	-	-	-	-	-	-
Su et al (35)	-	93.7	-	60	22.2	40	53.3	100	68.8
Talbot et al (9)	-	-	-	100	-	-	-	-	-
Turgut et al (36)	-	-	-	-	-	-	-	-	-
Weng et al (6)	-	100	84	16	58	63	84	92	-

All values are presented as % of patients except as noted otherwise in line 1. Abbreviations: TST: Tuberculin Stimulation Test ; RGNA: Radiologically Guided Needle Aspiration; MRI: Magnetic Resonance Imaging, performed.
°% of TST-positive on total of patients;
*% of biopsies performed on total of patients;
§% on total of biopsies performed;
+ % of positive results on biopsies performed;
^% on total of patients.

In the study conducted by Colmenero et al.[17] findings compatible with vertebral osteomyelitis were evident in 95.5% of MR scans vs. 85.7% of plain radiographs, confirming the limitations of conventional radiological studies for the diagnosis of TS.

Nevertheless, radiological investigations could be suggestive for diagnosis of TS, performing a vertebral biopsy whenever possible is mandatory to confirm diagnosis by isolation of *M. tuberculosis* and for the purpose of testing its antimicrobial sensitivity.

Radiologically guided needle aspiration (RGNA) is a simple, reliable, and practical approach for diagnosing TS, since it provides useful material for histopathological and microbiological studies[74,75]. RGNA is particularly indicated for patients who are candidates to chemotherapy alone, and it may also be used for drainage of paraspinal abscesses[33]. Otherwise, open surgical biopsy may be necessary if needle biopsy is unsuccessful, or in the cases in which surgical intervention is indicated for treatment[62].

More than 70% TS cases underwent a bioptic procedure in most of published studies[3,5,6,8,12,17,26,27,31,33,35], with a variable proportion between the surgical and radiologically guided techniques: although RGNAs have been more frequently used[5,9,27,29,31,33], surgical biopsy has been performed in more than 60% of cases in some reports[6,17,28].

Histological examination could reveal epithelioid cell granulomas, granular necrotic background with lymphocytic infiltration and, scattered multinucleated Langhans giant cells[74,75]; the proportion of suggestive histology is usually high, up to 90% of cases[24,26].

Microbiological investigation should include bacterial, fungal, and mycobacterial stains and culture. The definitive diagnosis of TS is obtained by culturing *M. tuberculosis* from pathological specimens (bioptic specimen, pus obtained from the drainage of paraspinal abscesses, and/or sputum for cases in which a concomitant active pulmonary infection is present). Since cultures on solid media require 3 to 8 week to show a visible growth, there are other techniques enabling faster results: acid-fast stain of specimen's smears could give a same-day result with the limitation to be less sensitive than culture and unable to distinguish *M. tuberculosis* from other *Mycobacteria*; nucleic acid amplification assays have a sensibility intermediate between acid-fast stain and culture and can identify *Mycobacterium* species belonging to *M. tuberculosis* complex. However, they require advanced laboratory techniques and cannot distinguish dead forms from viable organisms[55].

The diagnostic yield of the two bioptic procedures has been evaluated in different studies, and no significant differences have been reported between RGNA and surgical biopsy in terms of sensitivity for detection of granuloma, acid-fast bacillus smear on Ziehl-Neelsen's stain and/or culture, with rates of diagnostic success ranging from 20% to 90% for both the procedures[3,6,13,14,23,31,74]. According to these findings, and due to the low associated morbidity, RGNA should be recommended for diagnosis in patients with no indications for immediate surgery.

Treatment and outcome

Goals of management of TSs are to eradicate the infection, to prevent or treat neurological deficits, to correct or avoid the occurrence of spinal deformities and to achieve normalization of patient's daily activities as soon as possible. On the basis of current evidences, TSs are a medical condition, unless accompanied by surgical complications[57,62,76,77]. Medical treatment, duration of anti-mycobacterial regimens, surgical treatment and outcome in 29 different observational studies are reported in Table V.

Indications for surgical intervention are presence of neurological deficits caused by spinal cord compression, spinal deformity with instability, severe or progressive kyphosis, no response to or failure of anti-TB therapy, large paraspinal abscesses and non-diagnostic biopsies, even if repeated[8,10,76,78].

A Cochrane review of randomized controlled trials regarding the use of routine surgery in addition to chemotherapy for TS has been conducted by Jutte et al[79] in 2006, and no significant benefits have been demonstrated for any of the outcomes measured: kyphosis angle, neurological deficits, bony fusion, death from any cause, activity level regained, change of allocated treatment or bone loss. However, partially, these results could be due to a less severe disease of patients included in the review. Several studies suggest that the risk of deformity, instability, and progression to neurologic lesions or deficits correlates with the size of the vertebral lesions[80-82].

Table V. Medical treatment, duration of anti-mycobacterial regimens, surgical treatment, and outcome in 29 different observational studies.

Author (reference)	Medical treatment	Duration (months)	MDR TB	Surgery	Improvement	Relapse	Neurological sequelae
Alothman et al (3)	100	-	-	46	91.3	-	27.5
Alavi et al (16)	100	-	-	31.9	76.8	-	-
Colmenero et al (12)	100	10	-	76.2	76.2	7.3	49.3
Colmenero et al [2](17)	100	-	1.3	70.5	-	5.1	-
Cormican et al (5)	100	13	6	28.7	52.4	-	14.2
Dharmalingam (18)	100	-	-	61	-	-	-
Goldwana et al (19)	-	-	-	-	-	-	-
Hadadi et al (20)	-	-	-	-	-	-	-
Hayes et al (21)	100	12-24	-	47.6	91	9.5	-
Jalle et al (22)	-	-	-	41.9	-	-	-
Janssens et al (23)	100	-	-	34.6	-	-	26.9
Khorvash et al (24)	100	12	-	50	-	-	11
Kim et al (13)	100	7-10	-	85.1	-	-	-
Leibert et al (25)	-	12	0	-	-	-	-
Luzzati et al (14)	100	9	-	40.7	30.8	0	0
Maeda et al (26)	100	12	-	91.3	-	-	-
Mulleman et al (27)	-	-	-	-	-	-	-
Mwachaka et al (28)	100	9	-	25.6	70	-	18.4
Nene et al (29)	100	12-27	4.3	1.4	98.5	-	-
Nussbaum et al (8)	100	-	-	86.2	-	-	34
Park et al (30)	100	-	-	71.5	81	-	1.7
Pertuiset et al (31)	100	14	0	24	70.8	1	-
Ramachandran et al (32)	100	-	-	55.5	-	11.7	5.9
Rezai et al (33)	100	18-12	5	55	95	0	5
Solagberu et al (34)	85.1	5.7	-	0	-	-	-
Su et al (35)	100	12	5.3	62.5	70	-	-
Talbot et al (9)	100	-	-	13.8	-	-	-
Turgut et al (36)	99.4	-	-	98.4	44.5	-	-
Weng et al (6)	100	11	2.6	84	71	0	26

All values are presented as % of patients except as noted otherwise in line 1. Abbreviations MDR: multi drug resistant; TB: tuberculosis. Where absent, data were not available.

Conservative management of TSs consists of antimicrobial therapy and non-pharmacological treatments such as immobilization with orthopedic corsets, which is required when pain is significant or there is the risk of spinal instability[83,84].

The basic principles underling the treatment of pulmonary TB also apply to TSs. When the diagnosis of TS is correctly formulated, anti-mycobacterial therapy should be initiated, with a 2-months initial phase of combination of four first line anti-mycobacterial agents (i.e. isoniazid (INH), rifampin (RIF), pyrazinamide, and ethambutol), followed by the continuation phase of either 4 or 7 months with isoniazid and rifampin[85,86] (in Table VI drug dosage and administration are reported). First line anti-mycobacterial agents have been demonstrated to have a good bone penetration[87].

The issue of drug resistance has to be taken into account, and definitive anti-mycobacterial regimen should be based on susceptibility tests which should be always performed on initial isolate of *M. tuberculosis*; patients harboring strains of *M. tuberculosis* resistant to first line antimicrobial compounds (mostly INH and/or RIF) are at high risk for treatment failure and further acquired resistance, and they must be referred to a specialist in infectious diseases[85,86] (in Table VII second line anti-mycobacterial drugs are reported).

The duration of treatment remains controversial. The American Thoracic Society (ATS) and the Center for Disease Control (CDC) advocate short course treatment: 6-9 months for adults and 12 months for children with uncomplicated TS caused by a fully sensitive *M. tuberculosis* isolate[85,88]. Medical Research Council (MRC) studies showed that a 6-month regimen for TS, when combined with surgery, is as effective as a 9-month regimen[89-91]. Other studies have reported similar findings in adults, regardless combination with surgical treatment[30,35,92-94].

Table VI. First line anti-mycobacterial drugs: preparation and daily doses. Modified from CDC, Treatment of Tuberculosis, 2003[86].

Drug	Preparation	Daily doses	
Isoniazid	Tablet, elixir, aqueous solution for i.v. or i.m. injection	Adult (max) Children (max)	5 mg/kg (300 mg) 10-15 mg/kg (300 mg)
Rifampin	Capsule, powder for o.a., aqueous solution for i.v injection	Adult (max) Children (max)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)
Pyrazinamide	Tablet	Adult* (mg/kg) Children (max)	1,000 (18.2–25.0)[a]; 1,500 (20.0–26.8)[b]; 2,000† (22.2–26.3)[c] 15–30 mg/kg (2.0 g)
Ethambutol	Tablet	Adult* (mg/kg) Children (max)	800 (14.5–20.0)[a]; 1,200 (16.0–21.4)[b]; 1,600† (17.8–21.1)[c] 15–20 mg/kg (1.0 g)
Rifabutin	Capsule	Adult (max) Children (max)	5 mg/kg (300 mg) Appropriate dosing for children is unknown

i.v.: intra venous; i.m.: intra muscular; o.a.: oral administration; *Based on estimated mean body weight: [a]40-55 kg, [b]56-75 kg, [c]76-90 kg; †Maximum dose regardless of weight.

In contrast, a longer course of anti-mycobacterial therapy for TS has been administered in other studies[3,25,31,33]. In addition, in the retrospective study performed by Ramachandran et al[32], they found an alarming rate of relapse with the 6-months regimen, thus suggesting that treatment should be continued for at least 9 months. In addition, Cormican et al[5] have suggested that a longer duration of treatment could be required in cases with persistent abnormal MR scans, even in presence of apparent clinical disease resolution.

In general, younger age[3,30,31,35] and early diagnosis have been reported as factors associated with a good outcome, whereas presence of paraplegia at presentation has been recognised as the most negative prognostic factor[3].

Conclusions

TS is a rare but serious clinical condition which may lead to severe deformity and early or late neurological complications. In western countries TS is a health issue mostly concerning elderly people and immigrants, whereas in many developing nations, where patients in a young age are the most affected, it is still a source of clinical and socio-economic problems, also considering the lack of instrumentation, surgical expertise, and economical resources. Despite the actual availability of more effective diagnostic tools, early recognition of TS remains difficult and a high index of suspicion is needed due to the chronic nature of the disease and its insidious and variable clinical presentation. Patients presenting with chronic back pain and neurological symptoms, with or without a story of previous or active TB infection, should be investigated in order to rule out TS. A prompt diagnosis, indeed, is required to ensure improved long term outcome, and a microbiological confirmation is recommended to enable appropriate choice of anti-mycobacterial agents. Although TS is essentially a medical condition, surgery has an important role in alleviating pain, correcting deformities and neurological impairment, and restoring function, and it is indicated in selected group of patients. Further studies are required to assess the more appropriate duration of anti-microbial treatment, also in regarding of a combined surgical approach.

Table VII. Second line anti-mycobacterial drugs.

- Cycloserine
- Ethionamide
- Streptomycin
- Amikacin/Kanamycin
- Capreomycin
- P-Aminosalicylic-Acid (PAS)
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

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