

Multi-drug resistant tuberculous spondylitis: A review of the literature

Quratulain Fatima Kizilbash^{1,2,3}, Barbara Joyce Seaworth^{1,2,3}

¹Department of Medicine, University of Texas Health Northeast, ²Department of Medicine/Infectious Diseases, University of Texas Health Science Center, ³Heartland National TB Center, San Antonio, TX, USA

Address for correspondence:

Dr. Quratulain Fatima Kizilbash, Texas Center for Infectious Disease, 2303 SE Military Drive, San Antonio, TX 78223, USA. E-mail: quratulain.kizilbash@dshs.state.tx.us

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Abstract:

While tuberculous vertebral osteomyelitis is an ancient scourge, multi-drug resistant-tuberculosis (MDR-TB) is a modern major public health concern. The objective of this study was to review and summarize the data available on MDR-TB spondylitis. An extensive search of the PubMed database was conducted for articles in English relevant to MDR-TB spondylitis by December 2015. Tuberculous spondylitis accounts for 0.5–1% of all TB cases, and it is estimated that there are probably 5000 MDR-TB spondylitis cases each year worldwide. The diagnosis of MDR-TB spondylitis requires a high index of suspicion based on epidemiologic, clinical, and radiologic features. Cultures and susceptibility testing remain the gold standard for the diagnosis of MDR-TB, but this can take several weeks to obtain. Medical treatment is the mainstay of therapy, and ideally, it should be based on drug susceptibility testing. If empiric treatment is necessary, it should be based on drug exposure history, contact history, epidemiology, and local drug resistance data, if available. The total duration of treatment should not be <18–24 months. Clinical, radiographic, and if possible, bacteriologic improvement should be used to assess the treatment success. Surgery should be reserved for neurologic deterioration, significant kyphosis, spinal instability, severe pain, and failure of medical management.

Key words:

Diagnosis, medical, multi-drug resistant tuberculosis, spine, surgical

Features of tuberculous spondylitis (TB spondylitis) or tuberculosis (TB) of the vertebrae have been identified in Egyptian mummies dating back to 9000 B.C.,^[1] and in an analysis of 483 pre-Columbian skeletons in Chile, 2% showed lesions consistent with bony TB.^[2] Sir Percivall Pott described a disease of the vertebrae, most likely tuberculous vertebral osteomyelitis, in which the bones soften and collapse resulting in a hunched back, eponymously termed Pott's disease.^[3]

Tuberculous vertebral osteomyelitis, an ancient scourge, continues to be a significant public health concern; limited data exist on multi-drug resistant tuberculosis (MDR-TB) spondylitis.

Methods

A search of the PubMed database was conducted using the terms; "MDR TB and arthritis," "MDR TB and skeletal," "MDR TB and osteoarticular," "MDR TB and spine," "MDR TB and vertebrae," "MDR TB spondylitis," "MDR TB and bone," and "MDR TB and joint." Articles in English, which had a mention of MDR-TB spondylitis by December 2015, were reviewed.

Epidemiology

Extrapulmonary TB accounts for 15–20% of all TB cases; skeletal TB comprises about 10% of these cases. TB spondylitis accounts for 50% of the skeletal TB cases. Hence, in all, osteoarticular TB

represents 1–2% and TB spondylitis represents 0.5–1% of all TB cases.^[4] Immunosuppressed persons have a higher likelihood of skeletal TB. Moon noted up to 60% of skeletal involvement in those with TB who are HIV co-infected.^[5] The 2015 World Health Organization (WHO) global TB report estimates that there were 480,000 pulmonary MDR-TB cases worldwide and 15,000 cases of MDR-TB in the Eastern Mediterranean Region in 2014, but there is no mention of the incidence of extrapulmonary TB.^[6] Based on the extrapolation of these limited data, there are probably 5000 cases globally and about 150 cases in the Eastern Mediterranean Region of MDR-TB spondylitis each year. Most studies reported are from countries with a high TB burden; India, China, and South Africa. MDR-TB spondylitis can be due to acquired resistance

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from the past inadequate treatment or to primary resistance as a result of direct transmission from patients with MDR-TB.

Diagnosis

The diagnosis of MDR-TB spondylitis, such as pulmonary MDR-TB, requires a high index of suspicion. Important clues include contact with a known MDR-TB patient, history of treatment for TB, history of poor adherence or being lost from treatment, lack of clinical and radiographic improvement with standard TB treatment, or history of travel to a country or region with high MDR-TB incidence. Clinical and radiologic features associated with TB spondylitis may include classical symptoms of pulmonary TB such as cough, hemoptysis, fever, weight loss, and night sweats. However, these symptoms may be absent. TB spondylitis may present with chronic back pain, typically for more than 3 months, local kyphosis, and a neurologic deficit, i.e., bowel or bladder incontinence, lower extremity weakness, sensory deficits, or paraplegia.^[7] A sinus tract can appear distant from the involved vertebrae by tracking along the fascial planes or the neurovascular bundles.^[8] In a report of 111 patients with drug-resistant TB of the spine, the thoracic spine was the most common site of involvement in 68 (61.2%) patients followed by the lumbar spine in 34 (30.6%) patients, but any part of the vertebral column from the cervical spine to the sacrum may be affected by TB.^[9]

Radiologic features of TB spondylitis typically include anterior vertebral body involvement with endplate irregularities and loss of anterior vertebral height. Two or more adjacent vertebral bodies are usually involved with loss of the intervening disc space. The presence of a paravertebral or psoas abscess shadow is highly suggestive of TB spondylitis.^[7] Noncontiguous or skipped spinal lesions are more common than previously recognized. The pathophysiology of these “skipped” lesions is thought to be that once the first tuberculous focus is established in the spine, retrograde flow of bacilli through the valveless venous system occurs with changes in abdominal pressure, which allows the bacteria to establish “skip lesions.” A South African study found that 16 out of 98 cases of TB spondylitis had noncontiguous spinal involvement. Two of these cases had MDR-TB, but no statistically significant association was found between TB spondylitis and MDR-TB, HIV, or chronicity of disease. The authors recommend imaging of the entire spine in patients with TB spondylitis; preferably a whole spine sagittal magnetic resonance imaging (MRI).^[4] It is unknown if MDR-TB spondylitis presents differently, clinically, or radiologically from drug-susceptible TB spondylitis.

The most important method of identifying drug resistance is performing culture and drug susceptibility testing (DST). Obtaining samples for culture in patients with suspected TB spondylitis often poses a challenge. As a result, as demonstrated in two studies from India, the diagnosis of MDR-TB spondylitis is often delayed on an average of 7–8 months.^[9,10] Another systematic review noted delays that ranged from 6 months to 2 years.^[11]

The largest study that evaluated drug susceptibility patterns in drug-resistant TB spondylitis was a cross-sectional study from 2013 conducted at a tertiary spine care institute in Mumbai, India.^[9] One hundred and eleven out of 686 (16%) positive cultures for *Mycobacterium tuberculosis* had resistance to at

least one antituberculous drug and 90 of the *M. tuberculosis* isolates were MDR-TB. Resistance was most frequently found to isoniazid (92.79%), followed by rifampicin (81.98%) and least often found to pyrazinamide (46.8%). Among the second-line drugs, resistance was most frequently found to ethionamide (35.1%) and ofloxacin (32.4%) and least often found against kanamycin (4.5%), amikacin (4.5%), and capreomycin (0.9%). No isolate was resistant to clofazimine despite the relatively high incidence of Hansen’s disease in India. The greatest risk factors for MDR-TB were previous TB treatment and a history of being lost or nonadherent to treatment. The authors cautioned that their study could not be used to calculate the epidemiological incidence of drug resistance in TB spondylitis, since most referred cases were failing standard TB treatment.

Although cultures and DST remain the gold standard for diagnosing MDR-TB, they take 4–6 weeks or longer to obtain. Xpert[®] MTB/RIF has been endorsed by the WHO for the diagnosis of pulmonary TB in high incidence settings, but it is not validated for the diagnosis of musculoskeletal TB. A South African study from 2014^[7] attempted to evaluate the diagnostic accuracy of the Xpert[®] MTB/RIF for TB spondylitis compared to liquid culture. They had a total of 71 spine samples from 69 patients; two had repeat biopsies. These 71 spine samples were sent for acid-fast smear, liquid culture, and Xpert[®] MTB/RIF analysis. Thirty-six samples (50.7%) grew *M. tuberculosis* in liquid culture; Xpert[®] MTB/RIF was positive in 35 (97.2%). Eight samples had probable TB based on histology, but were culture-negative; Xpert[®] MTB/RIF was positive in all the eight samples. The sensitivity, specificity, positive and negative predictive values for Xpert[®] MTB/RIF were over 90% when histology and/or culture positivity was used as the reference standard. As expected, the specificity and positive predictive values fell considerably when only culture positivity was used as the reference standard. The test diagnosed was likely rifampicin-resistant TB in four patients who were subsequently started on MDR-TB treatment the day after their biopsy. In three of the four cases, the culture confirmed MDR-TB, but in one case, the culture did not grow. This case would have been missed without Xpert[®] MTB/RIF. In addition to the potential for more rapid diagnosis and initiation of correct treatment for MDR-TB, another Xpert[®] MTB/RIF benefit is increased sensitivity in samples with a lower bacterial burden, i.e., tissue samples. Xpert[®] MTB/RIF has a lower limit of detection of 130 CFU/ml of bacilli compared to culture, which requires 10,000 CFU/ml. The utility of Xpert[®] MTB/RIF testing in a low TB incidence setting may differ from that of a high incidence setting where this study was based.

Medical management

Limited data are available regarding the penetration of antituberculous medications into bone. Ethambutol and pyrazinamide have adequate concentrations in vertebral bone lesions, although the concentration in sclerotic lesions might be suboptimal. Streptomycin and ethambutol penetrate well into synovial fluid and skeletal cold abscesses. Linezolid and fluoroquinolones penetrate well into bone tissues and have been extensively used for the treatment of nontuberculous mycobacterial osteomyelitis. No studies have been found assessing amikacin or kanamycin, but other aminoglycosides

have a good penetration into synovial fluid and intervertebral discs.^[11]

In the absence of specific guidelines for the treatment of MDR-TB spondylitis, treatment should be based on the WHO^[12] or American Thoracic Society/Center for Disease Control and Prevention/Infectious Diseases Society of America^[13] guidelines for the treatment of drug-resistant pulmonary TB. Ideally, treatment should be based on DST. The regimen used should include at least four new drugs, which have not been used previously. At least 6 months of an initial injectable agent should be included. The total duration of treatment should not be <18–24 months. From the first-line drugs for TB, ethambutol and pyrazinamide can be used after DST is conducted, and *M. tuberculosis* is found to be susceptible to these drugs. Ethambutol is not used globally because many labs lack the ability to test for it and due to a lack of trust in the results of DST even when it is available. It is now recognized that DST in Mycobacterial Growth Indicator Tube (BACTEC MGIT 960 System Becton, Dickinson and Company 1 Becton Drive Franklin Lakes, New Jersey) liquid media misses some ethambutol resistance identified by molecular detection for drug resistance or solid media testing. Ethambutol susceptibility should be confirmed with one or both of these techniques whenever resistance to isoniazid or rifampin is noted. Moxifloxacin should be added for its excellent bone penetration, possibly better *in vitro* activity, and because the isolate is less likely to be resistant to moxifloxacin than to ofloxacin/levofloxacin. Linezolid has recently been identified by the WHO as a core drug, and its excellent bone penetration should be considered for inclusion in the treatment regimen.^[14] Para-aminosalicylic acid or ethionamide can be used, if needed, but their concomitant use should be avoided if possible. Clofazimine may be an important and useful adjunct.^[10]

Outcomes of medical management

A cohort study from Mumbai, India, published in 2009^[10] assessed the treatment and outcomes for 25 cases of culture-proven MDR-TB spondylitis between 2004 and 2007. The patients received a mean of six drugs during their intensive phase and a mean of 4 second-line drugs during the remainder of their treatment. An aminoglycoside was almost always part of the treatment for the first 5–6 months. Interestingly, seven out of the 25 patients were children who tolerated the medications exceptionally well without a significant toxicity. About 60% of the patients required regimen changes during treatment due to adverse reactions. Surgery was needed in four patients for neurologic deterioration and mechanical instability and two patients required recurrent aspirations for subcutaneous abscesses. At the time of publication, 19 were cured and six were still on treatment. Those who were cured had received a mean of 2 months of an intensive phase and 24-month total treatment. Positive predictors for success were evidence of clinical/radiographic improvement, initial resistance to three or fewer drugs, use of three or less second-line drugs, and regimens that did not have to be changed during treatment.

A New Delhi series published in 2012^[15] attempted to assess the treatment outcomes. They included 15 cases of MDR-TB spondylitis, suspected based on the failure of standard antituberculous therapy for over 5 months. Twelve of the

15 patients had surgical debridement of tubercular lesions, and in one patient, pus from a draining sinus from a prior surgical scar was obtained for culture and sensitivity. In all, 13 of 15 patients had tissue sent for culture and only three had positive cultures; two with MDR-TB and one with no evidence of resistance. Cure was achieved in 13 of 14 presumed drug-resistant cases on the basis of MRI with or without positron emission tomography scans following treatment with isoniazid, rifampicin, ofloxacin, ethionamide, cycloserine, and kanamycin/amikacin. Treatment was supplemented by immunomodulation using levamisole and Bacillus Calmette-Guérin (two intradermal and one deep intramuscular injection). One patient was still on treatment at the time of publication.

The response to treatment of MDR-TB spondylitis may be difficult to assess bacteriologically due to the difficulty of obtaining repeated specimens for culture. As a result, clinical and radiographic improvement is often used to assess the treatment success. Radiographic improvement may lag behind clinical improvement and would include resolution of marrow edema, fatty replacement of bone marrow, and resolution of abscesses [Figure 1].^[15]

Surgical management

Although the mainstay of treatment is medical management, drugs alone may not adequately address bone destruction that may occur with TB spondylitis. Indications for surgical intervention include spinal deformity with significant kyphosis, neurological dysfunction (i.e. bowel or bladder incontinence and paraplegia), pulmonary insufficiency related to deformities, restoration of spinal stability, failure of medical management with progressive bone destruction, or presence of persistent, severe pain.^[8] A relative indication would be a massive psoas abscess or enlarging fluid collections during treatment; however, these may improve with medical management alone. It is not known whether surgery is needed more frequently in those with MDR-TB or whether the indications should differ from that of drug-susceptible TB spondylitis. The specific surgical procedure indicated will vary from patient to patient depending on the site of involvement,

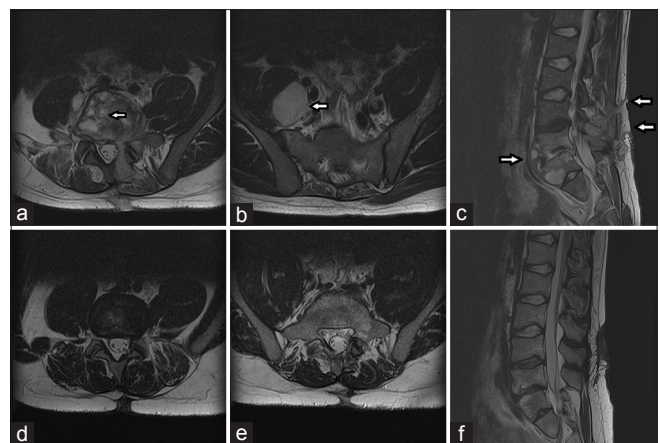


Figure 1: (a) Axial T2 magnetic resonance imaging from 7/17/14. (b) Axial T2 magnetic resonance imaging psoas 7/17/14. (c) Sagittal T2 magnetic resonance imaging 7/17/14. (d) Axial T2 magnetic resonance imaging 7/8/15. (e) Axial T2 magnetic resonance imaging psoas 7/8/15. (f) Sagittal T2 magnetic resonance imaging 7/8/15

surgical center, expertise of the surgeon, and other factors. An anterior or posterior surgical approach may be utilized to perform debridement, decompression, and/or fusion.

Outcomes of surgical management

Two studies, both from Chinese surgical centers, specifically addressed the surgical management of drug-resistant TB spondylitis. The first study from 2011^[16] looked retrospectively at 35 cases of drug-resistant TB, of which 12 were MDR-TB. Eight of the 12 MDR-TB spondylitis cases were retreatment cases and five were resistant to fluoroquinolones. The surgical procedures performed included anterior and/or posterior debridement of the involved vertebrae, instrumentation, and fusion, and in three procedures, drainage was followed by local chemotherapy. The authors did not mention what drugs were used locally and stated that the purpose of the local chemotherapy was to decrease the burden of *M. tuberculosis* organisms. All the patients achieved cure at 18–24 months with individualized chemotherapy; follow-up information was not provided. The second study retrospectively evaluated 19 patients with drug-resistant TB spondylitis, 16 of which had MDR-TB^[17] and absolute indications for surgery; various combinations of anterior and/or posterior debridement, fusion, and instrumentation were done. The remaining three patients underwent computed tomography-guided drainage and local chemotherapy.

Conclusion

A high index of suspicion must be maintained to diagnose MDR-TB spondylitis. Medical treatment is the mainstay of therapy, and ideally, should be based on DST. If empiric treatment is necessary, it should be based on the past drug exposure history, contact history, epidemiology, and local drug resistance data, if available. Surgery should be reserved for neurologic deterioration, deformity, spinal instability, severe pain, and failure of medical management.

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Conflicts of interest

There are no conflicts of interest.

References

- Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY, Gernaey AM, *et al.* Detection and molecular characterization of 9,000-year-old *Mycobacterium tuberculosis* from a Neolithic settlement in the Eastern Mediterranean. *PLoS One* 2008;3:e3426.
- Arriaza BT, Salo W, Aufderheide AC, Holcomb TA. Pre-Columbian tuberculosis in Northern Chile: Molecular and skeletal evidence. *Am J Phys Anthropol* 1995;98:37-45.
- Rogers K. Sir Percivall Pott. *Encyclopædia Britannica*; 2016.
- Polley P, Dunn R. Noncontiguous spinal tuberculosis: Incidence and management. *Eur Spine J* 2009;18:1096-101.
- Moon MS. Tuberculosis of the spine. Controversies and a new challenge. *Spine (Phila Pa 1976)* 1997;22:1791-7.
- WHO. Global Tuberculosis Report 2015. Geneva: WHO; 2015.
- Held M, Laubscher M, Zar HJ, Dunn RN. GeneXpert polymerase chain reaction for spinal tuberculosis: An accurate and rapid diagnostic test. *Bone Joint J* 2014;96-B: 1366-9.
- Agrawal V, Patgaonkar PR, Nagariya SP. Tuberculosis of spine. *J Craniovertebr Junction Spine* 2010;1:74-85.
- Mohan K, Rawall S, Pawar UM, Sadani M, Nagad P, Nene A, *et al.* Drug resistance patterns in 111 cases of drug-resistant tuberculosis spine. *Eur Spine J* 2013;22 Suppl 4:647-52.
- Pawar UM, Kundnani V, Agashe V, Nene A, Nene A. Multidrug-resistant tuberculosis of the spine – Is it the beginning of the end? A study of twenty-five culture proven multidrug-resistant tuberculosis spine patients. *Spine (Phila Pa 1976)* 2009;34:E806-10.
- Suárez-García I, Noguero A. Drug treatment of multidrug-resistant osteoarticular tuberculosis: A systematic literature review. *Int J Infect Dis* 2012;16:e774-8.
- WHO. Treatment of Tuberculosis: Guidelines. WHO Guidelines Approved by the Guidelines Review Committee. 4th ed. Geneva: WHO Press; 2010.
- American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR Recomm Rep* 2003;52:1-77.
- WHO. WHO treatment guidelines for drug-resistant tuberculosis. Geneva: WHO Press; 2016.
- Jain AK, Dhammi IK, Modi P, Kumar J, Sreenivasan R, Saini NS. Tuberculosis spine: Therapeutically refractory disease. *Indian J Orthop* 2012;46:171-8.
- Li L, Zhang Z, Luo F, Xu J, Cheng P, Wu Z, *et al.* Management of drug-resistant spinal tuberculosis with a combination of surgery and individualised chemotherapy: A retrospective analysis of thirty-five patients. *Int Orthop* 2012;36:277-83.
- Xu L, Jian-Zhong X, Xue-Mei L, Bao-Feng G. Drug susceptibility testing guided treatment for drug-resistant spinal tuberculosis: A retrospective analysis of 19 patients. *Int Surg* 2013;98:175-80.