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Literature Review

An Update of Tuberculosis Spondylitis and The Holistic Management by *Subroto Sapardan* Total Treatment: Literature Review Study

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Abstract

Tuberculosis spondylitis or Pott disease is a pathological condition that is caused by infection of Mycobacterium tuberculosis and manifests a combination of osteomyelitis and arthritis that usually involves more than one vertebrae. It has recently shown a significant resurgence in developed nations secondary to global migration. Concurrent with this phenomenon, multidrug-resistant bacterial strains of tuberculosis have been increasing in developing nations over the past decades. This reality causes TB spondylitis to be a serious disease with several diagnostic and treatment challenges. One of the treatment methods for tuberculosis spondylitis that has been established in Indonesia is the Subroto Sapardan Total Treatment Protocol, by emphasizing holistic from basic to advanced treatment, this protocol is effective in treating the spondylitis.

Introduction

Tuberculosis (TB) spondylitis, also known as spinal TB or Pott disease, is a form of skeletal TB – a subclassification of extrapulmonary TB. TB spondylitis is considered to be especially dangerous as it is strongly correlated to various neurologic complaints.[1] Although there is a reduction in the number of new TB incidences worldwide, the incidence of extrapulmonary TB, including skeletal TB, remains stagnant.[2] Estimates show that skeletal TB contributes to around 10% of all extrapulmonary TB cases. Of that 10%, TB spondylitis contributes to almost 50% of the cases, making it the most common manifestation of all skeletal TB cases.[3] Additionally, TB spondylitis has a high rate of complications, reaching around 10-43%.[1] Lower-income groups are at higher risk of TB spondylitis, specifically the younger age groups.[4,5]

The persistence of TB spondylitis is highly attributed to socioeconomic factors of the community and was given the title "a disease of poverty". In lower socioeconomic status, access to healthcare amenities is relatively more limited – this similarly applies to developing countries.[4] Additionally, the commonness of TB spondylitis risk factors contributes towards its persistency. Lack of education, imbalanced nutrition, alcohol or substance abuse, several chronic diseases, and immunosuppressive drugs are all considered predisposing factors.[6,7] Lastly, an environmental factor also plays a role in the spread and persistency of the TB pathogen; being directly proportionate to socioeconomic status, this further worsens the condition.

While TB spondylitis requires urgent treatment due to it having severe consequences, there are a handful of challenges that make the current treatment regimen difficult or inefficient. One of the biggest challenges lies in the varying growth kinetics and metabolic properties of the mycobacterial population in an infected region. In extrapulmonary sites, these pathogens are harder to eliminate, and inadequate treatment risks relapse.[8] Moreover, the increasing population of drug-resistant mycobacterial strains escalates the challenge further, rendering most current treatment regimens ineffective. The diagnosis of TB spondylitis itself has its own set of controversies.[9]

In essence, TB spondylitis is a serious disease with several diagnostic and treatment challenges. In pursuance of reducing the number of cases, severity of mortality, and morbidity of TB spondylitis, as well as finding a new method of management, this paper will extensively review a treatment regimen known as *Subroto Sapardan* Total Treatment. This method of treatment is developed and used in some hospitals in Indonesia.

Discussion

The Pathogen: Mycobacteria Tuberculosis

The pathogen responsible for TB is known as *Mycobacterium tuberculosis* (MTB), it is a resilient, aerobic, bacillus bacteria that primarily infects the lungs.[2] The resilience of MTB can be credited to its thick and abundant mycothiol cell wall; this protects MTB from acid and alkaline destruction and gives it resistance to some antibiotic agents. Aside from the cell wall, MTB exhibits numerous virulence factors, namely sulfolipid compounds that suppress phagocytosis and lipoarabinomannan which increases its pathogenicity.[10,11] These reasons along with several other virulence factors make the MTB pathogen highly contagious, it transmits from host to host through aerosol; an airborne transmission.[12] Though resilient, MTB has a complex and slow process of growth and generation, one example is the requirement of Rv3671c membrane protein.[10] This notable weakness can be exploited to eliminate the pathogen from a host.

Pathophysiology and Pathogenesis of TB Spondylitis

As previously stated, MTB spreads through aerosols and infection starts in the lungs of the host. Once it enters a human host, the pathogen can exist in four different types: extracellular rapid-dividing bacilli, extracellular slow-dividing bacilli, intracellular intermittent bacilli, and dormant bacilli.[9,12] It is important to note that even though MTB is the primary causative agent of TB and all its subvariants, there are a few other mycobacterium species that are capable of infecting the host and resembling TB, such as *M. bovis*, *M. africanum,* and *M. microti* to name a few.[2,13] While the lung is the most common site of infection, these pathogens can also be typically found in lymph nodes of the mediastinum, genitourinary tracts, mesentery, gastrointestinal system, and other viscera of infected hosts.[2] Cases of TB spondylitis are predominantly secondary infections, it is the result of the progressive spread of the pathogen from a primary lesion ordinarily of pulmonary or genitourinary origin.[6] The following diseases are thought to be assistive towards the spread of MTB: diabetes, HIV, micro- and/or macro-deficiency malnutrition, and chronic renal failure.[14] Certain usage of medication can also increase the rate of MTB spread, namely usage of TNF-alpha inhibitors and corticosteroids. It has also been hypothesized that genetic susceptibility may play a role in speeding up the spread, nevertheless, this claim has yet to be confirmed.[6,13,15]

Pathogenesis of TB in a host infected with MTB is fully dependent on the outcome of bacillary growth versus the host immunity.[13] Ingestion of the pathogen by alveolar macrophages normally results in the MTB continuing its proliferation inside the macrophages leading to its rupture.[10,13] Consequently, the further immune response will be activated, and eventually tissue damage will occur, either as a granuloma containing the infection (this specific reaction will typically result in sequestration, blocking bone formation) or caesious necrosis.[16] In the soft tissue, MTB can also form a cold abscess known as a psoas abscess. Unfortunately, cases in which the immune system proves to be adequate in eliminating MTB are unexpected. In the majority of cases, the pathogen will enter a dormant phase, placing those with a history of TB at risk of various TB manifestations. Considering both incidences of primary infection and reactivation of dormant phases, approximately 5% of patients will experience a rapid progression of TB disease.[13] The aforementioned ability of MTB to persist inside macrophages creates numerous opportunities for the pathogen to initiate extrapulmonary spread, this is complemented by the pathogens adhesin which has a high affinity to mammalian cells, enabling it to latch on extrapulmonary cells.[10]

Disseminated TB in extrapulmonary regions transpires from the hematogenous or lymphatic spread of the pathogen.[10] Specifically for TB spondylitis, the pathogen enters the vertebrae through a hematogenous route, using either Batson's venous plexus or spinal arteries.[13] When using the arterial route, MTB utilizes a complex of rich vascular plexus that branches off from anterior and posterior spinal arteries. Through it, the pathogen can invade the paradisal region of the vertebrae, initiating TB spondylitis in that location.[17] Meanwhile if MTB were to spread via Batson's venous plexus, it relies on the free-flowing ability of the blood in two directions, this process is fully dependent on intra-abdominal and intrathoracic activities. Aside from veins having lower pressure in comparison to arteries, this phenomenon can ensue due to the veins of Batson's plexus being valveless; a very atypical feature. Using this route MTB typically infects the central area of the vertebrae, furthermore due to the free-flowing feature of the blood, the pathogen can exploit this to infect multiple vertebrae.[6,13]

Based on the presence of disc involvement and the form of TB spondylitis, it was divided into two distinct types: classic spondylodiscitis and atypical spondylitis without disc involvement.[1] Meanwhile there exists a classification system of TB spondylitis based on the vertebral region involved, these are:

central (seen as skipped lesions in the vertebral column), anterior (this leads to kyphotic deformity, consequently forms respiratory problems and paraplegia), and posterior (invasion of laminae, pedicles, and processes).[2,13] As previously stated, the involvement of different regions is contingent on the type of hematogenous route MTB utilizes. In classic TB spondylitis, the infection generally starts with a hyperaemic exudative reaction, it will then progress to the destruction of the intervertebral disc, epiphyseal cortex, and adjacent vertebrae. If this ailment heals before the destruction of the structures, osteoporosis typically forms after the exudate is resorbed. Whilst in destruction, adjacent vertebral bodies may fuse leading to complications or deformities.[13]

Cases of atypical spondylitis without disc involvement could occur, these cases are usually seen in central lesions or elderly patients. It has been postulated that this is most likely due to age-related avascularity; complicating the spread of MTB via hematogenous route. In these cases, clinical manifestation is highly correlated to the collapse and complete compression of the vertebral body, known as vertebra plana.[6]

The previously described pathogenesis processes were all initiated by several chemokines, in the early phases of the infection where a small tubercle is being formed, MTB was discovered to activate chaperonin (CPN) 10 and CPN60. CPN10 is a potent osteolytic cytokine that recruits numerous osteoclasts leading to bone resorption, additionally, it also exhibits an inhibitory effect towards osteoblast proliferation. The effects can be prominently seen in the anterior region of the vertebrae. Meanwhile, the role of CPN60 is more on the induction of cytokine synthesis.[18] As the human body contains numerous cytokines, some may be present to aid immunity, while others may be detected as a sign of disease progression. Typically, when macrophagic phagocytosis of MTB occurs, the white blood cell will release IFN-ɣ which increases the synthesis of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α – this indicates that there is a pathogenic infection occurring in the body and also allows the utilization of IFN-ɣ as a diagnostic biomarker.[19] Recently, a study showed that IFN-ɣ has a strong synergistic effect with IL-7, an important T-cell cytokine, the study concluded that the addition of IL-7 may aid in the diagnostic performances of IFN-ɣ.[20] Once IL-1, IL-6, and TNF-α are released, a reaction cascade will then occur and activate Th1 cells which mediates protective functions against MTB; by repeating the IFN-ɣ cycle as one of its modes of action.[19] Specifically for IL-6 it will also increase the levels of C-reactive protein (CRP), which acts as an acute phase reactant in the reaction processes of cytokines during pyogenic infection, this allows CRP to act as an indicator for infection as well.[21] Despite this, some processes may instead benefit the pathogenicity of MTB, a 2012 study stated that the induction of IL-1β in some TB cases will lead to the increase of Th2 cell differentiation. Th2 cell differentiation has been observed to inhibit the protective function of Th1, consequently decreasing the levels of IFN-ɣ, suppressing inflammatory reactions which is important for the host immunity. This suppression will lead to the further proliferation of MTB in the host, progressing the disease.[22]

These forested damaging processes can be classed into 5 stages: implantation, initial destruction, progressive destruction, neurological involvement, and finally stage of deformity.[23] Eventually these processes lead to various insidious clinical manifestations of TB spondylitis. The earliest detectable signs are stiffness of the upper back during muscle contraction. Spinal rigidity may also be seen as a result of the destruction of vertebrae, though it is not considered to be a TB spondylitis-specific manifestation.[24] Backache is also a common symptom during active stages, other symptoms include rest pain, paraplegia, and spinal tenderness.[2,6] Common TB symptom of weight loss, fever, and malaise, though typically present in TB spondylitis, it is more associated with pulmonary TB. Hence, TB spondylitis has a diverse set of signs and symptoms.[2]

Diagnosis

Suspicion of TB spondylitis can arise from the identification of the common symptoms such as backache, rest pain, and paraplegia to name a few.[24] Radiological imaging can be done to aid the diagnosis, typically vertebral involvement known as Gibbs can be seen in the results, nonetheless radiological findings should be attentively differentiated from pyogenic vertebral osteomyelitis or spinal malignancy. Modalities viable for TB spondylitis include X-ray, CT scan for bone imaging, and MRI for tissue and abscess evaluation.[1] Each modality typically shows specific signs, X-rays can easily detect early erosive changes normally seen in the corner of the vertebrae.[25] However, MRI is still considered to be the method of choice in detecting early diagnosis as it has a higher sensitivity with a decent specificity, and it also allows anatomical localization of the abscess.[1,25] MRI typically shows 4 patterns of TB spondylitis: paradiskal, anterior, central, and posterior; with the majority being conforming to a paradiskal pattern. Lastly, CT scans were typically utilized to identify fragmentary bone patterns and calcification of caseating areas in later stages of the disease.[25,26] Hence, MRI and CT scans are considered to be important tools in assessing the early and later stages of the disease, respectively.[1,25,27] Laboratory examination through routine blood tests and microbial culture may help strengthen or confirm the diagnosis. Nevertheless, a histopathological assay

of samples obtained through biopsy is still considered to be a standard.[4] Confirmation can be made if the assay reveals: multinucleated giant cells, Langhans' giant cells, granuloma, or the acid-fast bacilli pathogen itself.[28]

Subroto Sapardan's Total Treatment Method

The *Subroto Sapardan's* Total Treatment is a regime for treating TB spondylitis that was developed in 1984 by Prof. Subroto Sapardan in *Cipto Mangunkusumo* Hospital, Jakarta, Indonesia.[23] Prof. Subroto Sapardan is a physician who specializes in orthopedic surgery, he is also active in the field of research and as an academic lecturer. Using his vast clinical and research experiences he arranged a treatment regimen for TB spondylitis with the following 5 points set as the goal of the regimen: to cure the infection, stabilize the spine, eliminate any pain and discomfort, correct the spine without any deformity, returning the functionality of the spine and any organ involved.[29] In total after thorough consideration and research, Prof. Subroto Sapardan made comprehensively 10 alternatives for the treatment methods.[23,29] These alternatives were all based on a few principles that rely on at least 14 different issues that stem from TB spondylitis. These problems are as follows: poor general condition, multiple lesions, instability, deformity, cold abscess, pain, infection, pathological fractures, progressive kyphosis, neurological deficits, cardiovascular complications, pulmonary disturbances, socio-economic-related and psychosocial-related problems.[29]

Prof. Subroto Sapardan formed this procedure in hopes of preventing medical practitioners from treating only the infection but also helping the patient retain their quality of life. The procedure was made very flexible and adaptable with opportunities in which the procedure itself can be improved if there were to be discoveries in the future – improvement of the original treatment method was encouraged in clinical practice [figure 1].[29]

He outlined the methodology of the treatment into 4 steps: identifying and clarifying the problem, listing the potential modalities ranging from conservative to aggressive procedures, and tailoring the stated problem with the most suitable treatment modalities. Finally, determining what treatment alternatives are used [figure 2] .[23,29]

As stated, Prof. Subroto Sapardan eventually composed 10 treatment alternatives using the 14 issues as a basis. He formulated the 1st alternative based on basic treatment (anti-tuberculous drugs, supportive treatment, plaster body jacket/spica or brace, bed rest, abscess drainage). This came about due to some patients in early cases with limited problems, refusing any type of surgery, or outright declining invasive procedures of being contraindicated from receiving such procedures.[23] The basic treatment is not only in the first alternative but also for supportive treatment of others. [23]

The 2nd alternative was targeted at stable-spine patients with good general condition, and large abscesses with minimal destruction (no instability and no deformity). [29] A guideline suggested that basic treatment with anterior debridement and evacuation of a paravertebral abscess.[23]

3rd alternative involved surgical procedures using anterior instrumentation, debridement, and fusion – this is typically reserved for cases of anterior thoracolumbar infection with minimal kyphosis and little to no pain. Prof. Subroto Sapardan was inspired by a Hong Kong method when He created this alternative, as such the two procedure shares a few similarities.[23,29]

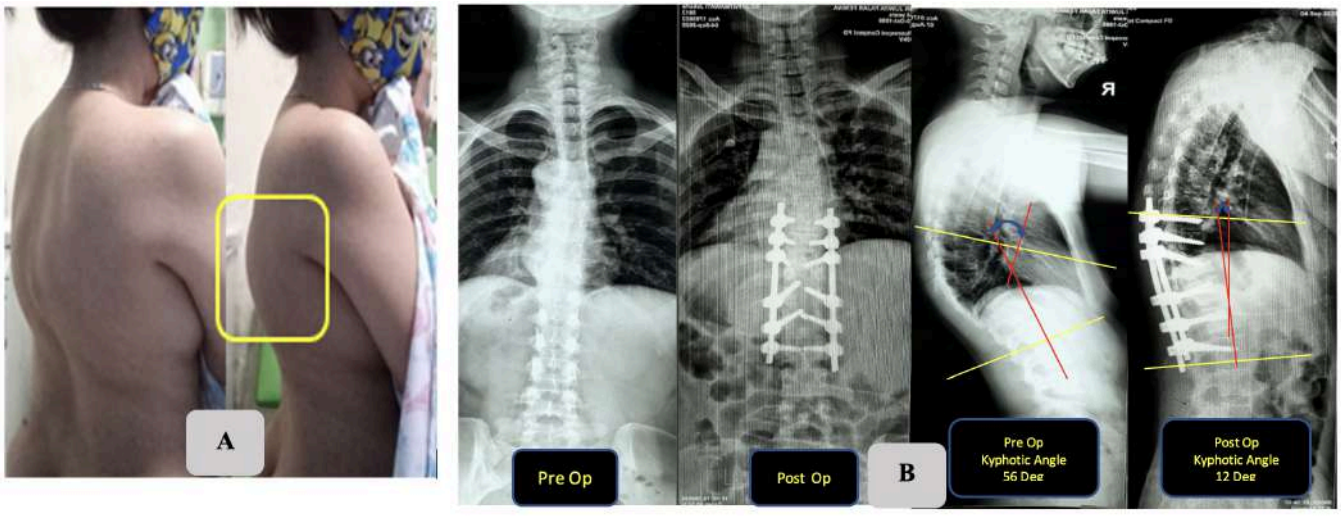

Figure 1. Subroto Sapardan's total treatment application in clinical practice; A. A female patient, 34, with back pain and kyphotic deformity, was diagnosed with TB spondylitis of Thoracal 11-12; B. She underwent decompression with laminectomy, posterior instrumentation, and kyphotic correction

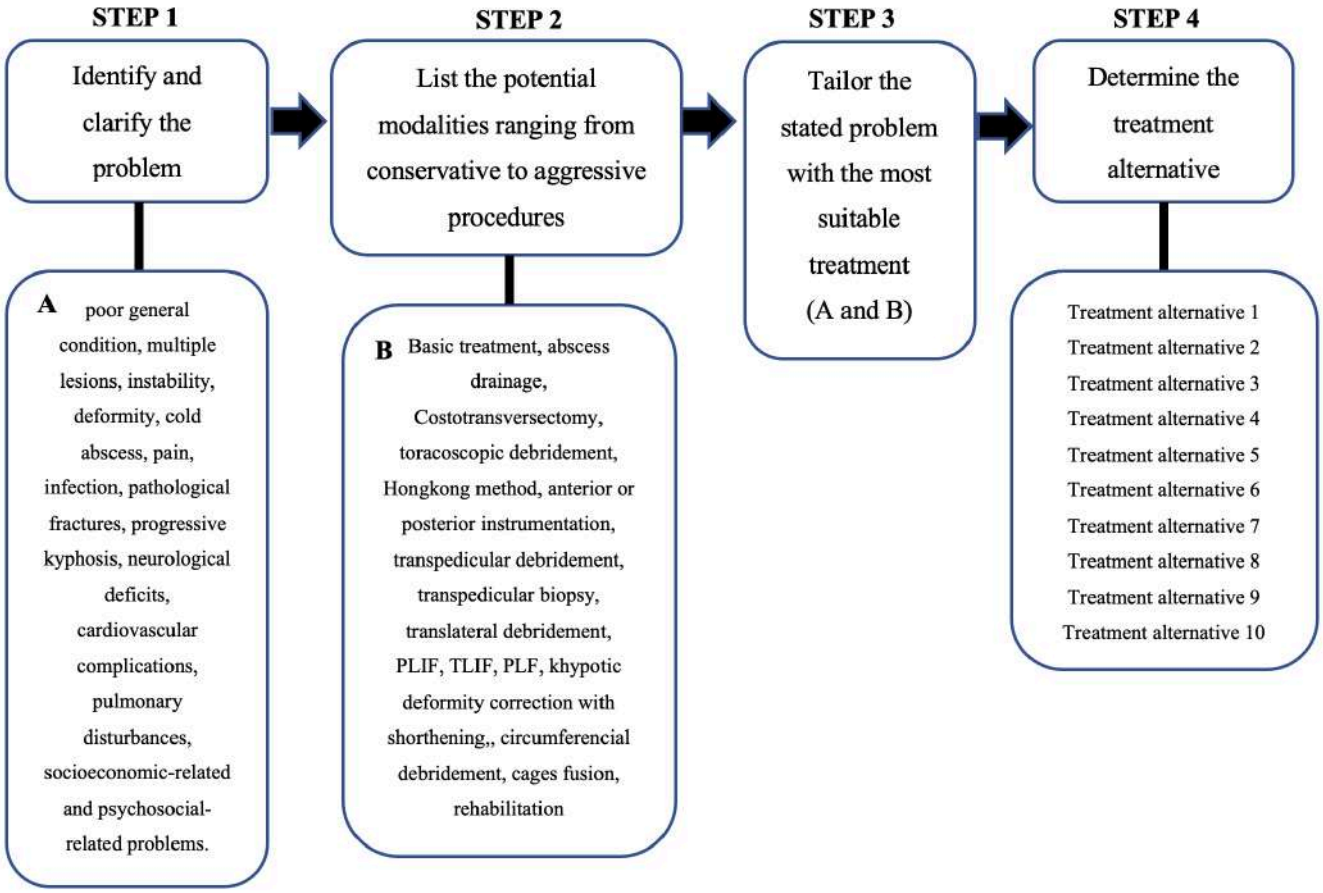

Figure 2. Subroto Sapardan's total treatment application in clinical practice; A. A female patient, 34, with back pain and kyphotic deformity, was diagnosed with TB spondylitis of Thoracal 11-12; B. She underwent decompression with laminectomy, posterior instrumentation, and kyphotic correction

The 4th alternative was a modification of the 3rd alternative, this procedure involved posterior instrumentation and correction of a nonrigid deformity followed by anterior debridement and fusion to achieve circumferential fusion. This procedure was targeted for patients with problems of infection, pain, instability, and deformity, with or without neurological deficit.[29]

5th alternative was made to be a continuation of the 4th procedure, the difference of 4th and 5th procedures is that the 5th alternative has a kyphosis deformity correction added. This alternative was tailored for patients with TB spondylitis on the cervical/thoracal/lumbar region with severe kyphosis that indicates correction.[23,30] This procedure included posterior instrumentation and anterior debridement and fusion which is removing the lamina facets, transverse process, and pedicles of the segments in the kyphosis until deformity is corrected. [23,29]

6th alternative was indicated in patients with stable anterior but unstable posterior, or those whose abscesses can only be reached through a posterior approach.[29] The procedure consisted of posterior decompression by laminectomy and costotransversectomy for debridement and evacuation of a paravertebral abscess followed by posterior instrumentation and fusion.[29]

Starting from the 7th alternative, the procedures were mainly reserved for more severe cases of spondylitis of the lumbar spine with hot paravertebral abscess. This alternative included laminectomy, limited shortening procedure, debridement, and fusion through translateral or posterior lumbar interbody approach. 7th alternative required rod and screw corrective manipulation. [23,29]

While the 8th required shortening and decompression procedures for spondylitis of the upper thoracic spine. This procedure consisted of laminectomy transpedicular debridement and biopsy, followed by posterior segmental instrumentation and fusion.[23,29]

The 9th required surgical repositioning of the spine, typically due to severe kyphosis (60° -90°) is still active or healed disease. This procedure consisted of removing lamina and facet joints, transverse processes, adjacent ribs, and middle segment until circumferential decompression of dura mater and cord is achieved correction by closing the posterior gap with posterior

segmental instrumentation.[23,29]

Lastly, the 10th procedure was applied for patients with extreme kyphosis (> 90°) without neurological complications, henceforth this procedure aims at preventing that from emerging.[23] This technique consisted of posterior instrumentation, debridement, distraction, and fusion.[23]

Finally, with the 10 alternatives formulated, Prof. Subroto Sapardan successfully formulated a new holistic treatment guideline for TB spondylitis. This procedure was then named after him in honor of his contribution and discovery. The total time taken for this method to be perfected was 5 years – whilst Prof. Subroto Sapardan introduced the treatment in 1984, it was not only until 1989 that the procedure, that has undergone various trials and improvements, reached a level of credibility that officiates its application in various hospitals in Indonesia.[29] 1989 marks the end of the long developmental history of the procedure, although minor improvements or modifications were made in the future, the general concept of the treatment was also officially finalized by that year.

Due to the credibility of *Subroto Sapardan* Total Treatment, as seen in a few published literature and case reports, the regimen is used in various hospitals throughout Indonesia. As previously described, each of the 10 alternatives listed in the guideline has its specific indication and goal, thus each alternative must be applied accordingly. This method is typically seen in practice at teaching hospitals, such as *Cipto Mangunkusumo* Hospital, and *Fatmawati* Hospital. It is also a widely spread procedure in orthopedic communities.[29] It is safe to say that as time progresses, this procedure will eventually be recognized further by the medical community, and as it has been proven to be quite effective and efficient, there may be an increase in its application in practicing hospitals.

As previously discussed, the *Subroto Sapardan* Total Treatment is a method of treating TB Spondylitis that has many strong assets. The holistic approach of the treatment is extremely beneficial for patients, as it takes into consideration not only the patient's disease but also their living condition – this can significantly improve patient's satisfaction and quality of life. The adaptability and flexibility of the procedure should also be complimented as it regards the possibility of medical advancements. The 10 alternatives that the regimen provided may be double-edged; one on side it benefits the patient and physician as it is very comprehensive, on the other, it may prove to be slightly inconvenient when a thorough consideration should be taken by clinicians under duress. One minor drawback of the treatment method is seen in the 6th alternative in which a guideline states that the procedure is inadequate if a patient exhibits an anterior abscess.[23] Meanwhile, one major weakness of this procedure is the lack of awareness in the medical community, though the procedure has been applied in several hospitals, it is not as widespread as it should be. In comparison to the majority of recognized treatment methods, there was a scarcity of published studies or reviews on *Subroto Sapardan* Total Treatment that could significantly increase its prestige.

Judging from the advantages and disadvantages of *Subroto Sapardan* Total Treatment, this review concludes that the method is positively applicable in clinical settings. With its holistic approach and having gone through years of application, the method holds both potential and credibility for clinical use.

Conclusion

TB spondylitis is the most common manifestation of skeletal TB, it is a severe condition that requires urgent care. TB spondylitis occurs when there is a hematogenous spread of MTB from a primary or dormant lesion. The *Subroto Sapardan* Total Treatment is an available method of managing TB spondylitis that is widely applied in Indonesian teaching hospitals. It has a very holistic approach towards TB spondylitis patients and it has a thorough 10 alternatives that can be suited to most of the 14 general issues TB spondylitis patients commonly face.

Recommendation

The application of *Subroto Sapardan* Total Treatment should be reinforced, its usage should be more widespread in hospitals throughout Indonesia. Awareness of both medical practitioners and patients on this treatment method should be amplified; as it may provide benefits for the medical practitioner in the form of expanding knowledge, and for the patients by increasing their satisfaction. The adaptability and flexibility of the method should also be used to both modernize and optimize the regimen. Lastly, it is highly recommended that more publications, in the form of articles or reviews, be made regarding the *Subroto Sapardan* Total Treatment to increase both its credibility and prominence.

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