REVIEW ARTICLE

Controversies in the Treatment of Extrapulmonary Tuberculosis

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Tuberculosis (TB) can spread to any tissue or organ of the body by way of hematogenous or lymphatic dissemination or contiguity. However, pulmonary TB is the most common presentation and the only form of the disease of epidemiologic importance. Consequently, the literature on the various forms of extrapulmonary TB (EPTB) is scant, and most of the published authors are specialists in specific extrapulmonary forms. As a result, in most of the major areas of study of EPTB, recommendations similar to those for pulmonary TB or others based on little or no evidence have been accepted. This lack of evidence is of particular concern in the case of treatment guidelines.

The present article reviews important work that has given rise to current treatment guidelines. While most of these guidelines reveal the lack of evidence available on this subject, it can, nevertheless, be concluded that a 6-month treatment regimen similar to that used in patients with pulmonary TB may be sufficient to treat all forms of EPTB, including meningeal disease. The role of steroids and surgery in the treatment of TB affecting different sites is also discussed. Other topics dealt with are the considerations that should be taken into account and the treatment modifications necessary in patients infected with the human immunodeficiency virus.

Key words: *Extrapulmonary tuberculosis. Treatment. Surgery. Steroids.*

Controversias en el tratamiento de la tuberculosis extrapulmonar

La tuberculosis (TB) puede afectar, por diseminación hematógena, linfática o contigüidad, a cualquier órgano o tejido del organismo. Sin embargo, la forma de presentación pulmonar es la más frecuente y la única epidemiológicamente importante. Esto ha motivado que las publicaciones sobre las diversas localizaciones de la TB extrapulmonar (TBE) hayan sido escasas, y casi siempre realizadas por especialistas de las diferentes presentaciones. Por tal motivo, en la mayoría de los grandes campos de estudio de la TBE se han aceptado recomendaciones similares a las efectuadas para la TB pulmonar, o se han seguido otras con escasa o nula evidencia; aspecto especialmente relevante en lo concerniente al tratamiento.

En el presente artículo se revisan importantes publicaciones que han dado lugar a las actuales recomendaciones sobre el tratamiento, detrás de la mayoría de las cuales resalta la falta de evidencia existente. En cualquier caso, se concluye que un régimen de 6 meses, similar al de la TB pulmonar, puede ser suficiente para tratar todas las formas de TBE, incluida la meníngea. Se discute, igualmente, el papel que los esteroides y la cirugía pueden tener en las diversas localizaciones de la TB, así como las modificaciones y/o consideraciones que deben tenerse en cuenta en los pacientes infectados por el virus de la inmunodeficiencia humana.

Palabras clave: *Tuberculosis extrapulmonar. Tratamiento. Cirugía. Esteroides.*

Introduction

Mycobacterium tuberculosis, the pathogen responsible for the worst epidemic that has ever plagued the human race in our long shared history, has acquired a number of characteristics that have helped it to perpetuate itself. One of these is its ability to disseminate from the first moment it infects a human being. During both the primary infection and subsequent reactivations, these disseminations—which are rather more common than might be expected—can spread to contiguous organs or to remote sites via the bloodstream or lymph system. Tuberculosis (TB) can, therefore, infect any organ or tissue in the body, and the disease can develop in nonpulmonary sites.[1-4] While pulmonary TB is the most important clinical manifestation of this infection, as it is both the most common presentation and practically the only form of the disease that is infectious,[4,5] the clinical importance of TB affecting other sites—known as extrapulmonary TB (EPTB)—should not be overlooked.

From the point of view of public health, the highest priority in TB control programs is the identification and treatment of the most infectious patients, who are mainly those with positive sputum smears. Since

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patients with EPTB are rarely smear positive, it is generally accepted that the contagious potential of this form is negligible and it has, therefore, never been a priority in the campaigns undertaken by national TB control programs.[4,5] Consequently, the literature on the various forms of EPTB is scant, and most of the published authors are specialists in specific extrapulmonary forms. As a result, in most of the major areas of study of EPTB, recommendations similar to those for pulmonary TB or others based on little or no evidence have been accepted. This lack of evidence is of particular concern in the case of treatment guidelines.

The various forms of EPTB share a number of characteristics that clearly differentiate them, as a group, from pulmonary TB: their incidence and epidemiology, the way *M tuberculosis* reaches the different organs or tissues, the pathogenic response produced, the possibilities of survival for the bacillus in each site, the clinical presentation, and the yield of the diagnostic techniques used. There has also been a great deal of discussion about whether EPTB should or should not be treated with the same regimens as pulmonary TB. Consequently, if clinicians are to deal appropriately with cases of suspected EPTB, they should be aware of the important differences between this entity and pulmonary TB.

Frequency of EPTB

As the incidence of EPTB is closely related to the prevalence of TB in an area, the rate varies between countries. However, a number of hypotheses have been advanced to explain the increase in the number of cases of EPTB reported in certain regions in recent decades: *a)* an increase in the diagnosis or reporting of cases, a phenomenon that may even have given rise to overdiagnosis; *b)* an improvement in diagnostic techniques that has facilitated the diagnosis of forms of EPTB with very low numbers of bacilli; and *c)* situations of severe immunodeficiency, of which the most important is human immunodeficiency virus (HIV).[6] With respect to HIV it is interesting to note that, while it has not been reported in some areas that acquired immunodeficiency syndrome (AIDS) has had any effect on the incidence of EPTB,[7,8] in most regions HIV infection is the main risk factor for progression from TB infection to disease.[4,9-16]

The number of reported cases of EPTB has been rising in both industrialized and developing countries, particularly in regions where the prevalence of HIV infection is high and in areas served by tertiary level hospitals staffed by specialized personnel and equipped with adequate resources to diagnose TB in different organs and systems. This phenomenon has been observed in various countries including Venezuela,[17] Malawi,[18] and Turkey.[19] In Venezuela, where there is a national TB control program and reporting is mandatory for all cases of TB, including EPTB, the number of reported cases of EPTB in recent years has been 5 times higher in the capital city, Caracas, than in the rest of the country.[17] In Malawi, the incidence of EPTB is higher in semi-urban than in rural areas,[18] and in Kocaeli (Turkey) 88.2% of the reported cases of EPTB came from urban areas.[19] When Sharma and Mohan[20] discussed this subject, however, they highlighted the factors associated with possible underreporting of cases, such as the difficulty of convincing patients—particularly those who are HIV positive—to undergo invasive procedures, while also pointing out that EPTB numbers can be overestimated because many diagnoses are only presumptive.

However, those authors report that the percentage of patients with extrapulmonary forms of TB in tertiary care centers in India was between 30% and 53%, while the percentage estimated by the national control program in India for HIV-negative adults is between 15% and 20%.[20]

Immunodeficiency also influences the site of EPTB. While the extrapulmonary forms of TB most often observed in immunocompetent patients are located in the pleura, the lymph system, and the urogenital system,[21-25] the most common site to date for EPTB in HIV-positive patients is the lymph system.[8,14,20-22,26-30]

Factors That Delay Start of Treatment

Early diagnosis and initiation of appropriate treatment are the keys to reducing morbidity and mortality in patients with EPTB, in particular in the case of miliary and meningeal forms of the disease—entities that constitute serious medical emergencies.[13,31] However, this is not always possible. As the clinical signs of EPTB are generally quite nonspecific, a high level of suspicion on the part of the generalist physician or the specialist in the diseases of the affected organ is essential for the early diagnosis of EPTB. Once again, the situation differs enormously depending on the health care resources and epidemiological situation in each country. In countries with a low incidence of TB where the resources needed to diagnose extrapulmonary forms are available, EPTB is generally proposed as a differential diagnosis in certain unresolved cases, or is particularly suspected if the patient is an immigrant from a country with a high prevalence of TB.[32] While a higher diagnostic suspicion may exist in countries with a medium or high prevalence of TB—generally developing countries where economic resources are fewer—the delay in reaching a firm diagnosis is usually due to the scarcity of necessary diagnostic resources or the longer delay before initial consultation with a physician because of poorer access to health care.

The difficulty of diagnosing EPTB is well known. It is due to the lower bacillary counts present in almost all extrapulmonary presentations and the problems associated with obtaining valid samples for analysis. Consequently, unlike pulmonary TB (for which the smear test and sputum culture are the principal diagnostic procedures), the main tool for the diagnosis

of EPTB is histopathology. It should be borne in mind, however, that while certain histopathologic findings—for example Langhans' cells and granulomas with caseous necrosis—are highly indicative of TB, similar findings are associated with other diseases, in particular all of the mycobacterioses.[33] This means that all specimens obtained for histopathologic testing should also be cultured in the microbiology laboratory. Moreover, the results of histopathologic analysis should be confirmed by another diagnostic finding or criteria. This can be epidemiological, clinical, or the results of an imaging study (radiography, isotopic or magnetic resonance imaging, ultrasound, or computed tomography.[4,13,34]

The presence of *M tuberculosis* in fluids and tissues is detected in between 10% and 60% of cases depending on the site.[35-38] The relatively low yield of microbiological techniques has led to the use of other diagnostic strategies, including the measurement of biochemical markers in TB-affected serosal fluids (adenosine deaminase, gamma interferon, lysozyme, or C-reactive protein), and molecular biology techniques, such as polymerase chain reaction.[39-44] While these techniques can be of great help in the diagnosis of EPTB, they are not yet available in many parts of the world. Of particular interest among these techniques is the measurement of adenosine deaminase in fluids because this is an economical and reliable method (with high sensitivity and specificity) for diagnosing pleural and meningeal disease in areas where TB is highly prevalent.[4,40-42]

The difficulties associated with convincing HIV-positive patients to undergo invasive procedures has been mentioned above, and it is precisely among such patients that diagnosis generally takes longer and is the most difficult notwithstanding extensive tuberculous dissemination. Invasive diagnostic procedures should be considered as early as possible in view of the rapid progression from a disease that can be treated to one that may be fatal.[31,45-47]

Controversies in the Treatment of EPTB

The treatment regimen is one of the most controversial aspects of the management of EPTB. On the one hand, certain international bodies, such as the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD), recommend the same regimen for both EPTB and pulmonary TB.[48,49] This recommendation is based on the need to simplify practice guidelines in the context of national TB control programs and on the hypothesis that the behavior of the bacillus does not differ between sites.[4,5,49] However, other important scientific societies recommend a longer treatment period for certain forms, including osteoarticular,[50] miliary,[50,51] and meningeal[50-53] TB, and even regimens involving higher dosages of drug in the case of tuberculous meningitis.[54] The WHO, moreover, has recently recommended the use of streptomycin instead of ethambutol for patients with meningeal TB.[48] While the literature for pulmonary TB is ample, very few clinical trials have been undertaken to validate the use of different treatment regimens in EPTB.[55-59] Consequently, the rest of the recommendations are based on a few published studies and expert opinion.[60-76]

Before the advent of rifampicin, most experts were of the opinion that an 18- to 24-month regimen based on a combination of isoniazid plus other drugs was sufficient to obtain satisfactory results. Later, more comprehensive studies were carried out on the treatment of EPTB, and these demonstrated the excellent efficacy of a 9-month treatment regimen combining isoniazid and rifampicin.[71,72] Only a few studies on pleural,[66,67] lymphatic,[55-57,73,74] osteoarticular,[58,59] urogenital,[60] and meningeal[76] TB have used 6-month regimens with isoniazid plus rifampicin in large numbers of patients. Some of these studies, which were controlled clinical trials enrolling patients with lymph node or spinal TB,[55-59] demonstrated the validity of the 6-month regimen of isoniazid plus rifampicin. However, the very few published studies that deal with other extrapulmonary sites only involve small numbers of patients.[63-65,68]

On the other hand, the recommendations on the use of intermittent regimens in the joint statement of the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America[53] on the treatment of TB are based on expert opinion, and there are very few studies that demonstrate the validity of this treatment regimen.[71-75]

The largest study that has published results on the treatment of TB in extrapulmonary sites was carried out in Venezuela.[22] In that study 679 patients were treated with a 6-month treatment regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide for the first 2 months followed by a combination of isoniazid and rifampicin 3 times a week for the remaining 4 months. Medication was administered according to the criteria of the Venezuelan national TB program, which specifies that all treatment must be directly observed. In total, 99.5% of the patients who received over 90% of their therapy were cured. This group included 24 patients with central nervous system TB, 27 with osteoarticular TB, and 42 with miliary or disseminated TB. In addition to confirming the effectiveness of the 6-month treatment regimen for EPTB in different sites, the Venezuelan study also demonstrated the importance in the management of these patients of ensuring adherence through strict supervision of treatment—the so called directly observed short course (DOTS) strategy. This strategy, generally recognized as fundamental in the control of TB in developed countries[79,80] as well as in low- and middle-income countries,[4,5,77,78] has only exceptionally been studied in patients with EPTB.[22]

In light of the above, it can be concluded that there is ample evidence to support the hypothesis that a 6-month treatment regimen for EPTB is ideal if it

includes isoniazid plus rifampicin; this hypothesis is supported by randomized clinical trials that studied patients with lymph node[55-57] and osteoarticular TB,[58-59] and by trials involving a large number of patients with pleural,[66,67] urogenital,[60,64] and other forms of EPTB. In the case of meningeal disease, however, some controversy still remains concerning the ideal duration of treatment. While some organizations, for example the WHO[48] and the IUATLD,[49] recommend a 6-month regimen (a duration also endorsed by certain important journals[22,76]), other guidelines propose a regimen of 9- to 12-months,[50-53] although they do recognize that this recommendation is not supported by any evidence from randomized clinical trials.[53]

Limitations on the Monitoring of Patients With EPTB Receiving Treatment

A technique such as smear microscopy or specimen culture, as used in pulmonary TB, is not available for monitoring patients with EPTB.[4] For this reason, clinical evaluation is one of the principal tools in the management of most forms of EPTB, especially ocular, cutaneous, lymph node, and meningeal disease. Imaging techniques also provide important support in miliary, osteoarticular, pleural, pericardial, and abdominal TB, as well as in some forms of TB affecting the central nervous system. The use of invasive procedures (biopsies) in the context of management would only be justified in the case of a poor response or no response to treatment, and then only to establish differential diagnoses. Bacteriology is only of use in the case of urinary tuberculosis.

Specialists responsible for the management of patients with EPTB must receive appropriate training[78] to enable them to establish criteria for cure, treatment failure, and relapse. In spite of the fact that EPTB is known to be paucibacillary, the subjective nature of the treatment decision and fear of relapse have led many physicians to prolong treatment or to add additional drugs without justification in a large number of cases of EPTB. A good example of this is lymph node TB; the enlarged nodes tend to shrink very slowly and may even get bigger after treatment has been completed. This phenomenon has, in some cases, been interpreted to be evidence of reactivated disease whereas it is, in fact, caused by a local immune reaction.[4]

Controversy Concerning the Use of Corticosteroids in the Treatment of EPTB

Another controversial aspect of the treatment of EPTB is the use of adjuvant oral corticosteroid therapy. The greatest difficulty in recommending these drugs is that the studies supporting their use differ methodologically in many ways including site of TB, severity of disease, types of patients studied, treatment regimens used, and forms and timetables of drug administration.[53,20]

Meningeal TB is one of the presentations about which the largest number of controlled trials of corticosteroids has been published. These trials enrolled large numbers of patients and demonstrated a more favorable outcome and a decreased risk of disease-related death and sequelae when oral corticosteroids were administered concomitantly.[51,53,81,82]

In pericardial TB, corticosteroid therapy is only recommended for the first 11 weeks, with several trials demonstrating lower mortality and a reduced need for pericardiocentesis when these drugs are used during the early stages.[4,53,83] This favorable outcome was not, however, observed when corticosteroids were administered during more advanced stages of the disease.[84]

In a few prospective, randomized trials on pleural TB it has been demonstrated that a course of oral prednisone had no beneficial influence on the development of pleural thickening[85,86] or residual lung function.[87] Patients receiving prednisone in 2 trials did, however, experience much more rapid improvement of symptoms (chest pain, fever, and dyspnea) and radiographic resolution.[4,86] The evidence has been considered sufficient to support the recommendation of such therapy in the British Thoracic Society guidelines[51] and in the statement published jointly by the American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America.[53] In other forms of EPTB, such as miliary or abdominal TB, recommendations for treatment with corticosteroids are based solely on expert opinion.[51,53,80]

The limitation imposed by the paucity of evidence supporting the use of corticosteroids adjuvant to the usual treatment regimens for EPTB is reflected in most of the guidelines. However, the existence of these recommendations has enabled most specialists to continue to consider the use of corticosteroids on a case-by-case basis, generally in the form of short courses. Theoretically, the use of corticosteroids would be more justified in the case of intense symptoms or very severe disease, but they are not indicated as a prophylaxis for sequelae of the disease.

The Treatment of EPTB in Patients With HIV Infection

Certain aspects related to the treatment of EPTB in HIV-positive patients must be discussed in light of the importance, mentioned above, of HIV infection in the development and course of this form of TB. The scant level I and level II evidence supporting the therapeutic recommendations for EPTB in the guidelines of the different international health organizations has already been mentioned. This deficiency is even more obvious in the case of TB/HIV coinfection because there are only a few studies evaluating treatment regimens for pulmonary TB in HIV-positive patients that include patients with EPTB[73] or studies on treatment regimens for EPTB that include HIV-positive patients,[22,98] and there is very little research on the subject of TB/HIV coinfection that deals with any treatment-related

aspects.[77,88-97] Nor have any controlled clinical trials been published that deal with the question of treatment regimens for EPTB in HIV-positive patients.

The recommendations of the American Thoracic Society[53] and the British Thoracic Society[51] establish that the treatment of pulmonary TB should be based on the same principles in HIV-positive individuals as in patients not infected with HIV. Although no specific mention is made of EPTB, there has been a tendency to apply the same recommendations to this group of patients. The basic points that should be taken into account are as follows:

1. The interactions between antituberculous and antiretroviral drugs. The fact that TB has been diagnosed is not in itself an indication for starting antiretroviral therapy. It has been proposed that antiretroviral therapy should be postponed, if possible, until after completion of the antituberculous treatment, or at least of the first phase of this regimen, because of the difficulty of differentiating between side effects and paradoxical reactions and because treatment adherence tends to decrease in patients dealing with both regimens. In patients already receiving antiretroviral treatment on diagnosis of TB, it has been proposed that an antituberculous regimen including rifampicin should be used in conjunction with an antiretroviral regimen excluding protease inhibitors.[53]

2. Paradoxical reactions. Although they have been reported in HIV-negative patients, paradoxical reactions occur more frequently in HIV-positive patients. They are triggered by the reconstitution of the immune response, either as a result of antiretroviral therapy or of the TB treatment itself. They include the following manifestations: the appearance of new enlarged lymph nodes or an increase in the size and inflammation of existing adenopathies; worsening of central nervous system lesions; and increase in pleural effusion.[53,92,99,100] The appearance of these reactions is not a reason for modifying the treatment regimen. Nonetheless, the possibility that the patient is not complying with the treatment regimen or that treatment has failed must be ruled out, and the existence of comorbidities should be investigated.

3. Poor adherence to treatment. Patient adherence is the principal factor determining the success of antituberculous treatment, especially in HIV-positive patients, one of the groups in which a high level of nonadherence has been demonstrated.[101-107] However, this failure to adhere to treatment cannot be attributed solely to the fact that the patients are infected with HIV; rather it is due to a series of associated factors that include illegal drug use and low socioeconomic status.[101-104] While once again most of the research has been carried out in patients with pulmonary TB, a study undertaken in Malawi demonstrated that the percentage of patients with EPTB who completed treatment was low, and that this nonadherence was associated with a high percentage of HIV infection; the conclusion drawn from this study was that national TB control programs should pay more attention to this group of patients.[105] It is precisely among patients suspected of poor treatment adherence that the DOTS strategy[108,109] should be complemented by other social welfare measures (methadone programs, work incentives, financial aid for food, and accommodation in halfway houses or other residential facilities).[102,110]

The Role of Surgery in the Treatment of EPTB

With the advent of effective chemotherapeutic agents, the need for surgical treatment in TB patients has practically disappeared. Today, there are only 2 special clinical situations in which surgery is indicated in the management of EPTB: when it is necessary to obtain valid diagnostic specimens (biopsies), and as a therapeutic option under certain circumstances to deal with sequelae or complications arising from the disease.[4,96,111-119]

In the case of pleural TB, the main invasive diagnostic procedures are thoracentesis and closed pleural needle biopsy (Abrams or Cope needle); thoracoscopy is only necessary in very rare cases. In the case of massive pleural effusion, repeated thoracentesis is a therapeutic option used to improve symptoms. This procedure does not, however, help to cure the disease or prevent sequelae. The placement of a thoracic drainage tube is recommended in cases of empyema or bronchopleural fistula. If this strategy fails to resolve these complications, thoracotomy, decortication, or thoracoplasty should be considered. It is advisable to wait until 6 months after start of medical treatment to evaluate sequelae and the need for surgical treatment .[4,111-113]

TB in abdominal or pelvic sites (gastrointestinal, urogenital, peritoneal, or lymph node) can spread to other nearby sites, and each one of these forms can be acute, subacute, or chronic. The invasive diagnostic procedures (paracentesis, endoscopy, laparoscopy, exploratory laparotomy) are performed when required to obtain specimens that will guide appropriate medical treatment before any definitive surgical intervention is carried out.[114] The following are some of the indications for surgical treatment: obstructive complications, gastrointestinal fistulas or hemorrhage,[96,115-118] drainage of perinephritic abscesses, management of urethral stricture and tuboplasties in urogenital TB, and even nephrectomy in the case of nonfunctional kidneys.[96,119]

Hydrocephalus can be a late complication of meningeal TB, and referral is indicated when the signs and symptoms of high intracranial pressure persist in spite of appropriate medical treatment.[113] Surgery is also indicated in the treatment of certain processes, such as constrictive pericarditis, vertebral abscesses that may compress the spinal cord, superficial and accessible abscesses arising from osteoarticular TB, and the mechanical complications or sequelae of lymph node TB.[4]

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