RECOMMENDATIONS OF THE SPANISH SOCIETY OF PULMONOLOGY AND THORACIC SURGERY (SEPAR)

Diagnosis and Treatment of Tuberculosis

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INTRODUCTION

Unfortunately, advances in the management of tuberculosis (TB) occur all too slowly. It has, however, been quite a few years since the last guidelines on the diagnosis and treatment of TB were published by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). During the intervening period, not only have advances been made in the treatment and, above all, the diagnosis of TB, but the demographic profile of Spain has also changed significantly as a result of increased immigration. Today, 10% of the country's population is foreign born and 30% of TB cases involve immigrant patients. In this context, we considered it both timely and essential to update the society's guidelines and adapt the recommendations to take into account these changes in the composition of Spanish society..

To simplify access to the information, we decided to combine all the society's recommendations on the diagnosis and treatment of TB in a single practice guideline based on the scientific evidence currently available. Recommendations are graded as A, B, C, or D. A grade A classification indicates that the supporting scientific evidence is good or very good (level 1 trials); grade B indicates that the evidence is reasonably good (level 2 trials); grade C that the supporting evidence is scant (individual case reports and case series); and grade D that the recommendation is based on expert opinion or consensus.

We would like to thank SEPAR's Scientific Committee for their confidence in the ability of this group of experts to compile the new TB guidelines, and we hope that the resulting document will be of use in improving the management of TB.

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DIAGNOSIS OF TUBERCULOUS INFECTION

Tuberculin Skin Test

The tuberculin skin test recommended in Spain is based on tuberculin purified protein derivative (PPD)-RT23 with Tween 80 administered at a dose of 2 tuberculin units (TU) per 0.1 mL, which is biologically equivalent to the recommended dose (5 TU) of the international standard tuberculin (PPD-S). The chief disadvantage of the skin test is that PPD contains many proteins that are not specific to *Mycobacterium tuberculosis* and are also found in other mycobacterial species. The implication of this is that individuals sensitized through prior exposure to other mycobacteria or TB vaccination will also respond immunologically to PPD.[1-3]

Table 1 shows the indications for performing a skin test.[4] The method that should be used is the Mantoux technique, an intradermal injection on the dorsal surface

TABLE 1
Indications for Tuberculin Skin Testing

Household members and close contacts of patients with tuberculosis
Individuals with radiographic findings indicative of inactive tuberculosis
Individuals with clinical and/or radiographic findings giving rise to a suspected diagnosis of active tuberculosis
Individuals with a high risk of developing active disease if they are infected
Infection with human immunodeficiency virus
Parenteral drug addiction
Marginalization
Immunosuppressant disease: leukocytosis, lymphoma, and other neoplastic diseases
Prolonged immunosuppressive therapy, anti-tumor necrosis factor-α therapy. Transplantation candidates
Infected individuals who represent a social and epidemiological risk if they develop active tuberculosis
Personnel working in day nurseries
Teachers
Health care workers
Prison staff
Epidemiological studies and tuberculosis control programs

of the forearm at a sufficient distance from superficial veins and on skin with no prior lesions (evidence level D). When the test dose is properly administered just under the surface of the skin, a tense wheal appears at the injection site. The results should be read 48 to 72 hours after administration by measuring the diameter in millimeters of the induration at the injection site in a direction perpendicular to the long axis of the forearm. Only the diameter of the raised induration should be measured, and a reaction taking the form of erythema without induration should be recorded as 0 mm. If follow-up between 48 and 72 hours after testing is not possible, a valid result can still be obtained as long as the reaction is read within 7 days.[5]

Interpretation of the Skin Test Result

A tuberculin skin test is considered to be positive when the induration is 5 mm or larger. In individuals who have been vaccinated against TB, it is impossible to determine with absolute certainty whether a reaction is due to infection with *M tuberculosis* or to the residual effect of vaccination. In practice, however, prior vaccination should be ignored in high risk groups. A skin test reaction of 5 mm or greater is deemed indicative of *M tuberculosis* infection in vaccinated individuals who fulfill any of the following criteria: household member or close contact of a smear-positive patient with active disease; indications of inactive TB on chest radiograph (confirmed by bacteriological evidence and subsequent course); infection with human immunodeficiency virus (HIV); high risk for HIV infection; or presence of silicosis lesions. In vaccinated individuals who do not meet any of these criteria, test results should be interpreted on a case-by-case basis bearing in mind that—while it can never be ruled out that the reaction may be due to the TB vaccination—the greater the diameter of the induration, the more likely it is that the cause of the reaction is a natural tuberculous infection, particularly if the diameter of the induration exceeds 15 mm.[3] Vesiculation and necrosis should also be considered indicative of tuberculous infection. Conversely, false negatives may occur because of defects in the technique used or immunodeficiency secondary to a number of diseases or situations, including severe TB and pleural TB. It should also be remembered that it takes 2 to 12 weeks following infection with *M tuberculosis* for the sensitized T cells to pass into the blood stream and recognize the tuberculin deposited within the dermis, and that infected patients may not react to the skin test during this period. In general, infants younger than 6 months do not present positive skin test reactions.

The capacity to respond positively to tuberculin does not remain constant over the course of an individual's lifetime; although it may never disappear entirely, it can weaken over time. This waning of sensitivity is seen in both elderly patients who were infected in their youth and vaccinated individuals who have never been infected with *M tuberculosis*. In such cases, the individual's reaction to repeat skin testing may be boosted or reinforced by the initial test reaction, a phenomenon called the booster effect. To prevent eventual confusion between a booster effect and tuberculin conversion on subsequent testing, older patients and vaccinated individuals with negative initial test results should be retested within 7 to 10 days and the results of this second test should be recorded as the definitive result.[6] In this respect, however, it should be noted that repeated skin testing does not induce tuberculin sensitivity in patients who have never been infected. In practice, tuberculin conversion is defined as a positive reaction occurring within 2 years of a negative skin test result.

In Vitro Interferon-γ Techniques

In recent years, a number of new laboratory techniques for the diagnosis of tuberculous infection have been developed. These techniques are based on the detection of the interferon-γ (IFN-γ) released in response to in vitro stimulation of the sensitized T cells present in whole blood containing specific *M tuberculosis* antigens.[7] The following region of difference 1 (RD1) antigens are currently used to stimulate the T-cells: early secretory antigenic target-6, culture filtrate protein-10, and the RD11 RV2654 antigen.[8] All these antigens are present in the *M tuberculosis* complex but not in the TB vaccine or in any of the nontuberculous mycobacteria except *M kansasii*, *M marinum,* and *M szulgai* so these assays can discriminate between individuals infected with *M tuberculosis* and those who have been vaccinated against TB or exposed to nontuberculous mycobacteria (evidence level C).[9,10] Moreover, the tests incorporate controls capable of detecting anergy and excluding false negatives. They may be repeated immediately and do not give rise to any booster effect. Figure 1 shows an algorithm for the use and interpretation of the tuberculin skin test in combination with IFN-γ techniques.

Moreover, this in vitro technology has the following additional advantages over tuberculin skin testing[10-12]: the interpretation of results is not subjective; the test may be repeated if necessary; results are obtained rapidly; no second appointment is required to read the reaction; patients are not lost to follow-up because of failure to attend the second appointment; the test is easily standardized and the laboratory procedure is simple to perform; positive controls can be included to identify anergic patients; and the patient's privacy is preserved because the antigen assay is carried out in a laboratory and there is no visible sign like the induration produced by the skin test. The drawback associated with this technique is the higher cost. More studies are needed to determine the efficiency of these TB-specific assays, but they are already accepted as the most cost-effective option in countries with a high prevalence of TB.

DIAGNOSIS OF ACTIVE TB DISEASE

Risk Factors for Tuberculous Infection and TB Disease

Infection with TB generally requires prolonged and close contact with a smear-positive individual. Infection is influenced by a variety of factors, including the number of bacilli present in the sputum of the smear-positive

individual, the closeness of the relationship, the duration of exposure, the age of the contact (the risk is higher in children), and the immunological status of the contact.

The risk of developing active disease is highest in the following groups of infected individuals[13]:

a) individuals who present recent tuberculin conversion. The probability is highest during the first year after conversion, falls to between 5% and 8% in the first 2 years, and then tapers off. In patients with HIV coinfection who are not receiving antiretroviral treatment risk is between 5% and 10% per year.

b) HIV-positive individuals and other immunocompromised patients irrespective of whether immunodeficiency is due to disease or treatment with immunodepressants or biologic agents. Among the biologics, the tumor necrosis factor-α inhibitors stand out because of their growing importance in the treatment of numerous diseases.

c) individuals with residual pulmonary lesions secondary to untreated TB.

d) children younger than 15 years.

Patients with silicosis or clinically significant weight loss also should be included in this list.

TB can affect anyone, although the incidence is higher among certain groups and the risk of infection varies greatly (Table 2). It is generally accepted that belonging to a population with an annual incidence of more than 100 cases per 100 000 constitutes a risk factor. The classic risk factors can also be grouped into the following 4 broad categories[14]: *a)* biological (various diseases, HIV infection, and other immunosuppressive conditions, vitamin D deficiency, and genetic factors); *b)* behavioral (smoking, alcoholism, other substance addictions); *c)* social (unhealthy housing, poverty, sanitation problems, institutional settings); and *d)* environmental (silicosis, asbestosis).

TABLE 2
Risk of Developing Tuberculosis by Clinical Situation[14]

Clinical Situation	Relative Risk
HIV and AIDS	100-500
Silicosis	30
Gastric bypass	27-63
Transplantation: kidney, heart, lung, and other	20-74
Cancer	16
Hemodialysis/chronic renal failure	10.0-25.3
Gastrectomy	2-5
Diabetes mellitus	2.0-4.1

Abbreviation: HIV, human immunodeficiency virus.

Clinical Manifestations of TB

TB cannot be distinguished from other nosological entities on the basis of clinical signs and symptoms alone. Most cases are characterized by an insidious, not very alarming, and quite variable onset that depends on the virulence of the causal pathogen, the patient's age, the organ infected, and the host's immune status. Symptoms can be classified into 2 groups:

1. Systemic symptoms. The most common systemic symptoms are fever, loss of appetite, weight loss, asthenia, profuse nocturnal sweating, and general malaise.

2. Organ specific symptoms. These symptoms vary depending on the site of disease:

– Pulmonary TB. No correlation has been found between the extent of pulmonary TB and the intensity of symptoms, and disease is asymptomatic in 5% of adult patients.[15] The primary infection is generally subclinical or accompanied by only mild nonspecific symptoms. The most commonly reported symptom is a dry or productive cough, with either purulent or blood-tinged sputum or occasionally unmistakable hemoptysis. The patient may experience pleuritic pain. Dyspnea occurs when the disease has spread widely and only rarely in miliary TB. A special form of onset is tuberculous pneumonia, a condition associated with clinical and radiological findings similar to those of bacterial pneumonia.

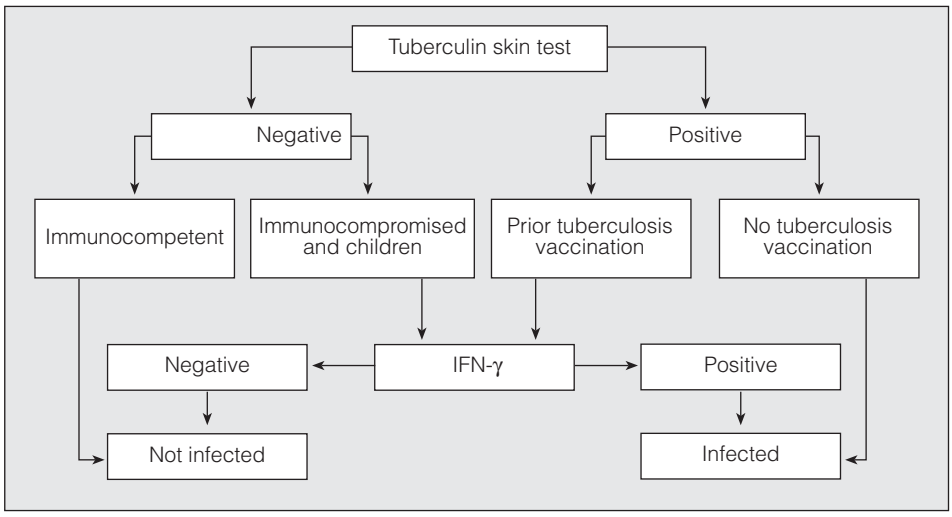

Figure 1. Algorithm for the combined use of the tuberculin skin test and in vitro interferon (IFN) γ techniques in the diagnosis of tuberculous infection.

In HIV-positive patients symptoms vary a great deal. Systemic symptoms predominate in severely immunodeficient patients, but the clinical picture in other HIV-positive patients is similar to that of the population in general.

– *Pleural TB*. Pleural TB may present as an acute pleuritis with high fever and pleuritic chest pain, but the most common presentation is chronic pleuritis with dull and/or pleuritic chest pain, low grade fever, dry cough, deterioration in general health, weight loss, asthenia, and progressive dyspnea.

– *Lymph node TB*. When TB affects the peripheral lymph node chain, a well defined painless swelling develops principally in the cervical and supraclavicular area (scrofula). Disease progression may give rise to inflammatory signs and fistulas with caseating drainage of material. If unrelated systemic symptoms should occur, HIV infection or other immunodepressive disease should be suspected.

– *Genitourinary TB*. The most commonly reported symptoms in genitourinary TB are pollakiuria, dysuria, hematuria, and flank pain, accompanied by pyuria with a negative culture. In women, genital TB can cause infertility, pelvic pain, and menstrual abnormalities. In men, it can give rise to orchitis and prostatitis, or it may affect the epididymis, where it manifests as a slightly painful mass.

– *Bone TB*. The spine, hips, and knees are the bones most often affected by TB. The chief symptom is pain. Mechanical abnormalities depend on the site of the disease. Swelling of the peripheral joints is common.

– *TB of the central nervous system*. The most common manifestation of central nervous system involvement is tuberculous meningitis accompanied by anorexia, general malaise, headache, decreased consciousness, neck rigidity, and vomiting. Involvement of the brain parenchyma (tuberculoma) is manifested by convulsions and focal signs.

– *Laryngeal TB*. The clinical manifestations of laryngeal TB are voice changes and aphonia, and occasionally throat irritation. Laryngeal involvement is almost always associated with pulmonary TB.

– *Miliary TB*. Miliary TB is a disseminated form of the disease most often found in HIV-positive patients although it can occur in any patient.[16] It is caused by the hematogenous spread of *M tuberculosis*, and symptoms include weight loss, anorexia, fever, night sweats, and poor general health.

The most common hematological finding in active TB is mild leukocytosis associated with lymphocytosis, although leukopenia or leukemoid reactions may occasionally develop. Anemia is a common finding in cases of disseminated disease or when the disease has been active for a long time. Pancytopenia may occur if bone marrow is directly affected. In severe cases of disseminated disease, biochemistry may reveal hyponatremia and hypochloremia secondary to secretion by lung tissue of an antidiuretic hormone-like substance.

Radiography

Neither extrapulmonary nor pulmonary TB has a pathognomonic radiographic sign, although in pulmonary disease, diagnostic suspicion is mainly based on indicative radiographic findings. Radiography is a sensitive but not highly specific diagnostic technique. High-resolution computed tomography (CT) currently plays an important role in differentiating between active lesions and evidence of prior disease.

– *Pulmonary TB*. Pulmonary TB almost always gives rise to abnormalities in the chest radiograph, although radiographic findings can be normal in endobronchial and miliary TB and in HIV-positive patients with severe immunodeficiency. Five radiographic patterns can be defined. The first, related to primary TB, occurs more often in immunodeficient patients (evidence level C).[17,18] Primary disease generally appears as a subpleural pulmonary infiltrate, sublobular in extent (the Ghon focus) in the middle or lower lobe and more rarely in the anterior segment of the upper lobe, alone or accompanied by enlarged hilar (the Ranke complex) or mediastinal lymph nodes, or as enlarged, mainly unilateral nodes with no infiltrate that may occasionally cause compression atelectasis. Pleural effusion and, very rarely, cavitation may also be found. The second pattern, typical of progressive TB, takes the form of extensive consolidation and cavitation in the primary pulmonary focus or in the apical or posterior segments of the upper lobes. The third pattern, that of postprimary TB, appears as heterogeneous and poorly defined parenchymatous opacities distributed across more than one segment, often associated with cavitation, which can be single or multiple (the walls may be fine and smooth or thick and nodular). The most common site is in the apical posterior segments of the upper lobes or in the apical segments of the lower lobes. Bronchogenic spread is seen as poorly defined nodules measuring between 5 and 10 mm with lobular or segmentary distribution distant from the cavitation located principally in the lower lung fields. The fourth pattern, that of miliary TB, comprises numerous noncalcified nodules measuring between 1 and 3 mm that are distributed throughout both pulmonary fields, predominantly in the lower lobes. They are more visible in the retrocardiac space on lateral projections and may be accompanied by consolidation, cavitation, and calcified or uncalcified adenopathies. The fifth pattern is associated with tuberculoma and demonstrates nodules of different shapes and sizes located predominantly in the upper lobes. These nodules are generally under 3 cm in diameter and have well defined smooth outlines (although they can occasionally be irregular and poorly defined) and surrounding satellites.

– *Pleural TB*. Pleural involvement is generally seen as a small or moderate unilateral pleural effusion, although the amount of fluid can be significant. In one third of these cases, parenchymatous disease is visible on the radiographic image in the same hemithorax as the effusion.

– *Lymph node TB*. When internal lymph nodes are involved, the most common sites are the right paratracheal, hilar, and mediastinal nodes. Enlarged nodes appear on CT scans with a slightly attenuated central area and an enhanced periphery in the form of a ring when contrast is administered.

– *Genitourinary TB*. When the kidneys are affected, calcifications inside the renal parenchyma and deformities of the renal calyx are seen. When the urethra is affected it appears dilated and irregular. Bladder involvement can be seen as a thickening of the bladder wall and a reduction in the lumen. Genital involvement in women gives rise to deformation and obliteration of the endometrial cavity and obstruction of the Fallopian tubes.

– *TB of the central nervous system*. In meningeal TB, CT scans may reveal intense and homogenous contrast uptake on the cortical surface extending into both hemispheres. On magnetic resonance images, uptake depends on the stage of the disease. Tuberculomata are seen on CT scans as rounded or lobulated masses showing ringed contrast uptake.

– *Osteoarticular TB*. A well-defined margin of destruction in the anterior vertebral body is usually observed. Disease progression gives rise to collapse of the anterior portion of the vertebral body, producing the characteristic gibbus. Paravertebral abscesses may be seen radiographically as posterior mediastinal masses.

Microbiological Diagnosis of TB

The microbiological study of samples is the only method that can establish a firm diagnosis of TB and, unfortunately, even these techniques are not 100% sensitive. In 10% to 15% of cases all the microbiological methods will yield negative results in spite of the presence of active TB. In such cases, diagnosis must be established on the basis of clinical and epidemiological parameters and imaging studies.[19]

All of the microbiological methods are highly specific, but their sensitivity depends heavily on the quality of the specimen obtained and how it is handled.

Conventional Diagnostic Microbiology

The conventional microbiological diagnosis of TB comprises the following techniques: smear microscopy, specimen culture, species identification, and susceptibility testing.[19,20]

1. Direct smear microscopy. Despite many advances in the diagnosis of TB in recent years, sputum smear testing using the Ziehl-Nielsen technique is still the basic tool for TB diagnosis and monitoring because it is a quick, simple, and low cost test that can be reproduced in any setting and used to detect infectious cases in the community, a task that constitutes the cornerstone of TB diagnosis and monitoring. The bacilli staining technique is based on the presence of mycolic acids in the cell wall of mycobacteria. These acids are present in all mycobacteria and persist when the bacillus dies. A positive smear test may, therefore, correspond to either dead or living *M tuberculosis* (a circumstance that complicates the interpretation of results when monitoring patients who are following treatment) or to another mycobacterial species.[19,20]

However, the chief limitation of smear microscopy is its moderate sensitivity; results can be affected by the site of disease, the degree of involvement, the quality of the specimen, and the time the technician spends determining that the result is negative. Sensitivity can be improved by concentrating the sample. The specificity of the technique is, however, very high (over 95%) and only limited by the false positives that can occur in the presence of environmental mycobacteria or, very rarely, due to technical defects. Consequently, while a negative smear does not rule out TB, a positive result almost confirms the diagnosis in over 95% of cases and is an indication for initiating treatment (evidence level D).[19,20]

Fluorescence smear microscopy (using auramine) has the advantage of facilitating the reading of the slide (a considerable time saving, with reading taking 3-4 minutes compared to 15-20 minutes in the case of a negative smear). This technique is particularly indicated as a screening tool in laboratories that process many specimens every day. Positive fluorescence smears must, however, always be confirmed using the Ziehl-Neelsen technique.[19,20]

The literature on the sensitivity of smear microscopy in HIV-positive patients indicates that sensitivity in these patients is similar or slightly lower.

2. Culture of mycobacteria. The other basic technique used to diagnose TB is the culture of specimens. When used in conjunction with species identification, culture is the only technique that reliably verifies the presence of TB and the only entirely valid method for monitoring the disease and confirming a cure. Cultures are also an essential part of the 2 other conventional microbiological techniques: species identification and susceptibility testing. Culture also offers the important additional advantage of being more sensitive than sputum smear microscopy. There are, however, 2 drawbacks that greatly limit the usefulness of culture as a basis for making clinical decisions: the long wait for results (a minimum of 2 to 4 weeks even with the fastest methods) and the complicated processing required. All too often the results of cultures serve only to confirm a diagnosis. They are not used to guide a clinical decision, which is usually taken on the basis of much faster techniques, such as the sputum smear test and chest radiograph. Nevertheless, in industrialized countries specimens should always be cultured.[19,20]

Cultures can be grown in either solid or liquid media. The solid media are the cheapest and most widely used, especially the egg-based preparations (Löwenstein-Jensen). However, the use of liquid media has gradually become more widespread because it offers several advantages including the shorter growth period required to obtain results (2-4 weeks as compared to 3-8 weeks), greater sensitivity, and the possibility of automation. The drawback of liquid media is that they are associated with higher rates of contamination (8%-10% vs 3%-5%). Even with liquid media, the time required to obtain culture results still precludes their use as a basis for clinical decisions.

Special techniques are required to process the blood cultures for mycobacteria indicated in the case of severely immunodeficient or feverish patients.

Although culture has always been considered to be the gold standard technique for the diagnosis of TB, the result may be negative in some smear-positive patients owing to the loss of viability of the bacilli or the process used to decontaminate the sample. Likewise, false positive results

may arise because of contamination of specimens in the laboratory. Despite these limitations, culture still plays a key role in the diagnosis and management of TB.

3. Species identification. Species identification confirms the diagnosis of TB because it can distinguish *M tuberculosis* complex from other mycobacteria. Species are identified using biochemical techniques, chromatography, and genetic probes. In industrialized countries, genetic techniques are the recommended method for identifying mycobacterial species because of the delays in obtaining results with biochemical techniques and the complexity of the procedures involved. Genetic methods can deliver results in 2 to 4 hours regardless of whether a direct specimen is used (polymerase chain reaction amplification techniques) or isolated colonies (hybridization techniques) (evidence level B).[19,20]

4. Drug susceptibility testing. Drug susceptibility can be determined using the proportion method, the most widely used technique on solid media. However, liquid media methods are much faster (a saving of 4-8 weeks including both the culture time and the test itself) and are therefore the techniques most often recommended in developed countries. It is important to stress that the results obtained are not 100% reliable and should always be interpreted in light of the characteristics and prior treatment of each patient. While the susceptibility tests for the first-line drugs (isoniazid, rifampicin, ethambutol, and streptomycin) are standardized and relatively simple to perform, those used for pyrazinamide are more complicated. The clinical reliability of the results for isoniazid and rifampicin exceeds 90%, but the results for ethambutol and streptomycin are more credible for susceptibility (over 80%) than for resistance, and the latter is always related to the resistance to these drugs in the community.[21,22]

Although their use has become more common, susceptibility tests for second-line drugs have not yet been completely standardized and in many cases the results obtained are not altogether reliable. The fluoroquinolone and aminoglycoside (amikacin) susceptibility tests are somewhat standardized and simpler than others. The reliability of the results obtained has not yet been clearly established, but they appear to be more reliable for resistance than for susceptibility. Tests for the other second-line drugs are not even standardized, and the scant clinical relevance of the results has been established.[21,22]

New Bacteriological Diagnostic Techniques

In spite of the many lines of research pursued in this field over the past 20 years, the results have contributed little to the routine diagnosis of TB and practically nothing that is useful in poor countries. The following new techniques can, however, be very useful in the facilities where they are available (evidence level B)[19,20]:

1. Molecular techniques that can rapidly detect resistance to rifampicin, which is usually linked to 1 or more mutations of the *rpo*β gene. The same techniques, which can be performed on direct samples and provide a result within a few hours, can also be used to detect genes linked to isoniazid resistance (*katG* and *inhA*), although such resistance is almost always associated with resistance to rifampicin.

2. Molecular amplification techniques used on smear negative direct specimens to increase the sensitivity of smear microscopy. The result can be obtained in 4 hours. However, it is very likely that the sensitivity obtained with these techniques will not exceed that of a culture. Positive results should always be interpreted in the context of the level of clinical suspicion.[23,34] On the other hand, a positive smear test associated with a negative result after amplification is indicative of nontuberculous mycobacteria.[23,34]

Other Diagnostic Methods

Histology

The typical pathological findings in TB are necrotizing or caseating granulomas and Langhans cells in tissue samples from infected organs. Histological analysis is the usual way of reaching a diagnosis in nonpulmonary forms of TB. However, since other diseases (sarcoidosis, leprosy, fungal infections, and syphilis) may give rise to similar granulomatous lesions, only a probable diagnosis can be established on the basis of histological findings alone. Note that samples for histology should be accompanied by fresh samples for mycobacterial culture and Ziehl-Neelsen staining for acid-fast bacilli (evidence level D). The typical granulomatous lesion is not usually observed in patients with HIV infection and/or a severe immune disorder.

Laboratory Tests

An elevated level of adenosine deaminase, an enzyme released by activated lymphocytes, contributes to the diagnosis of pleural, peritoneal, or meningeal TB. Adenosine deaminase levels above 45 U/L in pleural or ascitic fluid and greater than 8 to 10 U/L in cerebrospinal or pericardial fluid have a high sensitivity and specificity for TB (evidence level C), but are also found in other diseases. Such results must therefore be interpreted cautiously, especially in countries with a low prevalence of TB. The presence of IFN-γ in serum, pleural fluid, or bronchoalveolar lavage confirms tuberculous infection but not necessarily a diagnosis of active disease.

Specimen Collection

The best specimens for the diagnosis of pulmonary TB are spontaneous bronchial sputum samples. Samples should be collected on 3 consecutive days and can be stored in a refrigerator. In patients who do not produce sputum spontaneously, it may be possible to obtain samples after vapor humidification. Expectoration can also be induced with an aerosol of physiological saline solution, although great care should be taken because of the risk of contagion from contaminated aerosols. In children, 3 gastric aspirations may be performed, but in adults who do not produce sputum bronchoscopy is the method most often recommended (evidence level B). Microbiological

techniques should be used to study bronchial washings, bronchoalveolar lavage, and biopsies of any endobronchial lesions. The biopsies should also be studied histologically. Sputum obtained on bronchoscopy should also be studied (evidence level D).

In the case of pleural effusion and other serous complications, the fluid should be sampled for biochemistry, bacteriology, and cytology. In addition, specific markers, such as adenosine deaminase should be measured and, when necessary, a needle biopsy should be obtained either blind or using a pleuroscope.

In cases of nonpulmonary TB, fine needle aspiration for cytologic study or surgical biopsy for histological study are sometimes necessary. These techniques must always be complemented by smear microscopy, culture, and identification of any mycobacteria in the sample (evidence level D).[25,26]

TREATMENT OF TB

Based on the bacteriological fundamentals of the treatment of TB, the recommended treatment for first-time cases in Spain is the following 6-months regimen: 2 months with 4 first-line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) followed by 4 months with 2 drugs (isoniazid and rifampicin) (2HRZE/4HR) (evidence level A).[27-30] A first-time case is defined as a patient who has never been treated (new case) or has only received prior treatment for less than 1 month. The guidelines recommend prolonging this regimen to 9 months in cases of silicotuberculosis and to 12 months in patients with TB affecting the central nervous system (evidence level D); in the case of central nervous system TB a dose of 20 to 40 mg of corticosteroids should be added to the regimen during the initial phase (evidence level A).[30]

Ethambutol is included in the standard regimen for all patients for operational reasons and to cover the possibility of high primary resistance to isoniazid because the prevalence of such resistance throughout Spain has not as yet been determined with any precision. It is, however, very likely that the standardized regimen without ethambutol would be a valid treatment option for most Spanish-born patients with TB. Ethambutol may be removed from the regimen once susceptibility testing has indicated that the first-line drugs are effective.

The medication should be taken in a single morning dose while fasting, and no liquids or solids should be ingested during the following 30 minutes. In children, especially infants under 5 years of age, the dose of ethambutol should be 15 mg/kg daily (Table 3).[28]

Commercial preparations that combine fixed doses of the first-line drugs are now available. These combination tablets facilitate treatment compliance by reducing the number of pills to be taken and prevent the development of resistance by precluding selective monotherapy in patients who discontinue treatment. Current guidelines on the treatment of TB recommend the generalized use of combined drug preparations (evidence level C). Table 4 shows the fixed combinations available on the market and their dosage by weight.

The following 9-month treatment regimen may be used as an alternative to the 6-month regimen: 2 months with isoniazid, rifampicin, and ethambutol, followed by 7 months with isoniazid and rifampicin (2HRE/7HR). This regimen is particularly indicated in patients with gout. Other possible alternative treatments are 6-month intermittent regimens with administration 2 or 3 times a week. While effective, such regimens give rise to more side effects and require directly observed treatment (evidence level D).

TABLE 3
Dosage of Antituberculosis Drugs

Drug	Daily Dose
Isoniazid (H)	5 mg/kg. In children, 10-15 mg/kg. Maximum: 300 mg/d
Rifampicin (R)	10 mg/kg. In children, 10-20 mg/kg. Maximum: 600 mg/d
Pyrazinamide (Z)	20-30 mg/kg. Maximum: 2 g/d
Ethambutol (E)	25 mg/kg for the first 2 months followed by 15 mg/kg In children <5 years, 15 mg/kg. Maximum: 2 g/d
Streptomycin (S)	Intramuscular injection of 15-30 mg/kg
Capreomycin (Cp)	Maximum dose: 1 g/d or 750 mg in patients aged >50 years or weighing less than 50 kg
Kanamycin (K) Amikacin (Ak)	
Cycloserine Cs	15 mg/kg. Maximum dose: 1 g/d
Protionamide (Pt) Ethionamide (Et)	15 mg/kg. Maximum dose : 1 g/d
p-aminosalicylic acid (PAS)	200 mg/kg. Maximum dose: 12 g/d
Moxifloxacin (Mx)	400 mg/d
Ciprofloxacin (Cx)	750 mg/12 h
Ofloxacin (Ox)	400 mg/12 h
Levofloxacin (Lx)	500-1000 mg/d
Clofazimine (Cf)	100-200 mg/day
Rifabutin (Rb)	5 mg/kg. Maximum dose: 300 mg/d
Linezolid (lz)	1200 mg/d

Treatment of TB in Special Situations

The liver and kidneys are affected by the toxicity specific to each drug, and toxicity can be exacerbated if the metabolism or elimination of drug is deficient. Baseline function should be determined in patients with hepatic or renal insufficiency. While there may be no relationship with the degree of subsequent deterioration caused by treatment, the information will, nevertheless, orient the physician as to the functional reserve of the organ.

Liver Disease

Isoniazid, rifampicin, and pyrazinamide are all metabolized in the liver and can be hepatotoxic in the following descending order of frequency: isoniazid is associated with the greatest number of reported cases of toxicity; pyrazinamide has the greatest hepatocellular toxicity depending on the dosage; and rifampicin is responsible for jaundice and cholestasis. Combining pyrazinamide and rifampicin increases hepatoxicity, and

the addition of isoniazid to the combination further accentuates this effect. Of the second-line drugs, only protionamide and ethionamide have toxic effects. Chronic alcohol abuse, even in the absence of clinical signs of chronic liver disease, increases the likelihood of liver toxicity but does not contraindicate standard treatment if the patient has stopped drinking (evidence level D).[28,31] While standard treatment should be initiated in patients with disseminated TB and hepatic dysfunction, liver function should be closely monitored in these patients and the regimen modified if functional deterioration is observed (evidence level D).[27] In other acute diseases, such as hepatitis, treatment should be started with at least 3 drugs that are not hepatotoxic and continued with either streptomycin plus ethambutol or rifampicin plus isoniazid, depending on the clinical picture after the initial phase of treatment (evidence level D).[28] Treatment of patients with chronic liver disease, particularly when the process is advanced, poses serious problems, making specialist care essential. Pyrazinamide should be avoided, and clinicians should try to maintain a regimen of isoniazid plus rifampicin or at least rifampicin alone. With expert care and a stable clinical situation, standard treatment may be started with weekly monitoring of liver function using the criteria for drug-induced hepatitis. If necessary, attempts should be made to modify treatment by successively reintroducing rifampicin and isoniazid while maintaining the protection afforded by streptomycin, ethambutol, the fluoroquinolones, or cycloserine.

Renal Failure

Ethambutol, streptomycin, and all the second-line drugs are or may be nephrotoxic because they are all, except ethionamide, excreted by the kidneys in an active form. Ethionamide is excreted in the form of metabolites. The essential anti-TB drugs (isoniazid, rifampicin and pyrazinamide) are metabolized by the liver and eliminated in the form of inactive metabolites via the kidneys. Isoniazid, rifampicin, ethambutol, and especially pyrazinamide may be administered without dosage limitation to patients with renal failure because they are dialyzable.[27] In Spain, only the oral preparations containing isoniazid alone and 1 of the available combination tablets contain pyridoxine, a compound recommended for the prevention of peripheral neuropathy. Once drug resistance has been ruled out, the safest regimen is 2 months of isoniazid, rifampicin, and pyrazinamide, followed by 4 months of isoniazid and rifampicin (2HRZ/4HR); this regimen has no limitations (evidence level D).[28,31] In patients with renal failure, ethambutol, streptomycin, and even the second-line drugs can be administered when necessary, adjusting the amount of drug to be excreted according to the glomerular filtration rate. In general, even when creatinine clearance is less than 50 mL/min, conventional doses administered 3 times a week should be used to ensure the minimum inhibitory concentration required to maintain bactericidal activity (evidence level D).[27] When the clearance rate falls below 30 mL/min or the patient is in hemodialysis, the same regimen may be used but serum drug concentrations should be monitored. In patients receiving hemodialysis, medication should always be administered after dialysis because all of the first-line drugs except rifampicin are, to a greater or lesser degree, removed by hemodialysis.

TB and HIV Coinfection

The standard regimen (2HRZE/4HR) administered daily in fixed dose combination tablets is the most effective treatment for patients infected with HIV (evidence level B) and for those who may be HIV-positive but whose status is unknown (evidence level A). HIV serology should be ordered for all TB patients (evidence level D).[32] TB-HIV coinfection should always be managed by experts in both diseases (evidence level D).[30] In such cases, treatment problems generally stem from the greater prevalence of resistance to many anti-TB treatments in these patients, the severity and stage of both infections, and the pharmacological interaction between rifampicin and 2 groups of drug used in highly active antiretroviral therapy (HAART), namely, protease inhibitors and certain

TABLE 4
Treatment of Tuberculosis With Fixed-Dose Combinations: Number of Tablets by Patient Weight and Preparation

Weight, kg	Rifater (R 120+ H 50 + Z 300) 100-Tablet Pack	Weight, kg	Rimcure (R 150+ H 75 + Z 400) 100-Tablet Pack	Rimstar (R 150 + H 75 + Z 400 + E 275) 60-Tablet Pack
<40	3	38-54	3	3
40-49	4	55-70	4	4
50-64	5	>70	5	5
>64	6			
Continuation Phase: 4 Months				
Weight, kg	**Rifinah (R 300 + H 150) 60-Tablet Pack**		**Rimactazid (R 300 + H 150) 60-Tablet Pack**	**Tisobrif (R 600 + H 300) Pack of 30 Sachet**
50-90	2		2	1

Abbreviations: R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol.

non-nucleoside reverse transcriptase inhibitors. HIV-positive patients should be treated according to the guidelines for HIV-negative patients with multidrug resistant disease. Guidelines[32] and excellent reviews[33,34] dealing with this topic can be found in the literature. The primary objective is to maintain the use of rifampicin and to treat the TB before treating acquired immunodeficiency syndrome (AIDS) in order to avoid the development of immune reconstruction syndrome. The following regimens are, therefore, recommended: *a)* complete the 6 months of anti-TB treatment in patients with a $CD4^+$ count above 350 cells/μL before initiating HAART; *b)* treat the TB during the first 2 months in patients with $CD4^+$ values between 200 and 350 cells/μL and then start HAART with 3 of the drugs compatible with rifampicin, if possible; or *c)* in patients with a $CD4^+$ count under 200 cells/μL treat the TB for 2 to 8 weeks if the delay can be tolerated, and then start HAART applying the above criteria, or, when the patient's condition precludes any delay, administer combined treatment from the start with a HAART regimen based on the drugs compatible with rifampicin or rifabutin (evidence level D).[32,34] Anti-TB treatment without rifampicin is much less effective; if necessary, rifabutin may be given since it has few interactions, or the continuation phase with isoniazid and ethambutol may be extended for as long as 18 months (evidence level D).[34]

Pregnancy and Breastfeeding

No modification of the standard treatment regimen is required in either pregnant or breastfeeding patients (evidence level B),[30] although small doses of pyridoxine may be added to the regimen for nursing mothers (evidence level D).[27,28] Streptomycin, kanamycin, amikacin, and capreomycin are all prohibited during pregnancy because of fetal toxicity. Since very little is known about the possible effects in this context of the other second-line drugs, such as cycloserine, protionamide, and the fluoroquinolones, a case-by-case risk-benefit analysis is required before any of them can be used (evidence level D).[27]

Children and Older Patients

The only difference in the treatment of TB in children is that the dose must be adjusted according to body weight (evidence level B). Very little information is available about vision disorders that may be caused by ethambutol in children under 5 years of age. TB in children should be managed by experts in both specialist fields (evidence level D).[27,30] In older patients, who are often already receiving treatment with a variety of drugs for comorbid conditions and suffer from some degree of kidney dysfunction, drug interactions should be closely monitored.

Intolerance to Oral Medication and Loss of Consciousness

If the patient loses consciousness, the pharmaceutical formulation and the route of administration must be changed. The options are either percutaneous endoscopic gastrostomy or parenteral administration. In cases of gastric intolerance, it may be necessary to divide the daily dose into several doses, to administer antiemetics or anti-H_2 drugs, or even to change to parenteral administration. Isoniazid, rifampicin, ethambutol, streptomycin, amikacin, capreomycin, and the fluoroquinolones are the only anti-TB drugs available in parental formulations in Spain.

Adverse Effects of Medication

In most patients, anti-TB medication is usually well tolerated and presents no complications or clinically significant side effects.[27,31,35] Mild reactions, such as exanthema, urticaria, or cutaneous eruptions may develop, particularly at the start of treatment. These symptoms can usually be managed by changing the commercial preparation and/or prescribing symptomatic treatment (antihistamines or, very occasionally, corticosteroids). Mild gastrointestinal reactions may also appear (nausea, vomiting) without liver involvement. These disorders usually resolve with symptomatic treatment (antiemetics or anti-H_2 drugs) or modification of the timing of administration (dividing the daily dose into several fractions, administering each one close to a meal, or taking drugs with meals).

Anti-TB drugs can also affect the liver and cause elevated transaminase values (cytolysis) and/or alkaline phosphatase levels (cholestasis). These abnormalities may or may not produce symptoms. In such cases, treatment must be discontinued if transaminase levels reach 3 times the upper limit of normal in symptomatic patients or 5 times the upper limit of normal in asymptomatic patients. Otherwise, anti-TB treatment may be continued with strict clinical and laboratory monitoring and symptomatic medication when necessary. The most severe symptom is jaundice, and the condition may become life-threatening if the toxic medication is not discontinued.

Another possible complication is the reappearance of fever that had resolved after treatment (note that fever secondary to active TB may take several weeks to disappear). If drug-related fever is suspected, the drug responsible should be identified and discontinued; in some cases corticosteroids can be added to the regimen.

When a serious complication develops (usually hepatitis or fever), the clinician must identify the drug causing the adverse effect. This can be determined by interrupting treatment until fever disappears or liver function values return to normal (asymptomatic patients with transaminase values less than twice the upper limit of normal) and then reintroducing the drugs 1 by 1 every 3 days (the dose of rifampicin should be increased gradually: 150, 300, 450, 600 mg/day). The drug suspected of causing the problem should be introduced last (isoniazid is the drug that usually causes cytolysis while rifampicin causes cholestasis). Alternatively restart therapy without the drug suspected of causing the problem. Once the drug responsible for the side effects has been identified, the treatment regimen must be modified (note that the 6- and 9-month regimens require rifampicin or isoniazid and the 6-month regimen

TABLE 5
Adverse Effects Associated With First-Line Antituberculosis Drugs

Drug	Adverse Effects
Hydrazines	Exanthema Elevated transaminase values Hepatitis Peripheral neuropathy Interactions with antiepileptic medication (phenytoin) and disulfiram (antabuse) Joint pain
Rifampicin	Exanthema Hepatitis Thrombocytopenia Fever Flu-like syndromes Hemolysis Orange coloring of bodily fluids (urine, feces, tears)
Pyrazinamide	Gastrointestinal reactions Elevated uric acid Exanthema Hepatitis Joint pain Gout (rare)
Ethambutol	Optic neuritis Reduction in visual acuity Exanthema
Streptomycin	Vestibular and auditory toxicity Nephrotoxicity

cannot be used without pyrazinamide). If the standard regimen has to be discontinued, care of the patient should be the responsibility of a clinician with appropriate experience in managing TB.

It is important to warn patients about possible adverse events related to hearing (streptomycin) and vision (ethambutol), and about the interactions between rifampicin and oral hormonal contraceptives.

The main adverse effects of TB medication are shown in Table 5.

Drug Interactions

Possible interactions between anti-TB therapy and other medications the patient may be taking must always be reviewed since such interactions are common and sometimes clinically significant. When one drug inhibits or promotes the elimination of another, serum concentrations are increased or decreased, and this may render the prescribed dose either toxic or ineffective. The interactions of drugs administered in combination regimens may compensate one another if, like rifampicin and isoniazid, they have opposite effects. However, one usually predominates, in this case rifampicin.

Except for rifabutin, a drug very rarely used, none of the anti-TB drugs are changed in a clinically relevant manner through interaction with any other. One effect in the case of rifabutin is that serum concentrations of this drug are increased by indinavir and ritonavir, making it necessary to halve the daily dose of indinavir and to reduce that of ritonavir to 150 mg on alternate days.[27]

Anti-TB drugs do, however, interact with many other types of medication through the induction of various isoenzymes of the 3A system of cytochrome P450.

Rifampicin interacts with many widely used medications because of its potent induction of numerous 3A isoenzymes and inhibition of others (Table 6).[36,37] The dose must be modified in patients receiving treatment with the affected medications, and monitoring of drug serum concentrations will be necessary in some cases. Occasionally, rifampicin will have to be replaced by another anti-TB drug. It should be noted that a rebound effect is a possibility and that abnormal serum concentrations may persist for as long as 2 weeks after discontinuation of treatment with rifampicin or any other rifamycin. Only 2 of the interactions described in the literature—saquinavir and voriconazole—are formal contraindications to the use of rifampicin in combination regimens. Of the rifamycins, rifabutin is the least potent inducer of the P450 cytochrome.

Isolation and Prevention Measures

Since TB is generally spread from person to person through the air, early clinical suspicion, isolation, diagnosis, and start of treatment are all fundamental measures in preventing further spread of the disease. The bactericidal and sterilizing effect of treatment and its impact on the bacilli population have been studied. While these studies were not designed to investigate the transmission of TB and do not discuss the topic,[38] the findings they report suggest that patients with pulmonary TB rapidly become less infectious once treatment has started. The length of the interval that must elapse before a patient ceases to be infectious is not known with any precision, although empirical estimates range from 2 to 3 weeks.

The problem of transmission is particularly important in institutions settings, whether traditional hospitals and hospitalization units, or other locations such as clinics, emergency departments, nursing homes, correctional facilities, or home hospitalization settings.[39]

Patients suspected of having TB who come to a hospital emergency department should be immediately isolated and should remain in the department for as short a time as possible. Unnecessary hospital admissions should be avoided and length of stay should be kept to a minimum when hospitalization is unavoidable. Health care personnel who come into contact with TB patients must wear a particle filter mask, and patients who have to leave their room for some reason (for example, to have a radiograph) must wear surgical masks.[39] The reason for these measures should be explained to the patient.[30] Initially, patients should be admitted to a private room, but they can be taken out of isolation when a negative sputum smear result is obtained, a different diagnosis is established, or the diagnosis of TB is ruled out. If the diagnosis of TB is confirmed, the patients should remain in isolation. In the absence of clear evidence regarding how long a treatment period is necessary before a patient with TB stops being infectious, we prefer not to establish any schedule of fixed intervals for taking the patient out of isolation. While this

TABLE 6
Pharmacological Groups and Drugs That Present Significantly Reduced Serum Levels Following Interaction with Rifampicin, by Level of Evidence and Severity[36,37]

Pharmacological Group	Drugs That Present Reduced Serum Levels Following Interaction With Rifampicin			
	Demonstrated Interaction[a]		Probable Interaction: Observed and Published[b]	
	Intense	Moderate	Intense	Moderate
Cardiovascular agents		Digoxin	Amiodarone	Acetyldigoxin, bosentan, carvedilol, diltiazem, disopyramide, enalapril, losartan, metoprolol, nifedipine, propafenone
Broad-spectrum antibiotics			Telithromycin	Chloramphenicol, doxycycline
Anticoagulants				Dicumarol, warfarin
Anticonvulsants				Lamotrigine, phenytoin
Oral antidiabetic drugs		Pioglitazone, rosiglitazone		Chlorpropamide, gliclazide, repaglinide
Antifungal agents		Caspofungin, fluconazole	Voriconazole (contraindicated), itraconazole,	Ketoconazole
Other anti-infective drugs			Atovaquone	Mefloquina
Antineoplastic agents	Imatinib	Tamoxifen,		Bexarotene
Antiretrovirals				
Protease inhibitors	Saquinavir (contraindicated), atazanavir, lopinavir, nelfinavir		Amprenavir, fosamprenavir, indinavir	Ritonavir
Inverse transcriptase inhibitors			Delavirdine, efavirenz	Zidovudine
Bronchodilators				Theophylline
Hypolipidemic drugs				Atorvastatin, simvastatin
Hormones		Ethinylestradiol, etonogestrel, levonorgestrel. Other estrogens and progestogens		Levothyroxine
Immunodepressants			Cyclosporin, tacrolimus, temsirolimus, sirolimus	Betamethasone, cortisone, dexamethasone, leflunomide, methylprednisolone, prednisolone, prednisone
Narcotics		Morphine		Fentanyl, methadone
Psychotropic drugs				Buspirone, carbamazepine, citalopram, clozapine, haloperidol, sertraline, triazolam, valproic acid, zaleplon, zolpidem

[a]Controlled studies or experimental pharmacologic studies with area under the serum concentration curve, according to Drugdex System (Internet database).[37]
[b]Case series or published cases according to Drugdex System (Internet database)[37].

has been attempted in some guidelines,[30] others have chosen to define a series of conditioning factors.[39,40] We recommend that patients with TB should not share a hospital room with other patients (the ideal situation), or at least that isolation should not be discontinued until 3 weeks after the start of treatment and only when a response has been observed, sputum smear is negative, and the patient is adhering to treatment. The recommendations are shown in Table 7.

The most suitable setting for the treatment of TB from the point of view of preventing disease transmission is the patient's home. When home care is possible, the patient should remain at home for 2 to 3 weeks after start of treatment, and must avoid visits and contacts with unexposed persons during this period.

Treatment Monitoring

The aim of treatment monitoring is to ensure patient compliance, to assess treatment efficacy, and to detect adverse effects as early as possible. Monitoring should include the following components:

– *Clinical record*. A record should be kept of clinical improvement and any adverse effects that may occur. Compliance should be monitored, and every effort made to encourage the patient to continue treatment. Patients should be tested to verify compliance, and a random urine sample should be obtained without prior warning to confirm the presence of the characteristic orange coloring caused by rifampicin. The Eidus-Hamilton test can be used to detect the presence of isoniazid metabolites in urine.

TABLE 7
Hospital Isolation Measures (Evidence Level D)

Avoid hospitalization
Minimum necessary stay
Particulate mask for health care personnel
Surgical mask for patients
No room sharing while waiting for confirmation or exclusion of tuberculosis
If tuberculosis is confirmed: airborne isolation measures should be implemented.
Ideally the patient should not share a room
Isolation can be discontinued
After 3 weeks of treatment
When there is response and treatment adherence
And negative smear test results

Women of childbearing age should be warned about the interaction between rifampicin and oral contraceptives. It is important to monitor fluctuations in the patient's weight and to make the necessary dose adjustments. All patients should be followed up after 2 to 3 weeks to ensure early detection of treatment errors and toxicity, and monthly thereafter until treatment is completed.

– *Laboratory testing.* The workup should include a complete blood count, total white blood cell and differential counts, partial thromboplastin time, liver and kidney function tests, and a uric acid test. These tests should always be ordered during the first month of treatment. The complete blood count and liver function tests should be repeated on follow-up at 2, 4, and 6 months.

- *Bacteriology*. Sputum smear test and sputum culture should be performed at 2, 4, and 6 months, when samples can be obtained.

– *Chest radiography*. A chest radiograph should be obtained at 2 months, at the end of treatment, and whenever the clinician considers it to be necessary. In extrapulmonary TB, the imaging technique chosen will depend on the site of disease.

Adherence to Treatment

The fact that the treatment of TB still involves drug regimens that last many months means that some patients will abandon treatment. This phenomenon, which was observed when the modern anti-TB drugs were first introduced, led to the establishment in 1950 of the protocol for directly observed treatment (DOT).

In Spanish the term *cumplimiento del tratamiento* (drug compliance) refers to whether or not the patient is taking their medication, while *adherencia* (adherence) is a broader concept implying the patient's active cooperation, although in Spain the 2 terms have tended to become synonymous. The aim of a Spanish TB control program should be to achieve a rate of drug compliance greater than 90%. To achieve this clinicians must, in the first place, motivate patients by explaining to them the importance of completing treatment in addition to making the usual recommendations.[41] Studies have identified a number of strategies for promoting high levels of adherence and these are as follows in increasing order of complexity: self-administered treatment monitored monthly with or without incentives; supervised weekly treatment; bimonthly DOT; daily or intermittent outpatient DOT; daily DOT in institutional settings; and mandatory DOT.[42]

The Centers for Disease Control and Prevention in the United States of America recommend DOT in groups with a therapy completion rate under 90%.[43] In Spain, the factors most often associated with failure to complete treatment are alcohol and substance abuse, indigence, and imprisonment. DOT is recommended in these high risk groups. Furthermore, TB therapy completion rates of more than 95% can be achieved with improvements in coordination between clinics and patient follow-up by public health care nurses.[44] Prisoners who are released during treatment are very likely to abandon treatment. Because most prisoners with TB infection are also drug addicts, close coordination between prison methadone programs and municipal programs can help ensure that these patients complete their treatment.[45]

Nonstandard Treatment Regimens and Retreatment

A nonstandard regimen is one that includes a drug combination other than the regimen normally recommended for initial treatment (2HRZ plus ethambutol or streptomycin/4HR). The term retreatment is used to describe the use of a nonstandard regimen after either treatment failure or a relapse owing to the presence of bacilli resistant to a first-line drug; for all practical purposes the situations are comparable.

Nonstandard regimens are always longer than the 6-month standard dosage regimen. They last between 9 and 24 months and involve the administration of pyrazinamide, ethambutol or streptomycin for more than 2 months in the initial phase. Moreover, these regimens almost always include additional second-line drugs, which are less effective and more expensive than first-line agents, cause more side effects, and require strict adherence to treatment to prevent the development of resistance.

Reasons for Prescribing a Nonstandard Regimen

After TB is diagnosed or during the course of a standard treatment plan, the clinician may have to modify the initial treatment plan or prescribe a nonstandard regimen in the following high risk groups or circumstances:

1. Resistance. The resistance of *M tuberculosis* to any anti-TB agent can develop naturally by spontaneous mutation if there is a colony of more than 10^5 pathogens. To overcome this natural resistance, TB treatment plans must include a combination of at least 3 drugs. The genes involved in the development of most resistances to the first-line drugs are known, and this knowledge has led to the development of rapid laboratory tests that can quickly identify susceptibility and resistance to the 2 key drugs, rifampicin and isoniazid.

Resistance can be either primary or secondary. Primary resistance is generally the result of infection with resistant microorganisms and is found in patients who have never received anti-TB treatment. Secondary or acquired

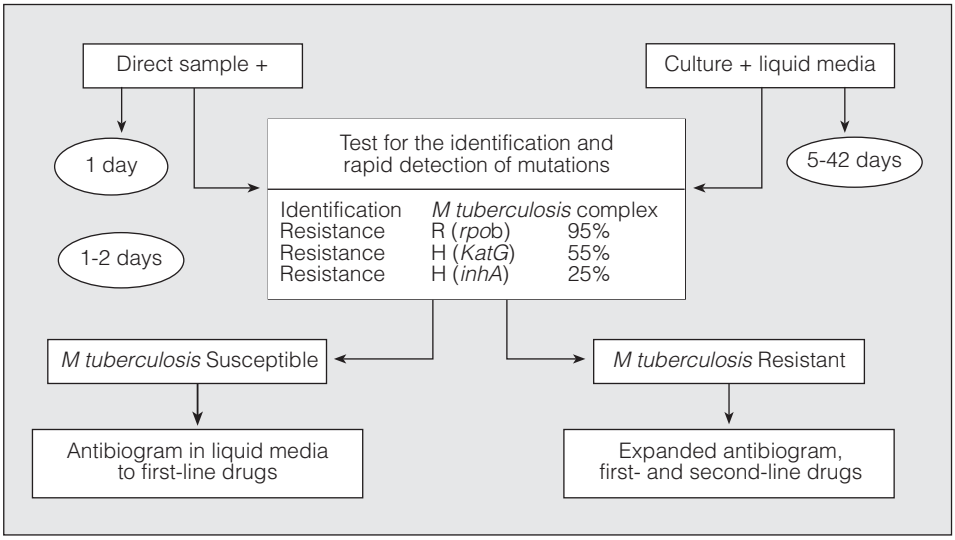

Figure 2. Laboratory analysis of mycobacterial resistance. H indicates isoniazid; R, rifampicin.

resistance develops in patients whose prior treatment has been inadequate, involving either prescribed or unintentional monotherapy or dual therapy due to undetected resistance to one or more of the drugs in the prescribed regimen. Patients with resistant disease may be classified into the following 3 categories: *a)* monoresistant, if the disease is resistant to a single drug, generally isoniazid; *b)* multidrug-resistant, if the disease is resistant to at least rifampicin and isoniazid; or *c)* extensively-resistant, if, in addition to being resistant to rifampicin and isoniazid, the disease is also not susceptible to either the quinolones or any of the parenteral drugs. Treatment is difficult and the prognosis uncertain in patients with multidrug-resistant and especially extensively-resistant disease, particularly when there is a concurrent immunosuppressive condition, such as AIDS.[46,47]

Due to the current trend toward increasing globalization, the risk of resistance may increase all over the world, even in countries like Spain where resistance is still uncommon. Resistance should, therefore, be suspected in any new case of TB, particularly if the patient presents with extensive lesions and a high bacillary density (evidence level B).[30] Suspicion should always be greater in the following patients and circumstances (evidence level B)[48,49]:

– Treatment failure, when a patient shows neither clinical nor radiographic signs of improvement and continues to produce culture-positive sputum with the same number of colonies after 4 months of treatment or develops positive cultures after several months of negative cultures. As this is a situation involving resistance to all of the drugs in the initial treatment regimen, treatment should be restarted with 3 or 4 drugs not previously prescribed. Treatment failure is rare in Spain as it only occurs when a patient fails to adequately adhere to a treatment regimen not based on the combined drug preparations normally prescribed in this country.

– Immigrants from developing countries and countries with high rates of resistance.

– Relapse in patients who have received prior treatment for TB disease or infection. If the prior treatment was adequate, resistance will generally not be found and the same standard treatment regimen can be repeated. However, if the prior treatment was inadequate, retreatment with a different combination of drugs should be started and maintained until the antibiogram is obtained.

– Close contacts of a patient with resistant TB.

– HIV-positive patients.

Resistance must be confirmed by the following mycobacteriological tests:

– Automated rapid test, with sequencing on positive culture and even on positive sputum smear. This test detects mutations of the genes associated with resistance to rifampicin (95%) and isoniazid (55%). Results are available in a few hours. This test should be ordered whenever it is available (Figure 2).

– Antibiograms of the 5 first-line drugs on positive culture in a liquid medium. The antibiogram is available a few days after a positive culture has been obtained. Ideally, this test should always be ordered. When this is not possible, it should be obtained at least for the patients in high-risk groups, and particularly for smear-positive patients.

– Expanded antibiogram including second-line drugs. Results may take between 3 to 5 weeks after a positive culture has been obtained. This test should only be ordered in cases of multidrug resistance and when extensive drug resistance is suspected (Figure 2).

2. Intolerance. If on initiating standard treatment the patient presents a gastrointestinal reaction with vomiting or severe digestive disease that renders safe treatment impossible, a nonstandard regimen should be given temporarily with drugs that can be administered parenterally (Table 3). The standard oral regimen should then be gradually reintroduced and is almost always tolerated after several weeks.

3. Toxicity. Anti-TB drugs have many toxic effects, some of which are potentially very severe. This toxicity may oblige the clinician to replace standard therapy temporarily or permanently with a nonstandard regimen.

4. In certain cases, there is a strong suspicion that one of the drugs involved will cause serious problems even before treatment is started and a nonstandard regimen is prescribed at the outset.

5. Interactions. Rifampicin is the drug most likely to cause problems because it is a potent P450 cytochrome inducer that increases the metabolism and reduces the half life of many drugs taken to treat concurrent diseases. In many of these cases, nonstandard regimens should be used.

Occasionally, resistance, toxicity, and drug interactions may all occur in the same patient, enormously increasing the difficulty of finding a treatment regimen that will cure the disease.

Guidelines

Recommendations based on the experience of groups of specialists should be followed to ensure the selection of the best retreatment regimen in each case(B).[26,30]:

1. Since resistance is irreversible, a drug to which the patient is known to be resistant should never be reintroduced, and a single new drug should never be added to an ineffective regimen.

2. At least 3 drugs should always be used in the initial phase of the treatment if the antibiogram is known, or 4 if no information is available concerning the susceptibility of each component. There is no evidence to suggest that combinations of more than 4 drugs produce better results. This initial phase should be continued until either a negative sputum smear has been obtained or, when sputum samples cannot be obtained, clear clinical and radiographic improvement has been observed. In the continuation phase, treatment with 2 useful drugs should be maintained for a minimum total treatment time of 12 months when using regimens without isoniazid and 18 months when the regimen does not include rifampicin, and between 18 and 24 months when neither rifampicin nor isoniazid can be used.

3. When tolerated, high doses of isoniazid can be added to retreatment regimens because isoniazid resistance is sometimes low level and the drug may sustain a certain level of activity when the dose is increased to 450 mg/d.

TABLE 8
What Antituberculosis Drugs Are Available?

Drug Groups	Drugs	No. That Can Be Used in an NSR[a]
1. First line drug	H, R, Z, E	4
2. Injectable drugs	S, Cp, K, Ak	1
3. Quinolones	Mx, Lx, Ox, Cx	1
4. Other antituberculosis drugs	Pt, Cs, PAS	3
5. Doubtful	Clarithromycin, Cf, amoxicillin-clavulanic acid, linezolid, thiacetazone, high doses of H	6

Abbreviations: NSR, nonstandard regimen; PAS, p-aminosalicylic acid. See Table 3 for definition of remaining drug abbreviations.
[a]There are 5 groups of antituberculous drugs and only those from groups 2 and 3 can be combined in a single regimen.

4. When selecting a retreatment plan after the results of the expanded antibiogram are known, the therapeutic regimen should be selected in the following order:

– An atypical combination with first-line drugs.
– Protionamide or quinolones (moxifloxacin, levofloxacin, ofloxacin, or ciprofloxacin).
– Aminoglycosides or capreomycin.
– Cycloserine or p-aminosalicylic acid.
– Other drugs with which there is little experience (Table 8).

The second-line drugs are more toxic, more expensive, and less effective than the first-line agents and they give rise more easily to new resistance if the patient does not adhere strictly to treatment. Consequently, the guidelines recommend DOT or else fortnightly or monthly monitoring and frequent toxicity checks.[50]

Although the resistant bacilli are less virulent, extreme isolation measures should be implemented and maintained until the patient's sputum smear is negative.

Regimens with second-line drugs should only be managed by clinicians with appropriate expertise.

In certain cases, surgery should be used as an adjunctive therapy to reduce the affected area and hence bacillary density. This measure will improve the efficacy of second-line regimens when pharmacological treatment alone has failed.[51]

Treatment of Tuberculous Infection

Tuberculous infection must be treated once active disease has been ruled out (on the basis of clinical or radiographic evidence, but never pending the results of cultures once samples have been collected). The possibility of latent tuberculous infection must also be studied with a view to initiating treatment in the cases and circumstances in which it has been shown to be effective.[14] The groups that benefit most from treatment of infection are the following: *a)* patients who have recently been infected (infected contacts and patients whose skin test results have become positive within the preceding 2 years); *b)* patients with HIV infection; and *c)* patients with radiographic evidence of residual lesions who have never received treatment. Special mention is due for the case of contacts with a previously documented positive tuberculin skin test because the risk of developing active disease in such circumstances is unknown; the decision to treat in such cases should be made on a case-by-case basis (after assessment of prior treatment, the patient's susceptibility, and the level of contact in terms of the duration and intensity of exposure).[41,52] Information concerning the recent transmission history of the index case should also be taken into account in the contact study and the treatment decision, such as whether a high proportion of the contacts were infected, evidence of secondary transmission, the presence of disease in low priority contacts, infection in patients younger than 5 years of age, cases of tuberculin conversion in the contact study.[52]

Other groups of patients in whom treatment of tuberculous infection is indicated are infected patients

TABLE 9
Treatment of Tuberculosis Infection

Indications (A)
Recent infection (contacts, tuberculin conversion)
HIV coinfection
Radiographic evidence of untreated inactive tuberculosis
Primary chemoprophylaxis (treatment of uninfected exposed individuals)
Children under 5 years of age (D)
HIV infection (D)
Children and adolescents (case-by-case basis). Young adults (D)
Immunodeficient patients
Type of treatment
1. Hydrazides for 6 months as a standard regimen (A)
2. Hydrazides for 9 months
HIV infection (B)
Children (B)
Evidence of old TB lesions on chest radiograph (B)
3. Rifampicin and hydrazides for 3 months (A)
A regimen other than hydrazides for 6 months
4. Rifampicin for 4 months, in patients without HIV infection (B), and in patients with HIV infection (D)
In cases of resistance to hydrazides

Abbreviation: HIV, human immunodeficiency virus.

about to start anti-tumor necrosis factor-α treatment,[53] patients awaiting a transplant, and patients on long-term treatment with high-doses of corticosteroids.

Patients who are found to have a negative tuberculin skin test during the course of a contact investigation should be retested after 8 to 12 weeks, and treatment should be started if the result of the second test is positive. Primary chemoprophylaxis (treatment of uninfected contacts of smear-positive patients) is indicated in children under 5 years of age and HIV-positive individuals because these patients are more susceptible to developing rapid and severe TB.[41,52] In such cases, treatment should be started and the tuberculin skin test should be repeated after 8 to 12 weeks. Other young people (children up to adolescence[41] and young adults) and immunodeficient contacts could also be included the group that should receive primary chemoprophylaxis.

As far as treatment is concerned, isoniazid is the most studied and most effective drug for treating such cases.[14] The effectiveness of this drug when administered for 6 months or more has been demonstrated, although efficacy appears to increase when treatment is extended for more than 6 months (to 9 or 12 months), but this result has not been clearly demonstrated in clinical practice.[54] The optimal duration of isoniazid treatment in patients coinfected with HIV has not been defined,[55] although the normal recommendation is to extend treatment for 6 to 9 months. Another possible regimen is treatment with rifampicin plus isoniazid for 3 months; this short course has an efficacy similar to that of single-drug therapy with isoniazid and achieves better compliance.[56,57] Another alternative to isoniazid, especially when there is resistance to this drug, is a 4-month regimen of rifampicin.[14] Treatment with a combination of rifampicin and pyrazinamide for 2 months is not recommended because of the risk of side effects.[58]

Since no regimen has been shown to be effective or is recommended in contacts of patients with multidrug-resistant TB, clinical monitoring is the preferred strategy.[59]

Our recommendations based on the above evidence are shown in Table 9. Patients who start treatment for tuberculous infection must be monitored clinically until treatment is completed in case they develop side effects. Laboratory tests are not strictly necessary although we recommend that clinicians order a workup before starting treatment and at 1 month and consider repeating the tests when the patient has completed treatment. Analysis is particularly indicated in patients at high risk for side effects (patients with liver disease, alcohol problems, HIV infection). Laboratory tests must always be ordered whenever symptoms indicative of treatment-related side effects are reported.

REFERENCES

1. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med. 2002;347:1860-6.
2. Lee E, Holzman RS. Evolution and current use of the tuberculin test. Clin Infect Dis. 2002;34:365-70.
3. Miret P, Pina JM, Juncosa S. Tuberculin reactivity in bacillus Calmette-Guérin vaccinated subjects. Tuber Lung Dis. 1996;77:52-8.
4. Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. Clin Infect Dis. 1993;17:968-75.
5. Pina JM, Domínguez A, Alcaide J, Álvarez J, Campos N, Díez N, et al. La respuesta a la prueba de tuberculina en enfermos tuberculosos. Arch Bronconeumol. 2002;38:568-73.
6. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion and reversion. Am J Respir Crit Care Med. 1999;159: 15-21.
7. Lalvani A, Nagvenkar P, Udwadia Z, Pathan AA, Wilkinson KA, Shastri JS, et al. Enumeration of T cells specific for RD1-encoded antigens suggests a high prevalence of latent Mycobacterium tuberculosis infection in healthy urban Indians. J Infect Dis. 2001; 183: 469-77.
8. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. Lancet. 2000;356:1099-104.
9. Domínguez J, Ruiz-Manzano J. Prueba de la tuberculina: ¿es la hora del cambio? Arch Bronconeumol. 2006;42:47-8.
10. Domínguez J, Ruiz-Manzano J, de Souza-Galvão M, Latorre I, Milà C, Blanco S, et al. Comparison of two commercially available interferon-gamma blood tests for immunodiagnosis of tuberculosis infection. Clin Vaccine Immunol. 2008;15:168-71.
11. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007;146:340-54.
12. Richeldi L. An update on the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2006;174:736-42.
13. Horsburgh CR Jr. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med. 2004;350:2060-7.
14. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med. 2000; 161:S221-S47.
15. Korzeniewska-Kosella M, Krys J, Muller N, Blas W, Allen E, FitzGerald JM. Tuberculosis in young adults and the elderly: a prospective comparison study. Chest. 1994;106:28-32.
16. Waite S, Jeudy J, White CS. Acute lung infections in normal and immunocompromised hosts. Radiol Clin N Am. 2006;44:295-315.
17. Jones BE, Ryu R, Yang Z, Cave MD, Pogoda JM, Otaya M, et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med. 1997;156: 1270-3.
18. Geng E, Kreiswirth B, Burzynski J, Schluger NW. Clinical and radiographic correlates of primary and reactivation tuberculosis. JAMA. 2005;293:2740-5.
19. Caminero Luna JA. Guía de la tuberculosis para médicos especialistas. International union against tuberculosis and lung disease. Paris: Imprimerie Chirat; 2003.

20. Palomino JC, Cardoso Leão S, Ritacco V. Tuberculosis 2007. From basic science to patient care. Available from: http://www.tuberculosistextbook.com/tuberculosis2007.pdf
21. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. Eur Respir J. 2005;25:928-36.
22. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J. 2005;25:564-9.
23. ATS Workshop. Rapid diagnostic test for tuberculosis; what is the appropriate use? Am J Respir Crit Care Med. 1997;155:1804-14.
24. Catanzaro A, Perry S, Clarridge JE, Dunbar S, Goodnight-White S, LoBoue PA, et al. The role of clinical suspicion in evaluating a new diagnostic test for active tuberculosis: results of a multicenter prospective trial. JAMA. 2000;283:639-45.
25. Caminero JA, Casal M, Ausina V, Pina JM, Sauret J. Normativa SEPAR sobre diagnóstico de la tuberculosis. Arch Bronconeumol. 1996;32:85-99.
26. Vidal R. Tuberculosis y micobacteriosis. In: Martín Escribano P, Ramos Seisdedos G, Sanchis Aldás J, editors. Medicina respiratoria. 2nd ed. Madrid: Aula Médica; 2006. p. 899-923.
27. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167:603-62.
28. World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 3rd ed. Geneva: World Health Organization; 2003.
29. Broekmans JF, Migliori GB, Rieder HL, Lees J, Ruutu P, Loddenkemper R, et al. European framework for tuberculosis control and elimination in countries with a low incidence. Recommendations of the World Health Organization (WHO), International Union Against Tuberculosis and Lung Disease (IUATLD) and Royal Netherlands Tuberculosis Association (KNCV) Working Group. Eur Respir J. 2002; 19:765-75.
30. National Collaborating Centre for Chronic Conditions. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London: Royal Collage of Physicians; 2006. Available from: http://www.rcplondon.ac.uk/ pubs/contents/dfb1d46a-bc32-4538-b631-1d82f4b6c8aa.pdf
31. Vidal R, Rey R, Espinar A, De March P, Melero C, Pina JM, et al. Recomendaciones SEPAR. Tratamiento y retratamiento de la tuberculosis. Arch Bronconeumol. 1996;32:170-5.
32. Tuberculosis care with TB-HIV co-management: Integrated Management of Adolescent and Adult Illness (IMAI). "WHO/HTM/HIV/2007.01", "WHO/HTM/HIV/2007.308". Geneva: World Health Organization; 2007. p. 33.
33. Fujiwara PI, Clevenbergh P, Diodio RA. Management of adults living with HIV/AIDS in low-income, high-burden settings, with special reference to persons with tuberculosis. State of the Art Series. Int J Tuberc Lung Dis. 2005;9:946-58.
34. Diodio RA, Fujiwara PI, Enarson DA. Should tuberculosis treatment and control be addressed differently in HIV-infected and uninfected individuals? Eur Respir J. 2005;25:751-7.
35. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al, on behalf of the ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174:935-52.
36. Lacy CF, Amstrong LL, Goldman MP, Lance LL. Drug information handbook. 12th ed. Hudson: Lexi-Comp; 2004-2005.
37. Drugdex® System (Internet database). Micromedex® Healthcare Series (Internet database). Greenwood Village: Thomson Micromedex; 2007.
38. Jindani A, Dore CJ, Mitchison DA. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. Am J Respir Crit Care Med. 2003;167:1348-54.
39. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Morb Mortal Wkly Rep. 2005;54:1-141.
40. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Controlling tuberculosis in the United States. Am J Respir Crit Care. 2005;172: 1169-227.
41. Grupo de trabajo del área TIR de SEPAR. Recomendaciones SEPAR. Normativa sobre la prevención de la tuberculosis. Arch Bronconeumol. 2002;38:441-51.
42. Grupo de estudio del taller de 1999 de la unidad de investigación en Tuberculosis de Barcelona. Documentos de consenso sobre tratamientos directamente observados en tuberculosis. Med Clin (Barc). 2000; 115:749-57.
43. CDC. Approaches to improving adherence to antituberculosis therapy. MMWR Morb Mortal Wkly Rep. 1993;42:42-81.
44. Rodrigo T, Caylà JA, Galdós-Tangüis H, García de Olalla P, Brugal MT, Jansà JM. Proposing indicators for evaluation of tuberculosis control programmes in large cities based on the experience of Barcelona. J Tuberc Lung Dis. 2001;5:432-40.
45. Marco A, Caylà JA, Serra M, Pedro R, Sanrama C, Guerrero R, et al. Adherence to tuberculosis treatment of prisoners. Predictors of adherence to tuberculosis treatment in a supervised therapy programme for prisoners before and after release. Eur Respir J. 1998; 12:967-71.
46. Ghandi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lallo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006;368:1575-80.
47. WHO. The global MDR-TB and XDR-TB. Response plan (20072008). Geneva: WHO; 2007. Available from: http://www.who.int/tb/publications/2007/global_response_plan.pdf
48. UITB. Prevención y control de las tuberculosis importadas. Med Clin (Barc). 2003;121:549-62.
49. ERS Task Force. Tuberculosis management in Europe. Eur Respir J. 1999;14:978-92.
50. Lobo Barrero CA, Pérez Escolano E. Control y supervisión del enfermo tuberculoso. Arch Bronconeumol. 2001;38:43-7.
51. Somocurcio JG, Sotomayor A, Shin S, Portilla S, Valcarcel M, Guerra D, et al. Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. Thorax. 2007;62:416-21.
52. Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis; recommendations from the National Tuberculosis Controllers Association and CDC, and guidelines for using the QuantiFERON®-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR Morb Mortal Wkly Rep. 2005; 54(RR-15):1-55.
53. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-a treatment. Thorax. 2005;60:800-5.
54. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 1999;1:CD001363.
55. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2004;1: CD000171.
56. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis. 2005;40:670-6.
57. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45: 715-22.
58. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations United States 2001.MMWR Morb Mortal Wkly Rep. 2001;50:733-5.
59. Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev. 2006;2:CD005435.