Tuberculosis: Current issues on diagnosis and management

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Abstract

In 1993, the World Health Organisation (WHO) declared tuberculosis (TB) a global emergency and in 1996, South Africa declared TB as a priority disease.

The most effective means of controlling TB is through rapid diagnosis by direct sputum microscopy for acid fast bacilli (AFB), or culture for *Mycobacterium tuberculosis* (MTB) and prompt initiation of the correct therapy by means of the Directly Observed Treatment, Short course (DOTS) strategy.

In 1997, it was estimated that 10 million of the 30 million people infected with the human immuno-deficiency virus (HIV) worldwide were co-infected with TB. This review article focuses on TB diagnosis, including newer laboratory tests, treatment, and chemoprophylaxis. Special issues such as extra pulmonary TB, childhood TB, BCG immunisation, and the deadly alliance between TB and HIV/AIDS are also considered. Tuberculosis is a treatable disease and the aim of any family practitioner should be to treat smear positive patients as soon as possible, and cure them at the first attempt. *(SA Fam Pract 2003;45(2):38-43)*

INTRODUCTION

The twentieth century brought major advances in tuberculosis (TB) management and control i.e. BCG vaccine, effective chemotherapy, new insights into the pathogenesis of the disease, and the introduction of Directly Observed Therapy Short course (DOTS) as a formidable management tool. Yet the burden of disease continues to rise unabated worldwide. Key factors in the global TB pandemic include:

a. The deadly alliance of tuberculosis with HIV/AIDS.
b. Patients' reluctance to take chemotherapy for extended periods resulting in the emergence of drug resistant strains.
c. The ability of tuberculosis to exploit conditions of poverty.
d. Failure of public health systems to identify and manage infectious patients rapidly and appropriately.[1]

Important issues in management of the disease and control of the pandemic are early diagnosis and appropriate treatment. This article will address some of the challenges, problems, and new developments in the field of tuberculosis pertinent to the family practitioner.

PULMONARY TUBERCULOSIS (PTB)

Clinical diagnosis:

The clinical picture of cough (of greater than 3 weeks duration), night sweats and weight loss is suggestive of pulmonary tuberculosis, but many other conditions may mimic tuberculosis clinically (Table I).[2] The chest x-ray findings of upper lobe infiltration/consolidation with cavitation are supportive of a diagnosis of PTB, but are not specific. The only definitive way to diagnose PTB is by direct sputum microscopy for acid-fast bacilli (AFB), or culture for *Mycobacterium tuberculosis*.[3]

Table I: Differential Diagnosis of Pulmonary Tuberculosis

- Pneumonia: bacterial, fungal
- Bronchiectasis
- Lung abscess
- Carcinoma of the lung
- Lymphoma
- Sarcoidosis
- Kaposi sarcoma
- Lymphocytic interstitial pneumonitis

Laboratory diagnosis:

Early morning sputa should be collected prior to initiating treatment. The yield is optimal in the morning, as bacilli accumulate overnight in the lungs.[3] Two sputa on consecutive days is cost-effective, increasing the sensitivity of microscopy results, but a third sputum does not have significant diagnostic benefit. Sputum collection should be conducted outdoors or in a well-ventilated room with no people standing close by. If no sputum can be obtained and PTB is still suspected, nebulized sterile hypertonic saline may be administered. Rarely, the latter may fail and the patient may need to undergo bronchoscopy and bronchoalveolar lavage. Good quality sputum specimens are essential as saliva is not useful for diagnostic purposes. The expectoration of sputum results in droplet nuclei containing viable TB bacilli circulating in the air and possible transmission to health care workers should not be underestimated.

Direct microscopy of the sputum, using special stains for acid fast bacilli is the cornerstone of diagnosis.[4] Smear positive patients are the most infectious and responsible for spreading the epidemic, and should therefore be identified early. Although non-tuberculous mycobacteria are also acid fast, they occur rarely in Africa, and if acid-fast bacilli are found, they are highly predictive of the presence of *M. tuberculosis*. It should be emphasised that microscopy will only identify about 60% of patients with PTB, as 10,000 organisms/ml of sputa are required to achieve a positive result. Good microscopy depends on the proficiency and dedication of the microscopist and the quality of the sputum. The yield will decrease in HIV disease (cavitation is less common although there is a high bacillary load), extrapulmonary tuberculosis (paucibacillary disease), and in childhood tuberculosis.

TB culture should be requested when microscopy is negative and pulmonary TB is still suspected. When only one smear is positive for direct microscopy, a chest x-ray should be performed to look for upper lobe cavitation and consolidation, and if present, the patient should be treated for TB. Ideally, in these cases, a culture for *M. tuberculosis* should be done to confirm the diagnosis of TB. The culture of sputum is more sensitive than microscopy and the only way to demonstrate viable TB bacilli, but also more expensive and difficult to perform. *M. tuberculosis* is a slow growing organism and results are usually only available after 3-4 weeks with liquid culture or 4-8 weeks with solid media e.g. Lowenstein Jensen.[5]

Newer laboratory tests

Molecular tests

Molecular tests e.g. Polymerase Chain Reaction (PCR), and molecular probes, performed directly on specimens amplify small amounts of mycobacterial DNA or RNA and provide rapid results.[6] However, they are expensive, less sensitive than culture, particularly in smear negative patients and may give false positive results under certain conditions due to amplicon contamination. They also do not differentiate between viable and dead bacilli. A negative result does not exclude tuberculosis and all molecular tests should be supported by TB cultures. Interpretation of results performed on blood specimens using these molecular tests is particularly problematic with both false positive and negative results.

Serology:

TB antibodies in blood are neither specific nor sensitive and are not recommended for diagnosis, or for guiding management of patients on treatment.[7] A positive result may not differentiate between previous TB disease, BCG administration, exposure to environmental mycobacteria, and active TB infection. Positive results may also occur in a number of other lung diseases. Sensitivity is adversely affected by HIV co-infection and negative results do not exclude tuberculosis.

Adenosine deaminase:

This is an enzyme secreted by mononuclear cells and is increased in body fluids in a number of diseases including tuberculosis. It is a useful supportive test in the diagnosis of TB pleural effusions if the level is above 70 units, but is not a definitive test.[8] A number of other conditions may lead to a raised ADA level, and the results must be viewed in the light of clinical findings. Serum ADA levels is non-specific and should not be measured.

Treatment:

Many trials have established short course chemotherapy as the preferred treatment for PTB with at least 97% efficacy, if compliance is assured, and in the absence of drug resistance. Short course treatment depends on using the potent anti-tuberculous drugs isoniazid (INH) and rifampicin (RIF) for a 6-months in addition to a two-month initial treatment with pyrazinamide (PZA) and ethambutol (EMB).[9,10] For re-treatment patients (previous TB treatment for longer than a month, treatment failures, relapsed TB, previous interrupted treatment), a re-treatment regimen is recommended for an eight-month period

Table II: New adult patients (New smear positive and other pulmonary tuberculosis) Regimen I*

2 Months Initial Phase (treatment given 5 times a week)	**Patient under 50 kg**	**Patient over 50 kg**
Combination tablet RHZE 120/60/300/200mg	4 tabs	5 tabs
4 Months Continuation Phase (treatment given 5 times a week)		
Combination tablet RH 150/100mg	3 tabs	
Combination tablet RH 300/150mg		2 tabs

R = rifampicin; H = isoniazid (INH); Z = pyrazinamide; E = ethambutol; S = streptomycin

* *(South African National TB Control Programme, 2000)*

with streptomycin included in the initial intensive two-month phase PZA for 3 months, and 8 months of INH, RIF and EMB. The addition of pyridoxine is recommended only in patients who are severely malnourished, alcohol dependent or those patients with peripheral neuropathy.[11]

The treatment should be supervised under the DOTS programme (Directly Observed Treatment Short course) to improve compliance. All confirmed TB patients should be notified to the local health authority. TB treatment is provided free of charge by the National TB Control Programme and patients should be managed on an ambulatory basis where possible. The drugs are administered as fixed combinations of drugs to improve adherence. A *"trial of treatment"* for suspected tuberculosis, without microbiological or histological proof is not recommended, as it leads to other treatable diseases being missed, misuse of available resources and may fuel drug resistance.[9]

Side effects of TB drugs:

These occur in 3-10% of patients. The majority are minor, such as mild skin rashes and nausea and are not indications for therapy to be discontinued.[12,13,14] Severe skin rashes such as Stevens Johnson syndrome may develop in HIV co-infected patients, most commonly associated with INH therapy. A small proportion of patients will develop toxic drug-induced hepatitis and the diagnosis of this side effect is one of exclusion of other diseases e.g. viral hepatitis. Routine monitoring of liver function tests is recommended in pregnancy, in patients with underlying liver disorders, malnutrition, the elderly and in those receiving other hepatotoxic drugs.[11] The development of severe nausea, jaundice or marked abdominal pain is an indication to perform liver function tests. INH, RIF and PZA are all hepatoxic and must be stopped immediately, if the serum levels of transaminases are three times the normal. Ethambutol and streptomycin can be given in the interim with careful reintroduction of standard TB drugs, one at a time at low dosage with monitoring of transaminase levels, until they return to normal. Rarely, ethambutol administration may be associated with visual field problems and colour blindness, which are dose-related and rare at a dose of 15-20mg/kg/day. Both are generally reversible if detected early. Drug interactions between anti-TB drugs and other drugs commonly occur e.g. phenytoin and INH, antacids and INH, oral contraceptives and rifampicin, anti-retroviral drugs and rifampicin.

OTHER ASPECTS OF TB MANAGEMENT

Symptomatic relief, weight gain, and decreased coughing and night sweats, will be noted about 2-4 weeks after initiating effective treatment. Raised temperatures may persist in disseminated and extensive TB for up to 4-6 weeks, but this is not in its own right an indication for a different sequence of antibiotics, or a change in TB treatment. Cough suppressants should be avoided as they are of no benefit.[13] Patients may remain infectious in the first two weeks after starting treatment but become less infectious thereafter. PTB is generally treated on an ambulatory basis but patients must be informed about coughing procedures to prevent the spread of the disease e.g. coughing into handkerchiefs. Repeat sputum for microscopy should be performed at the end of the intensive phase of treatment – if negative, the continuation phase of treatment should be commenced.[9] If sputum is still positive, a further month of intensive phase treatment should be given. When a patient does not respond to treatment, it is important to reconsider the initial diagnosis, or consider non-compliance or drug resistant TB. Indications for performing a chest x-ray before or while on treatment include shortness of breath, haemoptysis, severe sudden chest pain, or where a pleural effusion is clinically suspected. Hospitalisation is necessary in a small percentage of patients who are clinically ill, have haemoptysis, or are incapacitated. Patients who have successfully completed TB treatment may have residual lung damage, which can present as recurrent chest infections, but this is not an indication to restart TB treatment without microbiological evidence of relapse.

SPECIAL ISSUES IN TUBERCULOSIS

Pleural effusions and TB:

TB of the pleura is an important manifestation of primary or reactivation tuberculosis.[2] The differential diagnoses include lung carcinoma, mesothelioma and parapneumonic effusions following acute bacterial pneumonia. Pleural biopsies for histology and/or TB culture are useful but are invasive techniques and not always feasible. They are still the most useful procedures for the rapid diagnosis of tuberculous pleuritis. Microscopy of pleural fluid for acid-fast bacilli is insensitive. Culture is more sensitive, but results take several weeks. The aspiration of clear serous fluid with a high ADA (of greater than 70 IU) in a patient younger than 40 years of age is suggestive of TB.[8,15] If the fluid is

Key Messages

- Tuberculosis should be suspected in any person with cough of greater than 3 weeks duration, especially if night sweats and weight loss are present.
- Many diseases mimic tuberculosis and vice versa.
- Diagnosis of pulmonary tuberculosis must be confirmed by demonstrating the causative organism in the laboratory: acid-fast bacilli on smear microscopy or *Mycobacterium tuberculosis* on culture.
- Treatment is standardised, short course (6 months) and supervised for new PTB patients.
- Multidrug resistant tuberculosis is a laboratory diagnosis: isolation of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin.
- Tuberculosis is the most common opportunistic infection in HIV infected persons.
- All children below 5 years of age in contact with patients with active PTB should receive chemoprophylaxis.
- Early diagnosis and appropriate treatment are key issues in TB control.

bloody or the ADA is lower than 70 IU, and the patient is above 40 years of age, further tests are required to exclude other lung diseases.

Extra pulmonary Tuberculosis:

The manifestations of extra pulmonary tuberculosis are diverse and any system can be affected as a result of reactivation or disseminated disease.[2,15] Children and immunosuppressed patients are particularly affected. The signs and symptoms are non-specific. Conventional microbiology may be insensitive and the essential issue is to always consider tuberculosis as part of the differential diagnosis in patients with meningitis, lymphadenopathy, and hepatosplenomegaly. Tissue specimens should always be submitted where possible for mycobacterial culture as well as histology.

Non-tuberculous mycobacteria (NTM):

(Synonyms: atypical mycobacterial species, mycobacteria other than tuberculosis (MOTTS)). These mycobacteria are generally less virulent than *M. tuberculosis* and person-to-person transmission has not been documented.[15,16] They are environmental bacteria, found in soil and water. Diagnosis can be difficult because isolation of a NTM in a specimen from a non-sterile site may indicate contamination of the specimen from environmental sources, colonisation (especially of old TB cavities), or a true pathogen. Repeated isolation, absence of other pathogens, and a compatible clinical, radiological or pathological picture suggest a true pathogen. NTM are generally resistant to standard TB drugs and specific multi-drug treatment regimens are recommended dependent on the species isolated (and not on susceptibility testing). Clinical syndromes of NTM include lymphadenitis (*M. scrofulaceum*), pulmonary infections, (*M. kansasii* in miners), bronchiectasis in middle-aged women (*M. avium* complex - MAC), cutaneous infections (*M. marinum*) and disseminated disease (MAC in advanced HIV).

HIV and tuberculosis:

Approximately fifty percent of new adult cases of tuberculosis in South Africa are co-infected with HIV.[17] TB is the commonest opportunistic infection in patients with HIV/AIDS. Tuberculosis results from progressive primary disease, reactivation of a dormant focus (8-10% annual risk), or re-infection from an exogenous source. Tuberculosis may occur early in HIV disease when the immune system is relatively intact, and is often the first indication of an underlying immune problem.[2,18] Disease manifestations are dependent on the level of immune suppression, with characteristic upper lobe cavitations initially, pleural effusions and lymphadenopathy as immunity wanes, extra-pulmonary disease, disseminated (miliary) disease and atypical lung pathology with lower lobe consolidation late in HIV disease.[19]

The sensitivity of sputum microscopy and culture is diminished when atypical lung pathology is found, but is good early in HIV disease with cavitary PTB. Standard short course treatment is currently recommended, but may be prolonged in patients who show delayed bacteriological or clinical responses. Post-treatment prophylaxis is not currently recommended. Mortality is higher when compared to non-HIV infected patients with TB and may be due to other opportunistic infections or tuberculosis itself. A number of drug interactions are noted between rifampicin and anti-retroviral drugs, notably the protease inhibitors and non-nucleoside reverse transcriptase inhibitors and treatment modifications are then required. Chemoprophylaxis using six months of isoniazid has been shown to be successful in preventing TB in HIV positive patients who are tuberculin skin test positive. It is critical to exclude active TB before initiating prophylactic therapy.

Multidrug Resistant Tuberculosis (MDRTB):

MDRTB is defined as tuberculosis due to *M. tuberculosis* that is shown in the laboratory to be resistant to at least isoniazid and rifampicin - the two most powerful anti-TB drugs.[2] MDRTB is a "man made" problem and preventable by ensuring compliance with standard multidrug regimens. A person may be primarily infected with MDRTB strains from contact with patients with MDRTB, secondary to an inadequate drug regimen or as a result of poor adherence to standard therapy. About 1% of new cases of TB in South Africa and 4% of retreatment cases are MDRTB.[20] MDRTB should be suspected in a patient who fails to respond to therapy clinically and is microbiologically positive after 2 months of treatment, in patients who relapse, contacts of known MDRTB patients, non-compliant patients, and specific risk groups like Health Care Workers and Prisoners.

Patients who fail to respond to TB treatment because they were misdiagnosed in the first instance, should not be misdiagnosed as MDRTB. Sputum must be submitted for culture and susceptibility, to confirm the diagnosis. The treatment is complex, expensive and often toxic and should be undertaken by designated specialized centres. A multidrug regimen is administered for 18 months and drugs include amongst others ethionamide, the quinolones and kanamycin.[21] Treatment success rates are low i.e. in the region of fifty percent (unpublished data: Blumberg L).

Infection control and TB:

Smear positive PTB patients are most infectious, while smear negative PTB patients are less infectious. Early diagnosis and the institution of appropriate therapy is the best way to control the spread of the disease. With appropriate treatment, infectiousness will rapidly decrease in compliant patients, usually by the 14th day of treatment. Since infection may rapidly progress to disease, all children less than five years of age in close contact with a patient with PTB should be given chemoprophylaxis after exclusion of TB symptoms.[9] Contacts over five years should be followed for symptoms of PTB and be investigated should these arise. Routine CXR of these contacts, and skin testing is not recommended. In a health care setting, high-risk procedures for transmission include sputum collection, physiotherapy and nebulization.[22] Surgical facemasks do not offer protection to the health care worker performing any of these procedures, but specialised industrial dust masks offer some protection.

Childhood tuberculosis:

If children less than four years of age are infected with MTB, they may present with an exaggerated response to the primary infection: hilar lymphadenopathy with hoarseness, lobar collapse and wheezing.[9,23] Progressive primary pneumonia may occur, and there is the risk of extra pulmonary disease especially meningitis or disseminated disease in the weeks or months following infection. Childhood tuberculosis should be suspected in those with failure to thrive, chronic cough or pneumonia unresponsive to broad-spectrum antibiotics. The diagnosis of childhood tuberculosis is difficult as signs and symptoms are non-specific and the chest x-ray film is helpful but not specific. Supportive findings are hilar lymphadenopathy and bronchopneumonia, but cavitation is rarely seen. When in doubt, it is advisable to seek a second opinion from a paediatrian experienced in childhood TB. Childhood pulmonary tuberculosis is paucibacillary and therefore conventional microbiology is insensitive and sputa collection rarely successful. Tuberculin skin testing is a useful additional diagnostic tool for TB infection in children. If tuberculosis is suspected, it is important to enquire about a TB contact in the close environment, request a CXR, a tuberculin skin test and consider submission of three gastric aspirates for TB culture.

Tuberculin Skin Test:

The Tuberculin Skin Test (TST) has a role to play in the diagnosis of TB in children less than five years of age and for monitoring health care workers exposed to TB, but has virtually no role in the diagnosis of TB in adults in South Africa.[9,23,24] While a TST cannot differentiate between TB infection and TB disease in children, a positive test is likely to indicate recent infection, and a high risk of progression to active disease. The most reliable test is an intradermal Mantoux test using 0.1ml (5IU) purified protein derivative, which is read and interpreted according to the national guidelines.[9] The Monospot and Tine tests, although easier to perform are less reliable. The TST should be interpreted in the light of the clinical findings, exposure to TB cases, and previous BCG immunization. A negative TST does not exclude TB. Malnutrition, depressed cell mediated immunity, intercurrent viral disease, and disseminated TB may result in a negative TST in children with active TB.

Immunization against TB:

The current BCG vaccine is a live attenuated strain of *Mycobacterium bovis*. In South Africa, BCG is recommended at birth (or first contact with health services) and the World Health Organization does not encourage revaccination. Only symptomatic HIV infection or immunosuppression from other causes are contraindications for BCG administration. BCG is considered to provide appreciable protection against tuberculous meningitis and miliary disease, but not against TB infection.[25] A wide range of efficacy estimates (0-80%) exists for protection against adult pulmonary tuberculosis. In South Africa, intradermal BCG, which is more immunogenic, is now used. After its administration a scar remains in most cases and is a useful, though imperfect, indication of past BCG vaccination. Local injection-site abscesses may occur, typically as a result of an improper injection technique when the vaccine is administered into the subcutaneous layer of the skin. There may be resulting local or regional lymphadenopathy and systemic BCG-osis is a recognized but rare consequence. Most local reactions will heal without treatment. Management of local BCG complications is controversial.[26]

CONCLUSION

An effective TB control program requires early identification and effective treatment of persons who have active TB. The only definitive way to diagnose PTB is by direct sputum microscopy for acid-fast bacilli or culture for *Mycobacterium tuberculosis*. The treatment of new patients with PTB and HIV involves the use of proven anti-TB drugs for the recommended six-month duration. It must be noted that MDRTB is a "man made" problem that should be prevented by all family practitioners managing tuberculosis in their practices.❐

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