Guidelines for Tuberculosis Control in New Zealand 2010
Chapter 2: Clinical Features, Investigation and Assessment of Active Tuberculosis Disease
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Summary

This chapter gives a summary of the definitions of different states of TB infection, and an overview of the clinical features of active TB disease. The investigation of TB disease is also described. For a more comprehensive account, a list of further reading is supplied at the end of this chapter.

The most important aspect of making a diagnosis of active TB disease is to maintain a high clinical suspicion, especially in patients recently exposed to TB and with previous prolonged residence in a high incidence TB country, especially if they have recently arrived in New Zealand. The demographics of TB in New Zealand must be borne in mind, and are described fully in Chapter 1.

Active TB disease may be asymptomatic, but common systemic symptoms include fever, night sweats, weight loss, anorexia and malaise.

Pulmonary TB is the most common form of active TB, and is often present in those with extrapulmonary TB. Common symptoms include cough (initially non-productive) and haemoptysis. Chest pain may accompany pleural involvement and breathlessness may occur late when disease becomes extensive. Clinical signs are often few. Characteristically, upper lobe or apical lower lobe changes occur on chest X-ray, although overall chest X-ray changes are not specific and may not predict disease activity. Rapid diagnosis of pulmonary TB is essential as such patients are often infectious to others.

The most common form of extrapulmonary TB is lymphadenopathy, most commonly presenting in the cervical or mediastinal regions. Nodes may enlarge even during or after completion of successful treatment. Pleural TB is the next most common form and may present with chest pain or breathlessness, and without obvious pulmonary TB. Abdominal TB is often associated with prominent systemic symptoms and weight loss. Peritoneal or ileo-caecal disease are most common. Liver function tests may be abnormal due to presumed hepatic granulomatous inflammation.

Central nervous system (CNS) TB causes significant morbidity and mortality, and diagnosis is often delayed. Meningitis or focal signs and reduced conscious level may occur. Pericardial TB may also lead to permanent morbidity from constrictive pericarditis. Genitourinary TB is often silent and may thus cause renal impairment, bladder damage, or infertility. TB may also affect the larynx, eye, or endocrine organs. Finally, disseminated or miliary (blood borne) TB is a life threatening condition with the potential for serious morbidity and mortality.

Investigation for TB still relies on chest X-ray and examination of appropriate specimens for AFB smear, mycobacterial culture and the histological hallmark of necrotising granulomatous inflammation. Specimens may be obtained via sputum induction, bronchoscopy, fine needle aspiration and biopsy. Imaging such as CT, ultrasound or endobronchial/endoscopic ultrasound may help to guide needle aspiration. Despite newer laboratory techniques, TB culture still takes time so PCR techniques may provide additional more rapid information. Tuberculin skin testing and interferon gamma release assays may provide supportive evidence for a diagnosis of active TB in appropriate clinical settings.
Introduction

Primary pulmonary TB infection is usually asymptomatic. The only sign that infection has occurred is the conversion of the tuberculin skin test (TST) or interferon gamma release assay (IGRA) to positive (see Chapter 8). Occasionally, erythema nodosum (a characteristic skin rash) may occur during TST conversion, as may mediastinal lymphadenopathy as part of the primary TB complex. Development of subsequent TB disease only occurs in approximately 10% of otherwise healthy individuals, and the risk is highest early, in the first two years after primary infection.

‘Latent TB infection’ (LTBI) is the term used to describe a TST or IGRA positive individual who is asymptomatic with no signs of TB disease, and from whom TB organisms cannot be cultured. It is usually thought that such individuals harbour dormant or inactive TB organisms, although this is controversial. Such persons have normal or only trivial changes on chest X-ray, such as a small scar or patch of calcification.

The phrase ‘Inactive TB’ is sometimes used to refer to individuals with LTBI who have more extensive chest X-ray abnormalities, but who are found not to have evidence of active TB. Dependent on the extent of changes, such individuals are usually treated with a regimen as for active disease (see Chapter 3), as it is assumed they have a heavier burden of ‘dormant’ tubercle bacilli.

‘Active TB disease’ refers to individuals with evidence of replicating TB organisms, demonstrated either by smear and culture, or by histological evidence of characteristic granulomatous inflammation, or by other suggestive tests. Active TB may be asymptomatic particularly in the early stages of disease, but the usual clinical features are described in this chapter.
1 General Symptoms

The demographics of TB in New Zealand are presented in Chapter 1, and should be borne in mind when assessing patients with possible TB in New Zealand.

It is very important to maintain a high index of suspicion to make a diagnosis of TB. TB disease should always be considered in individuals with a history of contact with TB, or with previous prolonged residence in high-TB incidence countries, especially in those recently arrived in New Zealand.

TB may be asymptomatic until the condition is advanced. However, common systemic symptoms include malaise, fever, anorexia, weight loss and night sweats.
2 Pulmonary Tuberculosis

Pulmonary TB is the most common presentation of TB both worldwide and in New Zealand.

2.1 Symptoms

Active pulmonary TB may be asymptomatic initially, but as the extent and severity of the disease progress, symptoms appear. Cough is usually dry initially but may subsequently become productive. Haemoptysis may also occur, particularly in cavitatory disease, but may also occur in inactive (past) TB with bronchiectasis. Breathlessness is a late feature when parenchymal destruction or pleural effusion has occurred. Pleuritic chest pain may also occur in pleural TB.

Characteristically, TB causes few clinical signs on chest examination despite extensive radiological abnormality. Abnormal chest signs are usually the result of lung fibrosis, cavities or pleural disease.

A multivariate analysis described symptoms associated with culture positive TB in patients presenting with respiratory disease: the presence of TB risk factors and symptoms (odds ratio (OR) 7.9); a high temperature (OR 2.8); and upper lobe changes on chest X-ray (OR 14.6). The following were negatively correlated with active TB: shortness of breath (OR 0.2) and crackles on clinical examination (OR 0.29).

Endobronchial TB is uncommon, but it is important because it may result in tracheal or bronchial stenosis, which may be misdiagnosed as asthma or lung cancer. The incidence of involvement of the bronchial tree in pulmonary TB is unknown.

2.2 Chest X-ray appearances

Opacities are often seen apico-posteriorly in the upper and, albeit to a lesser extent, the apical segment of the lower lobes. As the disease progresses, there is more extensive consolidation and cavities develop, which then usually implies that the condition is infectious. Cavity formation is uncommon in primary TB. It is often seen in ‘reactivation’ TB where a heightened immune host response is more likely to occur. Vascular involvement is common in areas of active TB, and endarteritis obliterans may result in necrosis and cavity formation. Rupture of a vascular aneurysm (so-called Rasmussen's aneurysm) in the wall of a cavity may result in life-threatening haemoptysis.

A ‘miliary pattern’ describes the chest X-ray appearance of tiny, evenly distributed nodules. This pattern represents haematogenously disseminated TB.

Atypical or diminished chest X-ray appearances are seen in conditions associated with varying degrees of immunosuppression such as diabetes and HIV/AIDS.

Section 4.2 discusses the chest X-ray changes of TB in more detail. Pleural and mediastinal nodal disease are classified as extrapulmonary TB (see below).
3 Extrapulmonary Tuberculosis

3.1 Lymph node TB

In adults, TB is the most common mycobacterial cause of adenopathy in the neck and supraclavicular regions. In countries with low TB prevalence, mycobacteria other than tuberculosis are a more common cause of mycobacterial adenopathy in children.9 Women are more predisposed to develop TB adenitis than men (a ratio of 2:1), and TB occurs more commonly in non-Caucasians.

TB adenitis can involve any lymph node group. Mediastinal TB adenitis is commonly associated with extensive or severe local pulmonary TB. TB adenitis is often painless, but acute inflammation and pain can occur. Characteristically, nodes lack redness and warmth and are firm and discrete initially, but may become fluctuant as necrosis develops.

The progress of tuberculous adenitis can be unpredictable during treatment. Involved nodes may regress and disappear, or expand, develop into a lymph node abscess, and spontaneously perforate. The node perforation may cause a discharge onto the skin or, in the case of mediastinal nodes, into the mediastinum or one of its structures, a bronchus or the pleural space. Sometimes lymph nodes increase in size during treatment or even after completion of TB treatment. This is sometimes referred to as a paradoxical upgrading reaction.10,11

3.2 Pleural TB

Tuberculous pleuritis is the second most common form of extra-pulmonary TB. In two-thirds of cases, the onset of tuberculous pleuritis is acute. Tuberculous pleuritis occurs more commonly in adults than in children with TB.

A lymphocytic, exudative effusion is characteristic of tuberculous pleuritis, but initially neutrophils may predominate. TB requires exclusion in any lymphocyte-predominant exudative pleural effusion. A tuberculous empyema with the presence of frank pus on pleural aspiration may develop later in the course of pleural TB. This is uncommon, and a tuberculous empyema necessitatis (rupturing through the chest wall or into the lung) is now rare in Western countries.

3.3 Skeletal TB

Skeletal TB occurs in older people in developed countries, but is more common in younger people in other countries. Any bone or joint may be affected, but TB of the spinal vertebrae (Pott’s disease) is the most common. The collapse of bone may produce pain and kyphotic deformity, and the infection may spread locally (eg, paravertebral abscess formation) and then track through tissue planes to emerge as a lump or sinus at a more distant site.

Skeletal TB is often an insidious, late complication of lympho-haematogenous spread from unrecognised primary pulmonary disease. Delay in the diagnosis is common because of the often mild, chronic, non-specific nature of the symptoms.
3.4 Abdominal tuberculosis

Abdominal TB may present in peritoneal, enteric, hepatic and biliary forms. Systemic symptoms of weight loss, malaise and fever are prominent in this form of TB.

Peritoneal TB is the most common form of intra-abdominal TB. Peritoneal TB may follow the rupture of a small caseous peritoneal focus that has developed after haematogenous spread during primary infection. Peritoneal TB may also develop after the rupture of a larger focus within an abdominal viscus or lymph node. Symptoms of peritoneal TB are often insidious, with abdominal pain and systemic symptoms of TB. Occasionally, peritoneal TB presents as an acute abdomen. Ascites and omental thickening are common. Pleural effusion and pulmonary TB are commonly present. Tuberculous peritonitis is an occasional complication of peritoneal dialysis.12

Enteric TB may involve any part of the gastro-intestinal tract, but is most common in the ileo-caecal and ano-rectal regions. Abnormal liver function tests are commonly found in association with extensive TB, and usually settle within two weeks of the treatment starting. It is often uncertain whether this is due to tuberculous involvement of the liver – hepatic TB – or non-specific hepatotoxicity caused by the major infection. Hepatomegaly and upper abdominal pain and tenderness can occur. Biliary involvement may present with obstruction of the biliary tract by lymph node enlargement at the porta hepatis.

3.5 Genitourinary TB

Genito-urinary involvement in TB usually presents many years after haematogenous dissemination at the time of primary tuberculosis.

Renal TB is often silent, and systemic symptoms are uncommon. A finding of sterile pyuria should lead to sending of three early morning urine samples for TB culture. Renal tract involvement is more easily detected by intravenous urogram (or CT IVU) than by ultrasound. Later symptoms may include haematuria, dysuria or loin pain. If untreated, renal TB may lead to unilateral renal destruction, due to direct involvement of the kidney or indirectly from ureteric stenoses. TB cystitis is uncommon, but may cause dysuria and frequency. Bladder wall inflammation and then fibrosis may lead to permanent loss of bladder capacity.

Male genital TB may present as a cold abscess in the testicle or prostate, but epididymitis with local thickening is more common.

Female genital TB is often asymptomatic but menorrhagia may be reported. Female genital TB may involve the distal salpinges, ovary or endometrium, and is a cause of infertility, particularly in women in developing countries.

3.6 Neurological TB

TB can involve any part of the nervous system. TB meningitis in children is most common in children aged between six months and five years. TB meningitis tends to occur in adults who are elderly or partially immunosuppressed.
The onset of TB meningitis is often insidious and follows three stages of progression:

- **Stage 1**: low-grade fever, irritability and personality change.
- **Stage 2**: in association with raised intra-cranial pressure, meningitis, seizures and cranial nerve palsies (third, sixth and seventh).
- **Stage 3**: high fever, stupor and coma commonly followed by brain stem herniation and death. Even with chemotherapy, the mortality rate is high in this stage of the disease.

A review of 104 cases of TB meningitis at Auckland Hospital has recently been published. This review demonstrated that 36% of cases had a poor neurological outcome, and 12% were left with moderate disability. The diagnosis of TB meningitis and subsequent institution of treatment was sometimes delayed: the most common reasons were:

1. presentation with mild symptoms wrongly attributed to a systemic infection
2. incorrectly attributing CSF abnormalities to non-tuberculous bacterial meningitis
3. failure to diagnose extraneural tuberculosis associated with meningitis.

Unfortunately, delayed diagnosis leads to increased morbidity. Maori, Pacific and Asian patients were over-represented in the series compared to their proportion in the general population, emphasising that a high index of suspicion in high risk cases is very important. The most common presenting symptoms were headache (69%), fever (69%), altered mental state (58%) and drowsiness (28%). Non-specific symptoms such as nausea/vomiting, anorexia, lethargy, weight loss and cough were present in 35 to 61% of cases. More severe symptoms such as seizures, limb weakness and diplopia were present in less than 20%. The most common physical signs were fever (83%) and neck stiffness (69%). Mental state was abnormal in 65% of patients, but focal signs occurred in less than one-third – intra-cerebral tuberculomas are uncommon and may be asymptomatic or produce focal signs; they may progress to form a brain abscess.

Involvement of the ear in TB is rare.

Ocular involvement may occur in any part, but the cornea and choroidae are most commonly affected. The role of TB in eye disease is an evolving area, and it has been suggested that entities such as relapsing anterior uveitis and ocular vasculitis may be related to TB infection or an immunological reaction to TB infection. In such cases, treatment for TB is sometimes considered in addition to local or systemic corticosteroid therapy. Consultation with an ophthalmologist with a special interest in TB eye disease is advisable.
3.7 Cardiovascular TB

Cardiovascular TB is rare, but pericardial involvement is the most common. Tuberculous pericardial effusion usually occurs in extensive disseminated disease and should be considered when there is a substantial tuberculous pleural effusion or when cardiomegaly is present in active TB. A lymphocytic, exudative pericardial aspirate should be considered due to TB unless proven otherwise. Signs of pericardial effusion include oedema, pulsus paradoxus, raised venous pressure and hypotension with a narrow pulse pressure. The role of oral steroid treatment is discussed in Chapter 3. Constrictive pericarditis can be a late complication of TB pericarditis and presents with oedema, ascites and breathlessness.

3.8 Other forms of extrapulmonary TB

TB laryngitis usually accompanies extensive, cavitatory pulmonary TB, but isolated TB laryngitis may occur. TB laryngitis is a form of infectious TB with a normal chest radiograph. A cough, voice change and (later) throat pain are the main symptoms.

Isolated infiltration of the skin by tuberculous disease is uncommon and skin involvement is more often the result of the extension of TB osteomyelitis or the end of a sinus tract from another more deeply seated focus.

Endocrine involvement by TB includes adrenal, pituitary and thyroid TB. Adrenal TB usually occurs during haematogenous dissemination; adrenal insufficiency is uncommon as most of the adrenal tissue must be destroyed. Pituitary tuberculosis is rare, but hypopituitarism has been observed years after recovery from TB meningitis in childhood. This suggests that its involvement may be silent and easily overlooked during childhood TB meningitis. Thyroid TB is rare.

3.9 Disseminated and miliary TB

Disseminated TB involves multiple body systems and results from acute haematogenous spread. Disseminated TB occurs in about 3% of non-HIV TB cases in Western countries. 16 Disseminated TB carries an overall mortality rate as high as 38%, but the absence of miliary changes on the chest radiograph, in the presence of multi-system TB, is associated with a mortality rate of around 85%. Malnutrition is common in people with severe or extensive TB.

Miliary TB is the presence of multiple, small and uniformly-sized (usually less than 2 mm in diameter) nodules of active TB throughout the body. 17 All miliary TB is disseminated TB, but not all disseminated TB is miliary TB.
4 Investigation of Tuberculosis

This section describes clinical investigation for active TB disease. Techniques to assist with the early diagnosis of TB are also considered. The extent and severity of TB should always be documented as part of the clinical assessment. Investigation for latent TB infection (LTBI) is described fully in Chapter 8.

4.1 Introduction

Clinical investigation for TB initially requires a comprehensive history and physical examination. Important initial tests are a chest X-ray (CXR) and an examination of sputum or other specimens for acid-fast bacilli (AFB) and mycobacterial culture. A Mantoux test or an interferon gamma release assay (IGRA) may also be required.

4.2 Chest X-ray

Chest X-ray (CXR) is an essential test whenever TB is considered. Active pulmonary TB cannot reliably be ascertained by CXR features alone, but changes on a CXR may be suggestive.

An outline of common CXR features is shown in Table 4.1.18

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Favour active tuberculosis</th>
<th>Favour inactive tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Consolidation, variable size:</td>
<td>Linear scarring</td>
</tr>
<tr>
<td></td>
<td>• unifocal, commonly</td>
<td>Dense scarring</td>
</tr>
<tr>
<td></td>
<td>• ‘soft’, ‘fluffy’ areas with poorly defined margins</td>
<td>Volume loss</td>
</tr>
<tr>
<td></td>
<td>Cavities</td>
<td>Destroyed lobe or lung</td>
</tr>
<tr>
<td></td>
<td>Nodules:</td>
<td>Calcification</td>
</tr>
<tr>
<td></td>
<td>• focal, non-calcified; or</td>
<td>Nodules, calcified (tuberculomas):</td>
</tr>
<tr>
<td></td>
<td>• miliary pattern</td>
<td>• Ghon focus (scar from primary infection)</td>
</tr>
<tr>
<td>Mediastinum and hilar</td>
<td>Lymphadenopathy* – hilar and/or paratracheal</td>
<td>secondary (Simon) foci</td>
</tr>
<tr>
<td>Pleura</td>
<td>Pleural effusion/empyema</td>
<td>Pleural thickening:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• basal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• apical (irregular, &gt; 1 cm thickness)</td>
</tr>
</tbody>
</table>

Notes:
* Lymphadenopathy is very common in paediatric tuberculosis (TB).
Most of these chest X-ray features are not specific to TB.
High-resolution chest CT (computed tomography) is more sensitive at detecting cavities, lymphadenopathy, the factors contributing to ‘apical fibrosis’, and post-TB complications such as bronchostenosis and bronchiectasis.
4.2.1 Radiological criteria for induced sputum testing and bronchoscopy

The usual decision-making process is shown in Table 4.2, but the action taken for an individual case may vary, depending on the patient’s age and the presence or absence of risk factors for reactivation of disease.

Table 4.2: Radiological criteria for detailed mycobacteriological tests∗

<table>
<thead>
<tr>
<th>Chest X-ray shows</th>
<th>Do sputum (three times) (or bronchoscopy and broncho-alveolar lavage)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>No (except that in HIV-positive patients the chest X-ray in tuberculosis may be normal)</td>
</tr>
<tr>
<td>Calcified lymph nodes or pleura, with normal parenchyma</td>
<td>No</td>
</tr>
<tr>
<td>Minor apical pleural thickening only</td>
<td>No</td>
</tr>
<tr>
<td>Single granuloma less than 10 mm</td>
<td>No</td>
</tr>
<tr>
<td>Minor lobar scarring or several tiny less than 3 mm) dots of calcification</td>
<td>Yes</td>
</tr>
<tr>
<td>Larger focal areas of scarring</td>
<td>Yes</td>
</tr>
<tr>
<td>Possible patchy consolidation or infiltration</td>
<td>Yes and consider transbronchial lung biopsies</td>
</tr>
<tr>
<td>Definite infiltration or consolidation or cavitation</td>
<td>Yes and consider transbronchial lung biopsies</td>
</tr>
</tbody>
</table>

Notes:
∗ Induced sputum is the preferred procedure.
† Tests shown are for subjects at risk of tuberculosis who have no sputum or little sputum that is smear- or culture-negative.

A chest X-ray which is normal or lacks the typical features of TB makes a diagnosis of TB unlikely,19–21 and invasive tests for TB are unlikely to yield positive results. If TB remains strongly suspected, a repeat film should be obtained 2–3 weeks later. Immunocompromised or patients with HIV infection may have active TB in the presence of a normal chest X-ray or minor/atypical chest X-ray changes, and so immediate sputum testing is justified.

When inactive/fibrotic-type changes are seen on a chest X-ray, they should not be attributed to inactive TB unless detailed mycobacteriological testing for active pulmonary TB has been performed, or previous chest X-rays show that the abnormalities have been stable for at least six months, or up to two years if marked. This is of particular relevance in assessing candidates for ‘immigration clearance’ (see Chapter 10).

It is strongly recommended that subjects undergoing investigation for active pulmonary TB are kept in isolation until disease activity and smear status are determined.

4.2.2 Chest X-ray in extra-thoracic tuberculosis

TB pleural effusion is classified as an extra-pulmonary form of TB. The CXR appearance of the lung parenchyma is often normal in active pleural TB. Of 129 cases of TB pleural effusion in a Spanish study, 76% were considered primary, and the lung fields were thus normal.22 In Malaysia, 61% of 54 cases of TB pleural effusion had no CXR evidence of parenchymal disease.23
An abnormal chest radiograph is common in patients with other forms of extrapulmonary TB. CXR suggests current or past intra-thoracic TB in patients with extra-pulmonary TB in:

- 44–69% with meningitis\textsuperscript{24–26}
- 16–44% with superficial lymph node disease\textsuperscript{27–29}
- 26–50% with bone or joint disease\textsuperscript{26,29}
- 8–75% with genitourinary disease\textsuperscript{26,30,31}
- 32–78% with peritoneal or abdominal TB\textsuperscript{26,32–38}

A normal CXR does not exclude extrapulmonary TB, and testing for this should be pursued if there are suggestive systemic or site-specific symptoms.

4.3 Tuberculin skin test or interferon gamma release assay

The Mantoux test is the form of tuberculin skin test (TST) carried out in New Zealand. TSTs and interferon gamma release assays (IGRAs) are primarily tests for TB exposure and LTBI. They are required only for assistance in the diagnosis of active TB, if culture or histology are negative or inconclusive. These tests are described fully in Chapter 8.

TST and IGRAs are not needed if the diagnosis of active TB has been made or is likely to be easily confirmed (e.g., the CXR is strongly suggestive of infectious TB and the person has a cough and sputum). They should not be performed again if a previous TST or IGRA from within the last month is available, or if the person is known to have had a strongly positive TST reaction or has been treated for TB in the past (see Chapter 8).

Positive TST and IGRA results do not distinguish between active TB disease and LTBI. In addition, false negative TSTs and IGRA may occur in patients with active TB disease (up to 30% in patients with TB pleuritis in one previous series).\textsuperscript{39} False positive TSTs may also occur in patients with previous BCG vaccination or exposure to non-tuberculous mycobacteria (NTMs); the risk of false positives in this setting is less with IGRAs. The magnitude of the TST reaction does not predict the likelihood of current active TB disease.\textsuperscript{40} Therefore a positive TST or IGRA may help to support a diagnosis of active TB in appropriate clinical circumstances, but is never conclusive.

4.4 Sputum microscopy and culture

Three (preferably early morning) sputum specimens should be sent for TB testing. In general, all three samples are processed for both smear and culture.

Sputum samples may be incubated in a variety of media (see Chapter 11). Gene probes for \textit{M. tuberculosis} or MAIC may be applied to culture positive samples, to help provide early identification of TB or non-tuberculous mycobacteria. Probes for mutations conferring drug resistance are now available.
Polymerase chain reaction (PCR) for TB is also available (see Chapter 11). A positive result is useful as false positives are relatively rare. However, a negative result does not exclude active TB and so any sample on which PCR is performed should always be sent for TB culture. TB PCR is most commonly performed on nodal aspirates, pleural fluid or biopsies and cerebrospinal fluid (CSF).

4.5 Induced sputum

With induced sputum tests, a patient inhales a mist of 3–4% hypertonic saline (through a mouthpiece or face mask) generated by an ultrasonic nebuliser. Although specimens often appear more watery than sputum, these are acceptable for testing. Induced sputum testing has been shown to be more sensitive than bronchoscopy in the diagnosis of pulmonary TB in subjects who are sputum smear-negative.41 The procedure has a very high level of patient safety and acceptability.

Induced sputum testing for TB is a useful technique, with the following precautions. Respiratory isolation conditions are needed. The procedure must never be carried out in an open clinical area. Infected aerosols persist for a long time in a single room that is not equipped with an air extraction plus a high-efficiency particulate attenuation (HEPA) filtration system (see Chapter 11).

The principal patient safety concern is precipitating worsening of air-flow obstruction. Nebulised bronchodilator should precede the hypertonic saline in people with asthma and chronic obstructive pulmonary disease.

Patients must be supervised by a person who has experience with the procedure. Nursing or physiotherapy expertise is needed to optimise sputum elimination and collection. Staff must wear suitable face masks (see Chapter 11).

4.6 Bronchoscopy

Induced sputum is better than bronchoscopy for the diagnosis of active pulmonary TB.

4.6.1 Broncho-alveolar lavage

Expert opinion is that broncho-alveolar lavage (BAL) produces a better yield than ‘bronchial washings’ (the latter using 20–40 ml of lavage fluid), and should therefore be used at bronchoscopy. However, studies have not formally addressed this issue.

4.6.2 Preventing bronchoscopic transmission of tuberculosis

Bronchoscopy carries a greater risk of nosocomial infection from M. tuberculosis than induced sputum testing does, provided the latter is performed in respiratory isolation conditions. When bronchoscopy is performed where TB is a possible diagnosis, a room that meets TB isolation ventilation requirements should be used (ie, equipped with HEPA filtration air conditioning and, ideally with negative pressure).42,43 When TB isolation ventilation requirements are not available, a portable HEPA filter can be used. The efficacy of HEPA filters is discussed in Chapter 11.
The bronchoscopist and assistants must wear N95 masks, which limit the inhalation of droplets containing TB, when TB is a possible diagnosis (see Chapter 11). Bronchoscopes must be cleaned carefully to prevent the cross-contamination of specimens and cross-infection of patients with *M. tuberculosis*.

4.6.3 Indications for bronchoscopy

Bronchoscopy may be required, preferably when the diagnosis of TB has been made and infectious potential has been reduced or removed by treatment, in four circumstances.

- Intra-thoracic cancer needs exclusion.
- Endobronchial or endo-tracheal TB is possible (see section 2.1).
- Transbronchial lung biopsy is required because of lung infiltrates that are not typical of TB.
- Miliary changes are present, and sputum and induced sputum are smear-negative for AFB. In this situation, if there are risk factors for drug resistance or other differential diagnoses need exclusion, BAL and transbronchial lung biopsy should be done, provided there is no major contraindication.

Tissue should be sent separately in formalin for histology and in saline for TB culture.

4.7 Urine microscopy and culture

Do not perform urine mycobacterial culture unless sterile pyuria is present. There are multiple causes of sterile pyuria so the investigating clinician, whilst considering the possibility of tuberculosis, should also consider investigating and eliminating other common causes first.

Urine microscopy should be a routine test when TB is suspected or active TB needs to be excluded. In people with no urinary tract or abdominal symptoms, sterile pyuria, with or without red blood cells, is the main indication to proceed to early morning urine (EMU) TB tests. TB urine cultures are expensive, so should not be performed on the basis of a single abnormal midstream urine (MSU) test. In miliary TB, EMU tests may be culture positive without an anatomical urinary tract abnormality. EMU may be the only source of positive culture, especially in children.

MSU containing more than 20 white or red cells requires a repeat MSU test. If the abnormality persists, other causes should be excluded (eg, schistosoma serology in people who have resided in endemic areas) before performing urine TB cultures.

If the MSU is abnormal from an obvious cause (eg, menstruation or a bacterial urinary tract infection), repeat the MSU test once the condition has had time to resolve.

Sterile pyuria is also an indication for an intravenous urogram (IVU) or CT IVU, looking especially for urinary tract stenoses and other features of urinary tract TB. An IVU is often superior to ultrasound in this situation.
4.8 Gastric aspiration

A gastric aspiration examination is sometimes used in children when TB is suspected (or needs exclusion) and spontaneous sputum cannot be produced (see Chapter 5 for TB in children).

Bronchoscopy is an alternative if available. The choice between performing gastric aspirates and bronchoscopy in infants and children with abnormal CXRs is debated.\textsuperscript{28} Induced sputum examination may also be helpful in children, if tolerated.

4.9 Blood culture for mycobacteria

A blood culture for mycobacteria is important in patients with advanced HIV-infection, where 24–64\% of patients with TB have positive blood cultures. In up to 18\%, blood is the only site from which the organism is recovered.

4.10 Testing for HIV and other co-morbidities

An HIV test should be offered to every patient diagnosed with, or suspected of having, active TB disease, as each disease affects the course of the other. HIV is the single greatest risk factor for the development of active TB. Classical risk factors for HIV may not always be apparent.

For information on TB and HIV, see Chapter 6.

Patients starting treatment for TB also require baseline haematology, creatinine, liver function, hepatitis B surface antigen, and hepatitis C serology, together with regular monitoring of transaminases (see Chapter 3).

4.11 Pleural, pericardial and peritoneal investigations

In 90\% of tuberculous pleural and peritoneal effusions, the fluid is an exudate with a lymphocyte predominance. Other causes of lymphocytic effusions include lymphoma, other malignancies, collagen vascular diseases, and post-coronary artery bypass surgery. Early TB effusions may show neutrophil predominance and an eosinophilic pleural effusion is occasionally seen.\textsuperscript{44} A low pleural fluid glucose level is typical.

The sensitivity of the pleural and peritoneal fluid TB culture (10–35\%) is less than that of pleural or peritoneal biopsy culture (39–65\%). Mycobacterial blood culture bottles are more sensitive that standard TB culture systems for examining these fluids. Histology and culture of pleural biopsies can yield a diagnosis in up to 86\% of cases. Therefore, pleural biopsies are essential. In TB pleural effusions, induced sputum may be culture positive in just over 50\% of cases, so is a useful adjunct to investigations.\textsuperscript{45} Pericardial fluid has similar biochemical properties to pleural fluid, but pericardial biopsies may be required for histology and culture, and need to be obtained surgically.
A recent study of adenine deaminase (ADA) as an indicator of TB in lymphocytic effusions showed only rare false-positive results using an ADA level of 40 U/L or more. This test is therefore considered a very useful adjunct to diagnosis in suspected TB pleural effusion.

Thoracoscopic or laparoscopic pleural or peritoneal biopsy may be needed when other specimens (including sputum) fail to confirm a diagnosis especially in people from countries with a high prevalence of drug resistance where the drug susceptibility of the TB organism is essential.

4.12 Lymph node tuberculosis

Because pulmonary TB co-exists in 70% of cases of supra-clavicular and cervical TB adenitis, a CXR is indicated. When pulmonary disease is also present it may be easier to confirm the diagnosis with respiratory investigations (see earlier).

A New Zealand study showed that a fine needle aspirate (FNA) of tuberculous cervical and supraclavicular nodes was positive in 33% of cases – lower than in many other studies. This may be due to the small number of subjects or because cases present and are investigated earlier in New Zealand than in non-Western countries.

When an FNA is performed, AFB smears are essential and several FNA specimens should be cultured. TB PCR may also be requested. FNA cytology may show necrotic material, multi-nucleate giant cells and other findings suggestive of granulomata; it is important in detecting other causes of lymphadenopathy especially malignancy.

It is always desirable in this era of increasing drug resistance and given the propensity of TB lymphadenopathy to vary in size even during successful treatment, to obtain culture and sensitivity data. Therefore, if FNA smear and culture are negative and there is no clinical urgency, a core biopsy or excision biopsy should be performed with mycobacterial culture and cytology/histology. Treatment should not be started until a positive culture has been obtained or until an abnormal node has been excised and is being cultured for mycobacteria.

In mediastinal adenopathy where TB is strongly suspected, it may be possible to obtain transbronchial needle aspirate (TBNA) or an endobronchial ultrasound-guided TBNA (EBUS TBNA). If none of these tests is diagnostic, the patient should have a mediastinoscopy. Intraabdominal lymphadenopathy may be sampled via laparoscopy.

4.13 Central nervous system tuberculosis

TB meningitis or CNS disease should be considered in anyone seriously ill with disseminated TB: there should be a low threshold for performing a CT scan and/or lumbar puncture. CT is usually performed prior to lumbar puncture (if available), in order to exclude raised intracranial pressure, posterior fossa disease or obstructive hydrocephalus. It is difficult to exclude these with clinical examination alone, especially as performing fundoscopy may be hazardous in infectious patients.
Characteristic findings on CSF examination include a leucocytosis (usually lymphocyte predominant, although polymorphs may predominate in a minority of patients with early disease), a raised protein in almost all patients, and a low glucose. Acid-bast bacilli are found in less than 20% of cases. TB PCR has excellent specificity but low sensitivity of around 50–60%, and up to 45% of patients with presumed TB meningitis have negative CSF cultures. Routine blood test results are non-specific, but hyponatraemia is very common. It is important to search carefully for TB at other sites in patients with suspected CNS TB. Empiric treatment needs to be started early in patients with clinical features of CNS TB and characteristic clinical findings, without waiting for culture results.

4.14 Routine laboratory tests

Abnormal results that may be found with TB include the following.

- A mild leukocytosis – occasionally a leukemoid reaction or a leukopaenia or raised monocyte or eosinophil count.
- Anaemia is common, especially with disseminated disease, and iron studies show non-specific features of chronic disease.
- Pancytopenia, which may indicate extensive bone marrow involvement.
- Hyponatraemia, which occurs in about 10% of cases and is due to the production of an anti-diuretic hormone-like substance in diseased tissue. Hypo-adrenalism should be excluded by a short synacthen test.
- Hypercalcaemia in about 5% of cases of TB, but it is usually mild and responds to treatment of the TB.
- Mild hepatic dysfunction, which is common with moderately extensive TB. More severe hepatic dysfunction may be due to co-existing disease such as viral hepatitis or alcoholism.
- Hypoalbuminaemia and other non-specific features of severe chronic disease, especially in disseminated TB.
References


Further reading