Policy 1.2 Diagnosis of Tuberculosis: Clinical

Title | Diagnosis of Tuberculosis - Clinical
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Related WA TB Control Program Policies

1.1 Diagnosis of tuberculosis – Laboratory
1.2 Diagnosis of tuberculosis – Clinical
2.1 Medical treatment of tuberculosis (adults)
2.2 Case management of tuberculosis
3.1 Diagnosis of latent tuberculosis infection
3.2 Treatment of latent tuberculosis infection
4.1 Tuberculosis (active and latent) in children
4.2 Management of tuberculosis in prisoners and immigration detainees
4.3 Tuberculosis (active and latent) in pregnant women
4.4 Tuberculosis and HIV
5.1 BCG Vaccination
6.1 Contact tracing for tuberculosis
6.2 Active surveillance for tuberculosis in recent migrants
6.3 Tuberculosis and health care workers
6.4 Active surveillance for tuberculosis prior to anti-TNF alpha treatment
7.1 Notification of tuberculosis and enhanced surveillance data
8.1 Diagnosis and management of Hansen’s disease
9.1 Management of confidential information for the WA Tuberculosis Control Program
9.2 Client record management policy for the WA Tuberculosis Control Program
9.3 Fees and charges associated with tuberculosis and leprosy treatment

Document Control

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1.0 Introduction

The highest priority for tuberculosis control is the identification and cure of the infectious cases of tuberculosis. Therefore, any person with symptoms suggestive of tuberculosis, particularly cough for more than three weeks, should be investigated and the primary test should always be sputum microscopy and culture for acid-fast bacilli (AFB). It is, however, important to stress that active and even infectious diseases may be asymptomatic. A significant percentage of active pulmonary TB cases have negative sputum smears. Mycobacterial culture remains the gold standard for the definitive diagnosis of active disease.

2.0 Presentation of Tuberculosis

Tuberculosis is classified as pulmonary or extra-pulmonary. Pulmonary tuberculosis is more common and refers to disease involving the lung parenchyma and also includes disease involving the trachea. Extra-pulmonary TB is disease involving any other part of the body and includes lymph node TB, skeletal TB, urogenital TB and miliary TB. Tuberculosis disease of the pleura, with or without pleural effusion, and intra-thoracic lymphadenopathy (mediastinal and hilar), without radiological abnormalities in the lung parenchyma, are also classified as extra-pulmonary TB. This distinction is important from a public health perspective, as there is a risk of community transmission in untreated pulmonary TB. Conversely, the risk to community from extra-pulmonary TB is minimal (Hoffman & Churchyard, 2009).

A patient with both pulmonary and extra-pulmonary tuberculosis should be classified as a case of pulmonary TB.

2.1 Symptoms and signs

Clinical symptoms and signs that suggest active TB disease are:

- Cough with sputum for more than 2-3 weeks
- Haemoptysis
- Unexplained fever
- Night sweats
- Weight loss
- Lethargy and tiredness
- Chest pain
- Localised chest signs in upper/mid zones
- Enlarged lymph nodes, usually non-tender and most commonly around head and neck
- Localised symptoms related to anatomical site of extra-pulmonary TB e.g. back pain in vertebral TB, abdominal pain in peritoneal TB, headache in TB meningitis etc.
2.2 Special situations

**Human Immunodeficiency Virus (HIV) infection**

The clinical presentation of tuberculosis in HIV infected persons are influenced by:

i. The degree of immune suppression in the person; and

ii. The rate of disease progression.

In HIV-infected individuals with relatively preserved immunity, pulmonary TB presents in the typical adult pattern of upper lobe predominance and caviation. In patients with severe immune suppression pulmonary TB can present atypically e.g. with non-cavitary lower or mid zone infiltrates (Nachega & Maartens, 2009). Disseminated TB is also more common in immune suppressed patients.

TB progresses more rapidly in immune suppressed patients and therefore TB should be diagnosed and treatment initiated with minimal delay. Investigations for pulmonary TB should begin if cough persists for more than 1 week rather than 3 weeks in HIV affected patients (Nachega & Maartens, 2009). For more detail on tuberculosis in HIV affected persons please see the WA TB Control Program policy 4.4 *Tuberculosis and HIV*.

**TNFα antagonist therapy**

Patients who develop tuberculosis associated with TNFα antagonist therapy have a higher proportion of extra-pulmonary and disseminated forms of TB compared to manifestation of these forms of the disease in the non-immunosuppressed population (Keane, Gershon, & Wise, 2001). This difference in manifestations of TB may contribute to delays in investigating and diagnosing TB in patients undergoing TNFα antagonist therapy. For more detail please see the WA TB Control Program policy 6.4 *Active surveillance for tuberculosis prior to anti-TNF alpha treatment*.

3.0 Investigations for Tuberculosis

Direct microscopy examination and culture of clinical specimens are the first line investigations for tuberculosis. Mycobacterial culture remains the gold standard for the definitive diagnosis from an appropriate specimen (e.g. sputum, fine needle aspiration, tissue biopsy, cerebrospinal fluid, pleural/pericardial and peritoneal cavity fluid or urine). When microscopy for acid-fast bacilli and nucleic acid amplification testing (NAAT) is both positive, the diagnosis of tuberculosis can be considered to be established. The diagnosis is strongly supported by a histological appearance of caesating granulomas in tissue specimens prior to culture being available, in an appropriate clinical setting.

As treatment for TB treatment is prolonged, complex and with the potential for drug side effects, diagnostic specimens should be collected before treatment is initiated and confirmation of the diagnosis should always be sought. Culture is also important because
drug susceptibility testing for \textit{M. tuberculosis} isolates ensures the appropriateness of treatment.

Sputum collection for microbiological examination should be considered in all cases of TB, even when the primary presentation is with extra-pulmonary TB or the diagnosis is established by culture of an extra-pulmonary site. This is because of the potential for asymptomatic co-existent pulmonary TB and the public health implications of a positive result.

3.1 Sputum Microscopy

Sputum smear microscopy is the most reliable and cost effective method of diagnosing infectious cases of pulmonary tuberculosis cases. Whenever tuberculosis is suspected in a patient, three sputum samples should be collected on three consecutive days and examined by microscopy for acid-fast bacilli.

3.2 Sputum culture

Culture examination of sputum for acid fast bacilli is more sensitive and specific than direct smear microscopy and may be useful in detecting cases where the number of organisms are fewer than can be detected by direct smear microscopy. In general, cultures from microscopy smear-positive sites can become positive within 1-2 weeks, while cultures from microscopy smear-negative (mycobacteria-containing) specimens become positive within 2-4 weeks.

Pulmonary TB can be classified based on the microscopy and culture findings as follows:

3.2.1 Smear positive tuberculosis

- A patient with at least two sputum smears positive for acid fast bacilli (AFB) by direct smear microscopy \textit{OR}
- A patient with at least one sputum smear positive for AFB by microscopy \textit{and} chest x-ray abnormalities consistent with active pulmonary TB as determined by a clinician, \textit{OR}
- A patient with at least one sputum smear positive for AFB by microscopy and sputum culture positive for \textit{M. tuberculosis}.

3.2.2 Smear negative tuberculosis

- A patient with at least three sputum smears negative for AFB by microscopy and chest X-ray abnormalities consistent with active pulmonary tuberculosis, \textit{OR}
- A patient whose initial sputum smears was negative for AFB, but whose sputum culture is positive for \textit{M. tuberculosis}. 
3.3 Nucleic Acid Amplification Testing (NAAT)

Although microscopy is rapid, it is insensitive, requiring approximately $10^4$ organisms /ml for the test to be reliably positive and is not specific for *Mycobacterium tuberculosis*. On the other hand, culture is the most sensitive method for diagnosis, but may take 2-4 weeks to yield a positive result. Microscopy and culture for tuberculosis however, remains the first line tests for TB detection.

Nucleic acid amplification testing is usually laboratory-initiated following consultation with a consultant Clinical Microbiologist. All new smear-positive clinical samples, regardless of specimen origin and clinical presentation are considered for NAAT. Although NAAT is very sensitive and can technically detect a single organism, in practice organism load and sample volume factors come into play. The cut-off threshold for the sensitivity of the test seems to be the same as for microscopy, i.e. $\sim 10^4$ AFB/ml.

NAAT is largely a confirmatory test i.e. confirming *M. tuberculosis* when an AFB is seen or cultured. Occasionally NAAT is useful as primary diagnostic test e.g. with paucibacillary small volume samples like cerebro-spinal fluid or post hoc examination of fixed histological samples. It should not take preference over microscopy and culture for tuberculosis, especially if there is a limited amount of sample.

NAAT should not be used to monitor patients on anti-tuberculosis treatment. Tests may remain positive for an extended period of time regardless of whether DNA or RNA is the target for amplification. Costs, relative lack of sensitivity, plus concerns regarding technical issues that affect reliability and reproducibility currently preclude their use as a screening test. Microscopy and culture remain a mandatory component of mycobacterial investigations.

A rapid diagnosis of the presence of *M. tuberculosis* may be possible using Cepheid GeneXpert, which is a sensitive cartridge-based, automated real time assay that can detect MTB and resistance to rifampicin (a surrogate marker for MDR strains) within approximately 2 hours from receipt in laboratory. The test is available at Royal Perth Hospital, Fremantle Hospital and QEII PathWest sites. It should be noted that the GeneXpert assay is currently only accredited for use on respiratory samples and there is a lack of a true positive control for every assay. Confirmatory methods are therefore needed for both MTB and rifampicin resistance detections and comments to this effect are made at the time of reporting.

For more detail on laboratory methods of diagnosing tuberculosis please see the WA TB Control Program policy 1.1 *Laboratory Diagnosis of Tuberculosis*. 
3.4 Chest X-ray

Diagnosis of tuberculosis by means of x-ray alone is unreliable, because it lacks specificity. Abnormalities seen on a chest x-ray, even when characteristic of TB, may be caused by a variety of other conditions. In addition, x-ray changes do not necessarily distinguish between active and inactive TB. Conversely, if there is characteristic x-ray changes of TB in a patient considered at high risk for TB, then active TB should be assumed until an alternative diagnosis is proven. A chest X-ray should be requested for all patients suspected of having TB whether the primary site is pulmonary or non-pulmonary as the two forms of the disease may coexist.

Chest X-ray appearances that are suggestive of pulmonary tuberculosis would be:

- Patchy, mottling, miliary, nodular and/or linear shadows situated mainly in the apical/posterior segments of the upper, or the superior segment of the lower lobes.
- The above changes less commonly in the middle/ or lingular lobes.
- Bilateral distribution in the upper zones.
- “Soft” opacities that fluctuate over time suggest active disease.
- Cavities are usually thin-walled and if present indicate active and infectious disease.

The decision to start on anti TB treatment on patients should not be based solely on an abnormal chest X-ray and all efforts should be made to obtain a microbiological diagnosis.

3.5 Computed tomography (CT) scan chest

Computed tomography scan of the thorax is not performed routinely in the assessment of TB, except when investigating the possibility of differential diagnoses where indicated. It rarely adds any information beyond what is obtained on chest x-ray.

3.6 Tuberculin Skin Test (TST)

The tuberculin skin test has been used in the management of tuberculosis since the 19th century. It is an indirect test that indicates a cellular immune response from previous sensitisation with mycobacterial antigens and cannot distinguish between individuals with latent TB infection, active TB infection or past TB infection.

A positive result in the TST suggests tuberculosis infection. It does not however indicate the presence or absence of active tuberculosis disease. A positive TST may not indicate active disease and a negative result will not rule out active disease. The result of the TST must be interpreted with the patient’s history, clinical presentation and reason for testing. Generally, TST is not indicated as a diagnostic test for active TB.

The TST can be used as supportive evidence of the diagnosis of TB in cases where obtaining samples for microbiological examination is difficult e.g. small children (see the WA TB Control Program policy 4.1 Tuberculosis active and latent in children) or
paucibacillary extra-pulmonary TB (e.g. TB meningitis). If active TB disease is suspected than other additional testing is needed to confirm a diagnosis of active TB.

3.7 Interferon gamma Release Immunoassays (IGRAs)

Interferon Gamma Release Immunoassays (IGRAs) are blood tests that detect cell mediated immune responses to TB specific antigens that are secreted by the *M. tuberculosis* organism. The QuantiFERON-TB Gold In-Tube test (QIFN) is used in Western Australia. The antigens tested against are present in all *M.tuberculosis* but are absent from BCG vaccine strains and most non-tuberculous mycobacteria, with the exception of *M.kansasii, M.szulgai and M.marinum* (Mazurek et al, 2010).

Like the TST, a positive QIFN may not indicate active disease and a negative result will not rule out active disease. The results must be interpreted with the patient’s history, clinical presentation and reason for testing and the QIFN test should not replace the standard diagnostic investigations of active TB disease.

Compared to the TST, IGRAs have been in use for a very short period of time. Generally, IGRAs are not indicated as a diagnostic test for active TB. If active TB disease is suspected than other additional testing is needed to confirm a diagnosis of active TB.

Further discussion on tuberculin skin testing and IGRAs is discussed in the WA TB Control Program policy 3.1 *Diagnosis of Latent TB infection (adults)*.

4.0 Samples for Microbiological Diagnosis

Every effort should be made to obtain a microbiological confirmation of active TB disease and drug susceptibility testing through appropriate pathological specimens. Specimens need to be representative of the site of infection, be collected aseptically if possible, stored appropriately for the shortest possible time and transported to the laboratory as soon as able. Table 1 provides examples of common specimens for mycobacterial investigation according to disease site. As tuberculosis can affect any body site, this list is not exhaustive.
Table 1: Common clinical specimens for mycobacterial testing

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Specimen</th>
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<td>Pulmonary TB</td>
<td>Sputum&lt;br&gt;Induced sputum&lt;br&gt;Bronchoalveolar lavage&lt;br&gt;Gastric aspirate&lt;br&gt;Transbronchial biopsy&lt;br&gt;Percutaneous lung biopsy&lt;br&gt;Open lung biopsy</td>
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<tr>
<td>Pleural TB</td>
<td>Pleural fluid aspirate and/or biopsy</td>
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<tr>
<td>Lymph node TB</td>
<td>Fine needle aspiration biopsy&lt;br&gt;Open lymph node biopsy</td>
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<tr>
<td>TB meningitis</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>Miliary TB</td>
<td>Liver or bone marrow biopsy</td>
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<tr>
<td>Gastrointestinal TB</td>
<td>Peritoneal fluid aspirate&lt;br&gt;Colonoscopy with biopsies&lt;br&gt;Stool specimen</td>
</tr>
<tr>
<td>Bone and joint TB</td>
<td>Joint aspirate +/- synovial biopsy&lt;br&gt;Bone marrow aspirate</td>
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<tr>
<td>Uro-genital tract</td>
<td>Early morning urine (Sterile pyuria raises the possibility of TB)&lt;br&gt;Renal biopsy&lt;br&gt;Bladder biopsy&lt;br&gt;Prostate biopsy</td>
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<tr>
<td>Female Genital tract</td>
<td>Hysteroscopy and endometrial biopsy&lt;br&gt;Laparoscopy with biopsies, washings</td>
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The common clinical specimens used to diagnose TB are:

**Sputum**

Three sputum samples should be collected on three consecutive days and early morning samples are preferable. Patients should be advised to collect sputum after coughing following deep inspiration and it should not be saliva. Sputum samples should be collected in a well-ventilated space, e.g. outdoors or in a negative pressure isolation room, but NOT in the bathroom or toilet area.

**Induced Sputum or bronchoscopy**

Induced sputum collection or bronchoscopy may be indicated when the patient is unable to obtain a sputum sample by usual means. These two procedures have equal sensitivity (Conde et al, 2000 and McWilliams et al, 2002) so the choice is determined by weighing up the risk of complications, availability of the test and convenience with the patient.
Induced sputum collection must be performed in a room with negative pressure air-conditioning. It can be collected at any time of the day. Collection of induced sputum is performed on site at the WA TB Control Program located at the Anita Clayton Centre.

Bronchoscopy must be performed with appropriate precautions to prevent transmission of TB, both with respect to isolation of the patient in the hospital and within the bronchoscopy suite.

Fine needle aspiration biopsy

Fine needle aspiration biopsy is a quick and safe diagnostic tool in suspected extrapulmonary TB. It is especially useful in the investigation of suspected lymph node TB.

Excisional biopsies of lymph nodes may also be carried out to confirm diagnosis. It is important that the specimen is not placed in formalin.

Fasting gastric aspirates

Gastric aspiration is used to collect gastric contents containing swallowed sputum in order to culture for M.tuberculosis. Smear microscopy of gastric aspirates have a low yield (<15%) and the highest yield specimens are obtained first thing in the morning (Schaaf & Reuter, 2009). Gastric aspiration is usually reserved for use in young children who are unable or unwilling to expectorate sputum. A gastric aspirate should be obtained on each of three consecutive mornings and sent for smear microscopy and mycobacterial culture.
5.0 Works Cited


