TUBERCULOSIS (TB) SCREENING BEFORE INITIATING ANTI-TNF THERAPY

A resource guide for healthcare professionals

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ABOUT THIS RESOURCE GUIDE

THE PURPOSE OF THIS GUIDE IS TO INCREASE AWARENESS OF SPECIFIC SCREENING RECOMMENDATIONS FOR TB BEFORE INITIATING ANTI-TNF THERAPY AND IS BASED MAINLY ON INFORMATION AND RECOMMENDATIONS PROVIDED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION, THE AMERICAN THORACIC SOCIETY AND THE NICE CLINICAL GUIDELINE 117.

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WHY, WHO, AND HOW

Q. Why are there recommendations for TB screening for certain high-risk populations?

A. Globally, TB is a common and often deadly infectious disease.[1] The majority of individuals infected with *Mycobacterium tuberculosis* (M. tuberculosis) have latent TB infection (LTBI) rather than active TB disease. As such, identification and treatment of persons with LTBI has been essential in controlling the progression to active TB.[1,2]

Q. Who is at risk?

A. Individuals who are considered to be at risk of developing either active or latent TB infection[3]

- Adults, young people and children if they:
  - Have arrived or returned from high-prevalence countries within the last 5 years
  - Were born in high-prevalence countries
  - Live with people diagnosed with active TB
  - Have close contact with people diagnosed with active TB, for example at school or work
  - Are homeless or problem drug users
  - Are, or have recently been, in prison
- Adults and children who are immunocompromised because of:
  - Prolonged steroid use (equivalent to 15 mg prednisolone daily for at least 1 month)
  - TNF-α antagonists
  - Anti-rejection drugs such as cyclosporin, various cytotoxic treatments and some treatments for inflammatory bowel disease, such as azathioprine
  - The use of immunosuppressive drugs
  - Comorbid states affecting the immune system, for example HIV, chronic renal disease, many haematological and solid cancers, and diabetes.

Q. Is TB screening recommended with use of all TNF antagonists?

A. Yes. Evidence indicates that development of active TB can be a risk with the use of any agent that blocks TNF-α.[4] As such, all patients should be screened for LTBI prior to initiating a TNF antagonist.

Q. How do I go about the screening and treatment process? Are there guidelines?

A. Yes, NICE provides guidance on the screening of LTBI in patients receiving, or about to receive anti-TNF therapy. The British Thoracic Society provide recommendations for treatment in these patients.[5]

LATENT VERSUS ACTIVE TUBERCULOSIS

Q. How does LTBI differ from active TB?

A. Latent TB is defined by infection with mycobacteria of the *M. tuberculosis* complex, where the bacteria are alive but not currently causing active disease. LTBI and active TB differ primarily in the presentation of symptoms. A patient with LTBI usually has no symptoms, does not feel sick and cannot spread TB to others. Diagnosis of LTBI is demonstrated by a positive Mantoux test or TB blood test. Patients may have a normal chest x-ray or they could exhibit radiographic signs of LTBI, such as calcifications or pleural thickening.[6] Conversely, patients with active TB present with symptoms dependent on the region of the body where TB mycobacteria are growing; this may either be respiratory (including the lungs, pleural cavity, mediastinal lymph nodes etc) or non-respiratory (including in bone, joints, central nervous system, skin etc.).[3]

TB mycobacteria usually replicate in the lungs, and therefore may cause symptoms such as severe and persistent cough, pain in the chest, and coughing up of blood or sputum. Other symptoms include weakness or fatigue, weight loss, loss of appetite, chills, fever, and night sweats.

Diagnosis of active respiratory TB can be gained through abnormal chest x-ray, acid-fast bacilli in sputum, and/or positive sputum culture. Extrapulmonary signs and symptoms may be present and will depend on the organ system affected, such as lymph nodes, pleura, upper airways, genitourinary tract, bones and joints, central nervous system, gastrointestinal tract, pericardium, etc.[3]

Q. Will both LTBI and active TB show up on a Mantoux test or TB blood test (eg, interferon-gamma test [IGT]*)?

A. Mantoux test has been the most commonly used method to show if someone had been exposed to TB and may have had LTBI until recently. The test which is easy to use, however, has limitations. False positive results can occur because of prior BCG vaccination and false negative results can occur because of reduced immunity from co-infection with HIV or use of immunosuppressive drugs. Both active and latent TB infection usually produce a positive result by Mantoux test, and the test is not capable of distinguishing between the two.[3]

Interferon Gamma Tests were developed to be more specific as they detect antigens which are not present in BCG vaccination. They, therefore, remove the number of false positive results and are better at indicating latent TB infection.[7]

*AbbVie do not provide, carry out, recommend or finance either Mantoux or Interferon Gamma Tests

SYMPTOMS OF TUBERCULOSIS

Q. What should I tell my patients who are receiving TNF antagonist therapy about TB?

A. Physicians who prescribe any TNF antagonist therapy should educate their patients about the symptoms of TB.[6] Your patients should be counselled to report any symptoms of active TB, including*:

Respiratory symptoms of TB[8]
- A cough that lasts 3 weeks or longer
- Pain in the chest
- Coughing up blood or sputum (phlegm from deep inside the lungs)

Other symptoms of TB[8]
- Weakness or fatigue
- Weight loss
- No appetite
- Chills
- Fever
- Sweating at night

*This list is not meant to be comprehensive.

TREATING TUBERCULOSIS

Q. Who should be treated for TB?

A. Although the treatment regimens differ for active TB and LTBI, both individuals with active disease, as well as those with LTBI who are at high risk of developing TB, should be treated according to appropriate TB guidelines and / or standards of care.[3]

Q. If LTBI is dormant, why is it necessary to treat it?

A. While many individuals infected with *M. tuberculosis* will have LTBI and never develop active TB disease, those with a compromised immune system may not be able to contain the mycobacteria and are at risk of progression to active TB. Therefore, appropriate treatment is recommended for individuals who have LTBI and fall into a high-risk group.[3]

Q. Which high-risk groups should be treated for LTBI?

A. Once active TB has been excluded by chest X-ray and examination, treatment of latent TB infection should be considered for people in the following groups:[3]

- People identified through screening who are:
  - 35 years or younger (because of increasing risk of hepatotoxicity with age)
  - any age with HIV or any age and a healthcare worker if Mantoux test (Appendix D) is 6 mm or greater without prior BCG vaccination or 15 mm or greater with BCG vaccination.
- Children aged 1–15 years identified through opportunistic screening to be:
  - strongly Mantoux positive (15 mm or greater)
  - interferon-gamma positive (if this test has been performed)
  - without prior BCG vaccination.
- People with evidence of TB scars on chest X-ray, and without a history of adequate treatment.

Q. How is LTBI treated?

A. The typical treatment regimen for LTBI is either 3 months of rifampicin and isoniazid or 6 months of isoniazid. Exceptions to this regimen are patients with HIV infection (of any age) for whom 6 months isoniazid is recommended or those under 35 years of age in contact with people with isoniazid-resistant TB, for whom 6 months of rifampicin is recommended.[3]

PUTTING TUMOUR NECROSIS FACTOR ANTAGONISTS IN PERSPECTIVE

Q. What is the normal biologic role of TNF-α?

A. TNF-α is a naturally occurring proinflammatory cytokine involved in normal cell-mediated immune response against disease, including mycobacterial infection, such as TB.[9]

Q. How do TNF antagonists work in treating chronic inflammatory diseases?

A. Elevated levels of TNF-α play a key role in stimulating the pathologic inflammation underlying chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis.[10,11]

Q. What is the role of TNF-α in the immune response to TB?

A. Tumour necrosis factor plays an important role in protection against murine *M. tuberculosis* infection[12]. In vitro and in vivo studies demonstrate that TNF-α provides protective mechanisms in macrophages against *M. tuberculosis*. The studies further show that the absence of TNF-α has a detrimental effect on the ability of granulomas to contain and restrict the replication of *tubercle bacilli*.

Q. Why is screening for TB necessary with TNF antagonist therapy?

A. Any immunosuppressive agent, including TNF antagonists, can potentially result in reactivation of LTBI or progression of recently acquired mycobacterial infection to active TB.[2,13,14,15] For this reason, NICE and other experts, including the Health Protection Agency and British Thoracic Society, recommend screening for LTBI. They also recommend following through with appropriate management if infection is detected before initiating therapy with any TNF antagonist.

Q. Is screening important in managing the risk of TB?

A. Yes. Tuberculosis screening prior to initiation of TNF antagonist therapy has resulted in a decreased rate of progression of latent TB to active TB.[14,15] For example, in European clinical trials, implementation of TB screening prior to initiation of TNF antagonist therapy for the treatment of RA resulted in a reduction in the incidence rates of TB in the clinical trials.[14,15] Patients receiving TNF antagonist therapies should be monitored for signs and symptoms of active TB.[5]

GETTING DOWN TO BASICS – TUBERCULIN SKIN TESTING

Q. What is the standard TB skin test?

A. The Mantoux test (Appendix D), also known as the Tuberculine Skin Test (TST) or Purified Protein Derivative (PPD) test is a method used globally. It contains a tuberculin protein antigen.[16,17] The test is used to aid diagnosis of TB infection in persons at increased risk of developing active disease. However, the Mantoux test has limitations, particularly in the detection of LTBI. NICE guidance promote the use of dual strategy of Mantoux test in combination with IGT for people whose Mantoux test shows postive results, or in people whom Mantoux testing may be less reliable.[18] In specific groups, such as people who are immunocompromised, IGT alone or a dual strategy is recommended, but not Mantoux test alone.[18]
A Mantoux test alone is recommended for children as a false positive is unlikely due to lack of BCG vaccination.[18] Mantoux test and results should only be administered, read and interpreted by a trained healthcare professional.

Q. I am not trained to perform the Mantoux Test. Where can I send my patients for testing?

A. Infectious disease physicans, respiratory physicans and specialised nurses have been trained and routinely do Mantoux Tests (dependent on local infrastructure).

GETTING DOWN TO BASICS – INTERFERON-GAMMA TESTS

Q. What are IGTs?

A. Interferon-gamma tests are whole-blood tests that can aid in diagnosing both LTBI and active TB.[3] You will find general instructions on administering the test and interpreting the results at the back of this brochure for your reference.

Q. How do IGTs work?

A. Interferon-gamma tests measure a person's immune reactivity to *M. tuberculosis*.[3] They detect two tuberculosis antigens, 'early secretion antigen target 6' (ESAT-6) and 'culture filtrate protein 10' (CFP-10). These antigens are not present in BCG and are found in only a few species of environmental mycobacteria which explains the increased specificity, reduced likelihood of false positive results and better correlation with detection of latent infection of dormant organisms.[18] For more information, visit NICE **http://www.nice.org.uk/**.

Q. What are the advantages of IGTs?

A.
> Only requires one patient visit in comparison to Mantoux which requires two visits[19]
> Improved specificity in comparison to Mantoux, i.e. fewer false positive results which means it is less likely people will be unecessarily treated for presumed LTBI[19]
> Depending on your local infrastructure, results can be available within 24 hours[20]
> Does not boost responses measured by subsequent tests[20]

Q. What are the disadvantages and limitations of IGTs?

A.
> Blood samples must be processed within 8 hours after collection while white blood cells are still viable[21]
> Factors that decrease the accuracy of the test include errors in:[21]
  – Collecting blood samples
  – Transporting blood samples
  – Running and interpreting the test
> The Mantoux test is cheaper than the IGT[19]
> Patients may find a blood test less acceptable than an intradermal test[19]

Q. When should IGTs be used?

A. Interferon-gamma tests can be used in place of or in addition to the Mantoux test in all situations recommended by NICE. IGTs should be considered for people whose Mantoux test shows positive, or for whom Mantoux testing may be less reliable, e.g. BCG vaccinated people.[3,7] As IGTs are recommended by NICE for their specifity in detecting latent TB infection they are primarily recommended in patients being screened for LTBI. Specific recommendations and considerations for the use of IGT and Mantoux test in this setting are listed below:[3,7]

IGT alone or IGT and Mantoux test (dual strategy) is recommended for:[3,7]

- Immunocompromised patients (i.e. anti-TNF therapy, HIV and CD4 cell count less than 200 cells/mm^3)
- New entrants from high risk countries between 16 -34 years of age
- Employees of any age who are new to the NHS and are from a country with a high incidence of TB or have been in close contact with patients in a setting with high TB prevalence
- People from hard to reach groups* (single IGT only)

If either test is positive a clinical assessment to exclude active TB and for the consideration of treatment of latent TB is suggested.

*Hard to reach groups refer to children, young people or adults whose social circumstances or lifestyle, or those of their parents or carers that make it difficult to:[3,7]

- Recognise the clinical onset of TB
- Access diagnostic and treatment services
- Self administer treatment (or, in the case of children and young people, have treatment administered by a parent or carer)
- Attend regular appointments for clinical follow up

Q. When should IGTs not be used?

A. IGT should not be used as the initial test in children younger than 5 years of age. A Mantoux test only should be offered specifically to the following groups:[3,7]

- Children younger than 5 years of age who have recently arrived from a high-incidence country
- NHS employees of any ages who are not new entrants from a high incidence country or have not had BCG vaccination

REFERENCES

1. Centers for Disease Control and Prevention. A global perspective on tuberculosis [fact sheet]. Available at: http://www.cdc.gov/tb/events/WorldTBDay/resources_ global.htm. Accessed January 2013.
2. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit CareMed*. 2000;161:S221-S247.
3. NICE Clinical Guideline 117. Tuberculosis Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. March 2011. Available at: http://guidance.nice.org.uk/CG117/Guidance/pdf/English. Accessed January 2013.
4. Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha—California, 2002–2003. MMWR. 2004;53: 683-686.
5. 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-α treatment. *Thorax*. 2005;60:800-5.
6. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep. 2000;49:1-54.
7. NICE Clinical Guideline 117. Implementing NICE guidance, Tuberculosis Slide Set. March 2011. Available at: http://guidance.nice.org.uk/CG117/SlideSet/ppt/English. Accessed January 2013.
8. Centers for Disease Control and Prevention. Questions and answers about TB. Available at: http://cdc.gov/tb/publications/faqs/default.htm. Accessed January 2013.
9. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. Lancet Infect Dis. 2003;3:148-155.
10. Mease P. TNF-α therapy in psoriatic arthritis and psoriasis. Ann Rheum Dis. 2004;63:755-758.
11. Moore TL. Immunopathogenesis of juvenile rheumatoid arthritis. Curr Opin Rheumatol. 1999;11:377-383.
12. Flynn JL, Goldstein MM, Chan J, et al. Tumor necrosis factor-α is required in the protective immune response against Mycobacterium tuberculosis in mice. Immunity. 1995;2:561-572.
13. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Ann Rheum Dis. 2007;66(suppl III):iii2-iii22.
14. Perez JL, Kupper H, Spencer-Green GT. Impact of screening for latent TB prior to initiating anti-TNF therapy in North America and Europe [abstract]. Ann Rheum Dis. 2005;64(suppl III):86. Abstract OP0093.
15. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:889-894.
16. Tubersol® [package insert]. Toronto, Ontario: Sanofi Pasteur Limited; 2006.
17. Aplisol® [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; 2008.
18. NICE Clinical Guidance 117. New NICE guideline updates recommendations for diagnosing latent tuberculosis. Available at: http://www.nice.org.uk/newsroom/pressreleases/TBUpdate.jsp. Accessed January 2013.
19. Health Protection Agency. Interferon Gamma Release Assay (IGRA) testing for tuberculosis (TB): Questions & Answers (Q&As) for health professionals. Available at: http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis/Guidelines/TBGuid05IGRAQAprof/ Accessed January 2013.
20. Centers for Disease Control and Prevention. Guide for primary health care providers: targeted tuberculin testing and treatment of latent tuberculosis infection. Available at: http://www.cdc.gov/tb/publications/LTBI/default.htm. Accessed January 2013.
21. Centers for Disease Control and Prevention. Interferon-gamma release assays (IGRAs) – blood tests for TB infection [fact sheet]. Available at: http://www.cdc.gov/ tb/publications/factsheets/testing/IGRA.htm. Accessed January 2013.

APPENDICES

THE CONTENTS OF THE APPENDIX HAVE BEEN ADAPTED FROM AND DEVELOPED IN-LINE WITH INFORMATION FROM THE FOLLOWING SOURCES:

1. CENTERS FOR DISEASE CONTROL AND PREVENTION
2. NICE CLINICAL GUIDANCE 117
3. HEALTH PROTECTION AGENCY
4. THE BRITISH THORACIC SOCIETY

APPENDIX A: TUBERCULOSIS SCREENING CHECKLIST: ADULTS

This is a clinical practice tool, developed by AbbVie, adapted from Centre for Disease Control materials and updated in-line with recommendations from NICE Clinical Guidance 117, to assist with evaluating patients for the risk of developing active TB during therapy with a TNF antagonist. Consult your local TB guidelines for comprehensive information regarding TB screening and treatment recommendations in your area. *Please mark or fill out correspondingly*

_____ _____/_____/_____
Name of Patient Date of Birth

A Does the patient currently have any symptoms consistent with active TB such as:

	Yes	No	Comments
Cough ≥3 weeks	☐	☐	
Haemoptysis or sputum production	☐	☐	
Chest pain	☐	☐	
Fever	☐	☐	
Night sweats or temperature	☐	☐	
Weakness or fatigue	☐	☐	
Anorexia	☐	☐	
Weight loss ≥10% ideal body weight	☐	☐	

If one or more of the above is answered with "YES", active TB needs to be completely ruled out before initiation of therapy

B Immunosuppressive therapy (e.g. steroids, methotrexate, biologics) may increase the risk of active TB in patients with latent disease. Does the patient have this or other risk factors* for activation of latent TB including:

	Yes	No	Comments
Born or lived in TB endemic area	☐	☐	
Contact with people with sputum smear positive TB	☐	☐	
Resident or employee of a high risk residential facility e.g. prison, remand centre	☐	☐	
Mycobacteriology laboratory staff	☐	☐	
Child or adolescent exposed to adult in high risk category	☐	☐	
Immunosuppression due to treatment or another condition	☐	☐	
Homeless or problem drug user	☐	☐	
Diabetes	☐	☐	
Silicosis	☐	☐	
Organ transplant	☐	☐	
Chronic renal failure	☐	☐	
Gastrectomy or jejunoileal bypass	☐	☐	
Head or neck cancer, leukaemia, lymphoma	☐	☐	

**Medical consultation with Expert recommended in patients with a negative test but having risk factors for TB infection.*

C BCG vaccination:

	Yes	No	Comments
BCG vaccination	☐	☐	
Date of Chest X-ray	_____/_____/_____		

D Perform an IGT alone or IGT and a concurrent Mantoux Test. If either test is positive perform a chest examination and X-ray to exclude active TB**

Results of the Interferon Gamma Test	
Type of assay performed	_____
Date of assay performed	_____/_____/_____
Assay measurement / Interpretation	_____/_____
Date of LTBI treatment initiation	_____/_____/_____

D

Results of the Mantoux Test:	
Date of Mantoux Test application	_____/_____/_____
Date of Mantoux Test reading	_____/_____/_____
Induration at Mantoux Test site (in mm)	_____
Results of the Second Mantoux Test (if appropriate):	
Date of Mantoux Test application	_____/_____/_____
Date of Mantoux Test reading	_____/_____/_____
Induration at Mantoux Test site (in mm)	_____

***IGT and concurrent Mantoux Test must be performed in patients with HIV and CD4 counts < 200 cells/mm³. A Mantoux Test only should be offered specifically to NHS employees of any ages who are not new entrants from a high incidence country or have not had BCG vaccination.*

E Results of Chest X-ray Screening for TB:

	Yes	No	Comments
Normal	☐	☐	
Abnormal	☐	☐	
Latent TB	☐	☐	
Others (please specify test and normal/abnormal)	☐	☐	
Date of Chest X-ray	_____/_____/_____		

Referral to a TB specialist is recommended for any patient with positive results for the IGT or Mantoux tests or with abnormal findings on chest X-ray.

F Treatment should be initiated if the patient presents with a positive medical history and / or Mantoux shows an induration of ≥ 6 mm without prior BCG or ≥ 15 mm with prior BCG and / or IGT results are positive and / or the chest X-ray shows signs of LTBI

Mantoux or IGT	Chest X-ray	LTBI Treatment
< 6 mm or Negative	Normal	Not recommended*
< 6 mm or Negative	LTBI signs	Recommended
< 6 mm or Positive	Normal	Recommended
≥ 6 mm or Positive	Abnormal	Medical consultation with Expert recommended
≥ 15 mm or Positive	Normal	Recommended
Prescribed LTBI treatment regimen (drug/dose):		_____/_____
Date of LTBI treatment initiation		_____/_____/_____

G Does the patient have hepatic disease or any other risk factors for hepatic disease, which may require additional monitoring with LTBI treatment such as:

	Yes	No	Comments
Underlying liver disease (e.g. hepatitis B or C, history of heavy alcohol consumption)	☐	☐	
Pregnant or postpartum (within 3 months of delivery)	☐	☐	
Other risk factors for chronic liver disease	☐	☐	

_____ _____/_____/_____
Name of Doctor Date of evaluation

Abbreviations: IGT, interferon gamma test; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF, tumour necrosis factor

APPENDIX B: TUBERCULOSIS SCREENING CHECKLIST: PAEDIATRICS

This is a clinical practice tool, developed by AbbVie, adapted from Centre for Disease Control materials and updated in-line with recommendations from NICE Clinical Guidance 117, to assist with evaluating patients for the risk of developing active TB during therapy with a TNF antagonist. Immunocompromised children who are suspected of having LTBI should be referred to a TB specialist. Consult your local TB guidelines for comprehensive information regarding TB screening and treatment recommendations in your area. *Please mark or fill out correspondingly*

_____ _____/_____/_____
Name of Patient Date of Birth

A Does the patient currently have any symptoms consistent with active TB such as:

	Yes	No	Comments
Cough ≥3 weeks	☐	☐	
Haemoptysis or sputum production	☐	☐	
Chest pain	☐	☐	
Fever	☐	☐	
Night sweats or temperature	☐	☐	
Weakness or fatigue	☐	☐	
Anorexia	☐	☐	
Weight loss ≥10% ideal body weight	☐	☐	

If one or more of the above is answered with "YES", active TB needs to be completely ruled out before initiation of therapy

B Immunosuppressive therapy (e.g. steroids, methotrexate, biologics) may increase the risk of active TB in patients with latent disease. Does the patient have this or other risk factors* for activation of latent TB including:

	Yes	No	Comments
Born or lived in TB endemic area	☐	☐	
Contact with people with sputum smear positive TB	☐	☐	
Resident or employee of a high risk residential facility e.g. prison, remand centre	☐	☐	
Mycobacteriology laboratory staff	☐	☐	
Exposed to adult in high risk category	☐	☐	
Immunosuppression due to treatment or another condition	☐	☐	
Homeless or problem drug user	☐	☐	
Chronic disease e.g. diabetes, silicosis, chronic renal failure	☐	☐	
Organ transplant	☐	☐	
Head or neck cancer, leukaemia, lymphoma	☐	☐	
Gastrectomy or jejunoileal bypass	☐	☐	

**Medical consultation with Expert recommended in patients with a negative test but having risk factors for TB infection.*

C BCG vaccination:

	Yes	No	Comments
BCG vaccination	☐	☐	
Date of vaccination	_____/_____/_____		

D Perform Mantoux Test as initial diagnostic test if child has not received BCG vaccination**

Results of the Mantoux Test:	
Date of Mantoux Test application	_____/_____/_____
Date of Mantoux Test reading	_____/_____/_____
Induration at Mantoux Test site (in mm)	_____

D Results of the Interferon Gamma Test* :

Type of assay performed	_____
Date of assay performed	_____/_____/_____
Assay measurement / Interpretation	_____/_____

Results of the second Mantoux Test (if appropriate):

Date of Mantoux Test application	_____/_____/_____
Date of Mantoux Test reading	_____/_____/_____
Induration at Mantoux Test site (in mm)	_____

***Mantoux Test should be offered as the initial diagnostic test for LTBI in children younger than 5 years who have recently arrived from a high incidence country.*

E Chest Examination and X-ray is crucial to rule out active TB. Results of Chest X-ray Screening for TB:

	Yes	No	Comments
Normal	☐	☐	
Abnormal	☐	☐	
Latent TB	☐	☐	
Others (please specify test and normal/abnormal)	☐	☐	
Date of Chest X-ray	_____/_____/_____		

Referral to a TB specialist is recommended for any patient with positive results for the IGT or Mantoux tests or with abnormal findings on chest X-ray.

F Treatment should be initiated if the patient presents with a positive medical history and / or Mantoux shows an induration of ≥ 6 mm without prior BCG or ≥ 15 mm with prior BCG and / or IGT results are positive and / or the chest X-ray shows signs of LTBI

Mantoux or IGT	Chest X-ray	LTBI Treatment
< 6 mm or Negative	Normal	Not recommended*
≥ 6 mm or Positive	Abnormal	Medical consultation with Expert recommended
< 6 mm or Negative	LTBI signs	Recommended
≥ 6 mm or Positive	Normal	Recommended
< 6mm or Positive	Normal	Recommended
Prescribed LTBI treatment regimen (drug/dose):		_____/_____
Date of LTBI treatment initiation		_____/_____/_____

G Does the patient have hepatic disease or any other risk factors for hepatic disease, which may require additional monitoring with LTBI treatment such as:

	Yes	No	Comments
Underlying liver disease (e.g. hepatitis B or C, history of heavy alcohol consumption)	☐	☐	
Other risk factors for chronic liver disease	☐	☐	

_____ _____/_____/_____
Name of Doctor Date of evaluation

Abbreviations: IGT, interferon gamma test; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF, tumour necrosis factor

APPENDIX C: BRITISH THORACIC SOCIETY RECOMMENDATIONS

The British Thoracic Society released recommendations on TB and anti-TNF treatment in 2005, the summary of which is below[5]:

- Prior to initiation of anti-TNF treatment all patients should be clinically examined for active or latent TB infection as per NICE guidance

- If active TB is detected, either pulmonary or non-pulmonary, then chemotherapy must be inititated. Treatment with anti-TNF should then not be initiated until 2 months of anti-tuberculosis treatment with full compliance by the patient. Preferably anti-TNF therapy would be postponed until the full course of anti-tuberculosis treatment has been administered.

- If inactive or latent TB is detected the anti-TNF treatment protocol needs to be based on the patient's previous TB management:

  - Previous adequate treatment: If the patient exhibits abnormal chest X-ray consistent with previous TB infection but are considered to have received adequate treatment by a thoracic or infectious disease specialist then they may begin anti-TNF treatment but most be monitored every 3 months with a chest radiograph and sputum cultures.

  - Previous inadequate treatment: If the patient exhibits abnormal chest X-ray consistent with previous TB infection and is not considered to have received adequate treatment by a thoracic or infectious disease specialist then they may not begin anti-TNF treatment. Chemoprophylaxis for TB must be completed prior to initation of anti-TNF therapy.

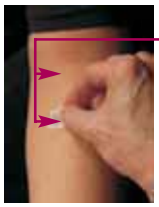
APPENDIX D: TUBERCULOSIS TEST INSTRUCTIONS

Mantoux Tuberculin Skin Test

1. Administration

For each patient, conduct a risk assessment that takes into consideration recent exposure and clinical conditions that increase risk for tuberculosis (TB) disease if infected. Prior to admistration inform your patient that 48 to 72 hours after they have been tested they are required to return to have the induration measured and interpreted.

1. Locate and clean injection site



2 to 4 inches (~5-10 centimeters) below elbow joint

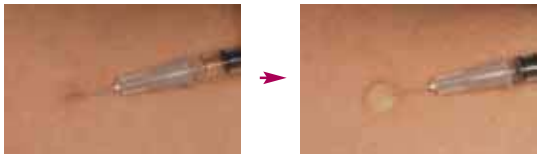
> Place forearm palm side up on a firm, well-lit surface
> Select an area free of barriers to placing and reading (eg, scars, sores)
> Clean the area with an alcohol swab

2. Prepare syringe

> Check expiration date on vial and ensure vial contains SSI tuberculin (2 TU per 0.1 mL)
> Use a single-dose (1 ml) tuberculin syringe with a 21G green needle with a short bevel
> Fill the syringe with 0.1 mL of tuberculin

3. Inject tuberculin

> Insert slowly, bevel up, at a 5- to 15-degree angle



> Advance needle through ~3 mm of epidermis, ensure needle is visible under skin

> After injection, a tense, pale wheal should appear over the needle just below skin surface

4. Check skin test

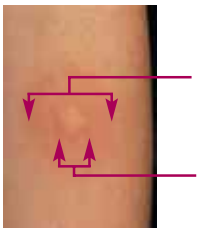
> Wheal should be 6 to 10 mm in diameter. If not, repeat test at a site at least 2 inches (~5 centimeters) away from original site

5. Record information

> Record all the information required for documentation by your institution (eg, date and time of test administration, injection-site location, lot number of tuberculin)

2. Reading

The skin test should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another skin test.



1. Inspect site

> Visually inspect site under good light

Erythema (reddening of the skin) — do not measure

Induration (hard, dense, raised formation) Only the induration should be measured

2. Palpate induration

> Use fingertips to find margins of induration

3. Mark induration

> Use fingertip as a guide for marking widest edges of induration across forearm

> If induration are irregular, mark and measure the longest diameter

4. Measure induration (not erythema)

> Using a mm ruler, place “0” ruler line inside left dot edge

> Read ruler line inside right dot edge (use lower measurement if between two gradations on mm scale)

5. Record information

> If no induration, record as 0 mm

> Do not record as “positive” or “negative”

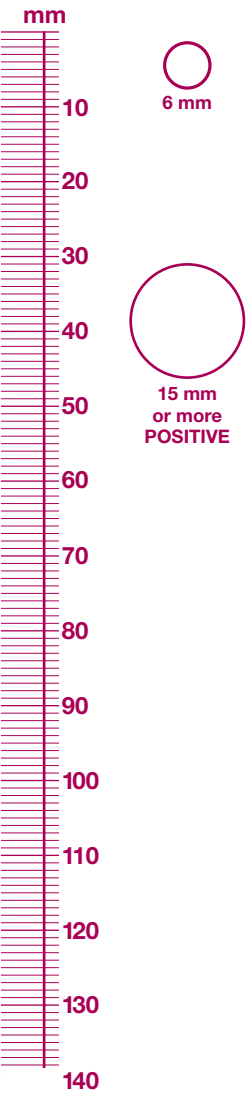
> Only record measurement in millimeters (mm)

Adapted from the Department of Health Publications, The Mantoux Test: Administration, reading and interpretation.

TUBERCULOSIS TEST INSTRUCTIONS

3. Interpretation

> When interpreting the results of the Mantoux Test the following should be considered:
> There is no correlation between the size of induration and likelihood of active disease.
> When risk factors to TB are absent, an induration of 6–15 mm is most likely to be due to previous BCG vaccination or infection with mycobacteria.
> HIV can cause false positive results.
> A person with a positive reaction should be tested with IGT and / or referred for a medical evaluation for latent TB infection and appropriate follow-up and treatment if necessary.
> A measurement of 0 mm or a measurement below the defined cut point for each category is considered negative.



INDURATION OF ≥6 MM IS CONSIDERED POSITIVE IN

> Human immunodeficiency virus (HIV)–infected persons
> Recent contacts of TB case patients
> Persons with fibrotic changes on chest radiograph consistent with prior TB
> Persons with organ transplants and other immunosuppressed patients (e.g. receiving the equivalent of ≥15 mg /d of prednisone for 1 month or more), patients receiving TNF blockers

INDURATION OF ≥15 MM IS CONSIDERED POSITIVE IN

> Recent immigrants (i.e. within the last 5 years) from countries with a high prevalence of TB
> Injection drug users
> Residents and employees* of the following high-risk residential facilities or institutions:
  - Prisons and jails
  - Nursing homes and other long-term facilities for the elderly
  - Hospitals and other healthcare facilities
  - Residential facilities for patients with acquired immunodeficiency syndrome (AIDS)
  - Homeless shelters
> Mycobacteriology laboratory staff
> Persons with the following clinical conditions that place them at high risk:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure
  - Some haematologic disorders (e.g. leukaemia and lymphomas)
  - Other specific malignancies (eg, carcinoma of the head, neck, or lung)
  - Weight loss of ≥10% of ideal body weight
  - Gastrectomy
  - Jejunoileal bypass
> Children less than 5 years of age
> Infants, children, and adolescents exposed to adults at high risk for developing active TB
> Persons with no known risk factors for TB

* For employees who are otherwise at low risk for TB and who are tested as part of an infection control screening program at the start of employment, a reaction of ≥15 mm is considered positive. Some healthcare workers participating in an infection control screening program may have had an induration >0 mm that was considered negative at baseline. If these healthcare workers have an increase in induration size upon subsequent testing, they should be referred for further evaluation.

Note: Reliable administration and reading of the Mantoux Test involves standardisation of procedures, training, supervision, and practice. Always follow your institution's policies and procedures regarding infection control, evaluation, and referral. Also remember to provide culturally appropriate patient education before and after administration, reading, and interpretation of the skin test.

For more information on tuberculosis, visit **www.nice.org.uk/**

Adapted from the CDC NCHSTP Office of Communications' Mantoux Tuberculin Skin Test Wall Chart 2004 incorporating measurements according to the NICE guideline, for more information please visit www.nice.org.uk.

TUBERCULOSIS TEST INSTRUCTIONS

Interferon-Gamma Tests

1. Administration

Confirm arrangements for testing in a qualified laboratory, and arrange for delivery of the blood sample to the laboratory in the time the laboratory specifies to ensure testing of samples with viable blood cells.

- > Draw a blood sample from the patient according to the test manufacturer's instructions
- > Schedule a follow-up appointment for the patient to receive test results, and to arrange for further medical evaluation and possible treatment for latent tuberculosis infection (LTBI) or active TB if needed
- > If you cannot locate a local laboratory to prove IGTs then contact your local Health Protection Agency: http://www.hpa.org.uk/web/HPAweb&Page&HPAwebContentAreaLanding/Page/1153822623816

2. Interpretation

- > Interpretation based on the amount of interferon-gamma (INF-γ) that is released or on the number of cells that release INF-γ
- > Both the standard qualitative test interpretation (positive, negative, or indeterminate) and the quantitative assay measurement should be reported
- > Interferon-gamma tests (like tuberculin skin tests) should be used as an aid in diagnosing infection with *M. tuberculosis*
  - o Positive test result: *M. tuberculosis* infection is likely
  - o Negative test result: *M. tuberculosis* infection is unlikely
  - o Indeterminate test result: uncertain likelihood of *M. tuberculosis* infection
  - o Borderline test result (T-Spot only): uncertain likelihood of *M. tuberculosis* infection
- > Diagnosis of LTBI requires that active TB also be excluded by medical evaluation, including:
  - o Checking for signs and symptoms suggestive of TB disease
  - o Chest radiograph
  - o Examination of sputum or other clinical samples for the presence of *M. tuberculosis*, when indicated
  - o Considerations of epidemiological and historical information

For more information on tuberculosis, visit http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/Tuberculosis/Guidelines/

Reference: Centers for Disease Control and Prevention. Interferon-gamma release assays (IGRAs)–blood tests for TB infection [fact sheet]. Available at: http://www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm. Accessed January 2013.

CONTACT INFORMATION

The current recommendations for targeted testing for TB and treatment regimens for LTBI have been endorsed by NICE. The HPA and the British Thoracic Society provide further information in the screening and management of TB.

Contact information for these 3 important national organisations are as follows:

TB information-National organisations

National Institute for Clinical Excellence
> 0845 003 7780
> http://www.nice.org.uk/

Health Protection Agency
> 020 7811 7000
> http://www.hpa.org.uk/

British Thoracic Society
> 020 7831 8778
> http://www.brit-thoracic.org.uk/

TB information - National Contact

Chest Clinic, Mater Dei Hospital, Msida
General no: +356 2545 0000

For any side effects please report to the Medicines Authority at http://www.medicinesauthority.gov.mt/adrportal or to the local representative of AbbVie Ltd.: V.J. Salomone Pharma Ltd. Upper Cross Road, Marsa MRS1542, Malta, Tel: +356 21 220 174.

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