Diagnosis of Tuberculosis Disease

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Quick Start Check List: Diagnosis of Tuberculosis Disease

The tasks listed below should be performed by licensed nursing, medical, and/or laboratory staff within the scope of their training and licensure.

Tasks for Diagnosis of Tuberculosis Disease	Instructions and Forms
Evaluate the patient with the following, as appropriate: ▪ Medical history (exposure, symptoms, previous treatment of tuberculosis (TB), risk factors) ▪ Human immunodeficiency virus (HIV) screening ▪ Physical examination ▪ Tuberculin skin test (TST) or interferon gamma release assay (IGRA)(in some circumstances) ▪ Chest radiography ▪ Bacteriologic examination (specimen collection and testing for AFB smear, NAAT, culture, and drug susceptibility))	Instructions: Consult local protocols and standing orders. Forms: See Chapter 17 for examples of forms that can be used.
Tasks for Follow up of Patients Diagnosed with Tuberculosis Disease	**Instructions and Forms**
Isolate the patient (if infectious)	Instructions: See Chapter 16, “Infection Control”
Report the case of suspected or confirmed tuberculosis to Public Health	Instructions: • Call the public health district serving the county in which the patient resides or the state TB program to report suspected or confirmed case. • If case is confirmed as having TB, public health district to complete Report of Verified Case of Tuberculosis (RVCT) electronic form when information is available.
Start the patient on treatment for tuberculosis disease	Instructions: See Chapter 6, “Treatment of TB Disease”
Manage the case	Instructions: See Chapter 9, “Case Management”
Conduct the contact investigation	Instructions: See Chapter 10, “Contact Investigations”

Introduction

Purpose

Use this chapter to understand and follow national and Idaho guidelines to

- Detect suspected cases of TB;
- Know when to report suspected or confirmed cases of TB; and
- Diagnose TB disease.

It is important to understand when a person should be evaluated further for TB disease. Not recognizing TB symptoms promptly leads to delays in treating a TB case—and to more infection, TB disease, and contacts to evaluate.

In the 2005 guideline, "Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America," one of the recommended strategies to achieve the goal of reduction of TB morbidity and mortality is early and accurate detection, diagnosis, and reporting of TB cases, leading to initiation and completion of treatment.[1]

Contacts are mentioned within this section, but their evaluation and follow-up and contact investigation are covered in more depth in Chapter 10, "Contact Investigation". For information on treatment, refer to Chapter 6, "Treatment of Tuberculosis Disease".

Improvement in the detection of TB cases is essential to progress toward elimination of TB in the U.S.[2] Case detection includes the processes that lead to the presentation, evaluation, receipt of diagnosis, and reporting of persons with active TB.[3] Detecting and reporting suspected cases of TB is the key step in stopping transmission of *Mycobacterium tuberculosis* because it leads to prompt initiation of effective multiple-drug treatment, which rapidly reduces infectiousness.[4]

TB is commonly diagnosed when a person seeks medical attention for symptoms caused by tuberculosis or a concomitant medical condition. Thus, healthcare providers, particularly those providing primary healthcare to populations at high risk, are key contributors to TB case detection.[5] The majority of pulmonary TB cases continue to be diagnosed at an advanced stage. Earlier diagnosis would result in less individual morbidity and death, greater success in treatment, less transmission to contacts, and fewer outbreaks of TB.[6]

A diagnosis of TB disease is usually based on positive cultures for *M. tuberculosis*. However, TB may also be diagnosed on the basis of clinical signs and symptoms, often with support from positive laboratory testing results (IGRA and/or NAAT) and/or response to treatment, in the absence of a positive culture.

Guidance

In Idaho:

- Persons who show or report signs and symptoms of TB should be evaluated for TB disease as described in the “Diagnosis of Tuberculosis Disease” section of this chapter and reported as suspected cases of TB as described in the “Reporting Tuberculosis” section of Chapter 2, “Surveillance.”
- Contacts should be evaluated as described in Chapter 10, “Contact Investigation.”

For roles and responsibilities, refer to the “Roles, Responsibilities, and Contact Information” section in Chapter 1, “Introduction“.

High-Risk Groups

Certain factors identify persons as being at high risk for tuberculosis (TB) infection; at high risk for progression to TB disease; or both (Table 2) (This table can also be found in Chapter 3 “Targeted Testing for Latent Tuberculosis Infection” and Chapter 7 “Diagnosis of Latent Tuberculosis Infection”.).

Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease are candidates for testing for latent tuberculosis infection in Idaho.

Persons with risk factors from both columns may be at much higher risk than those with risk factors in only one column. For example, an individual born in a high-TB-prevalence country with HIV infection is at much higher risk of having active TB than a U.S.-born individual with HIV infection.

TABLE 2: PERSONS AT HIGH RISK FOR TUBERCULOSIS INFECTION AND PROGRESSION TO TUBERCULOSIS DISEASE[7]

For Tuberculosis Infection	For Progression to Tuberculosis Disease[8]
▪ High-priority contacts such as housemates or coworkers or contacts of persons who have smear-positive pulmonary or laryngeal TB ▪ Infants, children, and adolescents exposed to adults in high-risk categories ▪ Recent immigrants (<5 years) from countries with high incidence of TB. (Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than U.S. rates.) ▪ Migrant workers ▪ Persons who have recently spent over 3 months in high-incidence countries (such as missionaries from the Church of Jesus Christ of Latter-Day Saints) ▪ Native Americans ▪ Persons with high rates of TB transmission: • Homeless persons • Injection drug users • Persons with human immunodeficiency virus (HIV) infection • Persons living or working in institutions with individuals at risk for TB such as: ▪ Hospitals, especially staff in nursing, emergency departments, and laboratories ▪ Long-term care facilities ▪ Homeless shelters ▪ Residences for acquired immunodeficiency syndrome (AIDS) patients ▪ Correctional facilities	▪ Persons with HIV infection ▪ Infants and children aged <5 years ▪ Persons infected with *Mycobacterium tuberculosis* within the previous 2 years ▪ Persons with a history of untreated or inadequately treated TB disease ▪ Persons with radiographic findings consistent with previous TB disease ▪ Persons who abuse alcohol or illegal drugs (such as injection drugs or crack cocaine) ▪ Persons with any of the following clinical conditions or other immunocompromising conditions: • Silicosis • Diabetes mellitus • End-stage renal disease (ESRD)/chronic renal failure, hemodialysis • Some hematologic disorders (e.g., leukemias and lymphomas) • Other malignancies (e.g., carcinoma of head, neck, or lung) • Body weight ≥10% below ideal body weight • Prolonged corticosteroid use • Use of other immunosuppressive treatments (e.g., methotrexate or tumor necrosis factor-alpha [TNF- α] antagonists) • Organ transplantation • Gastrectomy • Chronic malabsorption syndromes • Jejunoileal bypass

Source: Adapted from: CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR 2005;54(No. RR-17):4–5; CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6):7-9.

Case Finding

Identifying Suspected Tuberculosis Cases

The majority of tuberculosis (TB) cases are detected during the medical evaluation of symptomatic illnesses. Persons experiencing symptoms ultimately attributable to TB usually seek care not at a public health TB clinic but rather from other medical practitioners and healthcare settings.[9] Professionals working in the primary healthcare sector, including in ambulatory clinics, hospitals and emergency departments, should be trained to recognize patients with symptoms consistent with TB.[10]

Be alert for cases of TB among persons who have not sought medical care during evaluation of contacts of patients with pulmonary TB and of other persons with newly diagnosed infection with *Mycobacterium tuberculosis*. Screening for TB is also recommended during evaluation of any patient with immigrant or refugee status, and is required for any patient with a Class B1, Class B2, or Class B3 TB notification status. TB screening is also recommended during evaluations of persons involved in TB outbreaks, and for individuals working with populations with a known high incidence of TB. Also, screen for TB disease when the risk for TB in the population is elevated and when the consequences of an undiagnosed case of TB are severe, such as in jails, prisons, and other correctional facilities.[11]

Suspect pulmonary TB and initiate a diagnostic investigation when the historic features, signs, symptoms, and radiographic findings listed in Table 3 are detected. The clinical presentation of TB varies considerably depending on the extent of disease and the patient's response to the infection. TB should be considered in any patient who has persistent cough for more than two to three weeks, or other compatible signs and symptoms.[12]

Note that these symptoms should suggest a diagnosis of TB but are not required. TB should still be considered a diagnosis in asymptomatic patients who have risk factors for TB and chest radiographic findings compatible with TB.

All persons who have a persistent cough for more than two to three weeks[13] should be evaluated and be asked to use a mask or tissue to cover their mouth when in public. Hemoptysis, or coughing up blood, is a serious symptom, and patients who cough up blood should be evaluated as soon as possible. Be sure to have these patients use a mask and tissues.

TABLE 3: WHEN TO SUSPECT PULMONARY TUBERCULOSIS IN ADULTS[14]

Historic Features	▪ Exposure to a person with infectious tuberculosis (TB) ▪ Positive test result for *Mycobacterium tuberculosis* infection ▪ Presence of risk factors, such as immigration from a high-prevalence area, human immunodeficiency virus (HIV) infection, homelessness, or previous incarceration* ▪ Diagnosis of community-acquired pneumonia that has not improved after 7 days of treatment †[15]
Signs and Symptoms Typical of TB	▪ Prolonged coughing (≥2–3 weeks) with or without production of sputum that might be bloody (hemoptysis)§,[16] ▪ Chest pain[17] ▪ Chills[18] ▪ Fever ▪ Night sweats ▪ Loss of appetite[19] ▪ Weight loss ▪ Weakness or easy fatigability[20] ▪ Malaise (a feeling of general discomfort or illness)[21]
Chest Radiograph: Immunocompetent patients	▪ Classic findings of TB are upper-lobe opacities, frequently with evidence of contraction fibrosis and cavitation¶
Chest Radiograph: Patients with advanced HIV infection	▪ Lower-lobe and multilobar opacities, hilar adenopathy, or interstitial opacities, especially bilateral and widespread, might indicate TB

* See Table 2: Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.

† Patients treated with levofloxacin or moxifloxacin may have a clinical response when TB is the cause of the pneumonia.

§ Do **not** wait until sputum is bloody to consider a productive cough a symptom of TB. Sputum produced by coughing does **not** need to be bloody to be a symptom of TB.

¶ These features are not specific for TB, and, for every person in whom pulmonary TB is diagnosed, an estimated 10–100 persons are suspected on the basis of clinical criteria and must be evaluated.

Source: Adapted from: ATS, CDC, IDSA. Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR 2005;54(No. RR-12):33.

Extrapulmonary Tuberculosis

If a patient has a positive tuberculin skin test or interferon gamma release assay (IGRA), also consider signs and symptoms of extrapulmonary TB.

Follow-up on Suspected Cases of Tuberculosis

When a suspected case of TB is identified, the following should be done:

When a suspected case of pulmonary TB is identified, refer to “Diagnosis of Tuberculosis Disease” section of this chapter.

To formally report a suspected case of TB, see the “Reporting Tuberculosis” section in Chapter 2, “Surveillance”.

The patient should be masked with a simple surgical mask and immediately excluded from the workplace or placed in airborne infection isolation (AII) until confirmed noninfectious. For more information, see the “Isolation” section in Chapter 16, “Infection Control”.

Laboratories should report positive smears, positive PCR results, or positive cultures, and primary healthcare providers should report suspected or confirmed cases of TB to the health department, as specified in the “Reporting Tuberculosis” section in Chapter 2, “Surveillance”. Prompt reporting allows the health department to organize treatment and case management services and to initiate a contact investigation as quickly as possible.[22]

Diagnosis of Tuberculosis Disease

Consideration of tuberculosis (TB) disease as a possible diagnosis is the first step that must be taken before further evaluation, diagnosis, and management can occur. The diagnosis of TB disease is often overlooked because of the failure to consider it in the differential diagnosis. While a definitive diagnosis may involve the addition of laboratory and radiographic findings, a high degree of suspicion can be based on epidemiology, medical history, and physical examination. In considering TB disease, it is also important to consider factors that may affect the typical presentation of TB, such as the patient's age, nutritional status, coexisting diseases, and medications that the patient is taking.

An individual who is suspected of having TB disease requires a complete medical evaluation, including the following:

- Medical history, including exposure history or risk factors for exposure, symptoms, previous treatment for TB, and risk factors for developing TB disease
- Human immunodeficiency virus (HIV) screening
- Physical examination
- Tuberculin skin test (TST) or interferon gamma release assay (IGRA), if appropriate
- Chest radiography
- Bacteriologic examination

Medical History

The clinician should interview patients to document their medical histories. A written record of a patient's medical history should include the following:

- Exposure to infectious TB
- Symptoms of TB disease (as listed in Table 3: **When to Suspect Pulmonary Tuberculosis in Adults** and Table 4: **Symptoms of Tuberculosis Disease**)
- Previous TB infection or disease
- Risk factors (as listed in Table 2: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease**)
- Recent medical encounters (e.g., going to the emergency department for pneumonia)
- Previous antibiotic therapy

1. Exposure to infectious TB: Ask patients if they have spent time with someone with infectious TB.

Question patients about whether they know of any contact in the recent or distant past with persons diagnosed with pulmonary or laryngeal TB. It is important to note that patients often refer to latent TB infection (LTBI) as TB disease. Be aware that most persons become infected with *Mycobacterium tuberculosis* without knowing they were exposed. Clinicians should also consider demographic factors that may increase a patient's risk for exposure to TB disease and drug-resistant TB, such as country of origin, age, ethnic or racial group, occupation, and residence in congregate settings (such as a jail, homeless shelter, or refugee camp).

2. Symptoms of TB Disease: Ask patients about their symptoms.

Although TB disease does not always produce symptoms, most patients with TB disease have one or more symptoms that led them to seek medical care. When symptoms are present, they usually have developed gradually and been present for weeks or even months. Occasionally, however, TB is discovered during a medical examination or through medical imaging done for an unrelated condition.

The symptoms in Table 4 below may be caused by other diseases, but they should prompt the clinician to suspect TB disease. For historical features and chest radiograph results that should raise suspicion of pulmonary TB disease, refer to Table 3: **When to Suspect Pulmonary Tuberculosis in Adults.**

TABLE 4: SYMPTOMS OF TUBERCULOSIS DISEASE[23]

Pulmonary	General: Pulmonary and Extrapulmonary	Extrapulmonary
▪ Coughing ▪ Coughing up sputum or blood ▪ Pain in the chest when breathing or coughing	▪ Chills[24] ▪ Fever ▪ Night sweats ▪ Loss of appetite[25] ▪ Weight loss ▪ Weakness or easy fatigability[26] ▪ Malaise (a feeling of general discomfort or illness)[27]	The symptoms depend on part of body affected by tuberculosis (TB) disease: ▪ TB of the spine may cause pain in the back or a noticeable mass. ▪ TB of the kidney may cause blood in the urine. ▪ Meningeal TB may cause headaches or psychiatric symptoms. ▪ Lymphatic TB may cause swollen and tender lymph nodes, often at the base of the neck.

Source: Adapted from: ATS, CDC, IDSA. Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR 2005;54(No. RR-12):33.

3. Previous Latent TB Infection or TB Disease: Ask patients whether they have ever been diagnosed with or treated for TB infection or disease.

- **Patients who have had TB disease before** should be asked when they had the disease and how the disease was treated. Ask how many pills were taken per day or, if known, type, name, shape or color of medication and whether they received injections (to determine what treatment regimen was used). If the regimen prescribed was inadequate or if the patient did not follow the recommended treatment, TB may recur and may be resistant to one or more of the drugs used.
- **Patients known to have a positive skin test reaction or positive IGRA** probably have TB infection. If they were infected within the past two years, they are at high risk for TB disease if certain immunosuppressive conditions exist or if immunosuppressive therapies are being taken. (See Table 2: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease**.)[28]

4. Risk Factors for Developing TB Disease: Determine whether patients have any conditions or behaviors that are risk factors for developing TB disease.

For a list of behaviors and conditions that appear to increase the risk that TB infection will progress to disease, see Table 2: Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.

Human Immunodeficiency Virus Screening

Voluntary counseling and testing for human immunodeficiency virus (HIV) is recommended for all patients with TB. HIV counseling and testing has also been recommended for contacts of persons with TB.[29]

The Centers for Disease Control and Prevention (CDC) recommends the following:

- Routine HIV screening for all patients ages 13–64 seeking health care for any reason, without regard to any of the patient's known risks for HIV infection
- Annual HIV screening of patients known to be at high risk[30]

Physical Examination

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient's overall condition, other factors such as human immunodeficiency virus (HIV) infection that may affect how TB is manifested, and about the presence of extrapulmonary TB.[31]

Tuberculin Skin Test and Interferon Gamma Release Assays

Interferon gamma release assays (IGRAs) are available in Idaho through several commercial laboratories and hospital-based laboratories. Please see the section Chapter 11, "Specimen Collection and Laboratory Services".

Patients with symptoms of TB are sometimes evaluated with an IGRA or TST. However, a negative TST and/or negative IGRA does not rule out TB disease[32]—as many as 20% of patients with active TB disease have a negative TST reaction.[33] A negative result should not be used alone to exclude *M. tuberculosis* infection in persons with symptoms or signs suggestive of TB disease. Medical evaluation of such persons should include a history and physical examination, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus (HIV), and, when indicated, other tests or studies.[34]

For more information on the Mantoux TST and IGRAs, see the Chapter 7, "Diagnosis of Latent Tuberculosis Infection."

For additional information on IGRAs see: Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection --- United States, 2010

Chest Radiography

A posterior-anterior and lateral radiograph of the chest is the standard view used for the detection and description of chest abnormalities in adults. In some instances, other views (e.g., lordotic) or additional studies (e.g., computed tomography [CT] scans) may be necessary.

Children younger than 5 years of age should receive posterior-anterior and lateral radiographs.[35]

Certain abnormalities on chest radiographs are suggestive, but are not diagnostic, of TB. In pulmonary TB, radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, lesions may appear anywhere in the lungs and may differ in size, shape, density, and presence or absence of cavitation, especially in HIV-infected and other immunosuppressed persons.

In HIV-infected persons, pulmonary TB may present atypically on the chest radiograph. For example, TB may cause widespread opacities without cavities in any lung zone, especially if the patient has severe immunosuppression, or it may cause mediastinal or hilar lymphadenopathy with or without accompanying opacities and/or cavities. In HIV-infected persons, almost any abnormality on a chest radiograph may indicate TB. Also, the chest radiograph of an HIV-infected person with TB disease may appear entirely normal.[36]

For more information on chest radiography, see the Francis J. Curry National
Tuberculosis Center's Radiographic Manifestations of Tuberculosis: A Primer
for Clinicians (Second Edition, 2011) at
http://www.currytbcenter.ucsf.edu/products/radiographic-manifestations-tuberculosis-primer-clinicians-second-edition

Bacteriologic Examination

Refer to Table 5 below to determine the types of specimens needed to assist in the diagnosis of TB.

Table 5: SPECIMENS FOR DIAGNOSING TUBERCULOSIS DISEASE

Suspected Diagnosis	Specimen Needed
Pulmonary or laryngeal tuberculosis (TB)	Sputum (phlegm from deep in the lungs) samples for smear and culture examination for all specimens collected and nucleic acid amplification testing (NAAT) on at least the initial specimen. If adequate sputum sample cannot be obtained through coughing, other collection methods may be necessary, including sputum induction, bronchoscopy, or gastric aspiration.
Extrapulmonary TB	Depending on the anatomical site, other clinical specimens may be necessary, such as: ▪ Urine ▪ Cerebrospinal fluid ▪ Pleural fluid ▪ Pus or other aspirated fluid ▪ Biopsy specimens ▪ Blood (heparinized)

Refer to Table 6 below for information on the bacteriologic tests used to diagnose TB. See the Idaho Bureau of Laboratories website https://healthandwelfare.idaho.gov/Health/Labs/tabid/99/Default.aspx for information about *Mycobacterium tuberculosis* test availability, sampling and submission requirements, and turn-around times.

TABLE 6: BACTERIOLOGIC TESTS USED IN DIAGNOSING TUBERCULOSIS DISEASE[37]

Test	Description
Acid-Fast Bacilli (AFB) Smear	▪ Provides the physician with a preliminary confirmation of the diagnosis. It usually is the first bacteriologic evidence of the presence of mycobacteria in a clinical specimen. ▪ If positive, gives a semiquantitative estimate of the number of bacilli being excreted (which is of vital clinical and epidemiologic importance in assessing the patient's infectiousness).
Nucleic Acid Amplification (NAAT) Assay Testing*[38]	▪ A test done on sputum specimens for the direct and rapid identification of the *Mycobacterium tuberculosis* complex. ▪ Allows for the amplification of specific target sequences of nucleic acids that will be detected by a nucleic acid probe. ▪ Does not replace the need for routine AFB smear and culture.[39] ▪
Culture	▪ Usually necessary for species identification of all clinical specimens suspected of containing mycobacteria. ▪ Is required for growth-based drug susceptibility testing and genotyping.
Drug Susceptibility Testing	▪ Growth-based drug susceptibility testing can be done using a liquid medium or a solid medium method. Organisms that grow in media containing a specific drug are considered resistant to that drug. Molecular detection of drug resistance can be done on patient specimens or isolates from patient specimens and involves detection of mutations associated with drug resistance. Molecular tests can provide preliminary guidance on effective TB therapy, but cannot rule out all drug resistance and should always be done in conjunction with growth-based susceptibility testing.

* Identification of M. avium can also be performed if NAAT testing for MTB complex is negative.
IBL-Idaho Bureau of Laboratories
Sources: ATS, CDC, IDSA. Controlling tuberculosis in the United States: Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR 2005;54(No. RR-12):19; Tenover, R., et al. The resurgence of tuberculosis: is your laboratory ready? Journal of Clinical Microbiology 1993:767–770; and CDC Self-Study Modules on Tuberculosis, Modules 1-5, https://www.cdc.gov/tb/education/ssmodules/default.htm.

Laboratories should report positive smears, positive NAATs (or PCRs), or positive cultures and primary healthcare providers should report suspected or confirmed cases of TB to the health department as specified in the "Reporting Tuberculosis" section in Chapter 2, "Surveillance". Prompt reporting allows the health department to organize treatment and case management services and to initiate a contact investigation as quickly as possible.[40]

For information on reporting, see the “Reporting Tuberculosis” section in Chapter 2, “Surveillance.”

TB Genotyping

TB genotyping is a laboratory-based approach that determines the genetic pattern of a strain of *M. tuberculosis.* It is recommended that genotyping be done on all culture-positive cases of TB disease.[41]

Resources and References

Resources

(For easy access to references, hyperlinks are provided for online references in the list below.)

- Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children, *Clinical Infectious Diseases*, Volume 64, Issue 2, 15 January 2017, Pages e1–e33, https://doi.org/10.1093/cid/ciw694
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