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How to Diagnose

A diagnosis of pulmonary tuberculosis (TB) may be considered for any patient who has an abnormal chest x-ray consistent with TB or for any patient who has a persistent cough (i.e., a cough lasting 3 weeks or more) or other signs or symptoms compatible with TB (e.g., bloody sputum, chest pain, night sweats, easy fatigability, weight loss, anorexia or fever). A qualified medical provider should make the diagnosis. The index of suspicion for TB should be very high in areas or among groups of patients in which the prevalence of TB is high.

Approximately 19% of TB cases are exclusively extrapulmonary. The symptoms of extrapulmonary TB depend on the site affected. TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. Extrapulmonary TB should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB.

Persons for whom a diagnosis of TB is being considered should receive:

1. Medical History

A complete medical history should be obtained and should include questions pertaining to risk factors for TB exposure (including demographic history), infection or disease, symptoms of TB, underlying health conditions, risk factors for human immunodeficiency virus (HIV) infection or HIV antibody status, and information about contacts (especially high risk contacts, where immediate action may be necessary). If the patient received prior treatment for TB and the drug regimen was inadequate or if the patient did not adhere to therapy, TB may recur and may be drug resistant. Patients with an unknown or negative HIV status should be referred for HIV counseling and testing.

2. 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 and other factors that may affect how TB is treated.

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3. Tuberculin Skin Test (see “Tuberculin Skin Testing”)

Although a tuberculin skin test (TST) should be obtained on individuals for whom the diagnosis of TB is being considered, it is important to note that a negative TST does not exclude the diagnosis of active TB. On average, 10% to 25% of patients with active TB disease have negative TSTs at diagnosis.

4. Chest X-ray

Patients who have a positive TST result or symptoms suggestive of TB (**regardless of TST result**) should be evaluated with chest x-rays (PA and lateral views). Radiographic abnormalities that strongly suggest active TB include upper-lobe infiltration, particularly if cavitation is seen, and patchy or nodular infiltrates in the apical or subapical posterior upper lobes or the superior segment of the lower lobe. If abnormalities are noted, or if the patient has symptoms suggestive of extrapulmonary TB, additional diagnostic tests should be conducted.

Abnormalities on chest x-ray may be suggestive of, but are never diagnostic of, TB. Chest x-rays may be used, however, to rule out the possibility of pulmonary TB in a person who has a positive reaction to the TST and no symptoms of disease.

The radiographic presentation of pulmonary TB in HIV-infected patients may be unusual. Typical apical cavitory disease is less common among such patients. They may have infiltrates in any lung zone, a finding that is often associated with mediastinal and/or hilar adenopathy, pleural effusion or they may have a normal chest radiograph, although this latter finding occurs rarely.

Old healed TB can produce various radiographic findings such as pulmonary nodules, with or without fibrotic scars or visible calcifications. Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. Bronchiectasis of the upper lobes is a non-specific finding that sometimes occurs from previous pulmonary TB.

The CDPHE TB Program contracts with expert pulmonologists to provide chest x-ray interpretations for suspected/known active TB cases. Chest x-rays on these patients should be

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submitted to the TB Program rather than to a private radiologist for interpretation (CDPHE does not provide funds for chest x-ray interpretation). The program will contract with local public health agencies for a posterior-anterior (PA) and lateral chest x-ray views in adults and children with suspect or known active TB (see “TB Program Contracting and Reimbursement”). Exceptions to this policy may apply in certain circumstances; please call the TB Program for details.

5. Mycobacteriology Services

Mycobacteriology services for diagnostic and epidemiological purposes are available through the TB Program as follows:

- Smear examination - the specimen is concentrated, placed on a slide, and stained with a solution that detects acid-fast bacilli (AFB). Many TB patients have negative AFB smears.
- Culture of the specimen for AFB - the specimen is placed in special media that allows mycobacterial growth. Further biochemical tests are used to identify the type of AFB if growth occurs. Positive cultures for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex may confirm the diagnosis of TB. However, TB may also be diagnosed on the basis of signs and symptoms in the absence of a positive culture.
- Susceptibility testing from cultures positive for *M. tuberculosis* complex – the organism is tested for resistance to drugs commonly used to treat TB (isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide).
- DNA fingerprinting is used to identify specific strains of and is a tool to track TB transmission. Related isolates show the same pattern. In addition, DNA fingerprinting can be used to detect lab contamination.

Nucleic acid amplification tests (e.g. AMPLIFIED *Mycobacterium Tuberculosis* Direct Test—MTD; and polymerase chain reaction) are available through reference laboratories to facilitate rapid detection of *M. tuberculosis* complex. For further information about these tests, contact the TB Program.

Sputum samples should be obtained for smear and culture examination when pulmonary or laryngeal TB is suspected. Because TB can also occur in almost any anatomical site, a variety of

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other clinical specimens (e.g. urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) should be submitted for examination when extrapulmonary TB is suspected.

If a diagnosis of pulmonary TB cannot be established from sputum, other procedures may be necessary, including bronchoscopy and gastric aspiration. TB Program may be consulted when other procedures are considered (see, "How to Obtain" and "TB Program Contracting and Reimbursement").

We encourage providers to submit all specimens to the CDPHE laboratory for free bacteriological examination (see, "How to Obtain CDPHE Laboratory Services"). CDPHE laboratory provides a smear result in 1-2 working days and uses a rapid culture system. Cultures are incubated for 6 weeks. Negative results will be reported at the end of this six-week incubation period. A positive culture result may be reported earlier.

The following is a guide to specimen smear and culture results (continues on next page):

IF AFB SMEAR IS:	IF CULTURE IS:	INTERPRETATION AND ACTIONS
POSITIVE	POSITIVE for AFB, further identification pending	Assume <i>M. tuberculosis</i> complex until proven otherwise; may be later identified as non-tuberculous mycobacteria (NTM). Positive sputum smears are reportable within 24 hours (see, "Reporting Procedures")
POSITIVE	POSITIVE for <i>M. tuberculosis</i> complex	Diagnostic of active TB disease (see "Transmission prevention precautions" and "How to treat"). Reportable within 24 hours (see, "Reporting Procedures")
NEGATIVE	POSITIVE for <i>M. tuberculosis</i> complex	Same interpretation and actions as above.

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IF AFB SMEAR IS:	IF CULTURE IS:	INTERPRETATION AND ACTIONS
POSITIVE	POSITIVE for NTM	Not infected with <i>M. tuberculosis</i> , not contagious. Refer to primary care provider for treatment.
NEGATIVE	POSITIVE for NTM	No bacteriological evidence for <i>M. tuberculosis</i> ; not considered contagious. In many such cases the NTM is a contaminant or colonizer (see below).
NEGATIVE	NEGATIVE for <i>M. tuberculosis</i> complex and NTM	No bacteriologic evidence for <i>M. tuberculosis</i> . If patient has clinical symptoms not explained by another diagnosis and the suspicion for TB is high. Consult with TB Program.

A culture result of *M. tuberculosis* complex is diagnostic of TB disease. However, a false-positive culture should be considered when the results do not fit the patient's clinical status. Patients having only one positive culture should be re-evaluated for the possibility that the culture may be a false positive.

Other mycobacteria (*M. avium* complex (MAC), *M. kansasii*, *M. chelonae*) may cause pulmonary disease usually with a positive smear and culture for acid-fast bacilli (AFB) but are not contagious (see "Non-Tuberculous Mycobacteria," page 65). These organisms may also be present intermittently in small numbers and may not be pathogenic. Although uncommon, a person may be infected with more than one type of mycobacteria at any given time.

When a laboratory performs a culture that is positive for *M. tuberculosis* complex, the laboratory must save the isolate until it receives notification from the state or local health department that the patient has completed a full and appropriate course of treatment for active TB. In lieu of such storage, the laboratory may fulfill this requirement by submitting the isolate to either the state public health laboratory or for facilities located in Adams, Arapahoe, Boulder, Broomfield, Denver, Douglas, and Jefferson counties, to the Denver Public Health Mycobacteriology Laboratory at 605 Bannock St, Denver CO 80204, (303) 436-7366.

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When is an Active Case Contagious?

The factors that correlate with the contagiousness of an active case are:

1. Pulmonary or laryngeal TB
2. Presence of cough or cough-inducing procedures
3. Failure of patient to cover his/her mouth and nose when coughing
4. Positive sputum AFB smear
5. Cavitation on chest radiograph
6. Inappropriate or short duration of treatment adequacy
7. Poor clinical response to treatment

Patients are not considered infectious if they meet **all** the following criteria:

1. They are on adequate therapy
2. They have significant **clinical response to therapy** (i.e., reduction in cough, resolution of fever)
3. They have **three** consecutive negative sputum smear or culture results from sputa collected on different days

See "Transmission Prevention Precautions" for more information regarding patient placement issues.

Patients with extra-pulmonary TB usually are not infectious unless they have pulmonary or laryngeal TB in addition to their extra pulmonary disease or have an abscess or open lesion requiring treatment that may lead to aerosolization of wound drainage.

In general, children who have pulmonary TB are less likely to spread TB than adults because children do not usually develop a cough (so they cannot aerosolize TB organisms). However, transmission from children can occur in certain situations. Therefore, children with TB should be evaluated for infectiousness using the same factors as above for adults.

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Quarantine

State and local health departments have primary responsibility for preventing and controlling TB. To meet this challenge successfully, the Colorado Revised Statutes (25-4-503, 506 and 507) allow for the quarantine of patients with infectious TB who pose a risk to public health (see “Appendices”). The following is a brief summary of the statutes:

- Chief Medical Health Officers are directed to use every available means to investigate immediately and ascertain sources of known or suspected cases of TB in the infectious stage within his/her jurisdiction.
- Chief Medical Health Officers may issue an order requiring the medical examination of known or suspected cases of TB, regardless of the person’s religious denomination or beliefs, by a licensed physician of the examinee’s choice under such terms and conditions as the health officer shall specify.
- Chief Medical Health Officers determine when a quarantine or isolation order is necessary and shall make a quarantine or isolation order in writing which includes: name of patient to be isolated, initial period of time for isolation (not to exceed six months), place of isolation or quarantine, and other such terms and conditions that may be necessary to protect the public health.
- The patient under a quarantine or isolation order shall be examined at the time the order expires or at any other time the patient so requests, to ascertain whether or not the individual continues to be infectious.
- A patient with multidrug-resistant TB may be quarantined after missing one prescribed dose of anti-tuberculosis medications.
- When it has been medically determined that the patient’s disease is no longer

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infectious or communicable, the patient shall be relieved from all further liability or duty imposed by this statute.

State **and** local medical health officers who are licensed physicians have authority to enact the activities described above. For counties with a County Nursing Service, the County Medical Advisor should contact the State Chief Medical Health Officer (Dr. Ned Calonge, 303-692-2700) for quarantine orders.

Local efforts should be made to provide for adequate isolation of all persons with known/suspected infectious TB. Examples include, but are not limited to, restricting the patient to; a) a private, in-patient isolation room within a health facility where there is documented, adequate ventilation systems in place, b) home while wearing a mask when around other household members or staying in their room with the door closed and windows open, c) isolation outside of the home/health care facility in consultation with the TB Program. Isolation must be maintained until confirmation of non-contagiousness. If a patient has been or is at risk of being non-compliant with isolation, a state quarantine order or civil warrant procedure may be undertaken to protect the public.

Quarantine and Health Order Procedures

1. There are three different health orders available to enforce the statutes that are summarized above (see, "Forms"). These include:
 - Order for Patient to Submit to Medical Examination
 - Isolation/Quarantine Order
 - Order to Discontinue Isolation/Quarantine

2. When it is determined necessary or appropriate to serve one or more of the above orders, the Chief Medical Health Officer (local or state) is required to initiate and sign the appropriate form. The CDPHE TB Program must also be notified.

3. A health department representative, sheriff, or deputy sheriff must serve the form to the patient, and must explain the requirements of the order in the patient's primary language.

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4. After serving the form, explaining the order in the patient's primary language, and answering all patient questions, the order server requests that the patient sign the form. The patient has the right to refuse to sign the form, however, the order is still implemented.
5. The health department representative, sheriff, or deputy sheriff then signs the form and provides a copy of the order to the patient, the patient's medical record (if available), and CDPHE. The order server maintains the original form. If the order server is a CDPHE representative, the local health agency will be provided with a copy of the order.
6. The local health agency is responsible for fulfilling the requirements of the order. If the patient violates requirements specified in the order, the CDPHE Chief Medical Health Officer must be notified immediately. The Chief Medical Health Officers will then initiate appropriate civil warrant procedures.
7. The TB Program may provide reimbursement for quarantine services. Each request for reimbursement is reviewed on a case-by-case basis. Prior to authorization for reimbursement consideration, a written financial statement of need completed by a licensed social worker is required, indicating whether the client has other financial means to cover the costs of quarantine.

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Transmission Prevention Precautions

TB transmission prevention precautions **must** be followed for patients who are known or suspected of having active infectious TB. Patients may be identified as having infectious TB based on the patient's signs or symptoms of TB, a history of incomplete TB therapy, sputum smear and culture results, chest x-ray results, and/or the primary care provider's clinical opinion.

An effective TB infection control program requires the early detection, isolation and treatment of persons with known or suspect infectious TB. TB precautions should be based on a careful assessment of risk for transmission of TB in the facility or setting. The primary emphasis of the infection control plan should be on achieving these three goals through a hierarchy of control measures, including:

- Performing the **assessment of the risk** for transmission of TB in the particular setting or area, and for a specific occupational group which should be based on:
 - 1) The profile of TB in the community
 - 2) The number of infectious TB patients admitted to the area or ward or the estimated number of infectious TB patients to whom health care workers (HCWs) in an occupational group may be exposed
 - 3) The results of analysis of HCW skin test conversions (where applicable) and possible person-to-person transmission of *M. tuberculosis*;
- Use of **administrative controls** to reduce the risk of exposure to persons with infectious TB:
 - 1) Developing and implementing effective written policies and work practices to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB. Protocols should include at least the following TB prevention precautions:
 - a. Use triage to promptly identify patients who may have TB;
 - b. Promptly evaluate patients who have TB symptoms;
 - c. Place patient in a separate area apart from other patients and not in open waiting areas

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- (ideally in a room or enclosure with special ventilation maintained under negative pressure);
- d. Give patient a surgical mask to wear until he/she can be transported to an appropriate isolation room or until he/she leaves the building;
 - e. Give the patient a tissue and instruct them to cover their mouth and nose when coughing or sneezing;
 - f. Schedule appointments to avoid exposing other patients, especially HIV infected or immunocompromised persons;
 - g. Avoid performing a cough-inducing procedure (e.g. sputum inductions) on patients who may be infectious unless the procedure is absolutely necessary and performed using local exhaust ventilation devices such as booths or special enclosures or in a room that meets ventilation requirements for TB isolation;
 - h. Allow enough time to pass before placing another patient in a room or area previously occupied by an infectious patient (requires airflow analysis by a qualified engineer to define the length of time needed to remove at least 99% of airborne contaminants);
 - i. If the patient is placed in TB isolation and is not wearing a mask, all persons entering the room must wear special respiratory protection which meets minimum requirements for TB transmission prevention;
 - j. TB transmission prevention precautions can be discontinued if the diagnosis of TB is ruled out or if contagiousness is ruled out (see section 3, page 6);
- 2) Educating training, and counseling HCWs about TB;

This includes basic education regarding TB transmission, pathogenesis, diagnosis, difference between and therapy for latent TB infection and disease, signs and symptoms of TB, higher risks of disease associated with immunocompromised persons, prevalence of TB in the community and facility, transmission prevention precautions, situations that increase risk for exposure, purpose of TST, significance of a positive TST result and recommended follow-up, disease reporting procedures (including symptoms in health care workers), confidentiality, information regarding BCG vaccine associated with principles of TST, and options for work reassignments for immunocompromised HCWs;

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3) Screening HCWs for TB infection and disease;

This includes developing and implementing a tuberculin skin-testing program for persons in the facility with the potential for exposure to TB. Health care workers, including home health nurses, clinic workers and emergency medical technicians, should be included in a TB testing and prevention program if the risk assessment indicates that they are at risk for exposure. This means a TST upon employment and at repeated intervals determined by their risk of exposure thereafter. Any worker who develops symptoms of TB disease or whose TST result converts to positive should be evaluated promptly.

- Use of **engineering controls** to prevent the spread and reduce the concentration of infectious droplet nuclei in the air (adequate ventilation);
- Use of **personal (particulate) respiratory protection**, which has been certified by the National Institute for Occupational Safety and Health (NIOSH), including a respiratory protection program that teaches HCWs how and when to use the respirators.

TB Precautions in Hospitals and Other Inpatient Facilities

Hospitals and other inpatient facilities must initiate isolation in a private isolation room with special ventilation maintained under negative pressure relative to other parts of the facility (air flow from the corridors into the isolation room). The room must be monitored daily while in use to assure that appropriate ventilation is maintained, the door must remain closed, and the patient should only leave the room for medically essential purposes.

For the safety of all workers, the isolation room must be clearly identified as housing a potentially infectious patient. When the patient must leave the room, the patient should wear a surgical mask that covers the nose and mouth at all times.

Patients who are placed in isolation rooms should be educated about the transmission of TB, the reasons for isolation, and the importance of staying in their rooms. The patient should also be

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instructed to cover their nose and mouth when coughing or sneezing.

The number of persons entering the room should be limited and those entering the room must wear appropriate respiratory protective devices. These devices must adequately fit the worker or visitor and be fit checked before its use.

Patients evaluated at or admitted to an inpatient facility and determined to have suspected or known infectious TB cannot be released until the state or local public health agency has made arrangements for appropriate isolation/quarantine post discharge. Proper isolation procedures must be maintained while at the facility.

Isolation should only be discontinued when it is determined that the patient is no longer contagious (see, "When is an active case contagious?")

TB Precautions in Ambulatory-Care Settings and Emergency Departments

Some patients with suspected or known active TB may be evaluated or treated in an outpatient setting under the supervision of or directly provided by the local public health agency. All ambulatory-care settings and emergency departments must develop, implement and update a TB infection control plan in accordance with federal and state rules and/or recommendations (see above recommendations).

Home and Other Health Care Settings

Contact the TB Program for consultation regarding the appropriateness of home placement for individual patients. Patients who are placed at home should be instructed to cover their nose and mouth when coughing or sneezing and be instructed on the importance of taking prescribed therapy and administering directly observed therapy (DOT). Healthcare workers or visitors must wear appropriate respiratory protection when visiting patients with confirmed or suspect TB. Avoid performing cough-inducing procedures on patients who are infectious or use appropriate respiratory protection and perform in a well-ventilated area.

For further detail about transmission prevention, see "Guidelines for Preventing the

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Transmission of *Mycobacterium tuberculosis* in Health Care Facilities”, 1994, MMWR vol 43, No RR-13).

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How to Treat Active Tuberculosis - Basic Guidelines

1. The responsibility for successful treatment is clearly assigned to the public health program or private provider, not to the patient. The prescribing physician (private or public) is carrying out a public health function with responsibility not only for prescribing an appropriate regimen, but also for successful completion of therapy.
2. It is essential that treatment is tailored and supervision be based on each patient's clinical and social circumstances (patient-centered care), with an adherence plan that emphasizes directly observed therapy.
3. Patients who have confirmed active TB (e.g. patients with positive cultures for *M. tuberculosis* or clinical diagnosis by a qualified health care provider) or patients who are considered highly likely to have active TB should be started promptly on appropriate treatment. It is not necessary to wait for laboratory confirmation of TB before starting treatment for patients highly likely to have TB. Patients with confirmed or suspect active TB must be under the medical supervision of a qualified health care provider.
4. Treatment regimens must contain multiple drugs to which the organism is susceptible. The administration of a single drug or the addition of a single drug to a failing regimen can lead to the development of a strain of TB resistant to that drug. All patients should be started on a four-drug regimen containing isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). See specific treatment regimens and first-line TB drug dosages that follow. Adjust weight-based dosages as weight changes.
5. Consult the TB program for information regarding the treatment of patients with drug-resistant TB.

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6. TB medications should be administered together as a single dose rather than in divided doses. A single dose leads to higher and potentially more effective, peak serum concentrations and facilitates DOT.
7. Although ingestion with food delays or moderately decreases the absorption of TB medications, the effects are of little clinical significance.
8. Pyridoxine (Vitamin B-6 25 mg) is recommended for some individuals receiving INH as part of their treatment regimen to prevent peripheral neuropathy. It should be used in persons at risk for neuropathy (nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism, and pregnant or breastfeeding women).
9. Research has shown that non-compliance with patient-administered treatment for active TB leads to high failure rates (e.g. failure to cure the TB and the development of multiple-drug-resistant TB). **Therefore, Colorado regulations require that DOT be provided to all patients with active pulmonary TB and is strongly recommended for active extra-pulmonary disease (due to risk of progression to pulmonary disease).** Exceptions for a particular patient from this DOT requirement must be per approval of the TB Program. Public health agencies are responsible for making arrangements to assure that DOT is provided.

DOT means observation of the patient by a health care provider or other responsible person (i.e., home health care worker, minister, school nurse, or migrant health worker) as the patient ingests antituberculosis medications (the observer should generally not be a family member). DOT may be administered to patients in the office or clinical setting, the patient's home, place of employment, school, or other mutually agreed-upon place.

10. Clinical experience suggests that patients being managed by DOT administered 5 days/week have a rate of successful therapy equivalent to those being drugs 7 days/week. Thus, daily therapy may be given on a 7 days/weeks (182 doses) or 5 days/week (130 doses) DOT schedule.

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11. Patients should be monitored bacteriologically for sputum conversion (e.g., one sputum smear and culture) at least every 4 weeks until two consecutive specimens are negative on culture. Patients under quarantine may be retested more often (e.g. every 2 weeks) to expedite release from public health restrictions, if no longer contagious. Please NOTE: Three consecutive negative sputum smears are needed to release a patient from quarantine. New AFB smears and cultures (including susceptibility testing) should be obtained if new symptoms develop during therapy. One sputum specimen for AFB smear and culture should also be obtained at the end of treatment.

12. Patients with persistently positive cultures after three months of therapy, with or without ongoing symptoms, should be evaluated promptly to identify the cause. Treatment failure is defined as continued or recurrent positive cultures after four months of treatment. There are multiple, potential reasons for treatment failure including non-adherence to therapy such as spitting out or deliberately regurgitating pills after DOT, failure of the health care system to reliably deliver the drugs, unrecognized drug resistance (inaccurate drug susceptibility testing), or malabsorption of medications. Consult the TB Program or clinical expert for further recommendations.

13. Careful attention should be given to measures that foster adherence to therapy (e.g incentives). See “How to Motivate People to Comply With Therapy.” National health statistics indicate that culturally inappropriate care and lack of understanding of cultural differences may negatively affect health outcomes. Thus, it is imperative to become culturally competent and guide other health providers towards culturally competent health care. A culturally competent system acknowledges cultural differences with regard to health care and incorporates appropriate care policy, provider and consumer levels. It is important to have an understanding of different conceptions of illness and healing when providing health care to culturally and ethnically diverse populations. It may be necessary to utilize the assistance of language/cultural interpreters and to alter the plan of care so that patients are treated with dignity and respect for their culture.

14. Because rifamycins (e.g. rifampin, rifabutin, rifapentine) may decrease the effectiveness of oral contraceptives (the “pill”), an alternate birth control method should be used.

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15. Other drug interactions can occur. It is important to notify the pharmacy when patients are taking other medications to learn about potential interactions. Consult the Apothecary Pharmacy for additional information at (303) 499-2879.
16. All patients with active TB should be offered HIV testing.
17. The determination of whether treatment has been completed is based upon the total number of doses taken and not solely on the duration of therapy. The initial phase of treatment should be completed within three months and the continuation phase completed within 6 months. Thus, the doses for a six-month regimen should be completed within 9 months.

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Treatment Regimens for Culture Positive, Drug Susceptible Pulmonary TB

Initial Phase			Continuation Phase			Range of Total Doses (minimal duration)	Rating ³ (Evidence) ⁴	
Regimen	Drugs	Interval & Doses ¹ (minimal duration)	Regimen	Drugs	Interval & Doses ^{1,2} (minimal duration)		HIV ⁻	HIV ⁺
1	INH RIF PZA EMB	7 days/week for 56 doses (8 wks) or 5 days/week for 40 doses (8wks)	1a	INH/RIF	7 days/wk for 126 doses (18 wks) or 5 days/wk for 90 doses (18 wks) ⁶	182 – 130 (26wks)	A (I)	A (II)
			1b	INH/RIF	2 x weekly for 36 doses (18 wks)	92 – 76 (26wks)	A (I)	A (II) ⁷
			1c ⁵	INH/RPT	Once weekly for 18 doses (18 wks)	74 – 58 (26wks)	B (I)	E (I)
2	INH RIF PZA EMB	7 days/week for 14 doses (2 wks) then 2 x weekly for 12 doses (6 wks) or 5 days/week for 10 doses (2 wks) ⁶ then 2 x weekly for 12 doses (6 wks)	2a	INH/RIF	2 x weekly for 36 doses (18 wks)	62 – 58 (26wks)	A (II)	B (II) ⁷
			2b ⁵	INH/RPT	Once weekly for 18 doses (18wks)	44 – 40 (26wks)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wks)	3a	INH/RIF	Three times weekly for 54 doses (18wks)	78 (26wks)	B (I)	B (II)
4	INH RIF EMB	Seven days/week for 56 doses (8 wks) or 5 days/week for 40 doses (8wks) ⁶	4a	INH/RIF	7 days per week for 217 doses (31wks) or 5 days/week for 155 doses (31wks) ⁶	273 – 195 (39wks)	C (I)	C (II)

Definition of abbreviations: INH = isoniazid; RIF = rifampin; EMB = ethambutol; PZA = pyrazinamide; RPT = rifapentine

1 When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although, there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.

2 Patients with cavitation on initial chest x-ray and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 272 daily doses or 62 twice weekly doses) continuation phase.

3 Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

4 Definitions of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

5 Options 1c and 2b should be used only in HIV negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest x-ray. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

6 Five-day-a-week administration is always given by DOT. Rating for 5/day week regimen is A (III).

7 Not recommended for HIV infected patients with CD4⁺ cell counts < 100 cells/ml.

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			4b	INH/RIF	2 x /wk for 62 doses (31wks)	118 – 102 (39wks)	C (I)	C (II)
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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
FIRST-LINE DRUGS						
Isoniazid (INH)	Tablets (50mg, 100mg, or 300mg)	Adults (≥15yrs or 40kg) (max dose) Children (max dose)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)	15 mg/kg (900 mg) -	15 mg/kg (900 mg) 20-30 mg/kg (900mg)	15 mg/kg (900mg) -
Rifampin (RIF)	Capsules (150mg or 300mg)	Adults (≥15yrs or 40kg) (max dose) Children (max dose)	10 mg/kg (600mg) 10-20 mg/kg (600 mg)	- -	10 mg/kg (600 mg) 10-20 mg/kg (600 mg)	10 mg/kg (600 mg) -
Rifabutin	Capsules (150mg)	Adults (≥15yrs or 40kg) (max dose) Children	5 mg/kg (300 mg) Appropriate dosing for children unknown	- Appropriate dosing for children unknown	5 mg/kg (300 mg) Appropriate dosing for children unknown	5 mg/kg (300 mg) Appropriate dosing for children unknown
Rifapentine (RPT)	Tablets (150mg, film coated)	Adults (≥15yrs or 40kg) (max dose) Children	- Not approved for use in children	10 mg/kg continuation phase (600 mg) Not approved for use in children	- Not approved for use in children	- Not approved for use in children

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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
FIRST-LINE DRUGS						
Pyrazinamide (PZA)	Tablets (500mg, scored)	Adults (≥ 15 yrs or 40kg) (max dose) Children (max dose)	1,000 mg if 40-55 kg 1,500 mg if 56-75 kg 2,000 mg if 76 kg or more 15-30 mg/kg (2,000 mg)	-	2,000 mg if 40-55 kg 3,000 mg if 56-75 kg 4,000 mg if 76 kg or more	1,500 mg if 40-55 kg 2,500 mg if 56-75 kg 3,000 mg if 76 kg or more
Ethambutol (EMB)	Tablets (100mg or 400 mg)	Adults (≥ 15 yrs or 40kg) (max dose) Children (max dose)	40-55 kg = 800mg 56-75kg = 1,200mg ≥ 76 kg = 1,600 mg 15-20 mg/kg (1,000 mg)	-	40-55 kg = 2,000mg 56-75 kg = 2,800mg ≥ 76 kg = 4,000mg	40-55 kg = 1,200mg 56-75 kg = 2,000mg ≥ 76 kg = 2,400mg
SECOND-LINE DRUGS						
Cycloserine	Capsules (250mg)	Adults (≥ 15 yrs or 40kg) (max dose) Children (max dose)	10-15mg/kg per day (1,000 mg in two doses, usually 500- 750 mg/day in two doses) 10-15mg/kg per day (1,000 mg/d)	No data to support intermittent administra- tion	No data to support intermittent administration	No data to support intermittent administra- tion

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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
SECOND-LINE DRUGS, CONT.						
Ethionamide	Tablets (250mg)	Adults (≥ 15 yrs or 40kg) (max dose) Children (max dose)	15-20mg/kg per day 1,000mg/day (usually 500- 750mg/day in two divided doses or single daily dose at HS or with a main meal) 15-20mg/kg per day (1,000 mg/day)	No data to support intermittent administra- tion in adults or children	No data to support intermittent administration in adults or children.	No data to support intermittent administratio n in adults or children.
Streptomycin (continued on next page)	Aqueous solution (1-g vials) for IV or IM injection	Adults (≥ 15 – 50 yrs) (max dose) (> 50 years) (max dose)	15 mg/kg/day (1,000mg/day) 10 mg/kg/day; (750 mg) Usual dose is 750-1,000mg IM or IV 5-7 days/week for 2-4 months or after culture conversion, then reduce to 2-3 times per wk	-	-	-

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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
SECOND-LINE DRUGS, CONT.						
Streptomycin, Cont.	Aqueous solution (1-g vials) for IV or IM injection	Children (max dose)	20-40mg/kg/d (1,000 mg)	-	20 mg/kg (1,000 mg)	-
Amikacin/ Kanamycin	Aqueous solution (500mg and 1-g vials) for IV or IM admin	Adults (≥15 – 50 yrs or 40kg) (max dose) (> 50 years) (max dose)	15 mg/kg/day (1,000mg/day) 10 mg/kg/day; (750 mg) Usual dose is 750-1,000mg IM or IV 5-7 days/week for 2-4 months or after culture conversion, then reduce to 2-3 times per wk 15-30mg/kg/d (1,000 mg) IV or IM as single daily dose	-		-
					15-30 mg/kg	

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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
SECOND-LINE DRUGS, CONT.						
Capreomycin	Aqueous solution (1-g vials) for IV or IM admin.	Adults (≥15 – 50 yrs or 40kg) (max dose) (> 50 years) (max dose) Children (max dose)	15 mg/kg/day (1,000mg/day) 10 mg/kg/day; (750 mg) Usual dose is 750-1,000mg IM or IV 5-7 days/week for 2-4 months or after culture conversion, then reduce to 2-3 times per wk 15-30mg/kg/d (1,000 mg) as a single daily dose	-	-	-
p-Aminosalicylic acid (PAS)	Granules (4 g packets) can be mixed with food	Adults (≥15yrs or 40kg) Children (max dose)	8-12 g/day in 2 or 3 doses 200-300 mg/k/day in 2 or 4 divided doses 10 gm/day	-	-	-

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Doses of Anti-Tuberculosis Drugs for Adults and Children

Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
SECOND-LINE DRUGS, CONT.						
Levofloxacin	Tablets (250mg, 500mg, or 750mg); Aqueous solution 500 mg vials for IV injection	Adults (≥15yrs or 40kg) Children	500 – 1,000mg daily Long term use has not been approved. However, most experts agree the drug should be considered in children with multi-drug resistant TB. Optimal dose unknown.	- Long term use has not been approved. However, most experts agree the drug should be considered in children with multi- drug resistant TB. Optimal dose unknown.	- Long term use has not been approved. However, most experts agree the drug should be considered in children with multi-drug resistant TB. Optimal dose unknown.	- Long term use has not been approved. However, most experts agree the drug should be considered in children with multi- drug resistant TB. Optimal dose unknown.
Moxifloxacin	Tablets (400mg); Aqueous solution 400 mg/250 ml for IV injection	Adults (≥15yrs or 40kg) Children	400 mg daily Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.

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Drug	Preparation	Adults/ Children	Doses			
			Daily	Once Weekly	Twice Weekly	3 X Weekly
SECOND-LINE DRUGS, CONT.						
Gatifloxacin	Tablets (400mg); Aqueous solution 200mg/20 ml or 400 mg/40 ml for IV injection or	Adults (≥15yrs or 40kg) Children	400 mg daily Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.	- Long-term use (more than several weeks) has not been approved in children. Optimal dose unknown.

NOTE: CDPHE will initially provide a two-week supply of medication for daily therapy. Then, a 2, 4, or 6 weeks supply of medication will be provided in order to complete the initial 8-week treatment period (depending on patient's diagnosis status). Thereafter, CDPHE will provide a 4-week supply of medication at a time until treatment is complete.

*Repackaging of TB medications is prohibited by the Colorado Board of Pharmacy Rules and Regulations. TB medications must be dispensed by a nurse from multiple-dose bottles or by a nurse or outreach worker with daily pre-packaged medications (by the pharmacy).

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TB Treatment in Special Situations

Extrapulmonary TB

The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. Among patients with extrapulmonary TB, a 6-9 month regimen (2 months of INH, RIF, PZA, and EMB, followed by 4-7 months of INH and RIF) is recommended unless the organisms are known or strongly suspected of being resistant to the first line drugs. The exception to the recommended 6-9 month regimen is TB meningitis, for which the optimal length of therapy has not been established, but some experts recommend 9-12 months. Additionally, INH/Rifapentine (RPT) once weekly in the continuation phase is NOT recommended for treatment of any forms of extrapulmonary TB. Consult the TB Program for further information.

TB and HIV Infection

Management of HIV-related TB is complex. Therefore, care should be provided by or in consultation with experts in management of both HIV and TB. The treatment of TB in persons with HIV infection is essentially the same as for non-HIV infected persons. There are two important exceptions to this generalization: 1) Once weekly INH/RPT in the continuation phase should NOT be used in any HIV patient; and 2) Twice weekly INH/RIF or rifabutin should NOT be used for patients with CD4⁺ lymphocyte counts less than 100/ul. Providers must be alert to the potential for interactions among many of the anti-retroviral drugs and the rifamycins. Paradoxical reactions that mimic worsening of TB disease are more common in patients with HIV infection and may complicate therapy (see Section 6, "TB and HIV").

TB in Children and Adolescents

It is more difficult to isolate *M. tuberculosis* from a child with pulmonary TB than from an adult. Thus, treatment should be guided by the results of culture and susceptibility tests of specimens from the person presumed to be the source of the child's infection.

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Tuberculosis in infants and children younger than four years of age are is more likely to disseminate, thus treatment should be started as soon as the diagnosis is suspected. Children with TB are essentially treated the same way as adults with TB, except that dosages should be adjusted. The recommended duration of treatment in children is 6 months, with the exception of disseminated disease and TB meningitis, for which a 9-12 month regimen is recommended. Additionally, rifampentine is not approved for use in children.

The preferred method of treatment is to use tablets/capsules and not liquid medications to minimize side effects. Medications can be made into powder form: tablets can be cut into smaller pieces and crushed and capsules can be opened. Administer the powder in applesauce, yogurt or other food. INH can also be dissolved in a small amount of warm water and added to apple juice in a medicine cup (mixture amount should be no more than one or two swallows of liquid). Consult the TB Program for further recommendations.

Culture Negative Pulmonary TB in Adults

Persons with clinical or chest x-ray findings suspicious for pulmonary TB should have a thorough medical evaluation and a minimum of three sputum specimens collected. A diagnosis of active pulmonary TB should not be excluded in patients with 3 negative sputum culture results that are suspected of having pulmonary TB. Patients determined to have clinical pulmonary TB should start treatment with INH/RIF/EMB/PZA. A follow-up clinical and x-ray evaluation should be obtained after 2 months of therapy. If there is clinical or x-ray improvement and no other etiology is identified, treatment should be continued for an additional 2 months with INH/RIF (4 months total). A 4-month regimen for culture negative TB has been demonstrated to be successful. Note: If suspicion of pulmonary TB is high and the patient has positive AFB smears, even with negative cultures, he/she should be treated as if the culture is positive, using one of the recommended regimens.

TB in Pregnancy and Breastfeeding

Pregnant and lactating women with TB must be given adequate therapy as soon as TB is suspected. The preferred treatment regimen is isoniazid, rifampin, and ethambutol for 9 months

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(see, “First-line TB Drugs Dosages” and “Treatment Regimens”). A minimum of 9 months of therapy should be given since pyrazinamide cannot be used in pregnant patients. Pyridoxine (vitamin B-6) should also be given to prevent peripheral neuropathy. The following drugs should not be used because they have either been shown to have harmful effects on the fetus or because the effects on the fetus are unknown: pyrazinamide, streptomycin, capreomycin, ethionamide, cycloserine, ciprofloxacin, ofloxacin, amikacin, clofazimine.

The small concentrations of TB drugs in breast milk do not have a toxic effect on nursing newborns, and breast-feeding should not be discouraged. Conversely, drugs in breast milk should not be considered effective treatment for disease or infection in a nursing infant.

Because rifampin and rifapentine may decrease the effectiveness of hormonal birth control methods, an alternate method should be used.

TB in Renal Insufficiency and End-Stage Renal Disease

Renal insufficiency complicates the management of TB because some TB drugs are cleared by the kidneys. Management may be further complicated by the removal of some anti-tuberculosis agents via hemodialysis. Administration of all TB drugs immediately after hemodialysis will facilitate DOT (three times weekly) and avoid premature removal of the drugs. Consult the TB Program for further recommendations.

TB and Hepatic Disease

The treatment of TB in patients with unstable or advanced liver disease is problematic for several reasons. First, the likelihood of drug-induced hepatitis may be greater. Second, the implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life threatening. Finally, fluctuations in the biochemical indicators of liver function (with or without symptoms) related to the pre-existing liver disease confound monitoring for drug-induced hepatitis. Thus, clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease, and expert consultation is advisable in treating such patients. Consult the TB Program for further recommendations.

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TB Drugs - Adverse Reactions and Monitoring

Drug	Adverse Reactions	Monitoring*	Comments
Isoniazid	Hepatic enzyme elevation (can be asymptomatic) Clinical or fatal hepatitis Peripheral neurotoxicity Mild effects on central nervous system (dysarthria, irritability, seizures, dysphoria, inability to concentrate) Lupus-like syndrome Hypersensitivity reactions Monoamine poisoning Diarrhea Drug interactions (serum levels of phenytoin and carbamazepine may increase)	Baseline liver function tests for adults on treatment for active TB then monthly if baseline abnormalities or if increased risk of hepatotoxicity. Children do not require monitoring unless symptoms develop.	Hepatitis risk increases with age and alcohol consumption. Add pyridoxine (B-6 25 mg) if patient has conditions that may be associated with neuropathy (nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism, pregnant or breastfeeding women).
Rifampin	Orange discoloration of body fluids Cutaneous reactions (pruritis with or without rash) Hepatotoxicity GI reactions Severe immunologic reactions (thrombocytopenia, hemolytic anemia) Flu-like symptoms Several drug interactions (consult the TB Program Pharmacy at 303-499-2879)	Baseline liver and renal function tests, and platelet count. No routine monitoring is required, unless abnormalities in baseline measurements are present. Check for drug interactions.	Significant interactions with methadone, birth control pills, and other drugs (consult TB Program Pharmacy 3030-499-2879). Colors body fluids orange; May permanently discolor soft contact lenses.

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above may be reimbursable by the local public health agency for patients with no other means to pay (see, "TB Program Billing and Reimbursement").

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Drug	Adverse Reactions	Monitoring*	Comments
Rifabutin	Orange discoloration of body fluids Hematologic toxicity Uveitis GI reactions Polyarthralgias Hepatotoxicity Pseudojaundice Rash Flu-like symptoms Drug interactions (consult the TB Program Pharmacy 303-499-2879)	Baseline liver and renal function tests, and platelet count. No routine monitoring is required, unless abnormalities in baseline measurements are present. Check for drug interactions.	Interactions may occur with methadone, birth control pills, and other drugs (consult TB Program Pharmacy 3030-499-2879). Colors body fluids orange; May permanently discolor soft contact lenses.
Rifapentine	Orange discoloration of body fluids Cutaneous reactions (pruritis with or without rash) Hepatotoxicity GI reactions Severe immunologic reactions (thrombocytopenia, hemolytic anemia) Flu-like symptoms Drug interactions (consult the TB Program Pharmacy at 303-499-2879)	Baseline liver and renal function tests, and platelet count. No routine monitoring is required, unless abnormalities in baseline measurements are present. Check for drug interactions.	Interactions may occur with methadone, birth control pills, and other drugs (consult TB Program Pharmacy 3030-499-2879). Colors body fluids orange; May permanently discolor soft contact lenses.
Pyrazinamide	Hepatotoxicity GI reactions Transient morbilliform rash Dermatitis Non-gouty polyarthralgia Hyperuricemia (asymptomatic) Acute gout (rare)	Baseline uric acid and liver function testing for adults. Repeat if baseline abnormal, if patients have underlying liver disease, or if symptoms of adverse reactions occur.	

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above may be reimbursable by the local public health agency for patients with no other means to pay (see, “TB Program Billing and Reimbursement”).

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Drug	Adverse Reactions	Monitoring*	Comments
Ethambutol	Retrolubar neuritis Peripheral neuritis Cutaneous reactions	Baseline visual acuity and color vision. Question patient monthly for possible visual disturbances. Repeat visual acuity and color vision tests monthly for patients with renal insufficiency or if patient is taking a higher dose than is recommended. Refer patients with visual changes to their private provider immediately.	Used with caution in children too young to be monitored for changes in vision, unless TB is drug resistant.
Streptomycin	Ototoxicity (hearing loss or vestibular dysfunction) Neurotoxicity Nephrotoxicity	Baseline audiogram, vestibular and Romberg testing and serum creatinine. Question patient monthly for changes in renal function and auditory or vestibular symptoms. Repeat audiogram and vestibular testing if symptoms of 8 th nerve toxicity develop.	
Cycloserine	Mild to severe central nervous system effects (headaches, restlessness, psychosis, seizures)	Assess neuropsychiatric status monthly	Should not be used in pregnant women unless there are no suitable alternatives. Should be used cautiously in patients with impaired renal function.

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above may be reimbursable by the local public health agency for patients with no other means to pay (see, "TB Program Billing and Reimbursement").

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Drug	Adverse Reactions	Monitoring*	Comments
Ethionamide	GI reactions Metallic taste Hepatotoxicity Neurotoxicity Endocrine disturbances (e.g. gynecomastia, alpecia, hypothyroidism, impotence)	Baseline liver function and thyroid stimulating hormone (TSH) tests. No routine liver function monitoring is required, unless abnormalities in baseline measurements are present or symptoms develop. Obtain a monthly (THS).	Should NOT be used in pregnant women. Reactions may improve if doses are taken with food or at bedtime. Diabetes may be more difficult to manage. Use with caution in patients with hepatic disease and renal disease.
Amikacin/ Kanamycin	Ototoxicity Nephrotoxicity	Baseline audiogram, vestibular and Romberg testing and serum creatinine. Question patient monthly for changes in renal function and auditory or vestibular symptoms. Repeat audiogram and vestibular testing if symptoms of 8 th nerve toxicity develop.	Patients with severe hepatic disease may be at greater risk of nephrotoxicity. Should be used with caution in patients with renal function impairment. Contraindicated in pregnant women.
Capreomycin (Continued on next page)	Nephrotoxicity Ototoxicity	Baseline audiogram and vestibular and Romberg testing. Question patient monthly for changes in auditory or vestibular symptoms. Repeat audiogram and vestibular testing if symptoms of 8 th nerve toxicity develop. Baseline creatinine, serum potassium, and magnesium concentrations. Question patient monthly for changes	Should be avoided during pregnancy. Use with caution in patients with renal function impairment.

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above may be reimbursable by the local public health agency for patients with no other means to pay (see, "TB Program Billing and Reimbursement").

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Drug	Adverse Reactions	Monitoring*	Comments
Capreomycin (Continued from previous page)	Nephrotoxicity Otototoxicity	in renal function symptoms. Repeat serum potassium and magnesium concentrations monthly.	Should be avoided during pregnancy. Use with caution in patients with renal function impairment.
p- Aminosalicylic acid (PAS)	Hepatotoxicity GI symptoms (most common) Malabsorption syndromes Steatorrhea Hypothyroidism (esp. if used with Ethionamide) Coagulopathy (doubling of pro-time)	Baseline liver function and thyroid function testing. Repeat thyroid function every three months.	Safe to use during pregnancy. Marginal efficacy in TB meningitis. Contraindicated in patients with severe renal insufficiency, unless there is no alternative. Should be administered after dialysis.
Fluoroquino- lones (e.g. Levofloxacin, Ciprofloxacin, Moxifloxacin, Gatifloxacin)	GI symptoms Neurologic effects (dizziness, insomnia, headache, tremors) Cutaneous effects (rash, photosensitivity, pruritis) ** The above adverse reactions have been noted with use of Levofloxacin. Information regarding adverse effects of other fluoroquinolones is limited.	No specific monitoring is recommended.	Should be avoided during pregnancy. Do not administer within 2 hours of treatment with antacids and other medications containing divalent cations.

* Most third party payers will cover monitoring costs. However, costs for monitoring as described above may be reimbursable by the local public health agency for patients with no other means to pay (see, "TB Program Billing and Reimbursement").

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Management of Patients with Adverse Reactions to TB Drugs

Adverse Reactions Most Commonly Encountered*

Nature	Symptoms and Signs	Usual Causes
Dermatologic	Itching, rash, hives, fever, etc.	Pyrazinamide (most commonly), rifampin, rifabutin, rifapentine, rarely ethambutol, isoniazid, levofloxacin
Hepatitis	Anorexia, nausea, vomiting, jaundice	Isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, ethionamide, PAS
Gastrointestinal complaints	Anorexia, nausea, vomiting, epigastric pain, diarrhea, steatorrhea, malabsorption syndromes	Isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, ethionamide, PAS and levofloxacin
Neurotoxicity/CNS effects	Peripheral neuritis (numbness or paresthesia of feet or hands), anxiety, psychosis, depression, headaches, restlessness, seizures, circumoral parasthesias	Isoniazid, ethambutol, streptomycin, cycloserine, ethionamide, levofloxacin
Joint abnormalities	Gout-like symptoms, arthralgias, lupus-like syndrome, pain	Rifabutin, rifapentine, pyrazinamide, rarely isoniazid
Nephrotoxicity	Azotemia, hyperuricemia, proteinuria, hematuria, urinary casts, pyuria	Amikacin/kanamycin, capreomycin, pyrazinamide, streptomycin (less common)
Hematologic effects	Leukopenia, other Thrombocytopenia, thrombocytosis, neutropenia, lymphopenia, anemia, leukopenia, reduced creatinine clearance, potassium or magnesium depletion, doubling of pro-time	Isoniazid, rifampin, rifabutin, rifapentine, pyrazinamide, PAS

*See details on management of adverse reactions that follow table

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Adverse Reactions Most Commonly Encountered, Continued*

Nature	Symptoms and Signs	Usual Causes
Endocrine effects	Hypothyroidism, gynecomastia, alpecia, metallic taste, impotence	Ethionamide, PAS
Eye effects	Loss of vision and color blindness, uveitis, optic neuritis, retrobulbar neuritis	Rifabutin, ethambutol
Flu like illness	Fever, myalgias, malaise	Rifampin, rfiabutin, rifapentine
Hearing effects (8th nerve damage)	Hearing loss, ataxia, vestibular dysfunction	Streptomycin, amikacin/kanamycin, capromycin

*See details on management of adverse reactions that follow table.

Dermatologic Reactions

History and Examination:

1. The individual should be questioned about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible.
2. HIV-seropositive individuals are subject to a variety of dermatologic diseases either directly or indirectly related to HIV infection, or to other medications used for therapy or prophylaxis. Consultation with an appropriate infectious disease service or dermatology clinic is recommended.
3. There should be a careful examination to detect evidence of unrelated skin disease (scabies, contact dermatitis, childhood exanthem, acne, etc.).
4. Rash, particularly with other systemic symptoms, may be associated with hepatitis; measurement of AST (SGOT) should be considered.

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Follow up:

1. Unless an explanation is found for skin reaction unrelated to anti-tuberculosis medications, all anti-tuberculosis medications should be discontinued promptly and the individual examined each week until the skin reaction disappears.
2. CBC with platelet count may be indicated if there is evidence of petechiae.
3. Cases of severe dermatologic reactions, such as exfoliative dermatitis, and other cases of dermatitis associated with severe systemic reactions should be referred for hospital admission and for establishing a new anti-tuberculosis regimen or for rechallenge with the current medications while the patient is under daily surveillance as an inpatient.
4. Transient rashes that occur within 30-60 minutes of pyrazinamide administration and that last only 1-2 hours are usually due to pyrazinamide and are usually not treatment-limiting. If not severe and not associated with clinical or chemical hepatitis, treatment can be cautiously continued (preferably by direct observed therapy--DOT) and antihistamines used to reduce symptoms.

Restarting Anti-Tuberculosis Medications:

1. In cases managed in a clinic with a mild dermatological reaction, it is appropriate to rechallenge after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to restart the most important member or members of the regimen (isoniazid or rifampin) immediately, before trying pyrazinamide and/or ethambutol.
 - Single daily doses of isoniazid or rifampin should be given alone for three days with instruction to discontinue them promptly if the reaction recurs. The individual should be examined in three (3) to four (4) days.
 - If there is no reaction, the alternate drug, rifampin or isoniazid, should be given with similar instructions. The individual should be reexamined in three to four days.

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- Ethambutol or streptomycin should be given next, as these are unlikely to cause a rash.
 - If there is no recurrence of the skin reaction, pyrazinamide should be given, if this was in the initial regimen. If rash occurs with pyrazinamide but is not severe or associate with systemic symptoms, symptomatic management with the patient with the use with pyrazinamide with allow a 3-month shorter course of therapy.
2. If one of the initial drugs cannot be restarted because of an adverse reaction, treatment should be continued with the original regimen without the causative agent, with consideration about adding a new alternative drug (quinolone or aminoglycoside). If isoniazid, rifampin or pyrazinamide must be discontinued during the initial 2-months of treatment, a longer period of treatment is required. If treatment must be continued with a regimen that contains isoniazid or rifampin but not both, a 3-drug regimen may be needed for the remaining course. In such instances, the addition of a single agent to a successful regimen does not violate the rule of "do not add a single drug to a failing regimen."
 3. The same principles of management apply to cases with dermatologic reactions while on "retreatment" regimens for multi-drug resistant TB.

Drug-Related Hepatitis

History and Examination:

1. Individuals taking anti-tuberculosis medication(s) and who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) should be instructed to discontinue all medications promptly, be examined by their care provider, and have liver function tests (LFTs).

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Laboratory Evaluation:

1. If symptoms disappear quickly and LFTs are normal, anti-tuberculosis drug-induced hepatitis is unlikely. Another cause for symptoms should be suspected, and depending upon the nature, duration and severity of symptoms, a decision made regarding further diagnostic investigation. If evidence is secure that symptoms are unrelated to anti-tuberculosis medication(s), the entire regimen should be reinstated promptly and the individual followed closely for recurrence of symptoms.
2. If the LFTs are abnormal (SGOT/AST or SGPT/ALT is >3-5 times the upper limit of normal) with or without symptoms, drug-related hepatitis should be strongly suspected and all anti-tuberculosis medication(s) discontinued. Isolated mild bilirubin elevations without elevated AST (SGOT) may occur with rifampin and resolve with continued therapy; in most instances, treatment should be interrupted. Physicians/care providers should be strongly encouraged to consider cautiously continuing treatment for patients with known, pre-existing liver disease (e.g. chronic hepatitis or alcohol abuse).
3. The individual should be examined, and have LFTs repeated at least weekly. If symptoms persist for more than two (2) weeks without anti-tuberculosis medication(s), or if LFTs continue to worsen, either an unrelated cause for hepatitis, or progressive drug-related hepatitis should be suspected. Depending upon the severity of the hepatitis, judged by clinical findings and LFTs, hospitalization for closer observation and therapy may be indicated.

Restarting Anti-Tuberculosis Medications:

1. If the individual has severe pulmonary, or disseminated TB, or is HIV-seropositive, institution of a new regimen with lesser potential for hepatotoxicity (e.g. streptomycin, ethambutol, fluoroquinolone) may be indicated even before liver enzymes normalize, while sorting out the cause of toxicity.
2. Except for cases of liver toxicity unrelated to anti-tuberculosis therapy, and those included in item #1 immediately above, treatment should be withheld until symptoms

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resolve and the LFTs are normal, or have "plateaued" at a stable but elevated level. During this time, the individual should be followed closely with weekly examinations and test of liver functions. It is then appropriate to rechallenge with a single daily dose of one of the drugs in the prior regimen.

If AST (SGOT) elevation is greater than 500 IU/L and no other likely cause for elevation is present, isoniazid hepatotoxicity should be strongly considered. Some experts would avoid a rechallenge with isoniazid. If AST elevations are smaller and minimal symptoms are present, a rechallenge with isoniazid should be considered. Consult with the TB Program for further information regarding drug rechallenge.

2. Individuals who cannot take either isoniazid nor rifampin should be treated with a "retreatment regimen", usually streptomycin for four months after culture conversion, combined with pyrazinamide, ethambutol and a fluoroquinolone, and treated for a period of 12-18 months.
4. Although the specific cause for hepatitis cannot be identified by the pattern of LFT abnormality, in general, rifampin is implicated if the pattern is cholestatic (elevated bilirubin and alkaline phosphatase out of proportion to other enzyme elevations).
5. If the pattern is "hepatocellular" (AST and ALT enzymes elevated out of proportion to bilirubin or alkaline phosphatase), isoniazid, rifampin, or pyrazinamide may be the cause. Ethambutol, which very rarely causes hepatitis, can produce a hepatocellular pattern.
6. In some individuals, rifampin may cause gastritis with symptoms similar to those of hepatitis. In these, the LFTs remain normal or stable despite symptoms. Refer to: "Gastrointestinal Reactions" below.
7. Similar principles of management apply to cases of hepatitis induced by second-line drugs (e.g., ethionamide, PAS, rifabutin, and rarely fluoroquinolones).

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Gastrointestinal Reactions

Principles:

1. Almost any medication can cause gastrointestinal symptoms in susceptible individuals. Among first-line anti-tuberculosis medications, pyrazinamide is most often the cause for gastrointestinal symptoms, although rifampin may also be responsible.

Because rifampin is the most important member of combined chemotherapy, every effort should be made to reintroduce this drug without recurrence of gastrointestinal symptoms.
2. Because the gastrointestinal symptoms (anorexia, nausea, vomiting, epigastric distress) may be due to drug-related hepatitis, LFTs must be done on all individuals who present such symptoms.
3. Anti-tuberculosis medications should be absorbed within 1 hour if taken on an empty stomach and with 2 hours if taken on a full stomach. Doses cannot be counted if pills are visible in patient's emesis.
4. Anti-tuberculosis medications should be discontinued in such symptomatic individuals to improve symptoms, pending the results of liver function tests. If LFTs are normal or unchanged from baseline, and symptoms persist for 4-5 days without medication, unrelated GI disease (e.g. peptic ulcer disease, gastritis due to another cause, etc.) should be suspected and appropriate referral made for diagnostic investigation.

Restarting Anti-tuberculosis Medications:

1. If the individual is on isoniazid, rifampin, pyrazinamide, and ethambutol, pyrazinamide is the most likely the cause for gastrointestinal symptoms. After symptoms subside, it is appropriate to restart treatment with isoniazid, rifampin, and ethambutol. If gastric symptoms return, rifampin should be suspected as the cause and treatment should be attempted with isoniazid, pyrazinamide, and ethambutol.
2. If symptoms do not recur, it is usually possible to reintroduce pyrazinamide without

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recurrence of gastric symptoms by modifying the pattern of administration, such as giving all of the medication before bedtime, preceding the medication with a small meal, restarting pyrazinamide with a smaller dose and increasing it over a period of one to two weeks.

3. An H-2 blocker (e.g. Cimetidine) may be useful to help alleviate gastrointestinal symptoms. Antacids may also be useful. They may, however, interfere with the absorption of isoniazid and rifampin. When employed, antacids should be given one to two hours after isoniazid has been taken, and preferably, not used for prolonged periods.
4. When gastritis is caused by pyrazinamide, this drug can be omitted from the regimen with less risk than is the case with rifampin. If the individual has TB susceptible to isoniazid and rifampin, he/she can be treated with these two medications for a total of nine to twelve months.

Peripheral Neuritis

Predisposing Factors:

Isoniazid may cause peripheral neuropathy, especially in individuals with a predisposing cause such as alcoholism, diabetes, HIV infection, malnutrition, etc.

Role of Pyridoxine (Vitamin B6):

Pyridoxine (Vitamin B6) usually, but not invariably, prevents the emergence of isoniazid-induced peripheral neuropathy. Isoniazid should be assumed to be the primary cause for paresthesia and numbness of the feet and hands, with or without peripheral motor weakness, in isoniazid-treated subjects even if other predisposing causes are present. This drug should be discontinued, and large doses of pyridoxine given.

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Follow up:

Although the neuropathy usually subsides when the diagnosis is made early and isoniazid discontinued, neurologic injury may be irreversible if the diagnosis is delayed and the manifestations become severe. Neurologic consultation should be obtained if the diagnosis is not clear.

Joint Manifestations

Isoniazid:

Isoniazid can rarely induce active systemic lupus erythematosus (SLE) –like syndrome especially in subjects who have this disease in a subclinical stage. The individual may have only arthralgias or may present a full-blown pattern of SLE with arthritis and other systemic manifestations. The diagnosis requires clinical suspicion and positive antinuclear antibodies (ANA) markers of SLE. Isoniazid must be discontinued, and such individuals referred to an appropriate medical or rheumatology clinic. Usually the symptoms resolve with cessation of therapy.

Pyrazinamide:

1. Pyrazinamide may leads to increased levels of serum uric acid by impairment of renal excretion of uric acid.
2. Hyperuricemia without symptoms of gout usually does not provide a basis for discontinuing pyrazinamide.
3. Arthralgias and myalgias occasionally occur with pyrazinamide that are not due to gout or increased uric acid levels and need not prevent continuation of therapy.

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Renal Manifestations

Rifampin

Rifampin can cause acute or chronic nephritis, with or without symptoms, and evidenced by proteinuria, hematuria, and urinary WBCs. Acute or chronic renal failure has occurred.

Urinalysis, BUN, and creatinine should be monitored serially in individuals with underlying renal disease given rifampin, and similar studies obtained promptly in any individual who evidences symptoms consistent with acute or chronic nephritis (e.g. systemic symptoms, low back pain, or red/dark urine).

Aminoglycosides and Capreomycin

Aminoglycosides or capreomycin are a frequent cause of renal injury in individuals treated with these drugs.

Other Anti-Tuberculosis Medications

Isoniazid, pyrazinamide and ethambutol are not known to cause renal disease, although the blood levels of ethambutol (and cycloserine, aminoglycosides and capreomycin) may become markedly elevated in individuals with renal function impairment and may require additional monitoring.

Hematologic Manifestations

1. All first-line anti-tuberculosis agents rarely can lead to hematologic abnormalities. Thrombocytopenia is more often due to rifampin; although the other first-line drugs may depress platelets as well. A "flu-like syndrome" has been reported with rifampin, especially when it is used intermittently and is manifested by an acute episode with fever, chills, and muscle pain that may be associated with renal failure, severe anemia, thrombocytopenia and leukopenia.

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2. Leukopenia has been caused by rifampin, isoniazid and pyrazinamide, and rarely, ethambutol. Hemolytic syndromes and other types of anemia have been encountered rarely.
3. If an individual on anti-tuberculosis drugs develops symptoms, signs or laboratory evidence of significant anemia, leukopenia, or thrombocytopenia that cannot otherwise be explained, it is prudent to discontinue all anti-tuberculosis drugs and refer the individual promptly for hematologic consultation.

Visual Manifestations

1. Ethambutol-induced optic neuritis occurs only rarely, and usually regresses completely when ethambutol is discontinued. It may progress, however, to severe visual loss if diagnosed late. In general, optic neuritis most commonly occurs in patients receiving higher doses of ethambutol (doses of ethambutol greater than 15 mg/kg body weight), longer duration of treatment, or in individuals with impaired renal functions since the drug is cleared largely by renal excretion.
2. The usual symptoms are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.
3. Ethambutol should be avoided, or used with caution and with frequent monitoring of vision and renal function, in subjects known to have, or are at risk of renal function abnormality, such as the elderly, diabetics, hypertensives, etc., and those with preexisting non-correctable visual loss. Serum BUN and creatinine should be obtained before ethambutol treatment on all that are at risk of renal disease. Serial tests of visual acuity and color vision are indicated for early detection of signs of optic neuritis; in addition, the patient should be asked about visual changes on each follow-up visit.
4. Ethambutol should be discontinued immediately if optic neuritis is suspected, and the patient referred for ophthalmology consultation if the visual impairment does not reverse promptly.

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Drug Resistant TB

When an initial culture is identified as positive for *M. tuberculosis*, a drug susceptibility test is performed. In this test the organism is incubated in the presence of a panel of anti-tuberculosis drugs. If the organism grows, then it is considered to be resistant to that drug. The test may take two to three weeks after the identification of *M. tuberculosis*. It is crucial to identify drug resistance as early as possible to ensure appropriate treatment.

A person can either acquire a drug resistant strain of TB from another person (primary resistance) or can develop resistance as a result of inadequate treatment (secondary resistance). Non-compliance with drug treatment plays a major role in the development of drug-resistant TB.

Drug resistance presents difficult treatment problems. Treatment must be individualized and based on the patient's medication history and susceptibility studies. Clinicians who are unfamiliar with the treatment of drug-resistant TB should consult with the CDPHE TB Program or with a TB expert.

Isoniazid-Resistant TB

When isolated resistance to isoniazid is documented, the treatment regimen should be adjusted by discontinuing isoniazid and continuing rifampin, ethambutol and pyrazinamide. Adding a fluoroquinolone may strengthen the regimen for patients with extensive disease. A 6-month regimen has yielded $\geq 95\%$ success rates, despite resistance to isoniazid, if 4 drugs were used in the initial phase and rifampin plus ethambutol was used throughout.

Multi-drug resistant TB

Multi-drug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin. Patients with MDR TB are at high risk for treatment failure and further acquired resistance. They must be referred immediately to a specialist or consultation obtained from specialized treatment centers.

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Adequate data is not available on the effectiveness of various regimens and the necessary duration of treatment for patients with MDR TB. Many of these patients also have resistance to other first-line drugs (e.g. ethambutol, streptomycin, or pyrazinamide). Because of the poor outcome in such cases, it is preferable to give at least 3 new drugs to which the organism is susceptible. **Clinicians should never add a single drug to a failing regimen.** Commonly, these patients will require a total of 18 – 24 months of therapy.

Contact the TB Program for further information regarding recommended treatment regimens (including use of second line drugs).

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How to Motivate People to Comply with Therapy

Assuming appropriate drugs are prescribed, circumstances surrounding each TB patient that may affect his/her ability to complete treatment becomes the most important consideration in completion of TB treatment. Factors that interfere with adherence include cultural and linguistic barriers, life style differences, homelessness, substance abuse, and other conditions and circumstances that, for the patient, are priorities that compete with taking treatment for TB. Effective TB case management identifies the circumstances surrounding each patient and determines an appropriate care plan.

Poor adherence to TB medication regimens leads to inadequate treatment. The consequences of inadequate and incomplete TB treatment are serious:

- Prolonged illness and disability for the patient
- Infectiousness of the patient, causing continued transmission of TB in the community
- Development of drug-resistant TB
- Death

Many health care providers believe they can predict whether a particular patient will take medication as prescribed. However, research data indicate that providers, on the average, are correct only 50% of the time. Directly observed therapy (DOT) is therefore the standard method of providing treatment to all persons with active TB. In addition, DOT allows for the immediate detection of non-compliance so that actions can be taken to avoid treatment failure. Careful attention must be paid to ensure that ingestion of the medication is, in fact, observed.

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Health care providers must recognize that even with DOT, additional strategies and efforts are necessary for treatment success. It is important to use any tool available in order to promote adherence to therapy, including:

- Learn as much as possible about your patient's health history, beliefs and attitudes about TB, sources of social support, and barriers to treatment
- Work with an interpreter or a person of the same cultural background as the patient, if possible
- Look for early warning signs of future adherence problems (e.g., patient feels medicine is no longer needed because they are feeling well, difficulty in accessing health care)
- Designate a person to do DOT who does not have a strong emotional tie with the patient. Suitable designees might include school nurse/staff, employee health, public health, visiting nurse, work supervisor, clergy, or other responsible person
- Provide effective education to patients and key individuals in the patient's social environment
- Provide patient with needed health or social services or make referral to other health or social service agencies
- Use a team of personnel whose members work together to assist each patient in completing treatment
- Establish an efficient, patient-friendly clinic system for scheduling appointments, keeping records, and monitoring adherence
- Mutually agree on a time and location for DOT (be creative and flexible)
- Be aware of patients who may require techniques to assess for ingestion of medication

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(e.g., hiding pills in mouth, vomiting after pills swallowed)

- Encourage a social support system that enhances the patient's adherence to treatment
- Use incentives and enablers (see examples next page)

In summary, use all available strategies for maintaining adherence to treatment.

If, despite your best efforts, the patient does not adhere to DOT voluntarily, Colorado State statutes allow a public health official to require court-ordered DOT, involuntary quarantine, or isolation for treatment of TB (see, "Quarantine").

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Incentives and Enablers

Food Applesauce (in which to mix medicine) Fruit Chewing gum Homemade cakes/cookies Milk Big Macs French fries Chicken snacks and dinners Whole, uncooked chickens Bread Eggs Pickles Vienna sausages Ice cream Blow-Pops Shrimp Canned food Oatmeal cakes Pudding (in which to mix medicine) Steak dinner Sausage biscuits Beverages, soft drinks, juices Coffee/Tea Nutritional supplements (e.g., Ensure)	Clothing Socks Gloves Stockings Sweaters Coats Personal Care Contraceptives (e.g., condoms) Razor blades Shaving cream Face cream Powder Makeup Nail polish Obtaining non-TB medicines Household Wood stove Kerosene Fuel oil for heat Smoke alarm Cooking utensils Furniture Fishing Supplies Fishing pole Crickets Worms	Services Helping obtain birth certificate Washing patient's clothing Arranging building of wheelchair ramps Installing wood stove Helping obtain driver's license Repairing bicycle Automotive Battery Gasoline Motor oil Seasonal Homemade Valentine cookies Easter baskets Christmas baskets (food) Birthday cakes Thanksgiving hams Nurses dressed in Halloween costumes Birthday cards	Children Reading stories Painting child's nails Tea party with child Playing games Chewing gum Charts with stars and stickers Stuffed animals Grab bag with assorted treats School supplies Storybooks Basketball Crossword puzzle books Transportation Bus fare Bicycle Paying a friend for transportation Staff transporting patient to doctor Garden Flowers Flower bulbs Money
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Source: Using incentives and enablers in the TB control program.

Columbia: American Lung Association of South Carolina and South Carolina

Department of Health and Environmental Control, Division of Tuberculosis Control, 1989.

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Contact Investigation

Introduction

Contact investigation is an integral part of any TB program and one of the best ways to find people who have TB disease. According to the Centers for Disease Control and Prevention, 7-8 cases of disease are found for every 1000 contacts that are evaluated. Finding infected contacts that do not yet have disease and offering treatment for latent tuberculosis infection (LTBI) is important as well. On average, about 20% of contacts are found to have TB infection, but in some contact investigations as many as 80-100% of the close contacts may be infected.

Successful contact investigation requires skills in patient assessment, counseling, interviewing, and evaluation. **Results of all TB contact investigation activities should be documented on the “TB Contact Investigation Record” (see “Forms”) and submitted to the TB Program after initial testing of contacts and then again upon completion of contact investigation (including names and locating information for any out-of-state contacts identified). The information will be compiled and evaluated by TB Program management staff as part of ongoing program evaluation activities. This information is reported to the Centers for Disease Control and Prevention on an annual basis.**

Purpose

The purposes of contact investigation include:

- To identify persons who have TB disease so that they can be given treatment and stop further transmission
- To identify persons who have LBTI and offer treatment to prevent progression to disease
- To identify persons who are at high risk of developing TB disease and need treatment for LTBI until it becomes clear whether they have TB infection
- To identify the source of TB disease transmission
- To identify environmental factors that may contribute to the transmission of TB

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Who is a Contact?

Contacts are persons exposed to someone with infectious TB disease. Exposure to TB is time spent with or near such a person and is determined by the duration, proximity, and intensity of the shared time (see “Prioritization of contacts” below). Contacts generally include family members, roommates or housemates, close friends, coworkers, classmates, and others. Public health agency staff usually identifies contacts by interviewing the person with TB and by visiting the places where that person spends time regularly.

When Is a Contact Investigation Done?

A contact investigation is a systematic procedure for tracing, testing, and evaluating persons who have been exposed to someone with infectious TB. **In general, a contact investigation should be done whenever a patient is found to have or is suspected of having infectious TB disease (e.g. symptoms and chest x-ray consistent with TB disease).** Infectiousness depends on a variety of factors, but is more likely when patients have:

- Cough
- Hoarseness
- Other symptoms of pulmonary or laryngeal TB
- Positive AFB smear or culture results for *M. tuberculosis* (recent evidence suggests that transmission can occur in AFB sputum smear-negative cases as well)
- Cavity on chest x-ray
- Inadequate or no treatment

Young children with pulmonary TB disease are rarely infectious, so a contact investigation is generally not conducted for them. However, young children with pulmonary TB disease should be evaluated for infectiousness and contact investigation may be warranted in some circumstances.

In addition, a **source case investigation** (looking for the source of exposure) should be conducted to find the source of TB transmission when recent transmission is likely. This is usually done when:

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- A young child is found to have TB infection or disease
- A severely immunocompromised person who does not have a known history of TB infection is found to have TB disease
- A cluster of TST conversions is found in a high-risk institution (e.g. health care or correctional facility)

A source case investigation is conducted to determine who transmitted TB to the child, index patient or persons in the cluster of skin test conversions, whether this person is still infectious, whether this person was reported to the health department or if others were infected by the same source patient.

Supervisory clinical and management staff should make decisions regarding prioritization of contact investigations. Setting priorities between two or more contact investigations is a decision that should be made based on the likelihood of infectiousness of the index case. If program resources are limited, priority should be given to contacts that were exposed to the most infectious TB patients or to those who are at highest risk for progressing to disease, if infected. CDPHE TB Program DOES NOT PAY for testing or follow-up for non-contacts (persons who have not shared sufficient time or were not near a person with infectious TB).

Steps in a Contact Investigation

A successful contact investigation requires careful gathering and evaluation of detailed information, often involving many people. In general, contact investigations follow a process that includes these 9 basic steps:

1. Medical Record Review

Review of the TB patient's medical record/information and information from the clinician to determine whether the patient has been infectious and, if so, when. Knowing when the patient was infectious helps to determine which contacts are at risk. Information that should be collected includes site of disease, symptoms, approximate date of onset of symptoms, sputum smear and culture or other mycobacterial laboratory results

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(including dates of specimens and drug susceptibility results), chest x-ray results, TB treatment information (medications, dosages, and dates of treatment), and method of treatment (e.g. DOT vs. self-administered). Clinical and supervisory staff should determine the period of infectiousness after a complete assessment of the information is available.

2. Patient Interview (TB Case Interview)

The patient interview is one of the most critical parts of the contact investigation. If the interviewer does not communicate well enough with the patient to get accurate information about symptoms, places where patient spent time, and names of contacts, then people who need evaluation and treatment may be missed. The interviewer should keep in mind that the patient may first learn of their new TB diagnosis during the initial interview. The patient may be overwhelmed, fearful of their diagnosis, or still very ill and unable or unwilling to participate fully in an interview. Thus, follow-up interviews should be scheduled to educate patients and to complete a thorough contact investigation. Good communication (ask open-ended questions), good listening skills, patient education, and establishing and maintaining a trusting relationship are essential during all interviews.

The initial interview should occur **no more than 3 working days** after the case is reported. During the interview, the TB patient should be asked more about:

- Symptoms—type and onset; especially cough and sputum production
- Places where the patient spent time while he/she were infectious (e.g. household—including guests and visitors, work, school, leisure, recreation, transportation, incarceration, travel, medical/dental or beauty appointments)
- Any contacts
- How often and how long the contacts were exposed
- Locating information for the contacts

In addition, the patient should be asked about the characteristics of each place (room size,

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windows open or closed, time spent in each place, etc.) to help determine the risk that *M. tuberculosis* was transmitted in each place. Written educational materials regarding TB should also be provided to the patient.

Some patients may be reluctant to identify some or all of their contacts. For example, a patient may not want to identify people who use illegal drugs with him/her. The interviewer should be sensitive to the patient's fears, explain the importance of testing the contacts, and **assure the patient that all information will be kept confidential (including the patient's name)**. A patient interview checklist can assist the interviewer obtain the correct information (see Appendix 5).

3. Field investigation

A field investigation means visiting the TB patient's home or shelter, workplace (if any), and other places where the patient said he/she spent time while infectious to identify contacts and evaluate the environmental characteristics of the places where exposure occurred. The public health worker should assess for:

- room size
- crowding
- ventilation
- contacts (especially children) and their locating information
- evidence of other contacts who may not be present (e.g. pictures of others who may live in the place, shoes left by others who may live in the house, maintenance/cleaning workers in the home, toys left by children)

Close contacts (see "Prioritization of contacts" below) that are present should 1) receive a TST and arrange for reading of the results; 2) be educated about the purpose of the investigation, basic TB transmission, risk of transmitting TB to others, and importance of testing, treatment, and follow-up for LTBI and disease; and 3) be referred for medical evaluation, including chest x-ray and sputum collection if they have symptoms of TB.

4. Risk Assessment for *M. Tuberculosis* Transmission

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The infectiousness of the TB patient is dependent upon the duration of time when the patient was infectious and estimated degree of infectiousness. The degree of infectiousness is estimated from information regarding the patient's symptoms, sputum smear results, and other conditions identified during the medical record review and patient interview. The greater degree of infectiousness, the more likely transmission will occur.

The risk of transmission in a particular space depends on the concentration of infectious droplet nuclei in the air. Small room size, crowding conditions, poor ventilation (no or little fresh air to dilute the droplet nuclei in a room), and lack of air cleaning systems increase the risk of transmission of *M. tuberculosis*.

The length and closeness of exposure between the TB patient and a particular contact are key factors in assessing the contact's risk. Persons who frequently spend a lot of time with the TB patient or have been physically close to the patient are at higher risk of becoming infected.

5. Prioritization of contacts

Contacts are prioritized based on risk of progression to TB disease once infected and the risk of infection after exposure to an active pulmonary or laryngeal TB case (e.g. close, regular, prolonged contact with the TB patient while he/she was infectious, especially in small, poorly ventilated places). To use time and resources wisely, the contact investigation should be focused on the high-priority contacts.

- A. Contacts at high risk of developing TB, once infected, are considered high-priority and should be evaluated first. This includes household contacts, contacts living in congregate settings, children less than 4 years of age, HIV-infected or other immunocompromised persons, and contacts with certain other medical conditions (see Chapter 1, page 1 footnote). Contact the TB Program for assistance with identification of these contacts.
- B. Other contacts to an active pulmonary or laryngeal TB case should be evaluated

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in the order of their risk of infection after exposure.

- 1) High priority - Contacts to a source case who spend:
 - 8 hours or more in a small, poorly ventilated space
 - 16 or more hours in a small well-ventilated space
 - 24 hours or more in a classroom size space
 - 100 hours or more in a large, open space

- 2) Medium priority—Contacts to a source case who:
 - Are 4 to 15 years of age
 - Spend 4 or more hours in a small space
 - Spend 8 or more hours in a classroom size space
 - Spend 50 or more hours in a large, open space

- 3) Low priority – All other contacts.
These contacts have less intense, less frequent or shorter durations of contact with the TB patient and should be given lower priority for testing.

6. Evaluation of Contacts

Evaluation of TB contacts includes at least a medical history and TST. **Close contacts and high-priority contacts should be examined within 7 working days after the index case has been diagnosed.** Contacts should be asked about their history or treatment of previous TB infection or disease, documented previous TST, previous exposure to TB, risk factors for developing TB disease, and current symptoms of TB. All high-priority contacts should be given a TST. **A reaction of 5 mm or greater is considered positive for contacts.** Contacts with a positive reaction should be further evaluated for TB disease (see “Contact Investigation Guideline” next page). In some cases, sputum inductions are necessary to obtain an appropriate specimen.

Contacts who have a previously documented positive TST should not receive another test, but should be evaluated for symptoms of TB disease. Depending on the results of the evaluation, some of these contacts may be candidates for treatment of LTBI or

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disease. A recent chest x-ray should be obtained and interpreted before initiating any treatment.

Because it takes 2-12 weeks after TB infection for the body's immune system to react to tuberculin (window period), contacts that have a negative reaction on the initial TST should be retested 12 weeks after their last exposure to the infectious TB patient.

Infants under 6 months of age may have a false-negative TST reaction because their immune systems are not yet able to react to tuberculin. Thus, infants need careful clinical evaluation.

Contacts who have TB symptoms, are HIV-infected, have other immunosuppressive conditions, or are under 4 years of age should have a chest x-ray at the same time as the initial skin test to evaluate him/her for TB disease. This is because of their high risk of quickly developing TB disease. In addition, these close contacts should be considered for treatment of latent TB infection (LTBI) even if the initial TST reaction is negative during the window period. Treatment may be discontinued if the 12-week follow-up TST is still negative and the contact is not at continued risk for exposure to infectious TB.

Contacts who have an abnormal chest x-ray or symptoms of TB disease should have three early-morning sputum specimens, collected on three different days, for smear and culture examination, regardless of his/her TST reaction.

7. Treatment and follow-up for contacts

The following contacts should be offered treatment for LTBI:

- Contacts with a positive TST reaction and no evidence of TB disease
- High-priority contacts who have a negative TST reaction who may develop TB disease quickly after infection (e.g. children under 4 years of age, HIV-infected people, contacts with other immunosuppressive conditions)

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Contacts recently infected with *M. tuberculosis* are a high-priority for treatment for LTBI because they are at high-risk of developing TB disease (highest risk of developing TB disease is in the first 2 years after infection). HIV-infected contacts or other immunosuppressed contacts may be given a full course of treatment for LTBI, regardless of their skin test results, because of the possibility of a false-negative skin test result (inability to react to tuberculin due to a compromised immune system).

Contacts who have a positive sputum smear or chest x-ray result suggestive of current TB disease should begin treatment for TB disease.

Contacts who have started treatment for LTBI or TB disease should be monitored to ensure compliance and completion of treatment. Contacts with LTBI and at high-risk for progressing to TB disease should be considered for directly observed preventive treatment (e.g. children, HIV positive or immunosuppressed patients).

8. Decision About Whether to Expand Testing

After the highest-priority contact group has been evaluated for LTBI and TB disease, the contact investigation staff should evaluate the results of testing for evidence of recent transmission. Evidence of recent transmission is indicated by any of the following factors:

- High infection rate among contacts as compared to the local community positivity rate
- Infection in a young child
- A skin test conversion in a contact
- A secondary case of TB disease

To calculate the infection rate among a given priority group of contacts:

1. Determine the number of contacts with newly-identified positive skin tests.

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2. Determine the total number of contacts without a documented previous positive skin test. Subtract the number of contacts with a documented previous positive skin test from the total number of contacts.
3. Determine the infection rate. Divide the number of contacts with a new positive skin test by the total number of contacts without a documented previous positive skin test. Multiply by 100; the resulting percentage is the infection rate for that group of contacts.
4. Compare the level of skin test positivity rate in the local community (based on TB Program estimates) to the infection rate for the group of contacts.

When there is evidence of recent transmission of TB in the first priority group of contacts tested, the likelihood that *M. tuberculosis* has also been transmitted to contacts with less exposure, increases. The testing should, therefore, be expanded to the next priority level of contacts (“concentric circle approach”--see References, “Contact Investigations for Tuberculosis. Self Study Module 6, October 1999”). This should be done as soon as it becomes clear that transmission may have occurred. The decision about expanding contact investigation to the next group of contacts should be made by clinical and supervisory staff, based on an assessment of all available information.

On the other hand, if there is NO evidence of recent *M. tuberculosis* transmission among high priority contacts, testing should not be expanded to the next group of contacts (e.g. new positive skin test rate among contacts is lower than or similar to the level of infection in the community, no young children have a positive skin test reaction, no contact skin test conversions have occurred, no contacts have TB disease). Once the infection rate among the group being tested is the same as the infection rate in the local community and there are no other factors indicating recent transmission, testing can be stopped.

9. Evaluation of Contact Investigation Activities

An evaluation of the contact investigation activities should be conducted with or by a

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supervisor to determine such things as:

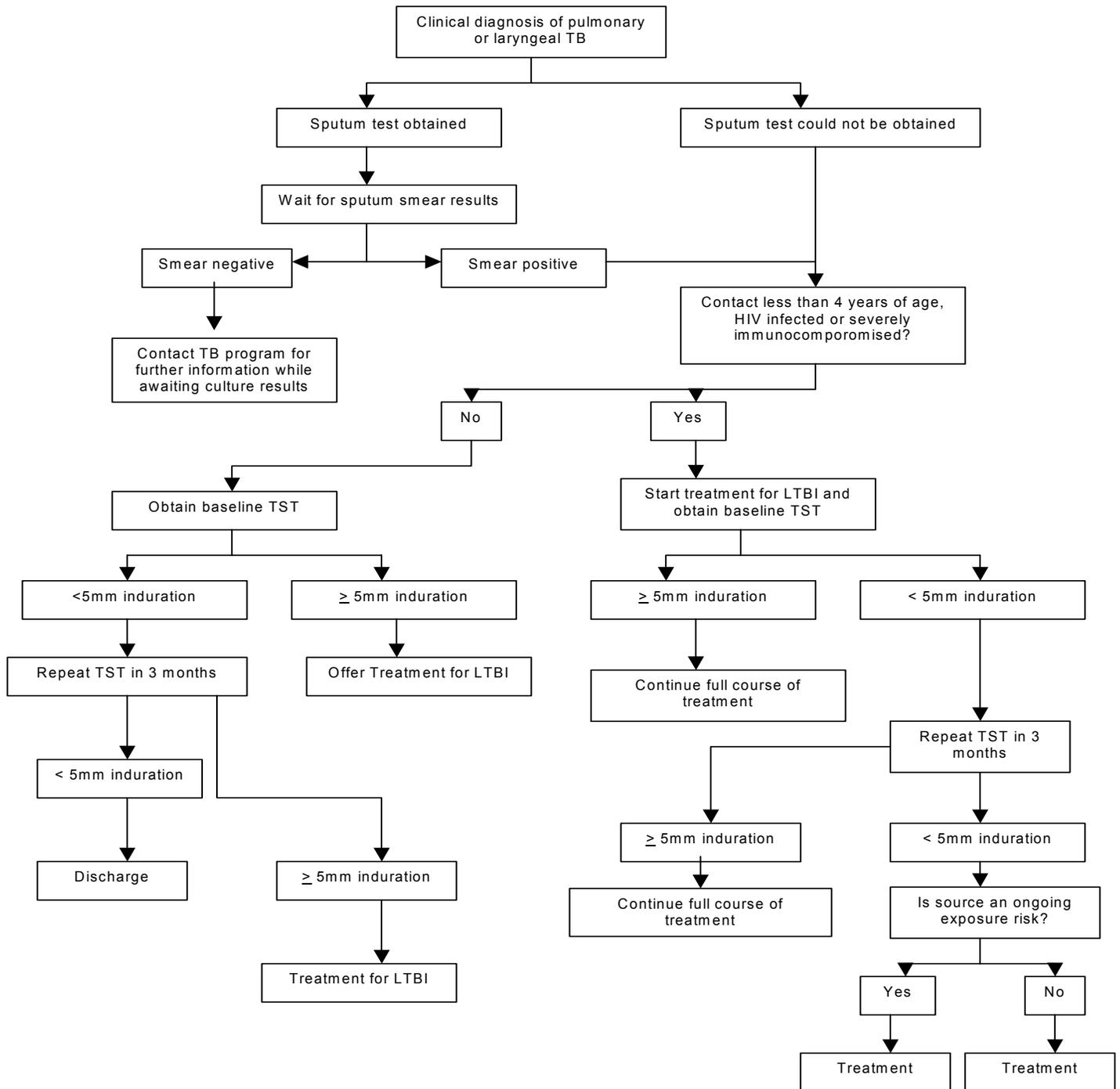
- Were an appropriate number of contacts identified?
- Were the highest-priority contacts located and tested?
- Was the contact investigation performed in all settings: household or residence, work or school, and leisure or recreational environments?
- Was the contact investigation expanded appropriately? Were contacts completely evaluated (including second skin test if needed) and given appropriate therapy if they had TB infection or disease?
- How many infected contacts completed a regimen of treatment for LTBI?
- Did all identified cases complete and adequate treatment regimen?

The answer to these questions will help determine how successful the contact investigation has been.

Results of all TB contact investigation activities should be documented on the “TB Contact Investigation Record” and submitted to the TB Program after initial testing and again after completion of the investigation (including names and locating information for any out-of-state contacts identified). The information will be compiled and evaluated by TB Program management staff as part of ongoing program evaluation activities.

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**CONTACT INVESTIGATION
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Post-treatment Evaluation and Follow-up

All individuals with pulmonary TB should be evaluated prior to completion of anti-tuberculosis treatment. At this evaluation:

- perform symptom review
- obtain PA and lateral chest x-ray
- attempt to obtain one sputum specimen for AFB smear and culture testing
- instruct patients to promptly report any new or recurring symptoms of TB post-treatment.

After the follow-up evaluation, you may follow-up after completion contact the TB Program to obtain further follow-up recommendations. Generally patients do not require of therapy, but should be instructed to return to clinic promptly, if signs or symptoms recur.

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Non-Tuberculous Mycobacteria

Mycobacteria other than tuberculosis (non-tuberculous mycobacteria-NTM) are bacteria widely distributed in nature, primarily found in soil, water, and domestic and wild animals. These bacteria may be found as contaminants, colonizers, or may cause human disease. Most human infections with NTM appear to be acquired by aspiration or inoculation of the organisms from an environmental reservoir. There is little evidence to support person-to-person transmission, if it occurs at all. These bacteria have also been referred to as atypical mycobacteria or mycobacteria other than tuberculosis (MOTT). Drug resistance is commonly found in NTM organisms.

Clinicians and patients have also often used the term “TB” to describe these infections, although TB should only be used to refer to *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum*). Therefore it is important to confirm the species of mycobacteria involved in a clinical situation. The TB Program provides services related only to *M. tuberculosis* treatment, prevention and control. All clinical treatment and follow-up of NTM infections should be referred back to the patient’s primary care provider. Consultation by an expert in the treatment of NTM infections is recommended because of the complexity and length of treatment required for these infections (call the TB Program for references). The cost of care for NTM infections, including antituberculous drugs, is the responsibility of the patient.

NTM can cause serious infections in immunocompromised individuals, particularly those with AIDS or other types of impaired cellular immunity, or in individuals with underlying lung disease. More than 95 percent of NTM infections in AIDS patients are caused by *M. avium* complex (*M. avium*, *M. intracellulare*). Other NTM infections may be caused by species such as *M. kansasii*, *M. chelonae*, *M. fortuitum*, etc. The table, next page, summarizes important features of NTM.

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Non-tuberculous Mycobacteria and Human Disease (Continued on Next Page)			
Mycobacterium	Environmental Source	Causes Human Disease?	Usual Site of Disease
<i>M. abscessus</i>	Water	Yes	Lung, skin
<i>M. asiaticum</i>	Animals	Yes	Lung
<i>M. avium</i> complex	Soil, water, swine, cattle, birds, fowl	Yes	Disseminated, lung, lymph nodes
<i>M. gastri</i>	Soil, water	Very rarely	-
<i>M. flavescens</i>	Soil, water	Very rarely	-
<i>M. fortuitum/M.</i> <i>chelonae</i>	Soil, water, animals, marine life	Yes	Skin, lung
<i>M. genavense</i>	Unknown	Yes	Blood, bone marrow
<i>M. gordonae</i>	Water	Very rarely	-
<i>M. haemophilum</i>	Unknown source	Yes	Skin
<i>M. kansasii</i>	Water, cattle, swine (rarely)	Yes	Lungs
<i>M. malmoense</i>	Unknown	Yes	Lungs
<i>M. marinum</i>	Fish, water	Yes	Skin
<i>M.</i> <i>mucogenicum</i>	Water	Yes	Catheter, wound

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Non-tuberculous Mycobacteria and Human Disease, Continued			
Mycobacterium	Environmental Source	Causes Human Disease?	Usual Site of Disease
<i>M. scrofulaceum</i>	Soil, water, moist or liquid food stuffs	Yes	Lymph nodes
<i>M. shimoidei</i>	Unknown	Yes	Lungs
<i>M. simiae</i>	Water, primate	Yes	Lungs
<i>M. szulgai</i>	?Fish	Yes	Lungs
<i>M. terrae complex</i>	Soil, water	Very rarely	-
<i>M. ulcerans</i>	Tropical grasses	Yes	Skin
<i>M. xenopi</i>	Water	Yes	Lungs

For additional questions about NTM, call the TB Program (303) 692-2638.

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Specimen Collection and Transport

Many different types of specimens may be submitted for mycobacterial culture. The majority of the specimens submitted are from the respiratory tract. Tissue, normally sterile body fluids, urine, and gastric aspirates are other commonly submitted specimens. Blood and stool specimens may also be submitted for mycobacterial culture. The quality of specimens collected and the proper transport of those specimens to the laboratory are critical to the successful isolation of AFB (acid-fast bacilli). There will be no charge for TB testing submitted by local public health agencies for patients with signs or symptoms consistent with TB.

Specimen Collection

Specimens should be collected and submitted in sterile, leak proof, disposable, appropriately labeled, laboratory-approved containers. All specimens can be collected in the sterile collection tubes supplied by the CDPHE Laboratory. Do not use waxed containers, as they may provide false-positive smear results. Specimens should be forwarded promptly to the laboratory after collection for optimal processing and result turn-around time.

Initial specimens should ideally be collected prior to the initiation of antimycobacterial chemotherapy. Specimens should be collected aseptically, or the collection method should bypass areas of contamination as much as possible in order to minimize contamination with indigenous flora. Avoid contamination with tap water or other fluids that may contain either viable or nonviable environmental mycobacteria, since saprophytic mycobacteria may produce false-positive culture and/or smear results.

Sputum: Sputum, both expectorated and induced, is the principal specimen obtained for the diagnosis of pulmonary TB. Collect an early-morning specimen, preferably 5-10 ml, from a deep, productive cough on at least 3, but usually not more than 5 or 6 consecutive days (24 or more hours apart). Processing of additional specimens does not seem to improve recovery. For expectorated sputum, patients should be instructed to cough deeply to produce specimens distinct from saliva or nasopharyngeal discharge. The patient should also be instructed to press the rim of the container under the lower lip at the time of expectoration to minimize the chance of contaminating the outside of the

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container. For induced sputum, use sterile hypertonic saline, and avoid sputum contamination with nebulizer reservoir water to avoid possible false-positive culture or smear results due to saprophytic mycobacteria. Indicate on the requisition whether the specimen is induced or expectorated to ensure proper handling, as induced sputa appear watery and much like saliva. Pooled sputum specimens are unacceptable specimens for mycobacterial culture because of increased risk of contamination.

Bronchoalveolar Lavage Fluids and Bronchial Washings: Bronchial washings, bronchoalveolar lavage fluid, transbronchial biopsy specimens, and brush biopsy specimens may all be collected during bronchoscopy. Collect at least 5 ml of bronchial washing or bronchoalveolar lavage fluid in a sterile container. Avoid contaminating the bronchoscope with tap water. Frequently, bronchoscopy causes the patient to produce sputum spontaneously for several days after the procedure, and specimens collected a day or two after bronchoscopy enhance detection of mycobacteria.

Gastric Lavage Fluids: Aspiration of swallowed sputum from the stomach by gastric lavage may be necessary for infants, young children, and the obtunded. On each of three consecutive days, collect 5-10 ml of fluid in a sterile container without a preservative. Fasting, early-morning specimens are recommended in order to obtain sputum swallowed during sleep. Gastric contents are initially collected with a sterile suction syringe connected to a tube inserted in the stomach. Sterile saline (20-30 ml) may then be introduced into the stomach and aspirated as lavage fluid. The gastric contents and lavage fluid may be pooled in a sterile container. These specimens should be processed within 4 hours. If the specimens cannot be processed within 4 hours, adjust fluid to neutral pH with 100 mg of sodium carbonate immediately following collection. Unneutralized specimens are not acceptable, as acid is detrimental to the mycobacteria.

Blood: Cultures for the isolation of mycobacteria from blood are usually reserved for immunocompromised patients. The BACTEC 13A bottle is specifically designed for the recovery of mycobacteria from blood (contains a lysing agent). The 13A medium can be directly inoculated with 5 ml of blood. If blood needs to be transported before inoculation of BACTEC medium, use sodium polyanetholsulfonate (SPS) or heparin as an anticoagulant. Blood collected in EDTA or blood that is coagulated is **NOT** acceptable.

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Urine: Collect the first morning specimens, either by catheterization or midstream clean catch, into a sterile container on three consecutive days. Appropriate cleaning of genitalia should precede collection. Organisms accumulate in the bladder overnight, and the first morning void provides best results. Specimens collected at other time are dilute and thus not optimal. A minimum of 40 ml of urine is usually required for culture.

Stools: Stool specimens (>1 g) should be collected in sterile, wax-free, disposable clean containers or transferred from a bedpan or from plastic wrap stretched over the toilet bowl and sent directly to the laboratory.

Body Fluids: Body fluids (cerebrospinal--CSF, pleural, peritoneal, pericardial, etc.) are aseptically collected by aspiration or surgical procedures. Collect as much as possible (10-15 ml minimum) in a sterile container or syringe with a luer tip cap. CSF culture requires at least 2 ml.

Tissues (Lymph Node, Skin, Other Biopsy Material): Aseptically collect at least 1g of tissue, if possible, into a sterile container without fixative or preservative. Do not immerse in saline or other fluid or wrap in gauze. For cutaneous ulcers, collect biopsy material from the periphery of the lesion. Specimens submitted in formalin are unacceptable.

Specimen Transport

All specimens should be refrigerated (except blood) prior to transport to the laboratory unless transport to the laboratory is anticipated within 1 hour of specimen collection. When shipping specimens:

1. Make sure that the specimen is in the appropriate sterile specimen collection container.
2. Seal the container and label appropriately.
3. Place the sealed specimen container and an appropriate laboratory requisition form into a second shipping container with ice packs (except blood).

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3. Send specimens to:

CDPHE
Laboratory and Radiation Services
For US Mail: PO Box 17123
Denver, CO 80217
For Courier: 8100 Lowry Boulevard
Denver, CO 80220-6928

Contact the Public Health Microbiology laboratory at 303-692-3480 for further information regarding specimen collection, submission and reporting.

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Resources

For questions about active TB, call the TB Program (303) 692-2638, Denver/Metro TB Clinic (303) 436-7286, Francis J. Curry National TB Center in San Francisco (415) 502-4600, or the National Jewish Center Consultation Line (303) 398-1279.