

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION
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GOALS

- Respiratory isolation of high suspect TB patients
- Prevent TB transmission among inmates, staff, and the community
- Initiate treatment early in symptomatic patients
- Monitor medication adherence and response closely to avoid treatment failure and relapse

ALERTS

- Breach in respiratory isolation protocol
- Nonadherence with medication
- Never add a single drug to a failing regimen

All TB disease treatment must be overseen by the Chief Medical Executive (CME) in consultation, by law, with the Local Health Department (LHD) TB Controller (TBC).

ALL high suspect tuberculosis (TB) patients must be promptly placed in respiratory isolation and immediately started on a 4 drug TB regimen. Do not wait for confirmation of *Mycobacterium tuberculosis* (MTB) before initiating treatment.

DEFINITIONS

- HIGH SUSPECT TB DISEASE.** • Disease with clinical features that are so highly characteristic or suspicious for tuberculosis that TB treatment is warranted.
- CONFIRMED TB DISEASE**
- LABORATORY CONFIRMED** • TB disease that is confirmed by the presence of MTB on culture.
- CLINICALLY CONFIRMED** • TB disease that is culture negative but confirmed by a physician based on the patient's clinical characteristics.
- PULMONARY TB** • TB disease that is confined to the lungs.
- EXTRAPULMONARY TB** • TB disease that occurs outside of the lungs. (Extrapulmonary TB is rarely infectious unless it affects the larynx. However, a full evaluation for pulmonary TB [including chest x-ray [CXR] and respiratory specimen collection] must be performed in all cases of confirmed extrapulmonary TB).
- MULTI DRUG RESISTANT TB** • TB caused by an organism that is resistant to (at least) both isoniazid (INH) and rifampin (RIF).
- TREATMENT TEAM** • TB treatment in CCHCS is always managed by a TB Treatment Team of physicians, nurses, and public health practitioners headed by the CME of the patient's institution under the legally mandated oversight of the LHD TB Controller.
- TREATMENT COMPLETION** • Ingestion of the prescribed number of doses within a specified time frame.

TB DISEASE DIAGNOSIS

- EXAMINATION** History, physical, or CXR suggestive of TB:
- collect three sputum specimens for acid-fast bacilli (AFB) smear and culture (see pages 2-4).
 - at least one specimen should be tested using a nucleic acid amplification test (NAAT).

TB DISEASE TREATMENT

- Start treatment immediately in high suspect or confirmed TB patients.
- Treat low suspect TB patients in whom TB disease is confirmed.

Two Phase TB Treatment

Standard treatment for the majority of persons with previously untreated pan-sensitive pulmonary TB consists of two phases of directly observed therapy (DOT).

Initial Phase: Four drugs given for two months* (see Dosing page 5):

Isoniazid/thiamine (INH/B ₆)	Pyrazinamide (PZA)
Rifampin (RIF)	Ethambutol (EMB)

*Directly observed therapy (DOT) all given together as a single daily dose

Continuation phase (see page 5):

Most patients with uncomplicated pulmonary TB	FOUR additional months of two drugs (INH/B ₆ / RIF)
Patients with cavitary disease or positive culture results at 2 months	SEVEN additional months of two drugs (INH/B ₆ / RIF)

Treatment in Other Cases

- Consultation with Local Health Department TB Controller (LHD TBC) and CCHCS Public Health Branch required (see page 5).

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DIAGNOSIS

HIGH SUSPECT TB DISEASE DIAGNOSIS—Requires assessment of the following:

- ◆ Medical History.
- ◆ Physical exam.
- ◆ Chest radiograph (CXR).
- ◆ Review test results for prior TB infection [e.g., tuberculin skin test (TST) or interferon-gamma release assays (IGRA)]. (Neither TST nor IGRA testing is required for diagnosis of TB disease but one should be done as part of the work up).
- ◆ Specimen Collection.
- ◆ Bacteriologic examination of clinical specimens (e.g., sputum stain and nucleic acid amplification test [NAAT] and culture).

MEDICAL HISTORY

- ◆ Assess for TB disease related symptoms.
(Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease).

<p>Pulmonary TB symptoms:</p> <ul style="list-style-type: none"> ➢ Cough, especially if ≥ 3 weeks duration w or w/o sputum ➢ Hemoptysis ➢ Chest pain ➢ Loss of appetite ➢ Unexplained weight loss ➢ Night sweats ➢ Fever ➢ Fatigue 	<p>Extrapulmonary TB symptoms: May present with the symptoms above, as well as with the following (depending on the affected site):</p> <ul style="list-style-type: none"> ➢ Hematuria ➢ Headache or confusion (TB meningitis) ➢ Back pain (spinal TB, Pott's disease) ➢ Hoarseness (laryngeal TB)
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- ◆ Duration of symptoms: TB is generally a chronic infection with symptoms lasting weeks to months.
- ◆ Exposure history: History of exposure to a person with known infectious TB.
 - Demographic risk factors may affect likelihood of exposure to TB (e.g., in California more than half of new TB cases are reported in foreign-born persons).
- ◆ Prior history of TB – History of prior TB disease or latent tuberculosis infection (LTBI). If yes, did the patient complete a full course of appropriate therapy?
 - A previously positive TST or IGRA signifies prior TB Infection, which may or may not have developed into TB disease. Persons with LTBI have *M. tuberculosis* in their system but they do not have TB disease and cannot spread the infection to others;
 - Results of prior TST and IGRA tests may help clinicians differentiate those infected with *M. tuberculosis* from those uninfected. However, a negative result to any of the tests does not exclude the diagnosis of TB disease or of LTBI.
- ◆ Patients with prior TB who have been inappropriately or partially treated are at risk for recurrence or possible drug-resistance.
- ◆ Underlying medical conditions that increase the risk of progression to TB disease (e.g., HIV, diabetes mellitus, chronic renal failure, silicosis, leukemia, or cancer of the head, neck, or lung; persons who have had a gastrectomy or jejunioileal bypass; persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, etc.).

PHYSICAL EXAM

- ◆ Cannot be used to confirm or rule out TB disease.
- ◆ Provides valuable information about the overall condition of the patient and possible site of infection.
- ◆ Assess for signs of pneumonia, pleural effusion, lymphadenopathy, and meningitis.

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DIAGNOSIS

CHEST RADIOGRAPH (CXR)

Pulmonary TB

- Radiographic abnormalities often seen in the upper lobe (apical and posterior segments) or lower lobe superior segments.
- Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation.
- With HIV or immunosuppression the CXR may be typical, atypical, or with no visible lesions.
 - Typical cavitory lesions are usually observed in patients with higher CD4 counts.
 - Atypical patterns are observed in patients with lower CD4 counts, including infiltrates in any lung zone, mediastinal or hilar adenopathy, or, occasionally, a normal chest radiograph.
 - **In patients with HIV and symptoms and signs of TB disease, a negative CXR does not exclude TB disease.**
- Note, the presence of mixed nodular and fibrotic lesions on CXR may signify “old” TB disease.
 - These lesions may contain slowly multiplying tubercle bacilli and have the potential for progression to TB disease. Persons who have “old” TB disease on a CXR and have a positive TST reaction or positive IGRA result should be considered high-priority candidates for treatment for latent TB infection (LTBI), but only after TB disease is excluded (by obtaining three sputum specimens for AFB smear and culture) because “old” TB cannot be differentiated from active TB disease based on CXR appearance alone.
 - Conversely, fully calcified, discrete, nodular lesions without fibrosis likely represent granulomas and pose a lower risk for future progression to TB disease.

Extrapulmonary TB — more common in HIV patients. May have normal chest radiograph.

SPECIMEN COLLECTION

Sputum specimens

- All TB disease suspects (pulmonary and extrapulmonary) shall have sputum specimens collected for AFB smear and culture, even those without respiratory symptoms.
- At least three consecutive sputum specimens are needed, collected at 8 to 24 hour intervals, with at least one being an early morning specimen (preferred), or by induction, or by bronchoscopy.
- Specimens should be obtained in an airborne infection isolation room (AIIR).

Collection

- Coughing is the most commonly used method of sputum collection.
- Coughing should be supervised to ensure that sputum is collected correctly.
- A health-care worker wearing the recommended personal protective equipment shall coach and directly supervise the patient when sputum is collected.
- For patients unable to cough up sputum, deep sputum-producing coughing may be induced in an AIIR by inhalation of an aerosol of warm, sterile, hypertonic saline (3%– 5%).

Other specimens

When extrapulmonary TB is suspected, clinical specimens other than sputum (e.g., urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) may also be submitted for examination as dictated by the history and clinical exam.

SPECIMEN TESTING

All sputum samples must be sent for testing for acid-fast bacilli (AFB) smear and culture.

- Smear microscopy is quick and easy to perform.
- Culture examinations should be done on all diagnostic specimens, regardless of AFB smear or NAAT results.
 - MTB can grow in culture specimens that were AFB smear and NAAT negative.
 - Culture is much more sensitive than smears to diagnose TB disease.
 - 5,000 to 10,000 bacilli per milliliter of specimen are required for detection of bacteria in stained smears.
 - In contrast, 10 to 100 bacilli are needed for a positive AFB culture result. Thus, patients with TB disease may have negative AFB smears with a subsequent positive culture.
 - **Negative AFB smears do not exclude TB disease.**

At least one respiratory specimen should be tested using a NAAT.

- A single negative NAAT result should not be considered to definitively exclude TB disease, especially when the clinical suspicion of TB disease is moderate to high.
- The negative NAAT result should be used as additional information in making clinical decisions, to expedite testing for an alternative diagnosis, or to prevent unnecessary TB disease treatment.

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DIAGNOSIS

CONFIRMING PULMONARY TB**CULTURE-CONFIRMED TB**

- A positive culture for MTB confirms the diagnosis of the disease.
- Culture remains the gold standard for laboratory confirmation of TB disease.
- Culture examinations must be done on all diagnostic specimens, regardless of AFB smear or NAAT results. MTB can grow in culture specimens that were AFB smear and NAAT negative.

DETERMINING THE SENSITIVITIES OF THE ORGANISM

- Growing bacteria are required to perform drug-susceptibility testing and genotyping.
- Drug susceptibility testing for first-line MTB drugs must be performed on at least the first isolate from MTB positive sputum cultures.
- If testing demonstrates resistance to first-line TB drugs, second-line drug susceptibility testing must be performed.
- In addition to conventional testing, some patients may require rapid testing for genes that may confer resistance to TB medications.
 - Rapid molecular testing is especially important for patients known to have had:
 - prior TB disease treatment; or
 - contact with a patient with known anti-TB drug resistant disease.
- A limitation of molecular testing for drug resistance is that the clinical relevance of some of the mutations identified in MTB genes remains unknown. Therefore, it is essential that conventional (growth-based) drug-susceptibility tests are done in conjunction with molecular testing. Providers should call the PHB for help in locating a reference laboratory for rapid molecular testing for drug resistance if drug resistance is suspected (e.g., because the patient had incomplete TB treatment the past).

CULTURE-NEGATIVE (CLINICALLY-CONFIRMED) TB

- In the absence of a positive culture, TB disease may be diagnosed on the basis of clinical signs and symptoms alone.
- The diagnosis is often based on the clinical response to TB treatment.
- The Local Health Department TB Controller (LHD TBC) must be consulted when respiratory specimen cultures from a high suspect TB patient are negative for MTB.
- It is the LHD TBC's responsibility to decide if the patient's clinical signs and symptoms warrant a diagnosis of clinically-confirmed TB.
- The patient's TB medications must not be discontinued before the LHD TBC thoroughly reviews the patient's clinical course.

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TREATMENT

TWO-PHASE TREATMENT OF PAN-SENSITIVE PULMONARY TB

TREATMENT GOALS	INITIAL PHASE		CONTINUATION PHASE		
	<ul style="list-style-type: none"> Render the patient non-infectious Reverse the symptoms of TB such as weight loss, fever, and productive cough 		<ul style="list-style-type: none"> Avoid treatment failure Prevent relapse Prevent the development of drug-resistant organisms 		
TREATMENT DURATION	Treatment duration depends on: <ul style="list-style-type: none"> whether the patient had a cavitory lesion on chest x-ray and, when the patient's cultures converted to negative 				
TREATMENT	DRUGS	INTERVAL AND DOSES FIRST 8 WEEKS	DRUGS	INTERVAL AND DOSES AFTER FIRST 8 WEEKS	TREATMENT COMPLETION
No cavitory lesions on CXR and culture-negative 8-week respiratory specimens	INH/B ₆ RIF PZA* EMB [†]	Daily for 56 doses (8 weeks) [§] Followed by →	INH/B ₆ RIF	Daily for 126 doses (18 weeks) [§]	182 total doses Total duration of therapy 26 weeks
Cavitory lesion(s) on CXR or culture-positive 8-week respiratory specimens	INH/B ₆ RIF PZA* EMB [†]	Daily for 56 doses (8 weeks) [§] Followed by →	INH/B ₆ RIF	Daily for 196 doses (28 weeks) [§]	252 total doses Total duration of therapy 36 weeks

RELEASE OF PATIENTS WITH PULMONARY TB FROM AIRBORNE ISOLATION

- Patients with pulmonary TB are released from respiratory isolation depending on their tolerance of TB medications and their clinical, radiologic, and laboratory findings (e.g., smear and NAAT results).
- The CCHCS PHB, along with the LHD TB Controller, must approve all releases from airborne infection isolation room (AIIR) of patients on TB medications.
- See CCHCS Care Guide: Tuberculosis Diagnosis and Isolation for more information.

* PZA is contraindicated in some patients, e.g., patients who are pregnant, who have active gout, or severe liver disease. For these patients, an alternative 39 weeks regimen should be discussed with the treatment team, including the PHB and the LHD TB Controller.

[†] Ethambutol (EMB) should be discontinued as soon as laboratory results indicate that the MTB is pan-sensitive.

[§] First line TB medications should be given together as a single dose by DOT. Split doses should be avoided.

TREATMENT

FIRST AND SECOND LINE TB DRUGS CURRENTLY USED IN THE UNITED STATES	
FIRST LINE TB DRUGS	COMMENTS
Isoniazid (INH) Rifampin (RIF) Pyrazinamide (PZA) Ethambutol (EMB) Rifabutin (RBT)	<ul style="list-style-type: none"> • Standard treatment for drug susceptible TB (INH, RIF, PZA, and EMB form the core of initial treatment regimen) • Safe, effective, inexpensive • Oral route • 95% cure rate • Based on solid scientific evidence from over 30 years of drug discovery and controlled clinical trials, 1943-72 • RBT can be substituted for RIF if organisms are known to be susceptible to this agent
SECOND LINE TB DRUGS	
Streptomycin (SM) Cycloserine Capreomycin p-Aminosalicylic acid Levofloxacin Moxifloxacin Gatifloxacin Amikacin/Kanamycin Ethionamide	<ul style="list-style-type: none"> • Reserved for special situations such as TB disease: <ul style="list-style-type: none"> ➢ Caused by drug resistant organism ➢ In patients intolerant to some first line drugs • Treatment decisions are based on laboratory drug resistance testing and epidemiological information

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TB TREATMENT IN SPECIAL CIRCUMSTANCES

The TB Treatment team may need to consult with other disciplines in some cases (e.g., patients who are pregnant, HIV-infected, who have renal insufficiency or hepatic disease). These experts do not replace, but work in conjunction with, the CME and the LHD TBC.

CULTURE-NEGATIVE (CLINICALLY-CONFIRMED) TB

For patients with smear and culture-negative TB, the California TB Controllers Association (CTCA) recommends a longer duration of therapy in the continuation phase than do national guidelines.

- The CTCA guidelines stipulate that patients with smear and culture-negative TB who are responding to therapy after 2 months and for whom no other etiology is identified, should continue treatment for an additional 4 months (for a total of 26 weeks and 182 doses of treatment).
- In addition, because of the high level of INH resistance in California, the CTCA guidelines recommend the continuation of at least three drug therapy with INH, RIF, and EMB throughout the continuation phase of treatment.

EXTRAPULMONARY TB

Evaluation:

- All patients with confirmed extrapulmonary TB require a full evaluation for pulmonary TB (including CXR and evaluation of three respiratory specimens).

Treatment:

- Extrapulmonary TB is generally managed in the same way as pulmonary TB.
 - A six month regimen (2 months on INH, RIF, PZA and EMB followed by 4 months of INH and RIF), unless the organisms are known or suspected of being resistant to first-line drugs.
 - The exception to this recommendation is TB involving the central nervous system (CNS), for which up to 12 months of therapy is recommended.

Monitoring:

- Response to treatment must often be measured by clinical and radiographic findings rather than by culture because of the relative inaccessibility of the sites of disease.

TB IN HIV INFECTED PATIENTS

Treatment:

- Patients with HIV infection and TB have a higher likelihood of:
 - paradoxical reactions, which may be misinterpreted as clinical worsening;
 - concomitant illnesses or infections that may complicate treatment;
 - drug resistance and drug interactions; and
 - malabsorption of drugs.
- As with all treatment of TB disease in CCHCS patients, daily dosing of TB medications is required.
- Every effort should be made to use a rifamycin-based regimen for the entire course of TB therapy in HIV-infected patients. The drug-drug interactions between the rifamycins and antiretroviral drugs must be managed appropriately, rather than using TB treatment regimens that do **not** include a rifamycin or by withholding antiretroviral therapy until completion of TB treatment. Rifabutin (sometimes with dose adjustments) can often be substituted for rifampin when a patient is on antiretroviral therapy.

TB IN PREGNANCY AND WITH BREASTFEEDING MOTHERS

TB treatment in pregnancy should be initiated when the likelihood of disease is moderate to high. Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does TB treatment.

- A three-drug, nine month regimen with INH, RIF, and EMB can be used in pregnant women who are HIV negative.
- Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and it should not be used.
- Because of the unknown risk of second-line drugs to the fetus, pregnant women being treated for multidrug resistant TB (MDR-TB) should be counseled accordingly and expert consultation should be sought.

TB IN PATIENTS WITH HEPATIC DISEASE

Patients with hepatic disease or abnormal baseline liver enzymes may develop hepatotoxicity from TB medications.

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TB TREATMENT IN SPECIAL CIRCUMSTANCES (continued)

TB IN PATIENTS WITH RENAL INSUFFICIENCY AND END-STAGE RENAL DISEASE

- TB medication doses and/or frequency of administration may need to be altered for patients with renal insufficiency or ESRD or patients on dialysis.
- Drug levels may need to be monitored.

MANAGEMENT OF TREATMENT FAILURE, RELAPSE, AND DRUG RESISTANT DISEASE

TREATMENT FAILURE

Continued or recurrently positive sputum cultures for ≥ 4 months after treatment initiation in a patient receiving adequate drug therapy.

- May be due to acquired drug resistance resulting from nonadherence to treatment regimens, malabsorption, or advanced HIV disease.
- Evaluation includes symptom review, CXR, repeat drug susceptibility testing on positive cultures, clinical assessment for malabsorption, and assessment of potential laboratory error.
- Treatment failure should be immediately reported to the LHD TBC, who must approve any change in the treatment regimen. Consultation with another TB expert, e.g., California Department of Public Health (CDPH) TB Control Branch (TBCB) may be necessary.
- The principles for changing a failing regimen include:
 - ◆ **never add a single drug, as acquired resistance is likely to occur, and**
 - ◆ **always add at least three new drugs, never previously used for treatment, to the failing treatment regimen.**

RELAPSE

Patient becomes and remains culture-negative throughout the course of therapy, but, at some point after therapy, either becomes culture-positive again or develops signs and symptoms consistent with active TB.

- May be secondary to a failure to sterilize host tissues or, less commonly, exogenous reinfection.
- Risk factors include advanced HIV disease (based on expert opinion), extensive TB with cavitory disease, and persistent positive sputum cultures two or more months after treatment initiation.
- In patients previously treated with DOT, relapse generally occurs with organisms having the same susceptibility profile as the pretreatment isolate. Management of these patients should be discussed with a TB expert and the LHD TBC.

DRUG RESISTANCE

Primary drug-resistant disease: Laboratory-confirmed drug resistant TB in a patient with no prior history of TB treatment.

Acquired drug-resistant disease: Laboratory-confirmed drug resistant TB in a patient whose isolate develops drug resistance after an unsuccessful course of treatment.

(Drug-resistant TB disease must always be treated with a daily regimen and under DOT).

MONORESISTANCE

With INH-resistance → RIF, EMB, and PZA should be given for a minimum of six months.

With RIF-resistance → INH and EMB should be given for 18 months (preferably with PZA for the first two months).

MULTIDRUG RESISTANT TB (MDR TB)

- Caused by an organism that is resistant to at least INH and RIF, the two most potent TB drugs.
- Patients with MDR TB are at high risk for treatment failure, relapse, further acquired resistance, or death.
- The CME must engage the LHD TBC and the CDPH TBCB. Other experts may be consulted as needed.
- Current drug susceptibility results and a history of previous treatment with anti-TB drugs must be considered when tailoring drug treatment regimens for patients with MDR TB.
- Treatment for MDR TB:
 - ◆ Shall include at least three to five drugs to which the organism shows in vitro sensitivity,
 - ◆ Must be administered for a prolonged period after culture conversion, and
 - ◆ Requires second-line anti-TB drugs that are often less effective and more toxic than the first-line drugs.

EXTENSIVELY DRUG RESISTANT TB (XDR TB)

Extensively drug resistant TB (XDR TB) is a rare type of MDR TB that is resistant to INH and RIF, as well as any fluoroquinolones, and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

- This rare circumstance requires immediate notification of the LHD TBC and the CDPH TBCB.
- Management shall proceed according to the recommendations of the TBCB.

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MONITORING

MONITORING THE PATIENT WITH PAN-SENSITIVE PULMONARY TB (see table, page 10)

- Monitor for:
- Response (including culture conversion)
 - Adverse reactions to TB medications

Monitoring Response to Treatment

- Follow-up bacteriologic examinations
 - Patients with smear-positive pulmonary TB should have a set of two respiratory specimens (collected at least 8 hours apart, and not more than 24 hours apart) evaluated every week until both specimens in the set have been documented as smear-negative. There must be at least 7 days between the smear-negative set of specimens and the last smear-positive specimen.
 - Once sputum smears become negative, or for those patients with smear-negative but culture-positive pulmonary TB, a set of two respiratory specimens (collected at least 8 hours apart, and not more than 24 hours apart) should be collected every 2-4 weeks until cultures have been documented as persistently negative (persistently negative is defined as: at least one set of two negative cultures without any subsequent positives, and the negative set must have been collected at least 7 days after the last culture-positive specimen was collected).
 - Additional surveillance cultures during treatment are not recommended for pan-sensitive pulmonary TB.
 - For culture-confirmed TB, additional isolate testing, to include second line MTB drug susceptibility testing, must be performed if cultures fail to convert to negative within three months of therapy or when the clinical and/or radiographic presentation does not improve or worsens with therapy.
- Assess subjective and objective measures of clinical improvement. This is true for both culture and clinically confirmed TB. Clinical improvements can be observed on follow-up chest x-ray, by weight gain, decrease in cough and other symptoms, and by patient report.

Monitoring for Adverse Reactions to TB Medications**Baseline Evaluation**

- **Clinical Evaluation and education:** Patients placed on TB medication require:
 - Evaluation for any conditions that place him or her at high risk for TB progression or for toxicity from TB medications, e.g., renal insufficiency.
 - Baseline tests for visual acuity (Snellen Chart) and color vision (Ishihara) because EMB has the potential for ocular toxicity manifesting as optic or retrobulbar neuritis.
 - Education regarding the possible visual side effects of EMB and instructions to immediately report vision changes to their health-care provider.
- **Laboratory Testing:** Baseline liver function tests (LFTs) (aminotransferases [AST, ALT], bilirubin, alkaline phosphatase), serum creatinine, platelet count. Tests for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) should be obtained on all patients with unknown HBV and/or HCV status.
- **Predicting Drug Interactions (with special attention to rifamycins):** TB medications, especially rifamycins, can interact with other medications. See table of drug-drug interactions involving rifamycins (see pages 13-14). Knowledge of the mechanisms of drug interactions can help predict the likelihood of an interaction, even if that specific combination of drugs has not been formally evaluated.

Monitoring During Treatment

- **Clinical Evaluation:** At least monthly during treatment to identify possible adverse reactions to medications and to assess adherence.
- Monthly repeat testing of visual acuity (Snellen) and color vision (Ishihara) is recommended for patients receiving an EMB dose exceeding 15-20 mg/kg (the recommended range) and for patients receiving EMB for more than two months. Patients receiving EMB should be questioned monthly regarding visual disturbances.
- **Laboratory Testing:** Patients with abnormal baseline LFTs, or who are HCV positive, should have liver enzyme testing at the end of the first month of treatment, every other month thereafter while on therapy, and at any time during the course of therapy if symptomatic. Repeat LFTs at least monthly if the patient is at high risk for adverse reactions or has symptoms of adverse reactions.

End of Treatment Monitoring

- **Chest X-Ray:** An end-of-treatment CXR should be obtained to provide a new baseline.
- **Respiratory Specimens:** Collect two sputum specimens (at least 8 hours apart) for smear and culture.
- **Follow-up after Treatment:** Symptom review and medical evaluations bimonthly for a minimum of six months after the completion of treatment.
 - After treatment for TB instruct patient to promptly report the development of any symptoms, particularly prolonged cough, fever, and weight loss.
 - Patients with MDR-TB, recurrent TB, extensive disease, or poor adherence to treatment need more intensive end-of-treatment and post-treatment monitoring (at least monthly).

MONITORING

MONITORING TB TREATMENT

BASELINE TESTS	MONTHLY MONITORING DURING TREATMENT	END OF TREATMENT
<ul style="list-style-type: none"> • Liver panel (AST, ALT, bilirubin, alkaline phosphatase) • Serum creatinine • Platelet count • HBsAg, HCV antibody • Sputum specimens as previously described • Chest X-ray • Patients who will be taking EMB: <ul style="list-style-type: none"> ➢ Visual acuity test (Snellen chart) ➢ Color vision test (Ishihara) • HIV-infected patients: <ul style="list-style-type: none"> ➢ CD4+ lymphocyte count 	<ul style="list-style-type: none"> • Assess for adherence to TB medications • Identify adverse reactions to TB medications • Sputum specimen* • Liver panel if necessary** • Patients taking EMB: <ul style="list-style-type: none"> ➢ Question patient regarding visual disturbances including blurred vision or scotomata ➢ Patients exceeding 15-20 mg/kg EMB or receiving EMB > 2 months: <ul style="list-style-type: none"> ▪ Visual acuity test (Snellen chart) ▪ Color vision test (Ishihara) 	<ul style="list-style-type: none"> • Chest X-ray • Two sputum specimens for AFB smear and culture • Clinical follow-up for at least 6 months after therapy ends

*A set of two respiratory specimens (collected at least 8 hours apart, and not more than 24 hours apart) should be collected every 2–4 weeks until cultures have been documented as persistently negative (persistently negative is defined as: at least one set of two negative cultures without any subsequent positives, and the negative set must have been collected at least 7 days after the last culture-positive specimen was collected).

Routine monitoring of liver function, renal function, or platelet count are **not necessary during treatment unless patients have baseline abnormalities or there are clinical reasons to obtain measurements.

Monthly liver panel should be obtained in patients with the following:

- Abnormal baseline liver panel results
- Liver disease (e.g., HBV, HCV, alcohol abuse)
- Pregnancy or in the first 3 months postpartum
- Taking other hepatotoxic medications

Hepatotoxicity

Liver injury can be caused by three 1st line TB medications: INH, RIF, PZA.

Significant liver toxicity is indicated by AST ≥3X Upper Limit of Normal (ULN) in the presence of symptoms or ≥5X in the absence of symptoms. In these cases, the LHD TBC should be consulted immediately (before the next treatment dose).

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COMMUNICATION, REPORTING, AND LEGAL AUTHORITY**LEGAL AUTHORITY TO REQUIRE TB EVALUATION AND TREATMENT**

In accordance with Penal Code 7573-7574 (see page 15), the CME has the legal authority to require an inmate with suspect or confirmed TB to comply with evaluation and treatment.

REQUIRED REPORTING OF CONFIRMED AND SUSPECT TB

The CME is responsible for ensuring that his or her institution meets the mandatory reporting requirements of California Health and Safety Code Section 121362 (see page 15), and the California Code of Regulations (CCR) Title 17 (see page 15), as well as the mandatory reporting requirements to CCHCS PHB (IMSP&P Volume 10, Chapter 2) (see page 15).

Specifically, the CME is responsible for ensuring that;

- All TB suspects and patients are reported to the LHD TBC.
- The Correctional Facility TB Patient Plan (CFTP)* with all information available is submitted within one working day for a suspect or confirmed case of TB to the LHD for the jurisdiction of the prison (California Health and Safety Code 121362 [see page 15]).
- The CFTP is submitted electronically to the CCHCS PHB within one working day (IMSP&P Volume 10, Chapter 2) (see page 15).
- The institution adheres to any additional reporting requirements for LHDs (in addition to the minimum requirements outlined by regulation).
- The required LHD TBC approval is obtained for the original TB treatment plan, as well as any subsequent changes in the treatment regimen.

*The Correctional Facility TB Patient Plan (CFTP) is the tool for reporting TB suspects and patients in CCHCS to the LHD as well as to the CCHCS PHB.

REQUIRED REPORTING OF TB TREATMENT

In accordance with California Health and Safety Code 121361 (see page 15), the CME is responsible for ensuring:

- That his or her institution maintains written documentation of the patient's adherence to the TB treatment plan; and
- That all TB medications are given by directly observed therapy (DOT); and
- That his or her institution resubmits updates of the CFTP to the LHD and the CCHCS PHB as indicated. Updates to be reported include:
 - notification of new respiratory specimen results,
 - medication changes and completion,
 - new crucial laboratory results such as an inmate's HIV status, and
 - notification of inmate hospitalization, transfer, parole, or discharge.

REPORTING PAROLE OR DISCHARGE

In accordance with California Health and Safety Code Section 121361 (see page 15), the CME is responsible for ensuring that:

- Before his or her institution discharges, releases, or paroles a patient on TB treatment or with suspect TB, the institution notifies the LHD TBC,
- A written treatment plan has been received and approved by the local LHD TBC,
- The LHD TBC is notified of the jurisdiction to which the TB patient will be discharged, released, or paroled, and
- A notification and written treatment plan are provided upon release to both the LHD for the county in which the parolee intends to reside and the LHD for the county in which the state correctional institution is located.

SUMMARY

DECISION SUPPORT

PATIENT EDUCATION

MEDICATIONS

TREATMENT OF TB IN ADULTS

- All indicated TB medications are given simultaneously at the same time of day by DOT (no splitting of doses).
- Patients who experience serious adverse reactions should be instructed to stop treatment and immediately consult health care provider.

MEDICATION	Dose	ADVERSE EFFECTS/ INTERACTIONS*	COMMENTS
isoniazid (INH) Tablet: 100 mg, 300 mg \$	<u>Once daily:</u> 5 mg/kg (max: 300 mg/dose)	<ul style="list-style-type: none"> • Adverse effects: Hepatotoxicity, nausea, vomiting, anorexia, jaundice, abnormal LFTs, neuropathy, neurotoxicity, CNS effects • Drug interactions: acetaminophen, phenytoin, carbamazepine, ketoconazole, theophylline, valproate 	<ul style="list-style-type: none"> • Black Box Warning: May cause serious or fatal hepatitis. Risk of developing hepatitis is age-related • Contraindications: hepatic disease, hepatitis. May be used in patients with stable hepatic disease • Administer with pyridoxine 25 mg/day to prevent neuropathy
ethambutol (EMB) Myambutol® Tablet: 400 mg \$\$	<u>40-55 kg:</u> 14.5-20 mg/kg once daily (max: 800 mg/day) <u>56-75 kg:</u> 16-21.4mg/kg once daily (max: 1200 mg/day) <u>76-90 kg:</u> 17.8-21.1 mg/kg once daily (max: 1600 mg/day) <u>Renal impairment:</u> CrCl <30 ml/min or hemodialysis: 15-25 mg/kg per dose three times per week (not daily)	<ul style="list-style-type: none"> • Adverse effects: optic neuritis, skin rash, nausea, vomiting, hyperuricemia • Drug interactions: aluminum containing antacids • Avoid concurrent administration of ethambutol with aluminum hydroxide containing antacids for at least 4 hours following ethambutol administration 	<ul style="list-style-type: none"> • Contraindications: optic neuritis, patients unable to report visual side effects or changes in vision • Caution in patients with renal impairment • Optic neuritis is very rare at 15 mg/kg if kidney function is normal and is reversible with discontinuation of medication
pyrazinamide (PZA) Tablet: 500 mg \$\$\$	<u>40-55 kg:</u> 18.2-25 mg/kg once daily (max: 1000 mg/day) <u>56-75 kg:</u> 20-26.8 mg/kg once daily (max: 1500 mg/day) <u>76-90 kg:</u> 22.2-26.3 mg/kg once daily (max: 2000 mg/day) <u>Renal impairment:</u> CrCl <30 ml/min or hemodialysis: 25-35 mg/kg per dose three times per week (not daily)	<ul style="list-style-type: none"> • Adverse effects: hepatotoxicity, nausea, vomiting, anorexia, jaundice, abnormal LFTs, polyarthralgia, hyperuricemia, gout (rare), rash 	<ul style="list-style-type: none"> • Contraindications: patients with severe hepatic damage or acute gout • Caution in patients with diabetes or liver disease • Generally not used in pregnancy
rifampin (RIF) Rifadin® Capsule: 150 mg, 300 mg \$	<u>Once daily:</u> 10 mg/kg (max: 600 mg/dose)	<ul style="list-style-type: none"> • Adverse effects: hepatotoxicity, nausea, vomiting, anorexia, jaundice, abnormal LFTs, orange discoloration of body fluids, flu-like syndrome, renal failure, bleeding abnormalities • May increase risk of sunburn • Drug interactions: Many—see chart on pages 13-14 	<ul style="list-style-type: none"> • Contraindications: patients receiving atazanavir, darunavir, fosamprenavir, saquinavir, or tipranavir • Caution in patients with diabetes or liver dysfunction; concomitant use with etravirine, nevirapine, or any protease inhibitor • Orange urine, sweat, saliva or tears may permanently stain dentures and contact lenses • May cause significant bleeding problems
rifabutin (RBT) Mycobutin® Capsule: 150 mg \$\$\$\$	<u>Once daily:</u> 5 mg/kg (max: 300 mg/dose) <u>Renal impairment:</u> CrCl <30 ml/min: reduce dose by 50%	<ul style="list-style-type: none"> • Adverse effects: neutropenia, uveitis, polyarthralgias, hepatotoxicity, rash, orange discoloration of body fluids, nausea, vomiting • Drug interactions: See chart on pages 13-14 	<ul style="list-style-type: none"> • Caution in patients with neutropenia or thrombocytopenia • Orange urine, sweat, saliva or tears may permanently stain dentures and contact lenses • Weaker inducer of hepatic microsomal enzymes than rifampin • Fewer drug interactions with HIV meds than rifampin

BOLD = Formulary

*For a complete list of significant side effects and drug interactions consult prescribing information.

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION
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CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS INVOLVING THE RIFAMYCINS* (e.g., rifampin, rifabutin)		
DRUG CLASS	DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	COMMENTS
Anticoagulants	Warfarin (Coumadin®)	May require two or threefold warfarin dose increase; monitor prothrombin time
Anticonvulsants	Phenytoin, lamotrigine	Monitor therapeutic drug concentrations and seizure activity; increase dosage if needed
Antiinfectives	Azole antifungal agents: Ketoconazole, itraconazole, voriconazole	Avoid concomitant use if possible; if necessary to use, increase dose and monitor response; separate ketoconazole and rifampin doses by 12 h; Subtherapeutic levels of ketoconazole, itraconazole and voriconazole may occur with any rifamycins. Fluconazole can be used with rifamycins, but may require increased dose fluconazole
	Doxycycline	May require use of a drug other than doxycycline
	HCV antivirals	Potential loss of antiviral efficacy and HCV treatment failure
	HIV nonnucleoside reverse transcriptase inhibitors (NNRTIs): delavirdine, efavirenz, nevirapine, rilpivirine	Avoid coadministration of delavirdine or rilpivirine with rifamycins due to potential for HIV treatment failure; if possible, avoid nevirapine with rifampin and consider using rifabutin; if efavirenz is used, rifampin is preferred
	HIV protease inhibitors: atazanavir, darunavir, fosamprenavir, lopinavir, nelfinavir, ritonavir	Avoid coadministration with rifampin due to potential loss of HIV antiviral efficacy and HIV treatment failure; consider using rifabutin, may require rifabutin dose reduction due to increase in serum levels
	HIV integrase strand transfer inhibitor (INSTI): raltegravir	Serum raltegravir levels may be reduced with rifampin and may require raltegravir dose increase; Consider using rifabutin
	Newer antiretrovirals	Seek expert opinion on interactions of new antiretrovirals and rifamycins.
	Macrolides: clarithromycin, erythromycin	May reduce effectiveness of clarithromycin and erythromycin; no interaction with azithromycin
Bronchodilators	Theophylline	Monitor serum theophylline concentrations and therapeutic outcomes; may require increase in dose
Cardiovascular agents	ACE inhibitors/ARBs enalapril, losartan	Clinical monitoring recommended; may require dose increase or change to an alternative drug
	Beta blockers propranolol, metoprolol	Monitor clinical response; consider changing to an alternative medication or increase dose
	Calcium channel blockers: verapamil, nifedipine, diltiazem	Monitor clinical response; alternative drug class should be considered; may require a dose increase
	Digoxin (patients with renal insufficiency), digitoxin	Monitor arrhythmia control, signs and symptoms of heart failure, monitor serum concentrations of digoxin; may require dose increase
	HMG-CoA Reductase Inhibitors: Atorvastatin, fluvastatin, pravastatin, simvastatin	Monitor lipid panel; may require alternative agent or increase dose for select HMG-CoA reductase inhibitors
	Quinidine	Monitor serum quinidine concentrations and arrhythmia control; may require quinidine dose increase
	Propafenone, mexiletine	Monitor clinically; increase in dosage may be needed or change to alternative agent

*For a complete list of drug interactions consult prescribing information.

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION
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CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTIONS INVOLVING THE RIFAMYCINS* (e.g., rifampin, rifabutin)		
DRUG CLASS	DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	COMMENTS
Hormone Therapy	Ethinyl estradiol, norethindrone	Patients on hormonal contraceptives should be advised to add secondary form of contraception when taking rifamycin
	Tamoxifen	May require alternative therapy or use a non-rifamycin containing regimen
	Levothyroxine	Monitor serum TSH; may require increase dose of levothyroxine
Immunosuppressive agents	Cyclosporine, sirolimus, tacrolimus	Monitor serum cyclosporine, sirolimus, and tacrolimus concentrations and clinical response; increased dosage or use of another agent may be needed
	Glucocorticoids: Prednisone, dexamethasone, methylprednisolone	Monitor clinically; may require two- to threefold increase of glucocorticoid dose
Opioids	Methadone	Methadone dose increase may be required with use of rifampin or rifapentine; rifabutin infrequently causes methadone withdrawal
Oral hypoglycemic agents	glimepiride, glipizide, repaglinide, glyburide	Monitor blood glucose; may require dose increase or change to an alternative diabetic agent
Psychotropic agents	Benzodiazepines: Diazepam, midazolam, triazolam	Clinically monitor; prefer to avoid use with rifampin; may require use of an alternative agent or a dose increase
	Antipsychotics: Haloperidol, quetiapine	Clinically monitor; may require the use of an alternative agent or a dose increase
	Tricyclic antidepressants: Amitriptyline, nortriptyline	Monitor clinically; serum concentrations may be reduced and may require a dose increase or use of an alternative agent

*For a complete list of drug interactions consult prescribing information.

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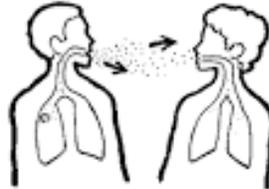
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PATIENT EDUCATION/SELF MANAGEMENT

TB DISEASE: WHAT YOU SHOULD KNOW

WHAT IS TB DISEASE?

- You have TB disease when you have active TB germs in your body.
- TB disease makes you sick.
- TB disease usually attacks the lungs.
- TB disease may also occur in other parts of the body such as kidney, brain, spine or other bones.
- People with TB disease can spread their TB germs to other people, especially to those they are close to.

**HOW DO I KNOW IF I HAVE TB DISEASE?**

Only your provider can tell if you have TB disease.

If the disease is in your lungs you may:

- Cough a lot.
- Cough up mucus.
- Cough up blood.
- Have chest pain when you cough.

You may also:

- Feel weak.
- Lose your appetite.
- Lose weight.
- Have a fever.
- Sweat a lot at night.



These symptoms may last for many weeks. They usually get worse without treatment.

TB disease outside the lungs may cause other symptoms.

HOW IS TB DISEASE DIAGNOSED?

TB disease is diagnosed by a medical provider using:

- The symptoms you are having.
- Your physical examination.
- Your chest x-ray.
- Collecting sputum and performing laboratory tests on the sputum.



PATIENT EDUCATION/SELF MANAGEMENT

TB DISEASE: WHAT YOU SHOULD KNOW CONTINUED

HOW IS TB DISEASE TREATED?

- TB disease can be cured with medicine.
- You will be separated from other people until you are no longer able to spread TB germs. This separation is usually not very long if you take your medicine as ordered by your health care provider.
- Missing doses will increase the duration of your treatment and it can cause your treatment to fail.
- Your health care provider may order laboratory tests or chest x-rays during your treatment.

WHAT SHOULD I DO?

Tell your health care provider if you have:

- A fever.
- A rash.
- Aching joints.
- Aches or tingling in fingers or toes.
- Stomach upset, nausea, or stomach cramps.
- Vomiting.
- Changes in eyesight such as blurred vision.
- Changes in hearing such as ringing in your ears.
- Dizziness.
- Bruising.
- Easy bleeding with cuts.
- Less appetite or no appetite for food.
- Tingling and numbness around the mouth.
- Yellow skin or eyes.



Tell your health care team right away if you think you are having any reaction to your treatment. Your health care provider will find a medicine plan that works for you. Most people can take their TB medicines without any problems.

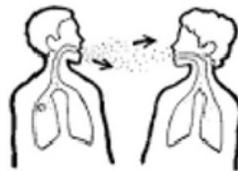
WHAT ELSE SHOULD I KNOW?

- Even if you feel better after a few weeks of treatment it does not mean the TB germs in your body are dead.
- Treatment for TB disease takes a long time (6 months or longer) because TB germs die very slowly.
- It is very important to take all of the medicines you are given exactly as they are prescribed and not to miss ANY doses.

EDUCACIÓN PARA EL PACIENTE / CONTROL PERSONAL DEL CASO LA TUBERCULOSIS (TB): LO QUE DEBE SABER

¿QUÉ ES LA TUBERCULOSIS?

- Usted tiene la tuberculosis si tiene gérmenes activos de la TB dentro de su cuerpo.
- La tuberculosis le enferma.
- La tuberculosis generalmente ataca a los pulmones.
- La tuberculosis también puede afectar otras partes del cuerpo como los riñones, el cerebro, la columna vertebral u otros huesos.
- Las personas que tienen la tuberculosis pueden propagar los gérmenes de la TB a otras personas, especialmente a aquellas con quienes tienen más contacto.



¿CÓMO SÉ SI TENGO TUBERCULOSIS?

Solamente su proveedor de atención médica puede decirle si tiene la tuberculosis.



Si la enfermedad está en sus pulmones, podría:

- Toser mucho.
- Tener una tos que produce moco.
- Tener una tos que produce sangre.
- Tener dolor en el pecho al toser.

También es posible que:

- Se sienta débil.
- Pierda el apetito.
- Pierda peso.
- Tenga fiebre.
- Sude mucho por la noche.

Estos síntomas pueden durar varias semanas y generalmente se empeoran sin tratamiento. La tuberculosis fuera de los pulmones puede causar otros síntomas.

¿CÓMO SE DIAGNOSTICA LA TUBERCULOSIS?

Un proveedor de atención médica diagnostica la TB mediante:

- Los síntomas que usted tiene.
- Un examen físico.
- Una radiografía de su pecho.
- Recoger muestras de su esputo y realizar exámenes de laboratorio sobre el esputo.



EDUCACIÓN PARA EL PACIENTE / CONTROL PERSONAL DEL CASO

LA TUBERCULOSIS (TB): LO QUE DEBE SABER (CONTINUACIÓN)

¿CUÁL ES EL TRATAMIENTO PARA LA TUBERCULOSIS?

- La tuberculosis se puede curar con medicamentos.
- Usted será separado de otras personas hasta que ya no es capaz de transmitir los gérmenes de la TB. Generalmente esta separación no dura mucho tiempo si se toma los medicamentos como lo ordene su proveedor de atención médica.
- Si no se toma alguna dosis, la duración de su tratamiento será aumentada y esto puede causar que fracase el tratamiento.
- Su proveedor de atención médica puede ordenar exámenes de laboratorio o radiografías del pecho durante su tratamiento.

¿QUÉ DEBO HACER?

Infórmele a su proveedor de atención médica si:

- Tiene una fiebre.
- Tiene una erupción cutánea.
- Le duelen las articulaciones.
- Siente dolor o hormigueo en los dedos de las manos o los pies.
- Tiene malestar estomacal, náuseas o calambres de estómago.
- Tiene vómitos.
- Hay cambios en su visión, tal como vista borrosa.
- Hay cambios en su audición, tal como un zumbido en los oídos.
- Tiene mareos.
- Le aparecen moretones.
- Sangra fácilmente cuando se corta.
- Su apetito disminuye o no tiene apetito para comer.
- Siente hormigueo o entumecimiento alrededor de la boca.
- Coloración amarillenta de la piel o los ojos.



Infórmele inmediatamente a su proveedor de atención médica si cree que está teniendo una reacción a su tratamiento. Su proveedor de atención médica buscará un plan de tratamiento que funcione para usted.

La mayoría de las personas pueden tomar los medicamentos para la tuberculosis sin ningún problema.

¿QUÉ MÁS DEBO SABER?

- Aunque se sienta mejor después de unas semanas de tratamiento, eso no significa que los gérmenes de la TB en su cuerpo están muertos.
- El tratamiento para la tuberculosis dura mucho tiempo (6 meses o más), ya que los gérmenes de la TB mueren muy lentamente.
- Es muy importante tomar todos los medicamentos que se le administren exactamente como son recetados y no perderse NINGUNA de las dosis.