

Consensus Statement of the TB Medical Advisory Board

Tuberculosis for Primary Care Physicians

Frequently Asked Questions

Indiana Tuberculosis Priorities

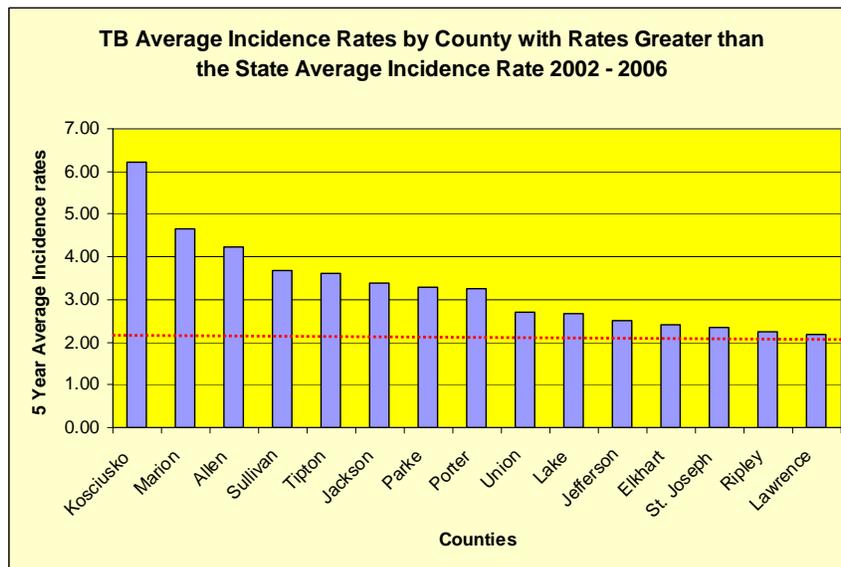
1. Early and accurate detection, diagnosis, and reporting of Tuberculosis (TB) cases leading to initiation and completion of treatment.
2. Identification of contacts of patients with infectious TB and treatment of those at risk with an effective drug regime.
3. Identification of other persons with LTBI at risk for progression to TB disease and treatment of those persons with an effective drug regime.

Is TB still an issue in Indiana?

Yes, TB is still a concern in Indiana. Although the numbers of cases of TB continue to decline within the state, we continue to have pockets of high-incidence in certain areas. During 2008, there were 118 new cases of tuberculosis reported to the Indiana State Department of Health. The overall TB case rate for Indiana was 1.9 per 100,000. TB was reported by 34 of the 92 counties. According to the 2000 census, the three most populous counties (Marion, Lake, and Allen counties) accounted for 54% of all new cases.

Over the previous ten year period 1999-2008, Indiana has had three extensive TB outbreaks in the northern areas of the state. These separate outbreaks have surrounded several infectious cases, each with their own unique social network, and involved hundreds of contacts requiring additional local, state and federal assistance to address. Without a continued coordinated effort between local public health departments, private medical practices, and the Indiana State Department of Health TB Program (ISDH) to continue to work with our infectious patients we will not be able to meet the challenges to TB elimination.

Table 1:



A diagnosis of tuberculosis should be considered in all patients with chronic cough (>2 weeks) and any general symptoms of TB including weight loss, fever or night sweats. HIV positive individuals (Chart 1) and children less than 5 years old (Chart 2) are especially vulnerable to progressing to active disease once exposed and should be medically evaluated promptly. In addition, persons that have lived or extensively worked in high-burden countries (Chart 3) continue to account for a greater portion of all reported cases each year. Of those non-U.S. born cases reported in 2008, the majority come from Central/South America.

Chart 1:

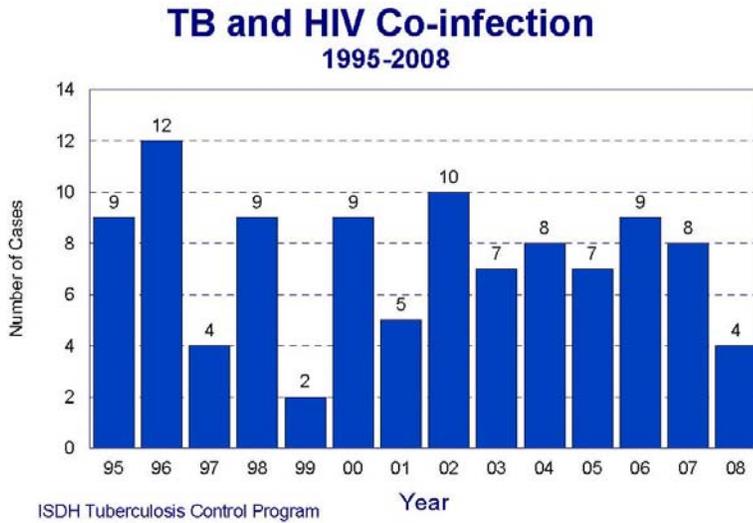


Chart 2:

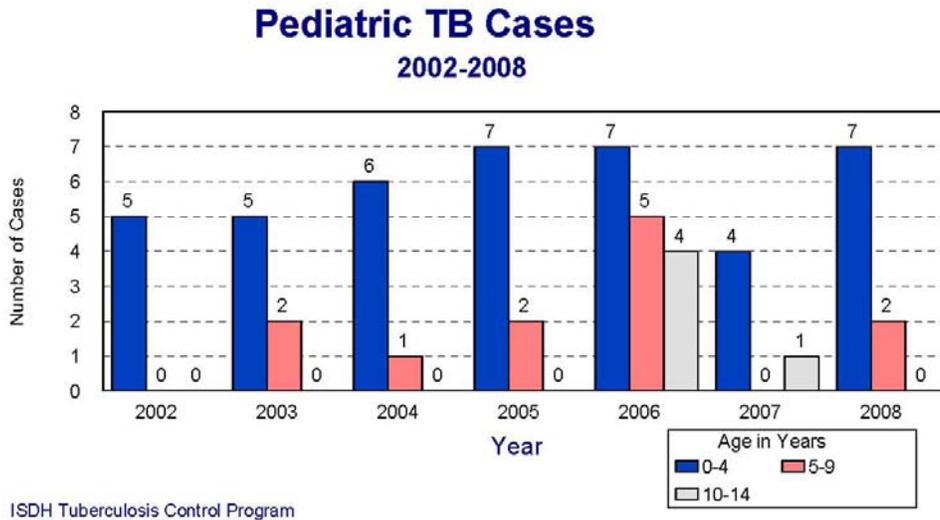
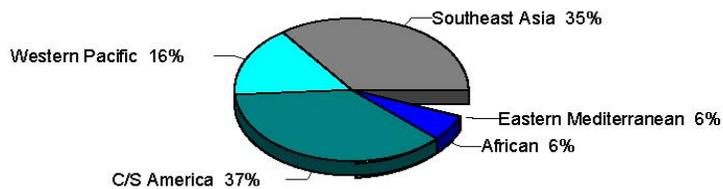


Chart 3:

Non-U.S. Born TB Cases Reported in 2008 by World Region (n=49)



ISDH Tuberculosis Control Program

What is Indiana's model for TB case management?

In Indiana, the control and eventual elimination of TB requires a coordinated effort between the patient, physician, local health department, and the ISDH TB Program. This broader view of TB control is the fundamental responsibility of the TB Case Manager, employed by the local health department. The TB Case Manager, which works as an agent of the Local Health Officer- who is ultimately responsible for TB control in their jurisdiction, is the primary liaison who links together the private physician, outreach worker, social services agencies, health care facilities and the patient. A listing of local health departments can be obtained from the ISDH Website at <http://www.in.gov/isdh/>

How should a person suspected of having TB be evaluated?

It is important for physicians to be knowledgeable of their local TB epidemiology when conducting a patient's history of TB exposure and symptoms. A complete medical evaluation for TB includes the following:

Medical history

Clinicians should ask about the patient's history of TB exposure, infection, or disease. It is important to consider demographic factors (e.g., country of origin, age, ethnic or racial group, occupation) that may increase the patient's risk of exposure to TB or to drug-resistant TB. Also, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increases the risk of latent TB infection progressing to TB disease.

Physical Examination

A physical exam can provide valuable information about the patient's overall condition and other factors that may affect how TB is treated, such as HIV infection or other illnesses. Extrapulmonary disease can have varied presentation based on site of infection.

BCG Vaccine

BCG, or bacilli Calmette-Guérin, is a vaccine for tuberculosis (TB) disease. Many foreign-born persons have been BCG-vaccinated. BCG is used in many countries with a high prevalence of TB to prevent childhood tuberculosis meningitis and miliary disease. However, BCG is not generally recommended for use in the United States because of the low risk of infection with *Mycobacterium tuberculosis*, the variable effectiveness of the vaccine against adult pulmonary TB, and the vaccine's potential interference with tuberculin skin test reactivity.

Testing for TB in BCG-Vaccinated Persons

The tuberculin skin test (TST) and interferon gamma release assay (IGRA) blood tests to detect TB infection are not contraindicated for persons who have been vaccinated with BCG. BCG vaccination may cause a false-positive reaction to the TST, which may complicate decisions about prescribing treatment. The presence or size of a TST reaction in persons who have been vaccinated with BCG does not predict whether BCG will provide any protection against TB disease. Furthermore, the size of a TST reaction in a BCG-vaccinated person is not a factor in determining whether the reaction is caused by LTBI or the prior BCG vaccination. TB IGRA Blood tests to detect TB infection, unlike the TST, are not affected by prior BCG vaccination and are less likely to give a false-positive result.

TB skin test or Interferon gamma Release Assays (IGRA)

The Mantoux tuberculin skin test (TST) and Interferon Gamma Release Assays such as the QuantiFERON-Gold test (QFT-Gold), the QuantiFERON-IN Tube (QFT-IN Tube), and the T-SPOT are used to test for *M. tuberculosis* infection. A TST is performed by injecting 0.1 ml of tuberculin purified protein derivative into the inner surface of the forearm (the injection should produce a pale elevation of skin 6 to 10 mm in diameter. The test is read within 48 to 72 hours by a trained health care worker, who measures in millimeters the induration (palpable, raised, hardened area or swelling) across the forearm. The reader should not measure erythema.

The IGRA is a blood test that requires live lymphocytes. It measures the patient's immune system reaction to *M. tuberculosis*. Once the blood samples are taken, they must be processed while white blood

cells are still viable. (Time frames from blood draw to incubation to the laboratory vary according to the specific IGRA test used. Please check with your local laboratory to obtain exact time frames for the test of your choice.) Blood samples are mixed with antigens including mixtures of synthetic peptides representing two *M. tuberculosis* specific proteins (ESAT-6 and CFP-10). These proteins, ESAT-6 and CFP-10, are absent from BCG vaccine and most environmental mycobacteria, and as a result ensure a more accurate prediction of TB infection. The Indiana State TB Medical Advisory Board has indicated that IGRAs can be used in place of the TB Skin Test. A medical provider should choose one method and not use an IGRA to validate the TST.

Chest x-ray

A PA and lateral chest radiograph is used to detect chest abnormalities. Lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest TB, but cannot be used to definitively diagnose TB. However, a normal chest radiograph may make pulmonary TB unlikely in a person who has had a positive reaction to a TST or QFT-Gold and no symptoms of disease.

Diagnostic Microbiology

The presence of acid-fast-bacilli (AFB) on a sputum smear or other specimen often indicates TB disease. Collection of three sputum specimens should be collected on three consecutive days or at least eight-hours apart and submitted to the laboratory for both AFB smear and culture. Acid-fast microscopy is easy and quick, but it does not confirm a diagnosis of TB because some acid-fast-bacilli are not *M. tuberculosis*. Therefore, a culture is done on all initial samples to confirm the diagnosis. (A positive culture is not always necessary to begin or continue treatment for TB.) Real time polymerase chain reaction (PCR) and nucleic acid amplification (NAA) rapid testing are available for rapid identification of TB DNA of specimens; however a positive culture for *M. tuberculosis* is needed to confirm the diagnosis of TB disease. Culture examinations should be completed on all specimens, regardless of AFB smear results.

Tips for non-specialists

- A high index of suspicion is needed in persons born outside the United States, immunocompromised patients, children <5 years old and persons with history of homelessness or incarceration.
- Check sputum for acid-fast bacilli if cough persists longer than three weeks despite broad spectrum antibiotics.
- Appearances on chest radiographs are often less specific in immunocompromised patients and children.
- To assist in the diagnosis of TB in children, all contacts <5 years old should receive both a lateral and posterior-anterior chest radiographs to properly detect chest abnormalities.
- Positive sputum cultures in children are difficult to obtain, as children are unlikely to cough and produce sputum. Gastric washings for AFB and cultures should be done if pulmonary specimens are unavailable or negative.

Drug sensitivities

For all patients, the initial *M. tuberculosis* isolate should be tested for drug resistance. It is crucial to identify drug resistance as early as possible to ensure effective treatment. Drug susceptibility patterns should be repeated for patients who do not respond adequately to treatment or who have positive culture results despite 3 months of therapy.

Clinical judgment should be used in evaluating and treating all symptomatic patients, even with smear negative and/or negative culture.

When should a case report of TB be completed?

Health care providers and laboratories are required to report suspected or confirmed cases of active TB (410 IAC 1-2.3-47), demonstrated by a positive acid fast bacilli (AFB) smear in a clinical setting compatible with disease due to *M. TB*; a positive culture for *M. TB*; or a clinical presentation compatible with disease due to *M. TB*, even with a negative or pending AFB smear or culture.

Providers should report to their local health departments using the “Report of Tuberculosis” state form 14058. Local health departments will then report to ISDH TB Program. Progress on treatment will continue monthly by local health departments using the “TB Monthly Follow-up Form”. Forms are available on the ISDH website at <http://www.in.gov/isdh/>

What drugs are used to treat active TB?

Recommended treatment of TB disease in HIV-negative adults

There are 10 drugs currently approved by the U.S. Food and Drug Administration (FDA) for treating tuberculosis (TB). Of the approved drugs, the first-line anti-TB agents that form the core of treatment regimens include; isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA). All persons diagnosed with TB disease, or suspected of having TB disease, should be started on **ALL** first line drugs. All TB medications should be taken together, split dosing should be discouraged.

Regimens for treating TB have an *initial phase* of 8 weeks (2 months), followed by a *continuation phase* of either 18 weeks (4 months) or 28 weeks (7 months). The continuation phase should be extended to 28 weeks (7 months) for patients who have cavitation on the initial chest film *and* positive sputum cultures at or after the *initial phase* of 8 weeks (2 months) of treatment. Treatment completion is determined by the number of doses ingested over a given period of time. Although basic TB regimens are broadly applicable, there are modifications that should be made under special circumstances (i.e., HIV infection, drug resistance, pregnancy, or treatment of children). Listed below are the basic regimens; please refer to *Treatment of Tuberculosis*¹ for all options for the treatment of drug-susceptible TB.

Preferred Regimen	Alternative Regimen I	Alternative Regimen II
Initial Phase Daily INH, RIF, PZA, and EMB* for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)	Initial Phase Thrice-weekly INH, RIF, PZA, and EMB* for 24 doses (8 weeks)	Initial Phase Daily INH, RIF, PZA, and EMB* for 56 doses (8 weeks)
Continuation Phase Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation Phase Thrice-weekly INH and RIF for 54 doses (18 weeks)	Continuation Phase Twice-weekly INH and RIF for 36 doses (18 weeks)
62 doses over 26 weeks	78 doses over 26 weeks	92 doses over 26 weeks

*EMB can be discontinued if drug susceptibility studies demonstrate susceptibility to first-line drugs.

A continuation phase of once-weekly INH/rifapentine can be used for HIV negative patients who do not have cavities on the chest film *and* who have negative acid-fast bacilli (AFB) smears at the completion of the initial phase of treatment.

Recommended treatment of TB disease in HIV-infected adults (pan-sensitive organism)

An **initial phase** of INH, a rifamycin (see Drug Interactions below), PZA, and EMB for the first 8 weeks (2 months). A **continuation phase** of INH and a rifamycin for the last 18 weeks (4 months).

Patients with advanced HIV (CD4 counts < 100/μl) should be treated with daily or three-times-weekly therapy in both the initial and the continuation phases. Twice weekly therapy may be considered in patients with less-advanced immunosuppression (CD4 counts ≥ 100/μl). **Once-weekly INH/rifapentine in the continuation phase should not be used in any HIV-infected patient.**

Twenty-six weeks of treatment (6 months with 62 to 182 doses depending on the Regimen) should be considered the minimum duration of treatment for adults with HIV, even for patients with culture-negative TB. Prolonging treatment to 36 weeks (extend continuation phase to 28 weeks for HIV-infected patients with delayed response to therapy (e.g., culture positive after 2 months of treatment) should be strongly considered.

What are the side effects, monitoring parameters, and major drug interactions of TB drugs?

TB Medication	Common Adverse Effects	Suggested Monitoring ^{*,Δ}	Potential Drug Interactions
Isoniazid (INH)	<p>Hepatotoxicity Asymptomatic aminotransferase elevations (10-20%)</p> <p>Clinical hepatitis (<1%)</p> <p>Peripheral neuropathy (<0.2%) – risk increased in patients with malnutrition, diabetes, HIV, renal failure, alcoholism, pregnancy, breastfeeding</p>	<p>Routine aminotransferase monitoring is not necessary. For patients with liver disease or those who develop asymptomatic elevations in aminotransferase levels, aminotransferase levels should be monitored monthly and when symptoms occur.</p> <p>Pyridoxine (25mg daily) is recommended in high risk patients for prevention of neuropathy.</p>	<p>Carbamazepine (CBZ) – ↑ CBZ levels</p> <p>Phenytoin (PHT) – ↑ PHT levels</p>
Rifampin (RIF)	<p>Orange discoloration of body fluids (sputum, sweat, urine, tears) – occurs in all patients so that patients should be warned about this effect; may permanently stain clothing or contact lenses</p> <p>GI reactions – nausea, anorexia, abdominal pain</p> <p>Cutaneous reactions Pruritus with or without rash (6%) – generally self-limiting, even with continued therapy</p> <p>Hypersensitivity (0.07-0.3%)</p> <p>Flu-like syndrome (0.4-0.7%) – more likely in patients receiving intermittent administration</p> <p>Hepatotoxicity – transient asymptomatic hyperbilirubinemia, cholestatic hepatitis; more common when given with INH</p> <p>Immunologic reactions (<0.1%) – thrombocytopenia, hemolytic anemia, acute renal failure, thrombotic thrombocytopenic purpura</p>	<p>No routine monitoring tests are required. Individual laboratory tests should be monitored in patients exhibiting clinical manifestations of adverse effects listed. In addition, routine serum concentration monitoring may be warranted for some drugs that interact with RIF.</p>	<p>INDUCES hepatic microsomal enzymes and ↓ serum concentrations of:</p> <ul style="list-style-type: none"> ▪ Antibiotics including clarithromycin, erythromycin, doxycycline, mefloquine ▪ Antiretrovirals including protease inhibitors[†], non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine)[†], maraviroc, raltegravir ▪ Benzodiazepines ▪ Cardiovascular drugs including verapamil, nifedipine, diltiazem, felodipine, propranolol, metoprolol, enalapril, losartan ▪ Cyclosporine, tacrolimus^{†,‡} ▪ Digoxin[†] ▪ Glyburide ▪ Haldol ▪ HMG CoA reductase inhibitors including simvastatin and fluvastatin ▪ Levothyroxine[†] ▪ Methadone[†] ▪ Oral contraceptives ▪ Phenytoin[†] ▪ Quetiapine ▪ Quinidine[†] ▪ Tamoxifen ▪ Theophylline[†]

			<ul style="list-style-type: none"> ▪ Warfarin[†] <p>[†] Rifabutin is the recommended rifamycin. The dose of rifabutin should be decreased when used with protease inhibitors.</p> <p>[‡] Routine serum concentration, TSH, or INR monitoring is recommended</p>
Pyrazinamide (PZA)	<p>Hepatotoxicity (1%)</p> <p>GI reactions – nausea, vomiting</p> <p>Polyarthralgias, non-gout (up to 40%) – especially in patients receiving daily PZA; usually responds to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs)</p> <p>Asymptomatic hyperuricemia - an expected effect but often without consequence</p> <p>Acute gouty arthritis – rare, except for patients with preexisting gout</p>	<p>Routine monitoring of serum uric acid concentrations is not recommended. However, serum uric acid concentration monitoring may be used as a surrogate marker for compliance.</p> <p>Routine aminotransferase monitoring is not recommended in all patients, but should be performed in patients with underlying liver disease or when PZA is used with RIF in treating latent tuberculosis.</p>	
Ethambutol (EMB)	<p>Retrobulbar neuritis – decreased visual acuity or decreased red-green color discrimination involving one or both eyes; dose-related with minimal risk using 15 mg/kg/d</p>	<p>Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara test). Patients should be questioned monthly regarding visual disturbances. Monthly visual acuity and color discrimination testing is recommended in patients receiving >15 mg/kg/d of EMB, in patients receiving EMB for longer than 2 months, and in patients with renal insufficiency. Patients should be instructed to notify their MD or public health clinic immediately if they experience any change in vision since EMB should be discontinued immediately..</p>	

* Baseline hepatic enzymes, bilirubin, serum creatinine, and a complete blood count are recommended prior to starting antituberculous therapy.

[▲] All patients receiving INH, RIF, or PZA should be instructed to immediately report any hepatitis-suggesting symptoms including nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin, or abdominal tenderness.

How can we ensure that a patient completes a full course of TB treatment?

The time to plan for completion is immediately on diagnosis. The provision of proper medications and Directly Observed Therapy (DOT) has been proven to improve patient compliance.

TB medications can be provided free of charge to all suspect, and active TB patients as well as for treatment for LTBI. State-funded TB medications are only provided through the local health departments. Prescriptions must be signed by a licensed practitioner who has prescription writing authority. Verbal or telephone orders that have not been countersigned will not be accepted.

In order to provide TB medications through the state-funded program, physicians must submit the following information to the local health department;

- Report TB patient to the local health department using the “Report of Tuberculosis” state form 14058,
- Provide copies recent chest x-ray, discharge summary and appropriate laboratory results, and
- Physician prescriptions (with correct doses and duration of treatment)

Studies demonstrate that adherence to medical regimens is invariably far lower than physicians suspect. Non-adherence to an anti-TB regimen can have major ramifications, not only for the patient, who may develop progressive, drug-resistant disease, but also for the patient’s family and other close contacts. Directly Observed Therapy (DOT) is the most reliable and effective way of administering anti-TB medications and assuring treatment completion. Ideally, every TB patient should received every dose of anti-TB medications within a program of DOT, in which a health care worker or other person watched the patient take the medication, DOT can be given at local health department clinics, by local health department outreach workers at a patient’s home or workplace, at school, at drug-treatment centers, or at community-based organizations, Intermittent dosing regimens, which are given twice or thrice weekly, are well documented to be at least as effective as daily regimens for patients with drug-susceptible organisms. Twice-weekly regimens can be started after two weeks of daily treatment. Intermittent dosing regimens should be given ONLY via DOT and should be used for patients with drug-susceptible isolates. For help in arranging DOT for your patients, call the local health department.

Physicians can support compliance by structuring all clinical services to be “patient-friendly,” and by assuring that the patient’s social service needs are met early in treatment, including HIV-related services, treatment for alcohol and drug addition, housing, and the provision of Medicaid.

NOTE: if a patient is started on TB medications in a hospital setting, please contact your local health department as soon as possible or at least prior to discharge. Although TB medications can be provided free of charge to TB suspects and cases, providing 7-10 days worth of TB medications to the patient prior to discharge maybe necessary to allow TB medications to be made available.

What follow-up tests are necessary for active TB patients?

Sputum specimens for microscopic examination and culture should be obtained from patients diagnosed with TB at a minimum of monthly intervals until two consecutive specimens are negative on culture. It is critical to obtain a sputum specimen at the end of the initial phase (2 months) to determine if the continuation phase should be extended. In addition, it is essential that patients have clinical evaluations at least monthly to identify possible adverse effects of the anti-TB medications and to assess adherence. All patients with TB should have counseling and testing offered for HIV. In order to document patient progress, the local health department TB case manager should submit a monthly TB follow-up report to ISDH and the medical provider.

How long should TB patients be isolated?

In general, patients who have suspected or confirmed TB disease of the lungs, airway, or larynx should be considered infectious if (a) they are coughing, undergoing cough-inducing procedures, or have positive sputum smear results for acid-fast bacilli (AFB); and (b) they are not receiving adequate antituberculosis therapy, have just started therapy, or have a poor clinical or bacteriologic response to therapy.

For patients in the hospital setting that are placed under airborne precautions because of suspected infectious TB disease of the lungs, airway, or larynx, airborne precautions can be discontinued when infectious TB disease is considered unlikely and either 1) another diagnosis is made that explains the

clinical syndrome, or 2) the patient has been on appropriate four-drug antituberculosis therapy and produces three consecutive negative sputum smears collected in 8- to 24- hour intervals (one should be an early morning specimen).

Patients that are on home isolation, should be instructed to remain at home and not go out to public places. People on home isolation should not leave their home except for needed medical care. This means the person is not allowed to go out in public, have visitors, return to work or use public transportation until cleared by a doctor or nurse from public health.

The contagious period depends on how well a patient's body responds to treatment. It may be as short as two weeks or it may be much longer. Additional sputum tests, chest x-rays and decreasing symptoms will be used to estimate possibility of infectiousness.

Physicians should educate their infectious patients about the need for follow-up contact investigation by the local health department. The local health department TB Case Manager will elicit the names of persons that may have been exposed during their infectious period. Exposed persons that are at high-risk should be evaluated for TB by their local health department.

Whom can we call for consultation?

Agency	Resource	Contact #	Website
Local Health Department	<ul style="list-style-type: none"> • Report suspect or active case of TB • Arrange for DOT 		www.in.gov/isdh/
ISDH TB Program	<ul style="list-style-type: none"> • Annual TB report • Forms • TB Medical Advisory Board Statements • Medical Consultation 	317.233.7434	www.TB.In.gov
New Jersey Medical School Global TB Institute	<ul style="list-style-type: none"> • Medical consultation 	1.800.4TB.DOCS	www.umdnj.edu/globaltb/home.htm
CDC	<ul style="list-style-type: none"> • Core Curriculum on Tuberculosis: What the Clinician Should Know (CDC) • Patient Educational Material • Diagnostic Standards and Classification of TB in Adults and Children (ATS/CDC) • Treatment of Tuberculosis (ATA/CDC/IDSA) 		http://www.cdc.gov/tb/pubs/default.htm

References

CDC Fact Sheet. Tuberculosis: General Information. July 2007

Centers for Disease Control and Prevention. Treatment of Tuberculosis. CDC MMWR 2003 (No. RR-11).

Centers for Disease Control and Prevention. Treatment of Tuberculosis. Controlling TB in the United States. CDC MMWR 2005 (No. RR-12).

Tuberculosis at a Glance: A reference for Practitioners on Basic Tuberculosis Information. Heartland National TB Center. December 2006.

Pulmonary tuberculosis: diagnosis and treatment. BMJ 2006; 332;1194-1197.

Orange County, CA. Home isolation fact sheet. 2008

What are the side effects, monitoring parameters, and major drug interactions of TB drugs was prepared by Sharon Erdman, PharmD

The Tuberculosis Medical Advisory Members are:

Co-Chairs

Crystal L. Jones, MD,
Marion County Health Department

Thomas P. Bright, MD
Anderson, IN

Members

Arthur Bentsen, MD
Evansville, IN

Anand Bhuptani, MD
Vigo County Health Department

Sharon Erdman, PharmD
Purdue University School of Pharmacy

Brian Foresman, DO, FCCP,
Indiana University Division of Pulmonology

Thomas Hayhurst, MD
Allen County Health Department

Rudolfo Jao, MD
Lake County

Richard Kohler, MD
Indiana University Infectious Disease

Amy Kressel, MD FIDSA
Indiana University Division of Infectious Disease

James Richardson, MD
Hendricks, IN

William Remington, MD
Kosciusko County Health Department

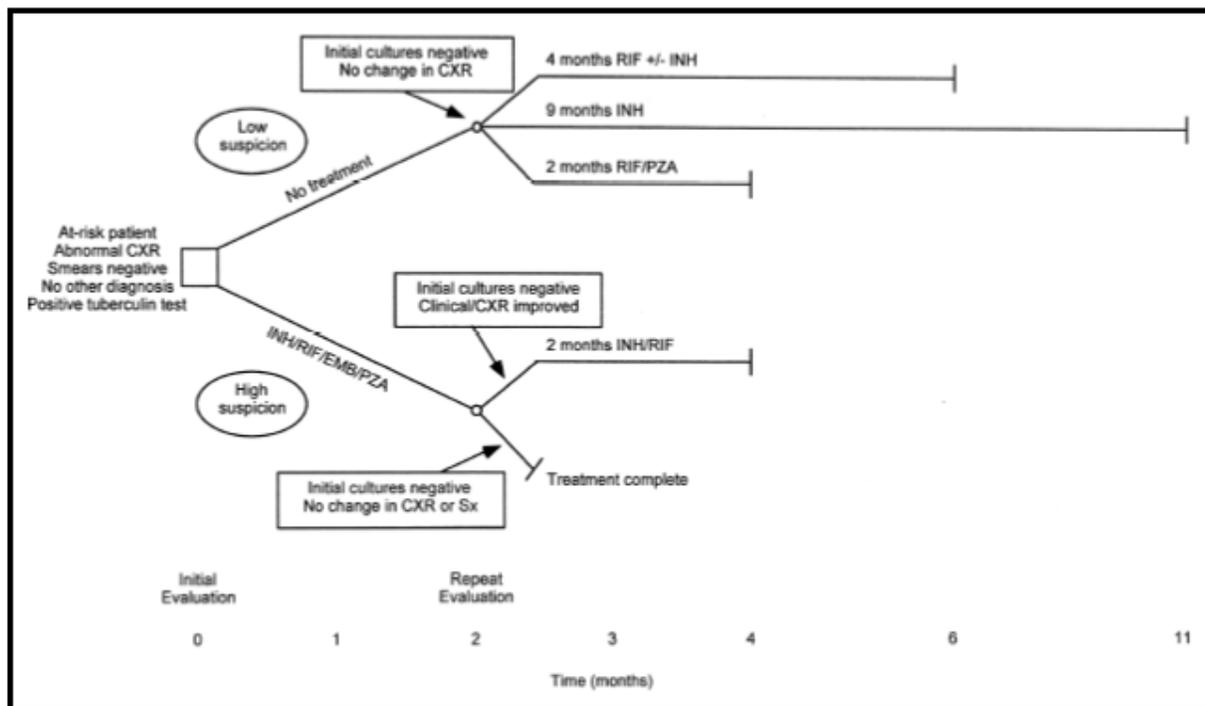
Sarah Sayger, MD
Purdue University Student Health Services

Robert G. Shellman, MD, FCCP
Beech Grove, IN

Stephen Wintermeyer, MD
Indiana University Health Services

The ISDH Tuberculosis Medical Advisory Board adopted this consensus statement in August 2009. This statement updates the previous Tuberculosis 10 Basics.

FIGURE 2. Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis



The decision to begin treatment for a patient with sputum smears that are negative depends on the degree of suspicion that the patient has tuberculosis. The considerations in choosing among the treatment options are discussed in text. If the clinical suspicion is high (bottom), then multidrug therapy should be initiated before acid-fast smear and culture results are known. If the diagnosis is confirmed by a positive culture, treatment can be continued to complete a standard course of therapy (see Figure 1). If initial cultures remain negative and treatment has consisted of multiple drugs for 2 months, then there are two options depending on repeat evaluation at 2 months (bottom): 1) if the patient demonstrates symptomatic or radiographic improvement without another apparent diagnosis, then a diagnosis of culture-negative tuberculosis can be inferred. Treatment should be continued with isoniazid and rifampin alone for an additional 2 months; 2) if the patient demonstrates neither symptomatic nor radiographic improvement, then prior tuberculosis is unlikely and treatment is complete once treatment including at least 2 months of rifampin and pyrazinamide has been administered. In low-suspicion patients not initially receiving treatment (top), if cultures remain negative, the patient has no symptoms, and the chest radiograph is unchanged at 2–3 months, there are three treatment options: these are 1) isoniazid for 9 months, 2) rifampin with or without isoniazid for 4 months, or 3) rifampin and pyrazinamide for 2 months. CXR = chest X-ray; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; Sx = signs/symptoms. (It should be noted that the RIF/PZA 2-month regimen should be used only for patients who are not likely to complete a longer course of treatment and can be monitored closely.)

Never Add a Single Drug To a Failing Regimen

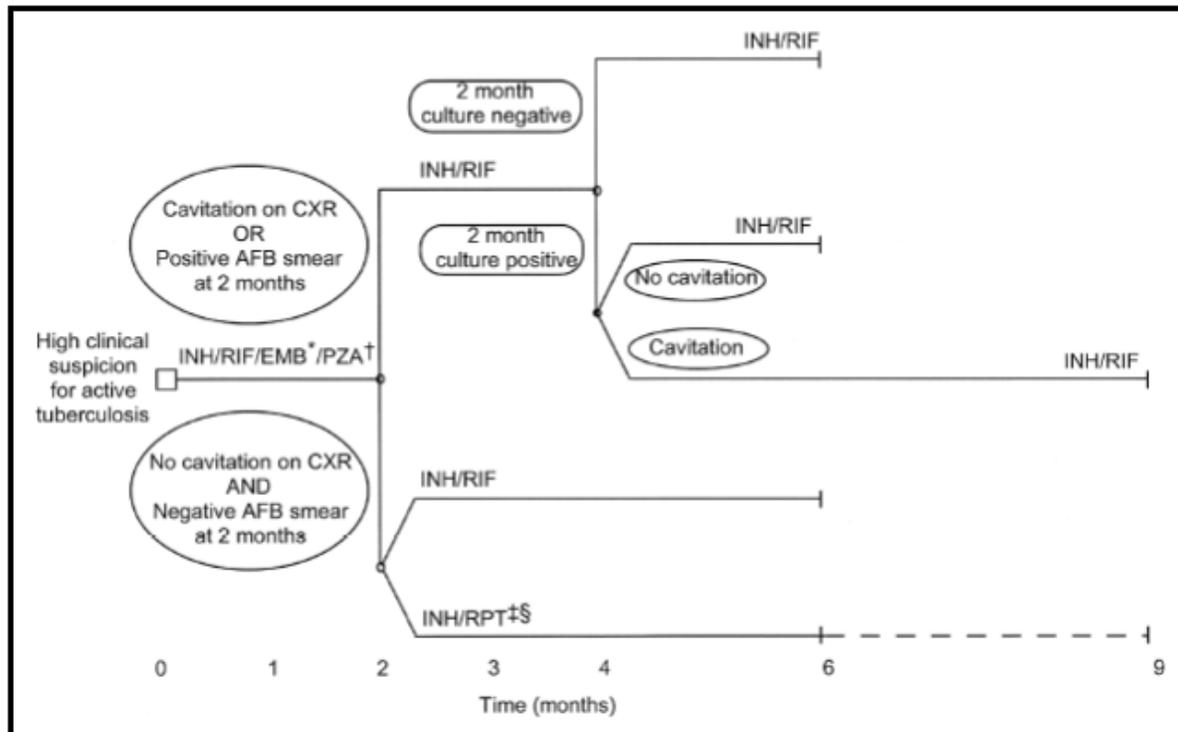
Treatment failure is defined by continued or recurrent positive cultures after 4 months of treatment in patients in whom medication ingestion was assured. Patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms and be treated with multiple agents that they have not received before. A single drug should never be added to a failing regimen. So doing risks development of resistance to the new drug, further complicating management.

TABLE 9. Antituberculosis drugs currently in use in the United States

First-line drugs	Second-line drugs
Isoniazid	Cycloserine
Rifampin	Ethionamide
Rifapentine	Levofloxacin*
Rifabutin*	Moxifloxacin*
Ethambutol	Gatifloxacin*
Pyrazinamide	<i>p</i> -Aminosalicylic acid
	Streptomycin
	Amikacin/kanamycin*
	Capreomycin

* Not approved by the Food and Drug Administration for use in the treatment of tuberculosis.

FIGURE 1. Treatment algorithm for tuberculosis.



Patients in whom tuberculosis is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months. A repeat smear and culture should be performed when 2 months of treatment has been completed. If cavities were seen on the initial chest radiograph or the acid-fast smear is positive at completion of 2 months of treatment, the continuation phase of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment. If cavitation was present on the initial chest radiograph and the culture at the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment). If the patient has HIV infection and the CD4⁺ cell count is <100/ μ l, the continuation phase should consist of daily or three times weekly isoniazid and rifampin. In HIV-uninfected patients having no cavitation on chest radiograph and negative acid-fast smears at completion of 2 months of treatment, the continuation phase may consist of either once weekly isoniazid and rifampin, or daily or twice weekly isoniazid and rifampin, to complete a total of 6 months (bottom). Patients receiving isoniazid and rifampin, and whose 2-month cultures are positive, should have treatment extended by an additional 3 months (total of 9 months).

* EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.

† PZA may be discontinued after it has been taken for 2 months (56 doses).

‡ RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.

§ Therapy should be extended to 9 months if 2-month culture is positive.

CXR = chest radiograph; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifampentine.