An Update on Tuberculosis

Dana G. Kissner, MD, Associate Professor of Medicine, Division of Pulmonary and Critical Care and Sleep Medicine, Wayne State University School of Medicine and Harper Hospital, Detroit, MI

Epidemiology trends: in 2015, for first time in 22 yr, number of active tuberculosis (TB) cases reported to Centers for Disease Control and Prevention (CDC) increased; percentage of cases of TB among foreign-born individuals continues to rise; incidence in United States low (3 cases per 100,000 individuals); ≈67% of cases of TB in foreign-born individuals, with incidence of 15/100,000; modeling shows that eradicating TB would require treating one-third of world population infected with TB (not possible); however, treating those with highest risk feasible

California TB Risk Assessment: screening tool for identification of TB infections (TBIs); asks about, eg, country of birth, risk factors for TB; immunosuppression — present or planned; eg, individuals with HIV infection, transplant recipients, those taking tumor necrosis factor (TNF)-α blockers, on prednisone or equivalent ≥15 mg/day for ≥1 mo; other history — contact with individuals with TB; prior positive tests for TB

Stages of infection: TBI either latent (LTBI) or active (cannot be both); starts with exposure or contact with case; TB airborne disease (bacteria in droplet nuclei from infected person); only one-third of individuals become infected; bacteria inhaled, resulting in TB pneumonia that presents as flu-like illness; infection spreads hematogenously and lymphatically; occasionally, diagnosis of primary TB in early stage of infection made in family member of active case; however, in most instances, primary TB heals without having been detected

LTBI: after exposure, immune cells become sensitized to TB antigens (Ags; healing starts during this period); results of TB skin test (purified protein derivative [PPD]), enzyme-linked immunospot (ELISPOT; eg, T-SPOT), or QuantiFERON TB Gold In-Tube (QFT-GIT) positive 3 wk to 2 mo later; at this point, patient asymptomatic and chest x-ray normal or may show small granuloma (LTBI, ie, no signs or symptoms of disease); ideally, treatment should be administered if test positive; after treatment, infection no longer latent; if LTBI not treated, active TB develops in 15% to 20% (ie, disease no longer latent); diabetes risk factor for TB; TB skin test, ELISPOT, or QFT-GIT remain positive after treatment because tests measure immune system, but LTBI no longer present

Testing: used to diagnose LTBI and active TBI; cannot distinguish LTBI from previously treated infection and current infection from previous treatment; not useful for determining whether treatment successful; interferon-γ release assays (IGRAs) — use series of peptides that simulate Ags of Mycobacterium tuberculosis (MTB) not present in most other mycobacteria and in Bacillus Calmette-Guérin (BCG); measure interferon-γ produced when sensitized immune cells from MTB-infected person exposed to peptides; BCG — TB vaccine used in other countries to prevent dissemination in infants and toddlers; does not prevent TBI; among nontuberculous mycobacteria (NTM), only Mycobacterium kansasii, Mycobacterium szulgai, and Mycobacterium marinum share peptides with MTB; PPD Ags shared with BCG and NTM, so TB skin test less specific

IGRAs: QFT-GIT — contains mixture of 3 types of peptides; 3 tubes (positive and negative controls and TB Ag tube) need to be filled properly and shaken vigorously enough to coat cells with Ag without causing breakage; “nil” (negative control) tube contains only heparin; TB Ag tube contains mixture of 3 peptides; mitogen (positive control) tube contains nonspecific stimulator of lymphocytes; ELISPOT test — separates only 2 of mixtures; first of 4 containers empty (nil); second container has only one peptide (ESAT-6) or panel A; third container has only CFP-10 (panel B); last container positive control containing mitogen; test evaluated by counting spots (each spot is immune cell producing sufficient interferon-γ to be recognizable); high nil or low mitogen represent invalid result; if invalid or indeterminate result obtained on ELISPOT and QFT-GIT, repeat test at least once; ≥8 spots in either or both panels is positive result; unlike QFT-GIT, borderline result (5-7 spots) possible and indication for repeat testing; QFT-GIT has single cutoff (no borderline); high number of spots likely valid result; if result close to borderline, consider clinical context

Confirmatory testing: IGRAs ideal for individuals who cannot or fail to return for reading of skin test; strongly positive PPD need not be repeated if appropriately performed and read; however, if test cannot be documented in individual who alleges prior positive test result, use IGRA to confirm; IGRAs useful for confirming infection after PPD screening of patients vaccinated with BCG

Treatment regimen recommended by CDC: 1) isoniazid (INH) daily for 9 mo; 2) rifampin (RIF) for 4 mo; 3) 3HP (12 once-weekly doses of rifapentine [RPT] and INH) given under direct observation; maximum dose of INH 900 mg and RPT 900 mg; total of 36 doses of INH (compared with 270 doses of INH in self-directed 9-mo INH regimen); normal-sized individual requires 9 pills per weekly dose (3 INH and 6 RPT) INH causes significant liver disease

Educational Objectives

The goal of this program is to improve the diagnosis and management of tuberculosis (TB) and interstitial lung disease (ILD). After hearing and assimilating this program, the clinician will be better able to:

1. Screen for latent TB infection.
2. Choose among options for treatment of TB recommended by the Centers for Disease Control and Prevention.
3. Obtain an adequate history when evaluating a patient with suspected ILD.
4. Recognize physical and radiographic findings that are consistent with ILD.
5. Recommend appropriate supportive therapy for the management of ILD.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose.

Ardizzoni E et al: 2011 Dec 8;365(23):2155-66; interferon-gamma release assay test — not appropriate for ruling out TB; if TB suspected, collect 3 sputum samples 28 hr apart (with one sample collected in morning), perform TB skin test or IGRA, and test for HIV; positive result on acid-fast bacillus (AFB) testing and culture of sputum — NAAT should be routinely performed; positive result reported as MTB complex-detected (indicates TB probably present); negative and positive predictive values excellent; suspected drug resistance — notify local health department; results obtained in 1 wk if specimens sent to CDC; accuracy of PCR — does not rule out TB; sensitivity and specificity unknown for bronchoscopy specimens and specimens other than sputum; release from isolation — NAAT (GeneXpert) labeled by Food and Drug Administration as alternative to serial smears; results equivalent to 1 or 2 sputum smears negative for AFB; however, clinicians have interpreted this to mean that one negative result on any PCR test can be used to release patients from isolation (additional smears and cultures still required); speaker believes this misunderstanding responsible for increase in TB rates.

**Questions and answers:** need for annual PPD test in patients treated for LTBI — once PPD, ELISPOT, or QFT-GIT positive, subsequent testing always positive; PPD results in patients who received BCG — BCG and PPD share same Ags; IGRA performed because of cost/availability; next test positive result on sequential testing; if PPD positive and read properly, IGRA unnecessary, but chest x-ray appropriate because asymptomatic TB possible; birth control for women on RPT — because of interaction with oral contraceptives, alternative method recommended.

**Suggested Readings**


**Interstitial Lung Disease for the Primary Care Provider**

**Eric S. White, MD, Professor of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan School of Medicine, Ann Arbor**

**Introduction:** interstitial lung diseases (ILDs) all characterized by decreased lung compliance, impaired gas transfer, and replacement of normal lung interstitium with inflammatory or fibrotic tissues; maybe named for etiologic agent (when known); interstitium is potential space bound by basement membranes in alveolus and vasculature; can be expanded by inflammatory cells, fluid from edema, reparative cells, fibroblasts, and scar itself; can extend into air spaces; has no blood vessels carrying red blood cells, so significant hypoxia often present.

**Causes:** inhaled agents; drugs (eg, amiodarone, bleomycin, methotrexate); radiation therapy; pneumonia (ie, any inflammation of lung); sarcoidosis; connective tissue diseases; lymphangioleiomyomatosis (LAM); eosinophilic granuloma (EG); also called pulmonary histiocytosis X or pulmonary Langerhans cell histiocytosis; smoking-related disease; treated with smoking cessation and anti-inflammatory drugs; sarcoidosis affects lung 95% of time; LAM is systemic disease.

**Diagnosis:** history — sex; age; symptoms; smoking history; previous use of medication; occupational and environmental history most important (including military service); family history; many ILDs associated with age (idiopathic interstitial pneumonias more common in individuals >50 yr of age); sarcoidosis more common in younger people (20-40 yr of age); some ILDs more common in one sex (eg, LAM seen only in women of child-bearing age); idiopathic pulmonary fibrosis (IPF) more common in men (tobacco-related disease).

**Symptoms:** dyspnea — most common; usually insidious; cough — usually dry and nonproductive; cough-variant syndrome common; tends to be chronic and constant; coughing jags classic symptom; no effective treatment available; constitutional symptoms — more common in systemic diseases than in local ILDs.

**Etiology:** smoking — increases risk for ILD (IPF; respiratory bronchiolitis-associated ILD; desquamative interstitial pneumonia; EG) but inversely correlated with development of sarcoidosis; previous medication — eg, bleomycin, antiarrhythmic drugs, antibiotics (especially macrodantin), nitrofurantoin (highly associated with development of pulmonary fibrosis); illicit drug use — www.pneumotox.com (provides information on association with ILD based on drug name, or pattern on computed tomography [CT] or x-ray); inhaled dust and antigens (Ags) — most common cause; eg, beryllium, coal, silica, cobalt, asbestos; air preferentially flows to zone 1 of lungs, while blood preferentially flows to zone 3, and mixture in zone 2; scarring of upper lobe clue for inhaled lung disease, except with asbestos-related disease (heavy fibers sink to lower lobe); military exposure — asbestos common in navy shipyards and motor pools; long-term exposure to burning pits; nuclear specialists, automotive workers, and telecommunications workers at risk; berylliosis — granulomatous inflammatory lung disease (also skin disease); noncaseating granulomatous inflammation with lymphocytes and histiocytes classic finding; distinguished from sarcoidosis by history (not possible microscopically); beryllium lymphocyte proliferation test can be ordered; treated with avoidance of Ag and corticosteroids; spouses exposed to same substances (brought home by workers).

**Hypersensitivity pneumonitis:** ask whether patient has birds and/or hot tubs (especially in enclosed environment); examples — sugar cane worker’s lung or bagassosis; potato riddler’s lung; ventilation and water-related contamination (humidifier fever); mummy handler’s lung; grain and flour processing; milling and construction; plastic manufacturing and painting; any substance to which individual exposed on regular basis that causes allergic reaction in lung.
Genetics: ≤10% of IPF familial; sarcoidosis in siblings not uncommon (genetic disease with environmental component); autoimmune disorders often familial

**Physical examination (PE) findings:** look for rash, synovitis, skin thickening and lesions, uveitis, and conduction defects in heart; if present, diagnosis sarcoidosis until proven otherwise (diagnosis of exclusion); digital clubbing not seen in chronic obstructive pulmonary disease (possibly IPF or lung cancer); lung examination largely nonspecific; crackles typically heard in lower lobes (site of most ILDs, except hypersensitivity pneumonitis [heard in upper lobes]); right ventricular heave with fixed split S2 present in pulmonary arterial hypertension which often accompanies ILDs; wheezing rare; no crackles heard in sarcoidosis; restrictive ventilator defect present, with low total lung capacity and low diffusing capacity of carbon monoxide (DLCO) because of decreased gas exchange

**Laboratory studies:** helpful for excluding systemic diseases; antinuclear antibody panels for connective tissue diseases; serum precipitants to bird or fungal Ags for hypersensitivity pneumoniosis; biochemical studies; blood counts for sarcoidosis; angiotensin-converting enzyme (ACE) test not useful

**Imaging:** start with chest x-ray (findings include hazy lung bases, scar tissue in mid and upper lung zones); high-resolution CT — radiologic test of choice; pattern recognition key; ground-glass appearance indicates inflammation or early fibrosis

**Histology:** surgical lung biopsy — gold standard; for infections and small granulomas, bronchoscopy adequate; diagnosis based on histologic patterns plus clinical history and radiologic findings; same-day procedure (using trocar) possible in 75% of cases (safe)

**Classification:** local vs systemic; those with known cause (hypersensitivity pneumoniosis), granulomatous ILDs, and other ILDs; idiopathic ILDs divided into IPF and non-IPF; “histology is not the disease itself”; “usual interstitial pneumonitis” pattern on biopsy seen in IPF and in other diseases (eg, chronic hypersensitivity pneumoniosis)

**Therapy:** directed at symptom relief; O₂ saturation <88% at rest or on exertion indication for O₂ therapy; administering O₂ to hypoxic patients for ≥18 hr prolongs life; pulmonary re- habilitation for deconditioning — only modality proven beneficial; antireflux therapy — for associated reflux disease; reflux significant problem in certain connective diseases (eg, scleroderma), but some data show chronic microaspiration or acid penetration into lungs can induce pulmonary fibrosis and other fibrotic lung diseases; Ag avoidance and abatement — for hypersensitivity pneumonia; immunosuppressive therapy — used for inflammation-based conditions; typically, corticosteroids and cytotoxic agents (eg, azathioprine, methotrexate, mycophenolate); disease-modifying antirheumatic drugs (eg, hydroxychloroquine); fibrotic lung disease — supportive care; for IPF; antifibrotic agents (nintedanib [Ofev] and pirfenidone [Esbriet]) slow rate of decline in forced vital capacity by ≤50%; neither drug improves symptom scores or DLCO, or slows rate of decline of DLCO; steroids and immunosuppressants contraindicated; lung transplantation — poor option; survival 50% at 5 yr; double lung better for ILD, and single lung better for COPD

**Suggested Readings**


**Acknowledgments**

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**Estimated time to complete the educational process:**

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
1. All the following statements about testing for tuberculosis (TB) are true, EXCEPT:
   (A) Positive in individuals with previously treated infection
   (B) Cannot distinguish latent TB infection from previously treated infection
   (C) Cannot distinguish current TB infection from previously treated infection
   (D) Useful for determining whether treatment successful

2. Which of the following nontuberculous mycobacteria share peptides with Mycobacterium tuberculosis?
   1. Mycobacterium kansasii
   2. Mycobacterium szulgai
   3. Mycobacterium marinum
   4. Mycobacterium bovis
   (A) 1,3  (B) 2,4  (C) 1,2,3  (D) 2,3,4

3. The minimum number of spots for a positive result on the ELISPOT (T-SPOT) test for TB is which of the following?
   (A) 2 spots in panel A and 2 spots in panel B  (B) 4 spots in panels A and B combined
   (C) 8 spots in panels A and B combined  (D) 12 spots in panels A and B combined

4. Which of the following drugs used to treat TB is most commonly associated with hepatotoxicity?
   (A) Isoniazid  (B) Rifampin  (C) Rifapentine

5. Which of the following is the most accurate statement about the use of nucleic acid amplification testing for TB?
   (A) Can be used in lieu of an interferon-γ release assay to diagnose TB
   (B) Routine after obtaining a positive result on acid-fast bacillus testing and culture of sputum
   (C) Has high specificity and sensitivity in bronchoscopy specimens
   (D) One negative test result obviates the need for serial smears and cultures when releasing patients from isolation

6. Which of the following interstitial lung diseases (ILDs) is seen only in women of child-bearing age?
   (A) Idiopathic pulmonary fibrosis  (B) Lymphangioleiomyomatosis
   (C) Eosinophilic granuloma  (D) Sarcoidosis

7. Which of the following is the most common symptom of ILD?
   (A) Cough  (B) Weight loss
   (C) Dyspnea  (D) Fatigue

8. Most ILDs occur in the _______ lobes of the lung, while hypersensitivity pneumonitis occurs in the _______ lobes of the lung.
   (A) Lower; upper  (B) Upper; lower

9. Which of the following tests is the gold standard for the diagnosis of ILD?
   (A) Pulmonary function tests  (B) High-resolution computed tomography
   (C) Bronchoscopy  (D) Surgical lung biopsy

10. Which of the following is an accurate statement about the treatment of fibrotic lung disease?
    (A) Nintedanib and pirfenidone slow the rate of decline in forced vital capacity by ≈50%
    (B) Nintedanib and pirfenidone improve symptom scores
    (C) Nintedanib and pirfenidone slow the rate of decline of diffusing capacity of the lung for CO
    (D) Steroids and other immunosuppressants are beneficial

Answers to Audio Digest Internal Medicine Volume 63, Issue 45: 1-C, 2-D, 3-C, 4-D, 5-D, 6-D, 7-A, 8-B, 9-A, 10-C

Attention, CME/CE Participants

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