



Center for Tuberculosis

Clinical Diagnosis of Tuberculosis

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Accreditation Statement



Accreditation Statement

In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

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UAN Number: UAN JA0000238-0000-26-089-L99-P.

ANCC

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A record of attendance will be provided to all registrants for requesting credits in accordance with state nursing boards, specialty societies or other professional associations.

For disclosure information regarding Mayo Clinic School of Continuous Professional Development accreditation review committee member(s) and staff, please go here to the course accreditation page.

Available Credit

- 18.25 ACPE,
- 18.25 *AMA PRA Category 1 Credit™*
- 18.25 ANCC
- 18.25 Attendance
- 18.25 IPCE

Disclosure:

No relevant financial disclosures to report and no mention of off-label use of any medications or products

Special thanks to Dr. Fida, some slides adapted from previous presentation

Learning Objectives

- Recognize typical presentation of tuberculosis and typical initial evaluation
- Understand variability in diagnostic methods for tuberculosis at different sites

Suspicion of Active TB Disease

- Should suspect/evaluate for TB based on combination of exposure, host factors, and clinical signs/symptoms of active disease



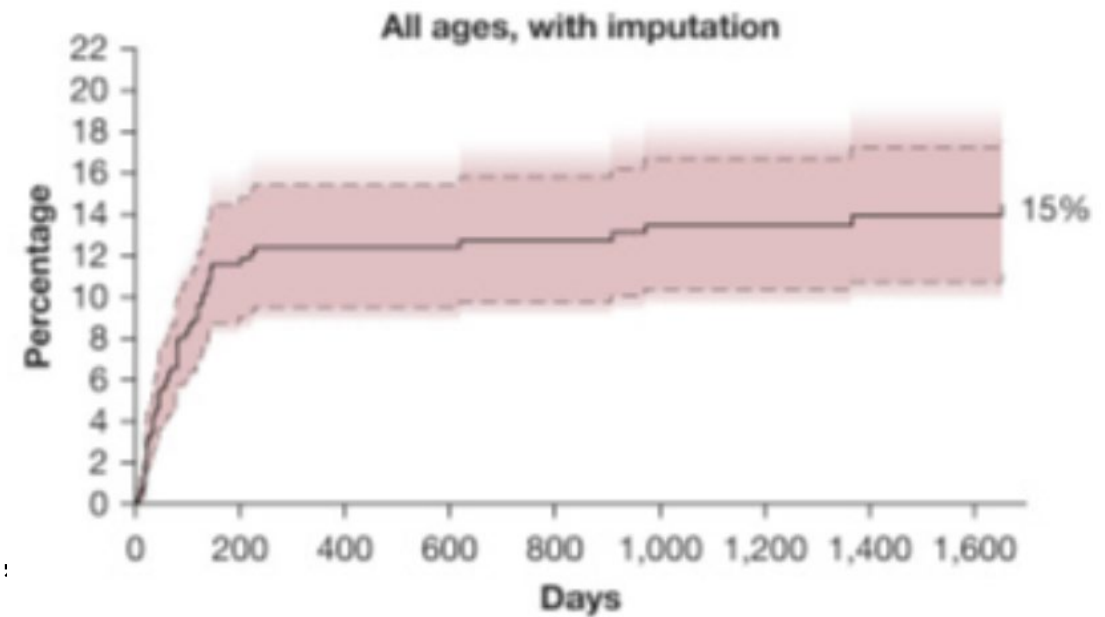
Exposure

- Recall of TB exposure: <10% in high-incidence vs 50-80% in low-incidence countries
- Risk of acquiring TB dependent on infectiousness of TB contact, environment (size of space, ventilation), and proximity and frequency/duration of exposure
 - More intense exposure = increased risk of acquisition **AND** active disease
- Active TB disease among close contacts with active case:
 - **3.1%** in low or middle-income settings vs 1.4% in high-income settings
 - **3-4%** with household contacts with smear-positive disease

Acuña-Villaroidia C et al. EurRespirJ 2018; Reicher MR et al. Clin Infect Dis 2020 Morrison 2008; Patterson 2025; Dowdy 2022; Young 2016; van de Berg 2025; Shah 2021

Exposure

- Classically, estimated that ~5% of persons infected with TB will develop active disease within first 2 years after infection, greatest risk w/in first 5 years, total lifetime risk ~10%
- Possibly underestimated?
 - Trauer et al, *Chest*, 2016
 - 10.9% developed active disease within study period, **estimated 5-year risk of 14.5%**
 - Greatest risk in **first 8 months** - ~10.2%



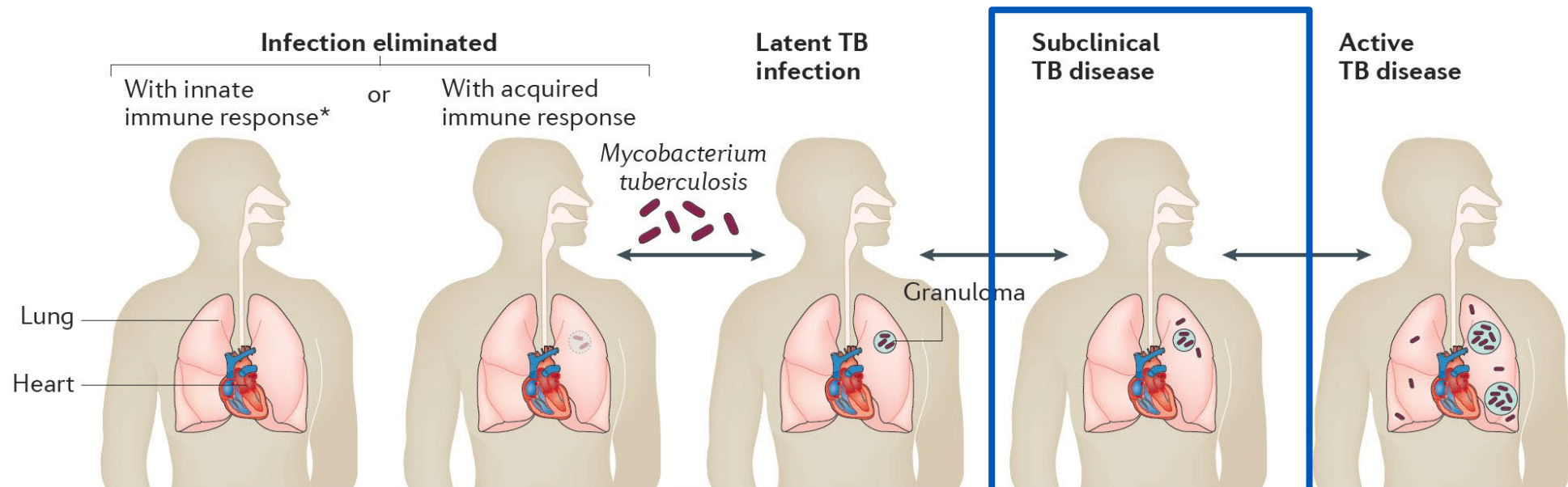
Host Factors

- Annual risk of progression to active TB
 - Untreated HIV – **7-10%**
 - TNF- α inhibitors – **1.5%**
- DM – 3x higher lifetime risk
- Age <5
 - Greatest risk <1yr (**up to 50%**), age 1-2 (**up to 25%**)

- Persons infected with HIV
- Children younger than 5 years of age
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years)
- Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease
- 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, or immunosuppressive drug therapy following organ transplantation
- Persons with diabetes mellitus
- Persons with silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung
- Persons who have had a gastrectomy or jejunioileal bypass
- Persons who weigh less than 90% of their ideal body weight
- Cigarette smokers and persons who abuse drugs and/or alcohol
- Populations defined locally as having an increased incidence of disease due to *M. tuberculosis*, including medically underserved, low-income populations

Clinical Symptoms

- Classic symptoms
 - Cough (typically >2-3 weeks) +/- hemoptysis, fevers, night sweats, weight loss, fatigue, chest pain
 - Majority of patients (~75%) report at least one symptom, but **prolonged cough only present in ~50% and fever in ~30%**
 - More likely to be symptomatic with smear-positive status, may be less likely with early disease, immunocompromise



	Infection eliminated	Latent TB infection	Subclinical TB disease	Active TB disease
TST	Negative	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Usually positive
Culture	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	Sporadically	Yes
Symptoms	None	None	Mild or none	Mild to severe
Preferred treatment	None	Preventive therapy	Multidrug therapy	Multidrug therapy

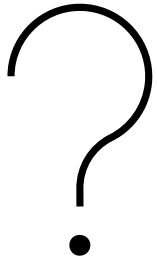
Pai et al., M. (2016, October 27). Tuberculosis. Nature.

Subclinical TB

- Frequency dependent upon definition of “subclinical” – true absence of symptoms in only ~20-25% of pts with active disease
 - Many have some symptoms but duration <2 weeks
 - Symptoms may be subtle, may only recognize after starting TB therapy
- Typically mild CXR abnormalities (non-cavitary)
- Less infectious, but may be delayed diagnosis with ongoing transmission risk

Stuck LK, et al. Lancet Infect Dis. 2022;22:1343-1354. doi:10.1016/S1473-3099(22)00181-6. Luo W, et al. BMC Pulm Med. 2020;20:146. doi:10.1186/s12890-020-01192-w. Lewinsohn DM, et al. Clin Infect Dis. 2017;64:e1-e33.

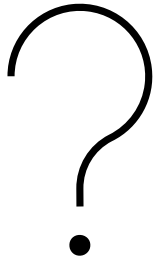
Polling Question



A 47 y/o male with PMH of obesity and uncontrolled diabetes mellitus presents with a 4 week history of cough, chest pain fatigue, and night sweats. He immigrated from Southeast Asia ~3 years ago. CXR is obtained with R upper lobe infiltrates, QuantiFERON-TB Gold Plus was obtained and was negative. What is your next best step in management?

- A. Obtain TST
- B. Treat empirically with amoxicillin/clavulanic acid and doxycycline for community acquired pneumonia
- C. Obtain AFB sputa x3 for smear, culture, and MTB NAAT
- D. No further workup/evaluation indicated

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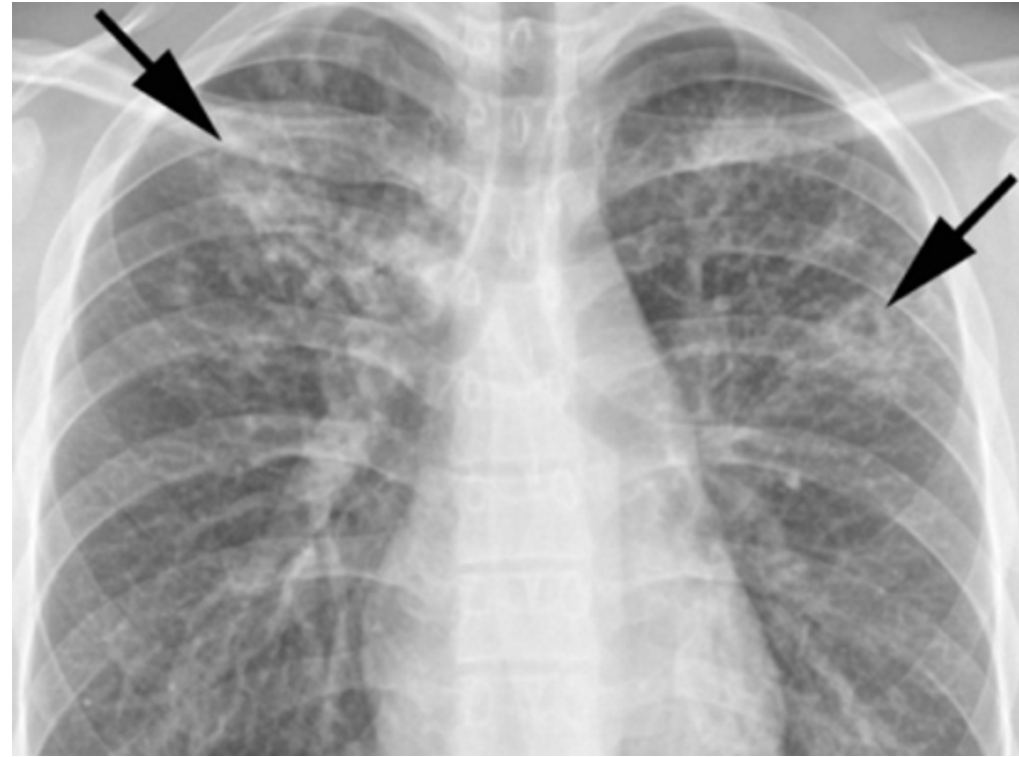
TB Screening Tests

- Tuberculin skin test (TST)
- Interferon-Gamma Release Assays (IGRAs)
 - QuantiFERON-TB Gold Plus
 - T-Spot
- Both can be falsely positive in active TB in up to 12-18% of pts – **greater risk in immunocompromised**

 5 or more millimeters	 10 or more millimeters	 15 or more millimeters
An induration of 5 or more millimeters is considered positive for • People living with HIV • Recent contacts of people with infectious TB disease • People who have fibrotic changes on a chest radiograph • Patients with organ transplants • Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/ greater than 15 mg per day of prednisone or those taking TNF-α antagonists)	An induration of 10 or more millimeters is considered positive for • People born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala • People who abuse drugs or alcohol • Mycobacteriology laboratory workers • People who live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities) • People with certain medical conditions that place them at high risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, or certain intestinal conditions) • People with a low body weight (<90% of ideal body weight) • Children younger than 5 years of age • Infants, children, and adolescents exposed to adults in high-risk categories	An induration of 15 or more millimeters is considered positive for • People with no known risk factors for TB

Imaging

- CXR at minimum as part of TB evaluation
 - Ideally 2 views (PA/lateral)
 - Classically – nodular or consolidative lesions and/or cavity formation, apical or posterior upper lobe or superior lower lobe involvement
- CT scans – improved sensitivity, may better detect more subtle findings (LAD, smaller nodular/cavitary lesions)
 - Cost/availability - limiting factor
 - May be utilized in cases of diagnostic uncertainty



Sputum Collection

- CDC recommends 3 samples for AFB sputum smear and culture, at least 8-24 hrs apart, at least one AM specimen
 - AM specimen: Increases sensitivity by ~12%
 - Volume – 5-10 mL recommended (decreased sensitivity w/volume <3-5 mLs)
- AFB smear sensitivity vs culture
 - Culture can detect TB from much fewer organisms (5000-10000 AFB/mL for smear vs 10-100 AFB/mL for culture)
 - ~50% sensitivity for 1st sputum, 2nd sputum adds ~10%, 3rd adds ~2%
- AFB smear – not specific (non-tuberculosis Mycobacteria)
- AFB culture – needed for phenotypic drug susceptibility testing

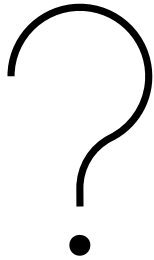
Induced vs Spontaneous Sputum

- Spontaneous samples – should still supervise/coach to obtain optimal samples
- Induced samples – cough after inhalation of aerosolized hypertonic saline
 - Strong performance with 3 samples, sensitivity is similar to bronchoscopy sampling

	1st Sample	2nd (Cumulative)	3rd (Cumulative)
AFB smear	64%	81%	91%
Mycobacterial Culture	70%	91%	99%

Luo W, Lin Y, Li Z, et al. *BMC Pulm Med*. 2020;20:146. doi:10.1186/s12890-020-01192-w.

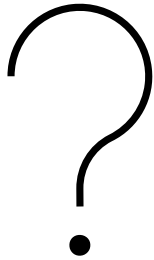
Polling Question



A 28 year old HIV-negative female recently completed a full 6 month treatment course with RIPE for pulmonary TB with DOT being performed. She cleared her cultures at one month and clinically improved on therapy, though had residual apical scarring present on CXR at treatment completion. 2 months after completing, she is admitted to your local hospital with fevers and symptoms and urinalysis consistent with pyelonephritis. Due to her abnormal CXR (stable from time of treatment completion), sputum sample is obtained and was noted to be MTB NAAT detected. What would you recommend?

- A. Restart on empiric RIPE therapy
- B. Start empiric BPAL-M with concern for MDR-TB
- C. Obtain AFB sputum samples x3 for smear/culture
- D. Observation

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- D. Observation

NAAT Testing

- Recommended to be performed on at least one respiratory specimen to aid in **initial** diagnosis
 - Recommended by WHO over AFB smear for initial diagnosis
- Can provide initial genotypic drug susceptibility information (e.g. rpoB mutations detected with GeneXpert MTB/RIF)
- Improved sensitivity and specificity compared to AFB smear
 - 95-99% sensitive for smear-positive, 60-90% for smear-negative
- Not for monitoring on/after therapy – **can remain persistently positive for years after treatment**



Bronchoscopy

- Can be beneficial when still attempting to confirm/refute diagnosis if negative induced sputum cultures
- May be beneficial for tissue/lymph node sampling, endobronchial or mediastinal disease

Specimen	Collection	Culture / NAAT	Smear
Bronchial Washing	Saline instilled & aspirated	50–79%	26%
Bronchial Aspirate	Direct suction from bronchial tree	96.5%	Similar
BAL	Large-volume lavage distal airway	85–100%	4%
Post-bronchoscopy Sputum	Expectoration after bronch	35–80%	9–73%
Gastric Aspirate	NG aspirate (often AM)	55–80%	21–30%

Kim YW *Clin Microbiol Infect* 2020¹; Eom JS *Clin Infect Dis* 2023²; Lewinsohn DM *Clin Infect Dis* 2017³; Boldi MO *Front Cell Infect Microbiol* 2023⁴; Musso M *BMC Infect Dis* 2025⁵; Lyu M *Biosci Rep* 2020⁶; Ahmad M *Int J Infect Dis* 2019⁷; Dickson SJ *Clin Infect Dis* 2003⁸; Park JH *Ann Med* 2021⁹; Brown M *Clin Infect Dis* 2007¹⁰; Shimoda M *J Infect Chemother* 2022¹¹

Other Pulmonary TB Diagnostics

- Urine LAM (lipoarabinomannan) – recommended by WHO (in addition to sputum testing) for use in PLWHIV
 - Not commercially available in US
- NAAT on tongue swabs – now endorsed by WHO when respiratory samples cannot be obtained
 - Sensitivity ranging from 45-78% compared to sputum culture



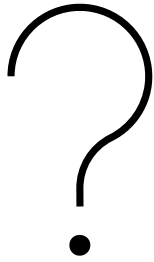
Extrapulmonary TB

							Extrapulmonary site of disease																
Year	Total pulmonary only cases ¹		Total pulmonary and extrapulmonary cases ²		Total extrapulmonary only cases ³		Total extrapulmonary sites ⁴	Pleural		Lymphatic ⁵		Bone or joint		Genitourinary		Meningeal		Peritoneal		Laryngeal		Other	
	No.	(%)	No.	(%)	No.	(%)		No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
2024	7,362	(70.9)	1,226	(11.8)	1,747	(16.8)	3,375	812	(24.1)	950	(28.1)	252	(7.5)	115	(3.4)	163	(4.8)	187	(5.5)	28	(0.8)	868	(25.7)
2023	6,732	(69.9)	1,135	(11.8)	1,728	(18.0)	3,223	743	(23.1)	861	(26.7)	282	(8.7)	132	(4.1)	182	(5.6)	184	(5.7)	17	(0.5)	822	(25.5)
2022	5,832	(70.0)	909	(10.9)	1,591	(19.1)	2,822	617	(21.9)	736	(26.1)	267	(9.5)	114	(4.0)	167	(5.9)	174	(6.2)	33	(1.2)	714	(25.3)
2021	5,190	(66.0)	994	(12.6)	1,682	(21.4)	3,002	586	(19.5)	818	(27.2)	368	(12.3)	120	(4.0)	157	(5.2)	210	(7.0)	25	(0.8)	718	(23.9)
2020	4,779	(66.7)	878	(12.2)	1,513	(21.1)	2,640	559	(21.2)	814	(30.8)	215	(8.1)	107	(4.1)	132	(5.0)	196	(7.4)	15	(0.6)	602	(22.8)
2019	6,073	(68.3)	1,006	(11.3)	1,813	(20.4)	3,126	675	(21.6)	1,008	(32.2)	269	(8.6)	115	(3.7)	164	(5.2)	187	(6.0)	27	(0.9)	681	(21.8)
2018	6,155	(68.4)	1,039	(11.5)	1,801	(20.0)	3,116	673	(21.6)	1,015	(32.6)	281	(9.0)	145	(4.7)	148	(4.7)	167	(5.4)	23	(0.7)	664	(21.3)
2017	6,214	(68.5)	966	(10.7)	1,883	(20.8)	3,138	635	(20.2)	1,054	(33.6)	279	(8.9)	137	(4.4)	150	(4.8)	183	(5.8)	21	(0.7)	679	(21.6)
2016	6,425	(69.5)	939	(10.2)	1,867	(20.2)	3,067	593	(19.3)	958	(31.2)	270	(8.8)	161	(5.2)	160	(5.2)	194	(6.3)	25	(0.8)	706	(23.0)
2015	6,624	(69.4)	1,007	(10.6)	1,904	(20.0)	3,167	697	(22.0)	994	(31.4)	302	(9.5)	142	(4.5)	168	(5.3)	191	(6.0)	16	(0.5)	657	(20.7)
2014	6,459	(68.8)	1,001	(10.7)	1,922	(20.5)	3,193	692	(21.7)	1,077	(33.7)	310	(9.7)	152	(4.8)	176	(5.5)	179	(5.6)	18	(0.6)	589	(18.4)
2013	6,657	(69.7)	926	(9.7)	1,972	(20.6)	3,125	648	(20.7)	1,032	(33.0)	325	(10.4)	156	(5.0)	181	(5.8)	171	(5.5)	19	(0.6)	593	(19.0)
2012	6,803	(68.5)	1,043	(10.5)	2,082	(21.0)	3,377	698	(20.7)	1,141	(33.8)	343	(10.2)	169	(5.0)	181	(5.4)	189	(5.6)	29	(0.9)	627	(18.6)
2011	7,272	(69.3)	1,052	(10.0)	2,169	(20.7)	3,476	758	(21.8)	1,134	(32.6)	355	(10.2)	178	(5.1)	226	(6.5)	186	(5.4)	26	(0.7)	613	(17.6)
2010	7,750	(69.5)	972	(8.7)	2,425	(21.8)	3,611	701	(19.4)	1,317	(36.5)	353	(9.8)	186	(5.2)	207	(5.7)	192	(5.3)	20	(0.6)	635	(17.6)

CDC reports cases of TB disease by site of disease in the United States from 2010 to 2024.

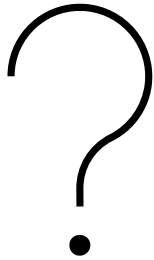
Tuberculosis in the United States, 2024 - CDC

Polling Question



- A 74 y/o male who recently immigrated from Sub-Saharan Africa presented to the ED with cough, dyspnea, and fever for several weeks. He was noted to have a large R pleural effusion – thoracentesis was obtained with lymphocyte predominant fluid with adenosine deaminase of 160. Cytology from pleural fluid with no malignant cells, routine culture from pleural fluid had no growth. QuantiFERON-TB Gold Plus is positive, but AFB smears x3 from sputa and x1 from pleural fluid are negative as is MTB NAAT from sputum and pleural fluid. He has no prior TB treatment history, no known MDR-TB contacts. You offer pleural biopsy for further evaluation, but patient refuses any further procedures despite education. What would you recommend?
 - A. Start empiric RIPE
 - B. Observation, await AFB cultures
 - C. Declare patient to lack capacity for medical decision making, proceed with pleural biopsy

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Pleural Tuberculosis

- Paucibacillary disease, only 6-8% smear positive, cultures 30-41%
 - Can improve sensitivity with pleural tissue biopsy
- MTB NAAT – sensitivity 23-51%
- Adenosine deaminase (ADA)
 - ~90% sensitivity, also positive with empyema, lymphoma
 - Can make presumptive diagnosis with ADA >40, lymphocyte predominant pleural fluid, and high clinical suspicion for TB



Porcel, *Ann Transl Med*, 2016. Philip KE, *BMJ Case Reports*, 2018

Lymphatic TB

- Lymph node aspirate – smear sensitivity 25-50%, culture + pathology/cytology leads to improved sensitivity
- NAAT - ~83% sensitivity in meta-analysis
- Plasma cell-free DNA – sensitivity 50% for probable cases, 70% for confirmed cases
 - May have role when lymph node sampling is difficult to obtain or inconclusive

Tadesse M et al 2014, Tiwari V et al 2003, Stadelman AM et al 2021, Jin *J Thor Dis* 2025,

TB of Other Sites

- Depending on site of involvement, AFB culture +/- NAAT testing often recommended (tissue, fluid, urine, feces)
- ADA may have role in diagnosis at other fluid sites (e.g. peritoneal TB, TB meningitis) with similar sensitivity ~90% but lacking specificity
- Ocular TB – paucibacillary and very small fluid volume, poor smear/culture and NAAT performance – often clinical diagnosis in collaboration with ophthalmologist



Thank you