

TB Suspect (Class 5) – General Approaches

Mayo Clinic Center for Tuberculosis

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Accreditation Statement



Accreditation Statement

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Available Credit

- 18.25 ACPE,
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- 18.25 ANCC
- 18.25 Attendance
- 18.25 IPCE

Disclosures

- No financial disclosures

Learning Objectives

- Differentiate between the five classes of TB
- Explain the clinical significance of Class 5 TB
- Identify the appropriate management steps for patients classified under Class 5 TB

TUBERCULOSIS CLASSIFICATION

Class	Type	Description
TB-0	- No TB exposure - Not infected	No history of exposure. Negative reaction to tuberculin skin test.
TB-1	- TB exposure - No evidence of infection	History of exposure. Negative reaction to tuberculin test skin test.
TB-2	- TB infection - No disease	Positive reaction to tuberculin skin test. Negative bacteriologic studies (if done). No clinical or radiographic evidence of TB.
TB-3	- Current TB disease	<i>M. tuberculosis</i> cultured (if done) or <i>both</i> a positive reaction to tuberculin skin test <i>and</i> clinical and/or radiographic evidence of current disease.
TB-4	- Previous TB disease	History of episode(s) of TB, abnormal stable radiographic findings in a person with a positive reaction to the tuberculin skin test, negative bacteriologic studies (if done) and no clinical or radiographic evidence of current disease.
TB-5	- TB suspect	Diagnosis pending (a patient should not be in this class for more than 3 months).

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“Possible TB” – A Common Referral to Infectious Diseases or TB practice/clinic

- Many cases referred to our Mayo/SE Minn TB clinic are for “evaluation of possible TB” or “TB rule out”
- 2-Tiered Decision Making
 - **Diagnostic**: Likelihood that TB disease present?
 - **Therapeutic**: Whether to preemptively start combination TB drug therapy (e.g. RIPE) vs delay/observation?
- More ‘time-sensitive’ for pulmonary cases
- Can be more complicated when assessing for CNS TB involvement

Class 5 -“Possible TB case”

– Why give a talk on this topic???

- **Common** referral to Public Health / TB clinic / Inf Dis provider
- **Challenging** set of patients to manage:
 - Patient care – want to get them better quickly
 - *When to treat??*
 - *When to observe / await culture data??*
 - Public Health – avoid transmission via untreated pulmonary TB

Class 5 – TB suspect:

Strength of TB suspicion based *on combination*:

1. **Clinical** presentation
2. **TB Risk factors** / patient demographics
3. **Radiologic** features
4. **Laboratory** (supporting) data

Remember:
“**The Four Horseman**” of
Notre Dame”



Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

1. *Is the Clinical* presentation / factors compelling for TB?
 - Whether typical (or atypical) symptoms or exam findings present – e.g.
 - a. Chronic coughing (e.g., lasting > 3 weeks), hemoptysis
 - b. Systemic symptoms – e.g. Fever, chills, weight loss, night sweats
 - c. Exam findings of extrapulmonary TB – including
 - Adenopathy (head/neck, axillary, etc)
 - Hepatosplenomegaly
 - Abdominal ascites

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

2. *Are TB Risk factors* present? – e.g.

- Patient demographics - Born/lived in TB-endemic country
- History of LTBI or active TB disease – treated or untreated
- Recent contact with person known to have pulmonary TB disease (untreated; e.g. identified via TB contact investigation)
- Other exposures (variable risk): Prison/jails; health care provider, congregate living settings, etc

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

3. *Are the Radiologic* findings c/w TB?
 - a. Upper lobe CXR, cavitary lesions (but acknowledging pulmonary TB can appear like anything)
 - b. Localized or systemic adenopathy
 - c. Hepatosplenic lesions
 - d. Bone lesions (e.g. vertebral lesions)
 - e. CNS lesions – (e.g. basilar meningeal enhancement on head MRI; tuberculomas, etc)

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

4. *Does Laboratory* (supporting) data support TB

- *Cultures and PCR pending, negative or NA*

- a. Reactive TST

- b. (+) IGRA (QuantiFERON or T. Spot)

- c. (+) AFB stain (sputum or tissue)

- MTB complex (including *M. bovis* – wild type & BCG *bovis*)
- NTM – e.g. MAC, *M. kansasii*, *M. abscessus* complex, etc
- Sometimes *Nocardia* & other mycolic acid containing bacteria
- *Morphologically different* compared to mycobacteria

- d. Tissue histology – necrotizing (or non-necrotizing) granulomatous inflammation

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

- 4. **Laboratory** (supporting) data – for TB
 - Cultures and PCR pending, negative or NA
 - e. GU TB – abnormal UA (usually with elevated protein and WBCs)
 - f. CNS TB (esp. meningeal) – elevated CSF protein, leukocytes (often lymphocytes), elevated ADA
 - g. Pleural fluid – pleocytosis (elevated WBC, often lymphocytes), elevated protein, ADA
 - h. Peritoneal TB – ascites with pleocytosis (often lymphocytes), elevated protein

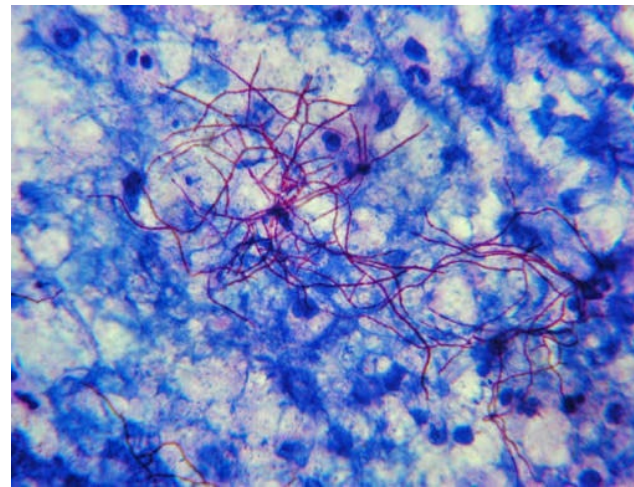
Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

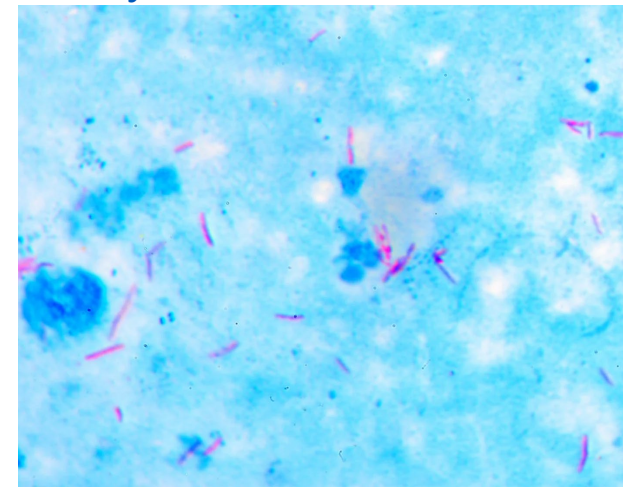
Confounders-I: Other AFB staining (+) organisms:

- a. Non-TB Mycobacteria (NTM)
- b. *Other mycolic-acid containing (AFB stain pos) bacteria – usual appear morphologically different/distinct:*
 - **Nocardia sp.*
 - *Gordonia sp.*
 - *Rhodococcus sp.*
 - *Tsukamurella sp.*
 - *Dietzia sp.*

Nocardia – Fite stain



Mycobacteria – AFB



Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

Confounders – II: Other Granuloma-forming pathogens in tissue (lungs or other tissue/liver, etc):

- a. Non-TB Mycobacteria (NTM)
- b. Fungal (histoplasmosis, blastomycosis, coccidiomycosis, etc)
- c. Other:
 - Brucellosis Rhodococcus
 - Q fever (C. brunetti) Syphilis
 - Bartonella Schistosomiasis (liver, bladder)
 - Toxoplasmosis
 - *Non-infectious (non-necrotizing): Sarcoidosis, Crohn's disease, temporal arteritis, etc

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

Confounders – III: other causes of adenopathy

Non-TB Mycobacteria (NTM)

- a. Fungal (*histoplasmosis, blastomycosis, coccidiomycosis, etc)
- b. Other:
 - Regional: Bartonella (Cat-scratch dis), GUD pathogens (syphilis chancroid, LGV, etc)
Tularemia, Yersinia Fungal (e.g. Histoplasma)
 - Systemic: Syphilis Brucellosis Toxoplasmosis
Lyme disease Fungal (histoplasmosis, cryptococcus HIV, EBV
 - *Non-infectious (non-necrotizing): Sarcoidosis, Lymphoma, Castleman's disease, etc

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

Confounders – IV: Other causes of cavitary lung disease

- a. Non-TB Mycobacteria (NTM)
- b. Fungal (histoplasmosis, blastomycosis, coccidiomycosis, Aspergillosis, Mucor grp., etc)
- c. Other:
 - *Nocardia* sp.
 - *S. aureus*
 - *P. aeruginosa*
 - Malignancy

Thin-walled cyst
Chronic aspiration



Clin Microbiol Rev. 2008 Apr;21(2):305-33

Class 5 TB – Suspect:

Likelihood of TB disease – considerations:

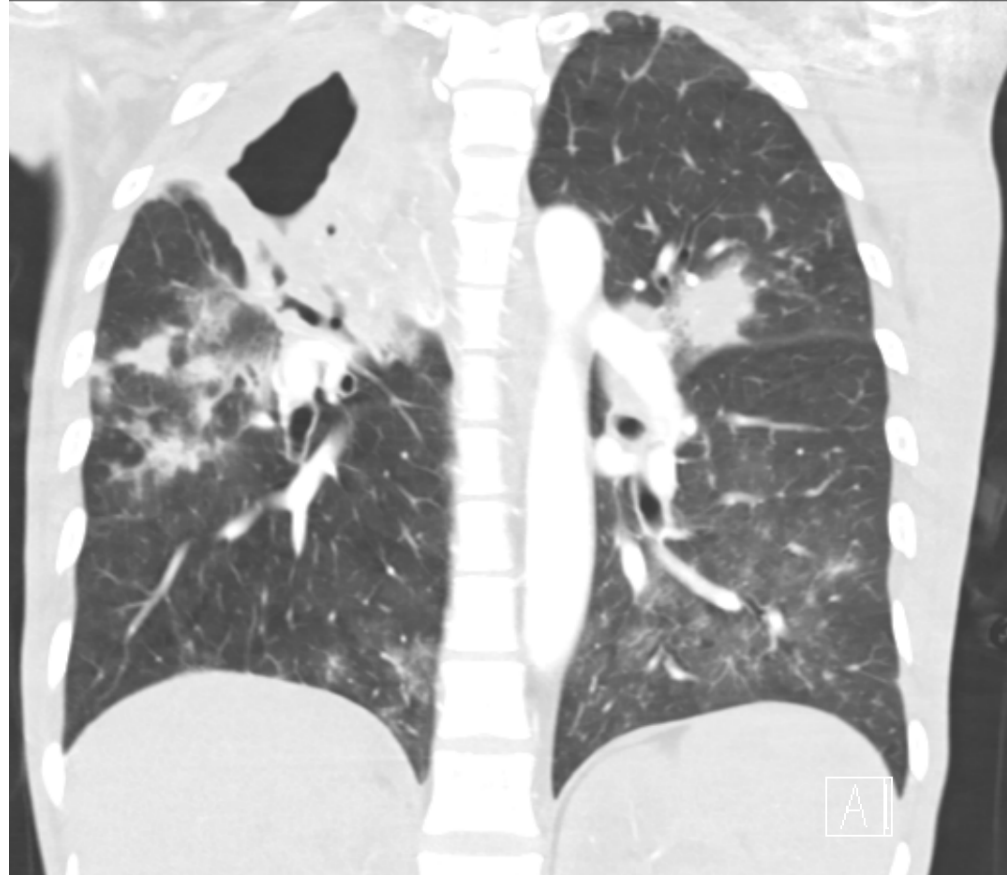
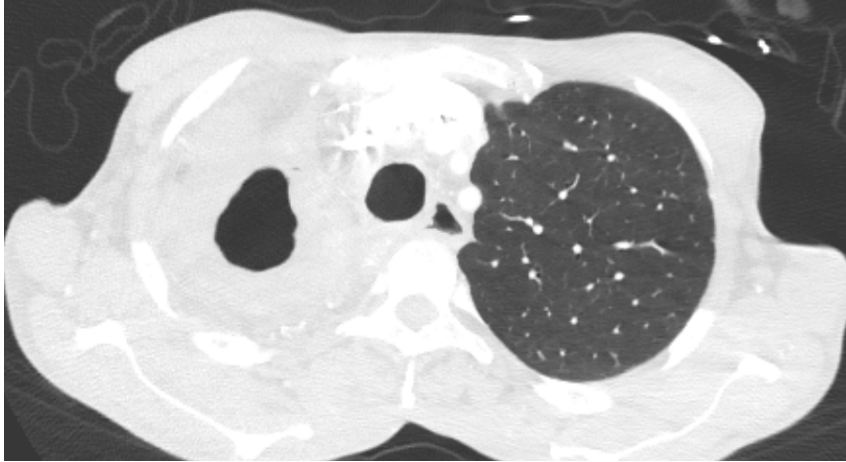
Non-TB Mycobacteria (NTM) – can be confounders:

- a. May produce reactive (+) TST
- b. Will stain pos (+) AFB (Ziehl-Neelsen, Kinyoun), Auramine-rhodamine, FITE, etc
- c. Select NTM that produce (+) IGRA:
 - *M. marinum* – extrapulmonary disease
 - *M. kansasii* – pulmonary disease
 - *M. szulgai*

Case - 1: 55 yo female from Central Africa

- History of pulmonary TB disease – treated back in 2001
- Summer 2023 – developed cough, hemoptysis
 - Progressed into productive, blood tinged
- October 2023: Hospitalized
 - CXR with RUL cavitary lesion
 - AFB (+) smear
 - CBC: 140,000 WBCs with (+)25% peripheral blasts
- Dx'd with acute myelogenous leukemia

Case - 1: 55 yo female from Central Africa



Sputum (multiple) and BAL cultures: ***M. abscessus complex***

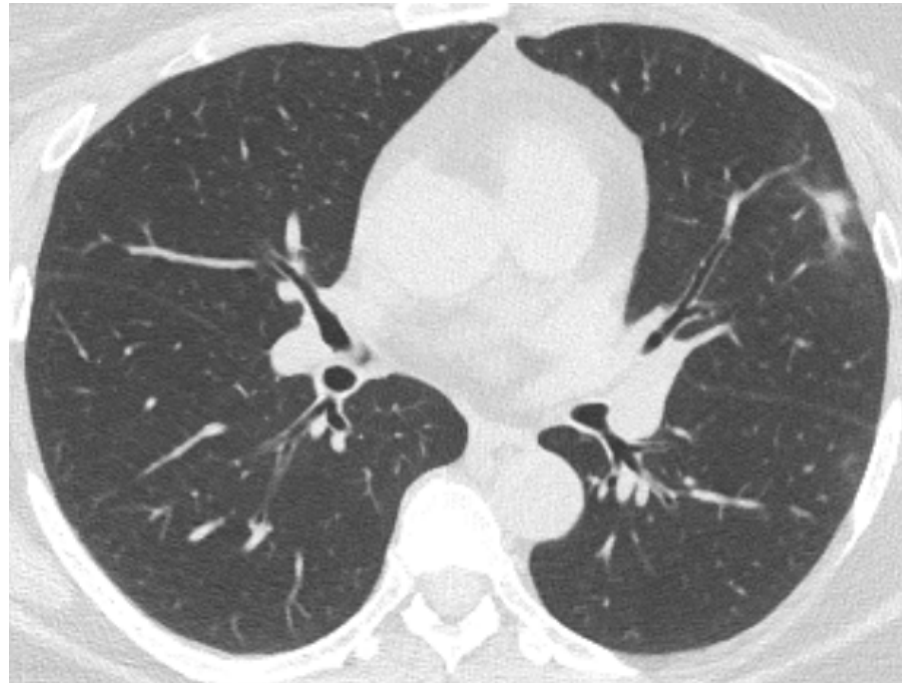
Case - 2: 45 yo female from Florida

- History of LTBI (reactive TST) – treated back in 2000 (6 mo. INH)
- Summer 2024 – Hospital pre-employment evaluation
 - Asymptomatic, immunocompetent
 - (+) QuantiFERON
 - CXR: small left mid lung opacity



Case - 2: 45 yo female from Florida

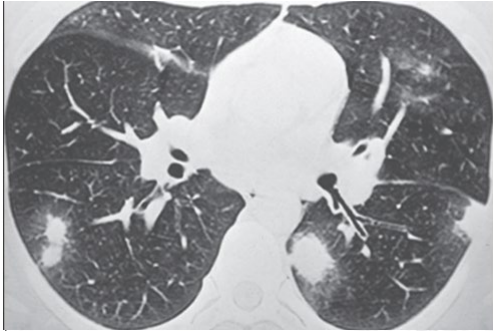
- CT chest:
 - “Stellate lingular density with a focal dilated bronchiole is likely a scar with local traction bronchiolectasis. Given a nodular component, a superimposed nodule/granuloma cannot be excluded and comparison with previous chest CT is recommended to ensure long interval stability.



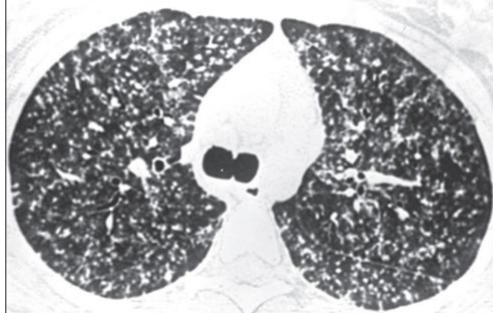
Case - 2: 45 yo female from Florida

- More information:
 - 2023 CXR did not show the left lung lesion – thus, presumptively new this year
 - Patient has long-standing morning cough (provider considered asthma)
 - Active TB contact recently by report (July 2024)
 - Patient has been working in a hospital - desk unit
 - Patient reports night sweats – granted could be perimenopausal, but not sure
 - Patient cannot produce sputum samples
- Bronch/BAL
- Preemptively treat for TB disease vs. observe and follow up CT chest or CXR
- Other approach?

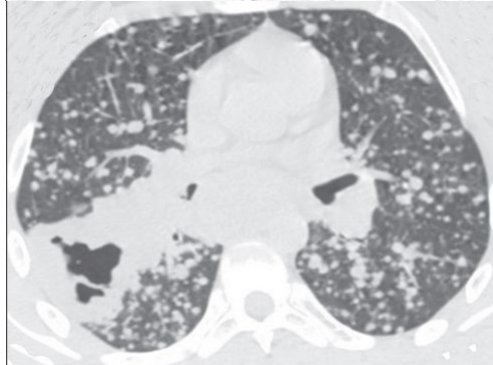
Cases - 3: The “many faces” of Pulmonary Histoplasmosis



47 yo female with nodular infiltrates and hilar adenopathy

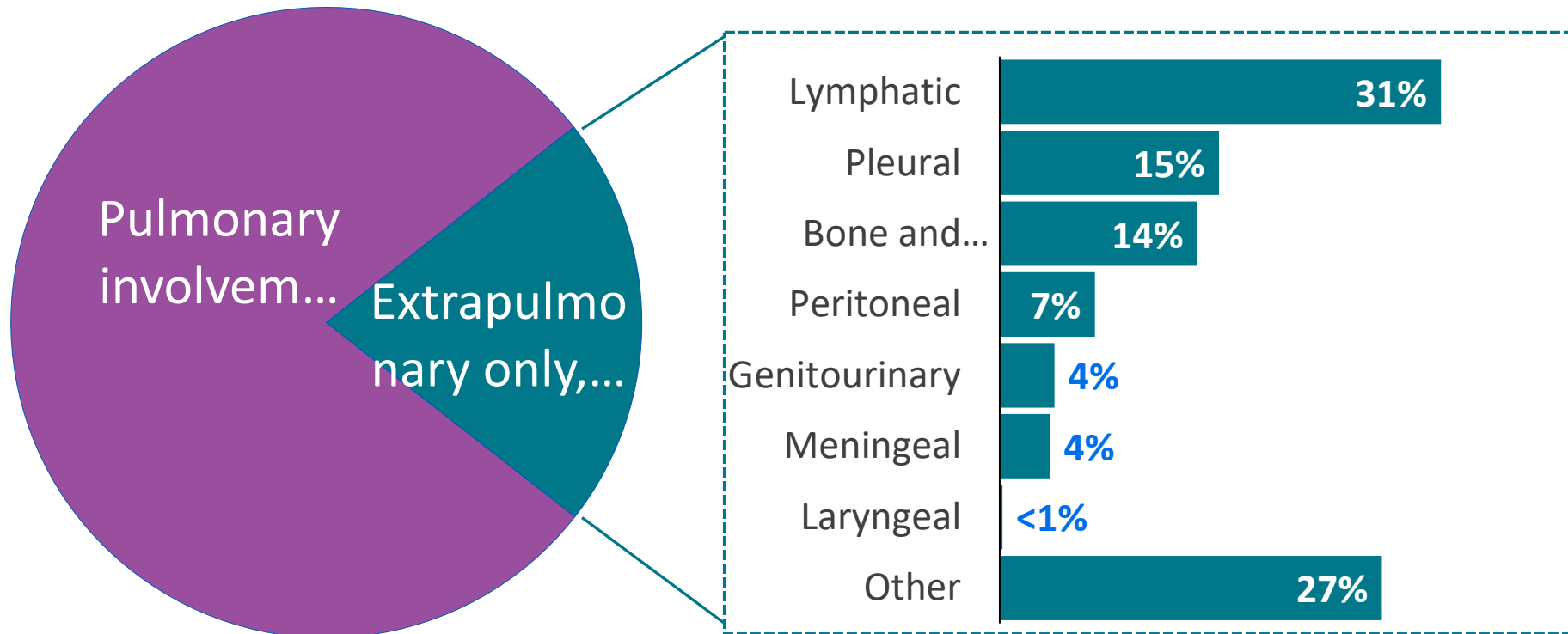


39 yo male with miliary pattern / diffuse pulmonary histoplasmosis



29 yo male with cavitary pulmonary histoplasmosis; miliary and nodular infiltrates

Percentage of TB Cases by Site of Disease,^{*} United States, 2021



^{*}Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

[†]Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

Lymphatic TB - “Scrofula”

- Age of patient: Children $\leq$ 12 yo: **65-80% MAC**
10-20% *M. scrofulaceum*
10% *M. tuberculosis*
Children > 12 yo: **>90% *M. tuberculosis***
- LN TB most commonly found on head & neck region (post cerv & SC chains)
- FNA or excisional biopsy preferred method of diagnosis
 - MTB not found in most specimens - this is a paucibacillary for of TB disease
 - Avoid I&D (risk of fistula development, poor healing)
- Unlike resected MAC LN disease in pediatric cases, chemotherapy is essential with lymphatic TB (6-month)

Cervical TB lymphadenitis



When to start treatment for TB disease?

- Confirmed M. tuberculosis disease: **Class-3**
 - Culture (+) MTB – typically delayed 2-4 weeks
 - Pos (+) rapid molecular test / NAAT
- Possible / Probable TB disease: **Class-5**
 - Can be challenging

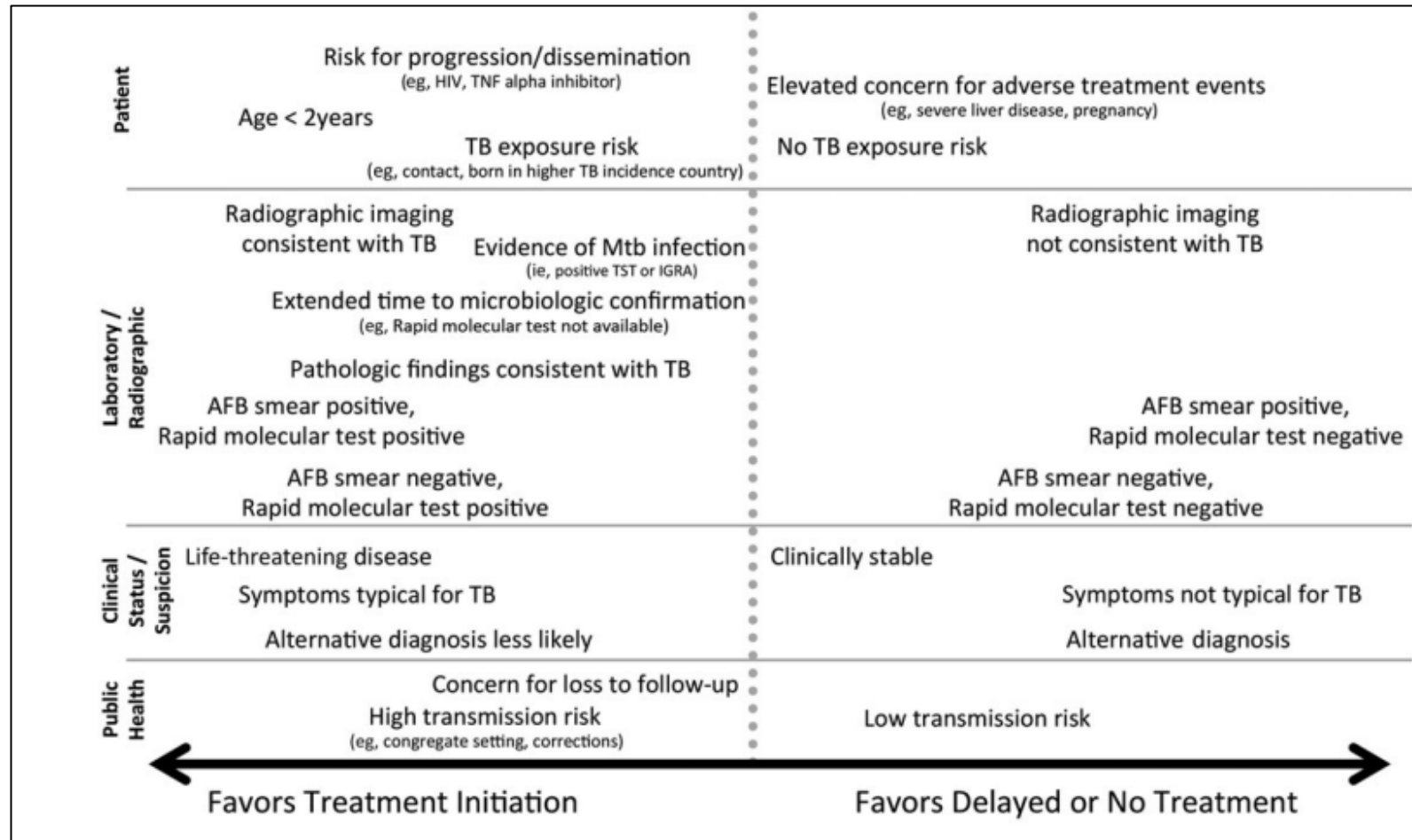
Class 5 TB – Suspect:

Urgency to start combination TB therapy

Considerations:

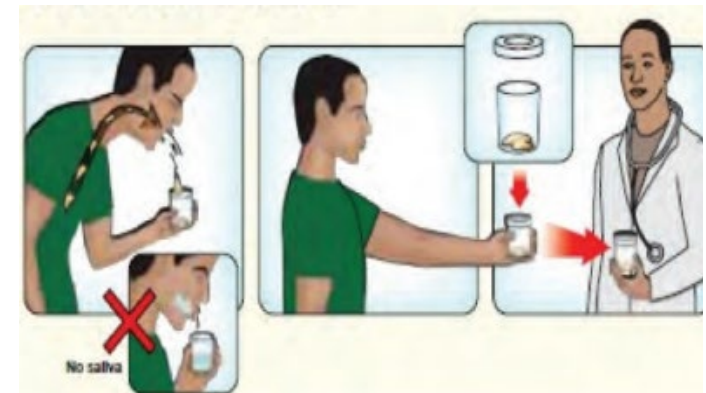
1. Patient's current health / *medical stability*?
 - The “sicker” patient - less time to wait (→it's “GO TIME”)
 - Especially concerning with CNS, disseminated/multiorgan disease
2. Risk of *spreading* TB to others
 - Pulmonary TB disease, especially when extensive
3. Risk of rapid disease *progression if untreated*
 - Immunosuppressive condition
 - Age < 5 yo; HIV, autoinflammatory condition, malignancy-chemotherapy, malnutrition
 - More virulent MTB strain

Factors to consider regarding preemptive treatment for active TB (Class-5)



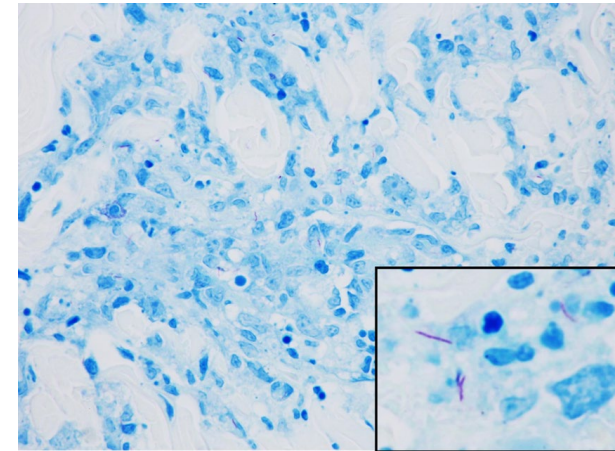
Culture Negative (-) TB

- 10-15% of pulmonary cases – many reasons:
 - Patient not able to produce quality sputum samples
 - Lower MTB bacillary burden (e.g. non-cavitary, more mild/localized disease)
 - Poor patient effort in producing sputum samples (often non-induced)
 - Note: Bronch/BAL can be option for patients not able to produce quality sputum samples, but not 100% sensitive for MTB detection (PCR, Stain, Culture)



Culture Negative (-) TB

- Extrapulmonary TB disease – often pauci-bacillary
 - Tissue biopsies may not demonstrate (+) PCR, AFB stain or cultures
 - Often ‘heterogenous’ distribution of MTB bacillary in diseased tissue (lymph node, liver, etc)
 - Supporting clinical and laboratory findings can be helpful:
 - Further exclude alternative causes/alternative pathogens
 - When appropriate – analysis of CSF, pleural fluid, peritoneal fluid, urine; tissue biopsies Histology); radiologic imaging, etc



Treating Class 5 TB (TB Suspect)

Impression: TB disease probable, less likely other diagnoses

- Start standard INH/RIF/PZA/EMB – while awaiting culture results
 - Important to ensure DOT for optimized patient compliance & monitoring
 - Usually more pressing need to preemptively start TB treatment in
 1. Patients with possible/suspected pulmonary TB disease
 2. Immunosuppressed patients
- MTB cultures monitored for 42 days:
 - A. Culture (+) Positive growth of MTB: confirmed active (class 3) TB disease
 - Complete full duration of TB therapy, guided by drug susceptibility testing (DST) results
 - B. No MTB growth after 6 weeks: possible “culture-negative” TB vs not TB disease
 - Next steps.....

Treating Culture-TB (TB Suspect)

- MTB cultures finalized at negative (at 6 weeks)
- Re-evaluation of patient after 8-10 weeks of RIPE treatment
 - Repeat CXR (or CT chest if done) – any improvement?
 - Clinical status (during the 8 weeks of RIPE) – any improvement?
- If cultures remain neg (-), AND
- There is *any clinical OR radiographic improvement* while on treatment during the first 2 months, then
 - *Clinical TB (Class 3) diagnosis made* → continue & complete treatment for active disease:

Culture-negative TB – different mgmt. options can apply

- **CDC/ATS/IDSA:** 4 months total therapy
 - 2 mo (INH/RIF/PZA/EMB)
 - 2 mo (INH/RIF)
 - **In Minnesota,** 8%-18% of TB cases are INH-resistant; large percentage of these patients are Somali
 - Concern for INH-resistant culture-neg. TB and risk of MDR TB development
-  ◦ Mayo/Olmsted Co: **Continue all 4-drug TB drugs** for 4-6 months therapy

FACTORS THAT INFLUENCE THE CLINICAL FEATURES OF TUBERCULOSIS

Host Factors	Microbial Factors	Host–Microbe Interaction
Age Immune status Specific immunodeficiency states Malnutrition Genetic factors (not yet defined) Coexisting diseases Immunization with bacillus Calmette-Guérin (BCG)	Virulence of the organism Predilection (tropism) for specific tissues	Sites of involvement Severity of disease

The End

*It may sometimes feel like it, but you're
never alone when managing TB*





Thank you