Diagnosis & Medical Management of TB Disease

Annie Kizilbash, MD, MPH

May 6, 2025

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

DIAGNOSIS & MEDICAL MANAGEMENT OF TB DISEASE

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Objectives

- Identify the process for diagnosis of TB
- Discuss current recommendations for the medical management of active TB

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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August 10th, 2016

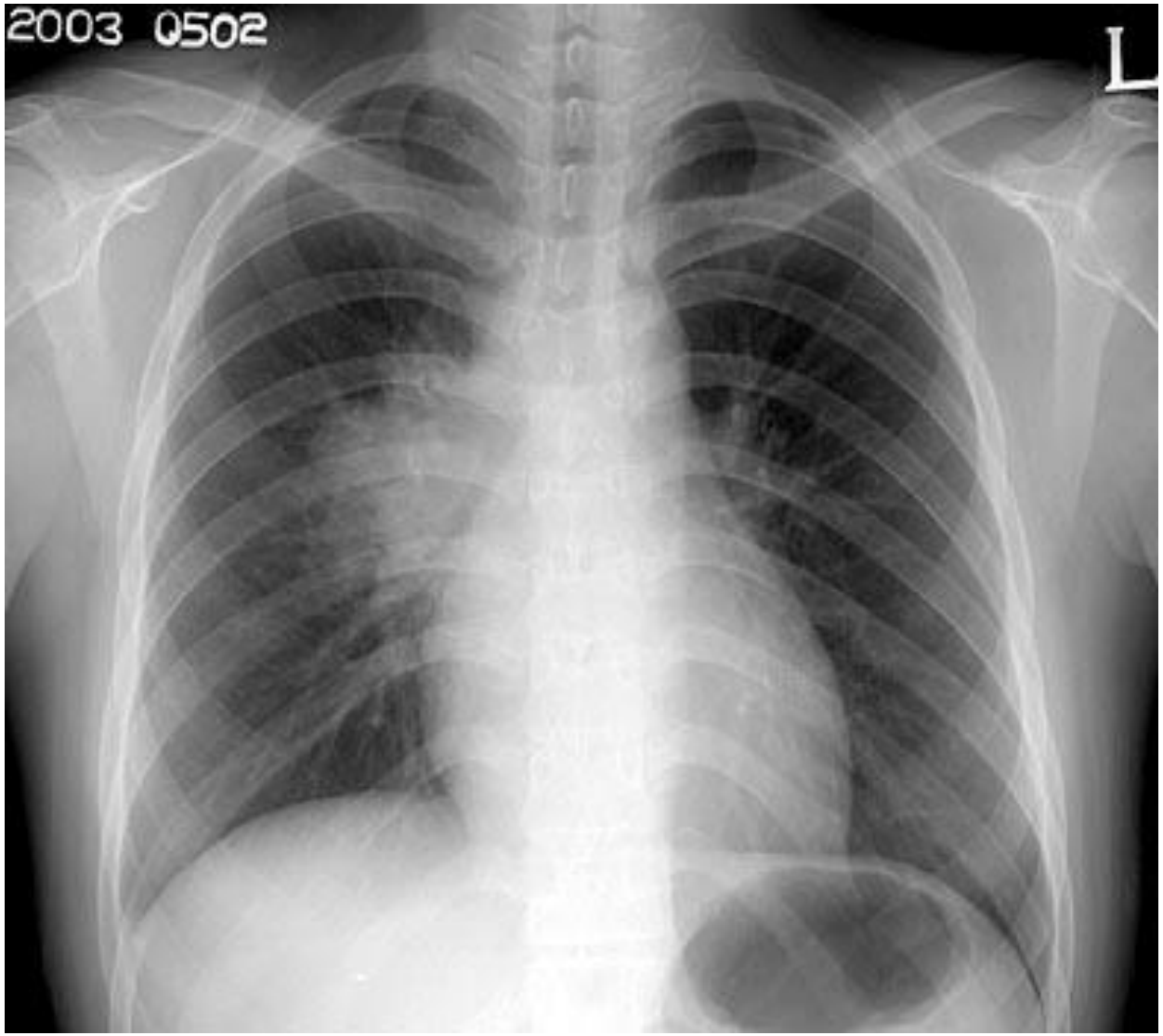
Clinical Diagnosis

Primary Tuberculosis

- TB is divided into primary and post-primary (or reactivation)
- Most primary TB resolves spontaneously, but reactivation may occur without treatment

Primary Tuberculosis

- Most are asymptomatic; fever and nonproductive cough may occur
- Opacities are in middle and lower lungs
  - Commonly unilateral
- Lymph node enlargement often occurs, and may cause bronchial compression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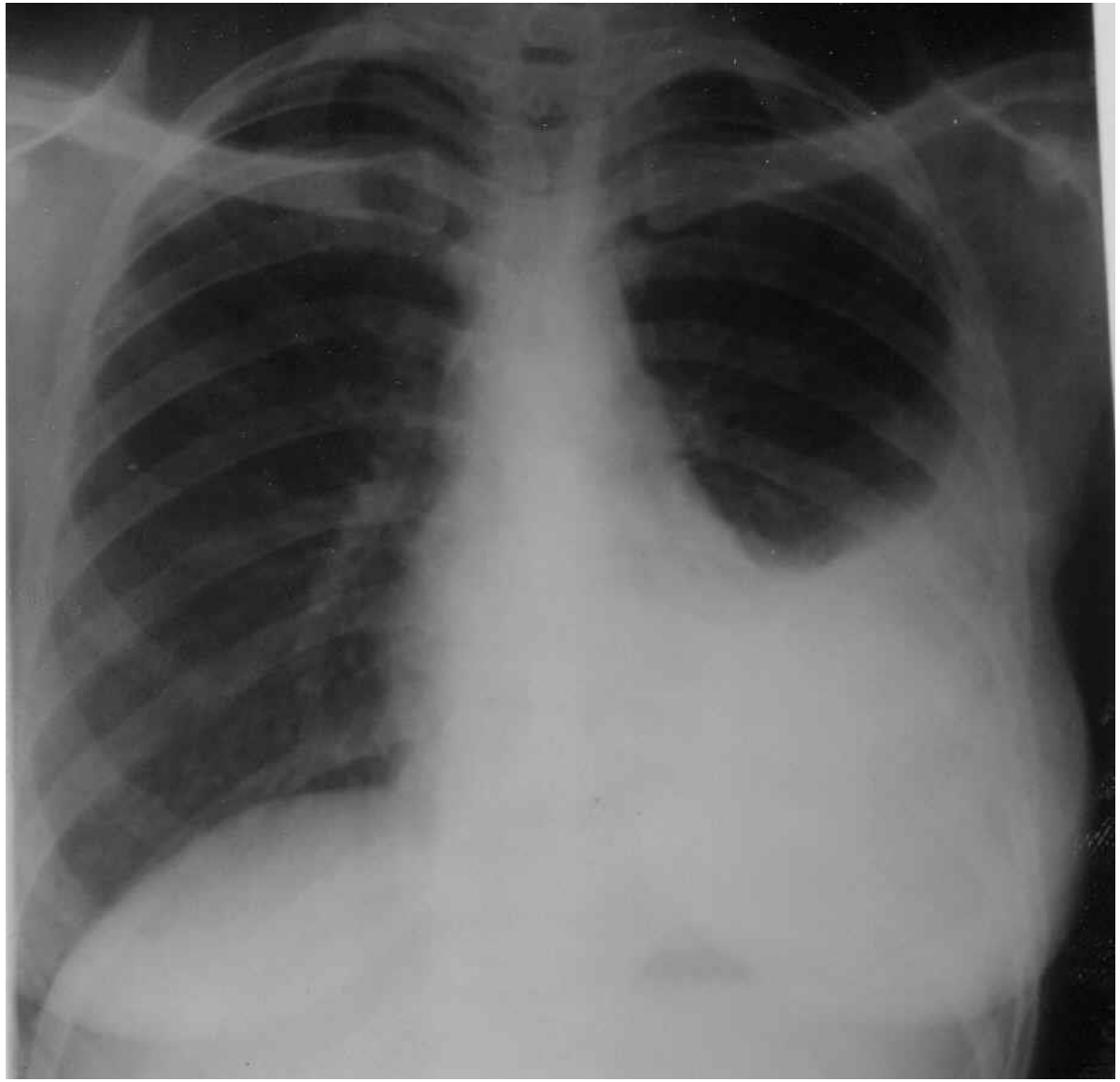
Primary Tuberculosis

- Pleural Effusion: Seen in up to 25% of those with primary TB.
- Often is the only manifestation.



Primary Tuberculosis

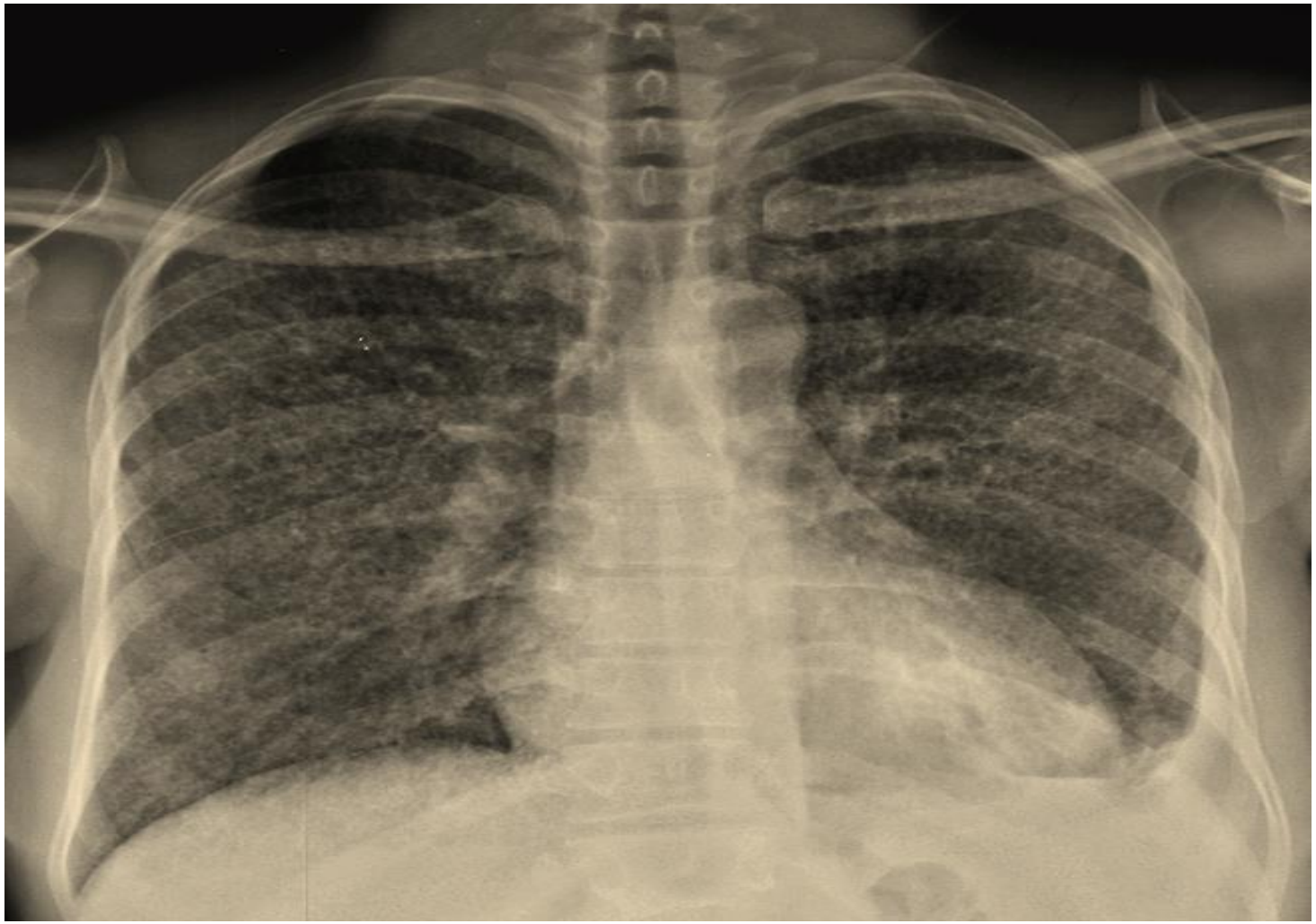
- The natural history of TB pleuritis is spontaneous resolution over 2 to 4 months
- May leave residual pleural thickening and calcification
- If not treated
  - High risk of reactivation
  - Rapid development of devastating disease in infants and immunocompromised persons

Primary Tuberculosis

- Miliary disease:
  - more commonly seen in the elderly, infants, and immuno-compromised hosts.
  - Usually seen within 6 months of the initial exposure

- Evenly distributed diffuse small 2-3 mm nodules, with a slight lower lobe predominance

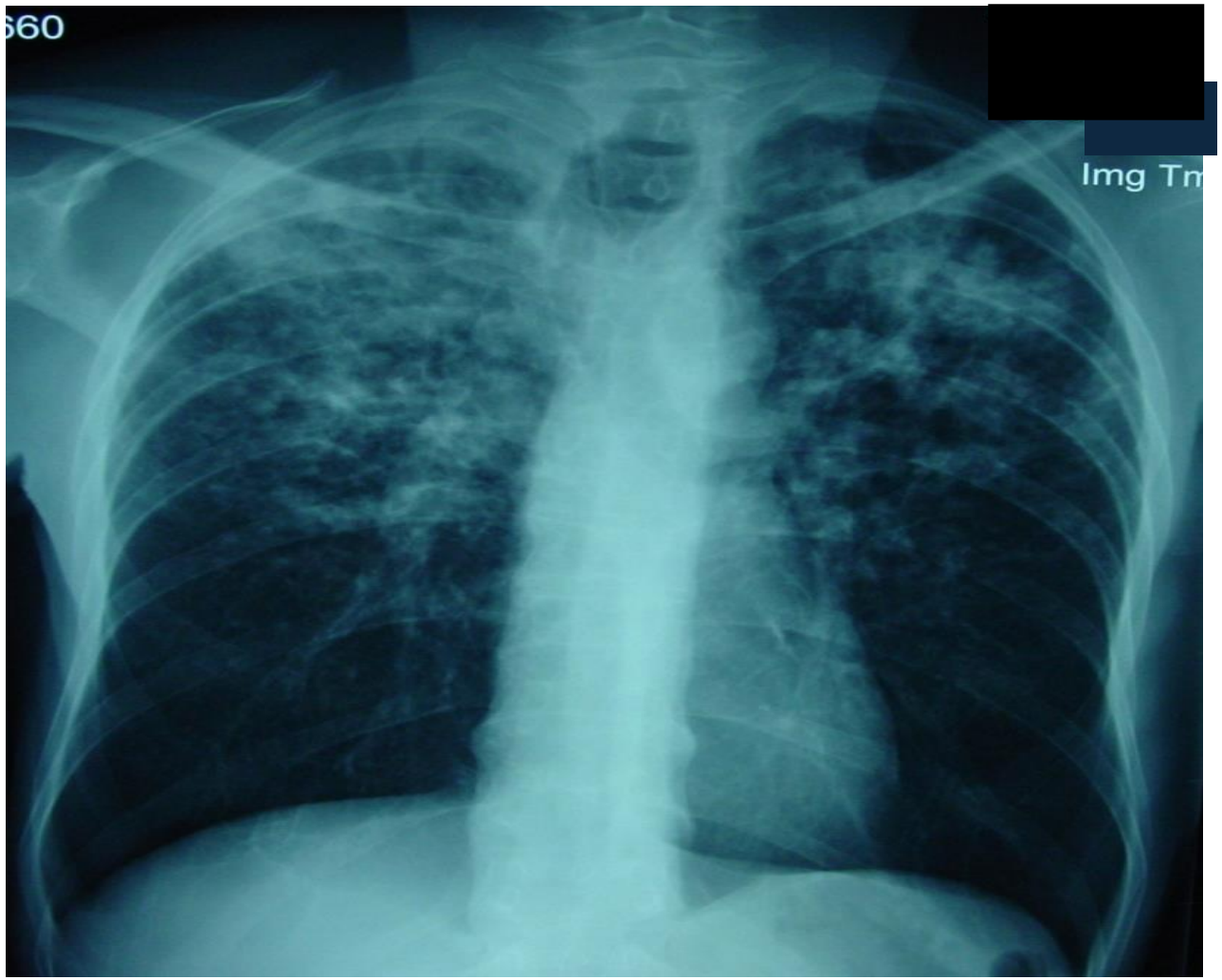
Miliary Tuberculosis



Post primary or reactivation tuberculosis

- Post Primary TB is progressive
- Upper lobes predilection, cavitation and absence of lymphadenopathy
- Fibrosis and calcification are seen after healing

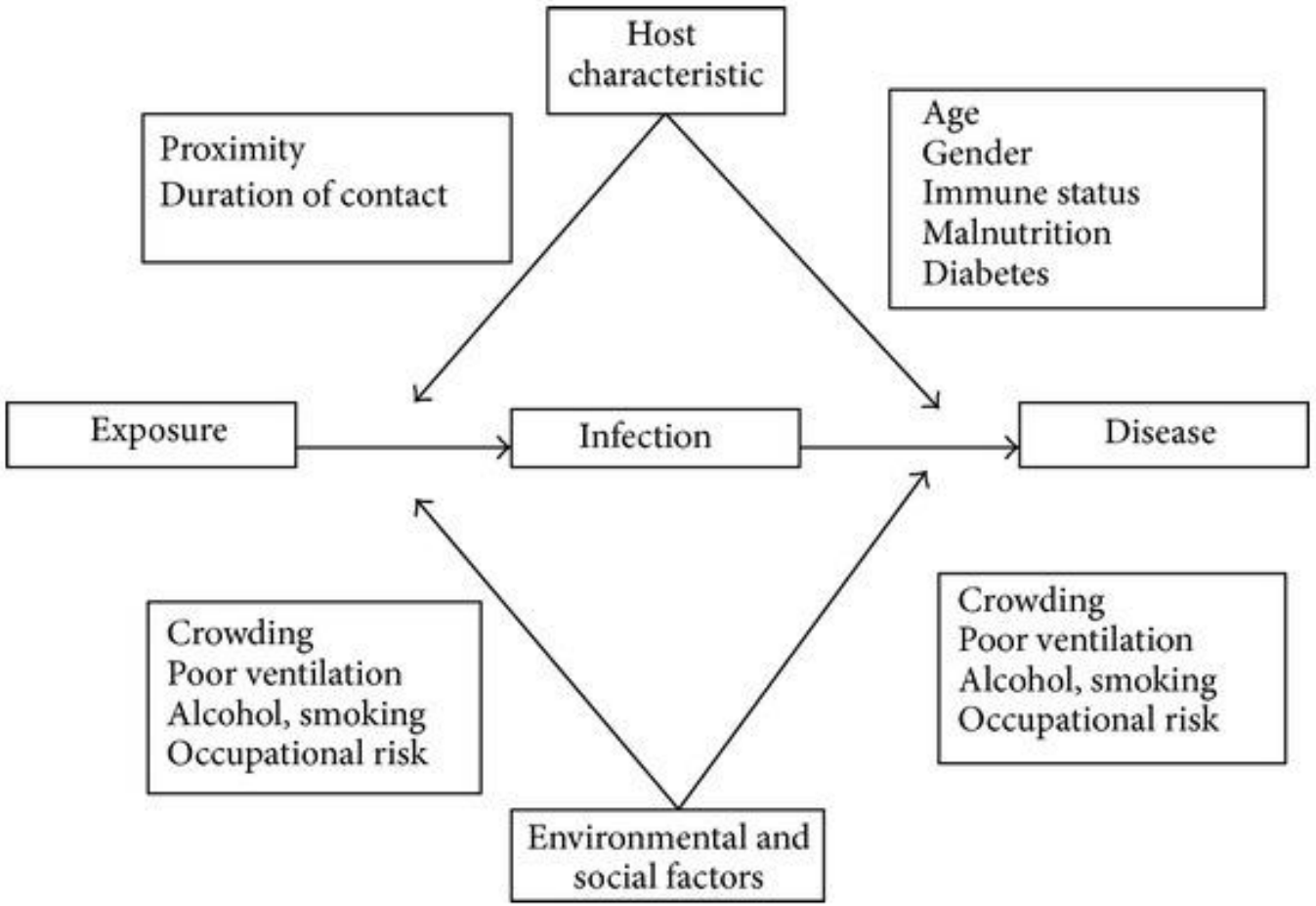
Reactivation Tuberculosis



Assessing the Possible Risk

- EXPOSED
- LATENT TB INFECTION (LTBI)
- TB DISEASE

Risk Factors for TB



Standard Components of TB Evaluation

- Patient History
  - Symptoms
  - History, co morbidities, demographics, family history
  - Hospital Discharge Information
- Physical examination
- Laboratory testing
  - Tuberculin Skin Test or Interferon Gamma Release Assays
    QTF Gold In Tube, TSpot TB
  - CBC, LFTs, sputum smears/cultures, Tissue histology
- Radiologic evaluation
  - CXR, (CT, MRI)

Sputum Collection

- Collect sputum specimens if:
  - Abnormal CXR consistent with TB
  - Presence of respiratory symptoms even if normal CXR

Mycobacterial Cultures

- Three initial sputum cultures within 24 hours
  - At least one first morning
  - At least one observed
- Cultures should be obtained monthly until negative on two consecutive months
  - Determine length of therapy
  - Identify delayed response (+ at 3 months)
  - Identify treatment failure (+ at 4 months)

CDC Recommendations for NAAT

- “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a
- (1) diagnosis of TB is being considered but has not yet been established, and for whom the test
- (2) result would alter case management or TB care and prevention activities.”

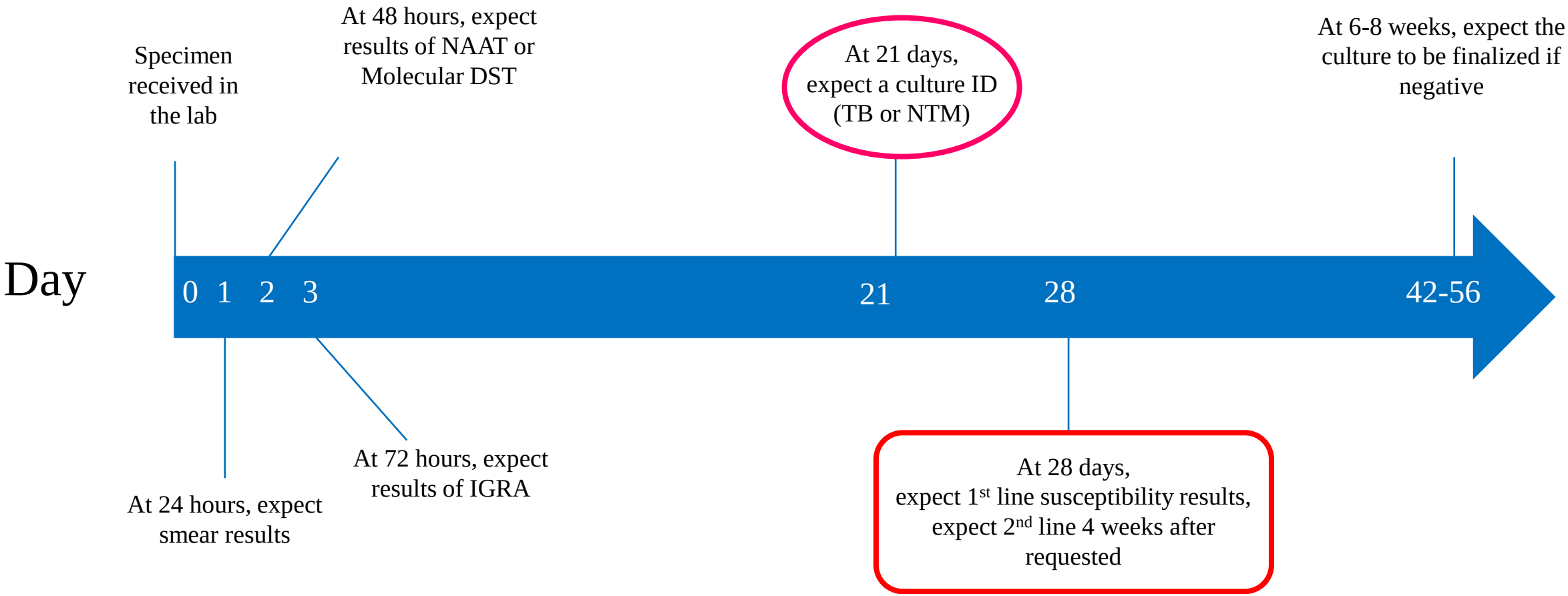
Why Use A NAAT ?

- Confirms AFB + patient as M TB

- If AFB + patient is NAAT negative on 2 specimens
  - **Less likely to have M TB**
    - Suspend Contact investigation and
    - Hold TB treatment unless TB is a strong consideration

- If patient is not strongly considered to have M TB and is NAAT negative x 2,
  - **Remove from isolation.**

When should I consider my specimen delayed?



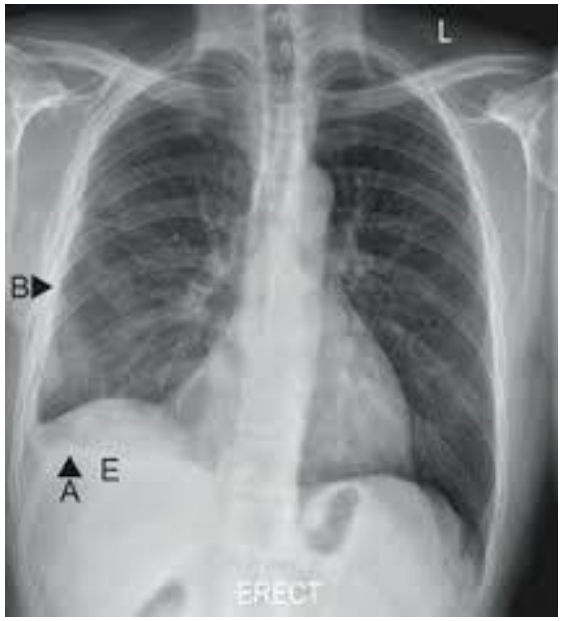
Chest Xray

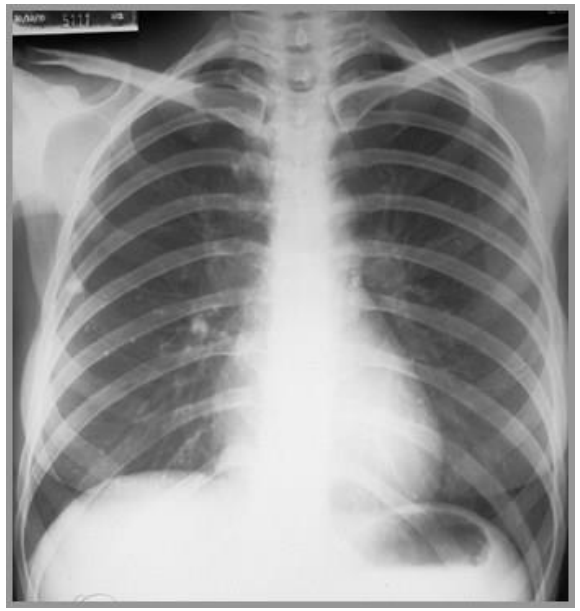
- Obtain a CXR in
  - Every person with a newly positive TST or IGRA
  - Any person at risk of TB who has symptoms and no other obvious diagnosis
  - May be indicated in some asymptomatic, TST/IGRA negative contacts at increased risk
    - Children 4 years and younger
    - HIV infected
    - Immunosuppressed

Differentiating Between LTBI and Disease when the CXR is abnormal

Abnormal CXR findings which could be consistent with LTBI

- Nodules/ Fibrotic lesions of old TB
- Calcified granuloma
- Pleural thickening
- Bronchiectasis





Management of TST + Persons With an Abnormal CXR and **– AFB Smear**

- Isolated CXR with nodules and/or fibrotic lesions:
- If no symptoms - wait
  - Collect sputum culture
  - Evaluate for symptoms
  - Repeat CXR
- If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: This person may have tuberculosis
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB

Management of TB Disease

Treatment Regimens for TB Disease

- **Initiation phase** of therapy
  - 8 weeks
  - INH, Rifampin and PZA +/-EMB

- **Continuation phase** of therapy
  - 16 weeks
  - INH and Rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- **General conclusions from the 2016 guidelines**
  - 6 mo (26 wk) is the ***MINIMUM*** duration of RX
  - **6 mo regimens require rifampin and INH throughout and PZA for the first 2 months**

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - **Without PZA** - minimum duration is **9 months**
  - **Without rifampin** - minimum duration is **12 months (up to 18 months)**

Why Give Ethambutol?

- A four drug regimen is recommended until susceptibility tests are reported
- Ethambutol can be stopped as soon as the lab reports an isolate susceptible to INH & rifampin.
- If treatment is being initiated after drug susceptibility tests are known and the organisms are susceptible, ethambutol is not necessary if the patient is given both INH and rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

Preferred Regimen *(HIV Uninfected)*

initial phase

2 mo I,R,Z,E daily (56 doses, 8wks) ***or***

2 mo I,R,Z,E 5x/wk (40 doses, 8wks) ***then***

continuation phase

4 mo - I,R daily (126 doses, 18 wks) ***or***

4 mo – I,R 5x/wk (90 doses, 18 wks)

Treatment of Culture Positive Pulmonary Tuberculosis

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

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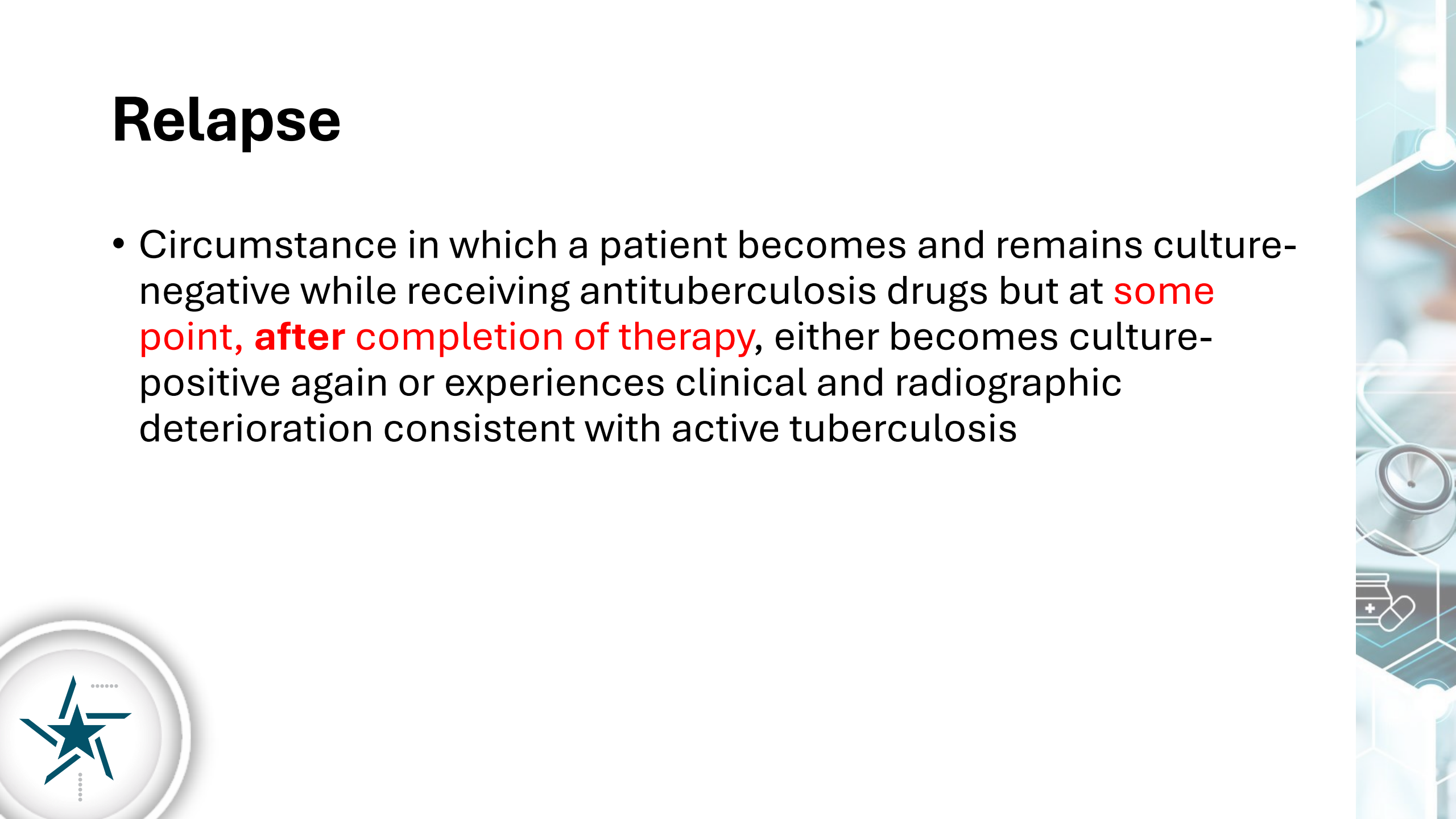
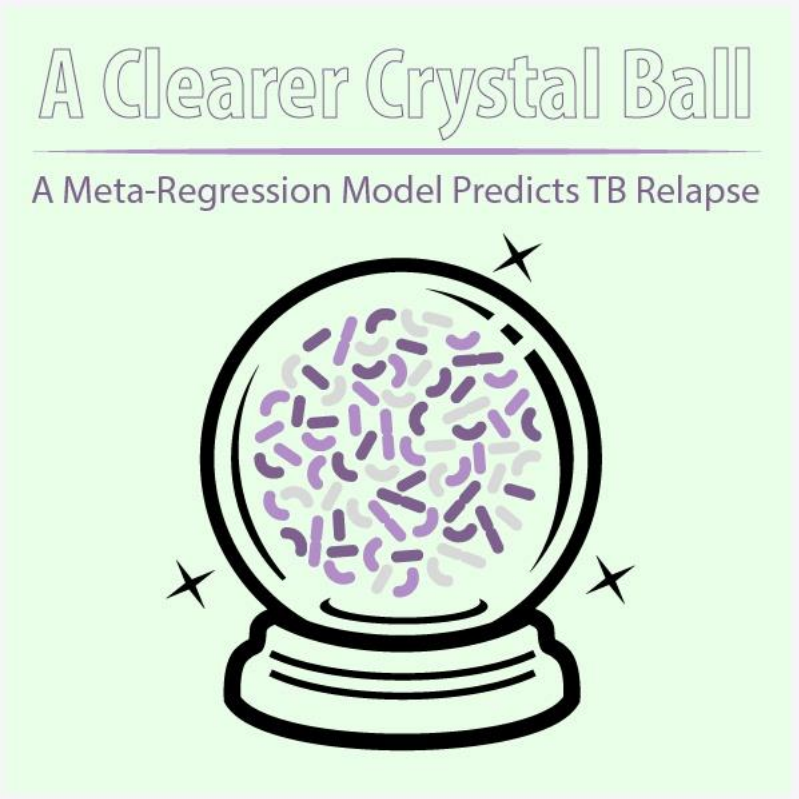
Relapse

- Circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but at some point, **after** completion of therapy, either becomes culture-positive again or experiences clinical and radiographic deterioration consistent with active tuberculosis



Patients at Risk of Relapse



- Who is more likely to have Relapse?
- What Can We Do Differently to Decrease the Risk?

Medical Factors Associated With Relapse

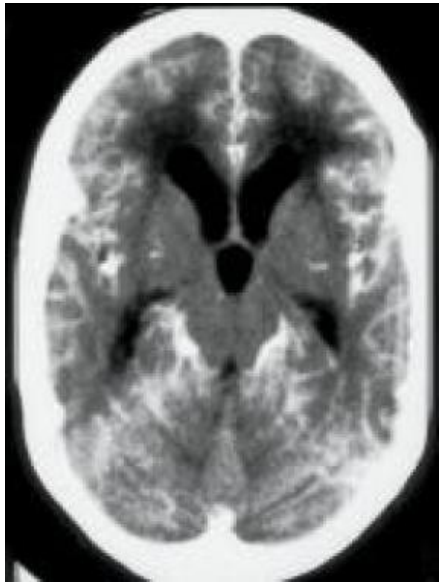
- Cavitary TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
  - Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
  - Drug resistant disease
    - Prior treatment for tuberculosis

Treatment Factors Associated with Relapse of Tuberculosis

- DOT
- Adherence
- Dosing intensity (Dose itself)
- Duration of therapy
  - Intensive phase
  - Continuation phase
  - Both
- Rifamycin containing regimen

Tailoring Treatment Regimens

- **Prolong** continuation phase when:
  - Positive 2 month culture with cavitary disease
  - Extrapulmonary disease
    - Meningitis, bone and joint
    - Disseminated disease in children
  - HIV TB in children and adolescents and in adults not receiving HAART during TB treatment



Relapsed Tuberculosis Management Strategies

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later
- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms

Treat with standard RIPE regimen

Relapsed Tuberculosis Management Strategies

- **Suspect drug resistance if:**
  - Patients treated with self administered therapy
  - Patient was poorly adherent
  - Patient deteriorates clinically or radiographically during initial weeks of treatment
- **Do molecular testing for drug resistance**
  - Consider expanded regimen, especially if immune suppressed
  - Add at least 2 drugs (fluoroquinolone and an injectable)

Treatment in Special Situations

“Delayed Response” Culture Positive at 3 Months

- TB lab should **automatically repeat** susceptibility studies on last positive culture - check to be sure
- Assess adherence
- Consider serum drug levels
- Evaluate response to therapy
  - Clinically and radiographically
  - By the time you know this it is 4 months into therapy!

“Treatment Failure” Culture Positive at 4 Months

Repeat susceptibility studies

- On last positive culture
- **And request on a “new sputum culture” now**
  - **Ask for molecular detection of drug resistance**
- Serum drug levels if not previously done
- Clinical evaluation

Augment therapy

- Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
  - Even if no clinical or radiographic evidence of failure

Active TB During Pregnancy

- Diagnosis may be difficult
  - Respiratory symptoms common in late pregnancy
  - Reluctance to do a CXR
  - Extra-pulmonary disease is even more difficult
- Outcomes for BOTH mom and baby are improved with treatment during pregnancy
- Infection control is important at time of delivery if mom is still infectious

Active TB During Pregnancy

- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
    - PZA recommended by WHO but controversial in U.S.
      - Case by case basis – benefit may exceed risk in HIV, extrapulmonary or severe TB
- Follow carefully for hepatotoxicity- risk is increased
  - During pregnancy
  - Three months postpartum

TNF alpha Antagonists

- Block TNF alpha activity which is required for granuloma formation and control of M TB infection
- Used for rheumatoid arthritis, Crohn's disease, psoriasis and a variety of other immune mediated diseases
  - Remicaid (inflixamab)
  - Embril (entanercept)
  - Humira (adalimubab)
  - Cimzia (certolizumab)

Warning: Risk Of Infections Infliximab

- Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), …and other opportunistic infections have been observed in patients receiving Remicade some of these infections have been fatal.
- Patients should be evaluated for LTBI with a TST.
- Treatment of LTBI should be initiated prior to therapy with Remicade.
- SEE WARNINGS

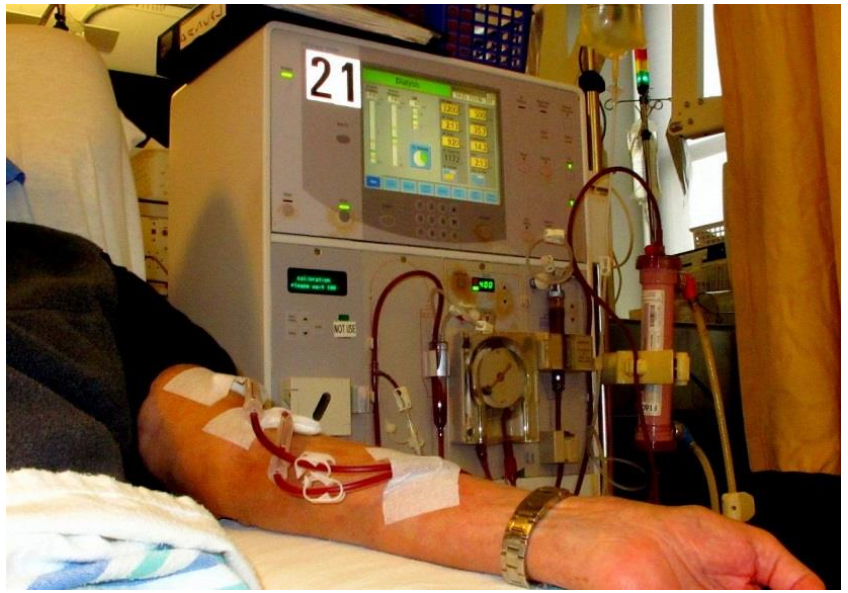
PDR 2004

TB Presentation in Dialysis Patient

- Pulmonary - Atypical presentation
  - Fever – most common sign!
    - Low or high grade
  - Weight Loss
  - Anorexia
  - Cough (may not be present)

TB Presentation in Dialysis patients

- Extra pulmonary TB
  - More common in dialysis patients
    - Pleural and lymph node – most common
    - Peritoneal/Abdominal
      - Can be indistinguishable from typical bacterial peritonitis
      - Peritoneal BX may show caseating granulomas
    - Any site – (Bone, Brain, Pericardium, etc.)
  - Don’t forget to do SPUTUMS!!



Treatment Regimen: Active TB

- Initial Phase (first two months):
  - INH 300mg po daily or 900 mg thrice weekly
  - Rifampin 600mg po daily or thrice weekly
  - Ethambutol 15-25mg/kg po Thrice weekly
  - PZA 25-35mg/kg po thrice weekly
  - Vitamin B6 50mg thrice weekly
- All doses should be given AFTER DIALYSIS

Table 12. Dosing Recommendations for Adult Patients With Reduced Renal Function[a]

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients With Creatinine Clearance <30 mL/min, or Patients Receiving Hemodialysis
Isoniazid	No	300 mg once daily, or 900 mg 3 times/wk
Rifampin	No	600 mg once daily, or 600 mg 3 times/wk
Pyrazinamide	Yes	25–35 mg/kg/dose 3 times/wk (not daily)
Ethambutol	Yes	20–25 mg/kg/dose 3 times/wk (not daily)
Levofloxacin	Yes	750–1000 mg/dose 3 times/wk (not daily)
Moxifloxacin	No	400 mg once daily
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 times/wk[b]
Ethionamide	No	250–500 mg/dose daily
Para-amino salicylic acid	No	4 g/dose twice daily
Streptomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Capreomycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Kanamycin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)
Amikacin	Yes	15 mg/kg/dose 2-3 times/wk (not daily)

Does Diabetes Impact TB Treatment Outcomes?

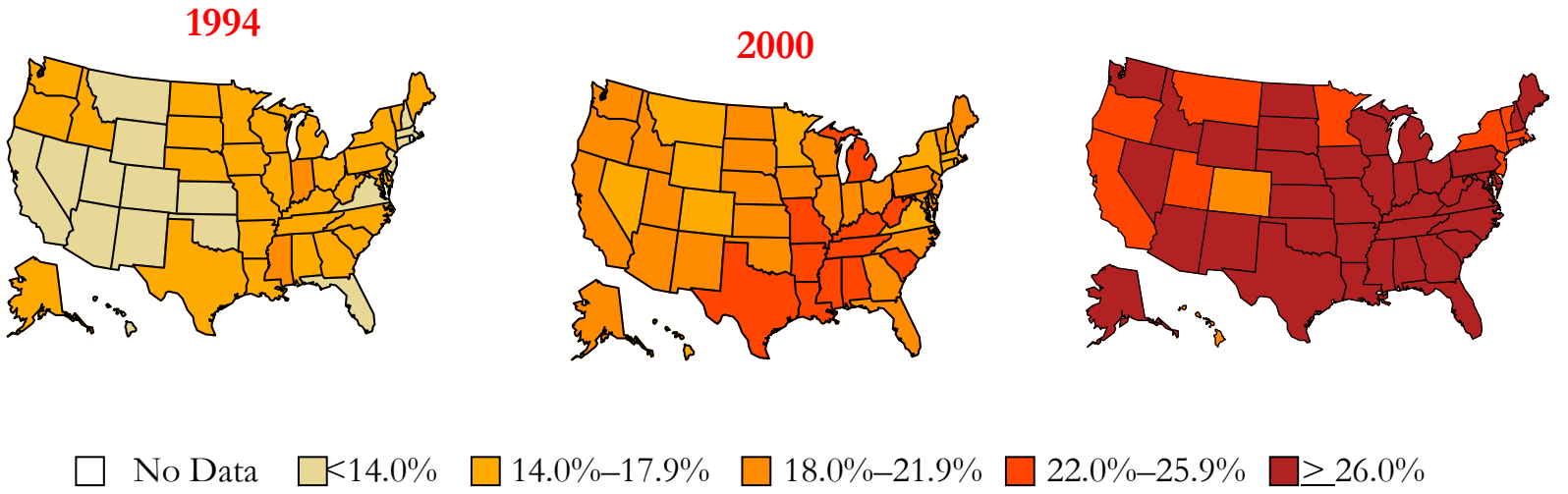
- A link between diabetes and TB has been recognized for centuries

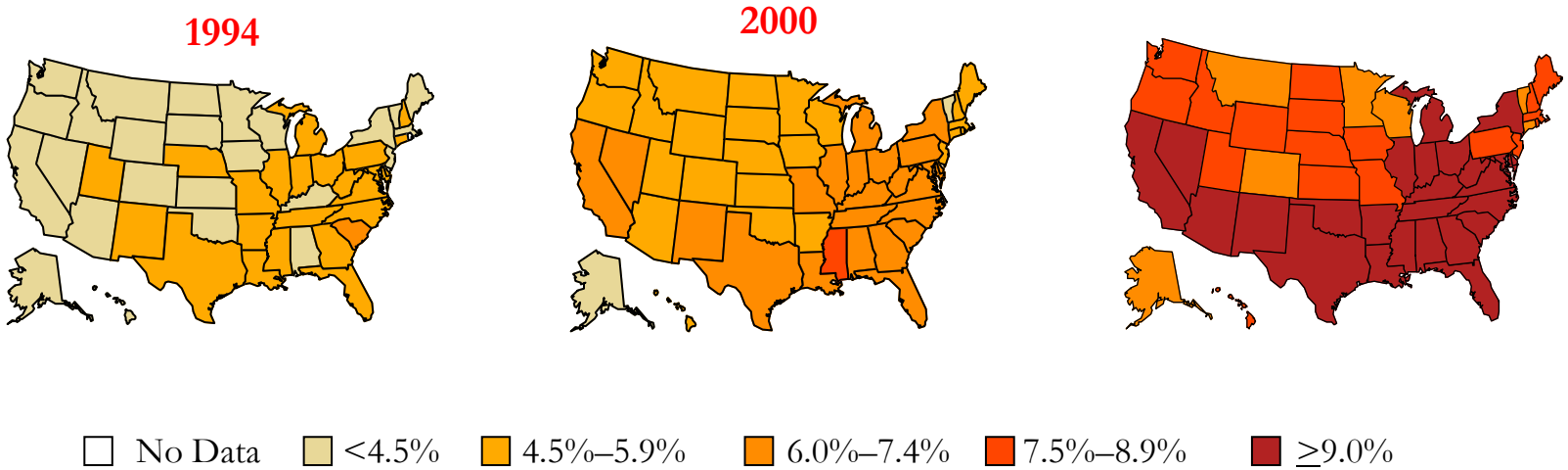
- Diabetics have increased risk of progression to disease, failure of therapy, relapse and mortality from TB

Richard Morton (1637-98) and his Phthisiologia

Tuberculosis and diabetes mellitus: convergence of two epidemics; Dooley K; *Lancet Infect Dis*. 2009 December; 9(12): 737–746.

Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults





CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Mycobacterium bovis

- A member of the M TB complex
- Is more common along U.S./Mexico border
  - Non-pasteurized milk and cheese – a food borne disease as well as respiratory
- Is associated with extra pulmonary disease and increased mortality
- Similar to other members but is resistant to PZA

Culture Negative TB

- A person who could have TB with positive TST or IGRA
  - Risk factors for TB
  - Abnormal CXR
  - Usually – clinical symptoms
- All cultures are negative
- Classify based on clinical and/or radiograph response to treatment at 2 months
  - **Clinical or CXR improvement – Culture Negative TB**
    - Treat for 4 months (children and HIV + 6 months)
      - RIPE for 2 months, then RIE +/- PZA dependent on INH resistance

Management of Treatment Interruptions

- Initial phase of therapy
  - <14 days –complete standard # of doses
  - >14 days – restart from the beginning
- Continuation phase
  - >80% doses by DOT – if initial smear–, may stop but if initial smear +, complete treatment
  - < 80% doses by DOT and lapse <3 months – complete therapy
  - < 80% doses by DOT and lapse >3 months – reevaluate and restart therapy from beginning

4-month Rifapentine-moxifloxacin TB Treatment Regimen

The 4-month TB treatment regimen consists of

- high-dose daily rifapentine (RPT) with
- moxifloxacin (MOX),
- isoniazid (INH), and
- pyrazinamide (PZA).

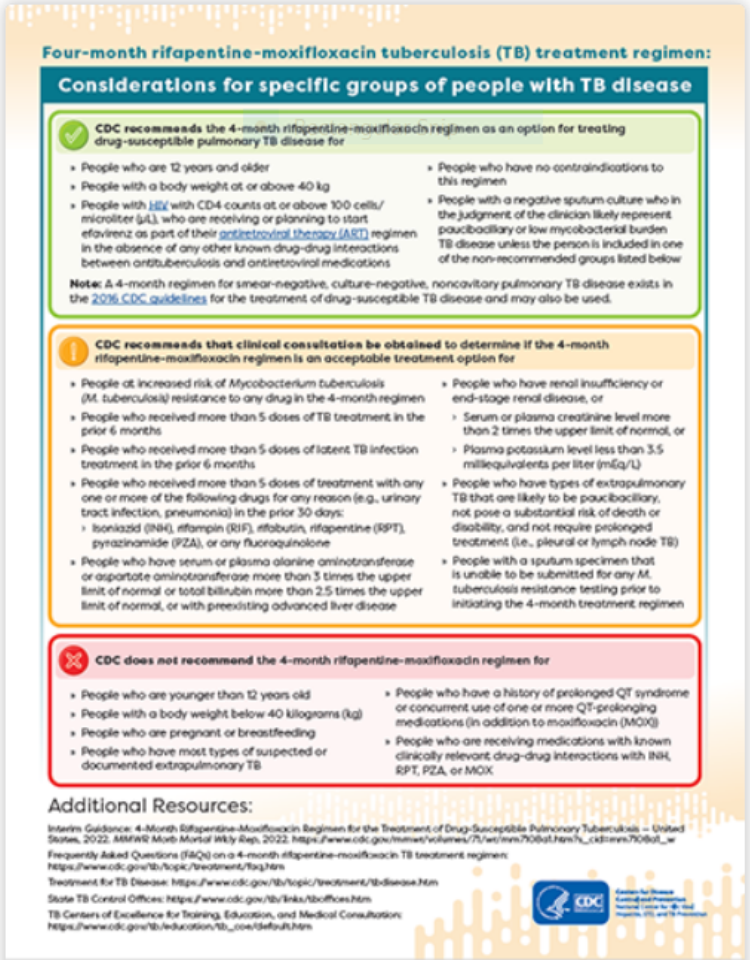
The 4-month rifapentine-moxifloxacin regimen has an intensive phase of 2 months, followed by a continuation phase of 2 months and 1 week (total 17 weeks for treatment).

Intensive Phase			Continuation Phase					
Drugs	Duration[a]	Frequency[b]	Drugs	Duration[c]	Frequency[b]	Total Doses	Comments[d,e]	Regimen Effectiveness
RPT MOX INH PZA	8 weeks	7 days/week for 56 doses	RPT MOX INH	9 weeks	7 days/week for 63 doses	119	Recommended for people ages 12 and older with body weight at or above 40 kg, with pulmonary TB caused by organisms that are not known or suspected to be drug-resistant, and who have no contraindications to this regimen.	The 4-month rifapentine-moxifloxacin TB treatment regimen is as effective as (noninferior to) the standard daily 6-month regimen in curing drug-susceptible TB disease.

Abbreviations: RPT= rifapentine; MOX= Moxifloxacin; INH = isoniazid; PZA = pyrazinamide

CDC recommends the 4-month rifapentine-moxifloxacin regimen as an option for treating pulmonary TB disease caused by organisms that are not known or suspected to be drug-resistant for

- People who are 12 years and older
- People with a body weight at or above 40 kg
- People with HIV with CD4 counts at or above 100 cells/microliter (µL), who are receiving or planning to start efavirenz as part of their antiretroviral therapy (ART) regimen in the absence of any other known drug-drug interactions between antituberculosis and antiretroviral medications
- People who have no contraindications to this regimen
- People with a negative sputum culture who in the judgment of the clinician likely represent paucibacillary or low mycobacterial burden TB disease unless the person is included in one of the non-recommended groups listed below



Considerations for the 4-month Rifapentine-moxifloxacin Regimen [PDF - 233 KB]

Note: A 4-month regimen for smear-negative, culture-negative, noncavitary pulmonary TB disease exists in the 2016 Treatment of Drug-Susceptible Tuberculosis Guidelines for the treatment of drug-susceptible TB disease and may also be used.

Open Forum Infectious Diseases

MAJOR ARTICLE

Experience With Four-Month Rifapentine and Moxifloxacin–Based Tuberculosis Treatment in San Francisco

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Background. A multicountry randomized controlled trial has demonstrated that pan-susceptible pulmonary tuberculosis (TB) can be successfully treated with a 4-month regimen of daily isoniazid, rifapentine, moxifloxacin, and pyrazinamide (HPMZ). We piloted HPMZ in San Francisco (SF) using a modified version of the US Centers for Disease Control and Prevention HPMZ treatment guidelines.

Methods. In this retrospective cohort, patients consecutively referred to SF TB clinic were evaluated for HPMZ eligibility based on preestablished inclusion/exclusion criteria. All underwent evaluation and management according to national recommendations. We reviewed the medical records of those initiated on HPMZ.

Results. From August 2021 to December 2023, 30 (18.8%) of 160 patients diagnosed with active TB met HPMZ inclusion criteria; of these, 22 (13.8%) started HPMZ. The median age (range) was 32.5 (14–86) years, 17 (77.3%) were otherwise healthy, and 19 (86.4%) had pulmonary TB, including 7 (36.8%) with cavitary disease. Eighteen (81.8%) patients had an adverse event, with 11 (50%) prematurely discontinuing HPMZ; the most common adverse events were vomiting, elevated transaminases, and rash. To date, 9 (40.9%) have completed treatment, with most achieving criteria for cure. One patient was diagnosed with possible TB recurrence and restarted standard TB treatment.

Conclusions. Our experience, with half of patients to date prematurely discontinuing HPMZ, illustrates the challenge of extrapolating findings from TB clinical trials commonly conducted in high-incidence, non-US settings to US clinical practice. Further experience may help identify best practices for implementing HPMZ, including identifying predictors of which patients may be most likely to benefit from and tolerate this regimen.

Keywords. tuberculosis; treatment; short-course; 4-month; SF.

In Summary: A Complete Assessment for the Diagnosis and Management of TB

…Is Essential to Good Patient
and Public Health Outcomes

Thank you!

Questions