Tuberculosis Treatment

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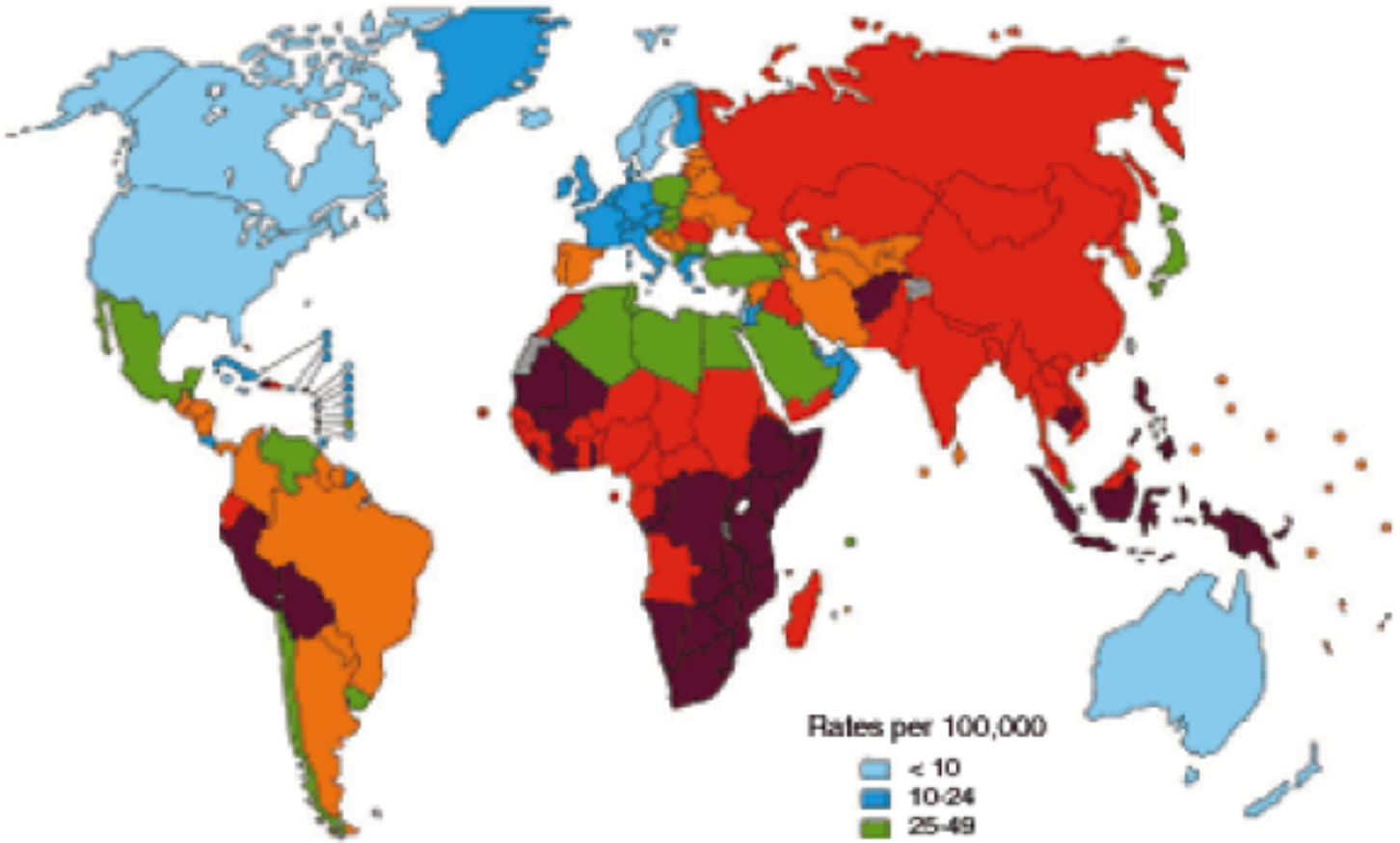
Outline

- Epidemiology
- Latent TB
- Active TB
- Special Treatment Situations
- Extra-pulmonary TB
- MDR & XDR TB

Estimated Rates of New Cases of Tuberculosis, 1997



Source: World Health Organization.

Global Impact

- About 2 billion people thought to have latent TB
- About 9 million new cases annually (new case every 17 sec) - incidence is decreasing last 5 years, as is mortality
- Causes more deaths than any other infectious disease (about 1.5 million deaths)
- Major health problem in developing countries
- Leading killer of youth and young adults
- Leading cause of death for women of childbearing age
- 10 million children orphaned by TB

World Health Organization

Current Anti-TB Drugs

- Four first-line drugs considered standard treatment:
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)

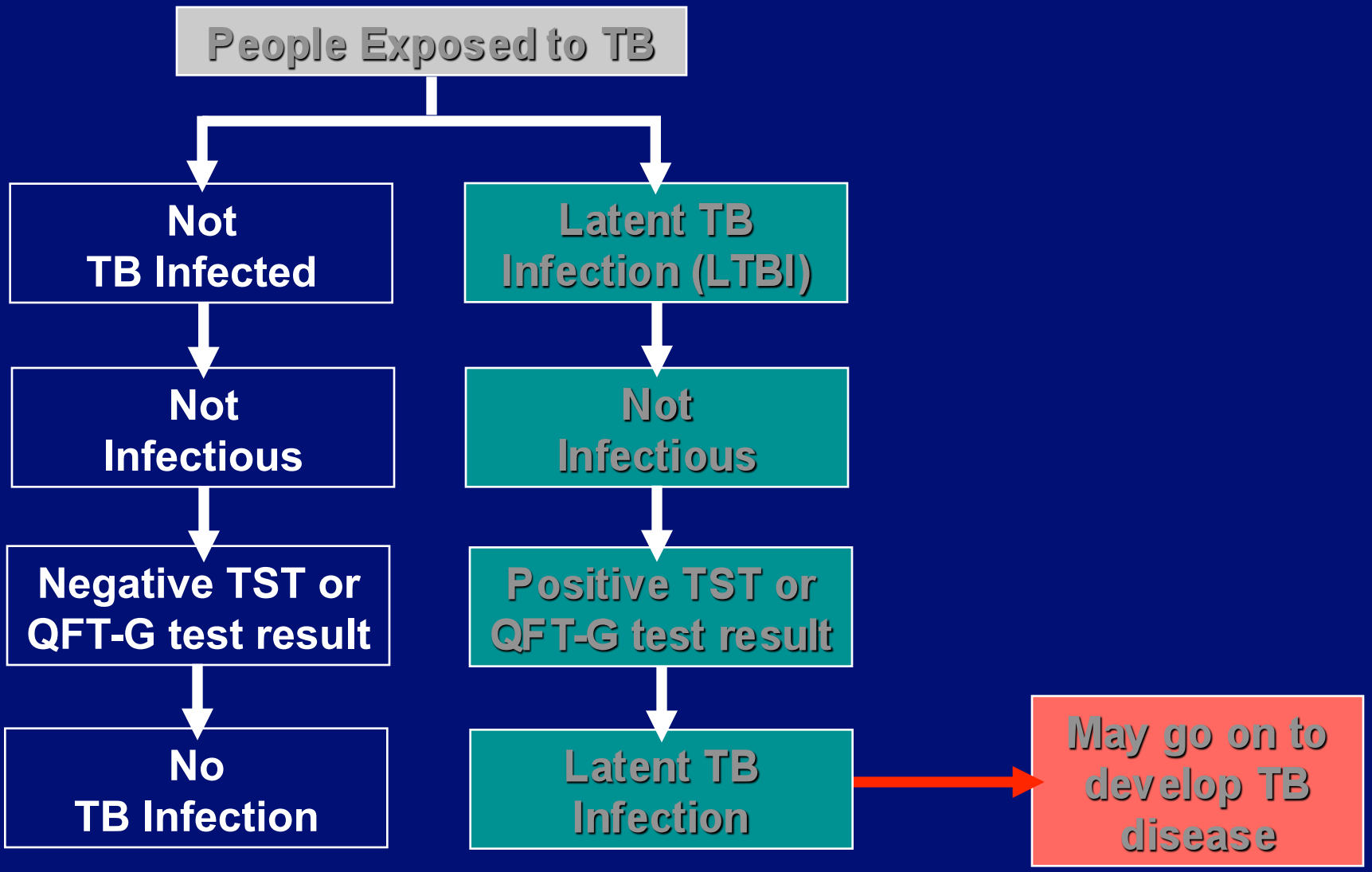


- Rifabutin and rifapentine also considered first-line drugs in some circumstances
- Streptomycin (SM) formerly first-line drug, but now less useful owing to increased SM resistance

Sites of TB Disease

	Location	Frequency
Pulmonary TB	Lungs	Most TB cases are pulmonary
Extrapulmonary TB	• Larynx • Lymph nodes • Pleura • Brain • Kidneys • Bones and joints •Peritoneum •Pericardium	Found more often in: • HIV-infected or other immunosuppressed individuals • Young children
Miliary TB	Carried to all parts of body, through bloodstream	Rare

Progression to TB Disease



LTBI vs. TB Disease

Latent TB Infection (LTBI)	TB Disease (in the lungs)
Inactive, **contained tubercle bacilli in the body**	Active, **multiplying tubercle bacilli in the body**
TST or blood test results usually positive	**TST or blood test results usually positive**
Chest x-ray usually normal	**Chest x-ray usually** abnormal
Sputum smears and cultures negative	**Sputum smears and cultures may be** positive
No symptoms	Symptoms **such as cough, fever, weight loss**
Not infectious	Often infectious **before treatment**
Not a case **of TB**	A case **of TB**

Diagnosis of Latent TB

Who should be tested?

Targeted Testing

- High-risk groups can be divided into two categories:
  - People who are at high risk for becoming infected with *M. tuberculosis*
  - People who are at high risk for developing TB disease once infected with *M. tuberculosis*

High Risk for TB Infection

- Close Contacts of people with infectious TB
- People from areas where TB is common
- Populations defined locally as having increased incidence of LTBI/TB
- People who live or work in high risk settings
- Healthcare workers
- Infants, children, and adolescents exposed to adults in high-risk groups

Progression to TB Disease

- Infection with HIV
- Chest x-ray findings suggestive of previous TB
- Substance abuse
- Recent TB infection
- Prolonged therapy with corticosteroids and other immunosuppressive therapy, such as prednisone and tumor necrosis factor-alpha [TNF-α] antagonists
- Organ transplant
- Silicosis
- Diabetes mellitus
- Severe kidney disease
- Certain types of cancer
- Certain intestinal conditions
- Low body weight

Diagnosis of LTBI

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs):
  - QuantiFERON®-TB Gold test (QFT-G)
  - QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  - T-SPOT

Mantoux Tuberculin Skin Test

0.1 ml of 5 tuberculin units of liquid tuberculin are injected between the layers of skin on forearm

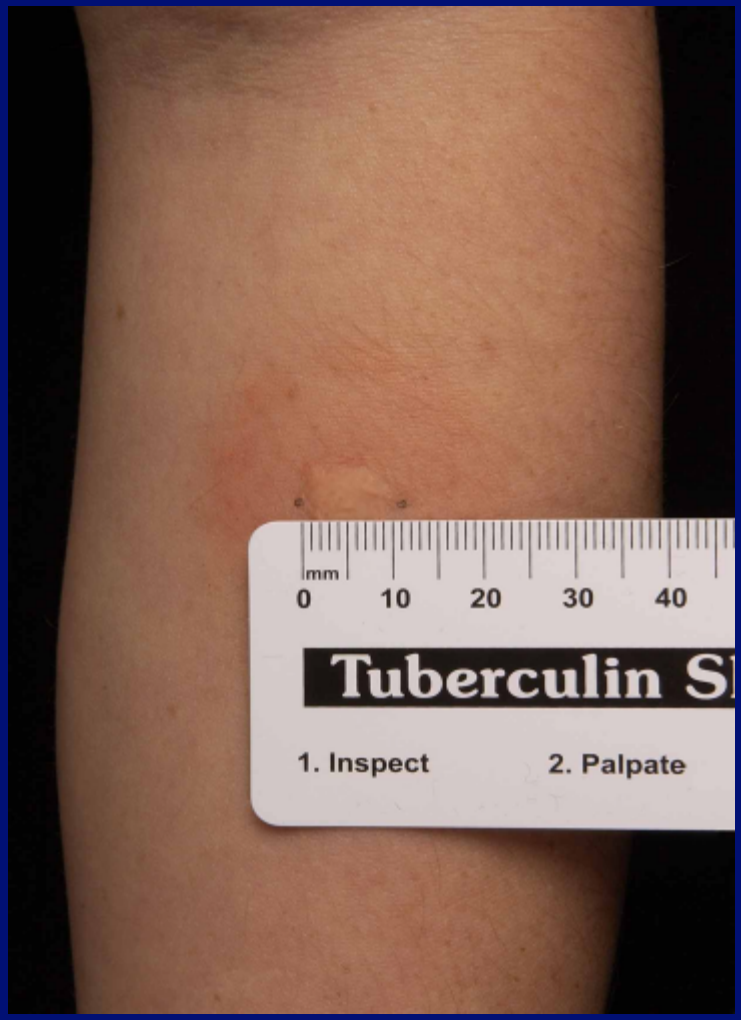


HCW administering Mantoux TST

CDC

Mantoux Tuberculin Skin Test

- Forearm should be examined within 48 - 72 hours by HCW
- Reaction is an area of induration (swelling) around injection site
  - Induration is measured in millimeters
  - Erythema (redness) is not measured



Only the induration is measured

CDC

Interpreting the Reaction

- Induration of ≥ 5 mm is considered positive for:
  - People living with HIV
  - Recent close contacts of people with infectious TB
  - People with chest x-ray findings suggestive of previous TB disease
  - People with organ transplants
  - Other immunosuppressed patients

Interpreting the Reaction

- Induration of ≥ 10 mm is considered a positive reaction for:
  - People who have recently come from areas where TB is common
  - People who inject drugs
  - People who live or work in high-risk congregate settings
  - Mycobacteriology laboratory workers

Interpreting the Reaction

- Induration of ≥ 10 mm is considered a positive reaction for:
  - People with certain medical conditions that increase risk for TB
  - Children younger than 4 years old
  - Infants, children, or adolescents exposed to adults in high-risk categories

Interpreting the Reaction

- Induration of ≥ 15 mm is considered a positive reaction for people who have no known risk factors for TB

False-Positive Reaction

- Infection with nontuberculous mycobacteria
- BCG vaccination
- Administration of incorrect antigen
- Incorrect measuring or interpretation of TST reaction

False-Negative Reaction

- Anergy
- Recent TB infection (within past 8 – 10 weeks)
- Younger than 6 months of age
- Recent live-virus (e.g., measles or smallpox) vaccination
- Incorrect method of giving the TST
- Incorrect measuring or interpretation of TST reaction

Interferon-Gamma Release Assays (IGRAs)

- Measure person's T-cell reactivity to *M. tuberculosis*
- Blood samples are mixed with antigens and incubated for 16 - 24 hours
- If infected with *M. tuberculosis*, T cells will recognize antigens and release interferon gamma (IFN-γ) in response
- Test results are based on IFN-γ concentrations

IGRA Advantages

- Requires single patient visit to conduct test
- Results can be available in 24 hours
- Less likely to have incorrect reading of results as compared to TST
- BCG vaccination does not affect results
- More specific to Mycobacterium Tuberculosis
- Does not cause booster phenomenon

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IGRA Disadvantages and Limitations

- Blood samples must be processed within 12 hours for some IGRAs
- Limited data on its use in certain populations
- Limited data on its use to determine who is at risk for developing TB disease

Treatment of LTBI

Patient Medical Evaluation

- Exclude possibility of TB disease
- Determine whether patient has ever been treated for LTBI or TB disease
- Find out if patient has any medical conditions that may complicate therapy
- Current medications
- Patients should be offered HIV testing

LTBI Treatment Regimens

Drugs	Duration (mo)	Interval	Rating* (Evidence)† HIV−	HIV+
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin–pyrazinamide	2	Daily	B (II)	A (I)
	2–3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.

† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

RIF/ PZA	RIF and PZA combinations generally should not be offered for treatment of LTBI

MMWR/CDC 2003; 52 (No. 31)

Special Considerations for LTBI

- Retest Close Contacts in 8-10 wks if initial TST/IGRA is negative
- Close Contacts at high risk of developing TB disease (children under 5, HIV, immunocompromised) should be treated even if initial testing is negative, then reevaluate at 8-10 wks.
- Severely immunocompromised Contacts might be treated for the full duration regardless of the results of 8-10 wks testing.
- Retreatment for patients with positive TST and documented completed treatment, in patients at high risk for reinfection or progression to TB disease

Special Considerations for LTBI

- Contacts of patients with MDR TB should be evaluated for the risk of developing TB disease. They can be either treated with alternative regimen for 6-12 ms, OR observed for symptoms of disease for a 2 year period without treatment
- In Pregnant Women, LTBI treatment can be delayed till after delivery, Unless, immunocompromised, HIV, or recent TB contact. Prefered regimen is INH x 9ms with B6 supplement
- Breast feeding women can take INH with B6 supplement. INH in breast milk is not enough to treat infant

Patient Monitoring

- Patients need to be evaluated at least monthly during therapy for:
  - Adherence to prescribed regimen
  - Signs and symptoms of active TB disease
  - Adverse reactions

- Liver function tests should be done before starting INH LTBI treatment and every month during therapy:
  - People living with HIV
  - People with history of liver disease
  - People who use alcohol regularly
  - Women who are pregnant or just had a baby
  - People taking medications that may increase risk of hepatitis

Treatment of TB Disease

Goals of Treatment

- Cure active disease
- Prevent reactivation of LTBI
- Prevent transmission
- Avoid resistance by ensuring adherence
- Minimize toxicity

General Rules

- Treatment must contain multiple drugs to which organisms are susceptible
- INH & RIF are the pillars of TB therapy
- Never add a single drug to a failing regimen
- Patients should take their medicines regularly under DOT
- Patients should take ALL their medicines
- If there is a possible adverse drug reaction, stop drugs altogether, and evaluate.
- Regimens can be given daily or 2 or 3 x/week

Treatment Outcomes

- Cured – smear negative at end of tx and 1 other previous smear negative
- Completed – finished full course
- Successful – either cured or completed
- Failed – remained smear +
- Defaulted - ≥ 2 consecutive months of tx interruption

Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT







Anti-tuberculosis Drugs

First-Line Drugs

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol
- Rifabutin
- Rifapentine

Second-Line Drugs

- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin
- Capreomycin
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Treatment of Susceptible TB

- Initial phase – 2 months
  - Start with 4 drugs pending cx results
  - INH, RIF, PZA, EMB
  - Can d/c EMB if sensitive to INH & RIF
- Continuation phase from 4 to 7 months

Regimens

- 4 basic treatment regimens
- All have same 4 drugs initially
- Difference is in number of doses/week and in duration of continuation phase

Regimens (cont)

- Use 7 months continuation if:
  - Cavitary TB with still + sputum
  - Initial tx did not include PZA at 2 mo
  - Once-weekly INH and RPT used but culture was + at end of initiation

Regimen 1

- Initial Phase – 2 months
  - INH, RIF, PZA, EMB (5 or 7 d/week)
- Continuation Phase – 4 months
  - INH, RIF daily (5 or 7 d/week)

  or
  - INH, RIF intermittent (2d/week)

  or
  - INH, Rifapentine (RPT) - (1d/week)

Regimen 2

- Initial Phase – 2 months
  - 4 drugs 5 or 7d/week for 2 weeks
  - then 2 d/week for 6 weeks
- Continuation Phase – 4 months
  - INH, RIF 2d/week

  or
  - INH, RPT 1d/week

Regimen 3

- Initial Phase – 2 months
  - INH, RIF,PZA,EMB for 3d/week
- Continuation Phase
  - INH, RIF for 3d/week

Regimen 4

- Initial Phase – 2 months
  - INH, RIF, EMB for 5 or 7 d/week
- Continuation Phase – 7 months
  - INH, RIF daily (5 or 7 d/week)

  or
  - INH, RIF 2 d/week

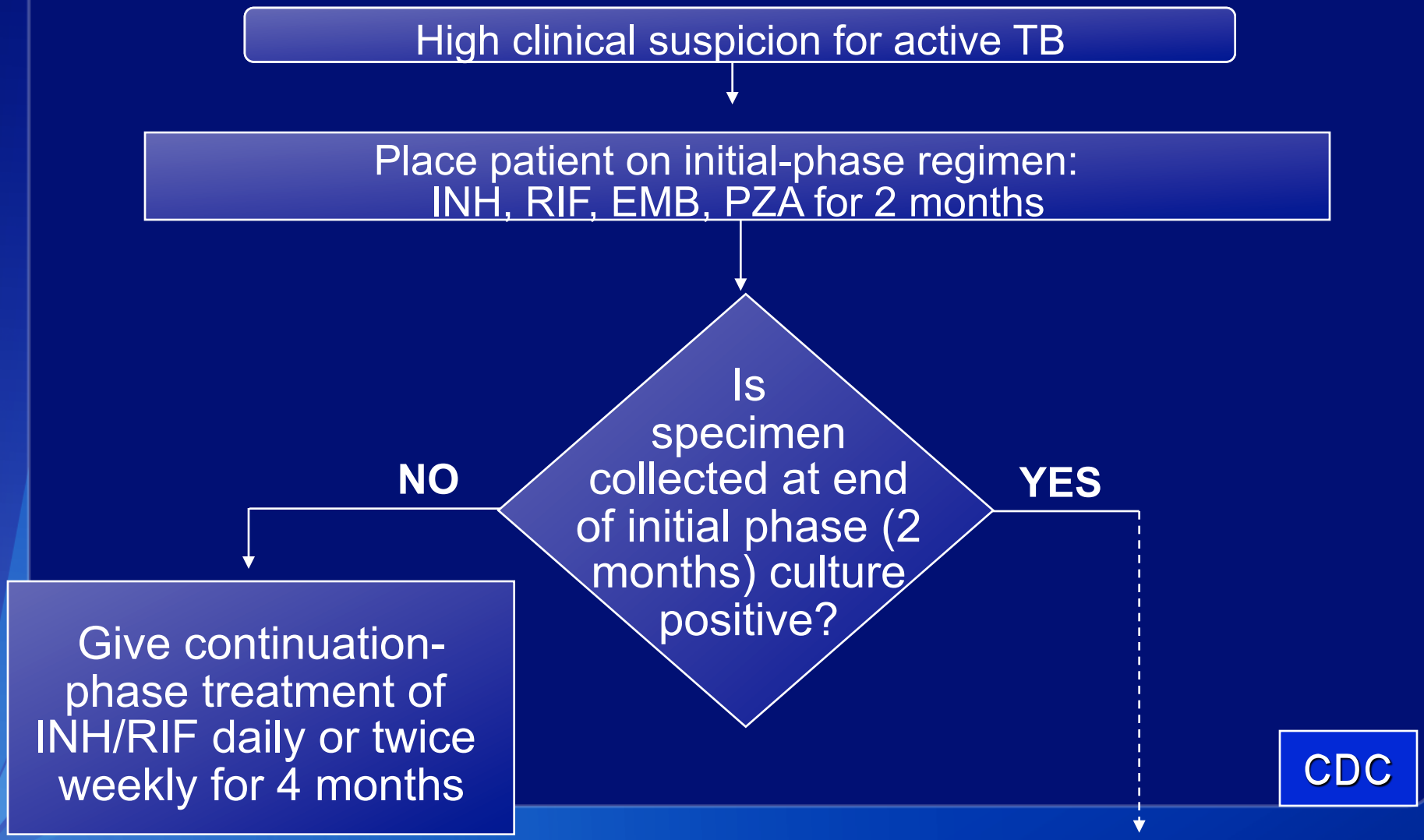
Drug regimens for culture-positive tuberculosis caused by drug-susceptible organisms

Initial phase		Continuation phase		Range of total doses (minimal duration)	Rating*
Drugs	**Interval and doses• (minimal duration)**	**Drugs**	**Interval and doses• Δ (minimal duration)**		
Regimen 1					
INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)◇	1a. INH/RIF	Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)◇	182-130 (26 wk)	A
		1b. INH/RIF	Twice weekly for 36 doses (18 wk)	92-76 (26 wk)	A
		1c. INH/RPT§	Once weekly for 18 doses (18 wk)	74-58 (26 wk)	B
Regimen 2					
INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk)◇, then twice weekly for 12 doses (6 wk)	2a. INH/RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)	A
		2b. INH/RPT§	Once weekly for 18 doses (18 wk)	44-40	B
Regimen 3					
INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a. INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B
Regimen 4					
INH RIF EMB	Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)◇	4a. INH/RIF	Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)◇	273-195 (39 wk)	C
		4b. INH/RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)	C

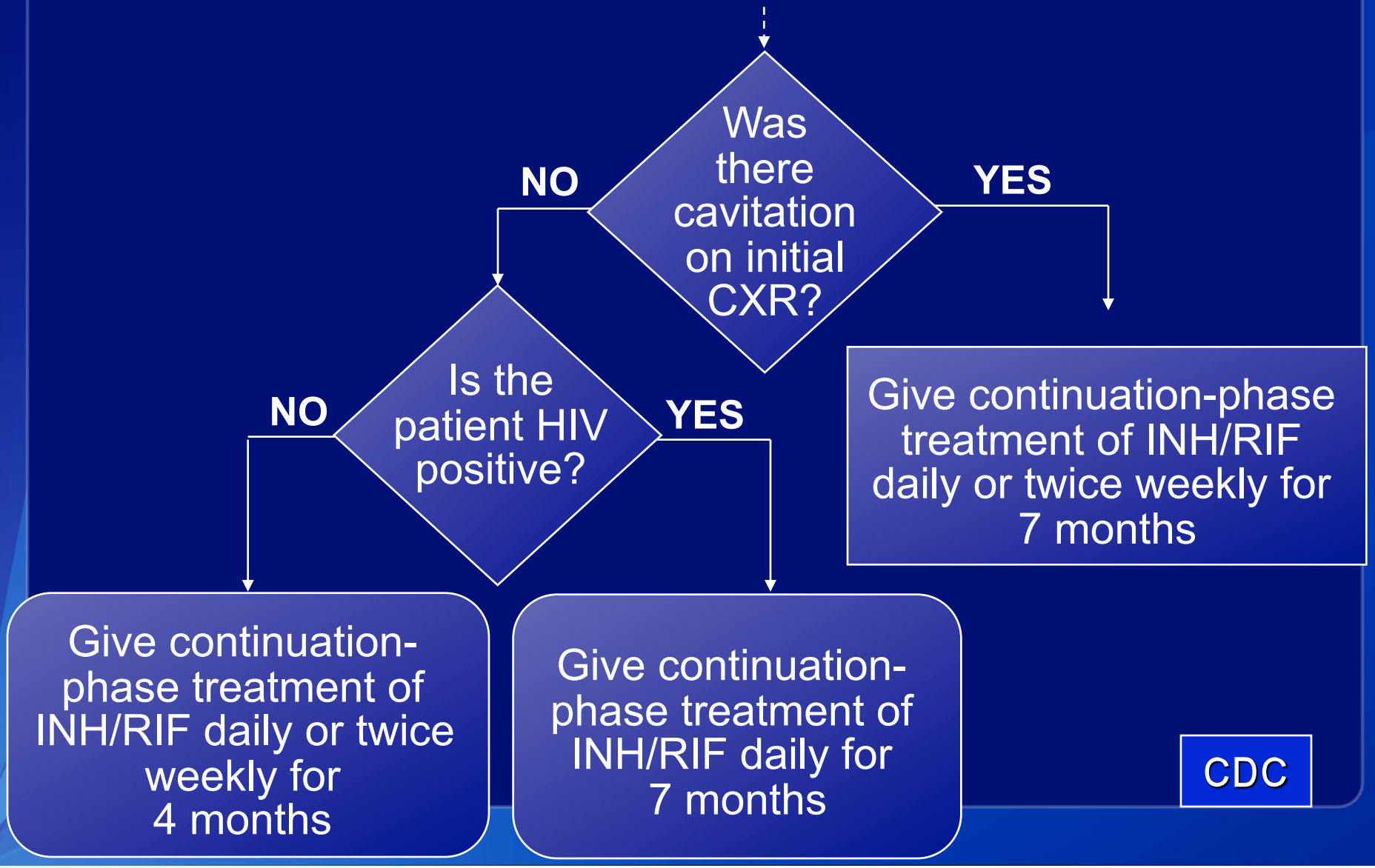
EMB: ethambutol; INH: isoniazid; PZA: pyrazinamide; RIF: rifampin; RPT: rifapentine.
* Definitions of ratings: A: preferred; B: acceptable alternative; C: offer when A and B cannot be given.
• When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
Δ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
◇ Five-day-a-week administration is always given by DOT.
§ Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the two month specimen, treatment should be extended an extra three months.
Data from Am J Respir Crit Care Med 2003; 167:603.

UpToDate

Culture-Positive TB Patients



Culture-Positive TB Patients (Continued)



Culture-Negative TB

High clinical suspicion for active TB despite negative smears based on:

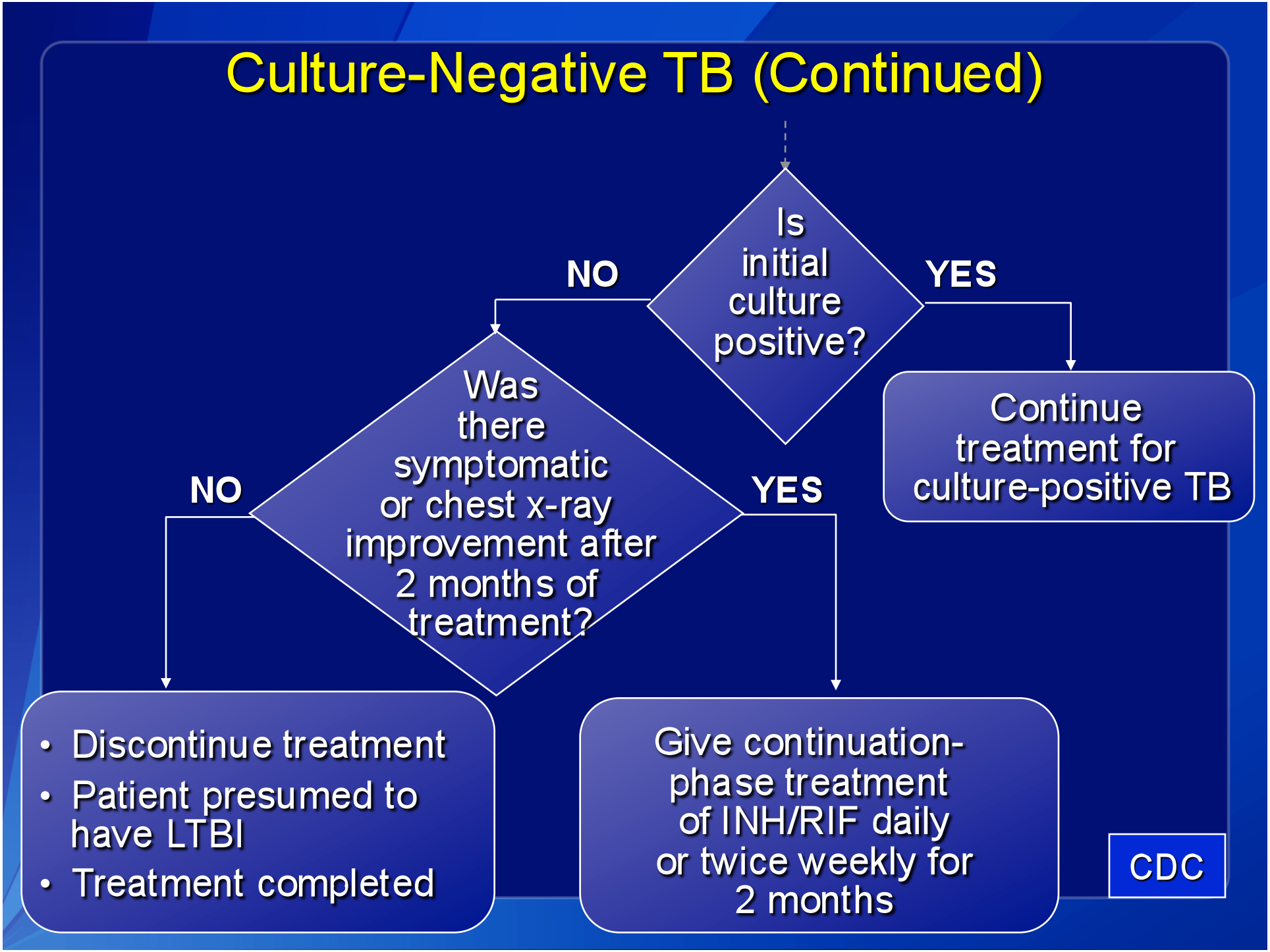
- Abnormal chest x-ray
- Clinical symptoms
- No other diagnosis
- Positive tuberculin skin test

Patient placed on initial phase regimen:
INH, RIF, EMB, PZA for 2 months



CDC

Culture-Negative TB (Continued)



Treatment Interruption

- Can be due to drug toxicity
- Can be due to patient non-adherence
- Most important to try to achieve continuous treatment in initial phase

  - lessens chance of resistance

Treatment Interruption – Initial Phase

- Interruption ≥ 14 days
  - Restart at beginning of initial phase
- Interruption < 14 days
  - continue to completion
- Important to get all initial phase doses done within 3 months

Interruption – Continuation Phase

- 80% or more of doses given
  - if initial smear negative, may stop tx
  - if initial smear +, continue therapy

Interruption – Continuation Phase

- Less than 80% of doses given
  - if possible repeat smear & culture
  - if interruption < 3 mos, continue tx
  - if interruption > 3mos, restart from initial phase
  - if repeat culture +, use 4 drugs until susceptibility returns

Treatment Monitoring

- Monthly sputum until 2 consecutive cultures negative
- Drug-susceptibility tests if culture-positive after 3 months of Rx
- Monthly visits to assess adherence and adverse reactions
  - LFT's, CBC, Vision

- Repeat chest x-ray:
  -At completion of initial treatment phase for patients with initial negative cultures
  -At end of treatment for patients with culture-negative TB
  -Generally not necessary for patients with culture positive TB

Treatment Monitoring

- Renal function, AST, ALT, bilirubin, and platelet count if abnormalities at baseline
- Visual acuity and color vision monthly if EMB used > 2 months or doses > 15-20 mg/kg

Common Adverse Reactions to Drug Treatment (1)

Caused by	Adverse Reaction	Signs and Symptoms
Any drug	Allergy	Skin rash
Ethambutol	Eye damage	Blurred or changed vision Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea Vomiting Yellowish skin or eyes Dark urine

Common Adverse Reactions to Drug Treatment (2)

Caused by	Adverse Reaction	Signs and Symptoms
Isoniazid	Peripheral neuropathy	Tingling sensation in hands and feet
Pyrazinamide	Gastrointestinal intolerance	Upset stomach, vomiting, lack of appetite
	Arthralgia	Joint aches
	Arthritis	Increased Uric Acid, Gout (rare)
Streptomycin	Ear damage	Balance problems
		Hearing loss
		Ringing in the ears
	Kidney damage	Abnormal kidney function test results

Common Adverse Reactions to Drug Treatment (3)

Caused by	Adverse Reaction	Signs and Symptoms
Rifamycins • Rifabutin • Rifapentine • Rifampin	Thrombocytopenia	Easy bruising Slow blood clotting
	Gastrointestinal intolerance	Upset stomach
	Drug interactions	Interferes with certain medications, such as methadone, and HIV protease inhibitors
	Orange discoloration	Urine, sweat, tears, contact lenses
	Photosensitivity	

Toxicity Related Interruption - Hepatic

- Stop all drugs if:
  - Clinical evidence of hepatitis not due to other causes
  - LFT's > 3X ULN with symptoms
  - LFT's > 5X ULN without symptoms

Toxicity Related Interruption - Hepatic

- If severe TB, continue treatment with aminoglycoside, quinolone, EMB
- Otherwise, when sx's/labs improve
  - Add RIF +/- EMB
  - if tolerates, then add INH
  - if tolerates and toxicity was not severe can add PZA

Toxicity Related Interruption – Rash or Fever

- Exclude other causes
- Stop all drugs
- If severe TB, alternative tx as in hepatic
- Once rash or fever better, restart 1 drug every 3 days

Special Treatment Situations

HIV/AIDS

- Treatment for HIV-positive patients same as for HIV-negative patients, except

  1) Once-weekly INH-rifapentine in continuation phase is contraindicated in HIV-positive patients
  2) Twice-weekly INH-RIF or INH-rifabutin should not be used in patients with CD4+ counts < 100

- Every effort should be made to use a rifamycin-based regimen for the entire course of therapy (unless patient is on a protease inhibitor)

- Rifabutin has interaction than RIF

HIV/AIDS

- When to start anti-HIV and anti-TB
- Risk of immune reconstitution syndrome
- Generally start TB therapy first
- Anti-HIV can be started 2-8 weeks later

HIV/AIDS

- CAMELIA – CD4 < 200
  - 2 vs 8 weeks post starting TB therapy
  - Early group mortality 18% vs. 27%
- ACTG A5221 – CD4 < 250
  - 2 vs. 8-12 weeks post starting TB rx
  - Subgroup with CD4 < 50 had lower mortality and less new AIDS illness

NEJM, October 20, 2011

HIV/AIDS

- SAPIT – CD4 < 500

  - 4 weeks post start of TB therapy vs. week 8-12

  - CD4 <50 had mortality benefit with early ART (but with > IRIS)

Children and Adolescents

- Use DOT
- Treat young children (<5 years old) with three (rather than four) drugs in initial phase (i.e., INH, RIF, and PZA)
- EMB not recommended unless increased likelihood of INH resistance or diagnosis of adult-like TB
- Thrice-weekly therapy not recommended

Extrapulmonary TB

- Similar treatment regimen for pulmonary TB, except for TB of the CNS, bone or joint; length of therapy is 9-12 months
- Corticosteroids used as adjunctive therapy for patients with TB meningitis and pericarditis
- If PZA cannot be used in the initial phase, continuation phase must be increased to 7 months

Pregnancy and Breastfeeding

- Initial phase treatment regimen should consist of INH, RIF, and EMB
- SM contraindicated & PZA teratogenicity unknown so not recommended for pregnant women
- If PZA not used, use 6 month continuation phase
- Add pyridoxine if using INH

Renal Insufficiency and End-Stage Renal Disease

- Dosage should not be decreased because peak serum concentrations may be too low; smaller doses may decrease drug efficacy
- Dosing interval of drugs could be increased
- Most drugs can be given 3 times weekly after hemodialysis; for some drugs, dose must be adjusted

Hepatic Disease

- Recommended regimens:

1) Treatment without PZA
   Initial phase (2 months): INH, RIF, and EMB
   Continuation phase (7 months): INH and RIF

2) Treatment without INH
   Initial phase (2 months): RIF, PZA, and EMB
   Continuation phase (4 months): RIF, PZA and EMB

Hepatic Disease

- Recommended regimens: (continued)

  3) Regimens with only one potentially hepatotoxic drug
     - RIF should be retained
     - Duration of treatment is 12-18 months

  4) Regimens with no potentially hepatotoxic drugs
     - Duration of treatment is 18-24 months

MDR TB

- Resistant to INH and RIF
- ~ 5% of TB cases in 2010
- Haiti had 41 new MDR cases in 2010 per WHO
- Drugs that can be used are less effective and are more likely to cause adverse reactions
- Treatment can last 2 years or more
- Surgery is sometimes use to remove infected site

MDR TB Risk Factors

- No response to appropriate therapy
- Patient previously treated for TB
- Close contact of patient with MDR TB
- Pt treated w/ multiple course of quinolones for CAP found to be TB
- Patient from high endemic areas

MDR TB Treatment

- If possible, should be guided by cultures
- Empiric therapy if suspect MDR
  - Standard 4 agents plus ≥ 2 other meds
- When get susceptibilities, stop resistant meds and add aminoglycoside and quinolone to remaining drugs
- Need to treat with 4 effective agents
- Treat for at least 18-24 months

MDR TB

- Surgery considered if:
  - Localized pulmonary TB
  - Lack of improvement with drugs
  - Highly resistant strain
- Give meds for 1 to 3 months pre-op
- Continue meds for 18 months post-op

XDR TB

- XDR TB is resistant to INH, RIF, all fluoroquinolones, and at least one injectable second-line drug (e.g., amikacin, kanamycin, or capreomycin)
- XDR TB patients have less effective treatment options
- XDR TB is very difficult to treat
- Consult with an expert

XDR TB Agents

- Cycloserine or other serine analogues
- Thionamides
- Para-aminosalicylic acid
- Capreomycin
- Amikacin, kanamycin
- Linezolid
- Amoxicillin-clavulanate
- Clarithromycin
- Meropenem
- Clofazimine

References

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