



# Treatment of Tuberculosis Disease

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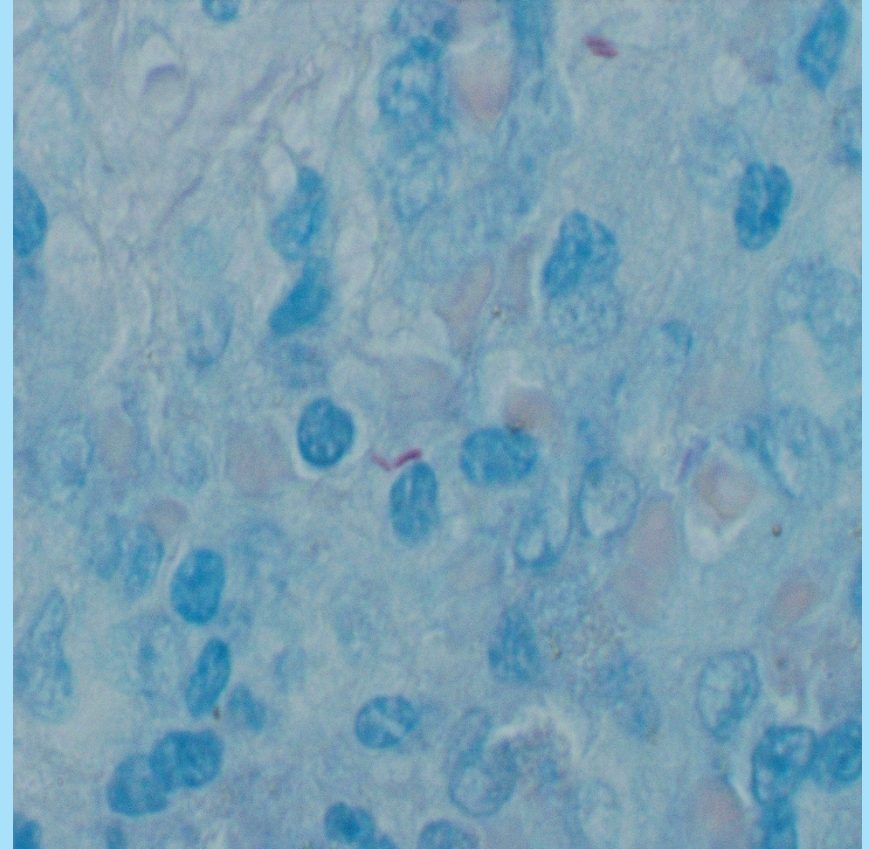
# Treatment of Tuberculosis

## Some Highlights of Most Recent Update

- The provider has primary responsibility
- Recommendations ranked by supporting evidence and strength
- Extend treatment for those with cavitation on cx-ray and (+) sputum cultures at 2 months
- Treatment completion defined by # of doses ingested as well as duration of therapy
- Guidelines for extrapulmonary disease  
(E-P TB increasing with shift to majority non-US-born cases)



# Decision to Treat





# Initiation of Therapy – 1

- **Treatment generally precedes definitive TB diagnosis (TB suspect)**
- **Treatment decision based on:**
  - Epidemiologic information
  - Clinical, pathological, radiographic findings
  - Results of microscopy, culture
- **Overcome unnecessary delays:**
  - Improved clinical acumen in diagnosis
  - Rapid diagnostic tests – nucleic acid amplification (NAA)
  - Early empiric therapy

*Am J Med* 1990; 89: 451-456

*Archives of Internal Medicine* 1994;154: 306-310



## Initiation of Therapy - 2

- Do not delay treatment waiting for smear and culture results in ill patients
- Absence of AFB on smear or granulomas on biopsy does not rule out TB, nor does negative TB culture (20% are culture-neg cases)
- TST is negative in 25% of active cases; IGRA test may also be false-negative



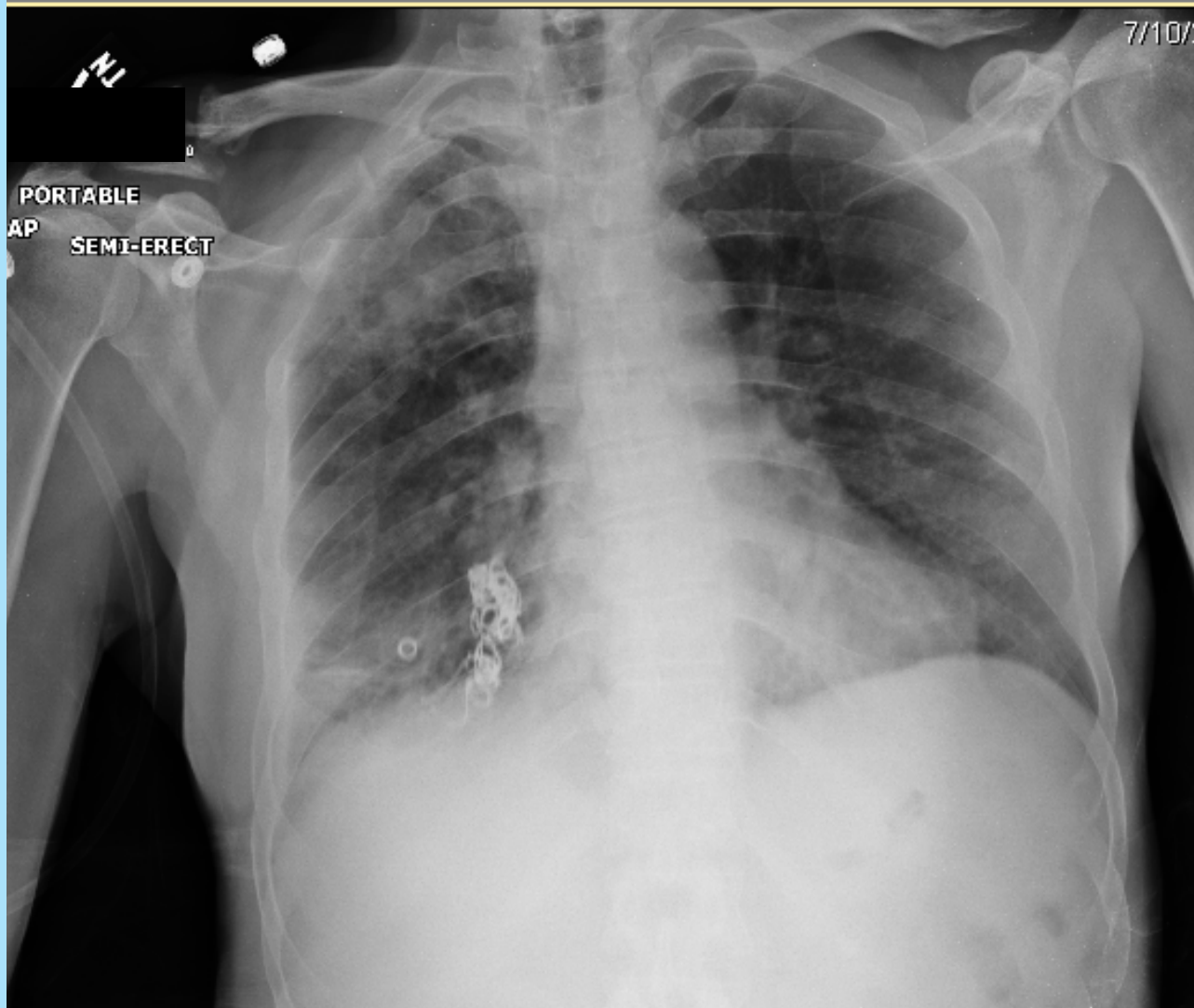


## Case Example – 1

- **6/22/10 - 52 yo Indian male presents to ED**  
**US x 2 yrs**  
**Alcoholic**  
  
**c/o shortness of breath, cough x 3 weeks,**  
**2 episodes of **hemoptysis****  
**Fever, chills, night sweats**  
**Anorexia, wt. loss 15 lbs.**
- **6/22/10 - Chest x-ray: **RUL** cavitary infiltrate c/w TB**



# Case Example - 2





## Case Example – 3

- 6/24, 25, 26      Sputum AFB smear (-)
- 6/24              ↑WBC, 16% M; ESR 61 mm/hr
- 6/25              TST (+) 17 mm
- 6/28              IGRA (-)
- 6/30              Bronchoscopy AFB smear (+)  
                         PCR (+)





# Estimated TB Burden

Global figures	Global estimates	US rank – Country of origin	# of new cases
<b>India</b>	<b>2,000,000</b>	1. Mexico	1,539
<b>Philippines</b>	<b>260,000</b>	2. Philippines	738
<b>Vietnam</b>	<b>180,000</b>	<b>3. India</b>	<b>877</b>
		4. Vietnam	518

WHO. *Global Tuberculosis Control*. WHO Report. 2010

CDC. *Trends in Tuberculosis --- United States, 2010*. MMWR 60 (11) 333-337



# Antituberculosis Agents

## First-Line Drugs

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- Rifabutin\* (RBT)
- Rifapentine (RPT)

## Second-Line Drugs

- Streptomycin (SM)
- Cycloserine (CS)
- p-Aminosalicylic acid (PAS)
- Ethionamide (ETA)
- Amikacin, kanamycin\*(AK, KM)
- Capreomycin (CM)
- Levofloxacin\* (LFX)
- Moxifloxacin\* (MOX)

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\* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB.



# Ratings – Guides to almost everything in the modern world

- **Electronics (energy saver)**
- **Films (PG, PG-13, R)**
- **Animal friendly ("No Animals Were Harmed"®)**



- **~1994: Infectious Disease/USPHS guidelines using ratings to help guide choices of therapies**



# Rating System – TB Regimens

## Part 1 (of 2)

### Strength of the recommendation

- A. Preferred, should generally be offered**
- B. Alternative; acceptable to offer**
- C. Offer when preferred or alternative cannot be offered**
- D. Should generally not be offered**
- E. Should never be offered**



# Rating System – TB Regimens Part 2 (of 2)

## Quality of supporting evidence

- I. At least one properly randomized trial with clinical end points
- II. Clinical trials that were either not randomized or were conducted in other populations
- III. **Expert opinion**





# Initial Regimens: Principles

- **4 currently recommended; similar outline**
  - Initial phase of 2 months
  - Continuation phase of 4 or 7 months
- **9 months total for**
  - Pulmonary cases with cavitation and culture (+) at 2 months (continuation phase, 7 mos.)
  - Persons unable to take PZA in initial phase
- **Caveats for HIV-infected persons**
  - RPT-containing regimens not advised
  - Thrice weekly RIF/RBT-containing regimens for patients with  $<100$  CD4+ cells (not 2x/wk)



# Anticipate Drug-Drug Interactions

- **Rifabutin/Rifampin considerations**

- Patients on drugs with potential for reduced activity
  - Patients on high dose methadone (withdrawal)
  - Corticosteroids, oral contraceptives, beta-blockers
- Dosage of Rifabutin (300 mg) = Rifampin 600 mg
  - RBT may cause less gastritis, hepatotoxicity

- **INH/RIF interactions with psychiatric drugs**

- Valproic acid (Depakoate<sup>®</sup>), oxcarbazepine (Trileptal<sup>®</sup>)



# Case Example: Rifamycin – steroid interaction – 1

- **50 yo Haitian female identified as a contact of case (spouse) with pan-sensitive TB**
- **h/o diagnosis of vasculitic renal disease, with renal failure 2009: treated with methylphenalate (Cell-Sept<sup>®</sup>) and Prednisone; currently on steroid taper**
- **(+) TST, abnormal chest x-ray**
- **Asymptomatic**



## Case Example: Rifamycin – steroid interaction – 2

- **RIPE begun; observe for steroid withdrawal**
- **Rifampin changed to Rifabutin to decrease interaction with steroid**
- **10 days later, severe headache, nausea, muscle aches, dizziness**
- **LFTs normal**
- **RBT d/c: symptoms resolved**



# Initial Regimen: 4 drugs

- **RIF, INH, PZA, EMB (“RIPE”) standard regimen**
- **PZA omitted in most pregnant females in USA, in persons with gout, severe liver disease (some experts advise caution with elderly)**
- **Combination of drugs needed over sufficient time**
  - To kill the TB bacilli rapidly (INH>EMB>RIF)
  - To prevent the emergence of drug resistance
  - To eliminate persistent bacilli to prevent relapse or failure





# Routine Examinations at Start of Treatment

- **Weight (doses calculated on mg/kg basis)**
  - Rifampin 450 mg for weight < 50 kg (110 lbs.)
- **HIV testing**
- **Baseline lab tests, at a minimum:**
  - Liver function tests (AST, ALT, alk phos and bilirubin)
  - Creatinine
  - Platelets



# Regimens for Culture (+) TB

**(refer to table in handout)**



# Adjunctive Therapy – 1

## Corticosteroids

- **Used for suppression of inflammatory phenomena**
  - When negative effects of inflammation operative, such as fluid expansion into closed space
  - May involve hypersensitivity to tuberculo-protein
- **“...it is the final judgment of treating physician to decide indications, duration and dosages”<sup>1</sup>....  
(of corticosteroids)**

<sup>1</sup>*Tuberculosis: A Comprehensive Clinical Reference.* H.Schaaf & A. Zumla, eds. Saunders. 2009, p. 671



# Monitoring during TB Treatment

**Monthly visits should include a brief physical exam and a review for:**

- Adherence
- Adverse drug reactions
- Use of alcohol and other potential hepatotoxins
- Follow up testing (sputum, LFTs, renal function, platelet count, visual acuity/color, x-rays)
- Drug susceptibility testing if culture (+) 3-4 months



# DOT Impact on Completion Rates

- **Non-supervised therapy (n=9) 61%**
- **Modified DOT (n=2) 79%**
- **DOT (n=4) 86%**
- **Enhanced DOT (n=12) 91%**

**DOT = Directly Observed Therapy**  
**Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized**  
**Enhanced DOT = Individualized incentives & enablers were provided in addition to DOT**





DOT: 7 days vs. 5 days per week?

**(see demonstration)**



# Special Treatment Situations

- **Special issues in E-P disease**
- **Paradoxical reaction (IRIS)**
- **Pregnancy**
- **Renal and hepatic disease**
- **Diabetes**
- **TNF-alpha inhibitors**

**(Other lectures to follow on drug toxicities, adherence, children, HIV, MDR-TB)**



# Extrapulmonary (EP) TB

- **Of 11,545 cases (US, 2009)**
  - 69 % pulmonary only
  - 21 % EP only
  - 9 % pulmonary & EP

<u>Site of disease</u>	<u>% cases</u>
Lymphatic	45%
Pleural	19%
Bone & Joint	10%
Peritoneal	6%
Genitourinary	6%
Meningeal	6%
Other	8%

<http://www.cdc.gov/tb/statistics/default.htm>



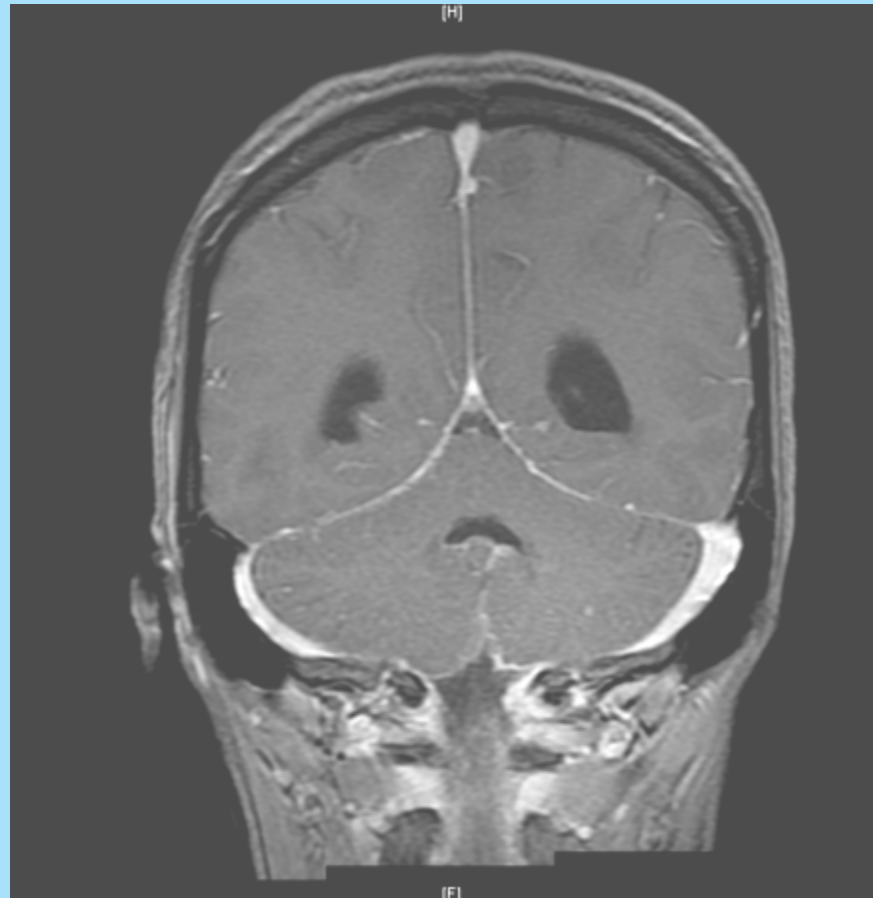
# Management of Extrapulmonary TB cases

- **Consult textbooks, guidelines, and experts<sup>1</sup>**
- **Do thorough literature review**
- **Interventions may be life-saving, especially in**
  - Central nervous system TB
  - Pericardial TB
  - Miliary TB, septic form

<sup>1</sup>Regional Training and Medical Consultation Centers (RTMCCs); National Jewish Medical Research Center; State medical consultants, other experts



# Central Nervous System TB: TB Meningitis - 1







# TB Meningitis – 2

- **Need CSF penetrating agents**
  - Good: INH, PZA
  - Less good: RIF, EMB
  - Consider available parenteral forms
- **Follow up imaging; prefer MRI (more sensitive)**
  - Ventricular enlargement may require shunting
  - Watch for development of tuberculomas on Rx



# TB Meningitis – 3

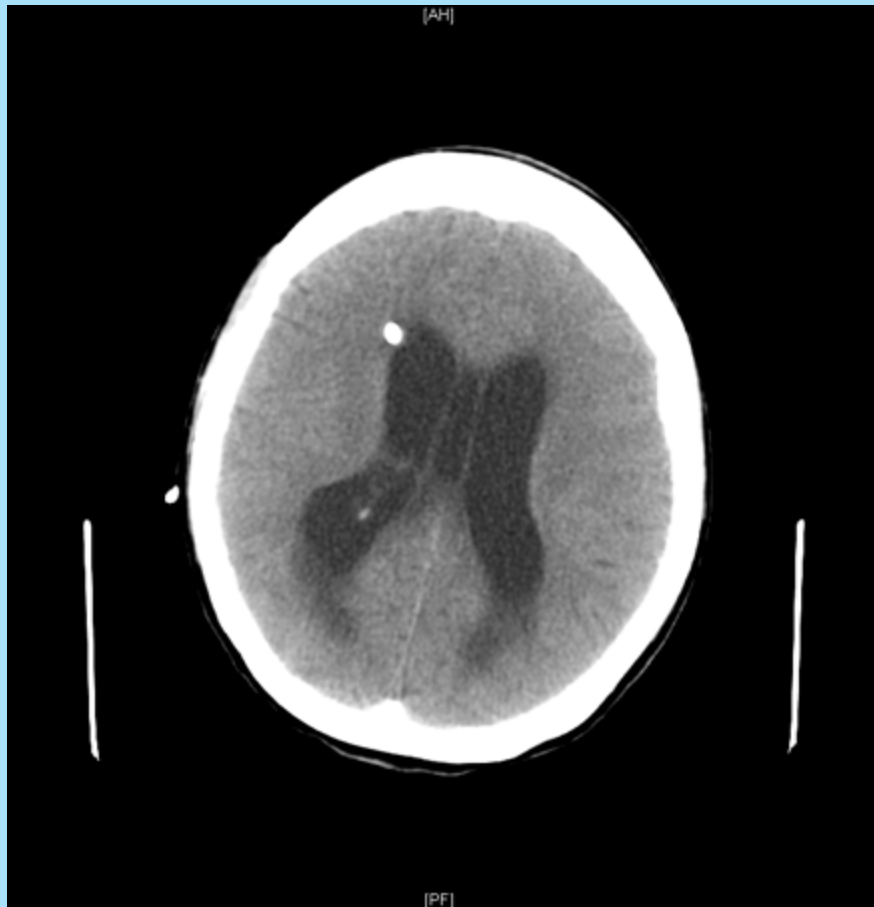
- **Adjunctive steroids**

- Limitations of studies (no large randomized controlled studies containing RIF); expert opinion
- Dexamethasone 12 mg/day x 3 weeks, followed by taper over 3 weeks
- Rifampin/steroid drug-drug interactions



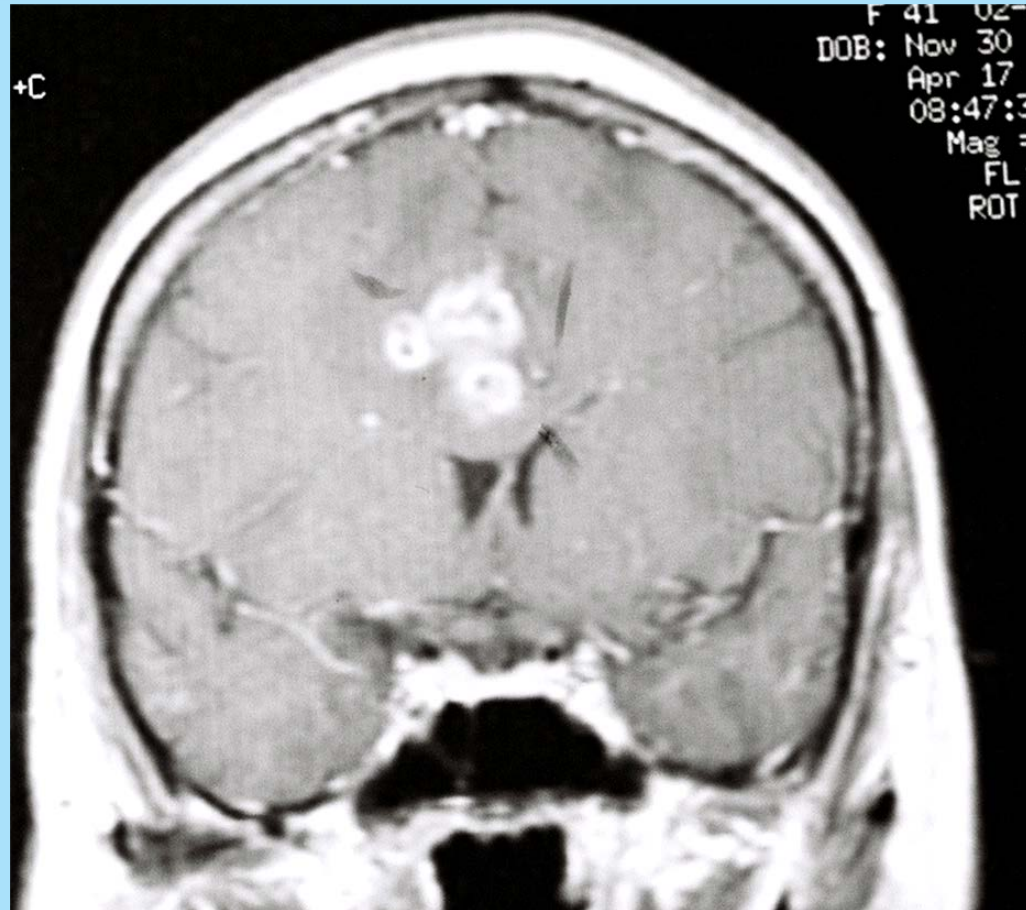
# TB Meningitis - 4

## Ventricular Shunting for Hydrocephalus





# CNS Tuberculoma





# Central Nervous System TB: Tuberculoma

- **Additional barrier for drugs to penetrate**
- **Maximize drug and steroid therapy**
- **Decisions:**
  - Surgical option?
  - Length of therapy?



# Lymphatic TB

- **Mass effect may be great if multiple nodes**
- **Excisional biopsy preferable**
- **Nodes often increase in size (IRIS) while on therapy, while biopsies culture-negative (not a failure)**
- **Longer treatment sometimes necessary**
  - Subset of patients with complicated courses
  - Evidence of LN response lagging TB at other sites





# Paradoxical Reaction – 1

- **Temporary exacerbation of symptoms, signs, or radiographic manifestations of TB after beginning anti-TB treatment**
  - High fevers
  - Esp. increase in size of lymph nodes/new lymph nodes
  - Worsening of infiltrates or pleural effusions
  - Expanding central nervous system lesions
- **Can occur in apparently immunocompetent persons, but more common among HIV-infected on highly active anti-retroviral therapy (HAART)**





# Paradoxical Reaction – 2 Enlargement of TB Lymph Nodes





# Paradoxical Reaction – 3 Treatment

- **Evaluate if other cause or Rx failure**
- **Mild – moderate:**
  - No change in anti-TB therapy
  - Symptomatic treatment: non-steroidal anti-inflammatory drugs (NSAIDs)
- **Severe**
  - May include airway compromise, sepsis syndrome
  - Prednisone 1 mg/kg, with taper after few weeks

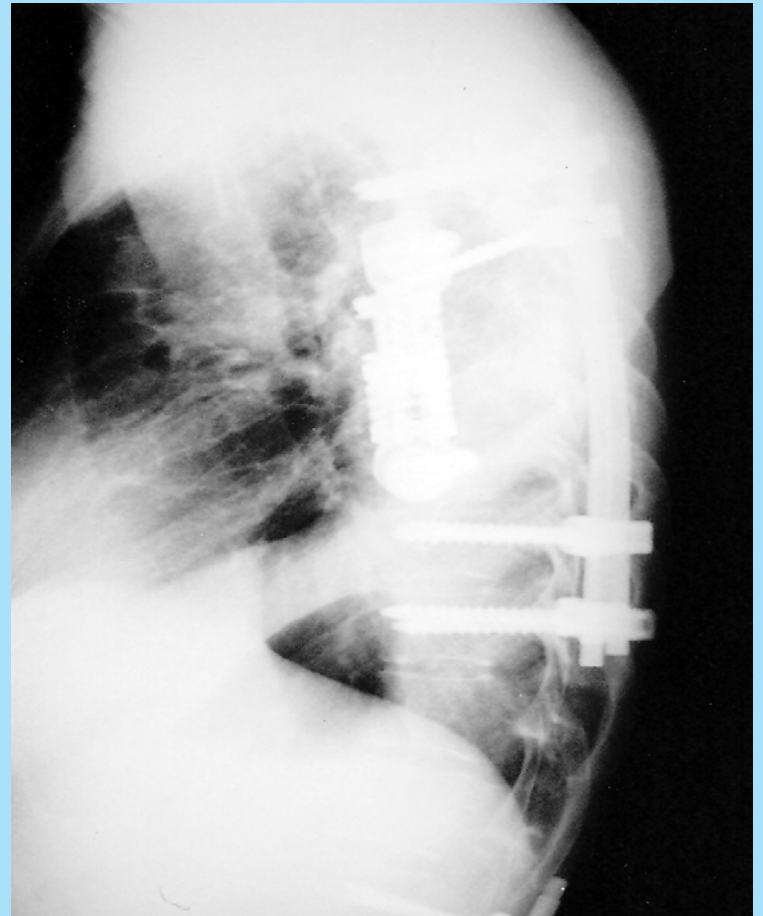
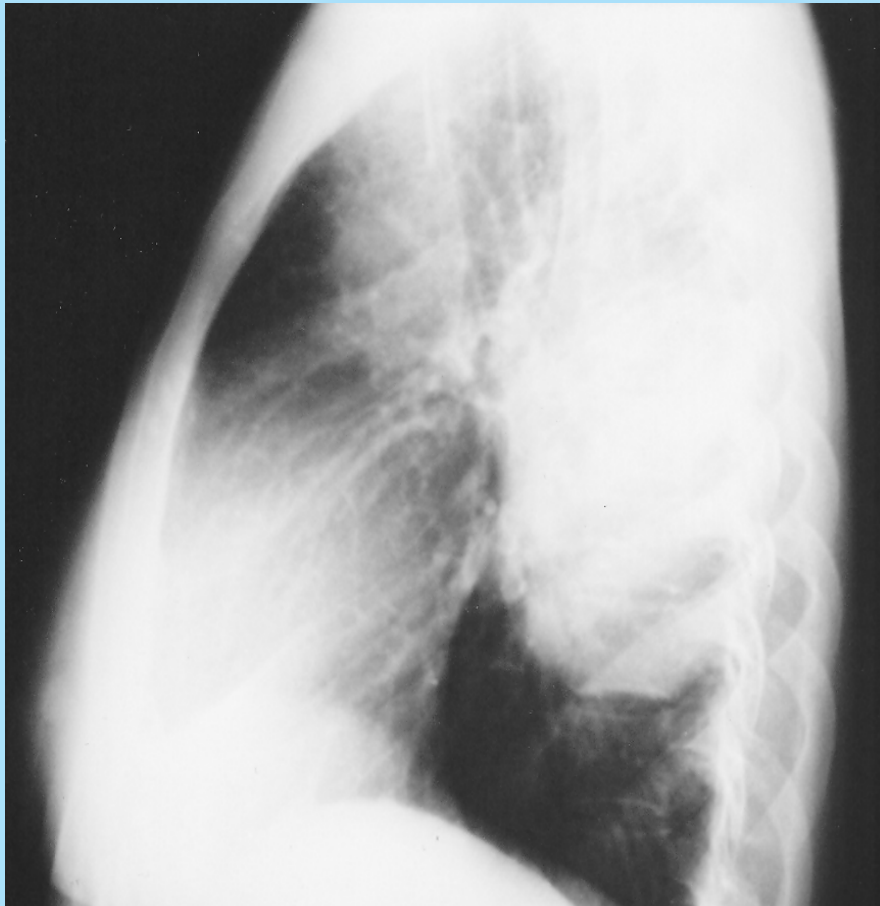


# Bone & Joint TB

- **Increasing in frequency: ~ 3-4% of all TB cases**
- **Serious forms affect mobility**
- **Vertebral most common**
  - Lumbar > thoracic; cervical rare; difficult to diagnose
  - Paraspinal abscesses common (Pott's disease)
  - Immediate and ongoing evaluation for neurologic deficits



# Vertebral TB with Paraspinal Abscess





# Extrapulmonary TB

## Other examples

**Pericardial**

**Corticosteroids indicated; monitoring, ECHO to r/o constriction; may require pericardiectomy**

**Peritoneal**

**May get false (+) CA-125: repeat test on or after TB Rx; steroid role unclear;**

**Pleural**

**Collect sputum even when no parenchymal infiltrate; yield high**

**Genitourinary  
(male)**

**Urology consult; image entire GU tract during Rx; monitor bladder symptoms**

**Genitourinary  
(female)**

**Major cause of infertility in women from high prevalence countries; do bx**



# Liver disease and TB – 1

- **Alcoholism most frequent underlying cause; chronic Hepatitis B or C; autoimmune**
- **Consider liver-sparing agents: EMB, FQN<sup>1</sup>, injectables, cycloserine (therapy duration extended)**

<sup>1</sup> *occasionally hepatotoxic*





## Liver Disease and TB - 2

- **Tolerate enzyme elevations to 5x upper limit of normal (ULN) if no GI symptoms**
- **Alcohol program often needed post hospital discharge**
- **Question arises for DOT worker of whether to give doses of TB meds if patient acutely intoxicated?**





# TB in Pregnancy

- **Treatment for TB is compatible with pregnancy**
- **If TB suspected pre-natally**
  - Expedite mother's diagnosis
  - Immediate treatment if active disease
  - Make preparations for examination of placenta after delivery for: pathology, AFB stains/cultures
  - Alert pediatrician to consider possible transplacental spread to infant
- **Watch for post-partum hepatotoxicity**



# Diabetes and TB - 1

- **Diabetes control more difficult with active TB, may improve as TB treated**
- **Low Rifampin in Type 2 diabetics; consider levels<sup>1</sup>**
- **Use insulin if necessary<sup>2</sup>**
- **Do not use Pioglitazone (Actos<sup>®</sup>) if ALT >2.5x nl<sup>3</sup>**

<sup>1</sup> *Clin Inf Dis.* 2006; 43:848-854

<sup>2</sup> Tuberculosis and Diabetes. *Frances J. Curry National Tuberculosis Center.* Webinar, Dec 10, 2009. (internet access next slide)

<sup>3</sup> City Health Information. *NYCDOHMH*, May/June 2010, p. 21 (access via [nyc.gov](http://nyc.gov), [DOHMH](http://DOHMH), diabetes)



# Diabetes and TB - 2

- **Summary of recent data in diabetics with TB<sup>1</sup>:**
  - delayed sputum conversion
  - higher incidence of relapse
  - greater mortality rate
- **Consider extending treatment to 9 months**

<sup>1</sup> Dean Schillinger and Gisela Schecter. Tuberculosis and Diabetes. *Frances J. Curry National Tuberculosis Center, Webinar Dec. 10, 2009. Access via [http://www.nationaltbcenter.ucsf.edu/training/arch\\_tbdm.cfm](http://www.nationaltbcenter.ucsf.edu/training/arch_tbdm.cfm).*



# Renal Disease

- **Adjustment for creatinine clearance < 30 ml/min**
  - ↑ dosing interval of renally excreted drugs (or those with renally-excreted metabolites) rather than dosage
  - No adjustment for INH & RIF
  - Lengthen interval for EMB & PZA (generally TIW)
  - If on dialysis, dose at completion of session
- **Anti-rejection agent/rifampin interactions in renal transplant patients;**
  - Cyclosporine (do levels); tacrolimus
  - Prefer rifabutin for less drug-drug interaction



# Creatinine Clearance ( $Cl_{cr}$ ) Formula

$$\frac{(140 - \text{age}) \times \text{weight in kg}}{\text{serum creatinine} \times 72}$$

**Note: for females, multiply result by 0.85**

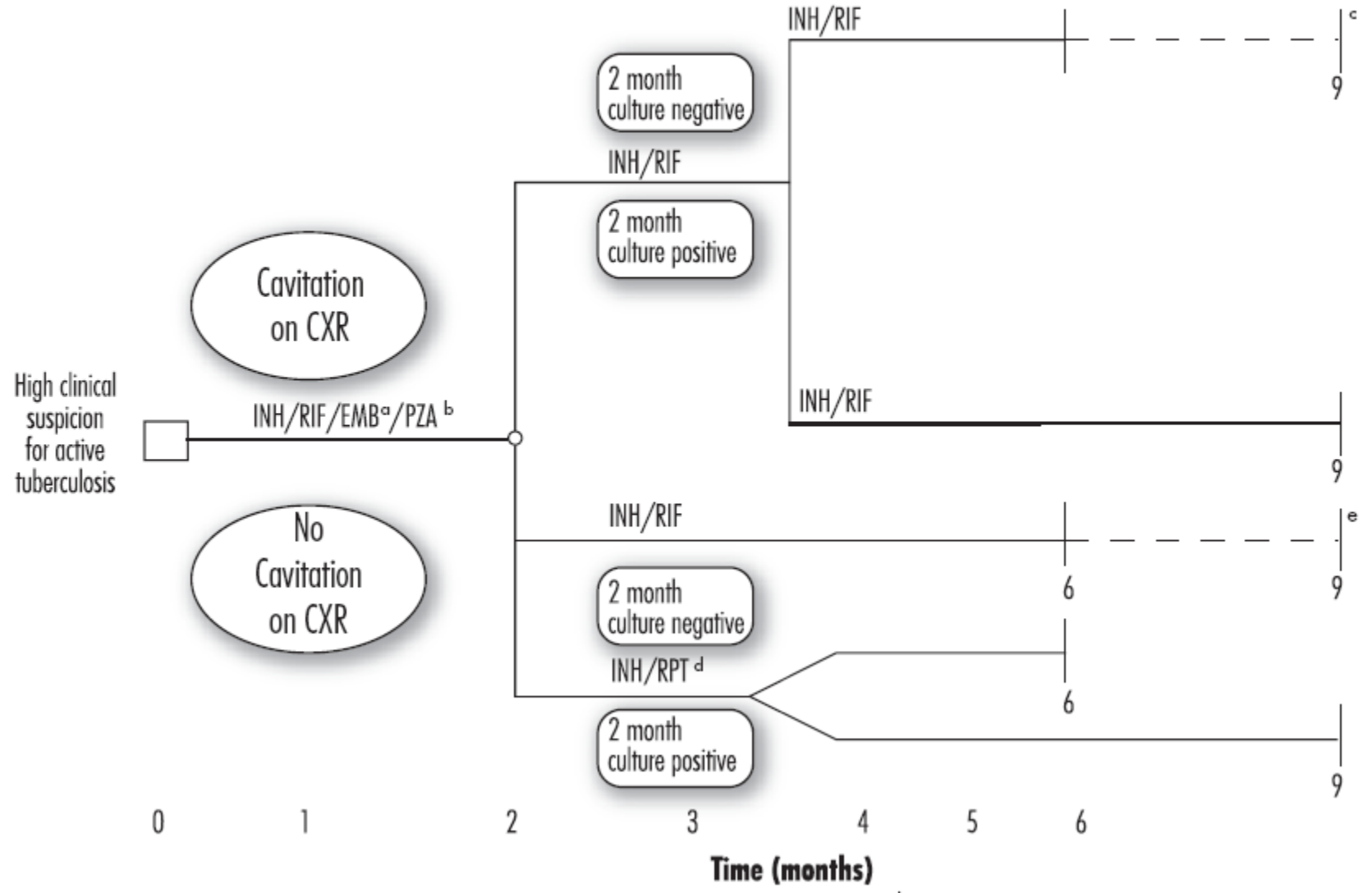


# TB in Patients on TNF-a Antagonists

- **Infliximab (Remicade<sup>®</sup>), Etanercept (Enbrel<sup>®</sup>), Adalimumab (Humira<sup>®</sup>), etc. used in rheumatoid arthritis, Crohn's disease, psoriasis, other conditions**
- **Inhibit or reverse granuloma formation**
  - Resultant TB often fulminant, disseminated
  - Early empiric therapy may be life-saving
- **Collaborate with rheumatologist on management**
  - Choice of alternate therapies
  - Re-introduction of TNF-a inhibitor?



# TREATMENT OF TUBERCULOSIS







# Rationale for Extending Continuation Phase:

## Relapse Rates – 6 months Rx

**Cavitary disease AND  
culture (+) at 2 mos**

**22% relapse**

**Non-cavitary disease,  
culture (-) at 2 months**

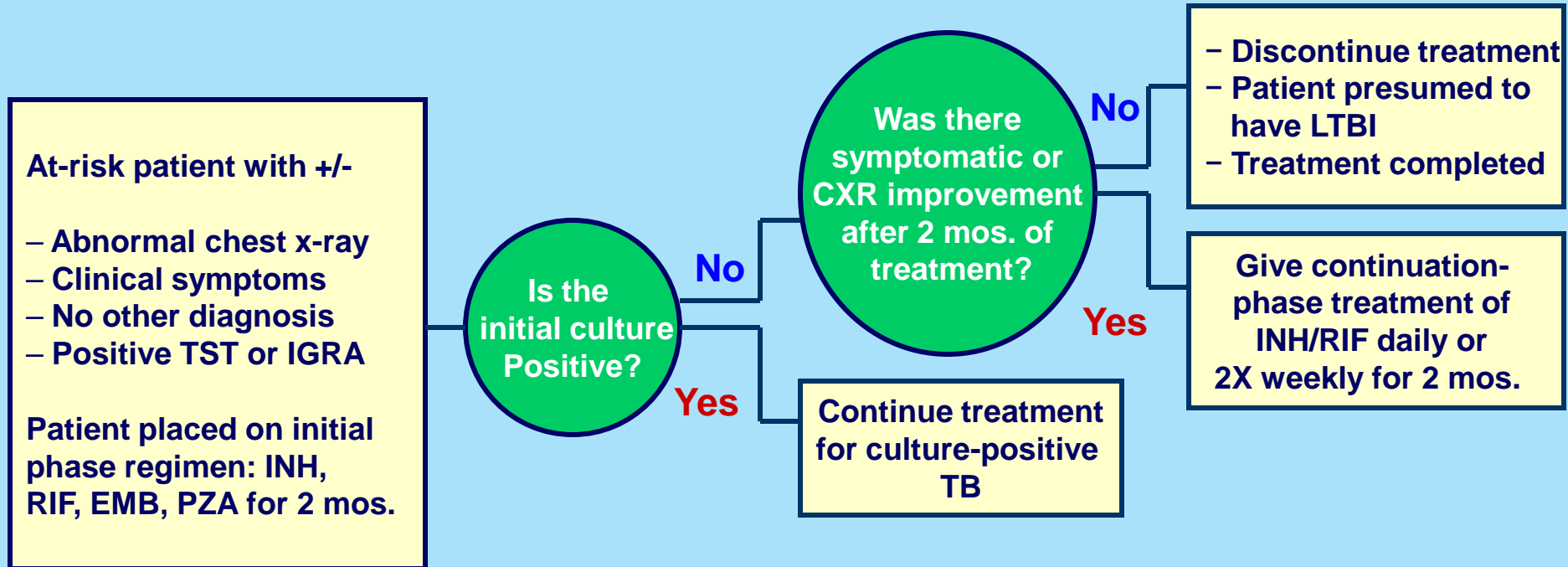
**2% relapse**

### **Note**

**5-6% relapse if either present**



# Algorithm to Guide Treatment of Culture-Negative TB





# Therapy Deviations

- **Avoid split dosing of first-line agents**
- **Analyze treatment interruptions**
  - Timing in course
  - Duration of interruption
  - Bacillary load at time of interruption (smear status)



# Therapy Deviations

- **Modify for drug toxicities**

- Follow regimens for drug-resistance<sup>1</sup>
- May affect duration of therapy
- Examples:
  - Loss of INH: 6-9 months; consider addition of FQN
  - Loss of RIF: add FQN; 12-18 months;  
consider injectable if extensive disease

<sup>1</sup>Francis J. Curry National Tuberculosis Center. *Drug Resistant Tuberculosis: A Survival Guide for Clinicians*. 2<sup>nd</sup> ed. 2008, p.34..



# Completion of Therapy Defined – 1

- **Completion of treatment primarily defined by number of ingested doses within specified time frame (not solely on duration of therapy)**
- **For example:**
  1. 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
  2. 6-month daily regimen (5 days/wk) = at least 130 doses



# Completion of Therapy Defined – 2

- **In cases of drug toxicity or non-adherence to regimen, all specified number of doses must be administered within:**
  - 3 months for initial phase
  - 6 months for 4-month continuation phase
- **If the specified number of doses are not administered within the targeted time period, patient is considered to have interrupted therapy**



# Continuation Phase Treatment Interruptions

- **If patient has received  $\geq 80\%$  of total doses:**
  - Consider bacillary load at time of interruption to decide if additional treatment needed (smear + or smear - ?)
- **If patient has received  $< 80\%$  of total doses:**
  - Consider duration of lapse and ability to complete full four months of Rx within 6 months time





# Rx Interruption Example – 1

- **12/20 19 yo dx TB meningitis in California**
- **1/02 Discharged with 7d supply RIPE & steroids**
- **1/07 No show clinic appointment**
- **1/16 Adm. to NJ hospital, altered mental status**

**Q – Continue treating? Restart?**



# Rx Interruption Example - 2

- **Time of interruption: initial phase (first 2 mos)**
- **Duration of interruption: (~8 days? - ~15 days?)**
- **Guidelines:**
  - If lapse  $>14$  days, restart from beginning
  - If lapse  $<14$  days, continue treatment to complete total doses warranted (if it can be completed within 3 months)
- **In this case, consequence of interruption can be serious; restart treatment**



# Relapse & Treatment Failure

- Relapse is defined as clinical deterioration or reversion to positive culture after treatment completion
- Treatment failure is defined as positive cultures after 4 months of treatment in patients for whom medication ingestion was ensured (by DOT)



# Role for Vitamin D?

- **Background:**

- Vitamin D used to treat TB in pre-antibiotic era
- Studies in humans showed enhanced macrophage microbicidal activity *in vitro*<sup>1</sup>

- **Contacts, Pakistan (n=128)**

- low vitamin D levels associated with 5-fold risk to TB progression<sup>2</sup>

- **Vitamin D supplementation during treatment controversial**

- Studies with conflicting results

<sup>1</sup> *Amer. Rev. Resp Dis.* 1989; 138: 768-770.

<sup>2</sup> Vitamin D deficiency and Tuberculosis Progression. *Emerging Infectious Diseases.* 2010; 16.



Reminder: treat a patient with TB,  
not just the disease

