Our Favorite TB Issues

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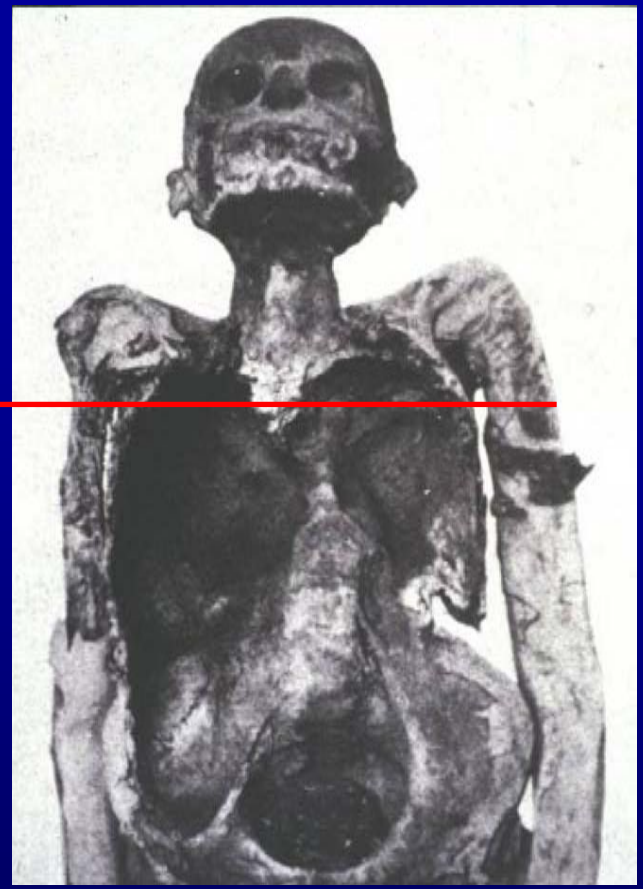
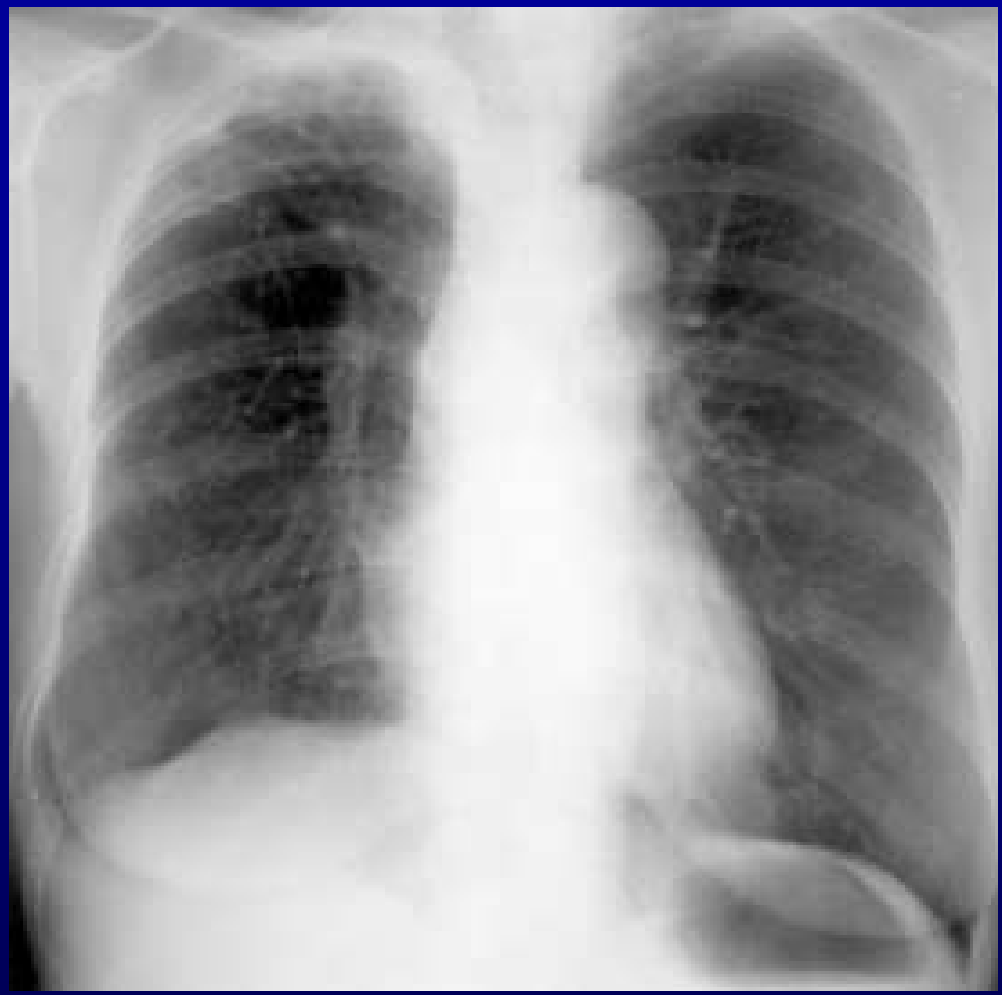
TB: Major Cause of Suffering and Death



- First human case 3400 BC
- Consumption, White Plague, scrofula, King's Evil, pthisis
- England 1815: 1 in 4 deaths
- France 1918: 1 in 6 deaths
- During 20thC, TB killed ~100 million
- Currently, 8.8 million cases and 2 million deaths each year

Case 1: Patient with TB Risk with Abnormal CXR

- 71W referred to your outpatient clinic for evaluation for active TB
- She immigrated from Botswana 1 mo ago
  - No symptoms of TB
  - No h/o of TB or significant PMH
- TST 13 mm (no previous TST)
- Abnormal CXR



Right upper lobe fibronodular opacities with volume loss and hilar retraction. Right apical pleural thickening.

Q1. Will an IGRA help you diagnose TB?

Sensitivity of IGRAs in Active TB: Independent Studies

- Pooled study data
  - QFT-G 55-88% (weighted pooled mean 75%), TST 77%[1], TSpot 83-97%, QFT-G 70-89%[2])
- Comparison TSpot vs QFT-G in S. Korea[3]
  - TSpot 96.6%, QFT-G 70.1%, TST 66.7%
- Conclusion: IGRAs should not be used to exclude active TB
  - Sensitivity in question for extra-pulmonary TB[4]

1. Pai and Menzies, CID 2007. 2. Richeldi et al, AJRCCM 2006. 3. Lee et al, Eur Resp J 2006. 4. Dewan et al, CID 2007

IGRAs are NOT for Diagnosis of Active TB

- CDC: IGRAs "cannot differentiate infection associated with TB disease from LTBI"
- If positive: no surprise and still can't conclude has active TB
  - Botswana TB rate >700/100,000
- If negative: doubt sensitivity of IGRA test
- Need specimens for smear and culture for TB diagnosis

Patient's Course

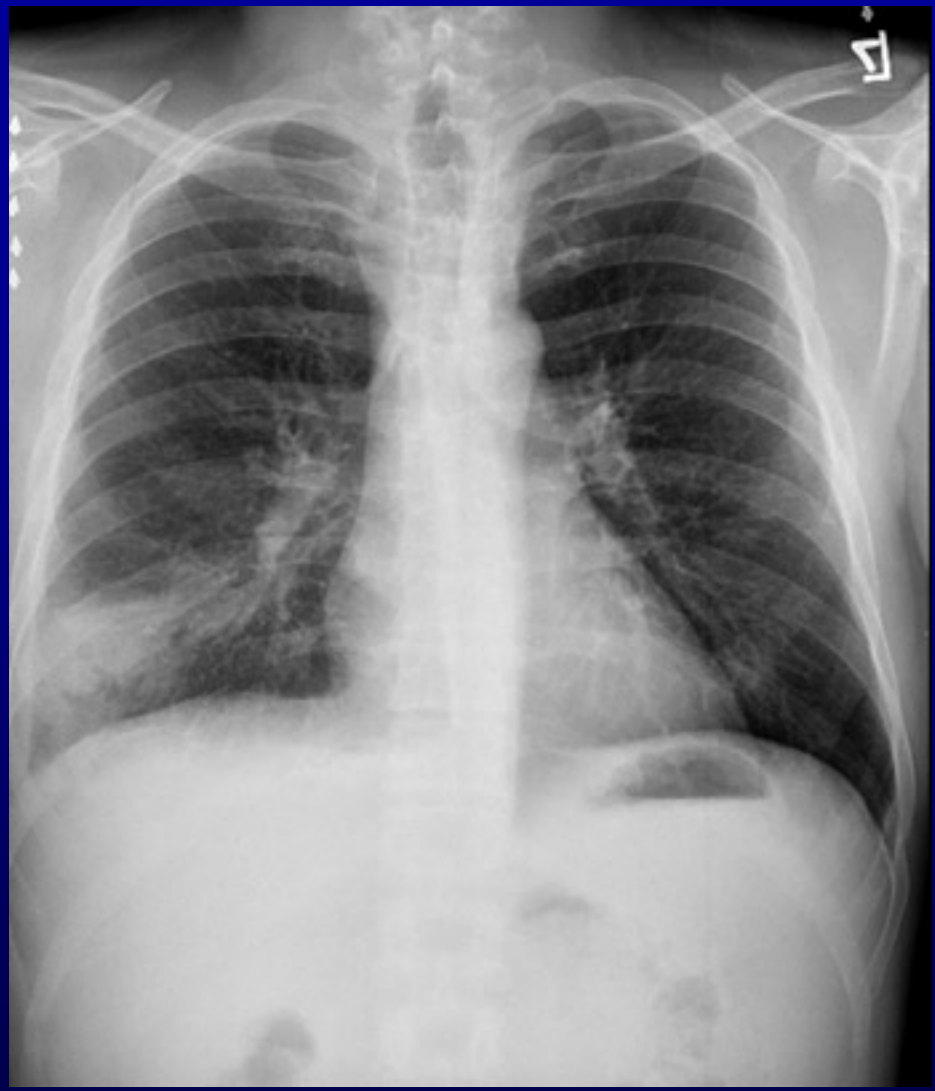
- Induced three sputa
- Started on isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA)
- At 8 weeks:
  - AFB smears and cultures negative
  - Remained asymptomatic
  - CXR unchanged
- Q2. Your differential diagnosis?

LTBI in Patient With Evidence of Past TB

- Without treatment, high risk for development of TB
- CXR: upper lobe opacities +/- volume loss
  - Less risk for active TB associated with
    - Calcified solitary nodules
    - Calcified hilar lymph nodes
    - Pleural thickening
- Differentiate between TB and LTBI based on symptoms and smears/cultures
- Treatment options
  - INH+RIF 4 months
  - INH 9 months

Case 2: Patient with TB Risk with Abnormal CXR

- 71W outpatient who immigrated from Botswana 1 mo ago
  - Symptoms of TB: dry cough and weight loss
  - No h/o of TB or significant PMH
- TST 13 mm (no previous TST)
- Abnormal CXR



Parenchymal consolidation in right lower lobe with loculated right-sided effusion

Patient's Course (1)

- Induced three sputa
- All three are scant positive, culture pending
- Q3. Would you start this patient on INH, RIF, EMB, PZA?
  - (Q3a. What is your differential diagnosis?)

Differential Diagnosis of +AFB Sputum

- Pulmonary pathogens
  - TB
  - NTM
  - *Nocardia* spp
  - *Actinomycoses*
- Some gi parasites are weakly acid fast, so modified acid fast stain (sulfuric acid instead of acid alcohol)
  - *Cryptosporidium* oocysts
  - *Sarcocystis* spp
  - *Isospora belli*

Empiric TB Treatment

- Decision to initiate empiric 4-drugs therapy based on
  - Epidemiology
  - Clinical signs compatible with TB
  - AFB smear status
  - Seriously ill (e.g., miliary TB)
  - High risk of transmission
- Most of world uses empiric or smear-only diagnosis to initiate treatment

Patient's Course (2)

- Started on INH, RIF, EMB, and PZA
- Within 1-2 weeks, cough worse, fevers develop, new SOB, new cervical lymphadenopathy
- Repeat CXR much worse with bilateral infiltrates and mediastinal lymphadenopathy
- Q6: What has happened (and how might it have been anticipated)?

Paradoxical Reaction

- **Exacerbation of manifestations of TB after beginning antiretroviral (ART) or TB therapy**
  - **More common among HIV-pos patients**
  - **In HIV-neg, especially when treat TB lymphadenitis**
- **Reconstitution of immune responsiveness**
- **Incidence uncertain**
  - **Narita et al[1]: in HIV+ patients on ART, 36% developed paradoxical worsening after beginning TB treatment compared with 7% of those not taking ARTs**
  - **Wendel et al[2]: only 7% of HIV+ TB patients developed paradoxical worsening, not associated with ART**

[1]Narita M, et al. Am J Respir Crit Care Med 1998;158:157–161

[2]Wendel KA, et al. Chest 2001;120:193–197

Paradoxical Reaction: Diagnosis and Treatment

- Signs: high fevers, lymphadenopathy, expanding CNS lesions, worse pulmonary infiltrations, and increasing pleural effusions
- Diagnosis of exclusion
- Treatment*
  - Mild: symptomatic mgt without change in antituberculosis or ART
  - Severe (e.g., airway compromise from lymph nodes, effusions, sepsis): prednisone or methylprednisolone 1 mg/kg and gradually reduced after 1 to 2 weeks

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)

Case 3: Patient with TB Risk with Abnormal CXR

- 71W outpatient who immigrated from rural Ivanova Oblask Russia 1 mo ago
  - Dry cough and weight loss
  - TST unknown
  - Abnormal CXR consistent with active TB
- PMH only significant for prolonged cough illness which was treated “for a long time”
- Q7: What questions might be helpful toward a diagnosis of relapsed TB?

Relapsed TB?

- Was he told it was TB?
  - No.
- How many pills (any injections)? Names?
  - One but doesn't know name.
- Did he have to go to the clinic to get everyday?
  - Maybe once a week.
- How long did he take them?
  - Months
- Did secretions turn red?
  - Doesn't recall reddish secretions while taking
- Did he take all prescribed?
  - Thinks so.

Q8. What is the significance of “one pill for months”?

Fixed Dose Combinations (FDCs)

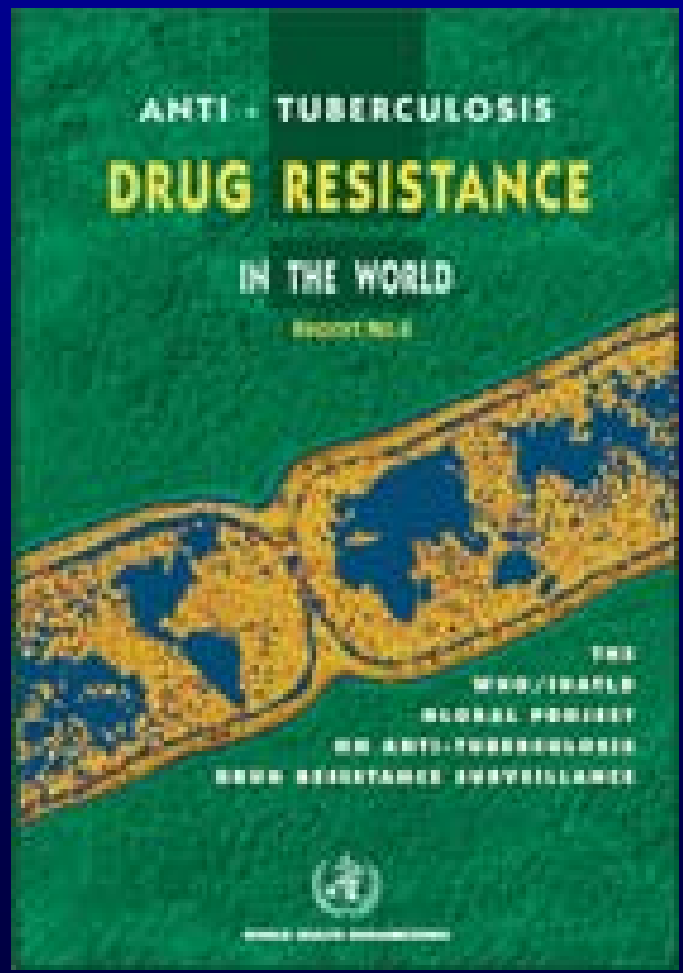
- WHO recommends FDCs for all new TB cases
- Justification includes simplicity, improved compliance, prevention of drug resistance
- Two FDCs available for use in US
  - Combination of INH and RIF (Rifamate®)
    - 2 Rifamate® provide conventional daily doses of INH (300 mg) and RIF (600 mg)
  - Combination of INH, RIF, and PZA (Rifater®)
    - Rifater® = INH (50 mg), RIF (120 mg), and PZA (300 mg)
    - 6 Rifater® = INH (300 mg) RIF (720 mg), PZA (1,800 mg)
      - RIF dose higher than typical because RIF is less bioavailable
- 4-drug combos of INH, RIF, EMB, and PZA available internationally

Patient's Course

- Induced three sputa
- All three are 1+ positive, culture pending
- Q9. Would you start this patient on INH, RIF, EMB, PZA?

High Suspicion for Drug Resistance

- Previous TB as evidenced by possible use of FDC
  - Relapse due to initial drug resistance or noncompliance?
- Rate of retreatment MDR TB in Ivanovo 58%
  - Even if not previous TB, primary MDR high 12.3%
- Excellent on-line source for regional and national drug resistance rates



Drug Resistant TB

- Drug resistant TB is created by
  - Patient: Not completing treatment
  - Clinicians: Not prescribing right drugs
  - Health system: Can't afford steady supply of drugs or sold sham drugs
- Drug resistant TB creates challenges
  - Patient: Longer, more toxic treatment
  - Clinician: Complicated regimens
  - Health system: Cost/case increased

First-line Drugs and Treatment of Susceptible TB

1. Isoniazid
2. Rifampicin
3. Pyrazinamide
4. Ethambutol
5. Aminoglycosides
6. Capreomycin
7. Quinolones
8. Thioamides
9. Cycloserine
10. PAS

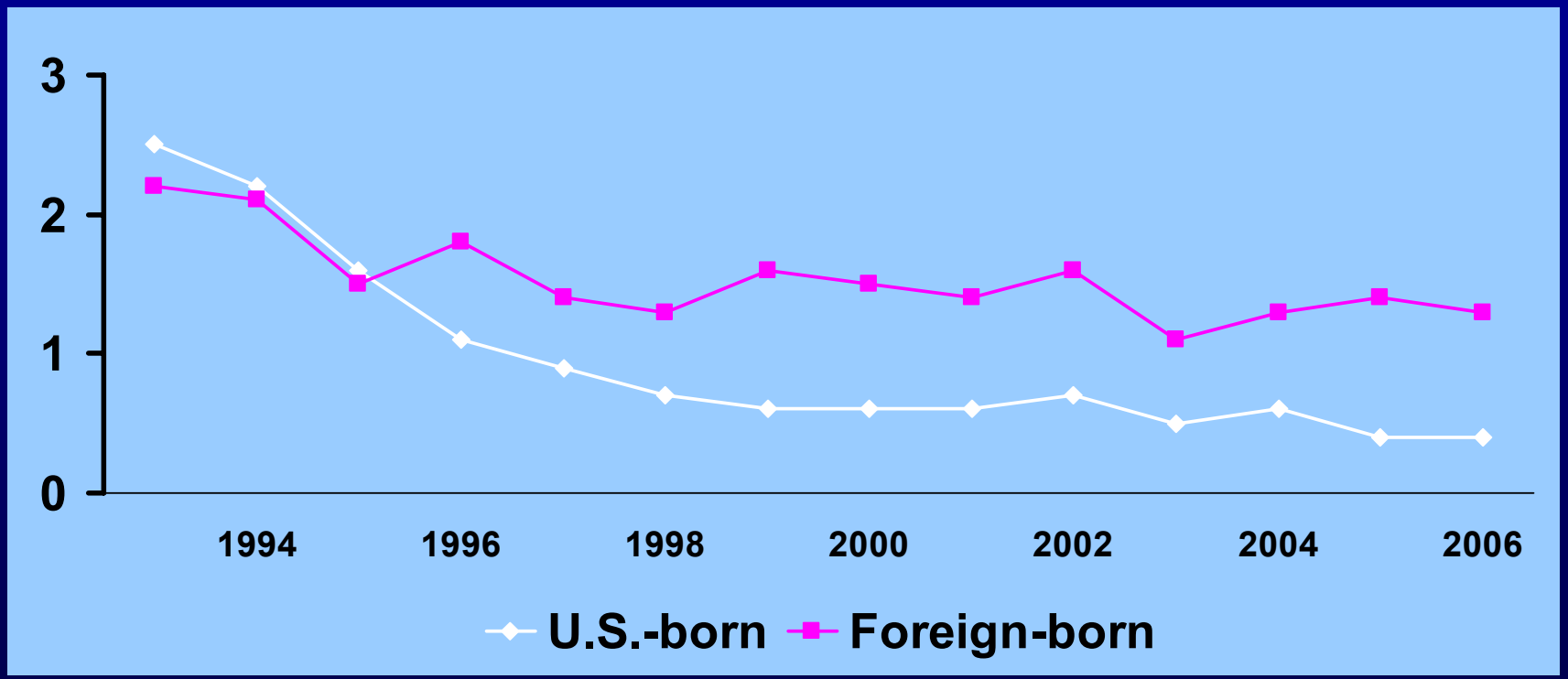
- Standardized TB treatment: 4 drugs x 2 months, 2 drugs x 4 months
- Based on evidence from ~ 30 years of clinical trials
- Safe
- 95% cure
- $20

Second-line Drugs and Treatment of Drug Resistant TB

1. Isoniazid
2. Rifampicin
3. Pyrazinamide
4. Ethambutol
5. Aminoglycosides
6. Capreomycin
7. Quinolones
8. Ethionamide
9. Cycloserine
10. PAS

- Treatment individualized, based on laboratory testing
- 4-6 drugs for 2 years
- No clinical trials
- Toxic
- <80% cure
- $3,500 - $5,000

Primary MDR TB in U.S.-born vs. Foreign-born Persons, United States, 1993–2006



Empiric Treatment for Relapsed TB

- In US, for patients with relapsed TB*:
  - If TB known to be initially drug-susceptible and treated by DOT
    - Standard four-drug initial phase regimen until results of susceptibility tests are known
  - If not DOT or had irregular treatment
    - Infer risk of acquired drug resistance
    - "Expanded regimen", especially in patients with impaired immunity, limited respiratory reserve, CNS involvement, or other life-threatening circumstances
- Global: std 4 drug+1 . . . but "never add one drug to a failing (failed?) regimen"

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)

Empiric Expanded Regimen Possible Drug Resistant TB

- No clinical trials to guide choice of agents for empiric expanded regimens
- Expert opinion* indicates
  - INH, RIF, and PZA
  - PLUS 3 drugs
    - EMB
    - Fluoroquinolone
    - Injectable agent
      - e.g., SM, amikacin, kanamycin or capreomycin

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)

Q10. Can you find out whether this isolate is drug resistant quickly?

Molecular Detection of Drug Resistance (MDDR) DNA Sequencing

- Sept 09, CDC offers DNA sequencing for id of drug resistance-associated mutations
- First, RIF and INH
- Then if resistant,
  - Fluoroquinolone (FQ), amikacin (AMK), kanamycin (KAN), and capreomycin (CAP)
- Isolates on solid media or pos MGIT cultures

Drug	Mutation	Sens (%)	Spec (%)
RIF	rpoB	96.1	97
INH	inhA/katG	88.6	98.7
FQ	gyrA	82.2	97
KAN	rrs + eis	86.8	96.9
AMK	rrs	87.9	99
CAP	rrs + tlyA	44.6	85.9

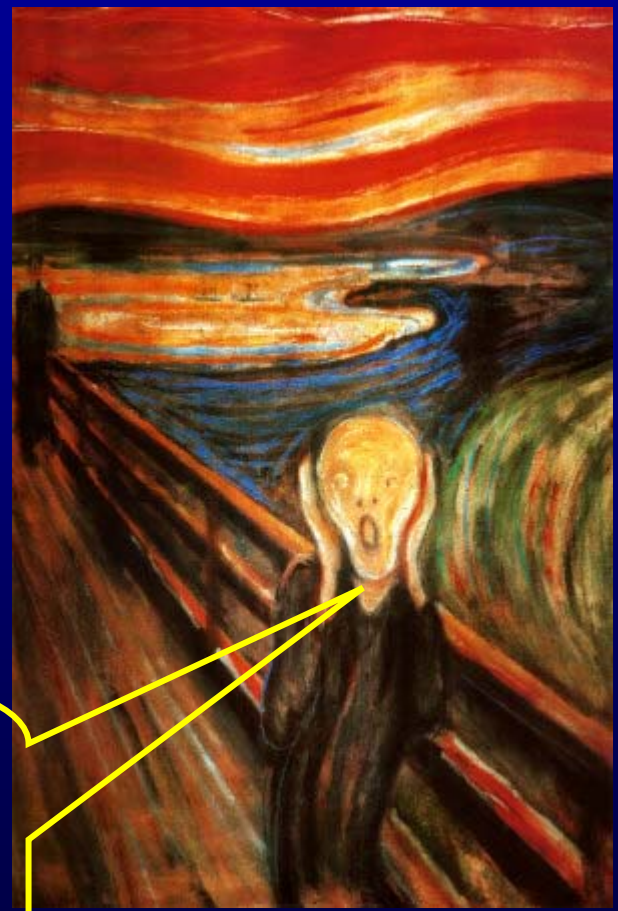
MDDR Submission Criteria

- High-risk of RIF resistance or MDR-TB
  - Previously treated TB case
  - Drug resistant TB contact
  - Foreign-born from area with high rates of MDR TB
- Known RIF resistant isolates
- High profile patients
  - e.g. daycare workers, nurses
- Adverse reactions
  - e.g. patient allergic to RIF
- Mixed or non-viable cultures
- Other situations on case by case basis

Initial MDDR results in days, and final results when conventional DST results are available!

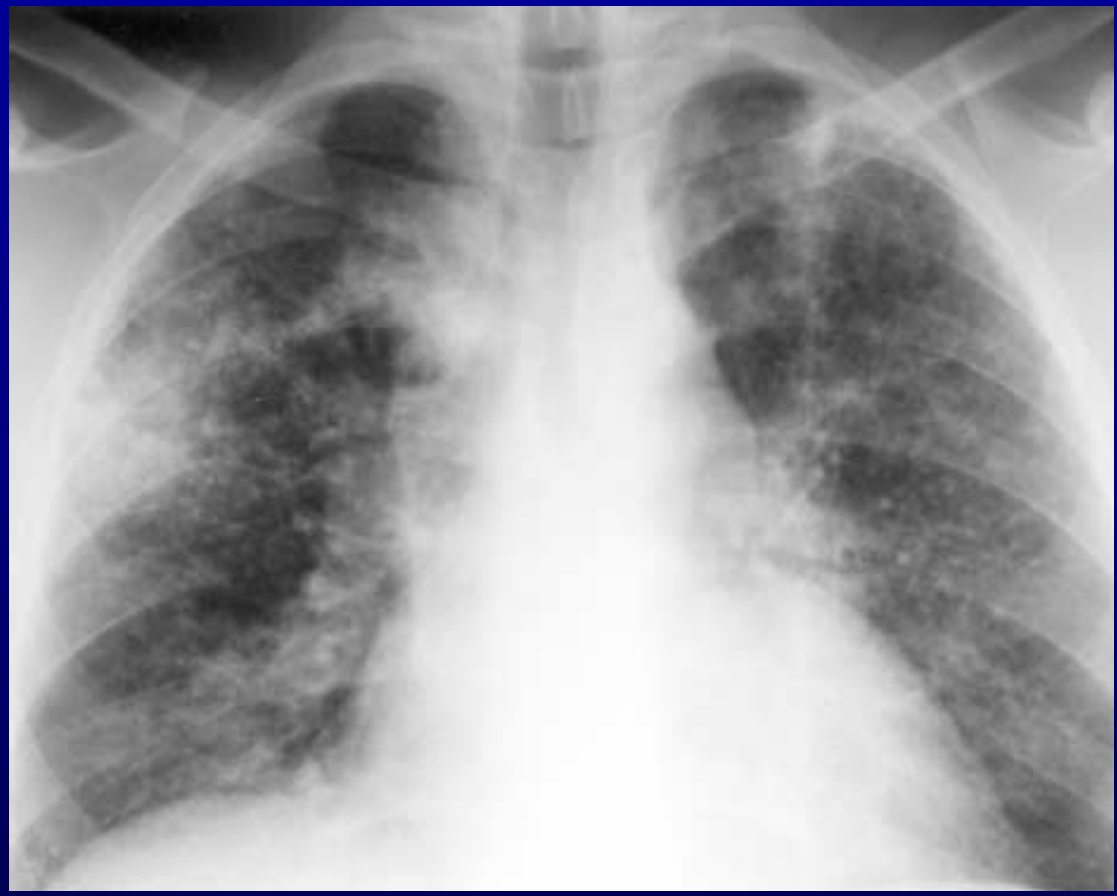
Case 4: SOB, Fever, Cough

- 71 yo man admitted for SOB
  - 1 month fever and prod cough
  - Weight loss 20 lbs
- 50 p-y history smoking
  - Vague h/o COPD
- No identified TB risk
- No history of LTBI evaluation
- Q11: Can you place TST or request IGRA without putting patient on Airborne Infection Isolation (AII)?



Yes: ". . . LTBI testing may be done for various reasons that may be incidental to the reason for hospitalization and do not necessarily indicate that the patient is an active TB suspect"*

*DHMC TB Control Policy



- TST 7mm
- CT scan multiple small nodules

Q12. Your Differential Diagnosis?

Diff Dx for Multiple Pulmonary Nodules

- Malignancy
  - Metastatic solid organ malignancies
    - Usually lung bases
  - Lymphoma
  - Kaposi's sarcoma in HIV+
- Rheumatologic and autoimmune: Wegeners
- Other: AVM, pneumoconiosis, silicosis
- Infectious
  - Bacteria: abscesses and septic emboli
  - Fungi (histoplasmosis, coccidiomycosis)
  - TB and nontuberculous mycobacteria (NTM)

Nontuberculosis Mycobacteria (NTM)

- Many mycobacterial species affect lungs: *avium, intracellulare, xenopi, abscessus, kansasi*, etc
- Distinguishing between TB and NTM aided by
  - Epidemiology: more common in
    - Male smokers
    - Middle-aged female nonsmokers (RML)
  - Growth characteristics and biochemicals
    - Microscopic appearance?
  - Genetic probes
  - Rarely radiographic features

Case Update and Issue

- Strong clinical suspicion for MAC
- Q13. Can you send three sputum for AFB without putting the patient on airborne infection isolation?

Not, really.
Doh!

NTM History

- 1860's: Avian form of TB recognized
- 1930's NTM cultured from environment
- 1939: Dutch den Dooren de Jong realized NTM more advanced than *M. tuberculosis*
- 1943: First case of recognized human infection in miner with silicosis
  - Repeated isolation of organism

Classification Chaos

- 1900's mycobacterial species exploded to 128
- 1950 Ernest Runyon restored order based on
  - Speed of growth
  - Production of pigments
- Runyon Class
  - I Photochromogens: slow growing, produce yellow-orange pigment in light
  - II Scotochromogens: slow growing, produce yellow-orange pigment in light or dark
  - III Nonchromogenic: slow growing, no pigment
  - IV Rapid growers: rapid (colonies in 5 days), no pigment

Runyon Examples

Runyon Group I (Slow-Growing Photochromogens)	
M. kansasii	Usually pathogenic
M. marinum	Usually pathogenic
M. simiae	Usually pathogenic
Runyon Group II (Slow-Growing Scotochromogens)	
M. szulgai	Usually pathogenic
M. scrofulaceum	Sometimes pathogenic
M. xenopi	Sometimes pathogenic
Runyon Group III (Slow-Growing Nonchromogens)	
M. avium complex	Strictly pathogenic
M. genavense	Strictly pathogenic
M. haemophilum	Usually pathogenic
M. malmoense	Usually pathogenic
Runyon Group IV (Rapid Growers)	
M. fortuitum	Sometimes pathogenic
M. chelonae	Sometimes pathogenic
M. abscessus	Sometimes pathogenic
M. mucogenicum	Sometimes pathogenic

NTM Infections 101

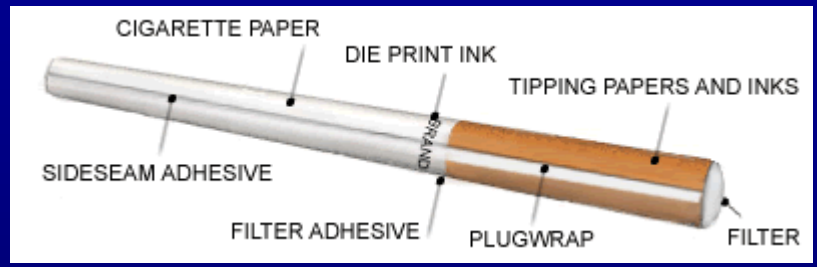
- Ubiquitous organisms in soil and water
  - Resistant to physical and chemical agents
- Exposure variable: 1950's, skin testing in healthy Naval recruits showed 30% exposure
  - Geographic distribution
    - 10-20% from north and west
    - >70% from southeast US
- No human to human transmission
- May be contaminant in clinical specimens
  - May persist on equipment (e.g., endoscopes) causing nosocomial and pseudo-outbreaks
- Pulmonary, cutaneous, disseminated or lymphatic

M. avium Complex (MAC) Runyon III

- ***M. avium ssp intracellulare***
  - **MAI**
- ***M. avium ssp paratuberculosis***
- ***M. avium ssp hominis***
- ***M. avium ssp avium***

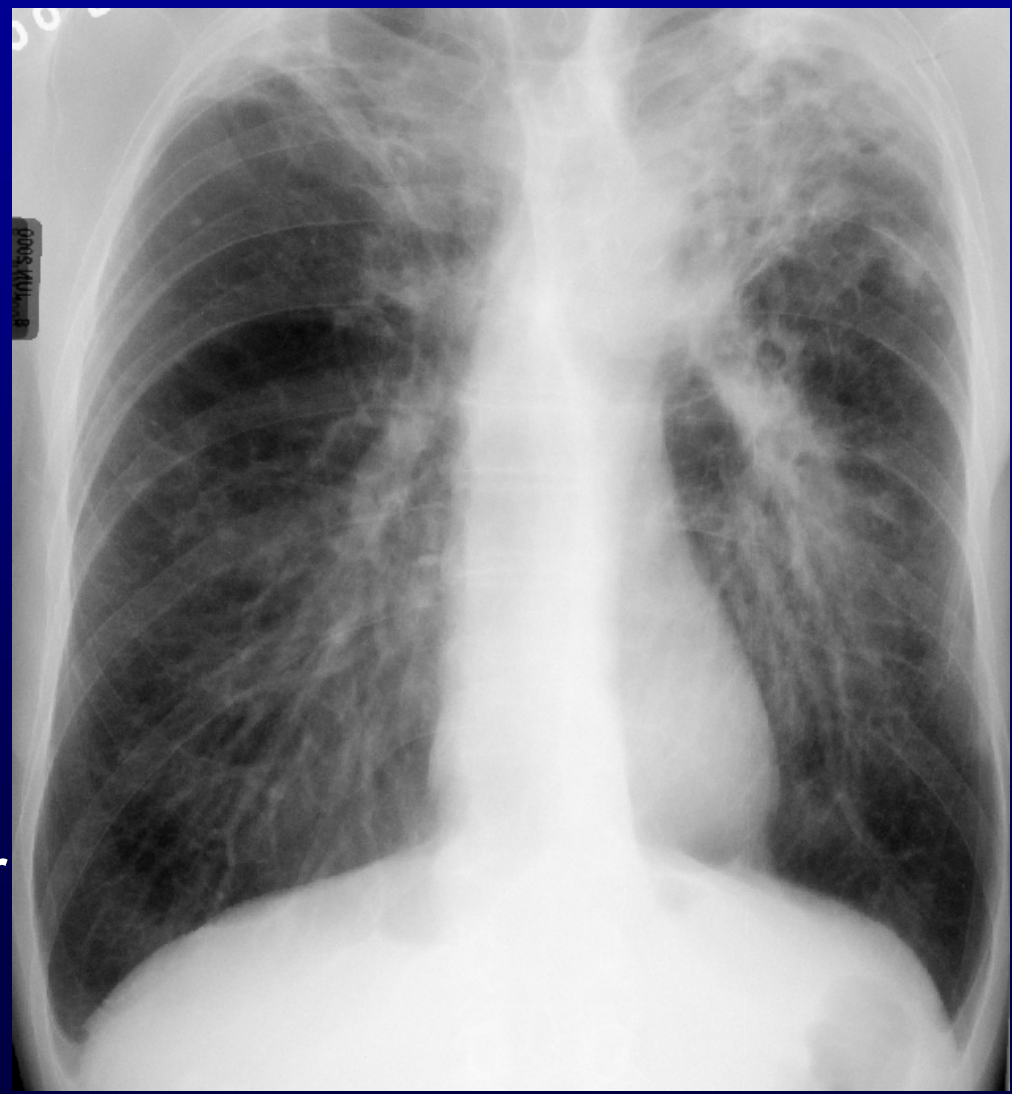
Environmental MAC Sources

- House dust
- Soil
- Birds (*M. avium*)
- Farm animals (*M. intracellulare*)
- Cigarette components
  - Tobacco, filter, paper
- 25% of water samples on East coast
  - Major source of infection is aerosolized water
  - Hypothesis for increasing prevalence: increased use of showers rather than baths



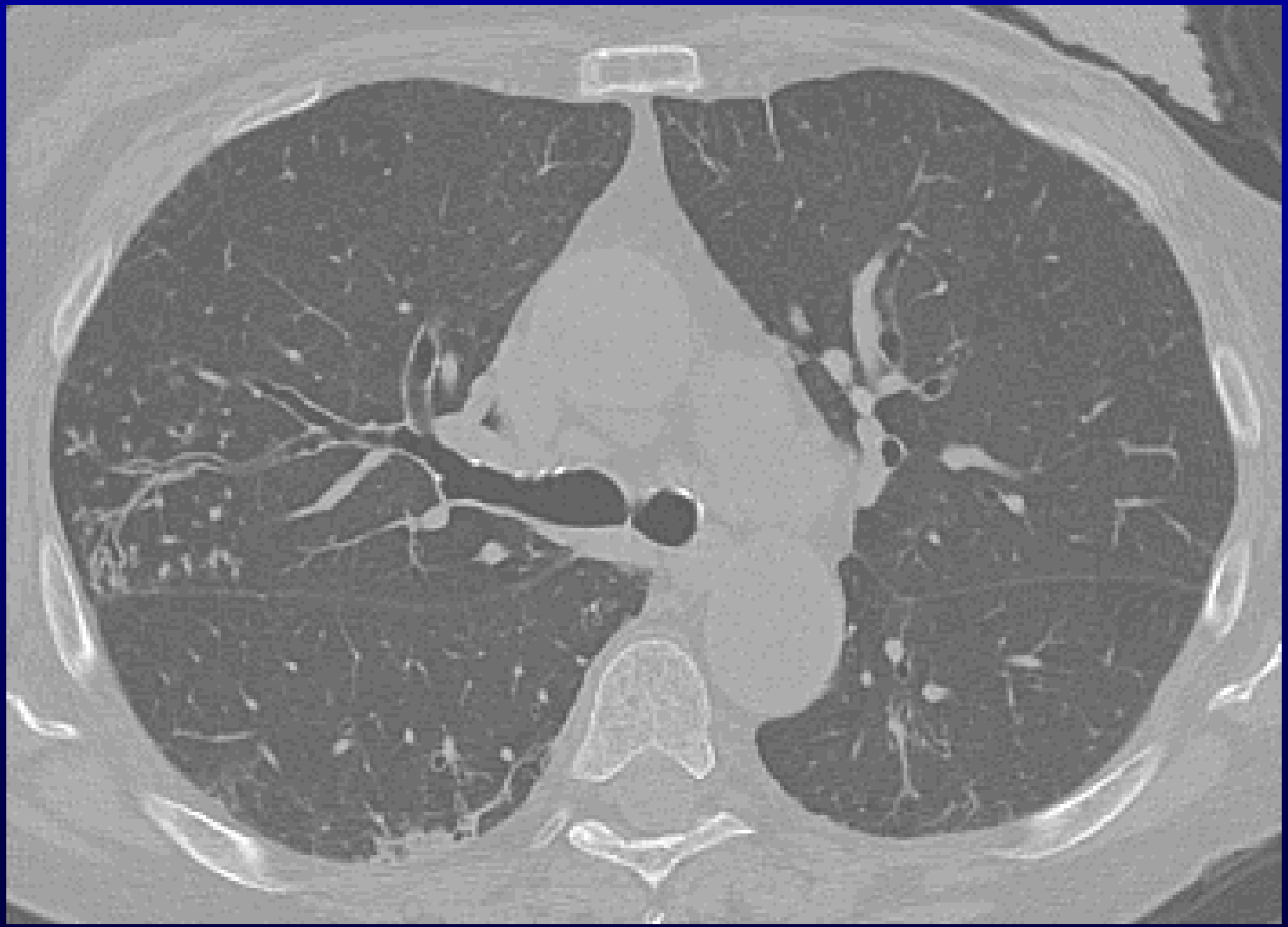
Clinical Spectrum with MAC

- Asymptomatic infection: 30-40%
- Symptomatic disease
  - Localized cervical adenitis age 1-5
  - Disseminated disease in AIDS
  - Pulmonary disease
    - Mimics TB, but slower and less virulent



Groups at Risk for Pulmonary MAC

- Preexisting lung disease
  - Acquired bronchiectasis
  - Cigarette smokers
  - Cystic Fibrosis
- Chest wall abnormalities
  - Thin, elderly women, no previous lung disease
    - "Lady Windemere's Syndrome"
  - Pectus excavatum
  - Scoliosis
- Hot tub users: hypersensitivity pneumonitis

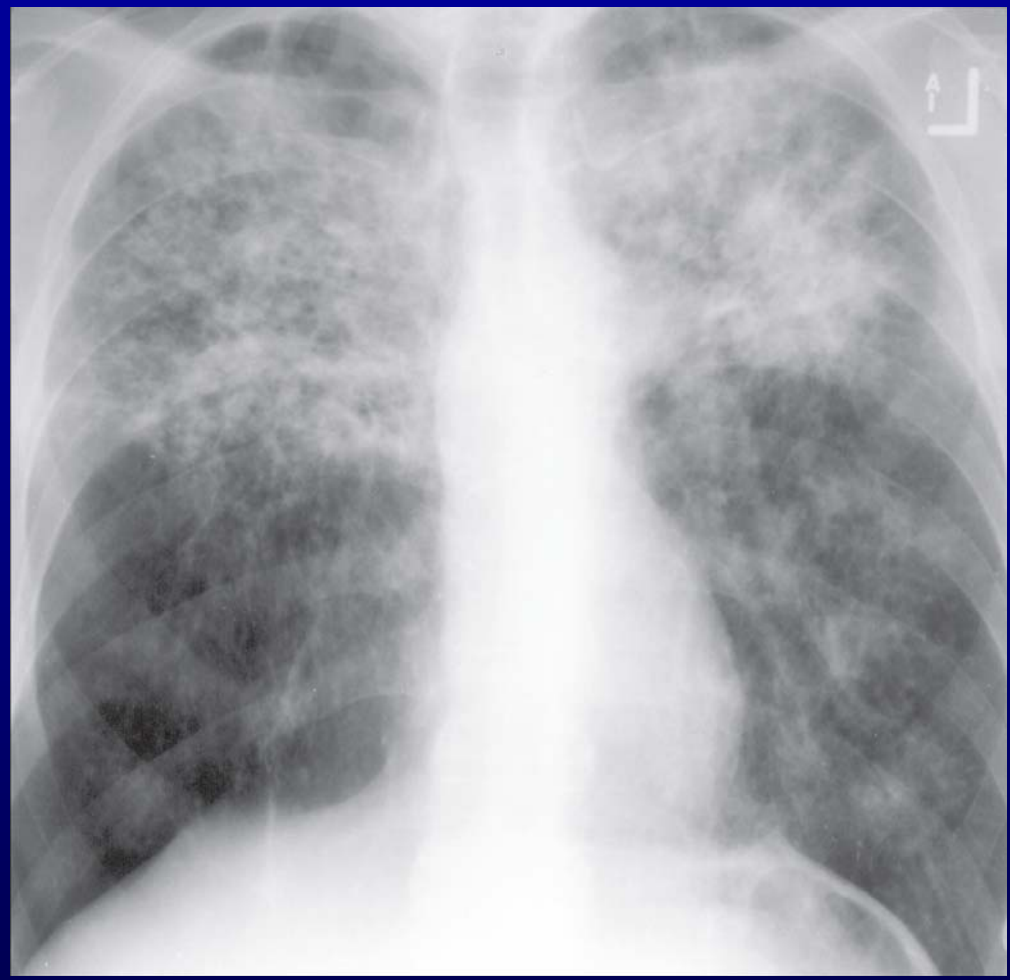


Case 5

- During jail intake, 49 yo male
  - Cough since 2004, increasing dyspnea
  - Weight loss 16 pounds over 2 years
  - Denied fever, night sweats, hemoptysis
- ?Latent TB infection (LTBI)
  - 2004: TST 12 mm, no treatment
- Relevant social history:
  - Homeless but denied shelter residence
  - Admitted smoking, alcoholism, occasional marijuana but no intravenous drug use

First Hospitalization

- Transferred from jail to local acute care hospital A
- AFB smear and *M. tuberculosis* culture positive
  - Fully susceptible isolate
- Laboratory exam: ALT 52 (ULN 42)
- CXR consistent with reactivation TB



Bilateral nodular infiltrates in both apices
Right hilar lymphadenopathy
No evidence for cavitation

First Complication

- Started on daily isoniazid, rifampin, PZA and ethambutol
- Treatment order served by NH DHHS, transferred to State Hospital for AII
  - Noted hepatitis C virus (HCV) positive
- On d18 of treatment, switched to biw
  - Sudden onset fever, myalgia, nausea
  - Transferred back to hospital A

Second Hospitalization

- Based on recurrence with re-challenge, diagnosed with ethambutol "flu-like reaction"
  - Reported in 4% taking RIF by intermittent dosing
    - Not reported with ethambutol
  - Patient refused to try again
- During hospitalization, RUQ pain noted
  - ALT >5 times ULN
- All TB meds stopped due to suspected DILI

Drug-Induced Liver Injury (DILI)

- Liver is vulnerable due to central role in drug metabolism and detoxification
- DILI accounts for 7% drug adverse effects and 30% of fulminant liver failure
- Asymptomatic to liver failure
- ALT/AST >3 times upper limit of normal (ULN) if symptomatic or >5 times ULN if asymptomatic
- Diagnosis of exclusion, with time to onset 5-90 days after start of drug known to be hepatotoxic
  - Recovery after drug cessation
  - Rapid re-injury after readministration

Drug	Incidence	Presentation
INH	≤20% have low-grade, transient elevation LTBI: 0.1-0.6%	Onset and recovery of hepatotoxicity weeks Recovery usually complete
RIF	Low, but few studies of monotherapy	Cholestasis Hypersensitivity Hepatocellular injury
PZA	Rifampin-PZA 2.6% Often implicated in multidrug regimens	Hepatoxicity Hypersensitivity Granulomatous
FQs	Moxifloxacin 0.9% ALT ≥1.5 times ULN	Varies with individual fluoroquinolone
EMB AGs Cycloserine	None	

DILI During Standard TB Therapy

- Asymptomatic elevation of AST in 20%
  - Levels usually normalize after treatment
  - Warrants increased clinical and laboratory monitoring
- Clinically significant DILI
  - Low incidence 0.1-0.15%
  - Time to DILI usually 2-3 weeks
    - 17.4 days (range 6-102 days) *

*Ungo et al. Am J Respir Crit Care Med 1998; 157: 1871–76.

Risk Factors for DILI During TB Treatment

- Pregnancy and postpartum; ?female sex
- Age >35 years
- Alcohol consumption
- Malnutrition
- HIV? Studies suggest increased risk, but few studies without confounding causes
- Underlying liver disease
  - Abnormal baseline transaminases
  - Liver transplant
  - Hepatitis B
  - HCV*?

*Ungo et al. Am J Respir Crit Care Med 1998; 157: 1871–76
Fernandez-Villar et al. Clin Infect Dis 2003; 36: 293-8.

Q14. How would you restart TB treatment?

Our Strategy to Restart Treatment

- Ensured dosages were correct
- Ruled out other causes
  - Viral hepatitis, alcohol, other drugs
- When AST <2 times ULN (or baseline), planned drug challenge Q 3-7 days
  - Rifampin, then isoniazid
  - If tolerated, assume PZA and embark on 9 month treatment protocol
    - FQ and aminoglycoside
    - "No ethambutol"

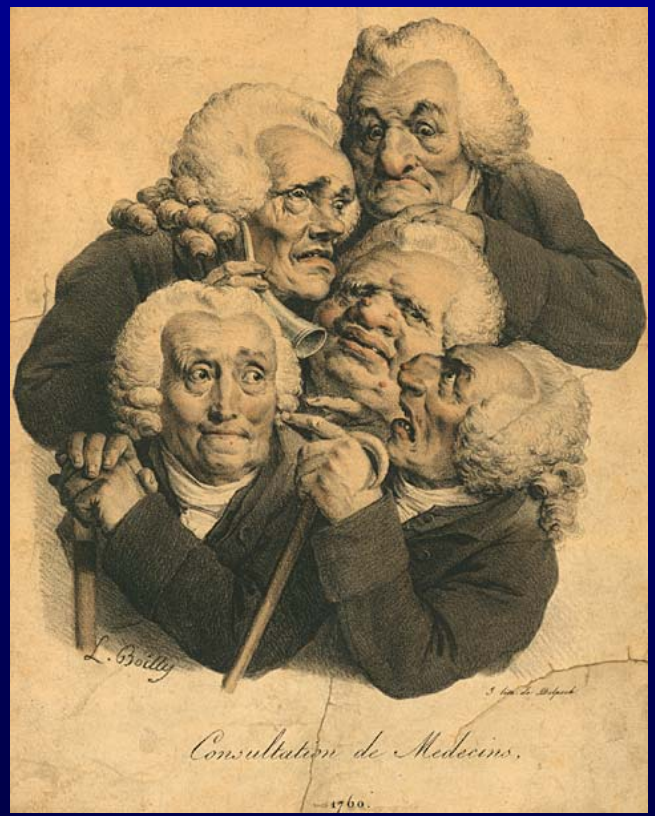
Refractory Hepatitis!

- 15d after treatment interruption, ALT still >2 times ULN
  - Expected resolution average 18.7d
    - Range 4-58d*
  - Differential included DILI and HCV flare
- Transfer from State Hospital to hospital B for monitored med restart

*Ungo et al. Am J Respir Crit Care Med 1998; 157: 1871–76.

Medical Consultation

- Outpatient and inpatient ID consultants
- Concurrent consultation with DHHS TB Medical Consultant
- Secondary consultation with Regional Training and Medical Consultation Center
  - In NJ: 1-800-4TBDOCS
- Authority? Ownership? Communication?



Second Hospitalization

- Recovery from transaminitis
- D0 Moxifloxacin and IM SM
- D5 Rifampin added
- D8 PZA restarted

- Q15: What potential error of medication reintroduction was made?

Fulminant DILI with PZA

- Influence of PZA on TB DILI ambiguous
- Some studies show no increased *rate* of DILI using PZA in treatment regimen
- "For those with prolonged or severe hepatotoxicity, rechallenge with PZA may be hazardous"*
  - Study of 18 fulminant DILI cases concluded PZA co-administration was associated with increased mortality**

* ATS Guidelines. Am J Respir Crit Care Med 2006; 174: 935-952
** Durand et al. Hepatology 1995; 21: 929-32.

Dose and Drug Escalation Without PZA

- Study of TB patients (HIV/HCV-) treated with standard first line drugs who developed DILI, defined as
  - 5 times ULN AST or ALT
  - Any increase in AST or ALT with anorexia, nausea, vomiting and jaundice
  - Total bilirubin >1.5mg/dl
- Randomized to 2 approaches to learn best approach to restart TB treatment after DILI

*Tahaoglu et al. Management of ATT drug-induced hepatotoxicity. Int J TB Lung Dis 5(1) :65-9

Two Strategies to Restart Meds

- Group I (N=20): dose and drug escalation without PZA
  - D1: strep 1000 mg or ethambutol 1500 mg
  - D3: + isoniazid 100 mg
  - D6: ↑ isoniazid to 200 mg
  - D9: ↑ isoniazid to 300 mg
  - D12: + rifampin 150 mg
  - D15: ↑ rifampin 300 mg
  - D18: ↑ rifampin 450 mg
- Group II (N=23): retreatment with full dose 4 drugs including PZA

Results

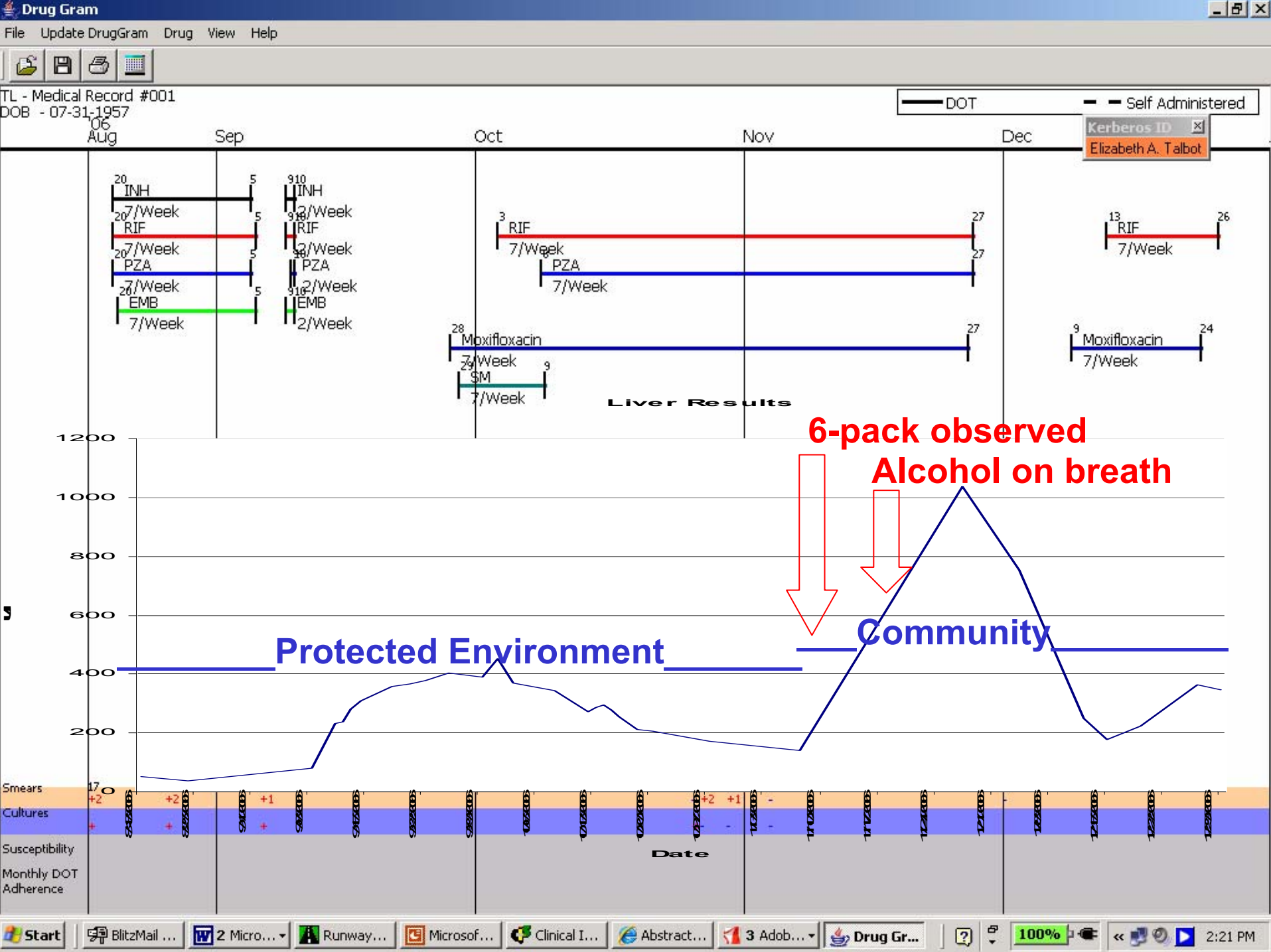
- No recurrence of DILI in Group I
- Recurrence in 24% of Group II
  - 6/7 crossed over to Group I and tolerated drugs
- Conclusion: dose and drug escalation without PZA may be an appropriate retreatment strategy after DILI

Recurrent DILI?

- 3 AFB smears negative, normalized LFTs on moxy, RIF and PZA
- Discharged to subsidized apt
- LFTs rose dramatically
- Second treatment interruption
  - Decline in transaminases
- Q16: Your differential, your approach?

Role of TB Drug-o-Gram

- Monitoring treatment and clinical progress
- Providing data for cohort analysis
- Teaching or presenting to other clinicians
- Discussions, papers, and/or consultations
- Available: http://www.umdnj.edu/ntbcweb/products/drugogram.htm


Drug Gram
File Update DrugGram Drug View Help
TL - Medical Record #001
DOB - 07-31-1957
DOT
Self Administered
Kerberos ID
Elizabeth A. Talbot
06
Aug
Sep
Oct
Nov
Dec
INH 7/Week
RIF 7/Week
PZA 7/Week
EMB 7/Week
INH 2/Week
RIF 2/Week
PZA 2/Week
EMB 2/Week
Moxifloxacin 7/Week
SM 7/Week
Liver Results
6-pack observed
Alcohol on breath
Protected Environment
Community
1200
1000
800
600
400
200
0
Smears
Cultures
Susceptibility
Monthly DOT Adherence
Date
Start
BlitzMail ...
2 Micro...
Runway...
Microsof...
Clinical I...
Abstract...
3 Adob...
Drug Gr...
100%
2:21 PM

Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy Guidelines

Am J Respir Crit Care Med 2006; 174: 935-952

www.thoracic.org/sections/publications/statements/pages/mtpi/hepatotoxicity-antituberculosis-therapy.html

Recommended Regimens for Pre-existing Liver Disease

1) Treatment without PZA
   Initial phase (2 mos): INH, RIF, EMB
   Continuation phase (7 mos): INH RIF
2) Treatment without INH
   Initial phase (2 mos): RIF, PZA, EMB
   Continuation phase (4 mos): RIF, EMB, PZA
3) Regimens with one hepatotoxic drug
   - RIF should be retained
   - Duration of treatment is 12-18 mos
4) Regimens without INH/RIF/PZA
   - Duration of treatment is 18-24 mos

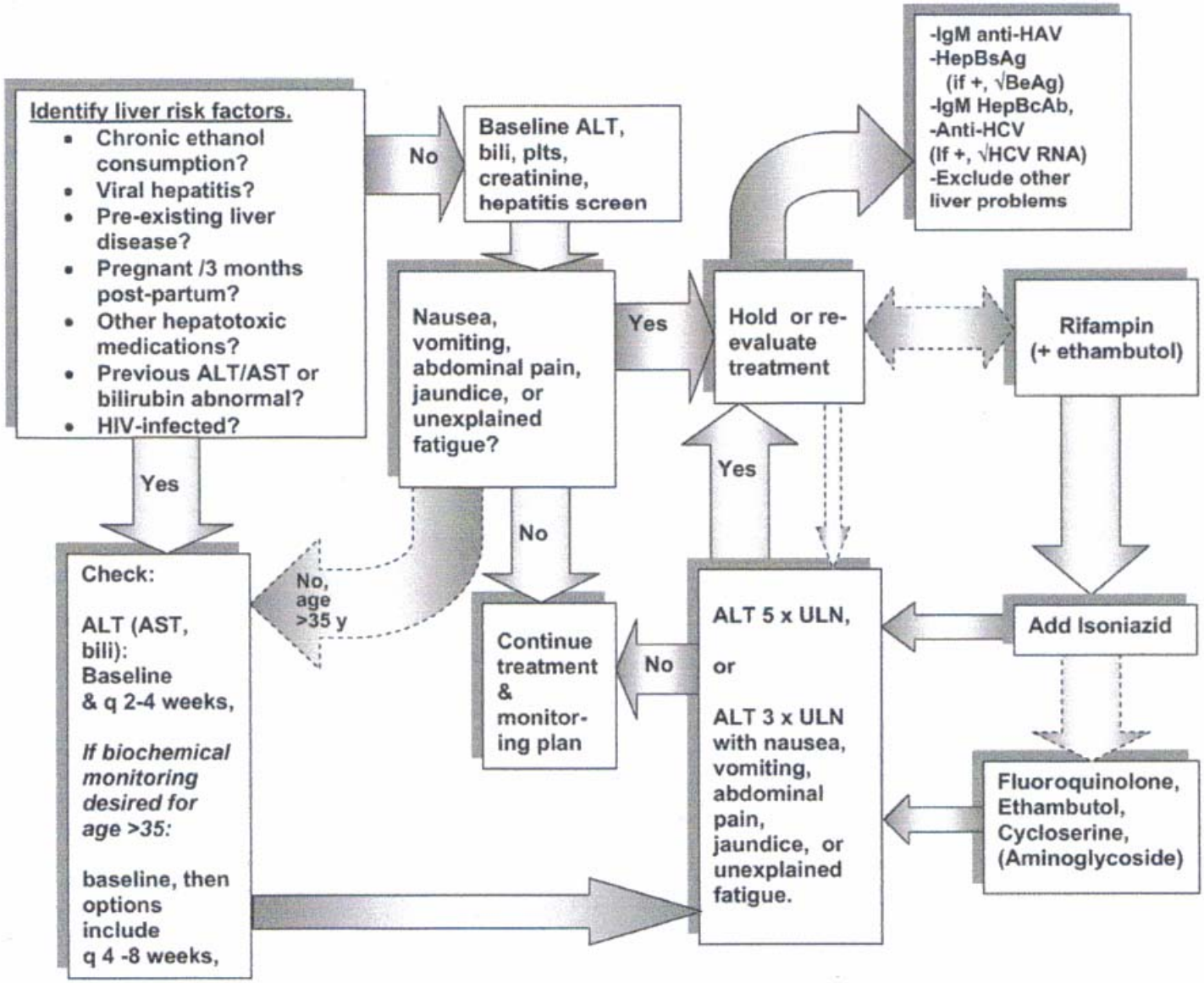


Figure 3. Monitoring for hepatotoxicity during treatment of TB disease. *Dotted lines* signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen.

Management of DILI While on TB Treatment

- First line drugs should not be stopped without adequate justification acc. to ATS/CDC/IDSA
  - >5 ULN for asymptomatic; >3 ULN ALT symptomatic
- Don't split dose to bid or tid
  - Uncertain pharmacokinetics
  - Possibility of treatment failure, resistance
- Toxicity less with intermittent regimens
- Management may require expert consultation
- Report serious adverse effects
  - 1800-FDA-1088 or www.fda.gov/medwatch

Summary

- TB is a great and formidable disease
- There are many resources out there to aid management
  - ATS Guidelines
  - Drug-o-gram
  - State Health Department TB Medical Consultant
  - Regional Training and Med Consultation Ctr
- Fill out your reviews carefully

Acknowledgements

- NH DHHS TB Program
  - J Fournier, L Roy, J Proctor
- Public Health Nurses
- Jose T. Montero