Is This Person Being Treated for TB Getting Better? Or Worse?
Monitoring Those on Anti-Tuberculous Therapy

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1

Monitoring of TB in the "pre-Drug" era: 1899

- Arthur Morgan, the protagonist of the video game Red Dead Redemption 2, gets infected with TB during a fight and later gets sick
- Treatment (from his Native American companion, Rain Falls): Ginseng, English Mace and Yarrow.
- Monitoring: Watch and see what happens

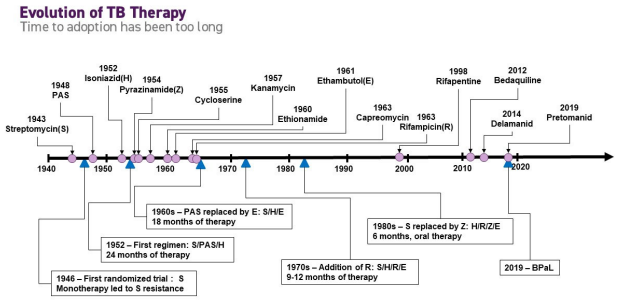
2

Fast Forward 30 Years: Monitoring TB Treatment in the US in the late 1920s

Source: https://www.saranaclake.com/history

3

Fast forward 100 or so Years…



- The Good: Much Less TB Disease
- More Drugs

➢But:

- More Complicated Patients
- More Drug resistance
- Less Expertise in Treating

https://www.tballiance.org/content/drugs-regimens-transforming-tb-drug-development

4

What can happen when you start someone on anti-tuberculous therapy?

On Treatment for TB Infection

- Stay the same (we hope)
- Get worse
  - Adverse effects of therapy
  - Development of TB Disease (rare)

On Treatment for TB Disease

- Get better (we hope)
- Stay the same
- Get worse (But why?)
- Get better in some ways and worse in others

5

Why isn't my patient getting any better, or maybe even getting worse?

Medication Related Issues

- Drugs not being taken
- Drug dosing
- Drug absorption issues
- Drug resistance
- Drug interactions
- Drug toxicity (adverse drug reactions, ADRs)

Disease Related Issues

- Severe TB disease
- New complications may develop
- New sites of disease may show up
- Increased inflammation/immune reconstitution syndrome (IRIS)
- Need for other interventions such as surgery for some complications

6

How do we assess response to treatment? What's in our Toolkit?

- Clinical evaluation (history and exam)
  - What are some of the objective components that we look for?
  - What do we ask the patient?
- Microbiologic evaluation (sputum)
  - How often? And how do we interpret the results?
- Chest radiograph (or other organ-specific imaging if extra-pulmonary)
- Laboratory evaluation
  - Are there any blood tests that are helpful?

7

Clinical Evaluation – Monthly

Clinical evaluations should be performed monthly, at a minimum

- Treatment efficacy
  - Assess symptoms of their TB disease, such as cough, fever, sweats, appetite, fatigue
  - Assess organ specific symptoms for extrapulmonary sites of disease
  - Measure and trend weight
    - A good measure of response to treatment, unless not eating from Meds
    - Also important for dose adjustment
  - Improvement often gradual, but if symptoms are not improving within the initial 2 months, consider causes of treatment "Failure"

➢Also assess for adverse effects of therapy (more later!)

8

Response to Treatment – Microbiologic

- Monthly sputa for smear and culture, until 2 consecutive specimens are negative
- **2-month** culture is vital in determining length of treatment➔ longer treatment if culture (not smear) still positive
- Drug susceptibility testing (DST) to Isoniazid, Rifampin, Ethambutol and Pyrazinamide at baseline
- Repeat DST if culture remains positive at **3 months**

Date	Smear	Culture	DST
1-5-17	1+	+MTB	Pansusceptible
1-23-17	-	+MTB	
2-20-17	-	-	
3-7-17	-	-	

9

What if you see this pattern?

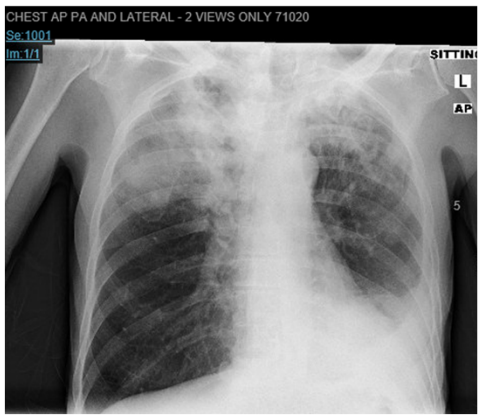
Date	Smear	Culture	DST
1-5-17	3+	+ MTB	Pansusceptible
1-23-17	4+	+ MTB	
2-20-17	3+	+ MTB	
3-7-17	3+	+ MTB	
4-4-17	1+	Pending	
4-6-17	2+	Pending	

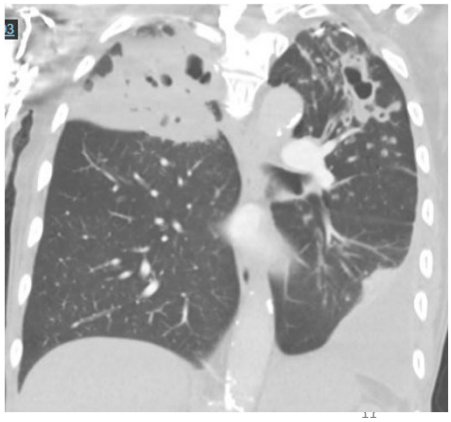
What does it mean? Should we be worried?

10

A recent case at my hospital

- 69 y/o US-born man with 9 months of 50 lb weight loss, fevers, night sweats and worsening of chronic cough
- Initial sputum specimens 4+ AFB positive
- Started on RIPE





11

We also send a GeneXpert® MTB/RIF - the result is available the next day and is shown below

Mycobacterium tuberculosis Complex Detection and Rifampin Resistance by PCR
ARUP test code 2010775

MTBRIF Source	Sputum	
Mycobacterium Tuberculosis by PCR	**Detected**	*
MTB Rifampin by PCR	Not Detected	
MTB Cmplx Interpretation	**Detected**	C
	MTBC detected. No rpoB gene mutations detected; probably rifampin susceptible.	

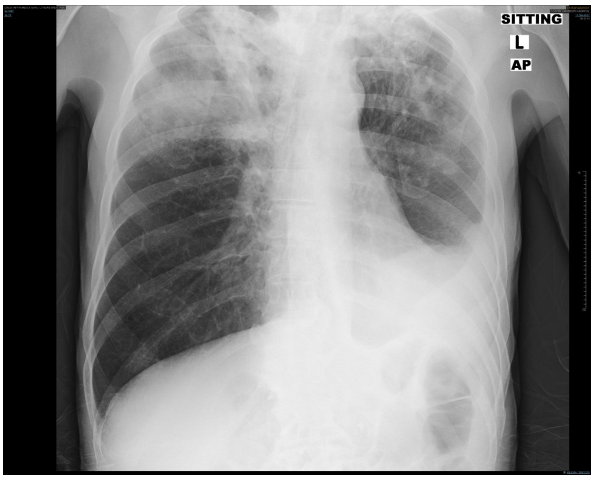
GeneXpert® information is often the only drug susceptibility data available until cultures grow unless Molecular susceptibility data is obtained.

12

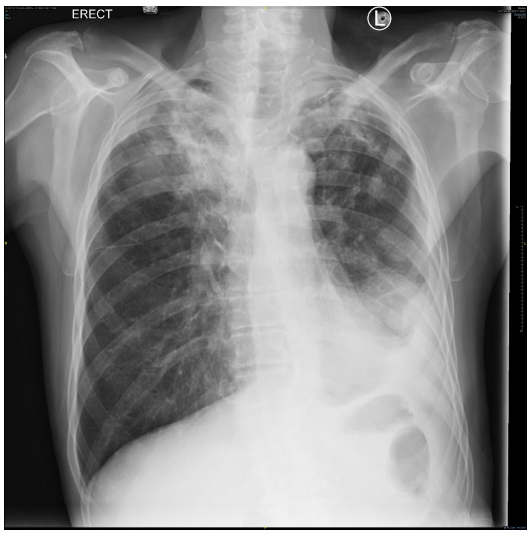
Fast forward 2 months:

- Still in hospital, coughing less, no fever or night sweats, but not gaining any weight
- Remains on RIPE, now at about 8 weeks (40 doses)
- Sputum specimens are all still AFB smear positive, at least 2 to 3+
- All samples from the first month are growing MTB, subsequent sputum AFB cultures pending
- Susceptibilities back on original isolate: Pan-susceptible
- Should we worry about the persistent positive sputum smears?
- What should we do?

13



1/17



3/17

14

One month later (3 months of treatment)

Date	Smear	Culture	DST
1-5-17	3+	+MTB	Pansusceptible
1-23-17	4+	+MTB	
2-20-17	3+	+ MTB	
3-7-17	3+	+ MTB	
4-4-17	1+	Pending	
4-6-17	2+	Pending	

Should we be worried now?

15

And at four months

Date	Smear	Culture	DST
1-5-17	3+	+MTB	Pansusceptible
1-23-17	4+	+MTB	
2-20-17	3+	+ MTB	
3-7-17	3+	+ MTB	
4-4-17	1+	+ MTB	Pending
4-6-17	2+	+ MTB	
5-1-17	2+	Pending	
5-2-17	1+	Pending	

Now should we be worried?

16

Poll 1
Persistent positive sputum AFB smears

Which of these is most likely to explain why this patient's AFB smears aren't clearing?

A) Extensive cavitary disease/high organism burden

B) Drug resistance

C) Poor absorption

D) Maybe he has an NTM in there, too

E) How do we know they are live organisms?

17

Persistent positive sputum AFB smears

What could explain why this patient's sputum AFB smears aren't clearing?

A) Extensive cavitary disease→ May need more time

B) Drug resistance→ Make sure getting DOT, and on an effective regimen, check susceptibilities at 3 months if still positive

C) Poor absorption→ Check drug levels

D) Maybe he has an NTM in there now→ Wait for the cultures to be identified

E) How do we know they are live organisms?→ Wait for the cultures to see if they grow

18

Case 1: Some data

- Sputum AFB cultures finally are negative at 4 months even though smears are still positive, and he is doing better. Drug levels for rifampin (2 hours post dose) are low and Rifampin dose is increased
- We decide to treat him for a total of 9 months (7 months of the continuation phase) due to slow response and persistent positive cultures at 2 months

➢Why do we extend the Treatment Course?

19

4 months with culture data now final

Date	Smear	Culture	DST
1-5-17	3+	+MTB	Pansusceptible
1-23-17	4+	+MTB	
2-20-17	3+	+ MTB	
3-7-17	3+	+ MTB	
4-4-17	1+	+ MTB	Pansusceptible
4-6-17	2+	Negative	
5-1-17	2+	Negative	
5-2-17	1+	Negative	

20

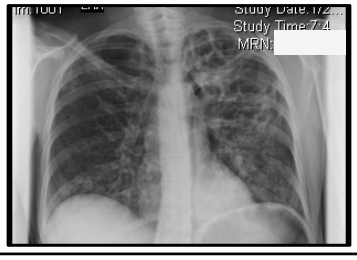
Drug Levels (Therapeutic Drug Monitoring, TDM)

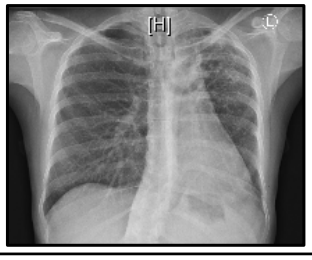
- Drug levels on “standard” medication doses may be low
- Certain patient populations may be more likely to have sub-therapeutic drug levels:
  - Diabetic patients
  - HIV infected
  - Malnourished and other sicker patients
- Sub-therapeutic levels have been associated with slower sputum sterilization rates
- Consider TDM (drug levels) in patients with slower clinical responses
- Adjust drug dosing based on levels, especially RIF and INH

21

Response to Treatment – Radiographic Evaluation

- In the patient with **positive** cultures
  - Chest radiograph at 2 months of treatment can be helpful but is not essential
  - Completion of treatment chest radiograph sets a new baseline for future comparison
- In the patient with **negative** cultures
  - 2 month chest radiograph is part of evidence to support TB diagnosis
  - An end of treatment chest radiograph is also helpful

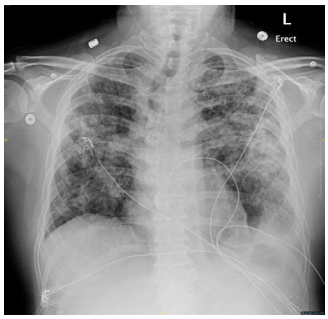


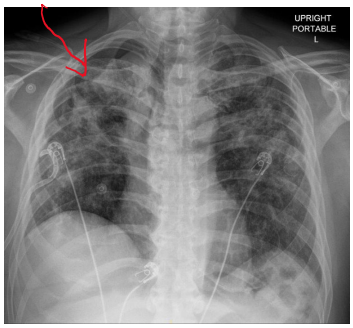


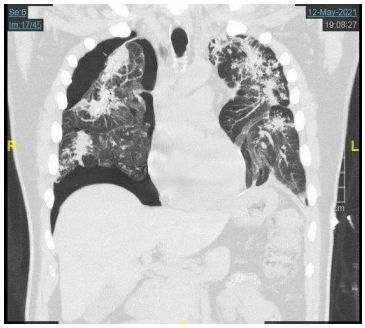
22

Other Reasons for Repeat Chest Radiographic Evaluation

- Significantly worsening pulmonary symptoms or changes on lung examination
  - Pleural effusions
  - Pneumothorax
  - Atelectasis from compression (e.g., large hilar lymphadenopathy)
  - Pericardial disease







23

Monitoring Summary

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

Nahid et al., Treatment of Drug Susceptible TB, CID 2016

24

Case 1: When do we Decide to Extend therapy?

➢**Reasons to extend the Duration of treatment beyond 6 months:**

- Did not get Rifampin plus PZA in the initial 2 months of therapy
- Resistance issues- depends on what specific resistance and Rx
- Positive cultures at 2 months: + cavitary disease (HIV negative), or if HIV positive even without cavitary disease
- Certain extrapulmonary syndromes: Central Nervous system disease and spinal disease, maybe Disseminated disease
- HIV with low CD4 and not on ART at start
- Clinical judgement: for some patients with extensive disease and/or slow clinical response

➢**Do we ever Treat for less than 6 months?**

25

When can you Treat for less than 6 months?

- Culture negative pulmonary disease
- Drug Susceptible Pulmonary Tuberculosis

Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Weekly / February 25, 2022 / 71(8);285–289

Wendy Carr, PhD[1]; Ekaterina Kurbatova, MD[1]; Angela Starks, PhD[1]; Neela Goswami, MD[1]; Leeanna Allen, MPH[1]; Carla Winston, PhD[1] (View author affiliations)

26

Case 2

- A 63 year old Vietnamese-born woman is diagnosed with smear-positive pulmonary tuberculosis, GeneXpert® MTB/Rif: MTB positive, RIF^R not detected
- She is started on 4 drug anti-tuberculous therapy with RIPE + Vit. B6 and is receiving her treatment by DOT.
- About two weeks into therapy she complains to her clinic nurse that the medications are "making me sick" and she wants to stop them
- What do you do now?

27

Prospective Monitoring for ADRs

- Collaboration between patient, prescribers, and TB program
- Patient education
  - Educate about potential serious ADRs from their regimen - *but <u>how</u> to educate without creating unnecessary anxiety?*
  - Educate about need to report symptoms (but don't presume they will)
- Staff education
  - Awareness of potential serious ADRs from different TB meds
  - Assess for ADR symptoms at each and every interaction
  - Document and communicate!
- Interactions: Monthly med pick ups, DOT visits, phone calls, any other

28

Prospective Monitoring for ADRs

- Medication interactions: Make sure you know about any changes in any other medications your client is taking - prescription AND all others
- Communication with other prescribers is critical, especially with patients on complicated medical regimens such as HIV co-infected and those with multiple co-morbidities
- Most drug interactions are related to Rifampin but there are a few others as well. In many instances, Rifabutin can be used in place of Rifampin
- Medication dosage adjustments:
  - Adjust for weight changes (usually wt gain on treatment)
  - Adjust for renal function

29

Common Types of Drug Toxicity (ADRs)

- **Gastrointestinal toxicity**
- **Hepatotoxicity**
- **Hypersensitivity (allergic) reactions**
- **Other dermatologic reactions**
- Joint symptoms
- Neuropathy
- Visual symptoms
- Drug fever
- Other: nephrotoxicity, hearing loss, cardiac

30

What Drug can do what?
ADRs to First Line Agents and Fluoroquinolones*

Reaction	INH	RIF	EMB	PZA	FQ
Gastrointestinal	X	X	X	X	X
Hepatotoxicity	X	X		X	X
Cutaneous	X	X	X	X	X
Periph. Neuropathy	X		X (rare)		X (rare)
Optic Neuritis	X (rare)		X		
Arthralgia	X	X (rare)		X	X
Gout			X (rare)	X	
Tendonitis					X
Flu-Like Syndromes		X			
Drug Fever	X (rare)	X (rare)	X (rare)	X (rare)	X (rare)
Hematologic	X	X	X (rare)	X (rare)	X (rare)
QT Prolongation					X
CNS	X				X

*Levofloxacin or Moxifloxacin

31

Poll 2
What symptom assessment, clinical, and laboratory monitoring are appropriate?

- Isoniazid
- Common ADRs
- Less common ADRs
- Monitoring plan

32

Poll 3

What symptom assessment, clinical, and laboratory monitoring are appropriate?

- Rifampin
- Common ADRs
- Less common ADRs
- Monitoring plan

33

Poll 4

What symptom assessment, clinical, and laboratory monitoring are appropriate?

- Ethambutol
- Common ADRs
- Less common ADRs
- Monitoring Plan

34

Poll 5

What symptom assessment, clinical, and laboratory monitoring are appropriate?

- Pyrazinamide
- Common ADRs
- Less common ADRs
- Monitoring Plan

35

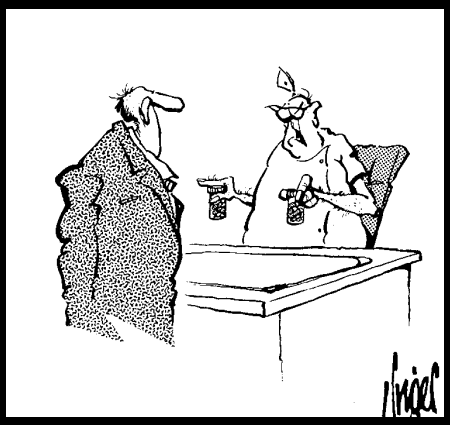
Poll 6

What symptom assessment, clinical, and laboratory monitoring are appropriate?

- Fluoroquinolones (Levofloxacin, Moxifloxacin)
- Common ADRs
- Less common ADRs
- Monitoring Plan

36

Management of Some Common ADRs to anti-Tuberculous Therapy: State of the Art



"Don't take any of these red pills, and if that doesn't work, don't take any of the blue ones"

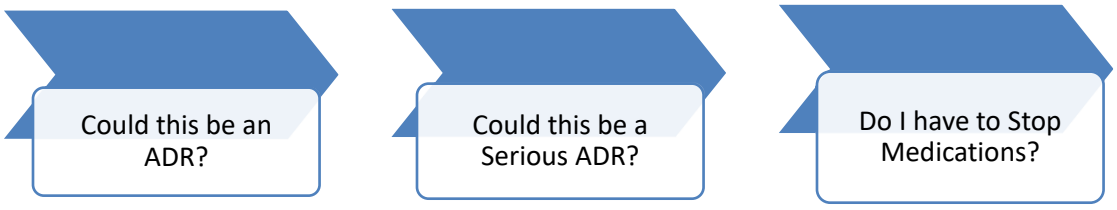
37

Back to our Client

- A 63 year-old Vietnamese-born woman is diagnosed with smear-positive pulmonary tuberculosis, GeneXpert® MTB/Rif: MTB positive, RIF^R not detected
- She is started on 4 drug anti-tuberculous therapy with RIPE + Vit. B6 and is receiving her treatment by DOT.
- About two weeks into therapy she complains to her clinic nurse that the medications are "making me sick" and she wants to stop them
- What do you do now?

38

Dr. F's Thought Process in Thinking Through Potential ADR Symptoms



Do I need to see them?
Do I need Lab work?
What do I tell them?

Do I Stop one/some/all Meds?
Do I need to start new Meds?
If I stop, When can I restart?

39

General Principles and Approach

- Pre-emptive monitoring for ADRs (baseline exam/labs)
- Evaluate likelihood that signs/symptoms due to a TB med
  - Any risk factors for toxicity?
- Rule out other common, or less common (but potentially more alarming) causes of the current presentation
  - Medication-induced nausea/vomiting vs. hepatotoxicity
- Evaluate severity of ADR → informs action plan
  - Self-limiting, supportive care, or need for alternative Rx
- Follow-up monitoring including treatment adherence

40

Case 2

- When further interviewed (using interpreter phone) our client says that when she takes her TB pills, she feels “sick to her stomach” like she might throw up and can’t eat. She has not vomited, does not have abdominal pain or dark urine. She has lost 2 lbs.
  - She has blood work done
  - ALT 51 (ULN 32, baseline was 23 before treatment); AST 38 (at the ULN), Bilirubin 0.9
- What do we do now?
- What interventions can we try?

41

Gastrointestinal (GI) Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain

➢ Overlap of GI toxicity and hepatotoxicity symptoms: Can’t tell difference without checking LFTs

42

Which Drugs are Most Likely to Cause GI toxicity (and When?)

- Almost any drug can potentially cause GI toxicity
- Often occurs early (first few weeks) of Rx
- Hierarchy: PZA > INH > RIF > EMB
- Fluoroquinolones can also cause GI toxicity but less commonly than PZA or INH
- Many of other 2nd line drugs can cause gastrointestinal toxicity (rarely injectables)
- May not have Sx with another agent from same class (Levofloxacin/Moxifloxacin, Rifampin/Rifabutin)

43

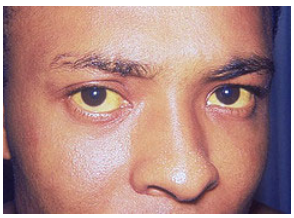
Management of GI Symptoms (after excluding hepatotoxicity)

- Change the timing of the dose
- Give meds with food (how much food?)
- Daily dosing with fewer pills rather than intermittent therapy with more pills
- Antacids 2hr before or after
- Anxiolytic if nausea occurs prior to swallowing pills
- Anti-emetics:
  - ondansetron (Zofran), prochlorperazine (Compazine), promethazine (Phenergan), hydroxyzine, metoclopramide

44

Back to our Cases

- What if her LFTs are elevated?
- What if her LFTs are:
  - ALT 90 (ULN 55)
  - AST 88 (ULN 50)
  - Bilirubin 0.5
- What if her LFTs are:
  - ALT 732 (ULN 55)
  - AST 444 (ULN 50)
  - Bilirubin 3.4



45

Hepatotoxicity: Drug Induced Liver Injury (DILI)

- Elevation in liver enzymes: ALT (AST, Bili)
- Confounders: Other drugs/supplements, alcohol, viral hepatitis, other liver/biliary tract disease, rarely TB involvement of liver
- Spectrum of hepatotoxicity
  - Can be symptomatic or asymptomatic
    - Asymptomatic, mild AST increases in up to 20% on INH
  - ATS **symptom related** threshold to **stop therapy** ALT 3x ULN
  - ATS **asymptomatic** threshold to **stop therapy** ALT 5x ULN
  - Fulminant Hepatitis (rare)
  - Fatal Hepatitis: Estimates 4-7/100,000 INH courses

46

Some Risk Factors for Hepatotoxicity from Anti-tuberculous Therapy

- Increasing age > 35
- Malnutrition or hypoalbuminemia
- PZA in regimen
- Other hepatotoxic agents
- Alcohol
- Pregnancy or post-partum (3 mos)
- Elevated baseline ALT
- HIV infection
- Multiple medical problems
- Pre-existing chronic liver disease
- Chronic Hepatitis: B and/or C
- Slow Acetylators
- Other genetic risks

47

Treatment Limiting Thresholds

- **Stop if ALT > 3 X ULN with N,V, abd. pain OR ALT > 5 X ULN in all**
- If moderate/severe TB, then continue at least 3 drugs
  - Rifampin, EMB, fluoroquinolone
  - Full Hepatic sparing regimen (no RiF): Example: EMB, FQ, linezolid
- Assess for confounders
  - Concomitant meds, OTC, supplements, herbals, EtOH
  - Acute viral hepatitis testing:
    - IgM anti–Hep A Ab; hepatitis B S Ag and IgM anti–Hep B core Ab; anti-HCV Ab and/or HCV RNA
    - Note: If Unstably housed or Injection Drug user, think Hepatitis A!!
- In rare instances, Increased LFTs can be due to TB disease

From: Am J Respir Crit Care Med. 174; 935–52, 2006

48

Monitoring on Therapy: Unexpected Events Pregnancy

- Pregnancy is not a contraindication to treating TB Disease
- May be a reason to delay treatment for TB infection
- Women of child-bearing age should be counseled to avoid becoming pregnant on TB Treatment, although most first line agents are considered safe in pregnancy
- Rifampin may interfere with efficacy of some contraceptive medications, especially oral contraceptives

49

So now we've stopped Rx, what then? Practical aspects of re-challenge

- Can restart once ALT falls to < 2 X ULN
- Many can even return to original regimen and tolerate it
- Weigh risks based on severity of hepatotoxicity
- Different strategies:
  - Sequential re-challenge: most useful to sort out hepatotoxicity cause; re-introduce a drug q. ~7 days with LFT monitoring
    - Start RIF +/- EMB, then INH, +/- PZA
    - If symptoms or LFTs ↑→ stop last drug added
    - If RIF and INH are tolerated, and **hepatitis was severe,** might not add back PZA

50

A few take home points

- Monitoring of those on anti-tuberculous therapy includes monitoring for response to therapy **and** for adverse effects of therapy
- Response to therapy can be followed by clinical, microbiologic and Radiographic assessments, especially for pulmonary disease
- Monitoring for extra pulmonary disease can be harder
- Worry about drug resistance, but there are many other reasons why patients may not be improving. Think about getting medication levels (TDM)
- Slower responses may be an indication for more prolonged treatment courses
- Adverse drug reactions to anti-tuberculous medications are common, especially on treatment for TB disease
- Monitoring for ADRs is an active and continuing process and what you monitor for may change depending on the specific treatment regimen

51