Severe TB Drug Toxicity: Unpleasant Truths and Modest Admonitions

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Objectives

After attending this lecture, participants should be able to describe:

- Serious side effects of selected TB drugs
- Predispositions for serious side effects from selected TB drugs
- Strategies to monitor patients and avoid serious side effects from selected common TB drugs

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Disclosures

- Insmed Inc.: Grant recipient, consultant, speaker
- Paratek Pharmaceuticals: Consultant

No Disclosures related to this talk

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The Wisdom of Steven Wright

- **If Barbie is so popular, why do you have to buy her friends?**

21 - Eagles may soar, but weasels don't get sucked into jet engines.

22 - What happens if you get scared half to death twice?

INH Hepatotoxicity

- Mechanisms: unknown
- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure): Approximately 4/100,000 persons completing therapy
- Generally occurs after weeks to months (rather than days to weeks)
- Risk factors: Age, alcohol consumption (> 4X î risk w/daily ETOH), pregnant and post-partum women, active hepatitis B, other hepatotoxic drugs

Am J Respir Crit Care Med. **2006** Oct 15;174(8):935-52

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Indications for LTBI treatment: a process in evolution

- Treatment for TST induration => 10 mm
- Treatment algorithm included size of TST induration and patient risk factors:
  - 5 mm: immunosuppression (HIV), contact to active case
  - 10 mm: HCW, underlying predispositions (DM), recent immigrants from high TB prevalence areas
  - 15 mm: age => 35 yrs and all other mortals
- IGRA guidelines: change with improving sensitivity and specificity of IGRA

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Evolution of Patient Monitoring for INH TBI Therapy

- 1960's to 1970's no standard monitoring
- Multiple INH-related deaths in 1970's: USPHS report
- Early/mid1980's routine clinical monitoring
- Significant fall in INH-related deaths
- Late 1980's/early 1990's Biochemical monitoring based on hepatitis risk stratification
- Mid 1990's/early 2000's no change
- Mid 2000s to now?

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56 year old female with "positive" TST Circa 2000

- Patient from Mexico, in the US for 2-3 years, living in Nacogdoches, TX
- Identified through employee TB screening in a local chicken processing plant
- Asymptomatic
- No known contact with active TB case
- Mild DM on oral agent
- **TST 12 mm induration**
- What to do?

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56 year old female with 12 mm TST Circa 2000 What to Do?

- Look for active cases and possible contacts to the patient among other workers in the chicken plant
- Discuss options (including no therapy) with the patient, through an interpreter if necessary, and provide educational material in her native language.
- Discuss risk of developing TB Disease
- Begin INH 300 mg/day with B6 25 mg/day
- ?Baseline liver enzymes, bilirubin etc.

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56 year old female with 12 mm TST Circa 2000 What Should You Do?

- No problems in first 2 months with INH
- Adherent with HD appointments and medication renewals
- After 2-3 months of INH, she develops rapid onset (days) abdominal pain, nausea and vomiting. No reported jaundice
- Does not immediately seek help, waits 2-3 days even after symptoms progress and continues INH
- What to do?

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56 year old female with 12 mm TST Circa 2000, with new onset vomiting What Should You Do (understanding that she is MIA)?

- Call in Phenergan suppositories and tell her to continue the INH
- Tell her that if she is not better by the next day to call someone who knows more than you about INH toxicity (Leave for your scheduled trip to Puerta Vellarta to do “TB field work” in Mexico)
- Tell her to stop INH immediately
- Tell her to go to an ED immediately
- Follow-up with the ED (if they do not contact you)
- HD staff unable to reach patient by phone, also attempted home visit/no one in the home

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56 year old female with 12 mm TST Circa 2000, with new onset vomiting and no contact with HD

What did she do?

- Patient visits community hospital ED and is sent home with antiemetic and no instruction to stop INH
- Patient cannot be contacted and in turn does NOT contact the HD
- She goes, instead, to a community hospital ED where she is found to have elevated AST, ALT and bilirubin, and is given IV fluid, sent home, and NOT told to stop INH
- Still no contact with HD. Goes back to community hospital ED and is admitted with ???
- To be continued….

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Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494–497.

- CDC project to monitor SAEs with treatment of LTBI 2004-2008
- 17 patients with SAEs, all hepatotoxicity
  - 2 children < 15 yrs of age
  - Adults median age 39
  - Diagnosed between 2nd and 9th month
  - One patient seropositive for Hep C, HIV
  - 5/17 liver transplant (one child), 5/17 died (one transplant)

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Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494–497.

- 10 patients who had CDC on-site investigation
- All patients with appropriate: indications for LTBI treatment, INH dosing, medication adherence, monthly clinical monitoring
- 5 patients baseline ALT WNL, Monthly ALT 2 patients

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Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494–497.

- Symptoms 1-7 months after INH started
- Fatigue, nausea, abdominal pain in 7 patients who waited for jaundice to seek medical attention
- 7/10 patients diagnosed by provider other than the prescriber of INH
- ***2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset, all after medical instruction***

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Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494–497.

- Death and liver transplantation approximately 1/150,000- 1/220,000 patients receiving LTBI treatment
- All patients monitored according to current guidelines
- SAEs idiosyncratic reaction, independent of dosing, possible anytime during treatment, can occur in children

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Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

Snider DE, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. Am Rev Respir Dis 1992;145:494–497.

- "Medical providers should emphasize to patients that INH treatment should be stopped immediately upon the earliest onset of symptoms (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

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56 year old female with 12 mm TST Circa 2000, with new onset vomiting and no contact with HD

- Patient admitted to Community Hospital with hepatic and renal failure
- Transferred to Tertiary Care Center in Houston for liver/kidney transplant
- Patient dies shortly after transfer to Houston hospital
- The patient's family brought wrongful death lawsuits against the TX Department of Health (including the TDH Commissioner, the Nacogdoches Regional TDH Director, the entire staff of the Nacogdoches TB clinic and David E. Griffith, MD, Medical Director of the Nacogdoches TB Clinic).

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56 year old female with 12 mm TST Circa 2000, with new onset vomiting What went wrong?

- Patient did not contact HD with onset of abdominal symptoms c/w hepatitis
- She continued INH while symptomatic
- She went to an outside health facility (rather than the HD) with no TB experience who did not stop the INH initially
- She did not stop INH until after admission to the Community Hospital with hepato-renal syndrome

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56 year old female with 12 mm TST Circa 2000, with new onset vomiting and no contact with HD

What did the HD do right?

- The patient met guidelines criteria for receiving INH
- She received extensive education before receiving INH that was DOCUMENTED!
- She had monthly clinical follow-up and biochemical follow-up with AST, ALT and bilirubin
- The HD documented several attempts to contact the patient by phone and a home visit.
- **CLINICAL FOLLOW-UP AND METICULOUS RECORD KEEPING ARE EVERYONE'S SHIELD AGAINST A LAWSUIT**
- The lawsuit was dropped and all defendants (including your humble narrator) were held harmless and also dropped with the lawsuit.

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TB Disease: Baseline Testing and Monitoring

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]	☐									

IDSA guideline 2016

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- **Monitoring. Routine monitoring is not necessary**. However, for patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of the drug, liver function tests should be measured monthly and when symptoms occur.

Blumberg HM, et al. ATS/CDC/IDSA: treatment of tuberculosis Am J Respir Crit Care Med. **2003** Feb 15;167(4):603-62.

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The Wisdom of Steven Wright

- **- I almost had a psychic girlfriend, ... But she left me before we met.**
  12 - OK, so what's the speed of dark?
  13 - How do you tell when you're out of invisible ink?

Isoniazid Hepatotoxicity: Interventions (AJRCCM, **2006;** 174: 935-952)

- **Baseline blood tests are generally not recommended for healthy patients treated with isoniazid or rifampin**. ALT alanine aminotransferase; DILI drug-induced liver injury; depending on the perceived hepatotoxicity risk, effectiveness of patient education, and the stability of ALT.
- **Baseline and follow-up serum ALT and bilirubin are recommended for patients with a possible liver disorder**; those with a history of chronic liver disease (e.g., chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis), patients with chronic use of alcohol, those with HIV infection treated with HAART, pregnant women, and those who are up to 3 months postpartum.
- **Baseline laboratory testing should be considered individually for patients receiving other medications and for those with chronic medical conditions .**
- Some experts recommend that healthy individuals **older than 35 years** treated with isoniazid or isoniazid with rifampin have baseline and scheduled monitoring of ALT.
- ALT is preferred for detecting and tracking hepatocellular injury

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Isoniazid Hepatotoxicity: Interventions (AJRCCM, **2006;** 174: 935-952)

- Patients with baseline transaminases more than three times the ULN should have ALT retested along with bilirubin,
- **The decision to treat LTBI, or more likely to defer, should be carefully made on a case-by-case basis, weighing the risk of progression to TB disease against the risk of isoniazid or rifampin-related DILI.**
- Factors influencing the latter include degree of baseline ALT elevation, alcohol consumption, age, and evidence of active replication of hepatitis virus. If treatment is started, some experts recommend measuring serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months, and as necessary.
- Some experts recommend monitoring transaminases in individuals treated with a combination of pyrazinamide hepatitis B virus; HCV hepatitis C virus; HepBsAg hepatitis B surface and a fluoroquinolone or ethambutol for contact with a patient with MDR TB.

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Isoniazid Hepatotoxicity: Interventions (AJRCCM, **2006;** 174: 935-952)

- "Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms"*
- "A rapid increase in ALT may be an indication for more frequent monitoring…"
- Consider rechallenge (many caveats)
- Where did this come from?

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Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. **2016** Oct 1;63(7):e147-e195.

- Drug-induced hepatitis is the most frequent serious adverse reaction to the first-line drugs. INH, RIF, and PZA can cause drug-induced liver injury (DILI), which is suspected when the **ALT level is ≥3 times the upper limit of normal in the presence of hepatitis symptoms, or ≥5 the upper limit of normal in the absence of symptoms.** In either situation, hepatotoxic drugs are stopped immediately and the patient is evaluated carefully.
- Other causes of abnormal liver function tests must be excluded before diagnosing drug-induced hepatotoxicity.
- An official American Thoracic Society statement on the hepatotoxicity of antituberculosis therapy (http://www.thoracic.org/statements/resources/mtpi/hepatotoxicity-of-antituberculosis-therapy.pdf (**guess what this is**)?

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Patient monitoring

Adverse Events During TB Treatment: for healthcare providers **April, 2025**

- Obtaining a detailed and accurate medical history and updating information at frequent intervals will identify persons who require close monitoring during TB treatment.
- The type and frequency of monitoring depends on the drugs used and the patient's risk for adverse reactions (e.g., age or alcohol use). **At a minimum, health care providers should conduct monthly examinations and ask patients about any side effects from medication.**

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Saukkonen JJ,. Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical PracticeGuideline. Am J Respir Crit Care Med**. 2025** Jan;211(1):15-33

There is insufficient evidence to support systematic testing of baseline liver function in people on regimens containing isoniazid and/or rifamycins.

- This is, however, strongly encouraged, where feasible and resources permit, for individuals with the following risk factors: history of liver disease, harmful use of alcohol, chronic liver disease, HIV infection, age > 35 years, pregnancy or in the immediate post-partum period (within 3 months of delivery).
- For individuals with abnormal baseline test results, sound clinical judgement is required to ensure that the benefit of TPT outweighs the risks, with routine testing at subsequent visits.

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TST and IGRA

- Intent to test is intent to treat
- Intent to test is intent to think (John Bernardo, MD, TB Icon, Chobian and Avedisian School of Medicine)
- TST/QFT are tests, not diagnoses

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DILI (Drug Induced Liver Injury)

- Isoniazid (INH)
- Rifamycins: Rifampin, Rifabutin, Rifapentine
- Pyrazinamide (PZA)
- Oxazolidinones: Linezolid, Tedizolid
- Ethionamide/Prothionamide
- Para-aminosalicylic acid (PSA)
- Rarely (Really?): Ethambutol, Streptomycin, Flouroquinolones

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DILI definition

- DILI: if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms
  - Saukkonen JJ,. Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical PracticeGuideline. Am J Respir Crit Care Med**. 2025** Jan;211(1):15-33
- "Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms"
- **Clinician experience and expert opinion: originally applied to INH but extrapolated to other TB medications**

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The wisdom of Steven Wright

- **The colder the x-ray table, the more of your body is required to be on it.**

33 - Everyone has a photographic memory; some just don't have film.

34 - If at first you don't succeed, skydiving is not for you.

35 - If your car could travel at the speed of light, would your headlights work?

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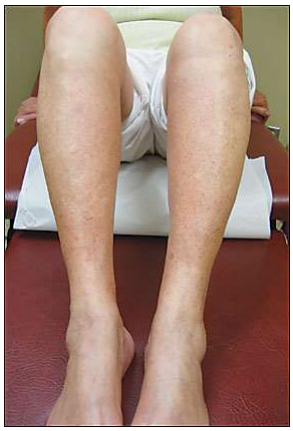
37 year old man started on IREZ 2 months ago,shows up in clinic with LE rash



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Thrombocytopenia—A Rare But Potentially Serious Side Effect of Initial Daily and Interrupted Use of Rifampicin

- Occurrence generally rare, < 1 % of patients receiving daily rifampin
- it is estimated that up to 6% of patients receiving high-dose twice-weekly rifampicin develop this condition.
- The risk increases significantly with high-dose intermittent therapy (e.g., twice weekly) rather than daily, low-dose administration.
- **Interruption Risk: Re-starting rifampin after a treatment gap increases the risk of severe reactions.**
- Mechanism: Rifampin induces the formation of antibodies that cause complement fixation and destruction of platelets.
- **Recovery: generally reversible upon discontinuation of the drug.**

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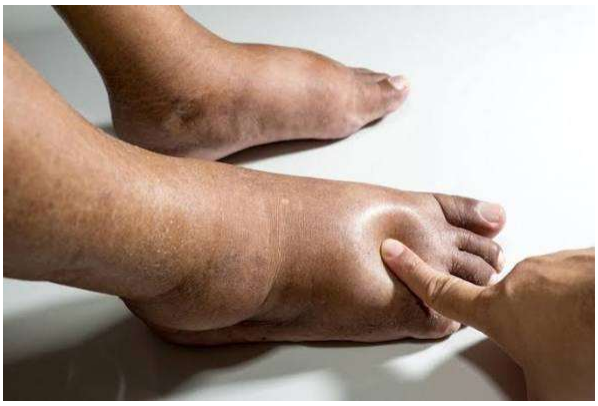
52 year old man shows up in clinic with nausea, and swollen feet/ankles



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Rifampin-induced acute kidney injury and hemolysis: A case report and literature review

Fateen A. Chest 2022 Dec 21;10(12):e6780

- Rare, some retrospective studies suggest an incidence of around 0.1% of TB patients.
- It is thought to be immune-mediated, frequently occurring with intermittent (twice-weekly) rather than daily therapy.
- Clinical presentation often includes "flu-like" symptoms, gastrointestinal distress, and fever.
- Prognosis is generally excellent, with up to patients achieving full renal recovery upon immediate discontinuation of the drug.
- Pathology: The injury is commonly associated with acute interstitial nephritis, though acute tubular necrosis is also seen.

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Guidelines for monitoring rifampin therapy

- Bupkiss, Nada, Zero, Zed
- ?routine CBC, CMP

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Ethambutol ocular toxicity: Case Report

- 60-year-old patient from Arkansas, diagnosed with MAC lung disease in August 2021 Started on azithromycin ethambutol and rifampin. Developed decreased hearing, switched from azi to clari early 2022
- Seen at NJH early October, 2022. Negative eye exam. She continued clarithromycin, rifampin and ethambutol at 17 mg/kg/day
- Soon after return to Arkansas from NJH she developed rapidly diminished visual acuity in November 2022.
- What to do?

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Ethambutol ocular toxicity: Case Report

- The ethambutol was discontinued but her visual acuity continued to decline from November 2022 to February 2023. She noted that she was "legally blind" for much of that time.
- Her visual acuity began to improve after February 2023. But it took many months before she could legally drive. At that point she was on rifampin clarithromycin and moxifloxacin.
- She was placed on ALIS with continued sputum culture neg meds 8/15/2023

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Drastically progressive ethambutol induced optic neuropathy after withdrawal of ethambutol:

Matsumoto T et al. Inter Med 2020; 60: 1785

- 85-year-old patient with bronchiectasis and extensive MAC lung disease.
- Initial antibiotic therapy: Clarithromycin 800 mg/day, rifampin 400 mg/day, and ethambutol 750 mg/day (body weight 62 kg, ethambutol 12 mg/kg). Normal renal function.
- **After starting ethambutol monitoring of visual impairment was left to him with private opthalmologist.**
- Initial ophthalmologic exam visual acuity 20/20 in both eyes and no color vision in impairment
- **Day 75 of treatment he experienced blurred vision.**
  - **Private ophthalmologist did not recommend discontinuation of ethambutol.**
  - **Referred to an ophthalmologist recommended by the authors**
  - **On day 85 of treatment; stopped ethambutol.**
  - **Total duration ethambutol administration 2.5 months.**

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Drastically progressive ethambutol induced optic neuropathy after withdrawal of ethambutol:

Matsumoto T et al. Inter Med, 2020; 60: 1785

- Ocular exam remained unchanged with the exception of:
  - Automated perimetry which showed mild enlargement of the blind spot.
  - Optimal coherence tomography showed the retinal nerve fiber layer thickness was within normal range.

Corrected visual acuity drastically worsened to 20/300 right eye and 20/1,000 left eye within 3 weeks. Brain MRI suggested optic perineuritis.

- 4 months after ethambutol, no significant change in vision
- There is no safe dose of which EOM can be avoided and therefore:
  - We may need to monitor for EOM even in cases of low dose ethambutol“
  - “It might have been better to choose a 3 times per week regimen in this case"

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Ethambutol induced optic neuropathy and mycobacterial disease

Yang S et al. Int J Tuberc Lung Dis 25: 2021: 680

- 237 patients taking ethambutol, mean age 73 years,
  - 18 (7.5%) reported visual changes
  - 219 patients without visual changes
- Of the 18 patients with visual changes 16 had an ophthalmology evaluation;
  - 5 (28%) had confirmed EOM,
  - 6 (33%) suspected,
  - 3 (17%) were inconclusive
  - 2 (11%) did not
- Main ethambutol dose was 16.5 mg/kg/day,
  - **Steady-state peak ethambutol serum concentration available for 7 (39%)**
  - **In the visual change cohort 1.55 mcg/mL**
  - **in the full visual change cohort 2.12**
  - **In those without visual changes 2.49 mcg/mL and.**

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Ethambutol induced optic neuropathy and mycobacterial disease

Yang S et al. Int J Tuberc Lung Dis 25: 2021: 680

- 1 patient received a comprehensive ophthalmic evaluation at baseline,
  - **only 5 (28%) patients receive color vision testing either at the initiation of ethambutol or at follow-up visits with primary prescribing physicians.**
  - All 18 patients had ethambutol adjustments due to self-reported visual changes:
  - 17 stopped ethambutol 1 lowered ethambutol dosage from 1000 mg to 800 mg/day
  - **the mean time to ethambutol termination due to vision changes was 290 days.**
  - Subsequently 2 restarted ethambutol
  - EOM affected vision after an average duration of 10 months with ethambutol of either 19.2 mg/kg daily over 21.9 mg/kg 3 times per week

- **There was no association but ethambutol serum levels within the first few months after treatment start and later visual complaints. Expected serum reference ranges 2 to 6 mcg/mL**

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Ethambutol ocular toxicity in treatment regimens for MAC lung disease

Griffith DE, AJRCCM, 2005: 172: 250

- 229 patients with MAC lung disease
- 50 patients with pre-existing ocular disease
- While on EMB 97 (42%) patients developed consulted and ophthalmologist: 90% with alternative diagnosis
- 24 (10%) stopped EMB temporarily
- 8/139 (6%) daily, 0/90 TIW had ocular toxicity (p= 0.05)
- None diagnosed during clinic toxicity exam
- All returned to baseline ocular status after stopping EMB

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Incidence of toxic optic neuropathy with low dose ethambutol

Yang HK, Int J Tuberc Lung Dis: 2016; 20; 261

- Retrospective study of 415 patients
- 3 (0.7%) develop toxic optic neuropathy over a 6-year period.
- Visual acuity, visual field, color vision and fundus examination was evaluated at baseline and every 3 months or whenever patient reporting any subjective symptoms of visual deterioration.
- **Of 289 patients prescribed a dose of ethambutol =< 15 mg/kg/day, only 1 (0.3%) developed toxic optic neuropathy**
- The incidence of ethambutol induced optic neuropathy among Koreans is estimated to be 0.7% and can be reduced with lower doses of ethambutol

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Factors affecting visual recovery in patients with ethambutol induced optic neuropathy

Srithawatpong S. et al. Clinical Opthalmology 2023: 17: 545

- Retrospective study of 5394 patient's treated with ethambutol. Uni-variant in multivariate relationships between various factors and visual recovery were evaluated using regression analysis.
- 23 patients (0.43%) diagnosed with ethambutol induced ocular neuropathy.
- **Logistic regression analysis on female gender was the categorical factor significantly associated with good visual recovery**
- **Linear regression analysis identified good initial visual acuity as the numerical factor significantly related to it.**
- **After adjustment with multivariate analysis, initial visual acuity was found to be the only significant factor associated with visual recovery**
- **All patients with initial visual acuity is better than 20/200 at the first visit achieved good visual recovery.**
- **The incidence of ethambutol ocular neuropathy treated with ethambutol was 0.43%. Good visual recovery was noted in 39% of these patients and initial visual acuity was the factor that affected visual recovery**

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Visual recovery time in patients with ethambutol induced toxic optic neuropathy

An HR et al. Korean J Opthalmologh 2024: 38: 91

- A retrospective cohort study of 35 eyes from 35 patients with EOM.
- Patients were observed following discontinuation of ethambutol with a mean follow-up period of 21±16 months.
- 21 (77%) showed significant visual recovery, the mean estimated time for visual recovery was 15±3 months, and 50% of the patients experience visual recovery at 8±2.2 months following ethambutol discontinuation.
- **Multivariate Cox regression analysis identified several significant risk factors for delayed visual recovery including**
  - **Duration of ethambutol medication equal to or less than 6 months,.**
  - **From symptom onset to ethambutol discontinuation greater than 14 days**
  - **Baseline peripapillary retinal nerve fiber layer thickness greater than 98 mm**
- **This study indicated a mean time of visual recovery of 15 months for EOM cases. Patients diagnosed with a EOM should be followed up for more than 1 to 2 years to evaluate their visual recovery.**

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Ethambutol dosing

- Dosing based on actual weight is acceptable in patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. Some clinicians prefer a modified IBW (IBW + [0.40 × (actual weight – IBW)]) as is done for initial aminoglycoside doses.
- Because tuberculosis drug dosing for obese patients has not been established, therapeutic drug monitoring may be considered for such patients.

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Monitoring ethambutol therapy

Blumberg HM, et al. ATS/CDC/IDSA: treatment of tuberculosis Am J Respir Crit Care Med. **2003** Feb 15;167(4):603-62.

- Patients should have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara tests).
- At each monthly visit patients should be questioned regarding possible visual disturbances including blurred vision or scotomata.
- Monthly testing of visual acuity and color discrimination is recommended for patients taking doses greater than 15–20 mg/kg, patients receiving the drug for longer than 2 months, and any patient with renal insufficiency.
- Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in vision. EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

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Monitoring ethambutol therapy

- Poor man's ocular toxicity monitoring
  - Weekly reading consistent font, distance from eyes
  - On-line color vision plates
  - The problem with opthalmologists
    - No experience with TB
    - They don't care about stopping EMB

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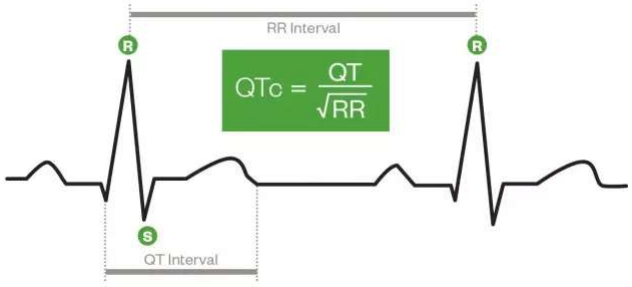
QTc Prolongation



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QTc Prolongation

- 73 year old college professor in Russia on sabbatical
- Arrested and convicted of espionage
- Sentenced to 5 years in a Russian prison but released after 2 years
- Returns to US with cough and weight loss
- CXR c/w TB, sputum 4+ AFB smear positive
- MDDR testing shows resistance to I,R,E,Z
- EKG shows QTc 490 msc
- What to do?

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QTc Prolongation

- **Key TB drugs include:**
  - **bedaquiline (BDQ)**
  - **delamanid (DLM)**
  - **clofazimine (CFZ)**
  - **fluoroquinolones like moxifloxacin (MFX).**
  - **Monitoring ECGs (especially if QTc > 500 ms) and electrolytes is crucial for safe management.**

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QTc prolongation

- For drugs that increase the QTc interval by less than 20 ms the data are inconclusive with regard to arrhythmic risk
  - **a change in baseline QTc of >20 ms should raise concern and a change of >60 ms should raise greater concern regarding the potential for arrhythmias**
  - **evidence from congenital long QT syndrome indicates that for every 10 ms increase in QTc there is a 5-7% increase in risk of torsades de pointes**
- drug-induced QT prolongation is often dose related and risk of torsades de pointes is increased with intravenous administration (particularly if given rapidly)

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QTc Prolongaton

- Female (~2 times increased risk ventricular arrythmia),
- QTc >500 ms (2 to 3 times increased risk ventricular arrythmia),
- QTc >60 ms over previous baseline (for every 10 ms increase in the QTc, there is a 5–7% increased risk for developing TdP),
- history of syncope or presyncope,
- history of TdP, bradycardia,
- liver or kidney disease (by increasing blood levels of QT-prolonging medications), medications that cause QTc prolongation (high doses, fast infusions, combination of medications), medications that inhibit CYP3A4, electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)

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TB Drug Monitoring

- It is challenging to the extreme trying to fit low incidence, serendipitous or idiosyncratic adverse events in a treatment decision algorithm
- The majority of people treated for TB do well without serious medication side effects.
  - Is this a cost/benefit question or zero tolerance question?
- What goals are we trying to accomplish with drug treatment monitoring and can we reach those goals?
  - Make our best effort to protect our patients from serious AE's (rhetorical question, of course)
  - Protect ourselves from Plaintiffs attorneys (non rhetorical/ visceral)
  - Are we fooling ourselves?

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The wisdom of Steven Wright

- **- If at first you don't succeed, destroy all evidence that you tried.**

26 - A conclusion is the place where you got tired of thinking.

27 - Experience is something you don't get until just after you need it.

28 - The hardness of the butter is proportional to the softness of the bread.

29 - To steal ideas from one person is plagiarism; to steal from many is research.

30 - The problem with the gene pool is that there is no lifeguard.