Treatment of NTM: Medication Side Effects

"Is the Treatment Really Worse Than The Disease?"

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National Jewish Health

NTM Provider Course

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Disclosures

- None

Overview

- The treatment of NTM should not be worse than the disease!
- You have a friend in National Jewish Health
- Take the time to understand the antibiotics
- Take time to understand your patient

Treatment of Slow Growing NTM

- Rifampin
- Rifabutin
- Ethambutol
- Azithromycin
- Clarithromycin
- IV Amikacin
- Inhaled Amikacin
- Clofazimine
- Moxifloxacin

Toxicity - Nausea and vomiting

Any Drug Can Cause a Rash

Rifampin Toxicity

- Hematologic
- Hepatotoxicity
- Nephrotoxicity
- Hypersensitivity
- “Influenza syndrome”
- “Respiratory syndrome”
- Other

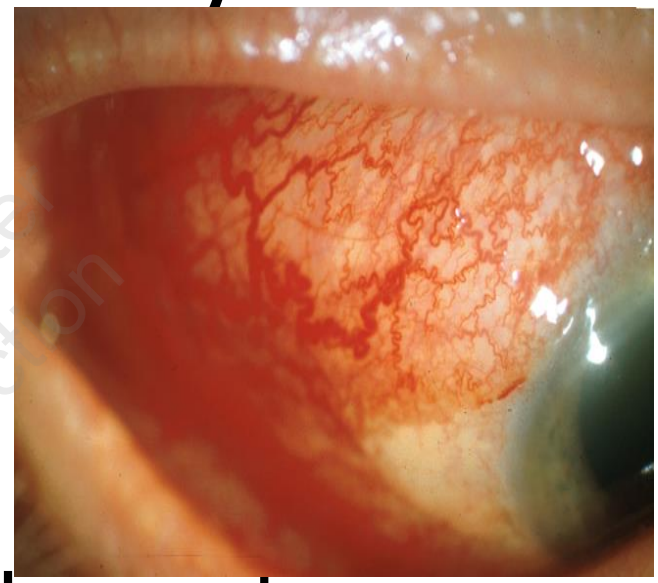
Rifampin Toxicity/Side Effects

- **Inactivates birth control**
- **Lowers endogenous/exogenous hormones**
- Hepatitis
- Drug induced lupus with positive antihistone antibody
- Fever
- Rash
- Leukopenia, Thrombocytopenia
- Nausea and vomiting
- Acute kidney injury

Toxicity - Rifabutin

- Hepatitis
- Uveitis
- Arthritis
- Fever
- Thrombocytopenia, Leukopenia
- Drug induced lupus
- Nausea and vomiting

Rifabutin Toxicity



- Hepatitis
- Uveitis
- Arthritis
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Case 1

- 55 y/o female started on rifampin, ethambutol, moxifloxacin and azithromycin for pulmonary M. chimaera infection
- 2 month f/u shows WBC of 2.0
- What are your thoughts about the WBC?

- What should you do?

What is the Cause of the Low WBC?

1. Rifampin
2. Moxifloxacin

What Would You Do Now?

1. Look at baseline WBC prior to starting treatment
2. Look at the platelet count as well
3. What is the ANC?
4. Stop the rifampin and recheck the CBC in 3 or 4 days

Unnecessary Bone Marrow Biopsy

Rifampin Drug Interactions

Very Potent Inducer of enzyme P450 3A4

As well as other P450 1A2, 2A6, 2B6, 2C8/9, 2C19

- **OCs/HRT/thyroid medications**
- **Glucocorticoids**
- **Clarithromycin**
- **Azole antifungals**
- Methadone
- Quinidine
- Theophylline
- Warfarin
- Verapamil, Diltiazem
- Sulfonylureas
- Digoxin
- Beta blockers
- Phenytoin, CBZ
- **Cyclosporine**
- Protease inhibitors
- Diazepam

Case 2

- 66 y/o male with Interstitial Pulmonary Fibrosis and sputum specimens are smear and culture positive for M. avium x 3. He is requiring 6 liters of supplemental oxygen in Denver. He is seen by ILD service and started on 40 mg of prednisone with minimal response at 2 weeks. Current medication are: rifampin, ethambutol, azithromycin, mycophenolate mofetil, pantoprazole
- Why might he not be responding to the prednisone?

Why might his oxygenation be prednisone unresponsive?

- Remember, if you are co-administering prednisone and rifampin, you must double the dose of desired prednisone to overcome the hypermetabolism of the prednisone because of the induction of the CYP450 3A by rifampin

Chen J; Ann Clin Microb. 2006:Feb 15;5:3

Case 3

- 51 year old male with refractory pulm M. avium
- Pneumonia 2009 – AFB smear positive
  - Placed in Isolation
  - CT done at that time showed thick walled RUL cavity extending to ssRLL
  - Started on clarithromycin, ethambutol and rifampin all administered thrice weekly
  - Thoughts?

CXR from 4/2016

Case 3

- Lost to f/u until 2011
- 6/2011 seen by Infectious Disease
  - Increased DOE, cough and fatigue
  - Urine histo Ag done - ? Result
  - Blasto, cocci, histo Ag done - ?result
  - Sputum smear and cx positive for M. avium
- 2/2012 – Started on rifampin, ethambutol and azithromycin daily

Case 3

- Bronchoscopy 2/2012
  - Culture positive for Histoplasma capsulatum
  - Started itraconazole liquid 200mg BID
- 4/2012
  - Itraconazole solution increased to 200mg TID
- 5/2012
  - Itraconazole solution decreased to 200mg BID secondary to side effects

Case 3

- 1/2013 – itraconazole discontinued after 1 year of treatment
- 9/2013- Sputum continues smear and cx positive for M. avium
  - ciprofloxacin, clarithromycin, rifampin, ethambutol
  - NEW SENSITIVITIES NOW SHOW CLARITHROMYCIN RESISTANCE
  - clarithromycin discontinued and linezolid is started (600mg BID)

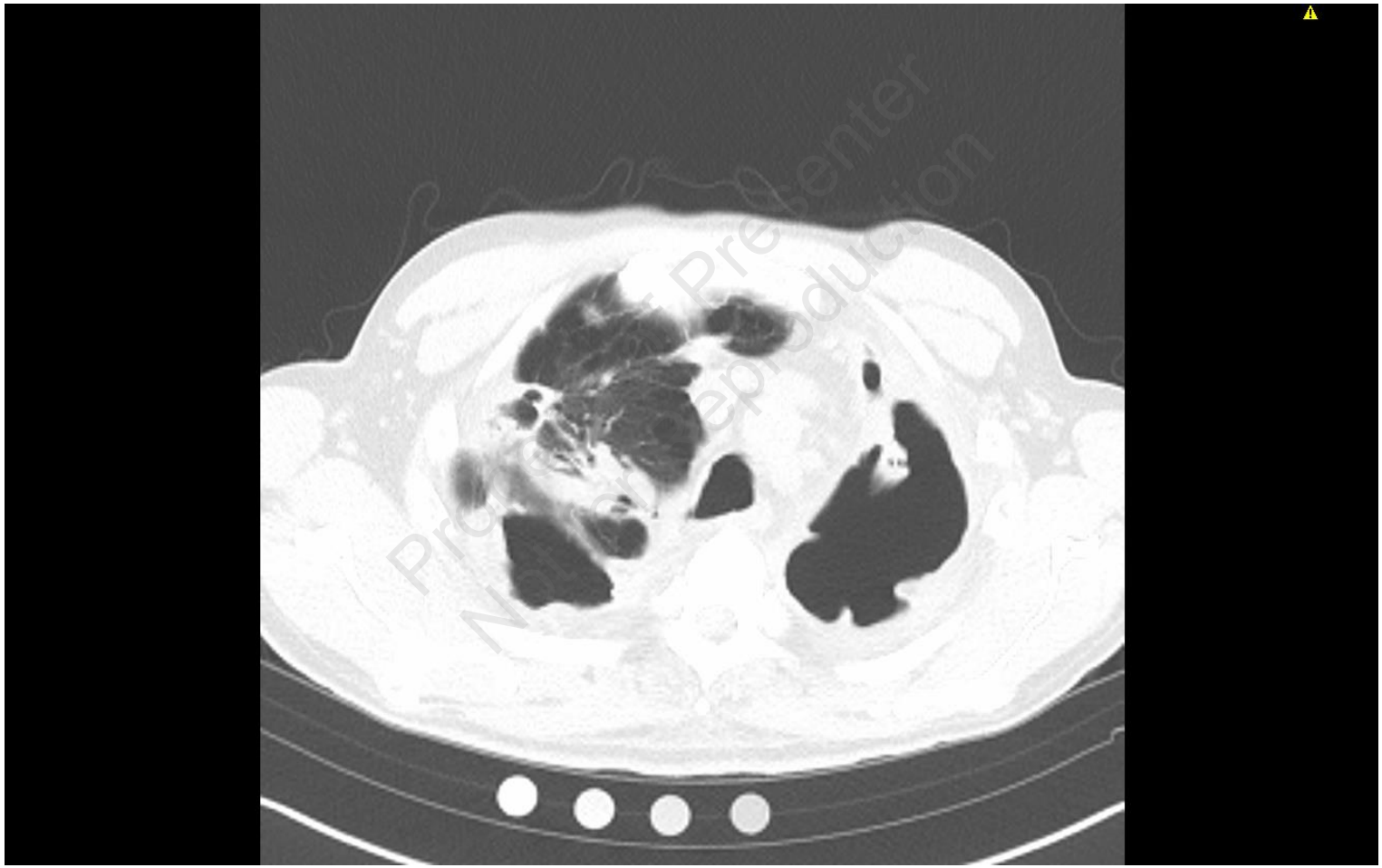
Case 3

- 1/2015 – ciprofloxacin discontinued and moxifloxacin started (400mg daily)
  - moxifloxacin/ linezolid/ ethambutol/ rifampin all daily
  - IV amikacin started and given M,W,F x 2 months
- 3/2015 – IV amikacin discontinued and started on inhaled amikacin
  - Severe coughing with inhaled amikacin
- Thoughts?

Case 3

- Admitted to NJH 9/14/16
  - Meds: Rifabutin/ Itraconazole/ inh Amikacin/ Ethambutol
- Labs
  - WBC 2.5 Hct – 40 Hgb – 12.9 Plt – 120K
  - RDW 19% 61% neut/ 9% bands/ 18% mono/ 12% lymphs
  - CRP 3.25 (< 0.4)
  - Biochems all normal
  - Vit D 34 (30-100)
  - Pre adm sputum: smear (-); 50 colonies of MACROLIDE RESISTANT M. avium; Histoplama capsulatum

Case 3 – CT scan 2016



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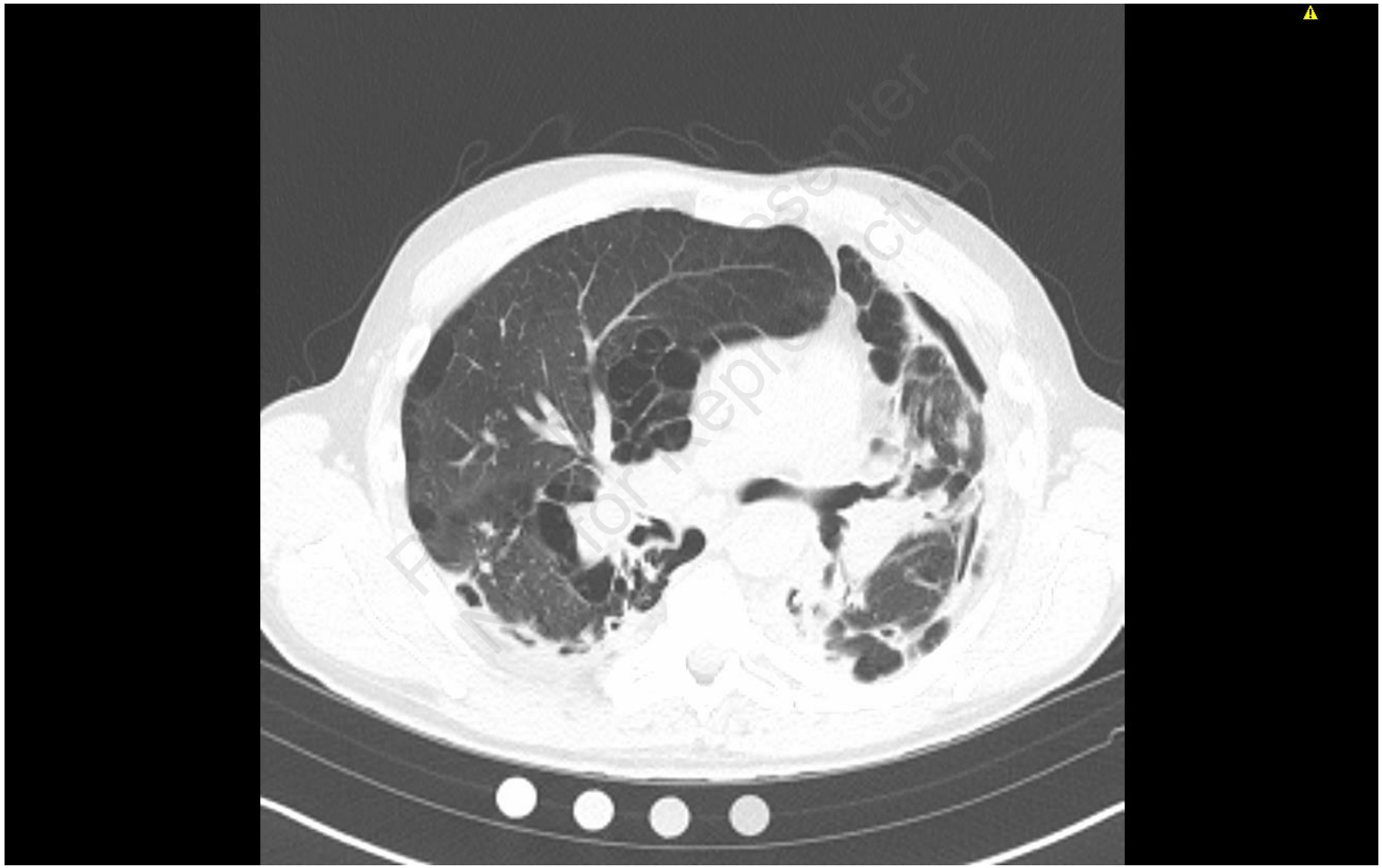
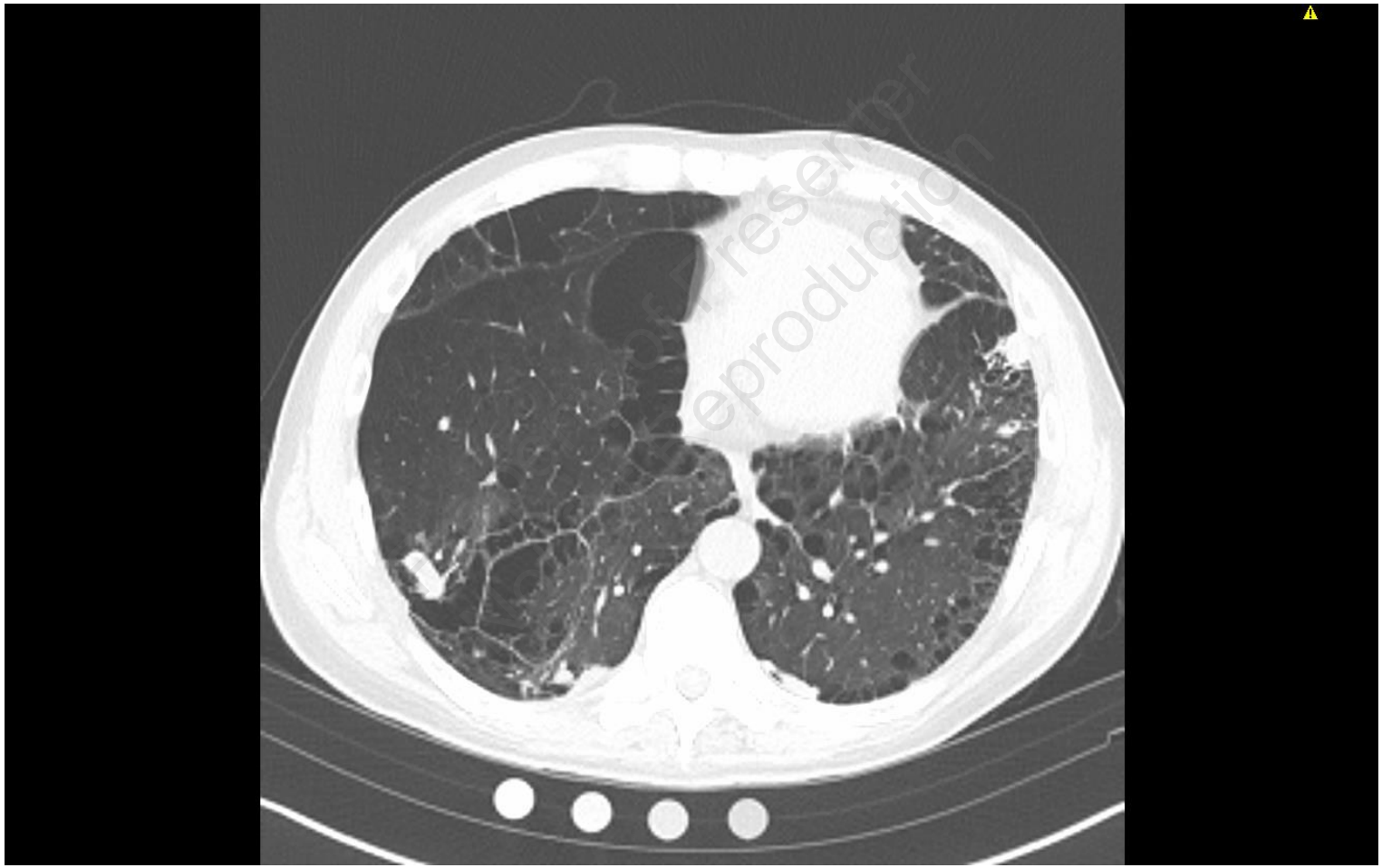
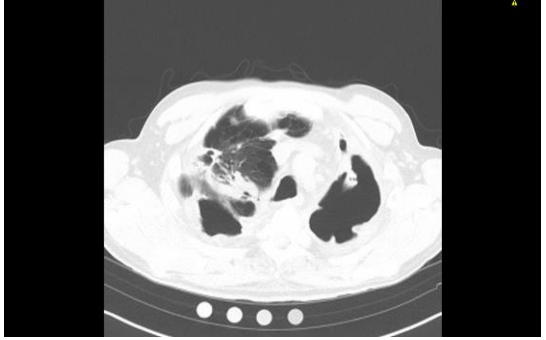


Case 3- CT scan 2016





Case 3

- What are the major medication issues?
  - What diseases do you treat?
    - M. avium
    - Histo
    - COPD
  - What medications do you use in this case?
    - What are major drug – drug interactions are important here?

Audience Response Question #1

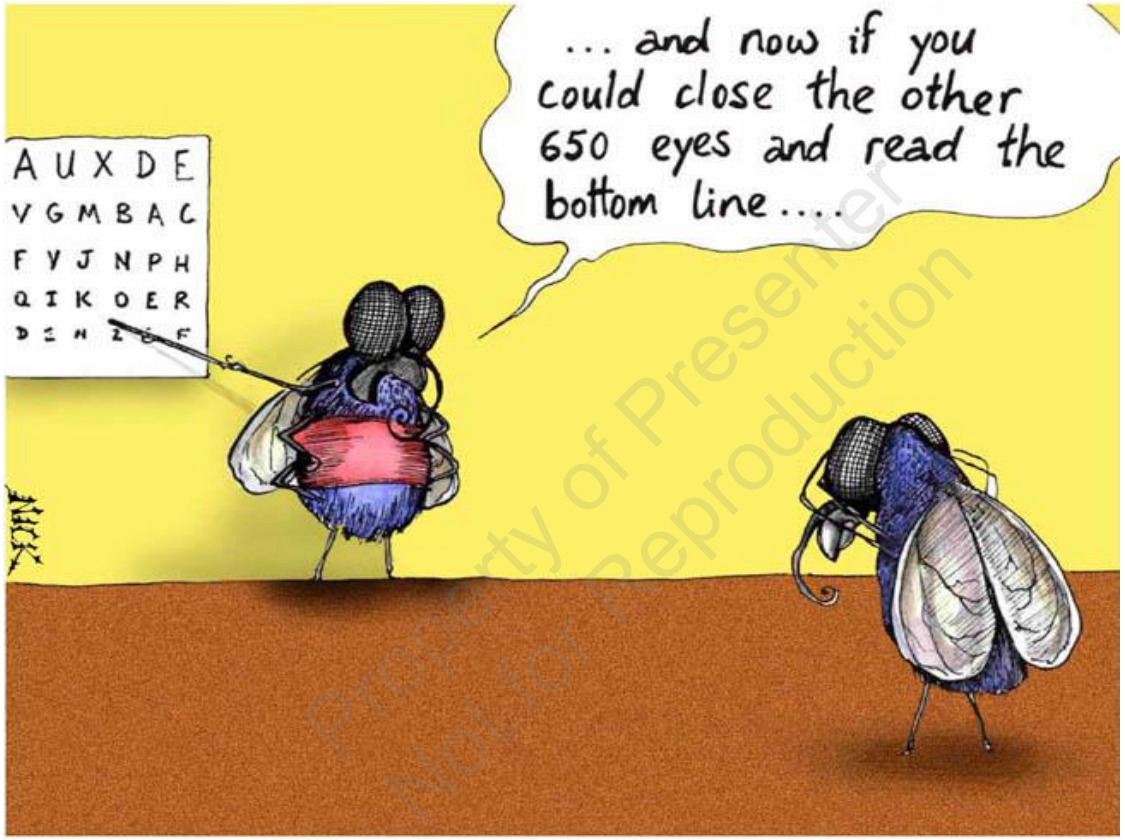
- Which medication can cause significant accumulation of rifabutin if given as part of a multidrug regimen for M. avium infection?
  1. Clarithromycin
  2. Ethambutol
  3. Azithromycin
  4. Imipenem

Case 4 - presentation

- 76 year old female on rifampin, ethambutol, and azithromycin each given once daily for M. intracellulare
- 2 months later reported visual changes to local MD, but no med changes were made. Told her this was likely secondary to (known) cataracts
- What would you do in this situation?

Case 4 - presentation

- At 2 months and 7 days, she could not read newspaper; legally blind
- Vision returned to normal over 1 years, and doing fine 2 years later.
- She had cataracts removed later.



Fly Hell.

Toxicity - Ethambutol induced optic neuritis

Ethambutol Toxicity

- Optic Neuritis (ON)
- Hyperuricemia
- Peripheral Neuropathy (PN)
- Hypersensitivity
- Hair loss

REMEMBER THAT ETHAMBUTOL IS CLEARED THROUGH THE KIDNEY!

Ethambutol Monitoring

- Regular self-assessment of color vision and acuity at home
- Referral to a neuroopthalmologist
- Visual evoked potential test show earliest changes
- Use with caution in renal failure

Kim KL, Park SP Cutan Ocul Toxicol. 2016 Sep;35(3):228-32

Audience Response Question #2

- If you suspect ethambutol induced optic neuritis, what is your first recommendation to the patient?

  1. Lower the frequency of administration from daily to thrice weekly
  2. Ask the patient to continue the antibiotic, and see an ophthalmologist as soon as possible
  3. Stop the ethambutol immediately and ask the patient to see an ophthalmologist as soon as possible
  4. Start prednisone and have the patient see an ophthalmologist as soon as possible

Azithromycin/Clarithromycin

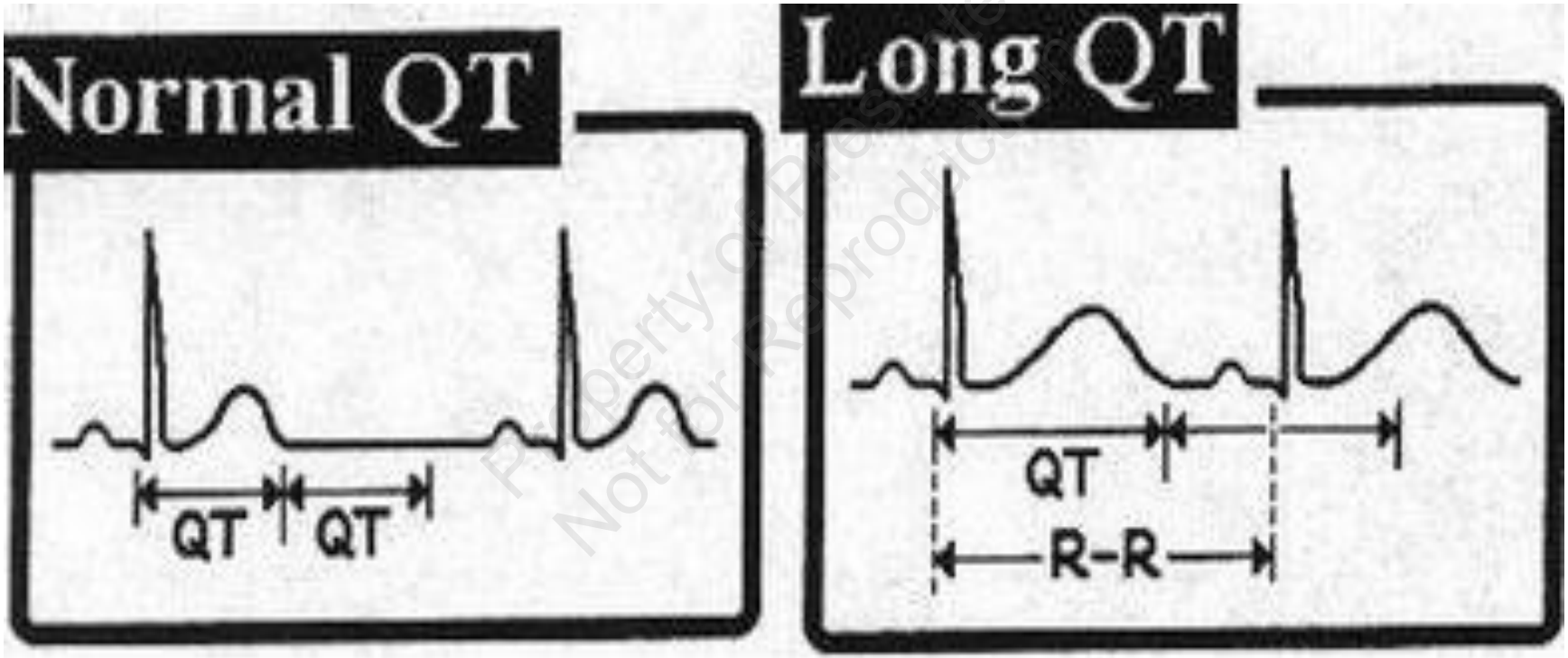
Azithromycin

- Long half life (68 hrs)
- Frequent bowel movements
- Hearing loss, tinnitus
- Prolonged QT
- No effect on CYP3A

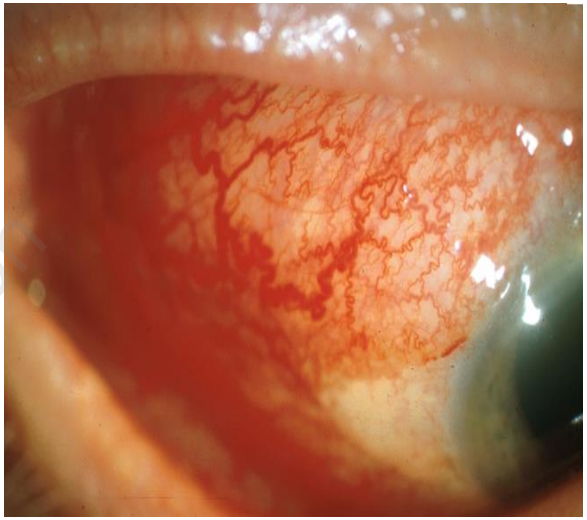
Clarithromycin

- Shorter half life (5-7hrs)
- Dysgeusia, diarrhea
- Hearing loss, tinnitus
- Prolonged QT
- Inhibits CYP3A
  - High concentrations of rifabutin, itraconazole, warfarin, digoxin,sotolol

Prolonged QT with Macrolides, Quinolones , clofazimine



Rifabutin + Clarithromycin Toxicity



- Hepatitis
- Uveitis
- Arthritis
- Fever
- Thrombocytopenia, Leukopenia
- Drug induced lupus
- Nausea and vomiting

Ideas for Rash Treatment

Drug Rash with Ethambutol or Rifampin

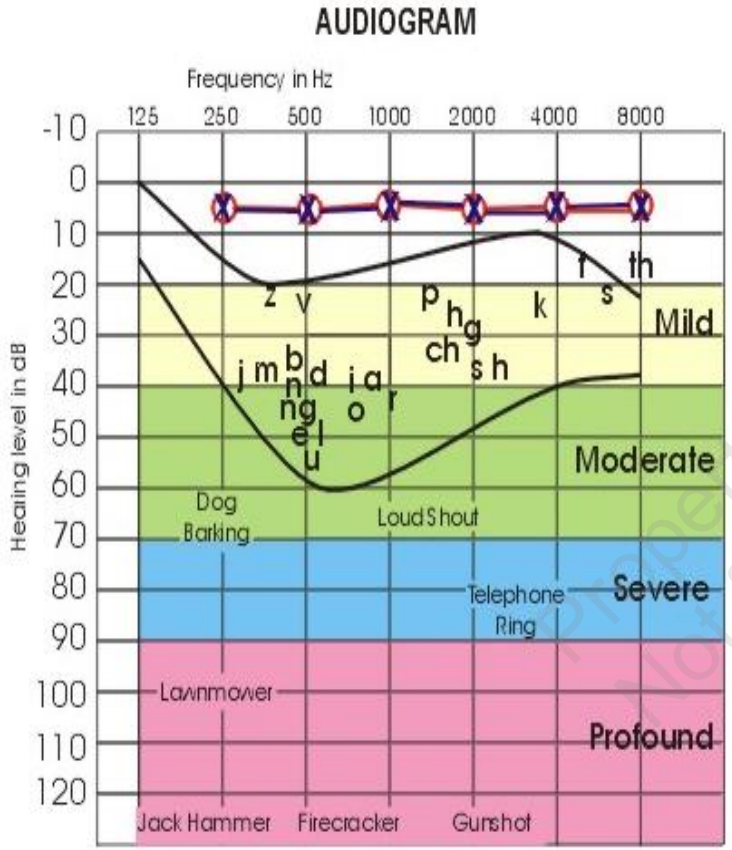
- After a rash occurs, it is best to let things quiet down for 2-4 weeks
- Then you can consider desensitization to either/both ethambutol and rifampin
- Consider starting H1/H2 blocker (cetirizine/ranitidine) as soon as possible and you may need to use prednisone as well to help rash resolve

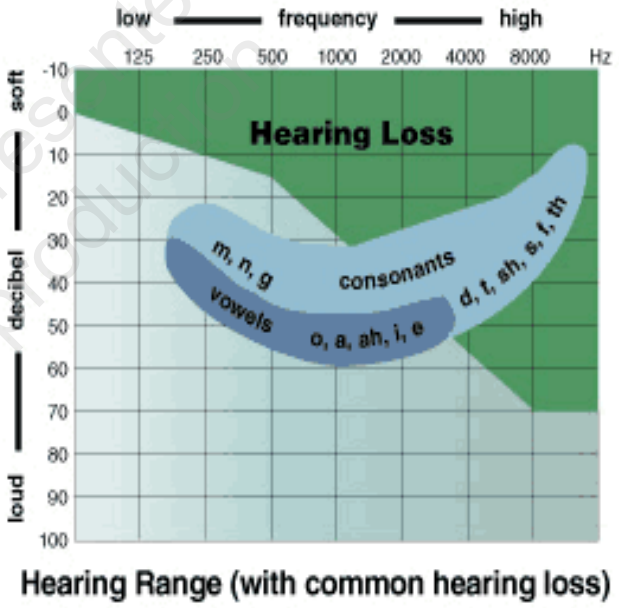
Kim JH, et al; Allergy; 2003 June; 58(6):540-1.

Inhaled amikacin

- Inhaled liposomal amikacin
  - 590mg once daily; eFlow vibrating nebulizer system
    - Watch for hypersensitivity pneumonitis or bronchospasm
    - Dysphonia is common; hearing loss
- Parenteral amikacin that is nebulized
  - 240mg(1 ml) diluted in 5ml of NS daily-thrice weekly
    - Bronchospasm; hearing loss; elevated creatinine

Hearing Loss Monitoring (aminoglycosides and macrolides)





Hearing Range (with common hearing loss)

Monitoring for Hearing loss

- No one knows the correct formal monitoring frequency
- We usually recommend formal audiogram testing at least once a month while on IV amikacin
- ? Frequency of monitoring while on inhaled amikacin
- What about concomitant macrolide and aminoglycoside use

Other Amikacin Side Effects

- Hypersensitivity- rash is rare but can happen
- Neurotoxicity
  - Circumoral paresthesias (slow IV infusion rate)
  - Decreased mental concentration
  - Post operative respiratory depression
  - Drug induced myasthenia gravis

MEDICATION SIDE EFFECTS FOR DRUGS USED TO TREAT RAPIDLY GROWING MYCOBACTERIA (RGM)

Ideas for Rash Treatment

Imipenem cilastin

Role: backbone for RGM treatment

Cleared: kidneys

Toxicity: rash, pancytopenia, hepatitis, C. diff, leukopenia; elevated CRP

Cefoxitin

Role: alternative to imipenem as backbone for RGM treatment

Cleared: kidneys

Toxicity: rash, C. difficile diarrhea, eosinophilia

Tigecycline

Role: alternative to imipenem as backbone for RGM treatment

Cleared: biliary excretion

Toxicity: nausea, vomiting, hyponatremia, hypoalbuminemia, elevated lft's

Prepare your patient for a rough ride with this medication!

Clofazimine

- It’s not as bad as it sounds!
- Starting dose of 100mg once daily
- Side Effects
  - Skin pigmentation (tan-brown); ichthyosis and dryness
  - GI (nausea, gastritis, diarrhea, epigastric pain)
  - Conjunctival and corneal pigmentation due to crystal deposits

Moxifloxacin

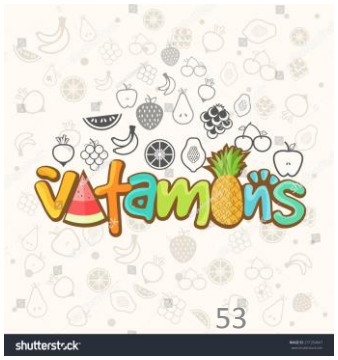
Action: inhibits DNA gyrase

Cleared: kidneys

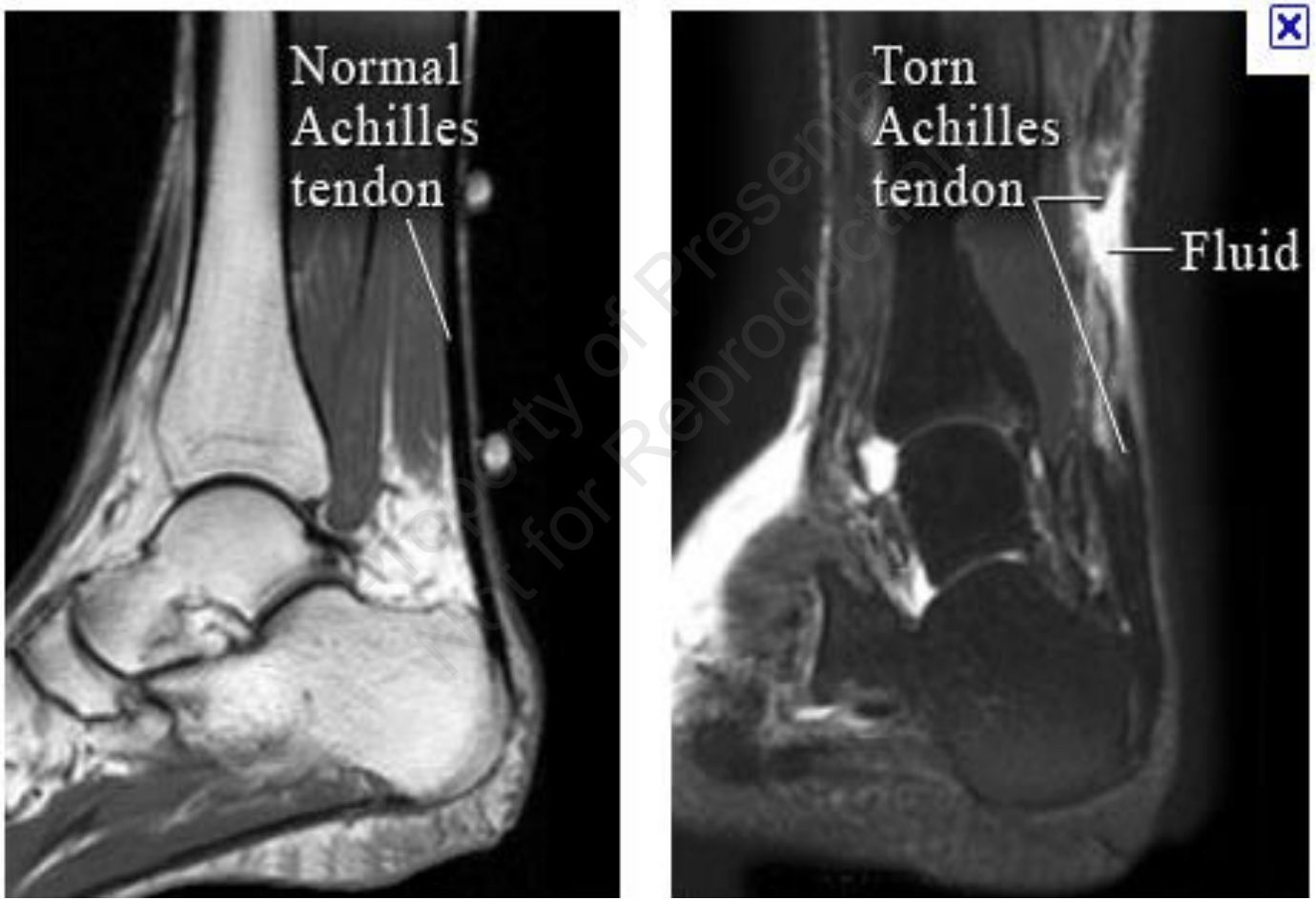
Toxicity: caffeine like effects, GI, tendonitis, hypoglycemia

Moxifloxacin

- Absorbed by dairy and all divalent cations
- We suggest taking 1 hour before breakfast
- Taking it at bedtime may cause significant insomnia
- Make sure that folks take all MVI and calcium supplements at lunch. No dairy within 2 hours of moxifloxacin
- Watch for CNS issues in older folks



Ruptured Achilles Tendon



Linezolid

Action: inhibits the initiation process of protein synthesis

Cleared: liver

Toxicity: myelosuppression, peripheral and optic neuropathy, serotonin syndrome

USA Trade Name	Generic Name
SSRIs	
Celexa	citalopram
Luvox	fluvoxamine
Paxil	paroxetine
Prozac	fluoxetine
Zoloft	sertraline
non-SSRIs	
Effexor	venlafaxine
Remeron	mirtazapine
Serzone	nefazodone
Wellbutrin (UK)	bupropion dothiepin

Audience Response Question #3

- You have an 80 year old patient on diltiazem, insulin, pantoprozole, and warfarin with newly diagnosed pulmonary non-cavitary M. avium infection based on 2 smear negative/culture positive sputums with moderate cough and fatigue. The CT scan shows only tree-in-bud changes. What diagnosis/treatment is most appropriate at this time?
  1. Do a bronchoscopy to gather more culture information
  2. Start azithromycin until you have final sensitivity results
  3. Start azithromycin,rifampin, and ethambutol (all given 3 times a week) while you wait for sensitivities
  4. Start moxifloxacin and azithromycin

Take Home Points

- The treatment of NTM should not be worse than the disease!
- You have a friend in National Jewish Health
- Take the time to understand the antibiotics
- Take time to understand your patient
- The treatment of NTM can be very taxing for your patients and you – but worth it!
- Thank you for caring

Questions?