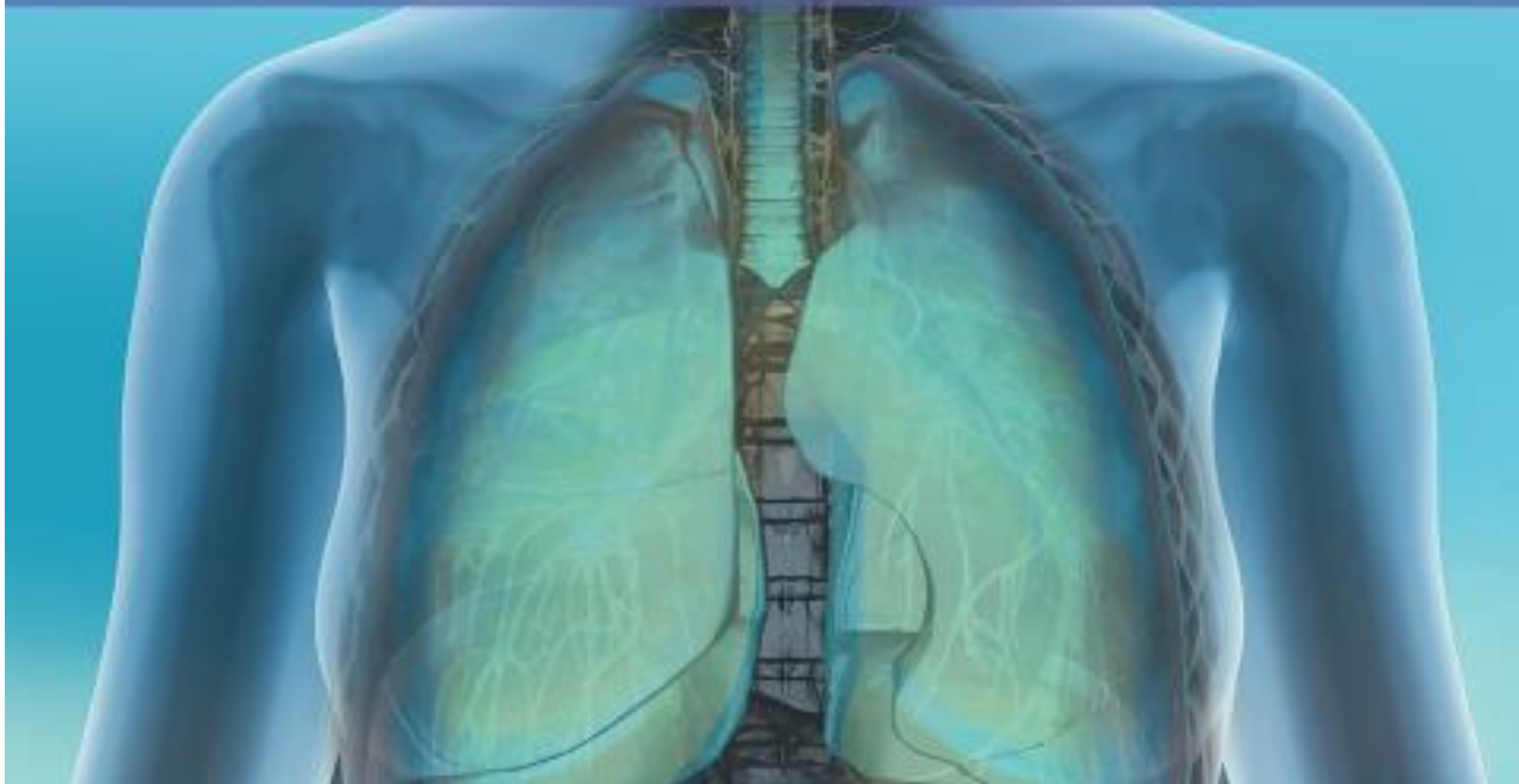
NTM Lecture Series for Providers

April 27-28, 2023
NATIONAL JEWISH HEALTH



NTM Medication Toxicity and Side Effects (or……)

David E. Griffith, MD

National Jewish Health

NTM Provider Course

April 2023

Drugs that make you….

Vomit, Barf, Blow chunks, Bow down before the porcelain god, Chuck your Cheerios, Cough up your cookies, Emesis, Empty your stomach, Flash, Heave, Hurl, Jersey yodel, Lose your lunch, Puke, Regurgitate, Retch, Spew, Spit up, Throw up, Tonsil toss, Toss your cookies, Up-chuck, Urp, Ralph, Calling dinosaurs, Technicolor yawn, Chunder, Talk on the big white telephone, Boot, Drive the porcelain truck

Disclosures

- Insmed Inc.: Consultant, Speaker
- AN2 Therapeutics: Consultant
- Paratek Pharmaceuticals: Consultant

I can’t prove it, but I know it must be true…

- The gene coding for antibiotic effectiveness is linked to the gene causing nausea.

  – Richard J. Wallace Jr., MD

“The Treatment is Worse Than The Disease”

- Do you believe that?
- Have you ever said that to a patient?

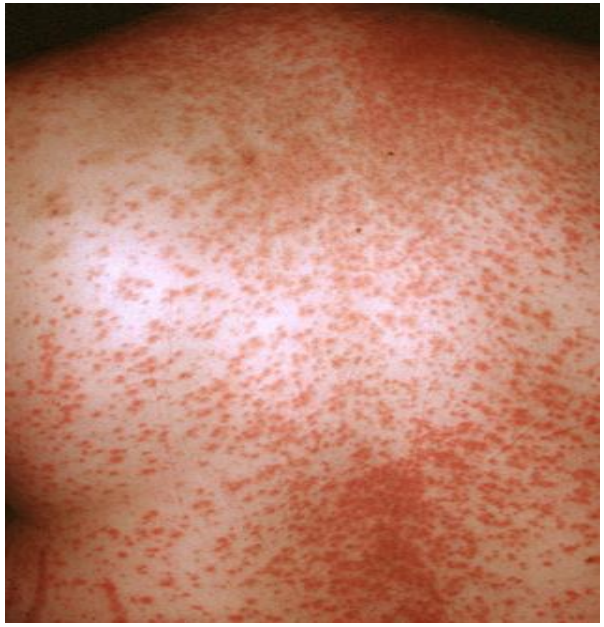
Treatment of Slow Growing NTM

MAC*, M. kansasii, M. xenopi*, etc.

- Macrolides: Azithromycin, Clarithromycin
- Ethambutol
- Rifamycins: Rifampin, Rifabutin
- Amikacin intravenous, nebulized liposomal, nebulized intravenous
- Clofazimine
- Bedaquiline
- Oxazolidanones (linezolid and tedizolid)
- Moxifloxacin

Any Drug Can Cause a Rash

In most instances a rash requires stopping all antibiotics and re-challenging with one drug at a time, starting with the most important drug in the regimen.



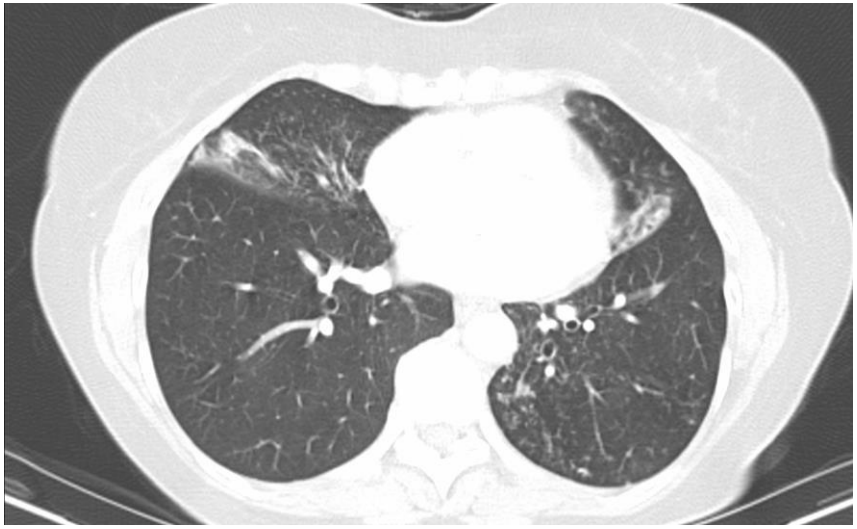
Hypersensitivity rash (urticaria, hives) with Ethambutol or Rifampin

- 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

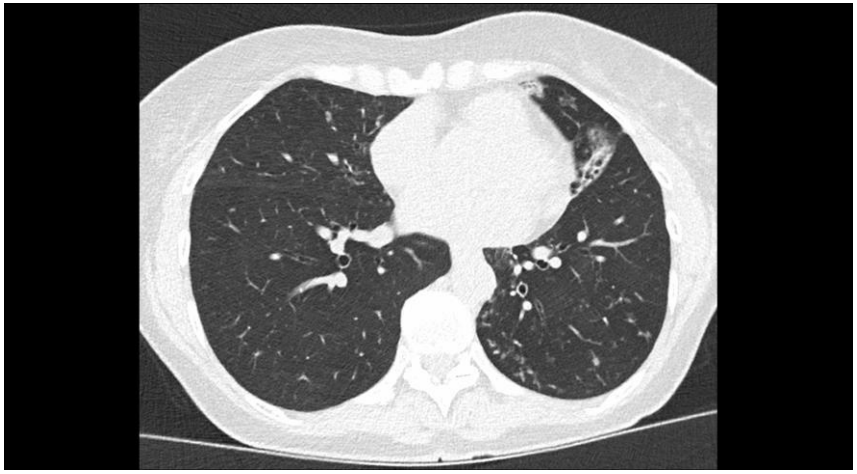
Kim JH, et al; Allergy; 2003 June; 58(6):540-1.

#1: 60 year old patient diagnosed with MAC lung disease Oct 2021, started on azithromycin, rmp, emb in 3/2022

Chest CT March 2022, sputum AFB culture positive for MAC



Chest CT July 2023, sputum AFB culture positive for MAC



Patient experiencing hearing loss and tinnitus, what do you do now with her MAC medications?

- Stop all MAC medications
- Stop azithromycin, continue other antibiotics
- Substitute clarithromycin for azithromycin
- Substitute clofazimine for azithromycin
- Substitute amikacin for azithromycin

Patient experiencing hearing loss and tinnitus. Question #1, what do you do now with her MAC medications? ANSWER: C

- A. Stop all MAC medications
- B. Stop azithromycin, continue other antibiotics
- C. Substitute clarithromycin for azithromycin
- Substitute clofazimine for azithromycin
- Substitute amikacin for azithromycin

Azithromycin/Clarithromycin

Azithromycin

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

THERE IS NOT COMPLETE OVERLAP BETWEEN CLARI AND AZI WITH REGARD TO HYPERSENSITIVIY AND TOXICITY

Clarithromycin

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

Monitoring for Hearing loss with azithromycin

- No one knows the optimal monitoring frequency
- We usually recommend audiogram testing at the beginning of therapy and then with the onset of symptoms.
- More frequent audiograms with pre-existing hearing problems
- What about concomitant macrolide and aminoglycoside use?

#2: 78 year old patient with treatment refractory MAC

- Patient was started on nebulized liposomal amikacin daily with azi, emb clofaz
- Had initial hoarseness that resolved after instituting saline gargle for 1 month
- Cough improved at month 2 of treatment
- On month 6 of nebulized liposomal amikacin she noted slight SOB that gradually worsened over the next 2 months
- A six minute oxygen walk test revealed O2 sat declined from 92% to 85% at 3 minutes

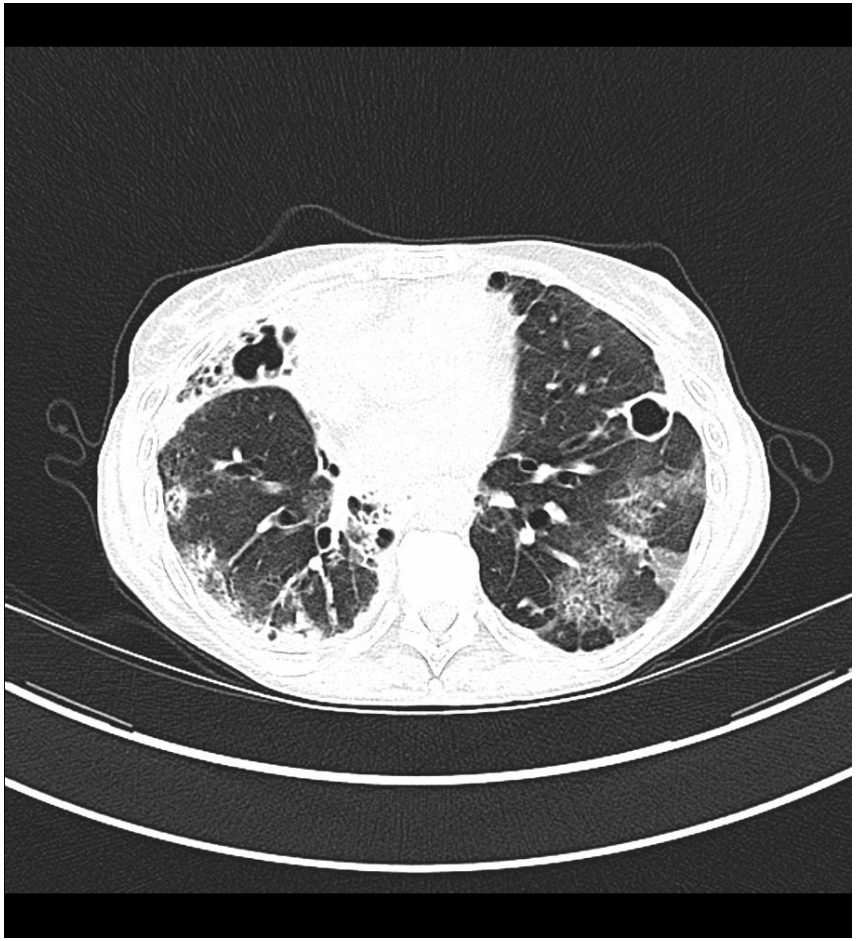
What should you do?

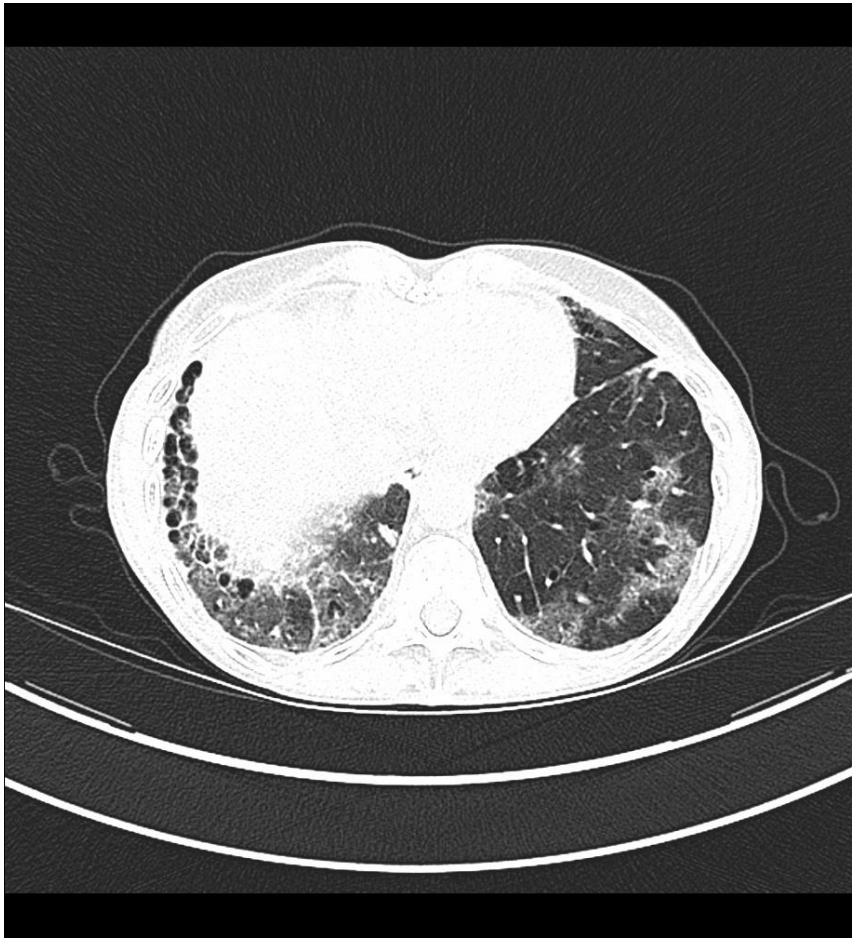
- Stop all MAC medications
- Stop Clofazimine
- Stop Ethambutol
- Stop inhaled liposomal amikacin
- Continue all MAC medications and add oral prednisone

Question # 2:
What should you do?

- 1 Stop all MAC medications
- 2. Stop Clofazimine
- 3. Stop Ethambutol
- 4. Stop inhaled liposomal amikacin
- 5. Continue all MAC medications and add oral prednisone

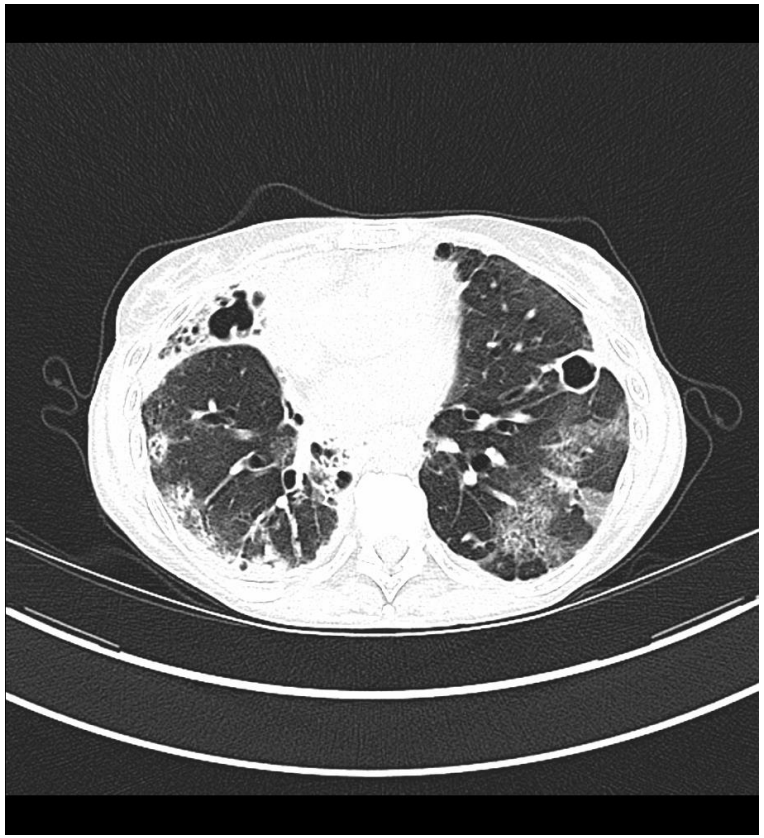
Chest CT when patient's breathing at its nadir, 4 months after starting inhaled liposomal amikacin. Significant decline in FVC and FEV1



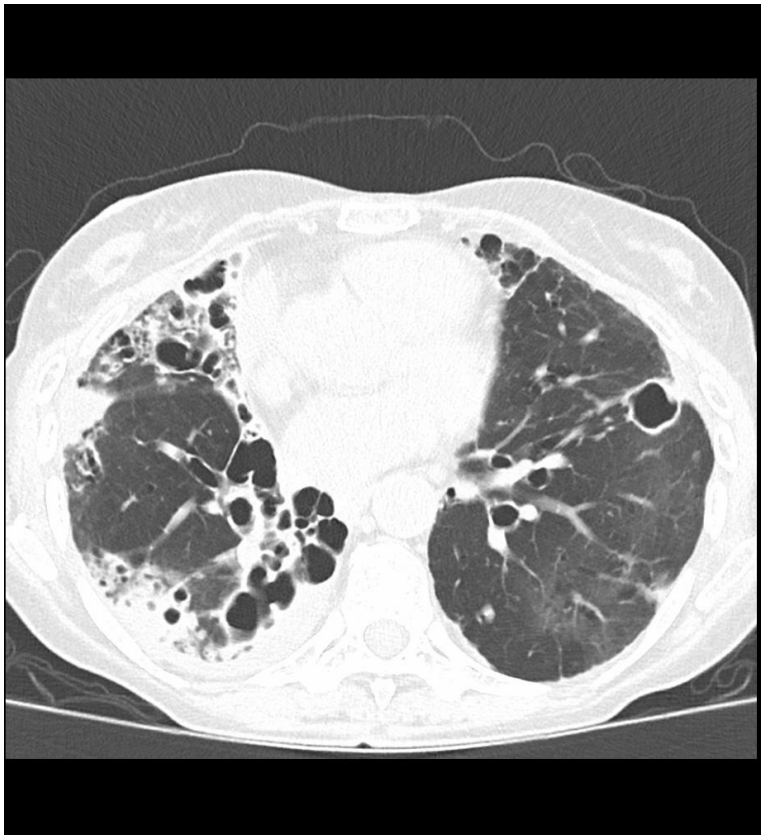


Chest CT scan 3 months after stopping inhaled liposomal amikacin

Chest CT at time of worst shortness of breath



Chest CT 4 months after stopping inhaled liposomal amikacin



Inhaled Amikacin

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

Intravenous Amikacin

- Amikacin (usually TIW dosing)
  - Ototoxicity: hearing disturbances, less vestibular dysfunction than Strep
    - Monthly audiogram while on IV amikacin
  - Nephrotoxicity: 3.4-8.7% of patients, increased risk with pre-existing renal disease, higher doses, other nephrotoxic drugs
  - Rash
  - Electrolyte disturbances: hypoklemia, hypomagnasemia (cardiac dysrhythmias)

Patient #1 returns 3 months after last visit. Cough, sputum production, fatigue improved

- Sputum AFB culture negative
- Gaining weight
- Exercise tolerance improved
- Sent home on clari, emb and rmp
- 2 weeks after NJH visit had precipitous loss of visual acuity

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

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

Question #3

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

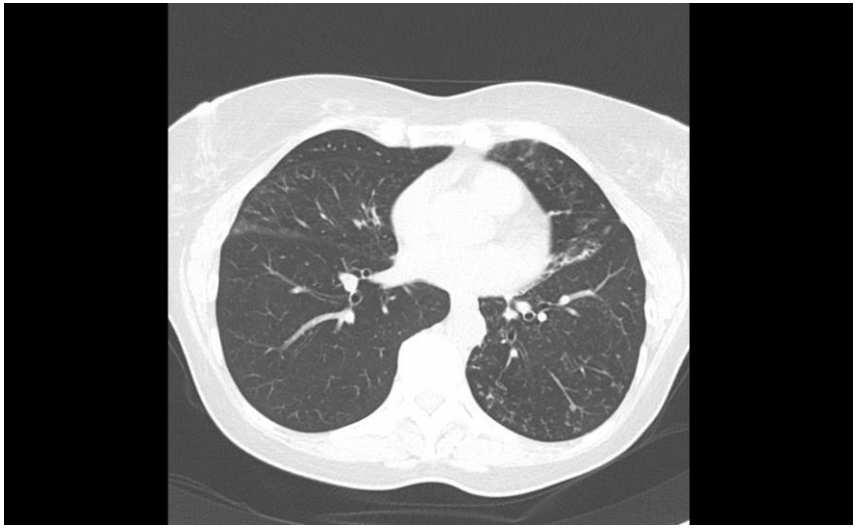
  1. Lower the frequency of administration from daily to thrice weekly
  2. Ask the patient to continue the antibiotic, and see an ophthalmologist as soon as possible
  3. Stop the ethambutol immediately and ask the patient to see an ophthalmologist as soon as possible
  4. Start prednisone and have the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

Patient #1

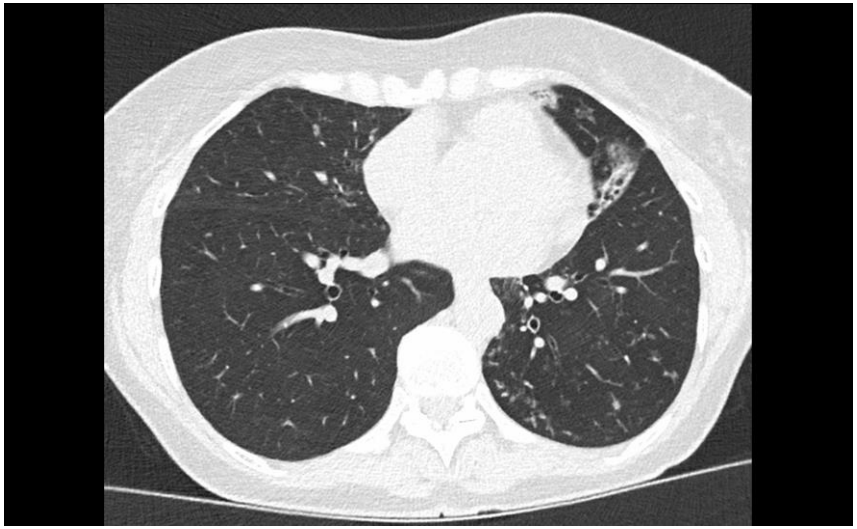
- No change in patient's vision for 3-4 months followed by gradual improvement
- 6 months after last ethambutol dose, vision considerably improved but not back to baseline levels.
- Patient on rmp/clofazimine/azithromycin
- Started on inhaled liposomal amikacin

Patient #1

Chest CT in October 2022



Chest CT in April 2023



EMB Toxicity

- **Retrobulbar neuritis**: decreased visual acuity or red-green color discrimination, dose related, unusual at dose 15 mg/kg. Increased risk with renal insufficiency.
- Peripheral neuritis
- Cutaneous reactions: < 1% of patients

Toxicity - Ethambutol induced optic neuritis

Ethambutol Optic Neuropathy

- May be unilateral or bilateral
  - Decreased visual acuity (blurriness), scotoma (partial vision loss/blind spots), and/or color blindness
- Usually reversible but may take several months(prednisone not indicated)
- Risk increases with dose(>20mg/kg) AND decreased renal function
- Monitor special groups and educate your patients
  - Recommend daily vision self-checks
  - Patients should promptly report to TB clinic personnel new vision changes and to stop the ethambutol immediately until they can be seen by ophthalmology

Griffith DE, Am J Respir Crit Care Med 2005 Jul 15; 172:2

EMB Toxicity: Monitoring

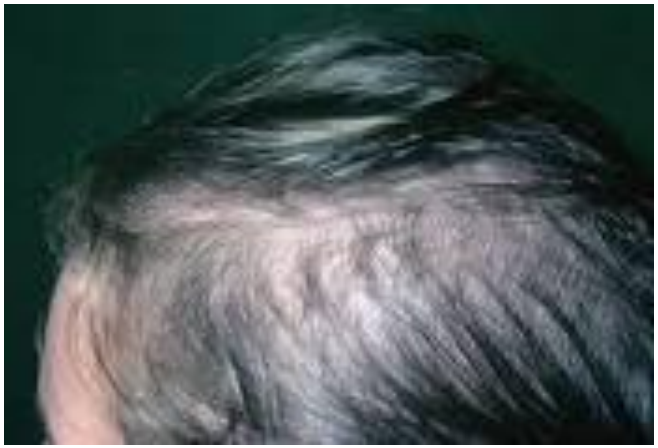
- All patients should have baseline visual acuity (**Snellen chart**) and testing of color vision discrimination (**Ishihara tests**).
- PATIENT EDUCATION
- Monthly symptom check (blurred vision scotoma)
- Monthly testing: high doses, treatment longer than 2 months, renal insufficiency
- Ophthalmology evaluation, no single diagnostic test for ethambutol ocular toxicity

EMB Ocular Toxicity

- Management
- Discontinue EMB immediately
- If severe, consider discontinuing EMB & any other ocular toxic drug
- Recovers over weeks to months, but defective color vision may persist longer.
- Refer to ophthalmology

Ethambutol Toxicity

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



REMEMBER THAT ETHAMBUTOL IS CLEARED THROUGH THE KIDNEY!

Rifampin Toxicity

Of the three drugs in the standard regimen, rifampin is the one most often associated with side effects and toxicity

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

Rifampin Toxicity/Side Effects

- Hepatitis (hepatic failure RARE)
- Drug induced lupus with positive antihistone antibody
- Fever
- Rash
- Leukopenia, Thrombocytopenia
- Nausea and vomiting
- Acute kidney injury

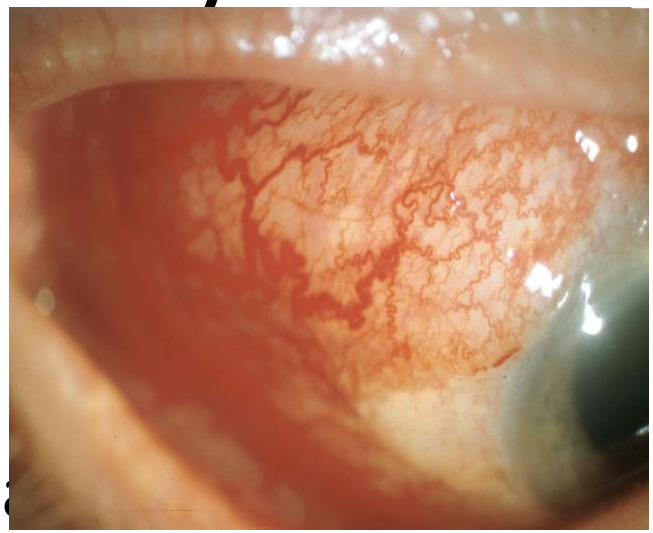
Rifampin Drug Interactions

Rifampin and rifabutin induce the CYP3A4 in cytochrome P450 enzymes
Rifampin causes and 80-fold induction and rifabutin causes a 20-fold induction in human hepatocytes

- **OCs/HRT/thyroid medications**
- **Glucocorticoids**
- **Clarithromycin**
- **Azole antifungals**
- Methadone
- Quinidine
- Theophylline
- Warfarin

- Verapamil, Diltiazem
- Sulfonylureas
- Digoxin
- Beta blockers
- Phenytoin, CBZ
- **Cyclosporine**
- Protease inhibitors
- Diazepam

Rifabutin Toxicity



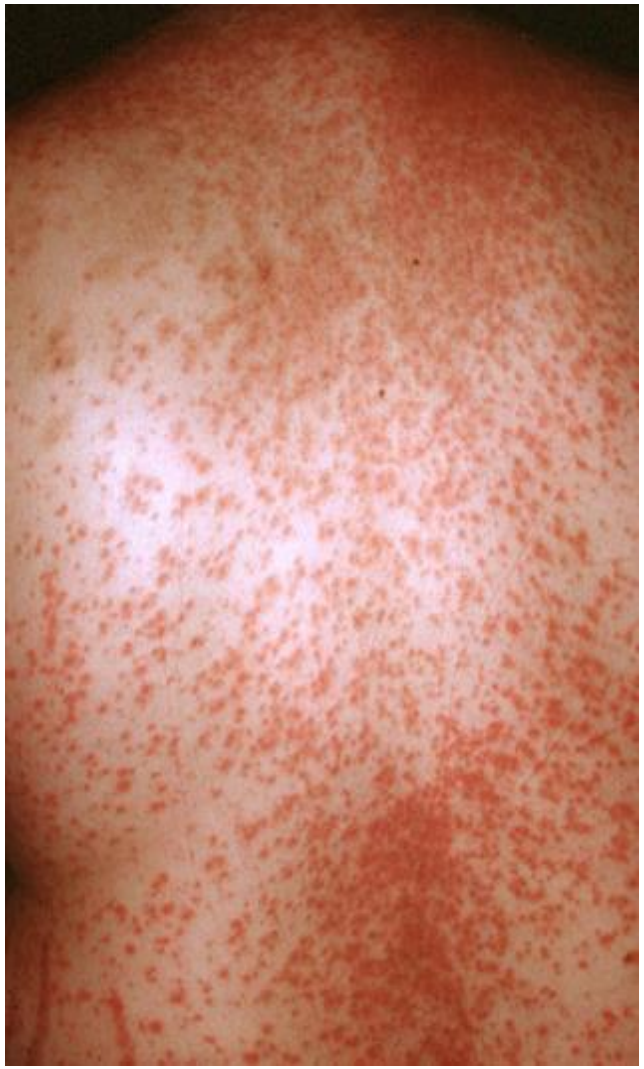
- Hepatitis
- Uveitis
- Arthritis
- Fever
- Thrombocytopenia, Leukopenia
- Drug induced lupus
- Nausea and vomiting
- Polyarthralgia/polymyalgia syndrome
- Skin hyperpigmentation
- Toxicity more common with concomitant use of clarithromycin

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

MEDICATION SIDE EFFECTS FOR DRUGS USED TO TREAT RAPIDLY GROWING MYCOBACTERIA (RGM) (*M. ABSCESSUS* SUBSPECIES)

Rash



Imipenem cilastin

Role: Foundation for RGM treatment

Cleared: Kidneys

Toxicity: Rash, pancytopenia, hepatitis, C. diff, leukopenia; elevated CRP, nausea, vomiting, diarrhea, headache, seizures

*Can try to switch to **meropenem** for minor reactions, But meropenem less active against *M. abscessus* than imipenem

Cefoxitin

Role: Alternative to imipenem as foundation for RGM treatment

Cleared: Kidneys

Toxicity: Rash, C. difficile diarrhea, eosinophilia, abdominal cramps or tenderness, back or leg pain, blistering of skin, blood in stool or sputum,

Ceftaroline

- Used in sequence with imipenem for RGM
- “Dual beta lactam” therapy
- Advanced cephalosporin
- Usually 600mg q 12 hours
- Adjust for renal impairment
- Rash, nausea, diarrhea, neutropenia (*21%), back or leg pain, headache, fatigue

*J Antimicrob Chemother 2016;71:2010

Tigecycline

Role: Alternative to imipenem as foundation for RGM treatment

Cleared: Biliary excretion

Toxicity: Nausea, vomiting, diarrhea, hyponatremia, hypoalbuminemia, elevated lft's, headache dizziness

Dosing should start low with gradual increase (the drug won't do much good if the patient won't take it)

(This drug can make a doorknob puke)

Omadacycline

- Tetracycline
- Nausea, vomiting, diarrhea, headache, elevated LFT's
- Fewer side effects and better tolerated than tigecycline
- Expensive
- Take at least 2 hours from anything with divalent cations(aluminum, iron, magnesium)
- ?A more effective and less toxic tigecyclline

Linezolid- Use 600mg once daily

Action: Inhibits the initiation process of protein synthesis
Cleared: Liver
Toxicity: Myelosuppression, peripheral and optic neuropathy, serotonin syndrome

Serotonin syndrome: Most cases have been associated with the concomitant use of LZD and an SSRI or tricyclic antidepressant.

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

Tedizolid

- Tedizolid phosphate (oxazolidinone)
- Bacteriostatic
- Weaker MAO inhibitor than linezolid
- No dose adjustments for renal insufficiency or hepatic impairment
- Nausea, headache, diarrhea; neutropenia and thrombocytopenia, and peripheral neuropathy ? less likely than with linezolid
- Expensive

Bedaquiline and Mycobacterial Disease

- There are concerns about QT interval prolongation (macrolide, FQ, clofazimine)
- Initial concerns about sudden death with bedaquiline NOT confirmed
- Good treatment responses and safety profiles have been substantiated by several studies
- Dose adjustment is not required in case of mild-to-moderate renal impairment

Bedaquiline For Mycobacterial Disease

Side effects:

- Nausea
- QT prolongation
- Headache
- Chest pain
- Weight loss
- Rash/skin discoloration
- Increase in LFTS/amylase

Monitoring for Drug Toxicity

- Azi/Clari/Emb, Rmp
  - Baseline CBC, CMP, visual acuity and color vision testing, audiogram
  - CBC, CMP, visual acuity and color vision testing after one month of therapy and then periodically
- For IV amikacin weekly CMP, amikacin levels
- For RGM therapy (in general) weekly CBC, CMP, periodic visual acuity and color vision
- Frequent patient interaction

Discontinuing MAC Antibiotics

- There is not a plethora of antibiotics that are active against MAC, even fewer for *M. abscessus* (not a lot of arrows in the quiver)
- The key antibiotics for MAC are, macrolide/ethambutol/amikacin
- The key antibiotics for *M abscessus* are, macrolide/amikacin
- If you stop them, how do you replace them?

Discontinuing MAC antibiotics
What will you replace them with?

- Macrolides: The most important drugs for treating MAC. Treatment success declines dramatically without a macrolide in the regimen (No comparably active replacement drug)
- Ethambutol: The most important drug for protecting against the emergence of macrolide resistance (amikacin, ?clofazimine, ?rifabutin)
- Amikacin: The only drug other than the macrolides where *in vitro* activity predicts clinical outcome (?rifabutin, ?clofazimine, ?oxazolidanone, ?bedaquiline)

Overview

- The treatment of NTM is usually not be worse than the disease!
- Know the limitations of current antibiotic choices
- Be familiar with antibiotic side effects and toxicity
- Preserve the most effective drugs in the regimen if possible
- Take time to help your patient stay on an effective treatment regimen