Treatment of NTM: Medication Side Effects

"Is the Treatment Really Worse Than The Disease?"

Gwen Huitt, M.D., M.S.

National Jewish Health
NTM Provider Course
November 5, 2021

Disclosures

- Insmed: Speaker

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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

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Treatment of Slow Growing NTM

- Rifampin
- Rifabutin
- Ethambutol
- Azithromycin
- Clarithromycin
- Amikacin (parenteral, nebulized liposomal, nebulized parenteral)
- Clofazimine
- *Moxifloxacin

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Toxicity - Nausea and Vomiting

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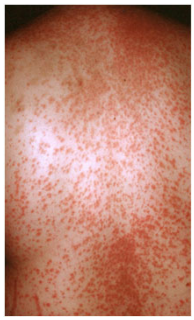
Any Drug Can Cause a Rash



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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

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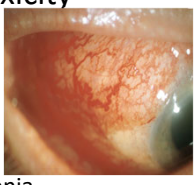

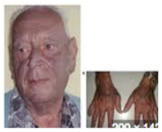

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Case 1

- 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?

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What is the Cause of the Low WBC?

1. Rifampin
2. Moxifloxacin

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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

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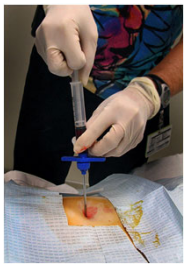
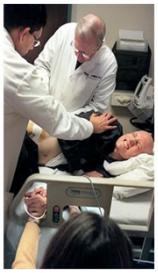
Unnecessary Bone Marrow Biopsy

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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

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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?

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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 17

Case 3

- 71 y/o female with refractory M. avium
- Has had consistently positive sputum cultures at 6 months despite a daily 3 drug regimen with azithromycin, rifampin and ethambutol
- Negative sweat test
- Negative CFTR analysis for cystic fibrosis mutations

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Case 3

- Patient was started on nebulized liposomal amikacin daily
- 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

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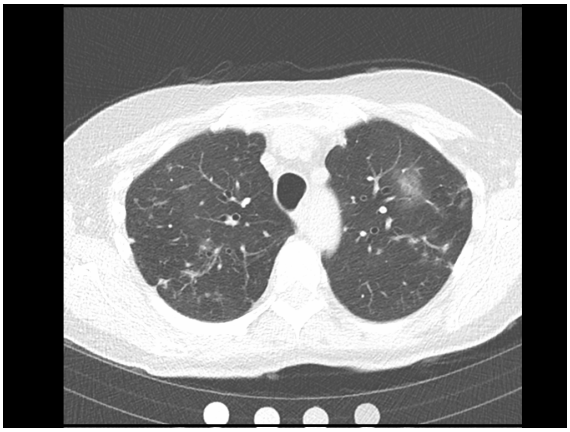

Case 3

- PFT's revealed FEV1 69% and FVC 77% with a DLCO of 73%
- What are your thoughts?

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Case 3

- The nebulized liposomal amikacin was discontinued and oral azithromycin, rifampin and ethambutol were continued
- The patient had achieved culture negative status on the third month of nebulized liposomal amikacin
- The patient returned 2 months after discontinuation of nebulized liposomal amikacin
- She was also given inhaled steroids for 2 months

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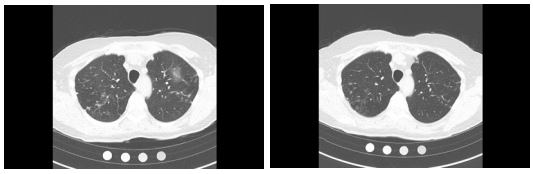
Hypersensitivity pneumonitis associated with nebulized liposomal amikacin

June 2021 September 2021



PFT comparison

On neb lipo amikacin

- FEV 1 - 69%
- FVC - 77%
- DLCO - 73%

3 months off neb lipo amikacin

- FEV 1 - 83%
- FVC - 89%
- DLCO – 79%

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Audience Response Question #1

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

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Audience Response Question #1

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  - Azithromycin
  - Imipenem

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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?

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Case 4 - presentation

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

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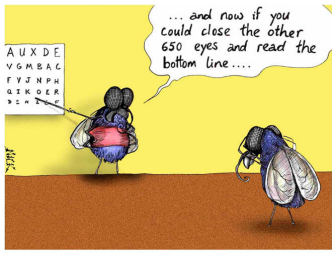

Fly Hell.

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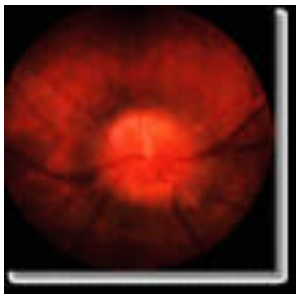
Toxicity - Ethambutol induced optic neuritis



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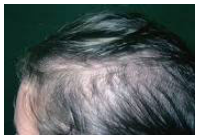
Ethambutol Toxicity

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



REMEMBER THAT ETHAMBUTOL IS CLEARED THROUGH THE KIDNEY!

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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

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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

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Audience Response Question #2

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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

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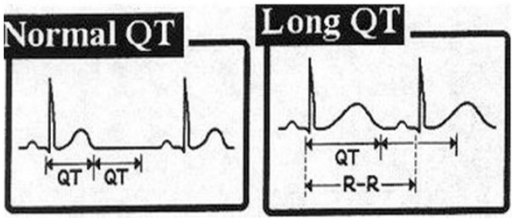
Prolonged QT with Macrolides, Quinolones , Clofazimine



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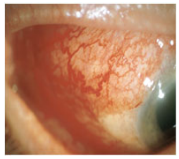
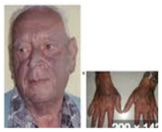
Rifabutin + Clarithromycin Toxicity

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





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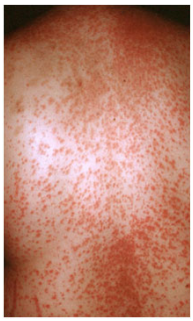
Ideas for Rash Treatment



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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.

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Inhaled Amikacin

- Inhaled liposomal amikacin
  - 590mg once daily; vibrating 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

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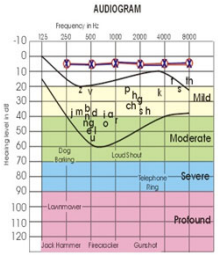
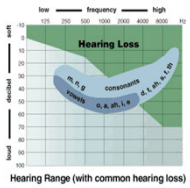
Hearing Loss Monitoring (aminoglycosides and macrolides)





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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

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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

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

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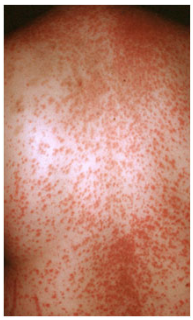
Ideas for Rash Treatment



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Imipenem cilastin

Role: Backbone for RGM treatment

Cleared: Kidneys

Toxicity: Rash, pancytopenia, hepatitis, C. diff, leukopenia; elevated CRP, "I feel like I going to die"

*Can try to switch to **meropenem** for minor reactions

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Ceftaroline

- Used in sequence with imipenem for RGM
- Advanced cephalosporin
- Usually 600mg q 12 hours
- Adjust for renal impairment
- Rash, nausea, diarrhea, neutropenia is not uncommon (*21%)

*J Antimicrob Chemother 2016;71:2010

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Cefoxitin

Role: Alternative to imipenem as backbone for RGM treatment

Cleared: Kidneys

Toxicity: Rash, C. difficile diarrhea, eosinophilia

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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!

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Omadacycline

- Tetracycline
- Nausea, vomiting, diarrhea, headache, elevated LFT's
- Expensive
- Take at least 2 hours from MVI, anything with divalent cations(aluminum, iron, magnesium)
- INR will increase (warfarin)

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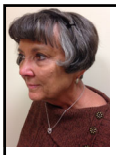

Clofazimine

- 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

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Moxifloxacin

Action: Inhibits DNA gyrase

Cleared: Kidneys

Toxicity: Caffeine like effects, GI, tendonitis, hypoglycemia

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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

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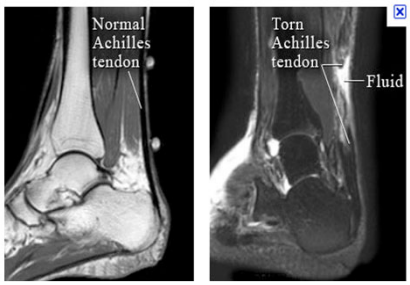
Ruptured Achilles Tendon



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Linezolid- Use 600mg once daily

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

Tedizolid

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

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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

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Questions?

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