

# NTM Medication Toxicity & Side Effects

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National Jewish Health  
NTM Provider Course  
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# Disclosures

- Insmmed 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 in NTM disease is linked to the gene causing nausea.

Richard J. Wallace Jr., MD

Under diagnosis

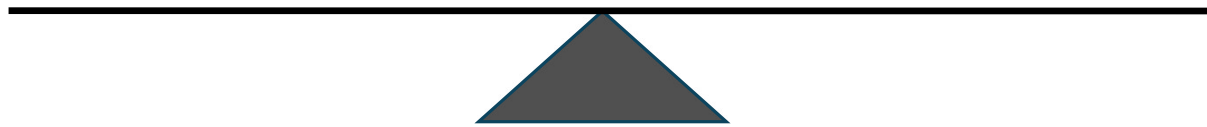


Disease  
Progression

Treatment



Drug  
toxicity



“The treatment is **worse** than the disease?”

# Considerations when managing NTM treatment drug toxicity

1. Not all NTM drugs are created equal
  - moxifloxacin cannot replace a macrolide
2. There is not a “deep bench” of effective NTM antibiotics to replace discontinued drugs as there is with TB drugs
3. In vitro susceptibility results have limited value for guiding drug choice
4. Must carefully consider the consequences of stopping an NTM antibiotics

MAC

Treatment medicine

MABC

Ethambutol  
Rifampin/  
Rifabutin

Macrolide  
Amikacin (IV, Neb)  
Clfazimine  
Linezolid/Tedizolid  
Bedaquiline

Imipenem  
Cefoxitin  
Tigecyclin  
Omadacylin

# Treatment of Slow Growing NTM (MAC)

Ethambutol  
Rifampin/  
Rifabutin

Macrolide  
Amikacin (IV, Neb)  
Clofazimine  
Linezolid/Tedizolid  
Bedaquiline

Imipenem  
Cefoxitin  
Tigecyclin  
Omadacylin

# Rash

\* Any Drug Can Cause a Rash!



1. Stopping all antibiotics
2. Re-challenging with one drug at a time
3. Starting with the most important drug in the regimen



# Hypersensitivity rash

(urticaria, hives) with Ethambutol or Rifampin

- ✓ Stop medications, let things quiet down for 1-2 weeks (or longer)
- ✓ Consider starting H1/H2 blocker (cetirizine/ranitidine)
- ✓ You may need to use prednisone as well to help rash resolve
- ✓ Then, consider desensitization to either/both EMB and RFP

## Case 1. 60 year old patient diagnosed with MAC lung disease

10/2021, started on azithromycin, RFP, EMB in 3/2022



Chest CT 3/2022

Sputum AFB culture; MAC +



Chest CT 7/2022

Sputum AFB culture; MAC +

Patient experiencing hearing loss and tinnitus.

**Question #1 ; What do you do now with her MAC medications?**

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

# Macrolide

Azithromycin	Clarithromycin
Rare hepatotoxicity	
Hearing loss, tinnitus	
Prolonged QT	
Long half life (68 hrs) ; take QD	Shorter half life (5-7 hrs) ; take BID
Frequent bowel movements	Dysgeusia, diarrhea
No effect on CYP3A	Inhibits CYP3A - High concentrations of rifabutin, itraconazole, warfarin, digoxin, sotalol

\* There is **not complete overlap** between CLARI and AZI with regard to hypersensitivity and toxicity!

## Monitoring for Hearing loss with azithromycin

- ✓ No evidence about optimal monitoring frequency
- ✓ Audiogram testing is recommended
  - At the beginning of therapy
  - Then with the onset of symptoms
- ✓ More frequent audiograms with pre-existing hearing problem
- ✓ What about macrolide + aminoglycoside use?

## **Case 2. 78 year old patient with treatment refractory MAC**

- ✓ Patient was started on nebulized liposomal amikacin (ALIS) daily  
with AZI, EMB, CFZ
- ✓ Had initial hoarseness that resolved after instituting saline gargle for 1 month
- ✓ Cough improved at month 2 of treatment
- ✓ On month 6 of ALIS 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

Patient experiencing SOB and Hypoxia after use of ALIS.

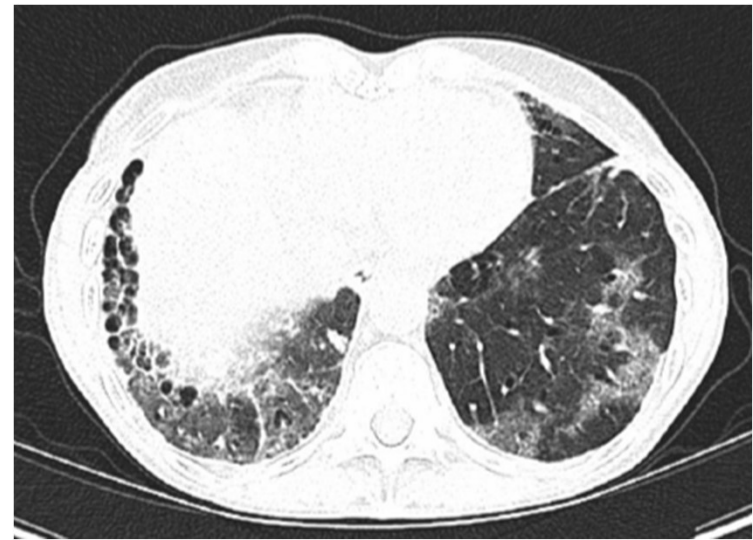
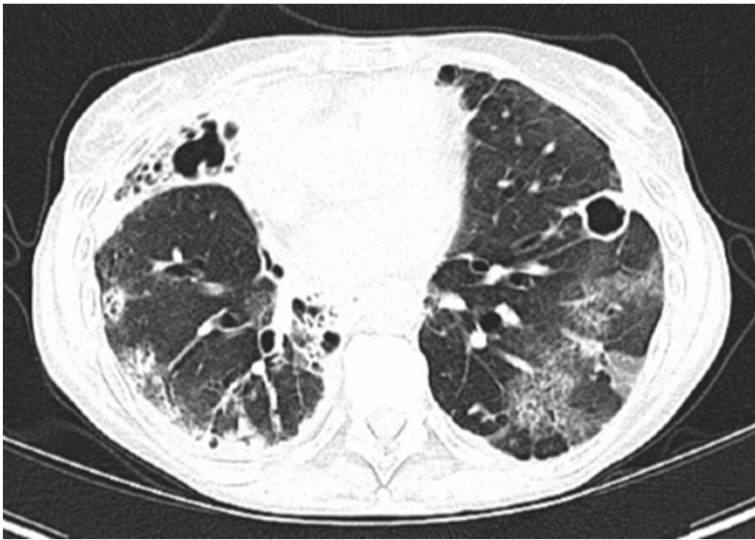
**Question #2 ; What should you do?**

- A. Stop all MAC medications
- B. Stop Clofazimine
- C. Stop Ethambutol
- D. Stop inhaled liposomal amikacin
- E. Continue all MAC medications and add oral prednisone

## Case 2. 78 year old patient with treatment refractory MAC

Start ALIS daily c AZI + EMB + CFZ → 6 months after treatment

SOB and Hypoxia after use of ALIS



- ✓ Chest CT when patient's breathing at its nadir
- ✓ Significant decline in FVC and FEV1



## Case 2. 78 year old patient with treatment refractory MAC

On ALIS daily c AZI + EMB + CFZ



Chest CT  
at time of worst SOB



4 months  
after  
stopping ALIS



Chest CT  
after stopping ALIS

# Amikacin (AMK)

## Inhaled Amikacin

Inhaled liposomal AMK

Parenteral AMK  
that is nebulized

590mg  
via vibrating system

240mg(1ml)  
diluted in 5ml of NS

Once daily

Daily - TIW

Ototoxicity

Nephrotoxicity

Bronchospasm

Hypersensitivity pneumonitis

Dysphonia (40%)

# Amikacin (AMK)

Inhaled Amikacin		Intravenous Amikacin
Inhaled liposomal AMK	Parenteral AMK that is nebulized	
590mg via vibrating system	240mg(1ml) diluted in 5ml of NS	15 – 25mg / kg
Once daily	Daily - TIW	Usually TIW
Ototoxicity		Ototoxicity (Monthly audiogram !!)
Nephrotoxicity		Nephrotoxicity
Bronchospasm		Rash
Hypersensitivity pneumonitis		Electrolyte disturbance (hypokalemia, hypomagnesemia)
Dysphonia (40%)		

## Case 1. 60 year old patient diagnosed with MAC lung disease

, started on azithromycin, RFP, EMB

→ Returns 3 months after last visit

- ✓ Cough, sputum production, fatigue improved
- ✓ Sputum AFB culture negative
- ✓ Gaining weight
- ✓ Exercise tolerance improved
- ✓ Sent home on azithromycin, RFP, EMB

→ 2wks after NJH visit had **precipitous loss of visual acuity**

Patient experiencing precipitous loss of visual acuity.

**Question #3 ; If you suspect EMB induced optic neuritis,  
what is your first recommendation to the patient?**

- A. Lower the frequency of administration from daily to TIW
- B. Ask the patient to continue the antibiotic, and see an ophthalmologist as soon as possible
- C. Stop the EMB immediately and ask the patient to see an ophthalmologist as soon as possible
- D. Start prednisone and have the patient see an ophthalmologist as soon as possible

## Case 1. 60 year old patient diagnosed with MAC lung disease

, started on azithromycin, RFP, EMB → loss of visual acuity

→ Stop the EMB & see an ophthalmologist ; optic neuritis

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

# EMB induced Optic Neuritis

Characteristics	
Unilateral or bilateral	Decreased visual acuity (blurriness) scotoma (partial vision loss/ blind spots) and/or color blindness (Red-Green color discrimination)
Usually reversible	But may take over weeks to months Defective color vision may persist longer Prednisone not indicated
Dose-dependent	Unusual at dose 15mg/kg Risk increases with dose (>20mg/kg) and decreased renal function Intermittent (TIW) dosing appears to be less associated with ocular toxicity than daily dosing

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

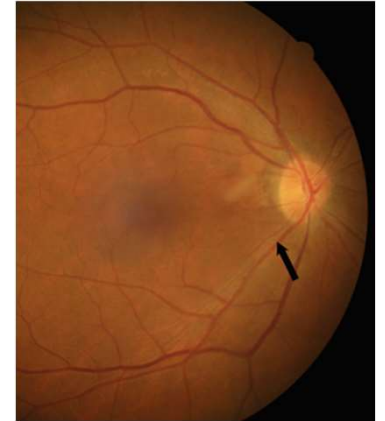
# EMB induced Optic Neuritis

Monitoring	
Baseline test (for all patients)	<b>Snellen chart</b> – visual acuity <b>Ishihara tests</b> – color vision discrimination
Patient education	Recommend daily vision self-checks Promptly report to TB clinic new vision changes and to stop EMB immediately
Monthly Sx check	Blurred vision, scotoma
Monthly testing	High dose (>20mg/kg), Tx longer than 2months, Renal insufficiency
Ophthalmology evaluation	No single diagnostic test for EMB ocular toxicity If suspect, refer to ophthalmology immediately



# EMB Toxicity

- ✓ Optic neuritis (ON)
- ✓ Hyperuricemia
- ✓ Peripheral neuropathy (PN)
- ✓ Hypersensitivity
- ✓ Hair loss



\* Remember that EMB is cleared through the kidney!

# Rifamycin

Rifampin (RFP)*		Rifabutin (RBT)**
Hepatotoxicity		
Hematologic (Leukopenia, Thrombocytopenia) <small>idiosyncratic</small>		
Drug induced lupus c antihistone Ab +		
GI upset (Nausea, vomiting)		
Hypersensitivity reaction		
Less frequent	Flu-like syndrome	More frequent
80-fold induction	Drug interactions	20-fold induction
Acute kidney injury <small>idiosyncratic</small>	Uveitis	
	Polyarthralgia/polymyalgia Syndrome	
	Skin hyperpigmentation	

\* Of the three drugs in the standard regimen, RFP is the one most often associated c toxicity

\*\*Toxicity more common c concomitant use of CLAR  
Toxicity primarily (not entirely) dose related

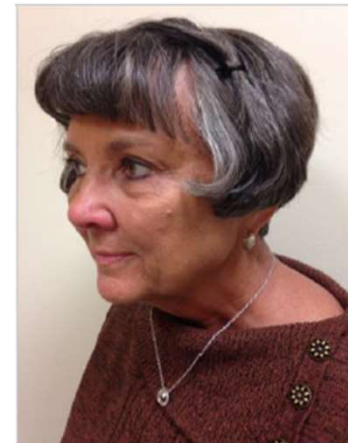
# Rifamycin Drug Interactions

RFP and RBT induce the CYP3A4 in cytochrome P450 enzymes  
**RFP** causes 80-fold induction vs **RBT** causes 20-fold induction

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

# 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 d/t crystal deposits



# Bedaquiline

- ✓ Concerns about QT prolongation (macrolide, FQ, clofazimine)
- ✓ Initial concerns about sudden death NOT confirmed
- ✓ Safety profiles have been substantiated by several studies
- ✓ Dose adjustment is not required in case of mild-to-moderate renal impairment
- ✓ Side effects
  - Nausea, QT prolongation, Headache, Chest pain, Weight loss, Rash/skin discoloration, Increase in LFTs/amylase

# Treatment of Rapid Growing NTM (MABC)

Ethambutol  
Rifampin/  
Rifabutin

Macrolide  
Amikacin (IV, Neb)  
Clfazimine  
Linezolid/Tedizolid  
Bedaquiline

Imipenem  
Cefoxitin  
Tigecyclin  
Omadacylin

# Rash

\* Any Drug Can Cause a Rash!



1. Stopping all antibiotics
2. Re-challenging with one drug at a time
3. Starting with the most important drug in the regimen

# Imipenem / Cefoxitin

	Imipenem*	Cefoxitin
Role	Foundation for RGM Tx	Alternative to imipenem for RGM Tx
Route/Dose	IV / 500-1000mg 2-3 times/day	IV / 2-4g 2-3 times/day
Cleared	Kidneys	
Toxicity	Rash, C. difficile diarrhea	
	Pancytopenia, Leukopenia, Hepatitis, Nausea, Vomiting, elevated CRP, Headache, Seizure	Eosinophilia, Abdominal cramps or tenderness, Back or leg pain, Blistering of skin, Blood in stool or sputum

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



# Ceftaroline

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

\* J Antimicrob Chemother 2016;71:2010

# Tigecycline / Omadacycline

	Tigecycline	Omadacycline*
Role	Alternative to <b>imipenem</b> for RGM Tx	Alternative to <b>tigecycline</b> for RGM Tx
Route/Dose	IV / 25-50mg 1-2 times/day	IV / 100mg QD
		Oral / 300mg QD
Cleared	Biliary secretion	?
Toxicity	N/V (Tige >> Omada), diarrhea, elevated LFT's, headache	
	Dosing should <b>start low with gradual increase</b> Can make a doorknob puke	Take at least 2 hours from anything with divalent cations (aluminum, iron, magnesium)

\* **Omadacycline** ; Fewer side effects and better tolerated than tigecycline  
 ? A **more effective** and **less toxic** than tigecycline, but **expensive!**

# Linezolid / Tedizolid

	Linezolid	Tedizolid**
Action	Inhibits the initiation process of protein synthesis	Bacteriostatic
Route/Dose	Oral / 600mg once daily or TIW	Oral / 200mg once daily
Cleared	Liver	?
Toxicity	Myelosuppression, Peripheral neuropathy, Serotonin syndrome* (Linezolid >> Tedizolid)	
	Optic neuropathy	Nausea, Headache, Diarrhea

\* Serotonin syndrome ; Most cases have been associated with the concomitant use of LZD and an SSRI or tricyclic antidepressant

\*\* Tedizolid; weaker MAO inhibitor than LZD / **Less toxic** than tigecycline, but **expensive!**

# Monitoring for Drug Toxicity

	MAC		MAB
Standard regimen	Ethambutol Rifamycin	Macrolide (Azi/Clari)	IV imipenem/cefoxitin
		± IV amikacin	
Monitoring	Baseline CBC, CMP, visual acuity and color vision testing, audiogram		
	→ After one month of Tx ; CBC, CMP, visual acuity and color vision testing → Then, periodically	Weekly CMP, amikacin drug level	In general, weekly CBC, CMP, periodic visual acuity and color vision
	Frequent patient interaction		

MAC

Key antibiotics

MABC

**Ethambutol**

Rifampin/  
Rifabutin

**Macrolide**

**Amikacin(IV, Neb)**

Clofazimine

Linezolid/Tedizolid

Bedaquiline

Imipenem

Cefoxitin

Tigecyclin

**?Omadacyline**

**\* If you stop them, how do you replace them?**

# Discontinuing **MAC** antibiotics What will you replace them with?

The **most important** drug!!!

**No** comparably active **replacement drug**!!!

~~Macrolide~~

**Ethambutol**

**Amikacin(IV, Neb)**

Rifampin/

Clofazimine

Rifabutin

Linezolid/Tedizolid

Bedaquiline

# Discontinuing **MAC** antibiotics What will you replace them with?

The most important drug for **protecting against the emergence of macrolide resistance !!!**

## Macrolide

~~Ethambutol~~ **Amikacin(IV, Neb)**

Rifampin/  
Rifabutin

Clofazimine

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# Discontinuing **MAC** antibiotics What will you replace them with?

The **only drug** other than the macrolides where  
**in vitro activity predicts clinical outcome**

## Macrolide

**Ethambutol** ~~Amikacin (IV, Neb)~~

Rifampin/  
Rifabutin

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# Discontinuing **MAC** antibiotics What will you replace them with?

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## Macrolide

**Ethambutol**

~~**Amikacin(IV, Neb)**~~

Rifampin/

?Clofazimine

?Rifabutin

?Linezolid/Tedizolid

?Bedaquiline

# Minimizing NTM Drug Side Effects

- Decrease drug dose (must maintain an effective dose)
- Increase interval between drug doses
- Split drug doses
- Drug administration with food
- Drug administration at night before bed
- Stomach acid reducing medication
- Anti-emetics
- Discontinue the offending drug (always last choice)

# Summary

- ✓ The treatment of NTM is usually **NOT** 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

Questions ?