NTM Medication Toxicity and Side Effects

David E. Griffith, MD

National Jewish Health

NTM Patient Course

April 2024

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 in NTM disease is linked to the gene causing nausea.

Richard J. Wallace Jr., MD

“The Treatment is Worse Than The Disease”

- Has a doctor ever said that to you?
- Do you believe that?

"The treatment is **worse** than the disease?"

Considerations when managing NTM treatment drug toxicity

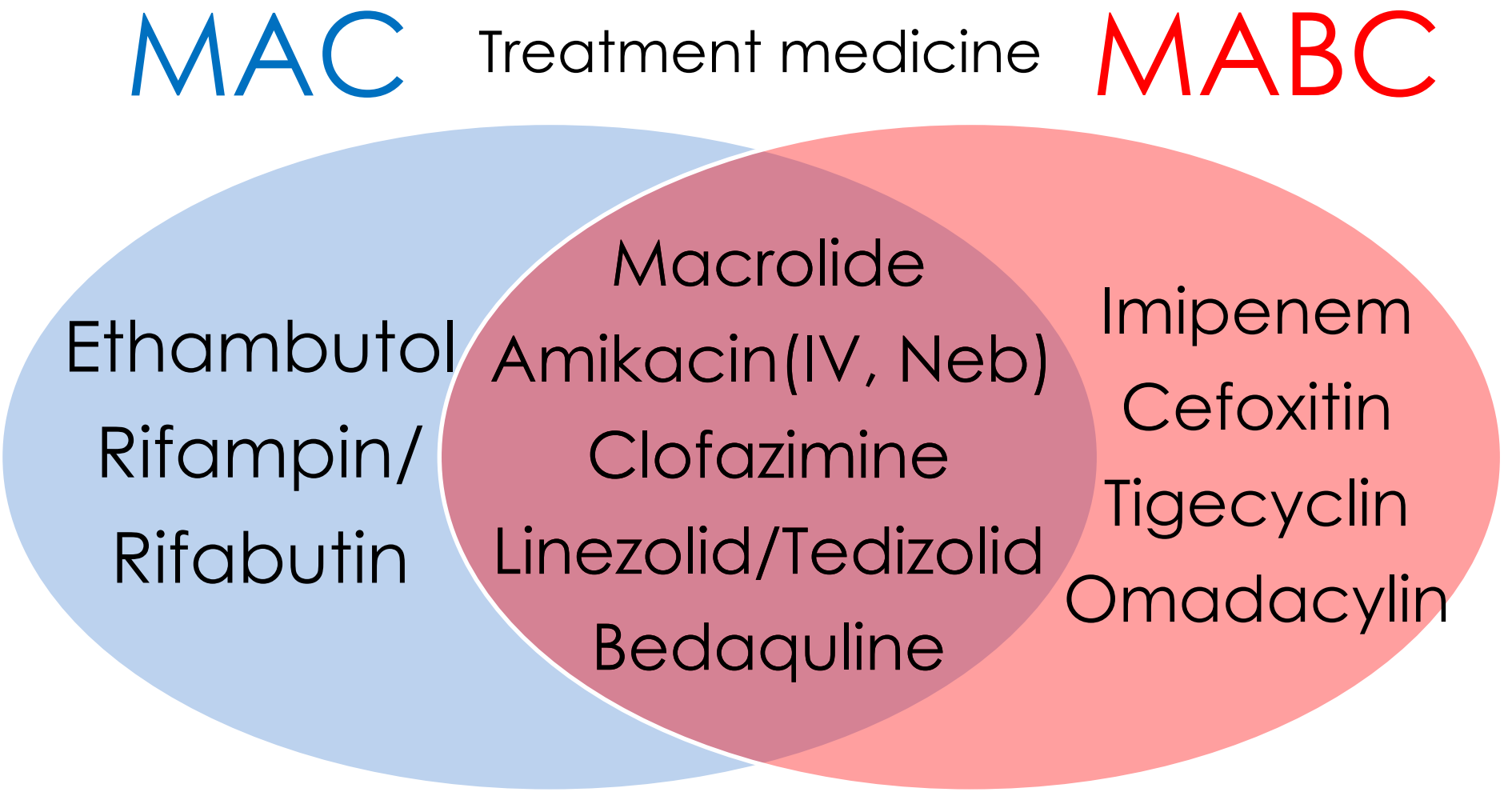
1. Not all NTM drugs are created equal

   - moxifloxacin cannot replace a macrolide

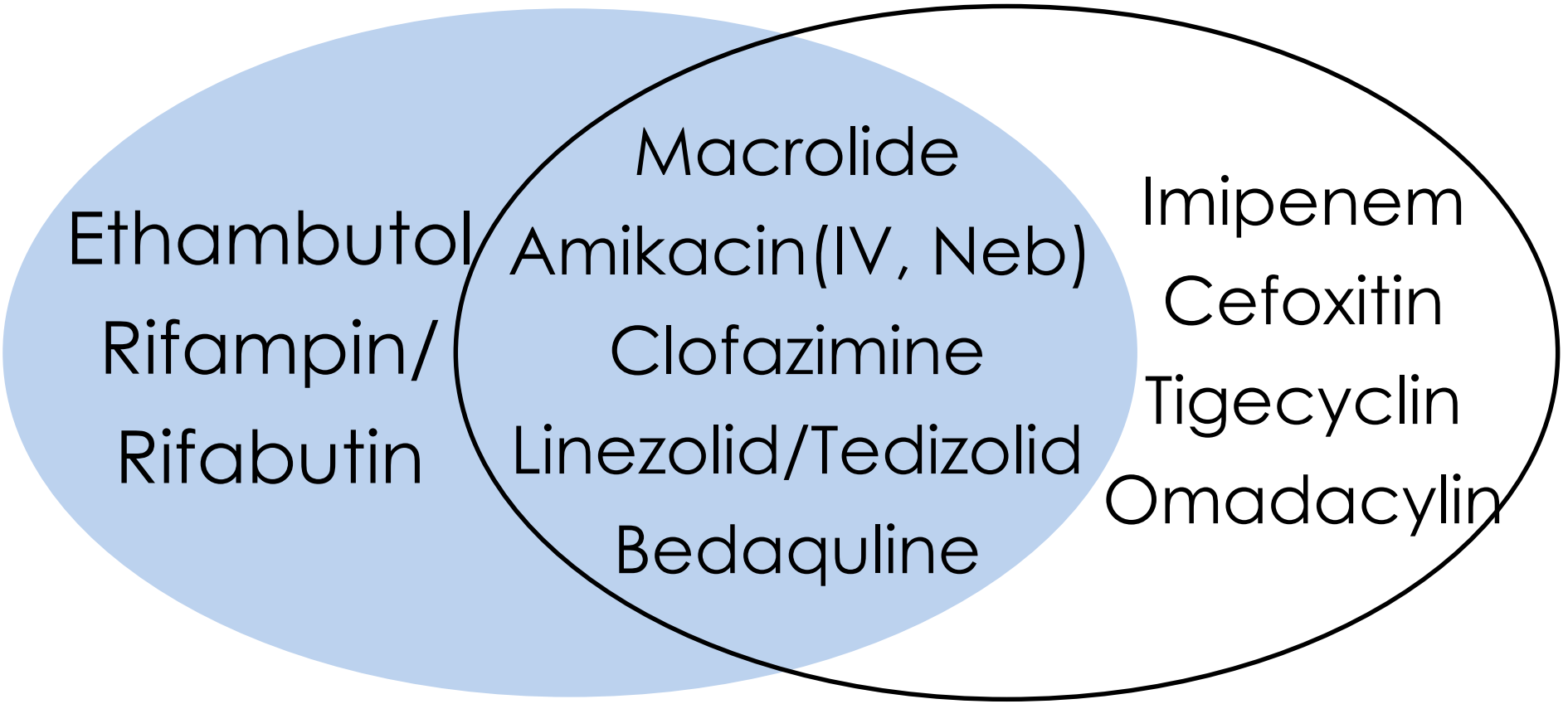
2. There is not a "deep bench" of effective NTM antibiotics to replace discontinued drugs as there is with TB drugs

3. In vitro susceptibility results have limited value for guiding drug choice

4. Must carefully consider the consequences of stopping an NTM antibiotics

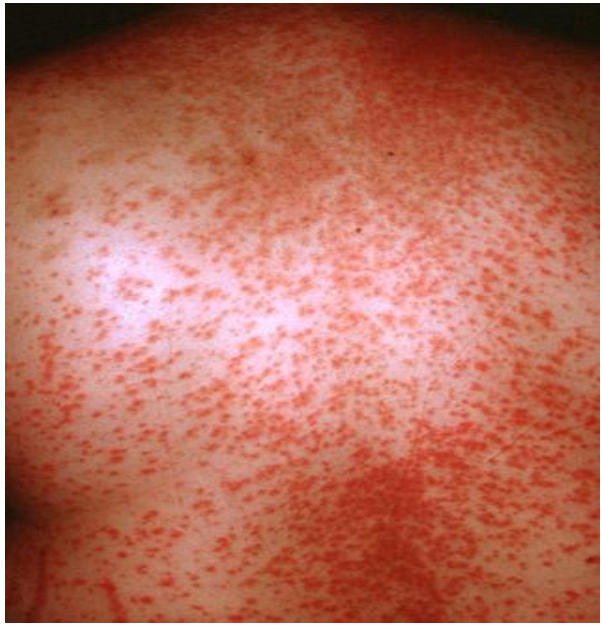

MAC
Treatment medicine
MABC
Ethambutol
Rifampin/
Rifabutin
Macrolide
Amikacin(IV, Neb)
Clofazimine
Linezolid/Tedizolid
Bedaquline
Imipenem
Cefoxitin
Tigecyclin
Omadacylin

Treatment of Slow Growing NTM (MAC)



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

- ✓ 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

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

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, sotolol

* 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?

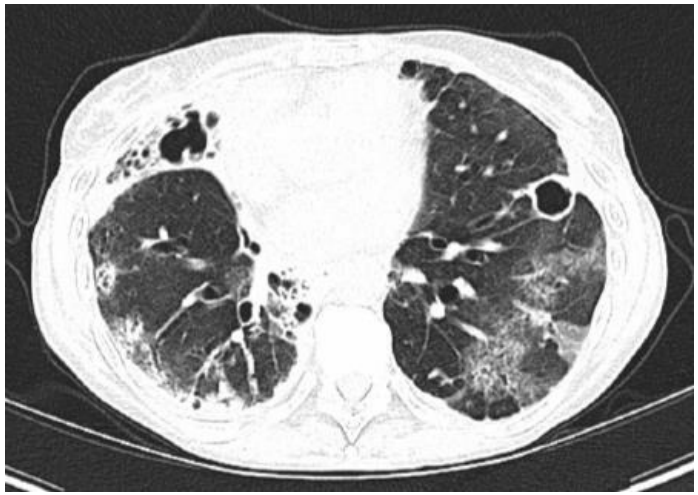
Inhaled Amikacin

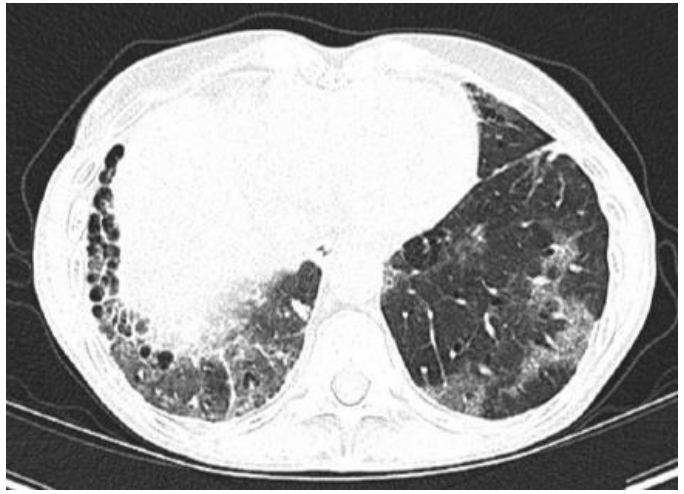
- Inhaled liposomal amikacin
  - 590mg once daily
    - Watch for hypersensitivity pneumonitis or bronchospasm
    - Dysphonia is common; hearing loss, tinnitus
- Parenteral amikacin that is nebulized
  - 240mg(1 ml) diluted in 5ml of NS daily-thrice weekly
    - Bronchospasm; hearing loss; elevated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

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

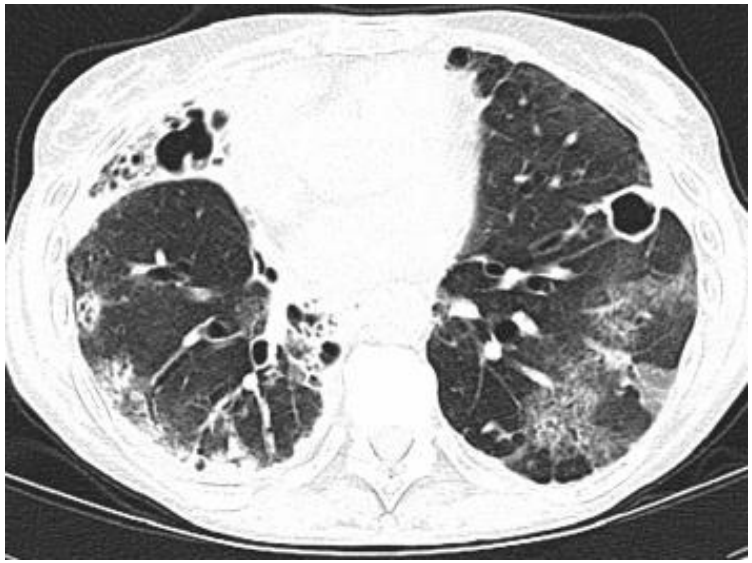




- ✓ Chest CT when patient's breathing at its nadir
- ✓ Significant decline in FVC and FEV1

Case 2. 78 year old patient with treatment refractory MAC

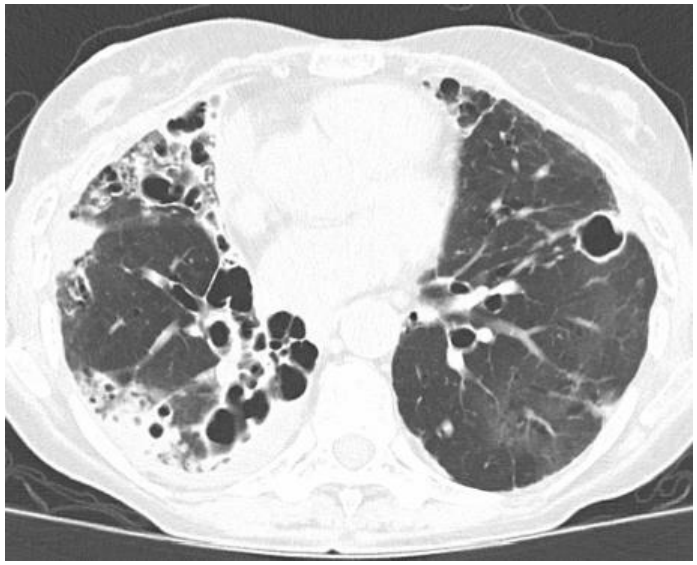
On ALIS daily c AZI + EMB + CFZ



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%)		

EMB induced Optic Neuritis

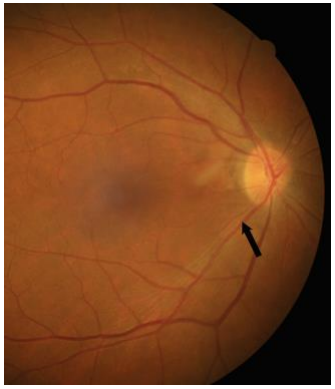
Characteristics	
Unilateral or bilateral	Decreased visual acuity (blurriness) scotoma (partial vision loss/ blind spots) and/or color blindness (Red-Green color discrimination)
Usually reversible	But may take over weeks to months Defective color vision may persist longer Prednisone not indicated
Dose-dependent	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

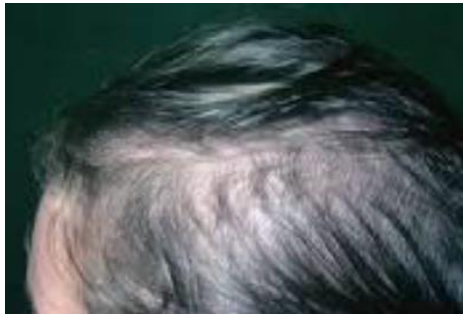
EMB induced Optic Neuritis

Monitoring	
Baseline test (for all patients)	**Snellen chart** – visual acuity **Ishihara tests** – 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 (<1% of patients)
- ✓ Hair loss



* Remember that EMB is cleared through the kidney!

Rifamycin

Rifampin (RFP)*		Rifabutin (RBT)**
Hepatotoxicity		
Hematologic (Leukopenia, Thrombocytopenia) idiosyncratic		
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 idiosyncratic		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

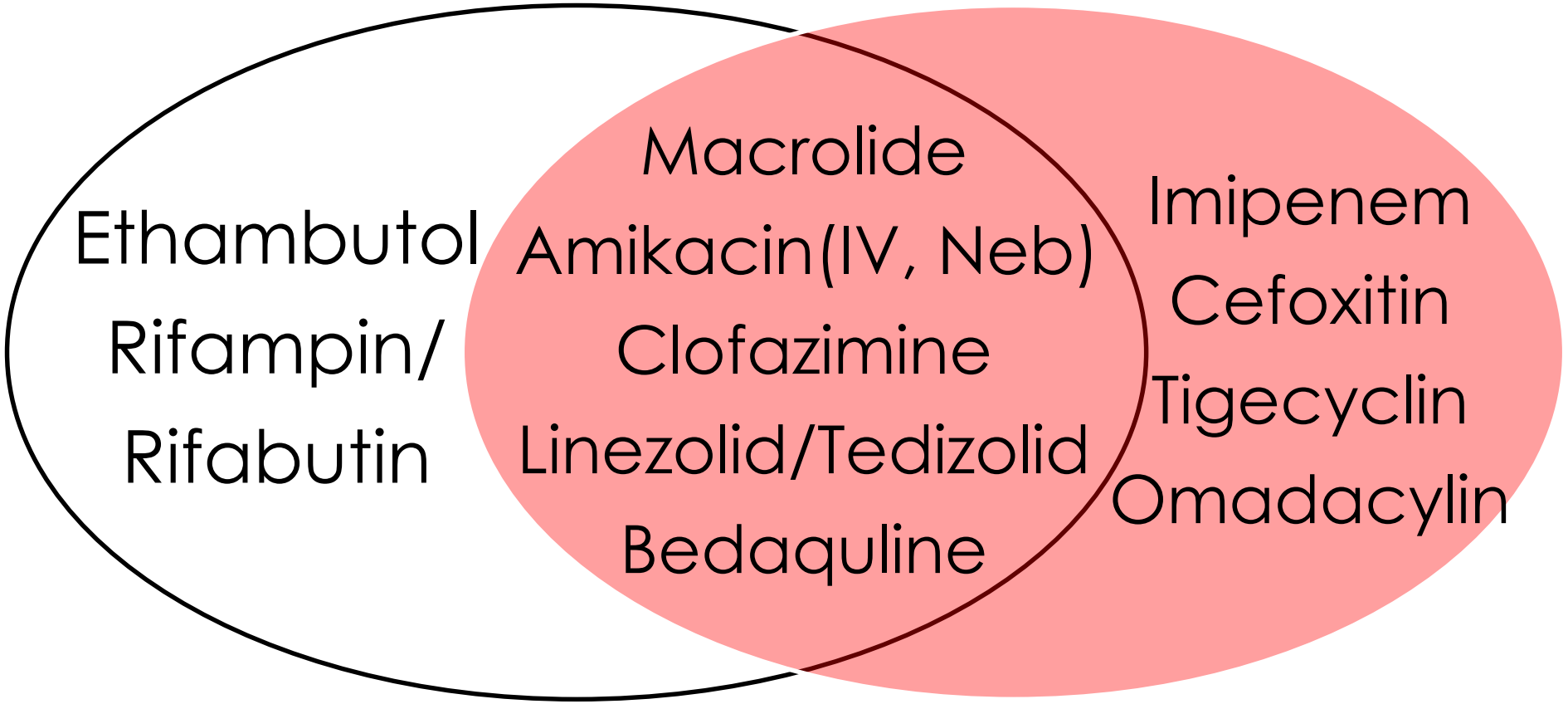
Clofazimine

- ✓ 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

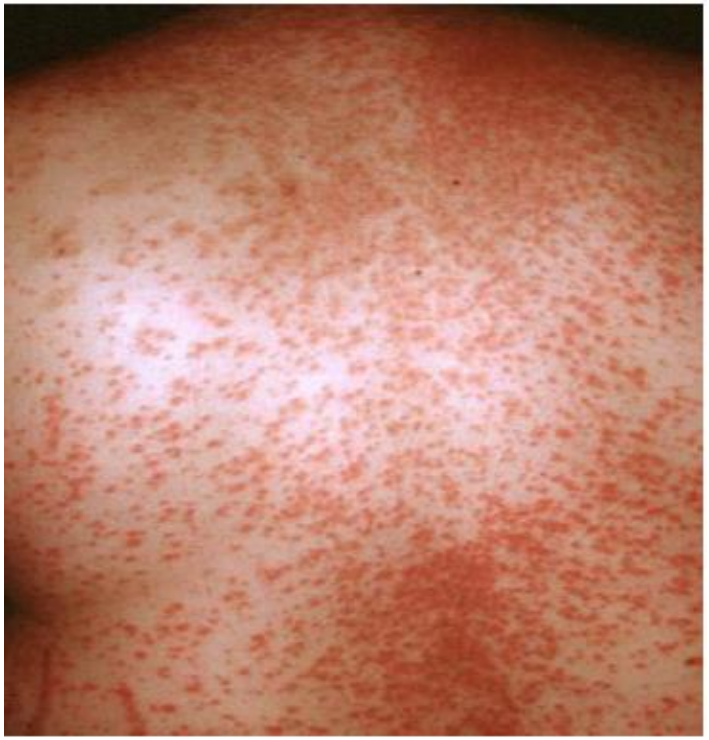
- ✓ Concerns about QT prolongation (macrolide, FQ, clofazimine)
- ✓ Initial concerns about sudden death NOT confirmed
- ✓ Safety profiles have been substantiated by several studies
- ✓ Dose adjustment is not required in case of mild-to-moderate renal impairment
- ✓ Side effects
  - Nausea, QT prolongation,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

Treatment of Rapid Growing NTM (MABC)



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 imipenem for RGM Tx	Alternative to tigecycline 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 start low with gradual increase 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

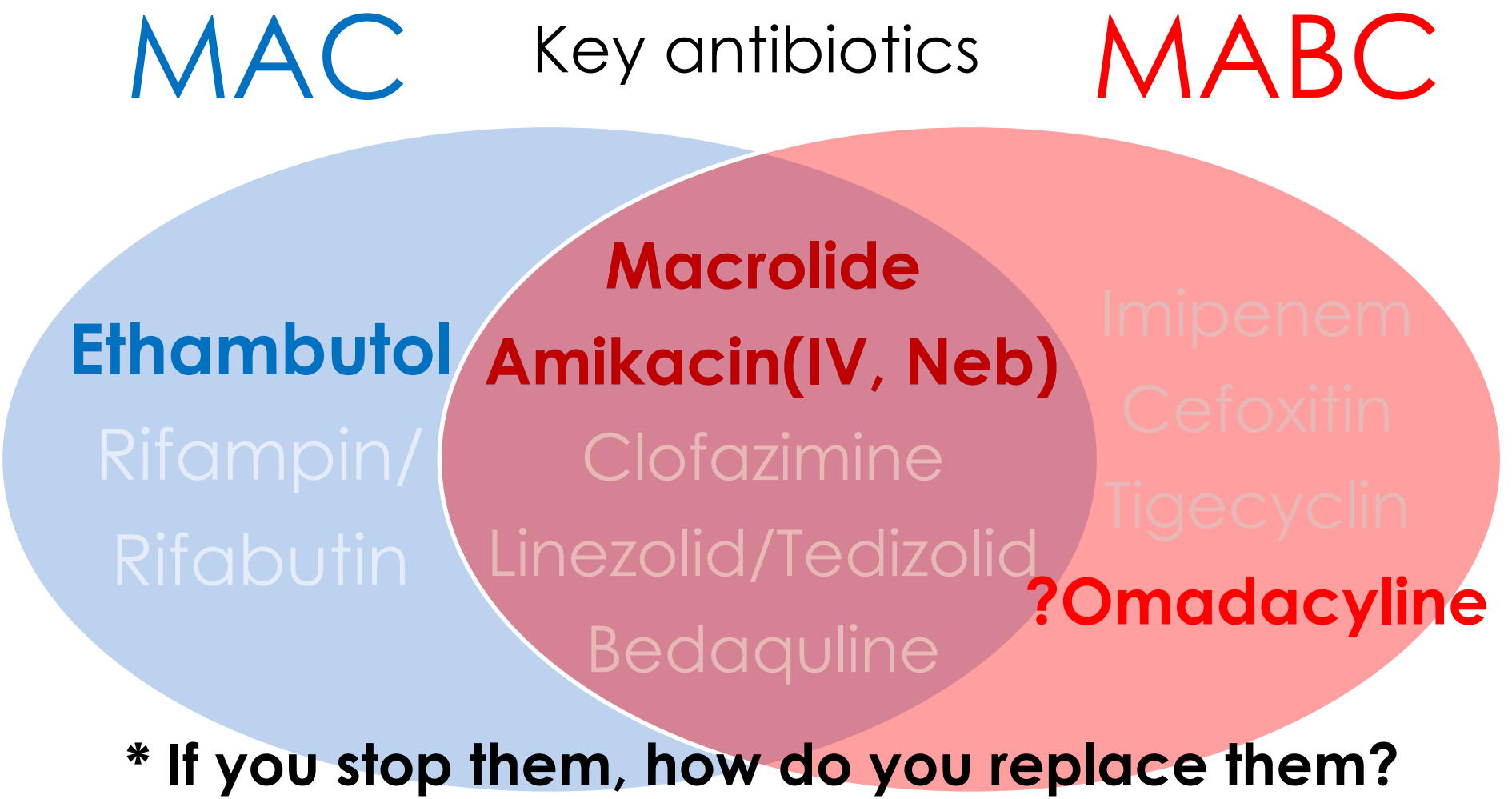
	Linezolid	Tedizolid**
Action	Inhibits the initiation process of protein synthesis	Bacteriostatic
Route/Dose	Oral / 600mg once daily or TIW	Oral / 200mg once daily
Cleared	Liver	?
Toxicity	Myelosuppression, Peripheral neuropathy, Serotonin syndrome* (Linezolid>>Tedizolid)	
	Optic neuropathy	Nausea, Headache,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

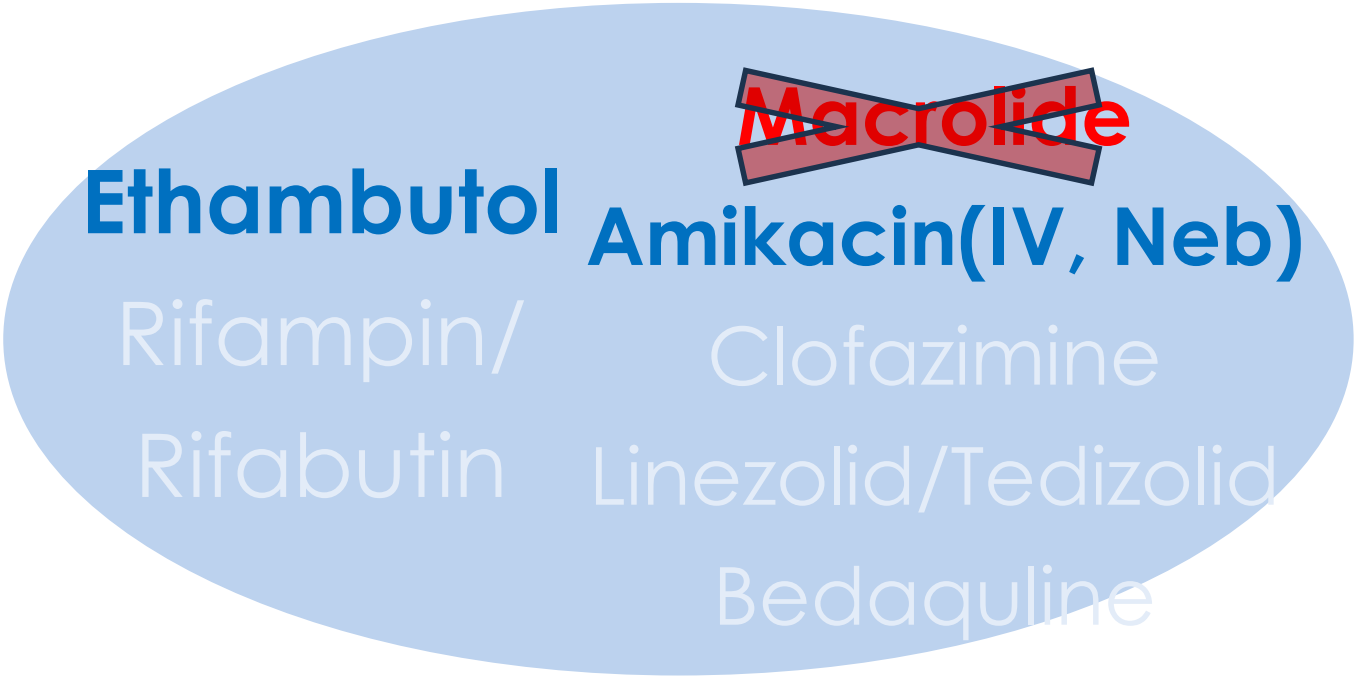


*** If you stop them, how do you replace them?**

Discontinuing MAC antibiotics
What will you replace them with?

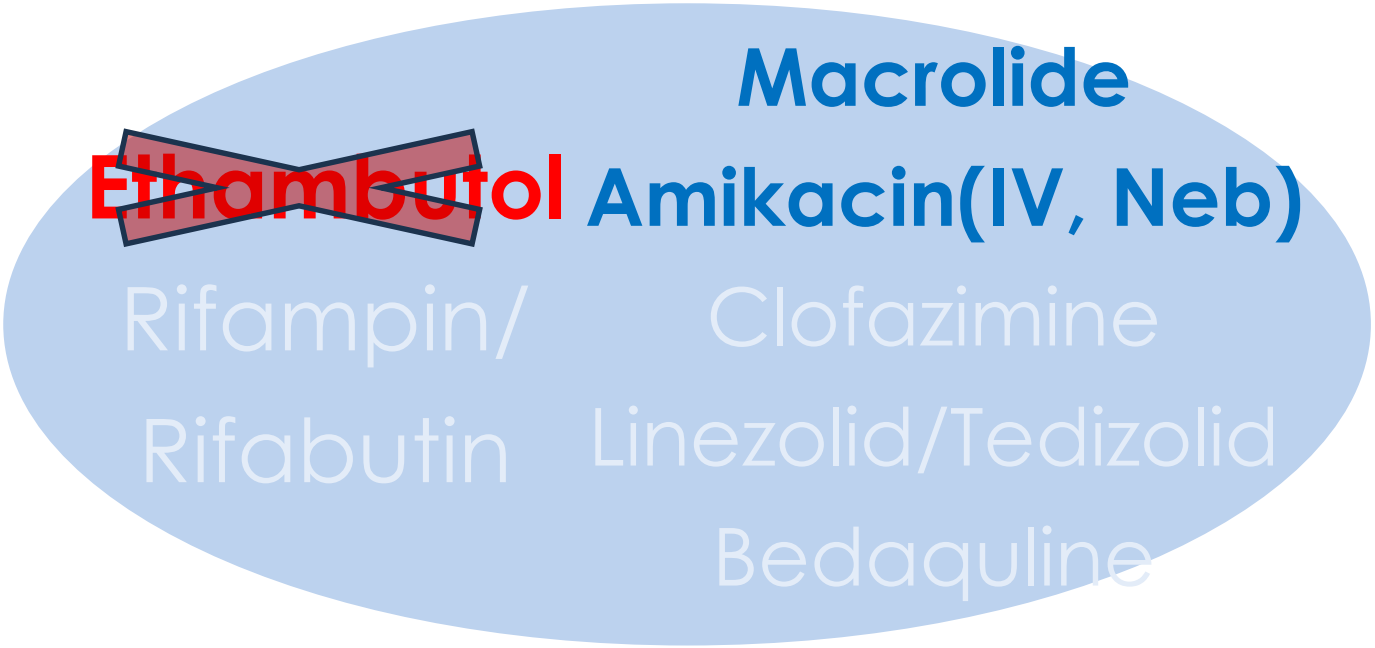
The **most important** drug!!!

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



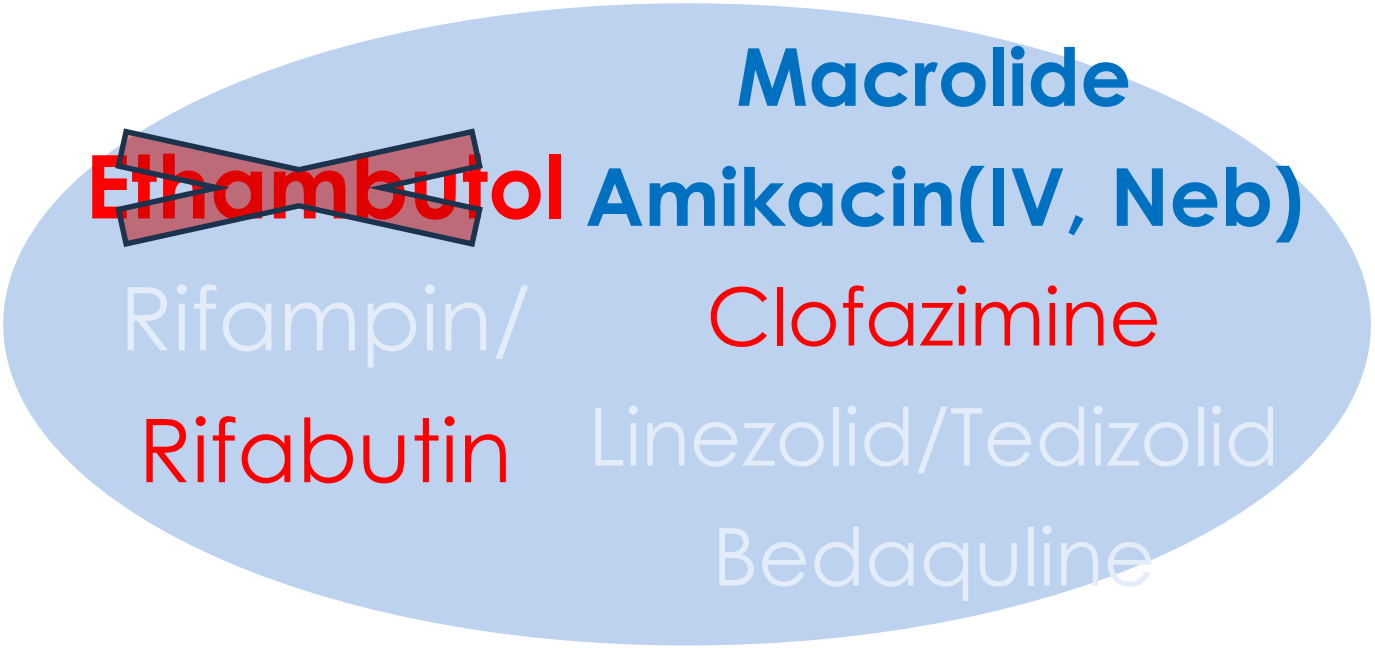
Discontinuing MAC antibiotics
What will you replace them with?

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



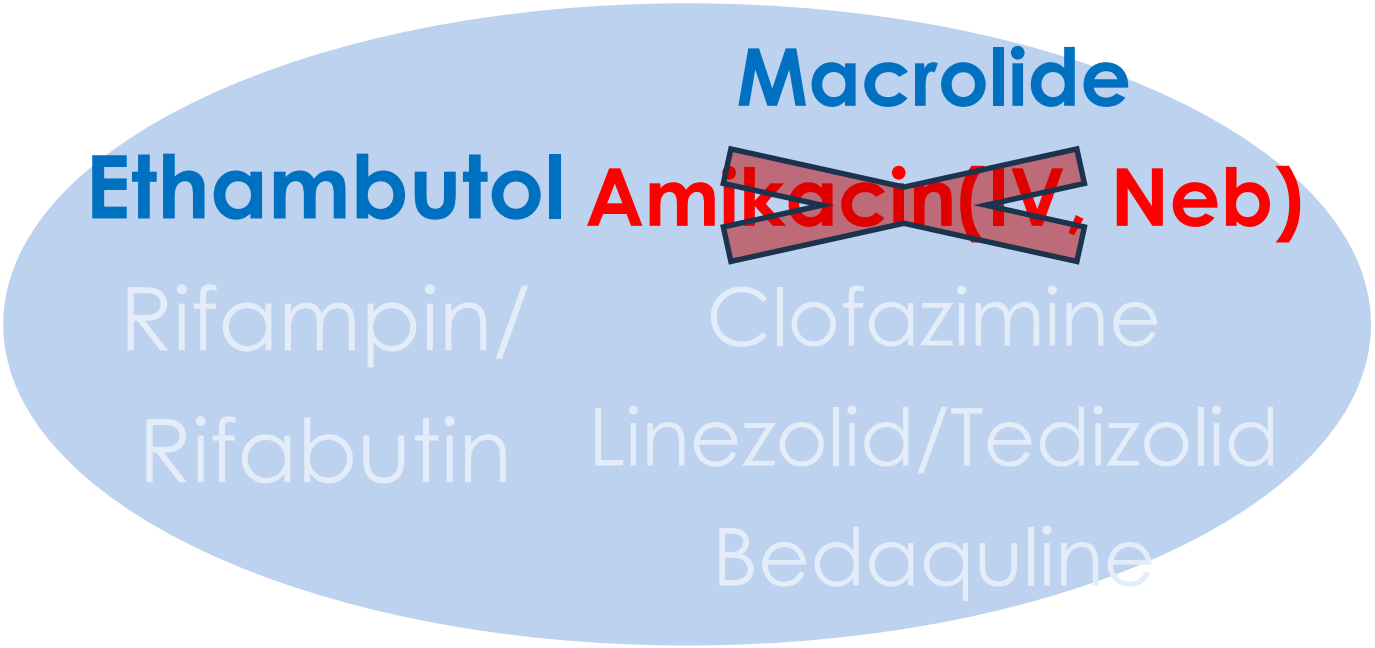
Discontinuing MAC antibiotics What will you replace them with?

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



Discontinuing MAC antibiotics
What will you replace them with?

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



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

Rifampin/

?Rifabutin

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

?Clofazimine

?Linezolid/Tedizolid

?Bedaquline

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 ?