

# Managing Side Effects

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**UTHealth**

The University of Texas  
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NTM Info & Research, Inc.

**THE TREATMENT OF NTM LUNG  
DISEASE SHOULD NOT BE WORSE  
THAN THE DISEASE**

# Managing Side Adverse Effects

## Macrolides, Rifamycins, Ethambutol and Fluoroquinolones

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# Managing Adverse Effects

## *- Objectives*

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Summarize and describe approaches toward common or severe drug-related AEs encountered in treating NTM using:

- Macrolides – Azithromycin / Clarithromycin
- Ethambutol
- Rifamycins – Rifampin / Rifabutin
- Fluoroquinolones – Moxifloxacin / Ciprofloxacin / Levofloxacin
- Drug interactions

# Macrolides

- azithromycin / clarithromycin

Cornerstone of therapy for MAC and critical for susceptible *M. abscessus* isolates

Useful agent for *M. xenopi*, *M. kansasii*, *M. malmoense*, etc.

Generally well tolerated, but usually some AEs (more so with clarithromycin)...

# Macrolides

## - azithromycin / clarithromycin

### Problems

### Guidance

#### Common (>1%)

- Diarrhea, nausea, abdominal pain (much more common with clarithromycin)
- Abnormal metallic taste, fatigue

Take with food, probiotics, dietary adjustment, dose /schedule adjustment, anti-nausea drugs\*, loperamide\*

Dose reduction if feasible

#### Uncommon (<1%)

- Hearing loss / tinnitus (more common?)
- Chest pain
- Bloody stool / colitis (C. difficile)
- Jaundice
- Vaginal yeast infection
- Kidney inflammation
- Dizziness, headache, vertigo
- Skin rash, itch, photosensitivity

Dose reduction if feasible

?

Depends on severity of colitis and NTM infection

Rare, typically avoidance

Topical (clotrimazole, etc.) vs systemic (fluconazole\*)

Rare, typically avoidance

Dose reduction if feasible

Avoid sun exposure, topical steroid

\*Potential for QTc prolongation

# Macrolides

## - azithromycin / clarithromycin

### Rare, serious problems

Allergic reaction, hives, difficulty breathing, skin rash – severe allergic reactions occur in much less than 1%

Irregular heart rhythm – very uncommon (much less than 1%) risk of potentially life threatening irregular heart rhythm

#### Azithromycin studies

- Tennessee Medicaid observational study (30-74 yr olds) - sudden death occurred in 47-245/1,000,000 (0.0047 – 0.0245%) with 5-day course

NEJM 2012

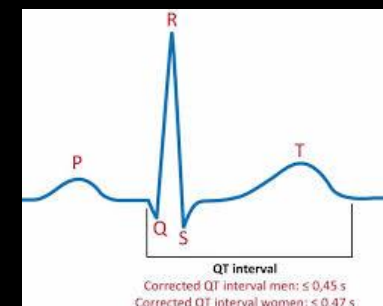
- Danish observational study (18-65 yr olds) – no increase in risk

NEJM 2013

### Guidance

Immediate discontinuation and treatment of allergic response  
Supervised careful desensitization may be used if drug subsequently required

Recognize that it is rare; likely greater in older people and with heart disease  
Cause related to effect on heart's electrical conduction system measured by the QTc interval



EKG before and periodically after starting (esp. with addition of other drugs that prolong QTc\*)

\*Fluoroquinolones (moxi-, levo-, ciprofloxacin), clofazimine, many others...

## Ethambutol

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Most important agent preventing macrolide resistance in MAC (this is *really* important)

Role less certain in other NTM species, but used commonly for *M. xenopi*, *M. kansasii*, *M. malmoense*, etc.

Generally well tolerated, but AEs may occur...



# Ethambutol

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## Optic neuropathy (vision changes)

- Decreased visual acuity (blurriness), scotoma (partial vision loss/blind spot), and/or color blindness
- Usually at least partly (and slowly) reversible
- Risk increases with dose (daily dosing >17-20 mg/kg higher risk)
  - Daily 15 mg/kg → likely >5%
  - Thrice weekly 20-25 mg/kg → likely ~1%
- Recommendations
  - Avoid higher daily doses if feasible
  - Test vision monthly (online, self testing), eye specialist exams periodically
  - Patients report promptly new vision changes; usually withhold drug until assessed

# Ethambutol

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## Less common AEs (likely <5%)

## Guidance

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Numbness / tingling of extremities  
(peripheral neuropathy)

Electrophysiologic testing helps confirm presence of  
neuropathy  
Dose reduction if feasible  
Occasionally severe requiring discontinuation (uncommon)

Anaphylaxis, severe dermatitis

Immediate discontinuation and treatment of allergic reaction  
Supervised careful desensitization may be used if drug  
required

Anorexia, nausea, vomiting,  
abdominal pain

Dietary adjustments, take with food, probiotics, dose  
reduction if feasible, anti-nausea drugs\*, loperamide\*

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\*Potential for QTc prolongation

# Rifamycins

- rifampin / rifabutin

Very commonly used for MAC; particularly important for *M. xenopi*, *M. kansasii*, *M. malmoense*, etc.

Interactions between rifampin and many drugs will occur

Though usually well-tolerated, AEs are common (typically more so with rifabutin)

- Universal orange-like urine discoloration; also other body secretion (sweat, tears); disappears when drug stopped
- Other AEs in minority...

# Rifamycins

- rifampin / rifabutin

Problems	Guidance
- GI distress, reflux, flatulence, diarrhea	Administration with food, dietary adjustments, probiotics, gastric acid suppression*, anti-nausea drugs†, loperamide†
- Flu-like symptoms – may include fever, headache, fatigue	Often dissipates If severe and persistent may require discontinuation
- Rash, eye inflammation, joint pain	Possibly severe immunologic reaction Cessation of drug with careful assessment and consideration whether future use required
- Liver inflammation	Monitor blood tests periodically Stop drug if significant abnormality If not severe, may restart at lower dose / intermittent dosing
- Low blood counts – platelets, white blood cells	Monitor CBC periodically If mild, observation vs dose reduction If severe, stop drug, consider whether safe to restart at lower dose
- Anaphylaxis / severe allergic reaction	Immediate discontinuation and treatment of allergic response Supervised careful desensitization if drug subsequently required

\*Acid suppression reduces rifamycin absorption; †May prolong QTc

# Fluoroquinolones

## - Moxifloxacin (or levo/ciprofloxacin)

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Relatively commonly used (likely more important for *M. xenopi*, *M. kansasii*, *M. malmoense*, some rapid growers)

Though usually well-tolerated AEs are common...

- GI distress → dietary adjustments, probiotics, anti-nauseants, acid suppression...
- Musculoskeletal pain → if moderate/severe may require discontinuation
- Tremulousness, anxiety – avoid caffeine within a few hours of dosing

Less common / rare but potentially severe

- Tendinopathy – tendon rupture (rare) – cessation of drug
- QTc prolongation – baseline and periodic EKG (esp with other QTc prolonging drugs)
- Psychiatric manifestations – withhold drug, other drug in class may be tolerated
- Colitis – uncommon, potentially very severe, withhold drug when possible
- Neuropathy – uncommon
- Avoid in patients with myasthenia gravis, may precipitate myasthenic crisis...

# Drug Interactions

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## Rifampin (much less commonly rifabutin)

- Increases liver's metabolism of many drugs and thus reduces their effect
- Must check for interactions with all other medications and consider monitoring, dose adjustments, other drugs

## Clarithromycin

- Inhibits liver's metabolism of many drugs (including rifamycins) and thus increases their effect (and toxicities)
- Azithromycin preferred; check for interactions when clarithromycin used

## Other drugs and issues

- Antifungals ("azoles") – increase levels of several drugs (rifamycins, macrolides)
- QTc prolongation – may occur with several antibiotics used for treating NTM (macrolides, fluoroquinolones, etc.), and many other drugs; combining multiple QTc prolonging drugs increases risk of an AE

# **Managing Adverse Side Effects: Inhaled/IV amikacin, Bedaquiline and Linezolid/Tedizolid**

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# Inhaled amikacin

- Historically available by drawing up a vial in a syringe and administering 250mg-500mg by a Pari-LC nebulizer
- Arikayce – new formulation available as of Fall 2018. 590 mg delivered by a Lamira nebulizer system which is delivered with the medication.





# Common side effects with inhaled antibiotics

- Cough
- Dysphonia
- Bronchospasm
- Coughing up blood
- Sore throat
- Ringing in the ears or hearing loss (possible)

# Tips for taking inhaled antibiotics

- Taking an inhaler or nebulizer of albuterol or the like before use may help
- Hot tea or other warm liquids may ease throat discomfort
- Practice patience – it is often normal to have side effects. These often improve with use!

# Intravenous Amikacin

- Dosed according to your weight
- Monitored with drug levels

## Side effects:

- Hearing loss/ringing in the ear
- Kidney impairment
- Nausea

# Bedaquiline and Nontuberculous Mycobacterial Disease

The FDA approved bedaquiline for treatment of drug resistant Tuberculosis (TB) in 2013. Some lab studies show it also works for NTM.

- Dispensed from ONE pharmacy in the U.S.



# Bedaquiline and Nontuberculous Mycobacterial Disease

- Administer orally with food
- Oral 400 mg once daily for 2 weeks, followed by 200 mg 3 times weekly.

# Bedaquiline

- Nausea
- Vomiting
- Diarrhea
- Increased liver enzymes
- Irregular heart beat or rhythm
- Headache
- Rash
- Joint aches

# Bedaquiline

Tell your doctor if you have:

- Irregular heart beat or chest pain
- Yellowing of the skin or discolored stool
- Severe abdominal pain
- Rash
- Headache

# Bedaquiline

## Monitoring:

- EKG of your heart at periodic intervals
- Routine blood work to monitor blood counts and liver function



# Tedizolid (Sivextro)



200 mg daily

# Linezolid (Zyvox)



300-600 mg daily-  
twice daily

# Tedizolid (Sivextro)      Linezolid (Zyvox)

Oral drugs used to treat NTM in certain cases

Side effects:

- Rash
- Changes in blood counts
- Neuropathy
- Nausea/vomiting/diarrhea
- Changes in the liver

# Tedizolid (Sivextro)      Linezolid (Zyvox)

Monitoring:  
Blood work

Notify your doctor:

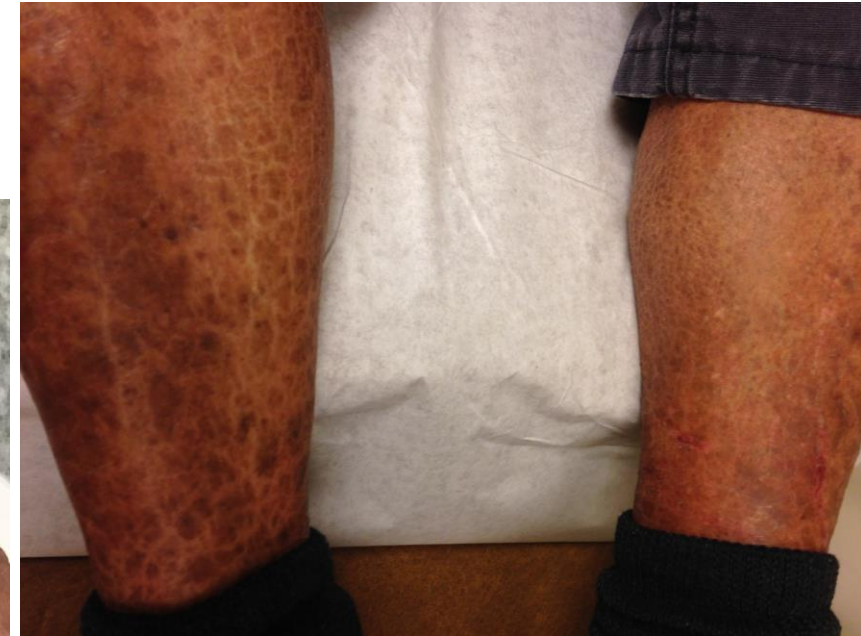
- Rash
- Numbness/tingling of your hands or feet
- Bruising
- Fever
- Abdominal pain

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

# What about clofazimine:

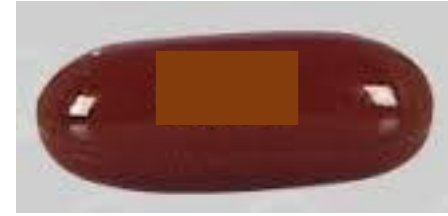


# Clofazimine



- New, old drug
- Currently only available in the USA through application with the pharmaceutical company Novartis in partnership with the FDA
- Your physician has to fill out the application, the application (IND) must be presented to an IRB (Institutional Review Board). If approved, you will get the medication for free
- This can be a very cumbersome process for your physician

# 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, abnormal liver function tests)
  - Conjunctival and corneal pigmentation due to crystal deposits
  - Discolored dental plaque; discolored hard contact lenses

# Clofazimine



- Starting dose is 100mg once daily however if side effects develop, decreasing the dose to 50mg once daily or even 50mg three times a week will often help
- Most common side effect is gradual skin tanning. This skin discoloration will begin to fade away once the medication is discontinued
- Some patients complain of stomach upset or intestinal cramping although this is not common
- A baseline EKG and periodic repeat testing should be done while on this medication



# Any Drug Can Cause a Rash



# Imipenem-Cilastin

- role: Backbone for RGM treatment
- action: inhibits protein synthesis
- dosage: I.V.
- dose: 500mg BID or TID
- cleared: kidneys
- toxicity: rash, pancytopenia, hepatitis, C. diff, leukopenia; elevated CRP

# Imipenem-Cilastin

- An intravenous medication that must be administered with a PICC line
- Given for the Rapidly Growing Mycobacteria such as *M. abscessus* but also for other “Respiratory Bacteria” such as *Pseudomonas*
- Usually administered twice a day
- Side effects are rash, diarrhea (*C. diff*), and rarely liver inflammation

# Imipenem-Cilastin

- Rarely, patients will have an “allergic” reaction that is best described by patients as “I just want to die”. They may have fever, body aches, terrible fatigue
- These symptoms will resolve within a day or two once the medication is stopped
- You should have blood monitoring with CBC and Biochem panel every week or two while on this antibiotic

# Cefoxitin

- role: Alternative to imipenem-cilastin as backbone for RGM treatment
- action: inhibits bacterial cell wall synthesis
- dosage: I.V.
- dose: 2 GM BID or TID
- cleared: kidneys
- toxicity: rash, C. diff, eosinophilia

# Cefoxitin

- This is an intravenous antibiotic used to treat the Rapidly Growing Mycobacteria such as *M. abscessus*
- It has a much higher risk of rash (it is a close cousin of penicillin) than imipenem, so we don't use it as often
- Common side effects are rash and *C. difficile* diarrhea
- You should have a CBC and Biochem panel done every week or two while on this medication because elevated liver function tests or low white blood count are not uncommon