Treatment of NTM: Medication Side Effects
“Is the Treatment Really Worse Than The Disease?”
Gwen Huitt, M.D., M.S.

NTM Lecture Series for Providers
October 20, 2017
Disclosures

• None
Treatment of Slow Growing NTM

- Rifampin
- Rifabutin
- Ethambutol
- Azithromycin
- Clarithromycin
- IV Amikacin
- Inhaled Amikacin
- Clofazimine
- Moxifloxacin
Toxicity - Nausea and vomiting
Any Drug Can Cause a Rash
Rifampin ( RIF )

role: Backbone for SGM

action: DNA – dependent RNA synthetase

dosage: oral, I.V.

dose: 600 mg once daily on empty stomach
450 mg once daily for <50 kg

cleared: liver >> kidneys

toxicity: hepatotoxicity, flu – like syndrome, acute renal failure
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
Rifabutin (RBN)

role: instead of RIF for HIV+ patients, or in patients with drug–drug issues

action: DNA–dependent RNA synthetase

dosage: oral

dose: 300 mg once daily

cleared: liver >> kidneys

toxicity: neutropenia, thrombocytopenia, uveitis, skin discoloration
Toxicity - Rifabutin

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

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

- 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?
What is the Cause of the Low WBC?

1. Rifampin
2. Moxifloxacin
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
Unnecessary Bone Marrow Biopsy
Rifampin Drug Interactions

Very Potent Inducer of enzyme P450 3A4
As well as other P450 1A2, 2A6, 2B6, 2C8/9, 2C19

- Warfarin
- OCs/HRT/synthroid
- Glucocorticoids
- Cyclosporine
- Azole antifungals
- Methadone
- Quinidine
- Theophylline

- Verapamil, Diltiazem
- Sulfonylureas
- Digoxin
- Beta blockers
- Phenytoin, CBZ
- Clarithromycin
- Protease inhibitors
- Diazepam
Case

- 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?
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
Drug-Induced Lupus Syndrome Associated with Rifamycin Therapy

• Serology:
  – 5 positive ANA ≥1:320
  – 1 positive anti-histone Ab
  – 3 negative anti-histone Ab (>2 mos off RIF)
  – 1 pt with positive ANA significant reduction in titer after D/C rif

• Conclusions
  – Lupus interactions may be seen with rifamycin therapy
  – May represent drug-drug interactions with altered degradation of rifamycins

Case- Hot off the Press -1

- 51 year old male with refractory pulm M. avium

- Pneumonia 2009 – AFB smear positive
  - Placed in Isolation
  - CT done at that time showed thick walled RUL cavity extending to ssRLL
  - Started on clarithromycin, ethambutol and rifampin all TIW
  - Thoughts?
Case - Hot off the Press - 2

- Lost to f/u until 2011
- 6/2011 seen by Infectious Disease
  - Increased DOE, cough and fatigue
  - Urine histo Ag done - ? Result
  - Blasto, cocci, histo Ag done - ?result
  - Sputum smear and cx positive for M. avium
- 2/2012 – Started on rifampin, ethambutol and azithromycin daily
Case- Hot off the Press -3

• Bronchoscopy 2/2012
  – Culture positive for Histoplasma capsulatum
  – Started itraconazole liquid 200mg BID

• 4/2012
  – Itraconazole solution increased to 200mg TID

• 5/2012
  – Itraconazole solution decreased to 200mg BID secondary to side effects
Case- Hot off the Press -4

• 1/2013 – itraconazole discontinued after 1 year of treatment

• 9/2013- Sputum continues smear and cx positive for M. avium
  – Cipro, Clari, Rifampin, ethambutol
  – NEW SENSITIVITIES NOW SHOW CLARITHROMYCIN RESISTANCE
  – Clari dc’d and linezolid is started (600mg BID)
Case- Hot off the Press -5

• 1/2015 – Cipro dc’d and Moxi started (400mg daily)
  – Moxi/ linezolid/ ethambutol/ rifampin all daily
  – IV amikacin started and given M, W, F x 2 months

• 3/2015 – IV amikacin dc’d and started on inhaled amikacin
  – Severe coughing with inhaled amikacin

• Thoughts?
Case - Hot off the Press -6

- Admitted to NJH 9/14/16
  - Meds: Rifabutin/ Itraconazole/ inh Amikacin/ Ethambutol
- Labs
  - WBC 2.5  Hct – 40  Hgb – 12.9  Plt – 120K
  - RDW 19%  61% neut/ 9% bands/ 18% mono/ 12% lymphs
  - CRP  3.25 (< 0.4)
  - Biochems all normal
  - Vit D  34 (30-100)
  - Pre adm sputum: smear (-); 50 colonies of MACROLIDE RESISTANT M. avium; Histoplama capsulatum
Case- Hot off the Press
Case- Hot off the Press
Case- Hot off the Press
Case- Hot off the Press -7

• What are the major medication issues?
  – What diseases do you treat?
    • M. avium
    • Histo
    • COPD
  – What medications do you use in this case?
    • What are major drug – drug interactions are important here?
Ethambutol (EMB)

role: Backbone of 3 or 4 drug treatment for SGM

action: inhibits cell wall synthesis

dosage: oral

dose: 15 – 25 mg/kg once daily (20mg/kg)

cleared: kidneys >> liver

toxicity: ocular toxicity, rashes
Audience Question #1

• Which medication can cause significant accumulation of rifabutin if given as part of a multidrug regimen for M. avium infection?
  1. Clarithromycin
  2. Ethambutol
  3. Azithromycin
  4. Imipenem
Case 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?
Case 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.
Fly Hell.
Toxicity - Ethambutol induced optic neuritis
Ethambutol Toxicity

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

• Different dosing regimens are used
• 25 mg/kg once daily x 2 months then decrease to 15 mg/kg daily to complete 18–24 months
• Griffith – Retrospective study of 229 patients  Mean age 63.8; 55% women
  • 139 pts with daily therapy
  • Mean duration of EMB tx 16.1 months
  • EMB daily 25 mg/kg/d x 2 mos then 15 mg/kg day
  • 6% developed ocular toxicity

Ethambutol Toxicity

- None of the cases were detected by routine ocular exam
  - Ishihara vs. visual acuity vs. visual field testing
- Visual acuity returned to normal after discontinuation of EMB
- 90 patients received Mon, Wed, Fri therapy with 25 mg/kg
  - None had ocular toxicity
  - Cum dose of EMB in daily significantly higher (P=0.0001)

Ethambutol Monitoring

- Regular self-assessment of color vision and acuity at home
- Referral to a neuro-opthalmologist
- 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
Audience 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
Azithromycin/ Clarithromycin

role: Backbone

action: inhibits protein synthesis

dosage: oral, I.V.

dose: 250mg once daily or 500mg 3x/week

cleared: liver

toxicity: ototoxicity, GI, prolonged QT
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
Prolonged QT with Macrolides, Quinolones, clofazimine
Rifabutin + Clarithromycin Toxicity

- Hepatitis
- Uveitis
- Arthritis
- Fever
- Thrombocytopenia, Leukopenia
- Drug induced lupus
- Nausea and vomiting
Ideas for Rash Treatment
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

Amikacin (AK)

role: Cavitary or severe nodular/bronchiectatic disease

action: inhibits protein synthesis

dosage: I.V., inhaled

dose: 12 – 15 mg/kg once daily 3x/week or 22mg/kg once daily 2x/week

cleared: kidneys

toxicity: ototoxicity, nephrotoxicity, cation loss, rash (rare)
Hearing Loss Monitoring

AUDIOMETRIC

Frequency in Hz
125 250 500 1000 2000 4000 8000

Hearing level in dB
-10 0 10 20 30 40 50 60 70 80 90 100 120

Mild
Moderate
Severe
Profound

Dog Barking
Loud Shout
Telephone Ring
Lawnmower
Jack Hammer
Firecracker
Gunshot

Hearing Range (with common hearing loss)
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
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
MEDICATION SIDE EFFECTS FOR DRUGS USED TO TREAT RAPIDLY GROWING MYCOBACTERIA (RGM)
Ideas for Rash Treatment
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
Cefoxitin

role: Alternative to imipenem 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
Tigecycline

role: Alternative to imipenem as backbone for RGM treatment

action: inhibits bacterial cell wall synthesis

dosage: I.V.

dose: 25mg or 50mg once or twice daily

cleared: biliary excretion

toxicity: Nausea, vomiting, hyponatremia, hypoalbuminemia, elevated lft’s
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
Moxifloxacin

action: inhibits DNA gyrase
dosage: oral, I.V.
dose: 400 mg once daily
cleared: kidneys
toxicity: caffeine like effects, GI, tendonitis, hypoglycemia
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
Ruptured Achilles Tendon

[Images showing comparison of normal and torn Achilles tendon, with annotations like "Normal Achilles tendon" and "Torn Achilles tendon" and "Fluid"]
Linezolid

action: inhibits the initiation process of protein synthesis

dosage: oral, I.V.

dose: 600 mg once daily

cleared: liver

toxicity: myelosuppression, peripheral and optic neuropathy, serotonin syndrome
Audience Question #3

You have an 80 year old patient on diltiazem, insulin, pantoprazole, and Coumadin with newly diagnosed pulmonary non-cavitary M. avium infection based on 2 smear negative/culture positive sputums with moderate cough and fatigue. The CT scan shows only tree-in-bud changes. What diagnosis/treatment is most appropriate at this time?

1. Do a bronchoscopy to gather more culture information
2. Start azithromycin until you have final sensitivity results
3. Start azithromycin, rifampin, and ethambutol (all given 3 times a week) while you wait for sensitivities
4. Start moxifloxacin and azithromycin
Thanks!