Nontuberculous Mycobacterial Infections of the Lung

Kenneth N Olivier, MD, MPH
Chief, Pulmonary Branch, NHLBI
Disclosures to Audience

For the three years preceding this presentation:

**Financial Relationships with Relevant Commercial Interests:**

- **Company name:** Beyond Air, Inc  
  **Type of relationship:** Research support, investigator initiated

- **Company name:** Matinas Biopharma  
  **Type of relationship:** Research support, industry initiated

- **Company name:** Spero Therapeutics  
  **Type of relationship:** Consultant

- **Company name:** Insmed, Inc  
  **Type of relationship:** Consultant

- **Company name:** AN2 Therapeutics  
  **Type of relationship:** Consultant

- **Company name:** Qrum  
  **Type of relationship:** Consultant

- **Company name:** Oricula Therapeutics  
  **Type of relationship:** Consultant

*Amikacin liposome inhalation suspension approved for treatment refractory *M. avium* complex lung disease

*All others not approved for NTM lung disease
Most approved for Rx of TB or other infections
Nontuberculous Mycobacteria

- Ubiquitous environmental organisms
- >190 species (http://www.bacterio.net/mycobacterium.html)
  - *M. avium* complex
  - *M. abscessus* group (3 subspecies)
  - *M. kansasii*

- Clinical
  - Lung
  - Skin, soft tissues
  - Disseminated
“Classic” NTM Lung Disease

- Male smoker
- Cavitary, lots of bugs
- Difficult to treat
- Pathogenesis
  - Structural disease
  - Disrupted barriers
  - Poor clearance
  - Opportunistic
## Susceptibility to Pulmonary NTM

<table>
<thead>
<tr>
<th>Category</th>
<th>Test/Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired local defenses</td>
<td>Clinical history, chest imaging, PFTs</td>
</tr>
<tr>
<td>COPD, bronchiectasis, pneumoconiosis, silicosis, previous cavitary tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Sweat chloride test, CFTR genotyping</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
<td>Nasal nitric oxide, cardinal clinical features, EM; genotyping (&gt;40 cilia structure/function genes)</td>
</tr>
<tr>
<td>Impaired systemic immunity</td>
<td>Total IgE, cardinal clinical features, family history, STAT3 genotyping</td>
</tr>
<tr>
<td>STAT3 deficiency</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant use</td>
<td>Drug history</td>
</tr>
<tr>
<td>Tumor necrosis factor-α blockers</td>
<td></td>
</tr>
<tr>
<td>Lady Windermere syndrome</td>
<td>Clinical history with exclusion of the above conditions, special body morphotypic features</td>
</tr>
</tbody>
</table>

Adapted from Wu. Lancet Infect Dis 2015
Guidelines

Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline

Eur Respir J 2020
Clin Infect Dis 2020

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

Thorax 2016

Supplement
Pulmonary Disease Criteria (Guidelines)

• Clinical (all 3)
  ▫ Pulmonary or systemic symptoms
  ▫ Radiographic – nodular or cavitary opacities (CXR) or bronchiectasis with multiple small nodules (CT)
  ▫ Exclusion of other diagnoses
  ▫ And...

• Microbiologic (any of these)
  ▫ At least 2 positive sputum specimens (same species)
  ▫ 1 bronchial wash/lavage
  ▫ Appropriate biopsy histopath & (+) respiratory culture

Nodular bronchiectasis

- 77yo woman
  - 2y persistent, productive cough
  - Caseating granulomas
  - Sputum smear AFB (+), cultures (+) MAC
Audience Response Question #1

• Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression (“watchful waiting”)?
  a. Antimicrobial therapy
  b. Watchful waiting

Audience Response Question #1

- Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression (“watchful waiting”)?
  - In patients who meet diagnostic criteria for NTM pulmonary disease, we suggest initiation of treatment rather than watchful waiting, especially in context of positive AFB sputum smears and/or cavitary lung disease.
Mycobacterium avium complex

- Nodular/bronchiectatic disease
  - Thrice weekly dosing
    - Clarithromycin or Azithromycin (preferred)
    - Ethambutol
    - Rifampin

**Mycobacterium avium complex**

- Nodular/bronchiectatic disease
  - Thrice weekly dosing
    - *Clarithromycin or Azithromycin (preferred)*
    - Ethambutol
    - Rifampin

*For MAC pulmonary disease, guidelines recommend susceptibility-based treatment for macrolides and amikacin*

Do current drugs work for Mac?

Failed to complete >6mos Rx or not evaluable (17%)

Failed to convert (17%)

Relapsed on Rx or Rx stopped <10 mos (29%)

Nodular bronchiectasis Rx episodes
n=424

Evaluable Rx
n=353

Sputum conversion
n=293 (83%)

Completed > 10 mos effective Rx
n=207

Post therapy “recurrences”
n=75 (36%)

New Infections (79%)

PFGE
n=65

Same Infection (21%)

Wallace. AJRCCM 2010 A2596
Wallace. Chest 2014
Nodular bronchiectasis

- 77yo woman
  - 2y persistent, productive cough
  - Caseating granulomas
  - Sputum smear AFB (+), cultures (+) MAC
  - Started thrice weekly
    - Azithromycin
    - Ethambutol
    - Rifabutin

- Referred to NIH 1 year later
  - AFB smear (+); heavy growth MAC
  - 40lb weight loss in prior year
  - Fatigue, decrease exercise tolerance
Audience Response Question #2:

- This patient is failing treatment. What is the most likely reason?

  a) Only taking meds three times weekly instead of daily
  b) She was prescribed the wrong medications
  c) Medication side effects led to poor adherence
  d) She has macrolide resistant *M. avium* complex and needs amikacin
Audience Response Question #2:

- This patient is failing treatment. What is the most likely reason?

  a) Only taking meds three times weekly instead of daily
  b) She was prescribed the wrong medications
  c) Medication side effects led to poor adherence
  d) She has macrolide resistant *M. avium* complex and needs amikacin
Tips for tolerance

- Stagger drug start
- Dose at bedtime
- Alter dose schedule
- Probiotics
- Drug substitution
# Drug toxicity monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides</td>
<td>Prolonged QT; auditory; resistance with monotherapy</td>
<td>EKG; discontinue monoRx with NTM isolation</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuritis; peripheral neuropathy</td>
<td>Visual acuity/color vision; [<a href="http://www.colorvisiontesting.com/is">www.colorvisiontesting.com/is</a> hihara](<a href="http://www.colorvisiontesting.com/is">http://www.colorvisiontesting.com/is</a> hihara)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Orange urine; hepatotox; drug-drug interaction (azoles)</td>
<td>LFTs; check for drug interactions and substitute</td>
</tr>
<tr>
<td>Amikacin/Streptomycin</td>
<td>Ototoxicity; nephrotoxicity</td>
<td>Baseline audiogram and monthly f/u on iv; every 3 mos on inhaled; monitor levels (amikacin)</td>
</tr>
</tbody>
</table>
Nodular bronchiectasis/CF

- 14 yo male with CF
  - MAC from sputum/BAL, AFB smear (-)
  - Diagnosed age 2
    - Positive sweat Cl⁻ (x2)
    - F508del/unknown
  - 1st iv antibiotics age 12, MSSA
  - FEV1 2.89 (77%)
Diagnosis/Rx of NTM in CF

- ATS/IDSA NTM diagnostic criteria apply to CF
  - With following caveat...
  - “Other CF pathogens & co-morbidities should be considered as contributors to symptoms and radiologic features when determining clinical significance of positive NTM cultures…”
- Treat other CF pathogens first and reassess clinical status
- Same regimen for MAC, but use **daily** dosing
Typical MAC treatment schedule

Floto. Thorax 2016
Cavitary *M. avium* complex

- 14 yo male with CF dx at 9 mos
  - F508del/G542X
  - *Pseudomonas* at time of dx
  - *M. avium* age 11 fevers, fatigue, wt loss
  - Started daily azithro, ethambutol, rifampin
- Referred to NIH with cavitary *M. avium*
  - Persistently 4+AFB, heavy growth culture
Mycobacterium avium complex

- Fibrocavitary or severe nodular bronchiectasis
  - **Daily dosing**
    - Clarithromycin *or* Azithromycin
    - Ethambutol
    - Rifampin or rifabutin
    - Amikacin or streptomycin for initial 2-3 months
      - (also for macrolide resistant disease)

Audience Response Question #3

- In patients with MAC pulmonary disease who have failed to respond after at least 6 months of guideline-based therapy, which of the following should be added?
  a. Oral quinolone
  b. Intravenous amikacin
  c. Inhaled amikacin (parenteral formulation)
  d. Amikacin liposome inhalation suspension (ALIS)
Audience Response Question #3

• In patients with MAC pulmonary disease who have failed to respond after at least 6 months of guideline-based therapy, which of the following should be added?
  a. Oral quinolone
  b. Intravenous amikacin
  c. Inhaled amikacin (parenteral formulation)
  d. Amikacin liposome inhalation suspension (ALIS)

Alternative drugs to consider - Mac

- Clofazimine
- Oxazolidinones (linezolid, tedizolid)
- Bedaquiline
- ?Quinolones
- Inhaled amikacin (parenteral formulation)
- Amikacin liposome inhalation suspension
Surgery?

- Retrospective - nonCF
  - n=134, focal bronchiectasis
    - 88% *M. avium* complex
- Thoracoscopic resection
  - No mortality/major complication
  - Minor complications – 12%
- Long term f/u – 23 mos
  - 92 (84%) culture negative
    - 8 relapse or reinfection
  - 18 (16%) failed to convert

Lung resection for NTM in CF

• “Lung resection should only be considered in extraordinary circumstances and in consultation with experts in the treatment of NTM and CF”

Floto. Thorax 2016
ARQ #4 *M. abscessus*: When to start treatment?

**A. 19 yo dx with CF**, hemoptysis, recurrent respiratory infections, bronchiectasis

BAL x2 AFB (-), culture (+) *M. abscessus*; biopsy: granulomas, focal necrosis, AFB (+)

**B. 6 mos after dx**, FEV1 88→86%, iv antibiotics *Pseudomonas/Staph*, no change FEV1;

culture (+) for *Mabs*, AFB (-)

**C. 4 yrs after dx**, FEV1 78→68%, iv antibiotics, FEV1 72%; culture (+) *Mabs*, AFB (-)

**D. 10.5 yrs after dx**, FEV1 68→56%, fevers, no response to iv antibiotics; BAL AFB (+),

*Mabs* heavy amounts, no other organisms, new cavity on CT
Cullen. Am J Respir Crit Care Med 2000
Colin. Pediatr Pulmonol 2010
Rx: *M abscessus* vs. *M massiliense*

<table>
<thead>
<tr>
<th></th>
<th><em>M. abscessus</em> (n = 24)</th>
<th><em>M. massiliense</em> (n = 33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>18 (75%)</td>
<td>32 (97%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Unchanged</td>
<td>4 (17%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>2 (8%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Radiographic response on HRCT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>10 (42%)</td>
<td>27 (82%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Unchanged</td>
<td>7 (29%)</td>
<td>5 (15%)</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>7 (29%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Microbiologic response</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial sputum conversion</td>
<td>6 (25%)</td>
<td>29 (88%)</td>
<td></td>
</tr>
<tr>
<td>and maintenance of conversion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial sputum conversion,</td>
<td>4 (17%)</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>with sputum relapse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to sputum conversion</td>
<td>14 (58%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

- 4 wks: iv amikacin bid + cefoxitin tid, oral clari, cipro, doxy
- 24 mos: oral clari, cipro, doxy

Koh. Am J Respir Crit Care Med 2011
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Resistance Gene</th>
<th>M. abscessus</th>
<th>M. massiliense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides</td>
<td>rrl (23S rRNA)</td>
<td>Point mutation adenine 2058/2059; Acquired resistance</td>
<td>Point mutation adenine 2058/2059; Acquired resistance</td>
</tr>
<tr>
<td>Macrolides</td>
<td>erm41</td>
<td>T28 sequevar (72%) inducible resistance</td>
<td>Deletion (100%) fully susceptible</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>rrs (16S rRNA)</td>
<td>1408 A→G (35%); 1491 G→T (48%); 1409 C→T (14%); 1406 T→A (3%); Acquired resistance</td>
<td>1408 A→G (35%); 1491 G→T (48%); 1409 C→T (14%); 1406 T→A (3%); Acquired resistance</td>
</tr>
</tbody>
</table>

M. abscessus group

- Should involve an **intensive phase** followed by a **continuation phase**

Floto. Thorax 2016
**M. abscessus** group

- **Intensive phase** should include:
  - Daily oral macrolide (preferably azithromycin)*
  - 3-12 weeks of iv amikacin plus ≥1 of following *guided, but not dictated by susceptibility tests*
    - Tigecycline
    - Imipenem
    - Cefoxitin
    - Consider dual beta lactams, newer beta lactamase inhibitor combinations
  - Duration of intensive phase should be determined by severity of infection, response to Rx & tolerability of regimen

*If acquired/inducible macrolide resistance – cannot count as an anti-mycobacterial drug*
**M. abscessus group**

- **Continuation phase should include:**
  - Daily oral macrolide (preferably azithro)*
  - Inhaled amikacin
  - 2-3 of the following oral antibiotics guided, but not dictated by susceptibility tests
    - Minocycline (*consider omadacycline*)
    - Clofazimine
    - Moxifloxacin
    - Linezolid (or tedizolid)
    - Rifabutin?

*If acquired/inducible macrolide resistance – cannot count as an anti-mycobacterial drug*  

Floto. Thorax 2016
Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease

Kenneth N. Olivier¹, Pamela A. Shaw², Tanya S. Glaser¹, Darshana Bhattacharyya¹, Michelle Fleshner¹, Carmen C. Brewer³, Christopher K. Zalewski³, Les R. Folio⁴, Jenifer R. Siegelman⁵, Shamira Shalim⁶, In Kwon Park¹, Elizabeth P. Sampaio⁷, Adrian M. Zelazny⁸, Steven M. Holland¹, and D. Rebecca Prevots¹

- Retrospective study n=20
- Inhaled amikacin + failing regimen
  - 250 mg/ml diluted 3 mL saline
  - Jet nebulizer
  - Started 250mg once daily → 500 bid
  - Dosing limited by dysphonia
    - 250 mg daily (50%)

<table>
<thead>
<tr>
<th>Sex, female</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>56 (16)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>10%</td>
</tr>
<tr>
<td>Cavitary disease</td>
<td>45%</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>75%</td>
</tr>
<tr>
<td>M. avium complex</td>
<td>25%</td>
</tr>
<tr>
<td>Months on Rx before inhaled amikacin, median (range)</td>
<td>60 (6, 190)</td>
</tr>
</tbody>
</table>

Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease

Kenneth N. Olivier¹, Pamela A. Shaw², Tanya S. Glaser¹, Darshana Bhattacharyya¹, Michelle Fleshner¹, Carmen C. Brewer³, Christopher K. Zalewski³, Les R. Folic⁴, Jenifer R. Siegelman⁵, Shamira Shallom⁶, In Kwon Park¹, Elizabeth P. Sampaio¹, Adrian M. Zelazny⁶, Steven M. Holland¹, and D. Rebecca Prevots¹

- Toxicity: 7 (35%) stopped

<table>
<thead>
<tr>
<th>Reasons for stopping</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ototoxicity</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Reversible increase in Cr</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Persistent dysphonia</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Amikacin liposomal inhalation suspension: Phase 2

Olivier. Am J Respir Crit Care Med 2017
Amikacin liposomal inhalation suspension: Phase 2

Olivier. Am J Respir Crit Care Med 2017
Amikacin liposomal inhalation suspension: Phase 3

Griffith. Am J Respir Crit Care Med 2018

![Chart showing patients with culture conversion over study months.](chart-image)
Amikacin liposomal inhalation suspension: Phase 3

Griffith. Am J Respir Crit Care Med 2018
## Toxicity monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Toxicity</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoxitin</td>
<td>Fever, rash, eosinophilia, cytopenias</td>
<td>CBC</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Skin discoloration, GI – enteropathy (rare), long half-life (~2 mos)</td>
<td>symptoms</td>
</tr>
<tr>
<td>Imipenem</td>
<td>hepatotoxicity</td>
<td>LFTs</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Cytopenias, optic neuritis, peripheral neuropathy</td>
<td>CBC; visual acuity and color vision; symptoms</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>GI, insomnia/anxiety, tendonitis, prolong QT</td>
<td>Symptoms; EKG</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Photosensitivity, GI, vertigo</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>GI, hypoprolinemia, bilirubinemia, pancreatitis (rare)</td>
<td>Symptoms, albumin, bili</td>
</tr>
<tr>
<td>Discovery</td>
<td>Phase I/II</td>
<td>Phase III</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>LCB01-0371</td>
<td>Clofazimine*</td>
<td>Liposomal amikacin for inhalation (LAI)</td>
</tr>
<tr>
<td>- Target 50S ribosome</td>
<td>- Target NDH-2</td>
<td>- Target 30S ribosome</td>
</tr>
<tr>
<td>- For <em>M. abs</em></td>
<td>- For <em>M. abs</em></td>
<td>- For refractory MAC PD</td>
</tr>
<tr>
<td>PIPD1</td>
<td>Tedizolid*</td>
<td>Liposomal amikacin for inhalation (LAI)</td>
</tr>
<tr>
<td>- Target MmpL3</td>
<td>- Target 50S ribosome</td>
<td>- Target 30S ribosome</td>
</tr>
<tr>
<td>- For <em>M. abs</em></td>
<td>- For NTM</td>
<td>- For refractory MAC PD</td>
</tr>
<tr>
<td>Indole-2-carboxamides</td>
<td>Bedaquiline*</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>- Target MmpL3</td>
<td>- Target ATP synthase</td>
<td>- Enhance host defense</td>
</tr>
<tr>
<td>- For <em>M. abs</em></td>
<td>- For NTM</td>
<td>- Produce reactive nitrogen intermediates</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>β-lactams with avibactam*</td>
<td>For CF patients with NTM (especially <em>M. abs</em>)</td>
</tr>
<tr>
<td>derivatives</td>
<td>- Target penicillin-binding</td>
<td>- From AIT therapeutics</td>
</tr>
<tr>
<td>- Target FAS-II</td>
<td>protein</td>
<td></td>
</tr>
<tr>
<td>dehydratase</td>
<td>- For <em>M. abs</em></td>
<td></td>
</tr>
<tr>
<td>- For <em>M. avium</em></td>
<td>- For <em>M. avium</em></td>
<td></td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Rifabutin*</td>
<td>Gaseous nitric oxide (gNO)(^5)</td>
</tr>
<tr>
<td>derivatives</td>
<td>- Target RNA polymerase</td>
<td>- Enhance host defense</td>
</tr>
<tr>
<td>- Target FAS-II</td>
<td>- For <em>M. abs</em></td>
<td>- Produce reactive nitrogen intermediates</td>
</tr>
<tr>
<td>dehydratase</td>
<td></td>
<td>- For NTM</td>
</tr>
<tr>
<td>- For <em>M. avium</em></td>
<td></td>
<td>- Thiolanox(^\circ) from novoteris</td>
</tr>
<tr>
<td>- For <em>M. abs</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mechanism of action**
- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid synthesis
- Other mechanisms
• Training and Career Opportunities at the NIH
  ▫ NIH Clinical Center – Critical Care Medicine Fellowship
  ▫ NHLBI/Univ of MD PulmCCM Research Track Fellowship
  ▫ *NHLBI/CC Advanced Lung Imaging Fellowship
  ▫ Lasker Clinical Research Scholars Program
    • Up to 12 years intramural/extramural career development funding
    • Tenure track/tenured Clinical Investigator positions