



# Nontuberculous Mycobacterial Infections of the Lung

Kenneth N Olivier, MD, MPH  
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# 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:** Insmmed, Inc

**Type of relationship:** Consultant

**Company name:** AN2 Therapeutics

**Type of relationship:** Consultant

**Company name:** Qrum

**Type of relationship:** Consultant

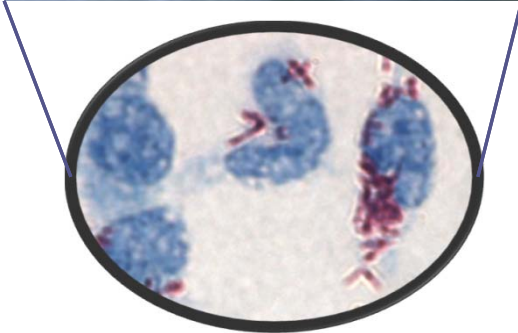
**Company name:** Oricula Therapeutics

**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
- Cavitory, lots of bugs
- Difficult to treat
- Pathogenesis
  - Structural disease
  - Disrupted barriers
  - Poor clearance
  - Opportunistic



# Susceptibility to Pulmonary NTM

Impaired local defenses COPD, bronchiectasis, pneumoconiosis, silicosis, previous cavitory tuberculosis	Clinical history, chest imaging, PFTs
Cystic fibrosis	Sweat chloride test, CFTR genotyping
Primary ciliary dyskinesia	Nasal nitric oxide, cardinal clinical features, EM; genotyping (>40 cilia structure/function genes)
Impaired systemic immunity STAT3 deficiency	Total IgE, cardinal clinical features, family history, STAT3 genotyping
Immunosuppressant use Tumor necrosis factor- $\alpha$ blockers	Drug history
Lady Windermere syndrome	Clinical history with exclusion of the above conditions, special body morphotypic features

# Guidelines

ERS OFFICIAL DOCUMENTS  
ATS/ERS/ESCMID/IDSA GUIDELINE

**New this month!**

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

Eur Respir J 2020  
Clin Infect Dis 2020

Charles L. Daley<sup>1,2,26</sup>, Jonathan M. Iaccarino<sup>3</sup>, Christoph Lange<sup>4,5,6,7,26</sup>, Emmanuelle Cambau<sup>8,26</sup>, Richard J. Wallace Jr<sup>9,26</sup>, Claire Andrejak<sup>10,11</sup>, Erik C. Böttger<sup>12</sup>, Jan Brozek<sup>13</sup>, David E. Griffith<sup>14</sup>, Lorenzo Guglielmetti<sup>15</sup>, Gwen A. Huitt<sup>1,2</sup>, Shandra L. Knight<sup>16</sup>, Philip Leitman<sup>17</sup>, Theodore K. Marras<sup>18</sup>, Kenneth N. Olivier<sup>19</sup>, Miguel Santin<sup>20</sup>, Jason E. Stout<sup>21</sup>, Enrico Tortoli<sup>22</sup>, Jakko van Ingen<sup>23</sup>, Dirk Wagner<sup>24</sup> and Kevin L. Winthrop<sup>25</sup>

Supplement

## 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

R Andres Floto,<sup>1,2</sup> Kenneth N Olivier,<sup>3</sup> Lisa Saiman,<sup>4</sup> Charles L Daley,<sup>5</sup> Jean-Louis Herrmann,<sup>6,7</sup> Jerry A Nick,<sup>8</sup> Peadar G Noone,<sup>9</sup> Diana Bilton,<sup>10</sup> Paul Corris,<sup>11</sup> Ronald L Gibson,<sup>12</sup> Sarah E Hempstead,<sup>13</sup> Karsten Koetz,<sup>14</sup> Kathryn A Sabadosa,<sup>13</sup> Isabelle Sermet-Gaudelus,<sup>15</sup> Alan R Smyth,<sup>16</sup> Jakko van Ingen,<sup>17</sup> Richard J Wallace,<sup>18</sup> Kevin L Winthrop,<sup>19</sup> Bruce C Marshall,<sup>20</sup> Charles S Haworth<sup>2</sup>

# Pulmonary Disease Criteria (Guidelines)

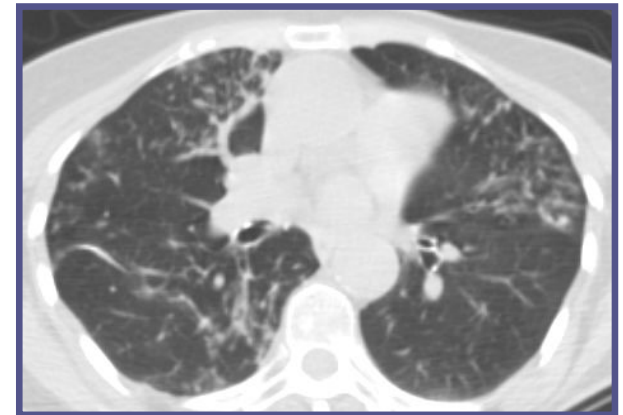
- Clinical (all 3)
  - Pulmonary or systemic symptoms
  - Radiographic – nodular or cavitary opacities (CXR) *or* bronchiectasis with multiple small nodules (CT)
  - Exclusion of other diagnoses
  - **And...**
- Microbiologic (any of these)
  - At least 2 positive sputum specimens (same species)
  - 1 bronchial wash/lavage
  - Appropriate biopsy histopath & (+) respiratory culture



[www.ntmfacts.com](http://www.ntmfacts.com)

# Nodular bronchiectasis

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





# Audience Response Question #1

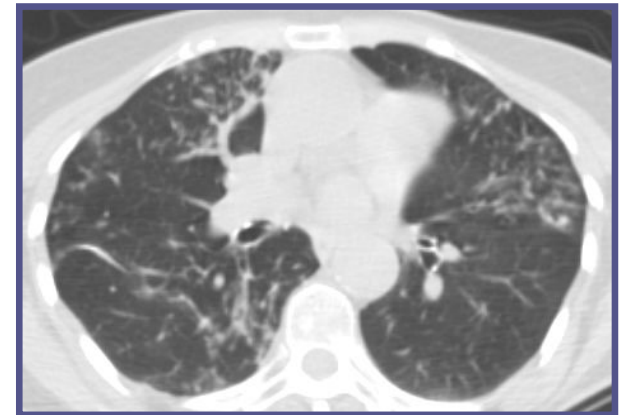
- Should patients with NTM pulmonary disease be treated with antimicrobial therapy or followed for evidence of progression (“watchful waiting”)?
  - a. Antimicrobial therapy
  - b. Watchful waiting

# 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

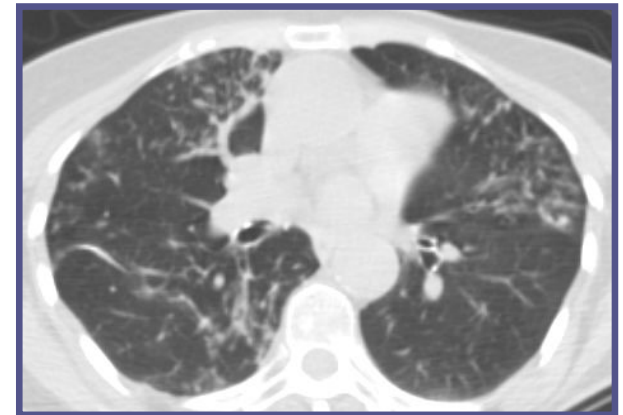
# *Mycobacterium avium* complex

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



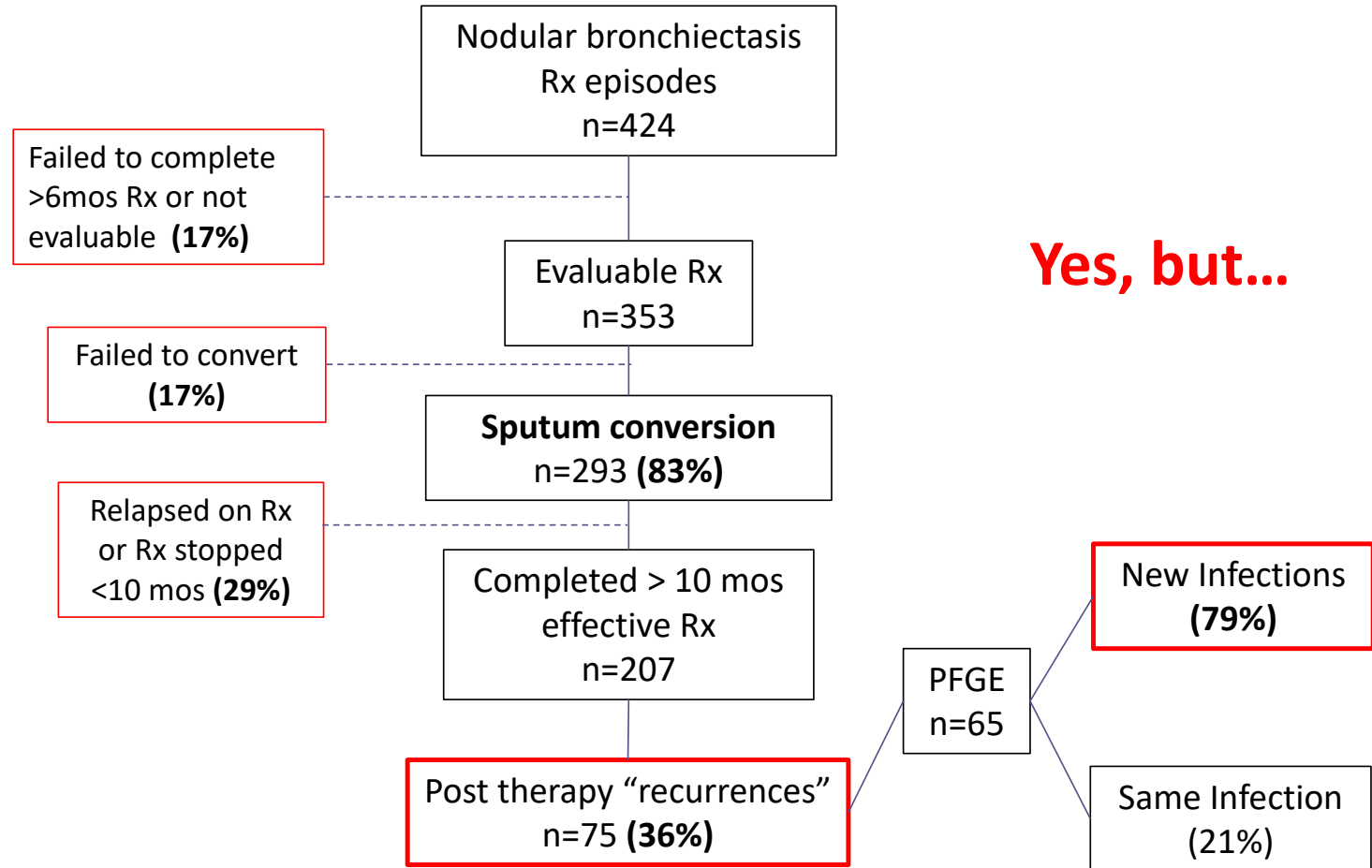
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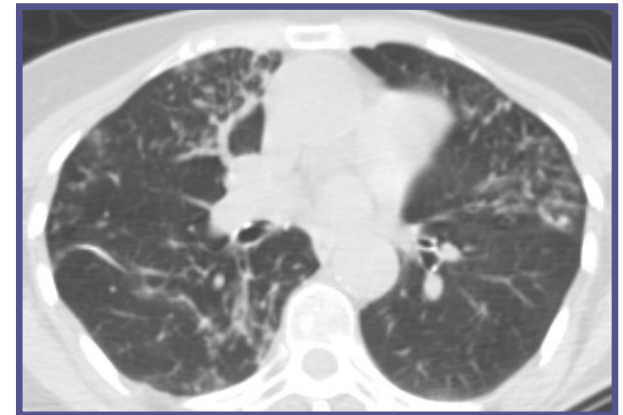
\*For MAC pulmonary disease, guidelines recommend susceptibility-based treatment for macrolides and amikacin

# Do current drugs work for Mac?



# 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:

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## Tips for tolerance

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



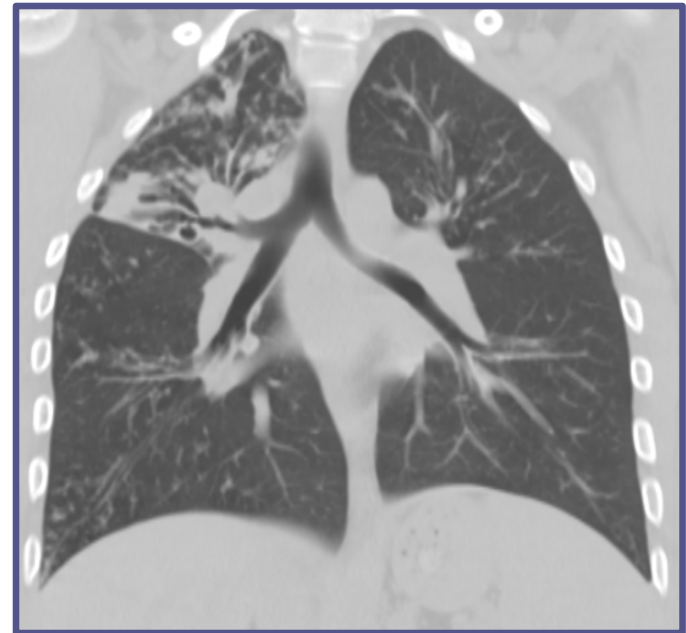
[www.themorningsun.com](http://www.themorningsun.com)

# Drug toxicity monitoring

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

# Nodular bronchiectasis/CF

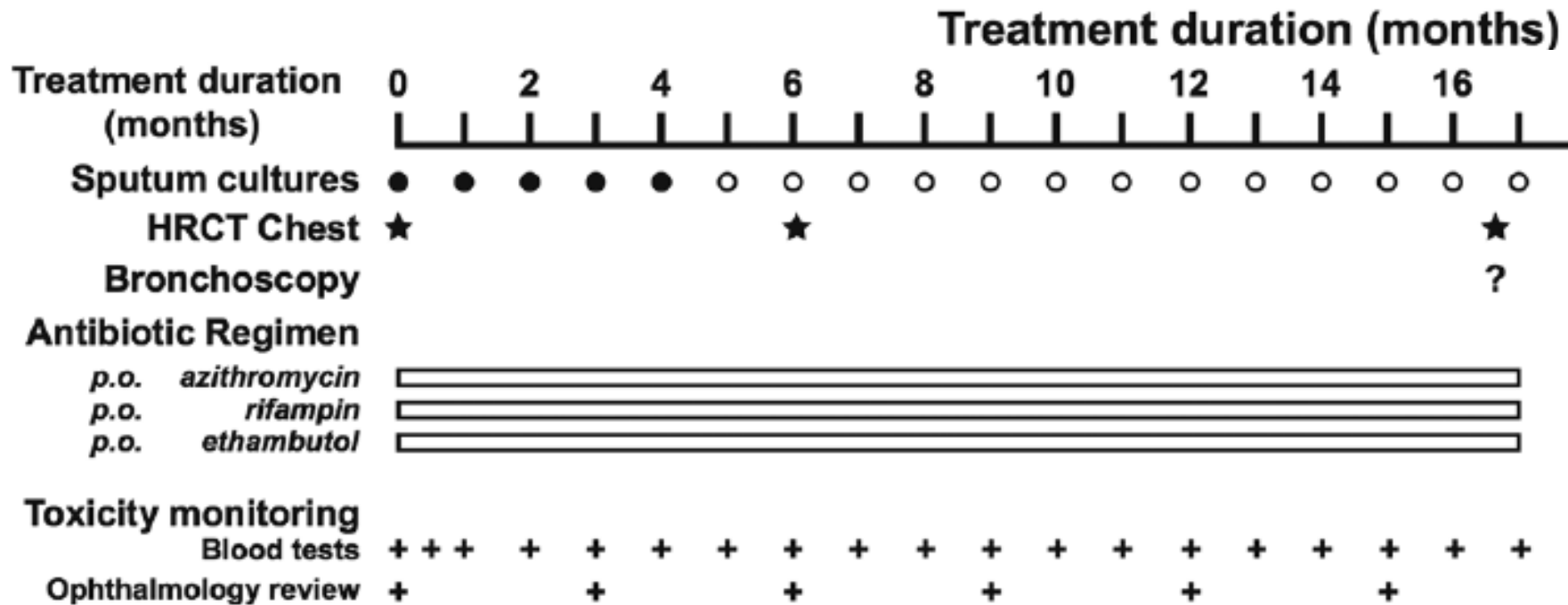
- 14 yo male with CF
  - MAC from sputum/BAL, AFB smear (-)
  - Diagnosed age 2
    - Positive sweat  $\text{Cl}^-$  (x2)
    - F508del/unknown
  - 1<sup>st</sup> iv antibiotics age 12, MSSA
  - FEV1 2.89 (77%)



## Diagnosis/Rx of NTM in CF

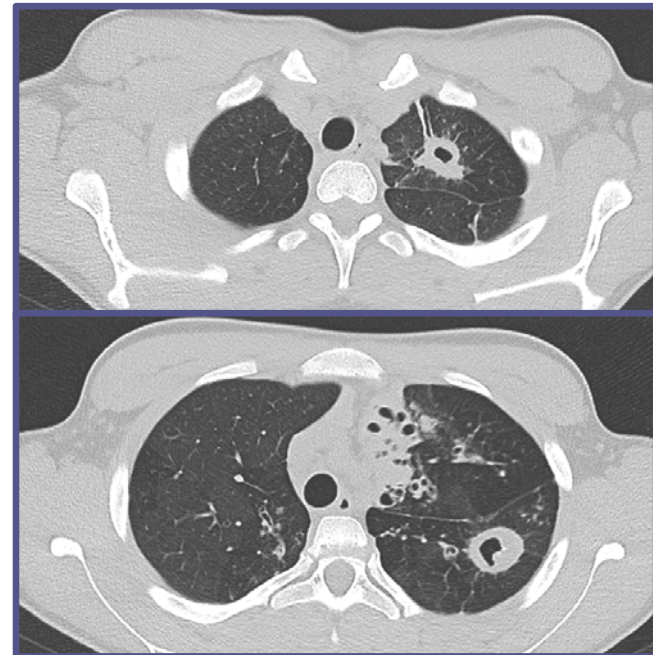
- ATS/IDSA NTM diagnostic criteria apply to CF
  - With following caveat...
  - “Other CF pathogens & co-morbidities should be considered as contributors to symptoms and radiologic features when determining clinical significance of positive NTM cultures...”
- Treat other CF pathogens first and reassess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

# Typical MAC treatment schedule



## 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

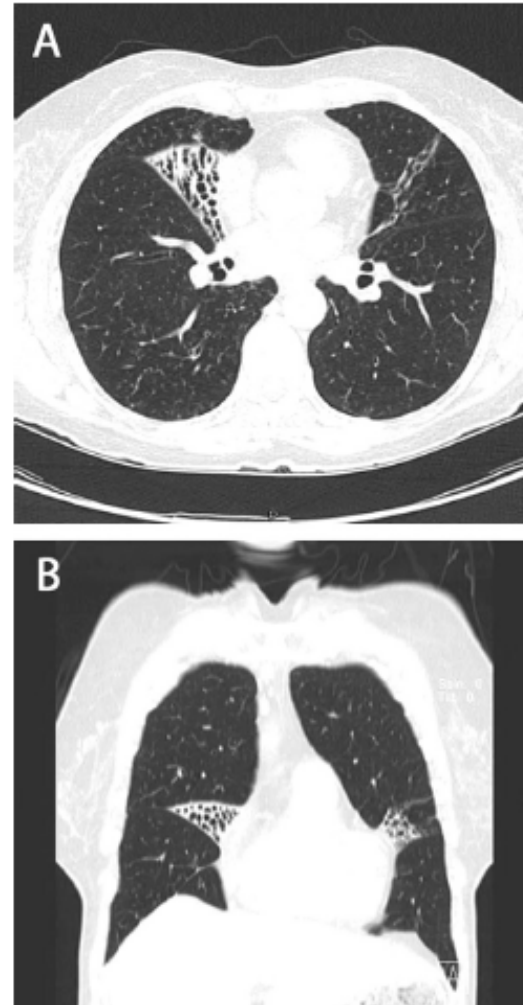
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  - a. Oral quinolone
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  - c. Inhaled amikacin (parenteral formulation)
  - d. **Amikacin liposome inhalation suspension (ALIS)**

## 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

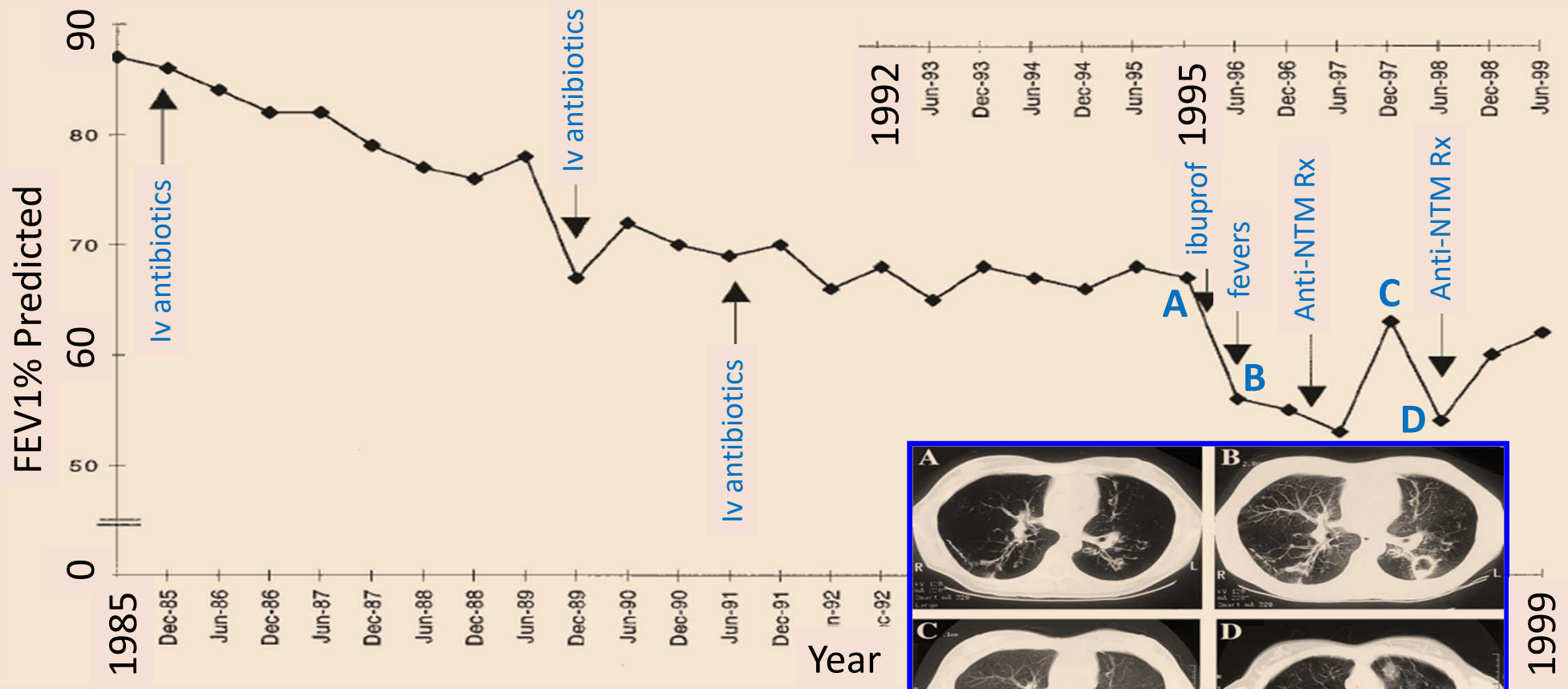


## Lung resection for NTM in CF

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

## 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 2000  
 Colin. Pediatr Pulmonol 2010

## Rx: *M abscessus* vs. *M massiliense*

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

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

Drug Class	Resistance Gene	<i>M. abscessus</i>	<i>M. massiliense</i>
Macrolides	<i>rrl</i> (23S rRNA)	Point mutation adenine 2058/2059; Acquired resistance	Point mutation adenine 2058/2059; Acquired resistance
Macrolides	<i>erm41</i>	T28 sequevar (72%) inducible resistance C28 sequevar (28%) fully susceptible	Deletion (100%) fully susceptible
Aminoglycosides	<i>rrs</i> (16S rRNA)	1408 A→G (35%); 1491 G→T (48%); 1409 C→T (14%); 1406 T→A (3%); Acquired resistance	1408 A→G (35%); 1491 G→T (48%); 1409 C→T (14%); 1406 T→A (3%); Acquired resistance

Wallace. Antimicrob Agents Chemother 1996

Bastian. Antimicrob Agents Chemother 2011

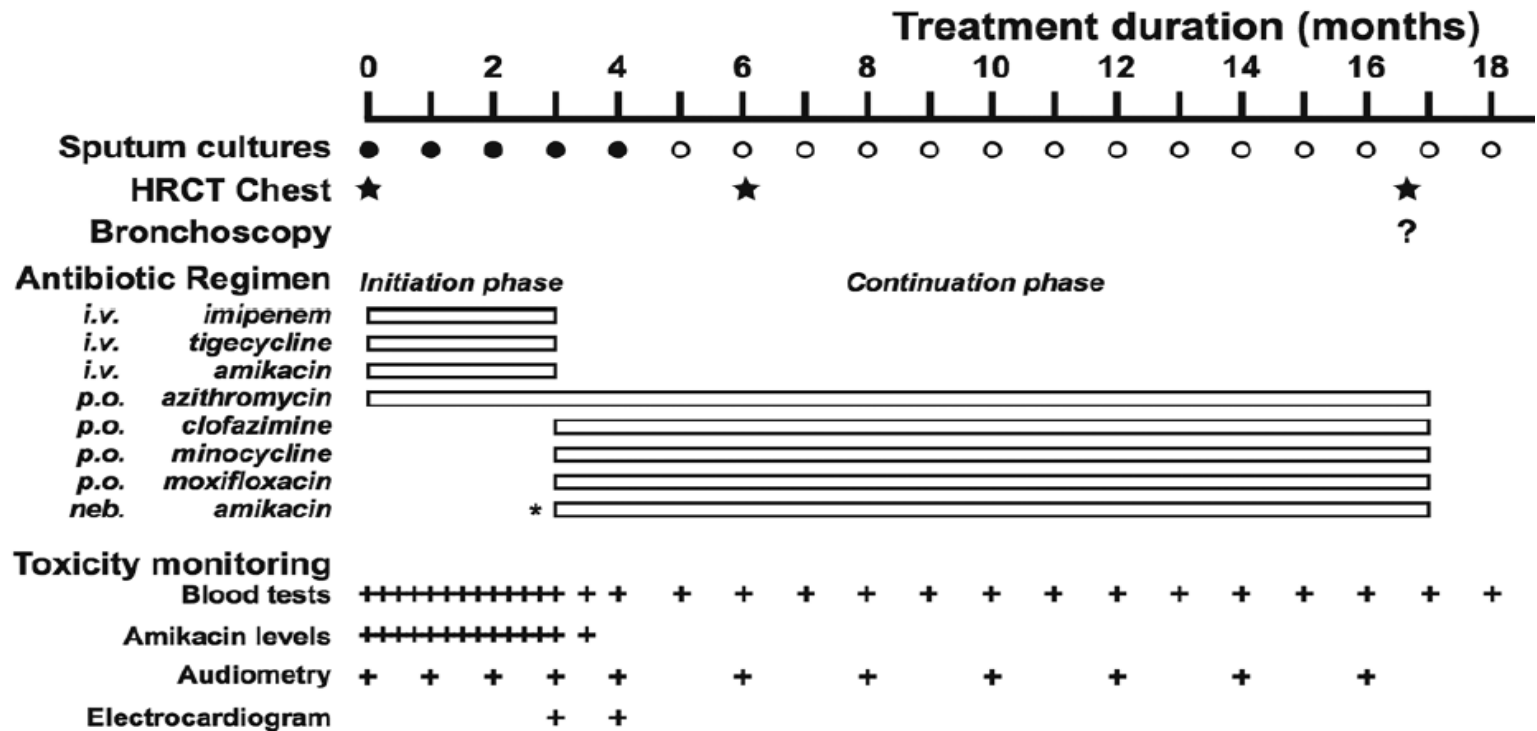
Prammananan. J Infect Dis 1998

Nessar. J Antimicrob Chemother 2011



# M. abscessus group

- Should involve an intensive phase followed by a continuation phase



## *M. abscessus* group

- Intensive phase should include:
  - Daily oral macrolide (preferably azithromycin)\*
  - 3-12 weeks of iv amikacin plus  $\geq 1$  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

## Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease

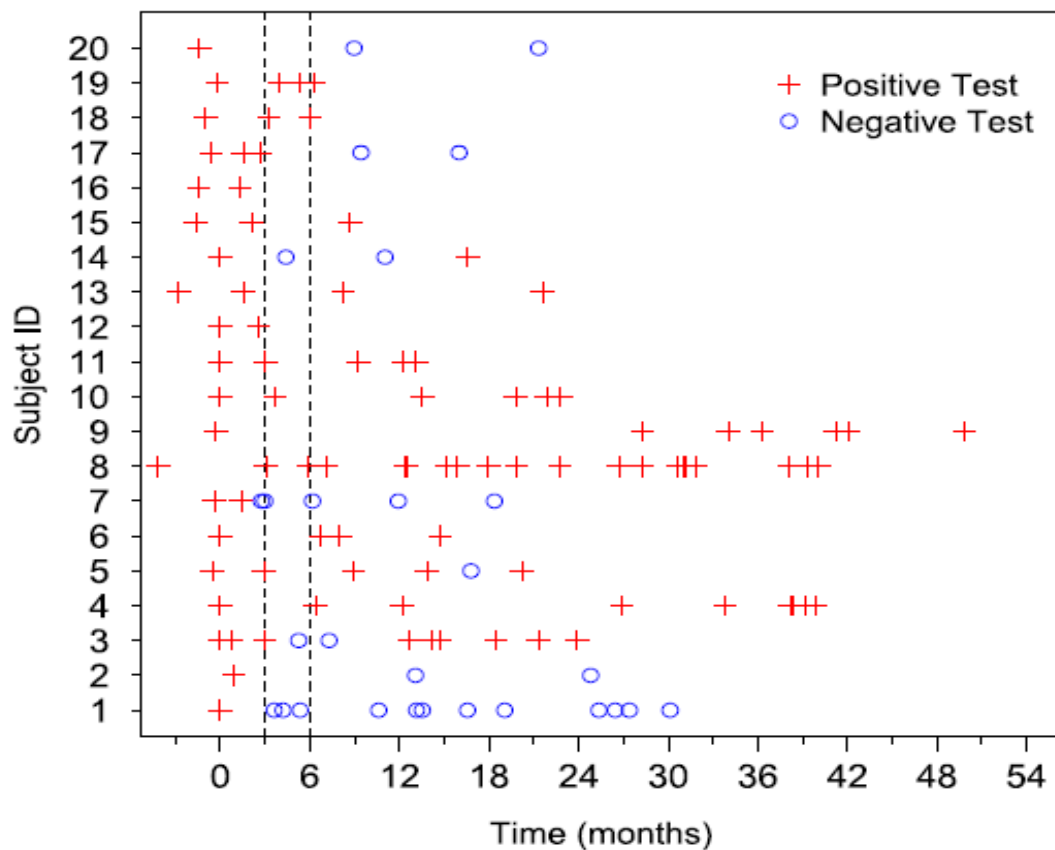
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- Retrospective study n=20
- Inhaled amikacin + failing regimen
  - 250 mg/ml diluted 3 mL saline
  - Jet nebulizer
  - Started 250mg once daily → 500 bid
  - Dosing limited by dysphonia
    - 250 mg daily (50%)

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

# Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease

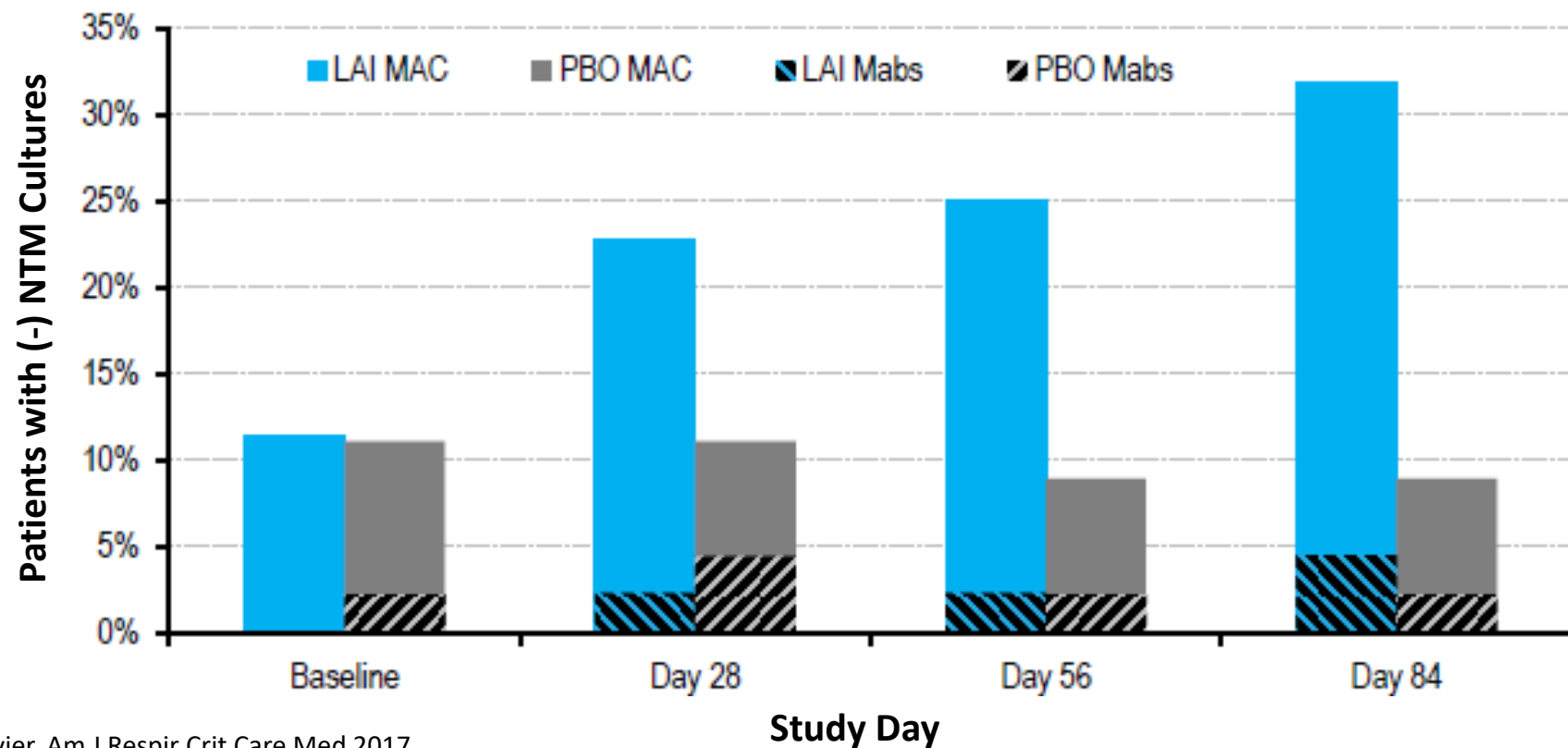
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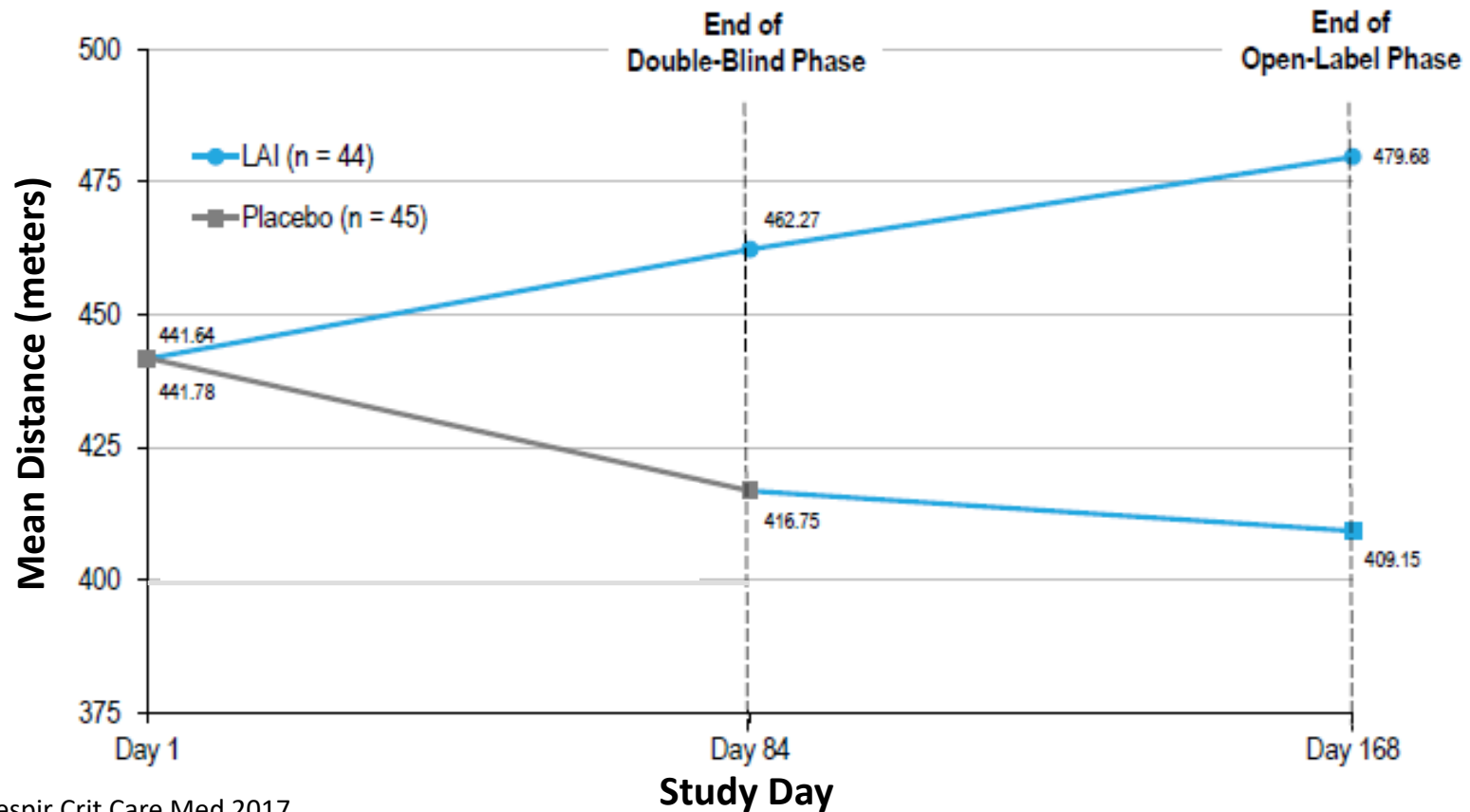
- Toxicity: 7 (35%) stopped

Reasons for stopping	n (%)
Ototoxicity	2 (10)
Hemoptysis	2 (10)
Reversible increase in Cr	1 (5)
Persistent dysphonia	1 (5)
Vertigo	1 (5)

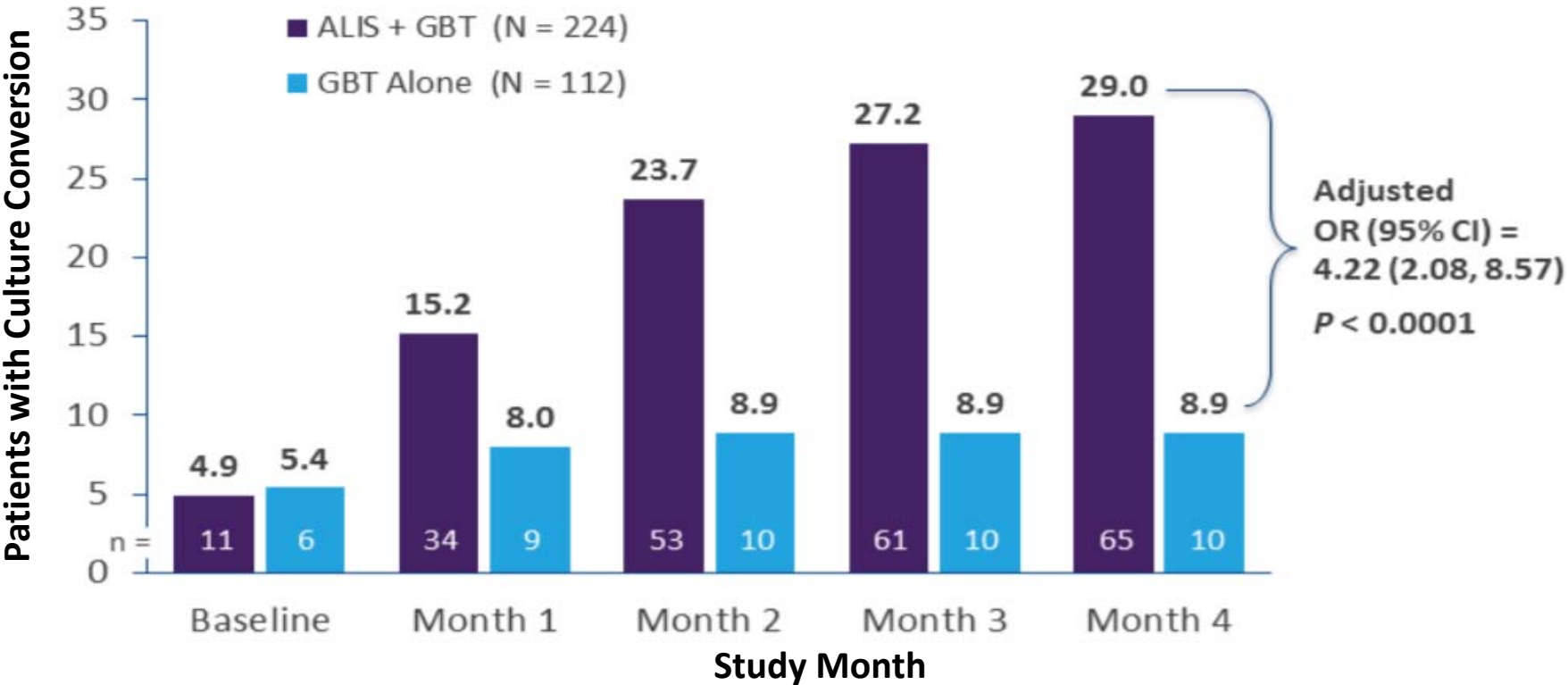
## Amikacin liposomal inhalation suspension: Phase 2



## Amikacin liposomal inhalation suspension: Phase 2



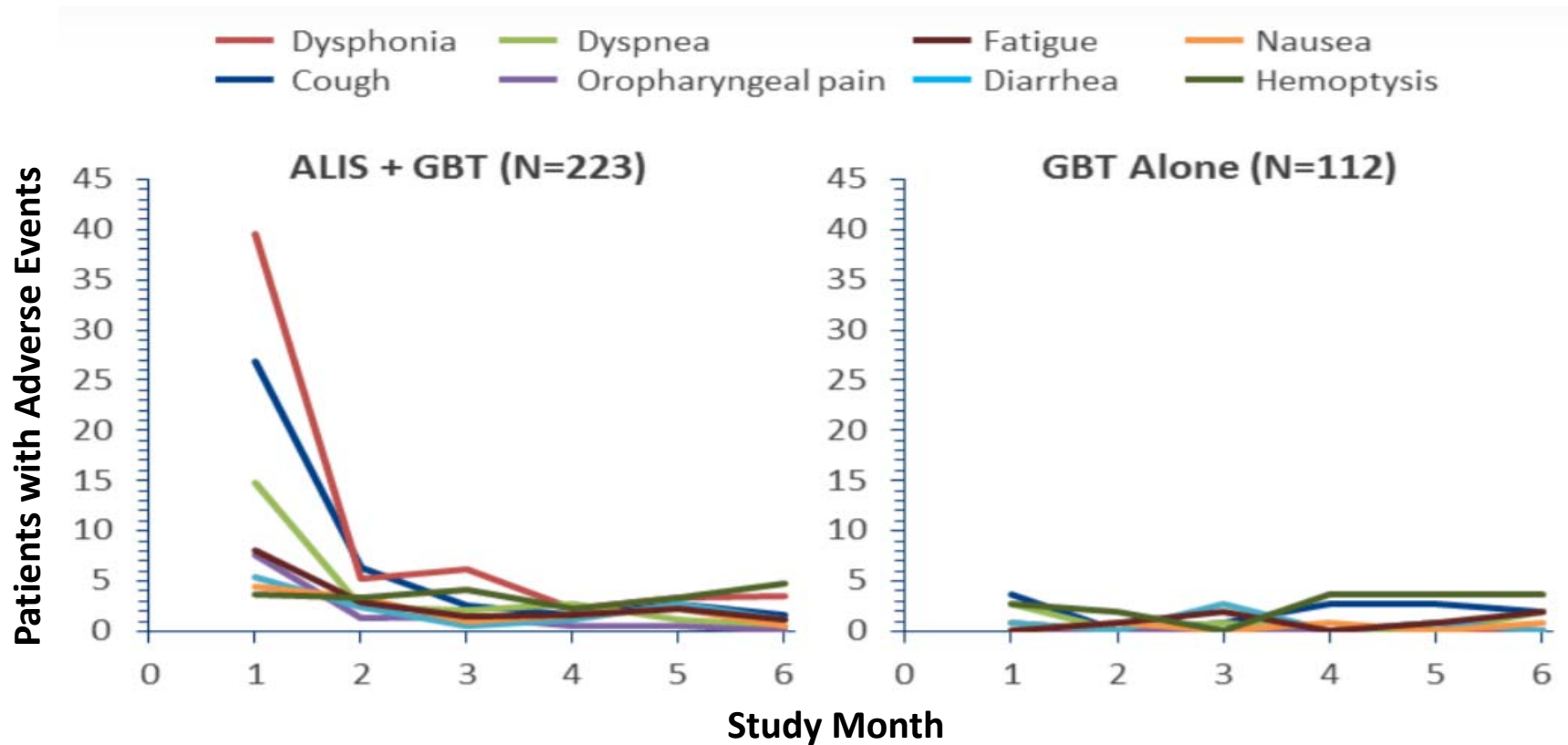
# Amikacin liposomal inhalation suspension: Phase 3



Griffith. Am J Respir Crit Care Med 2018



# Amikacin liposomal inhalation suspension: Phase 3



# Toxicity monitoring

Drug	Toxicity	Monitoring
Cefoxitin	Fever, rash, eosinophilia, cytopenias	CBC
Clofazimine	Skin discoloration, GI – enteropathy (rare), long half-life (~2 mos)	symptoms
Imipenem	hepatotoxicity	LFTs
Linezolid	Cytopenias, optic neuritis, peripheral neuropathy	CBC; visual acuity and color vision; symptoms
Moxifloxacin	GI, insomnia/anxiety, tendonitis, prolong QT	Symptoms; EKG
Minocycline	Photosensitivity, GI, vertigo	Symptoms
Tigecycline	GI, hypoproteinemia, bilirubinemia, pancreatitis (rare)	Symptoms, albumin, bili

## Discovery

## Phase I/II

## Phase III

## Phase IV

<p><b>LCB01-0371</b></p> <ul style="list-style-type: none"> <li>- Target 50S ribosome</li> <li>- For <i>M. abs</i></li> </ul>	<p><b>Clofazimine*</b></p> <ul style="list-style-type: none"> <li>- Target NDH-2</li> <li>- For <i>M. abs</i></li> </ul>	<p><b>Clofazimine</b></p> <ul style="list-style-type: none"> <li>- Target NDH-2</li> <li>- For <i>M. avium</i> PD</li> </ul>	<p><b>Liposomal amikacin for inhalation (LAI)</b></p> <ul style="list-style-type: none"> <li>- Target 30S ribosome</li> <li>- For refractory MAC PD</li> </ul>	<p><b>Linezolid</b></p> <ul style="list-style-type: none"> <li>- Target 50S ribosome</li> <li>- For NTM disease</li> </ul>
<p><b>PIPD1</b></p> <ul style="list-style-type: none"> <li>- Target MmpL3</li> <li>- For <i>M. abs</i></li> </ul>	<p><b>Tedizolid*</b></p> <ul style="list-style-type: none"> <li>- Target 50S ribosome</li> <li>- For NTM</li> </ul>	<p><b>Liposomal amikacin for inhalation (LAI)</b></p> <ul style="list-style-type: none"> <li>- Target 30S ribosome</li> <li>- For <i>M. abs</i> PD</li> </ul>	<p><b>Clarithromycin vs azithromycin</b></p> <ul style="list-style-type: none"> <li>- Target 50S ribosome</li> <li>- For MAC PD</li> </ul>	
<p><b>Indole-2-carboxamides</b></p> <ul style="list-style-type: none"> <li>- Target MmpL3</li> <li>- For <i>M. abs</i></li> </ul>	<p><b>Bedaquiline*</b></p> <ul style="list-style-type: none"> <li>- Target ATP synthase</li> <li>- For NTM</li> </ul>	<p><b>Nitric oxide</b></p> <ul style="list-style-type: none"> <li>- Enhance host defense</li> <li>- Produce reactive nitrogen intermediates</li> <li>- For CF patients with NTM (especially <i>M. abs</i>)</li> <li>- From AIT therapeutics</li> </ul>	<p><b>Clarithromycin vs moxifloxacin</b></p> <ul style="list-style-type: none"> <li>- Target DNA gyrase</li> <li>- For <i>M. xenopi</i> PD</li> </ul>	
<p><b>Thiacetazone derivatives</b></p> <ul style="list-style-type: none"> <li>- Target FAS-II dehydratase</li> <li>- For <i>M. avium</i> and <i>M. abs</i></li> </ul>	<p><b><math>\beta</math>-lactams with avibactam*</b></p> <ul style="list-style-type: none"> <li>- Target penicillin-binding protein</li> <li>- For <i>M. abs</i> and <i>M. avium</i></li> </ul>	<p><b>Gaseous nitric oxide (gNO)<sup>a</sup></b></p> <ul style="list-style-type: none"> <li>- Enhance host defense</li> <li>- Produce reactive nitrogen intermediates</li> <li>- For NTM</li> <li>- Thiolanox<sup>®</sup> from novoteris</li> </ul>		
	<p><b>Rifabutin*</b></p> <ul style="list-style-type: none"> <li>- Target RNA polymerase</li> <li>- For <i>M. abs</i></li> </ul>			

### 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