Diagnosis and Treatment of NTM Lung Infections

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Disclosures

- Principal Investigator/Grant support for clinical trials
  - Insmed (inhaled liposomal amikacin)
  - Bayer (inhaled ciprofloxacin)
  - Aradigm (inhaled liposomal ciprofloxacin)
  - Parion (investigational PCD therapy)
  - Zambon (inhaled colistin)
- Foundation support for Bronchiectasis Registry
  - COPD Foundation
- Consultant
  - Xellia
  - Bayer
  - Electromed

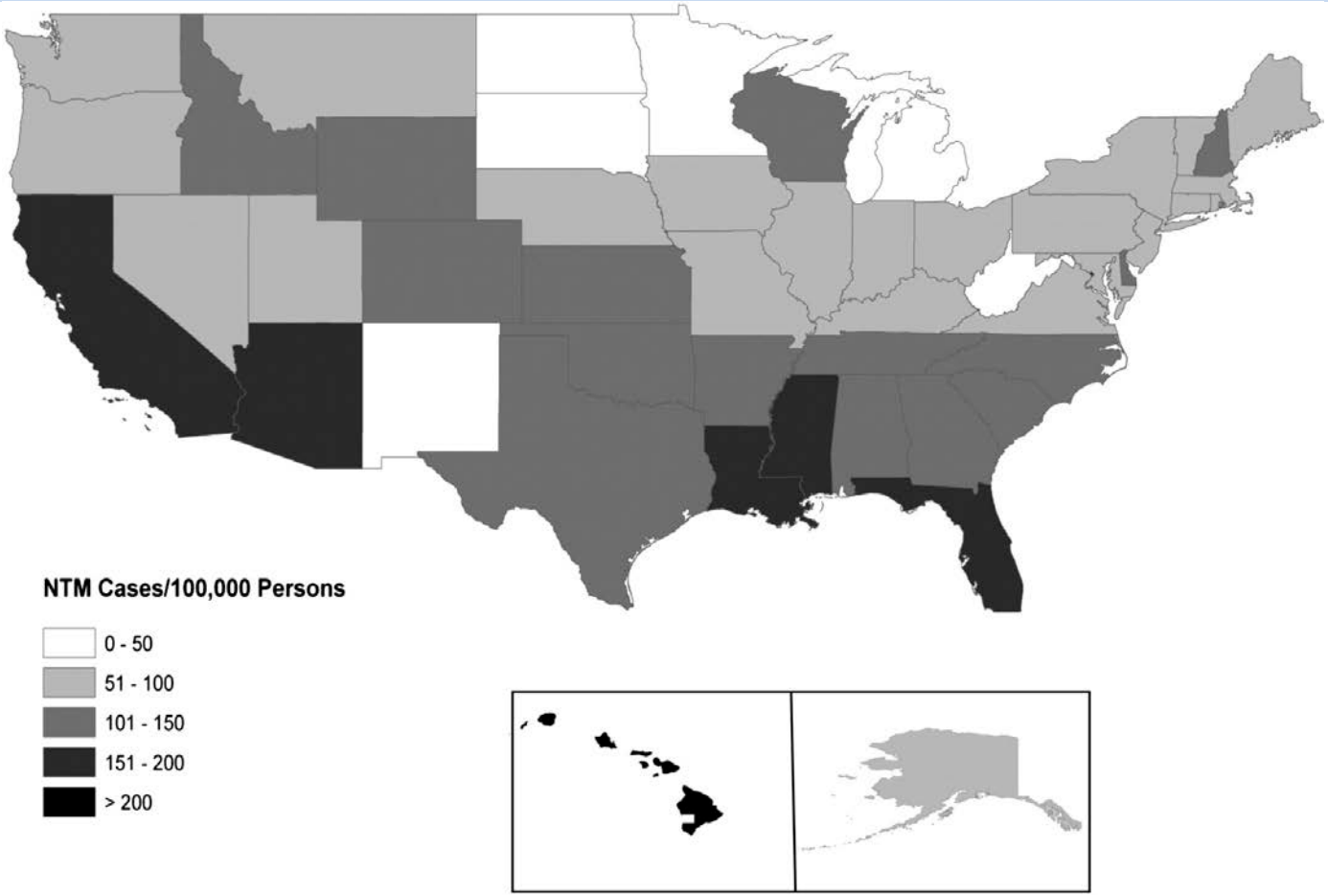
Diagnosis and Treatment of NTM Lung Disease

- Diagnosis
  - Clinical symptoms
  - Radiographic findings
  - Laboratory confirmation
- Treatment
  - Standard MAC treatment
  - “Standard” M. abscessus treatment
  - Salvage regimens
  - Pipeline
- Unmet needs

Burden of pulmonary NTM disease

- 2010 estimate: 86,244 US cases
  - Sources: Medicare and national survey data
  - Oceanic coastline and gulf states: 70%
  - Medication cost: 76% of expenditures
- 2014 projected estimates: 181,037 cases
- Disease of older adults, female predominant
  - » *Strollo SE et al. Ann Am Thorac Soc 2015;12:1458-1464*
- Similar reports from Queensland Australia
  - » *Thomson R et al. Ann Am Thorac Soc 2015;12:1425-1427*
- Increasing mortality in US
  - Disproportionately in older white women
    - » *Vinnard C et al. Ann Am Thorac Soc 2016;13:1951-1955*

Prevalence of disease
US Medicare beneficiaries



Adjemian J et al. Am J Respir Crit Care Med 2012;185:881-886

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NTM and Cystic fibrosis

- US CF Foundation data
  - 14% positive for NTM
  - Spatial clustering
    - » *Adjemian J et al. Am J Respir Crit Care Med 2014;190:581-586*
- European CF Society Patient registry
  - 2.75% positive for NTM
    - Risk factors: other organisms, chronic medications
      - » *Viviani L et al. J Cyst Fibrosis 2016;15: 619-623*
- Concern about patient to patient transmission
  - » *Bryant JM et al. Lancet 2013;381:1551-1560*

Diagnosis of NTM lung infection

- Clinical symptoms
  - Pulmonary symptoms
    - Chronic cough
    - Sputum production
    - Occasionally hemoptysis
    - Occasionally chest pain
  - Systemic symptoms
    - Weight loss
    - Night sweats, low grade fever
    - Fatigue, malaise

Diagnosis of NTM lung infection Underlying conditions

- Underlying conditions:
  - None, de novo disease
    - Abnormal body morphology: thin, tall, older, caucasian females
    - Multigenic predisposition
      - » *Szymanski EP et al. Am J Respir Crit Care Med 2015;192:618-628*
  - Pulmonary diseases
    - Bronchiectasis
    - COPD/emphysema
    - Fibrotic or fibrocavitary lung disease
      - Post infectious, including TB
      - Diffuse fibrosis, including sarcoidosis
  - Genetic disorders
    - Cystic fibrosis
    - Alpha 1 Antitrypsin deficiency

Diagnosis of NTM lung infection
Underlying conditions

- Immune disorders
  - Genetic—rare, often cause disseminated disease
    - IFNGR mutations
    - IL 12 mutations
    - Stat 1 mutations
    - GATA 2 mutations
    - Anti-IFN gamma autoantibodies
  - Acquired
    - Untreated AIDS
    - Chemotherapeutic agents
    - Anti-rheumatic agents
    - Transplant immunosuppressive therapies
    - Inhaled corticosteroids
      - » *Honda JR et al. Curr Opin Immunol 2018;54:66-73*
      - » *Liu VX et al. Ann Am Thorac Soc 2018;15:1169-1176*

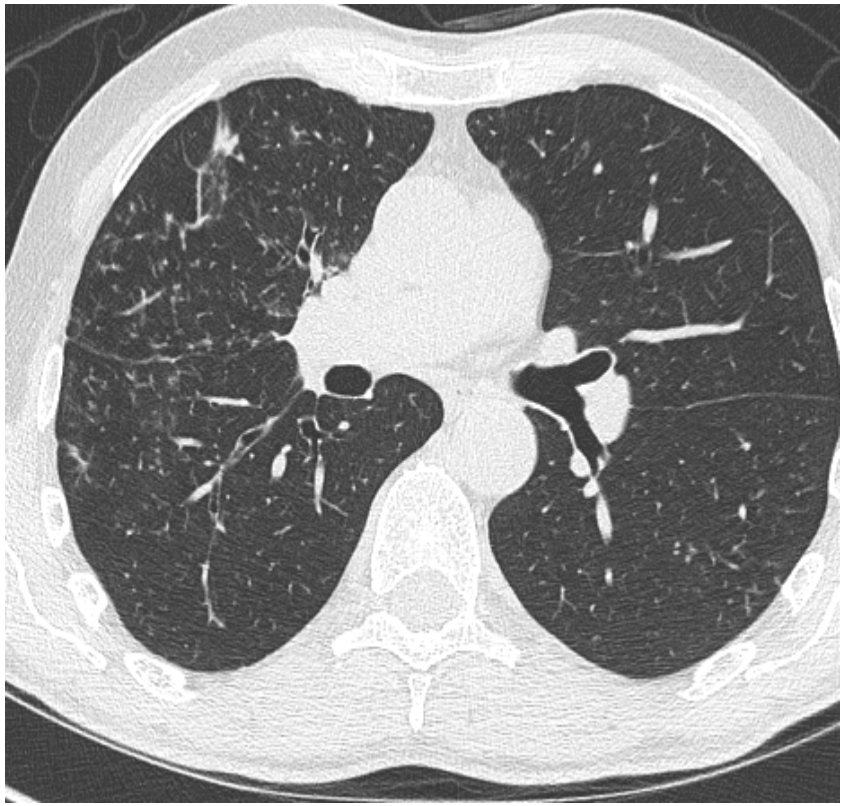
Diagnosis of NTM lung infection
Underlying conditions

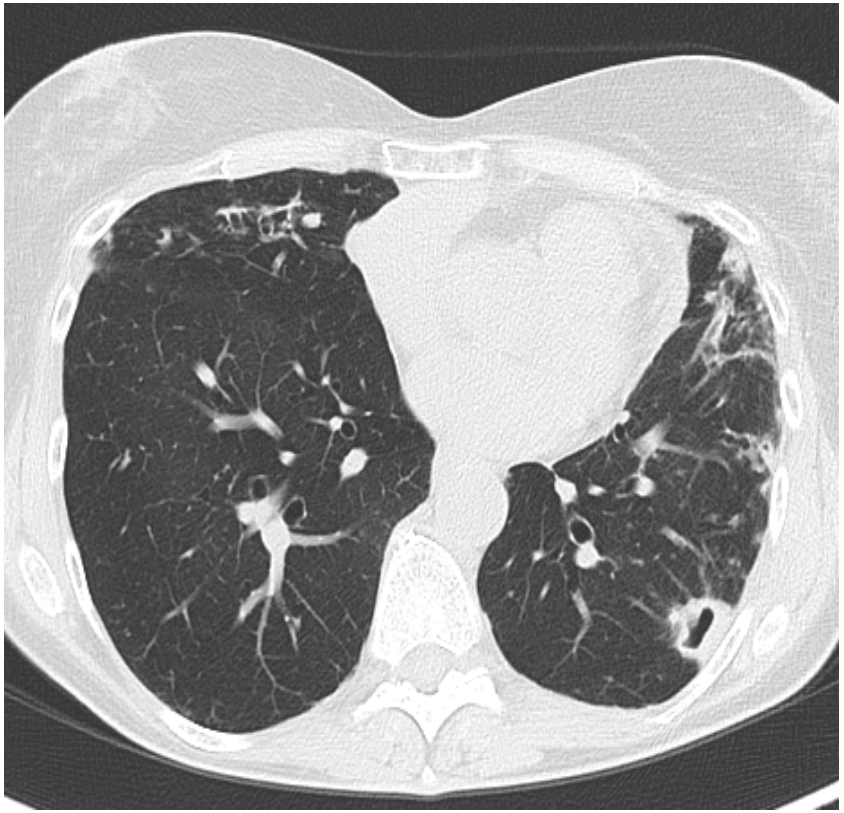
- Other disorders
  - Chronic reflux/aspiration
  - Rheumatologic disease
    - RA, Sjogren's
  - Inflammatory bowel disease
- "Why me/why now?"
  - Host susceptibility and environmental exposure
  - Soil/water exposure
    - » *Lake AM et al. BMC Medicine 2016;14:54*
    - » *Dirac MA et al. Am J Respir Crit Care Med 2012;186:684*
    - » *Marras TK. Am J Respir Crit Care Med 2012;186:585-586*

Diagnosis of NTM lung infection Radiographic findings

- Plain chest radiography may be suggestive
- CT chest (HRCT)
  - CT findings are not diagnostic
  - Fibronodular disease
    - “tree in bud” nodularity
  - Fibrocavitary disease
  - Disease progression
    - “waxing and waning” infiltrates/mucus plugging

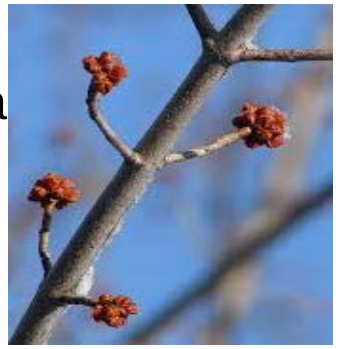
Fibronodular vs fibrocavitary

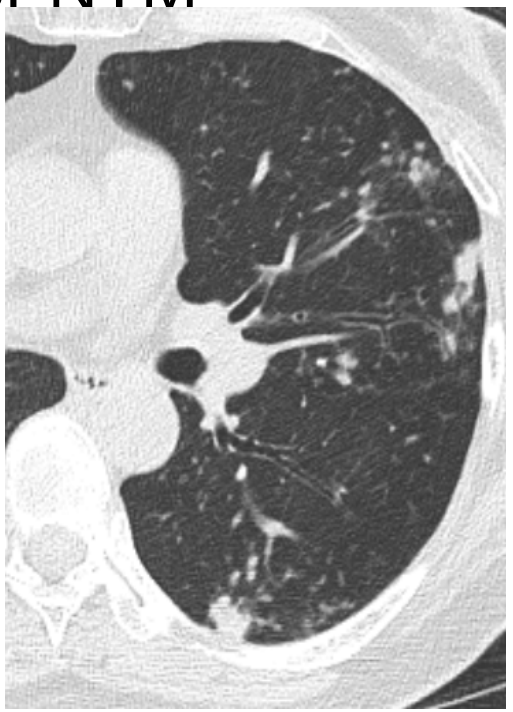




Radiographic manifestations

- Radiographic findings are not diagnostic of NTM infection
- “tree in bud” nodularity is not specific for NTM
  - Multiple causes of bronchiolitis
  - Infection/inflammatory
    - NTM but also “routine” bacteria
    - Inflammation
    - Mucus plugging





- *Miller WT et al. Chest 2013; 144:1883-1892*
- *Shimon G et al. Lung 2015; 193:823-829*

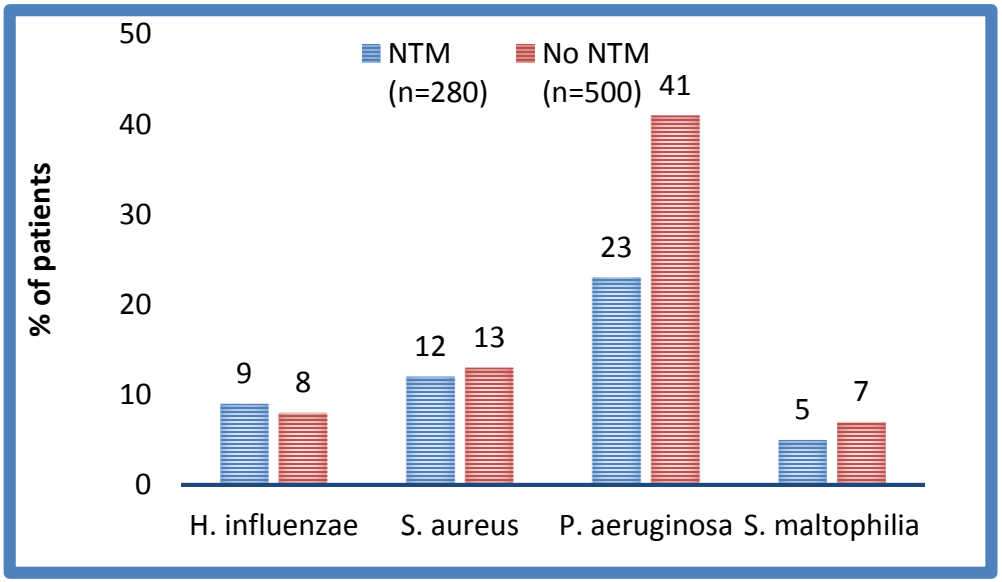
NTM lung infections

- Mycobacterium avium complex
  - M. avium
  - M. intracellulare
  - M. chimera
- Mycobacterium abscessus complex
  - M. abscessus subspecies abscessus
  - M. bolletii
  - M. massiliense
- Many clinical labs do not sub-speciate

NTM and *P. aeruginosa* co-infection

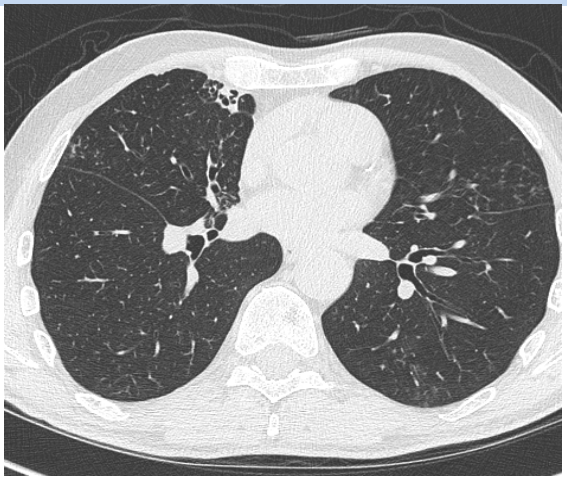
- In observational and retrospective studies, 23% to 52% of NCFB patients with NTM are co-infected with *P. aeruginosa*[1-4]

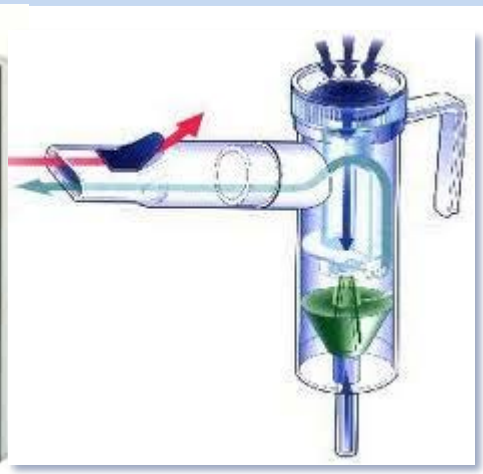
Co-infection rates in the BRR[4]*

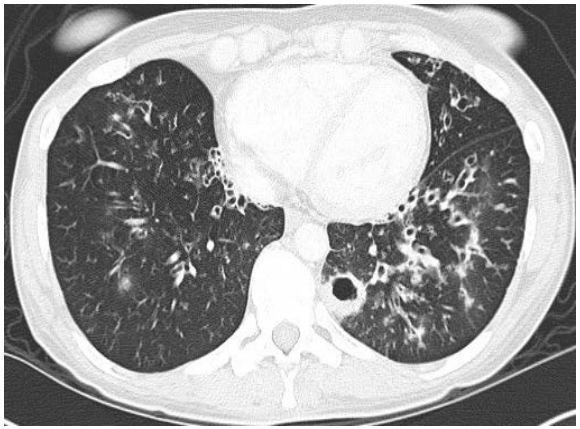


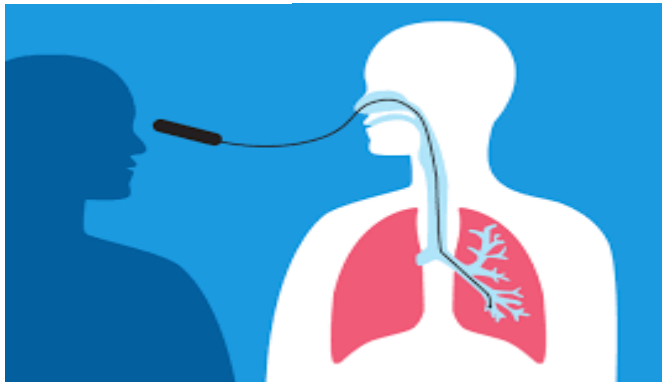
1. *Maiz L, et al. BMC Infect Dis. 2016;16:437.*
2. *Zoumat Z, et al. Respirology. 2014;19:714-22.*
3. *Bonaiti G, et al. Int J Mycobacteriol. 2015;4:68-9.*
4. *Aksamit TR et al. Chest 2017;151:982-992*

Obtaining pulmonary secretions









Confirming the diagnosis of NTM

- Clinical, radiographic, laboratory triad
- Clinical symptoms can be non-specific
- Radiographic findings do not always correlate
  - Specific organism
  - Monitoring for disease progression/regression
- Mycobacterial cultures are challenging
  - How many prove infection?
  - How to collect the specimens
    - Technique
    - Frequency
  - Laboratory issues

Confirming the diagnosis of NTM

- Laboratory issues
  - Organism speciation
    - Mycobacterium avium complex
      - Sub-speciation not routinely done
      - Clinical correlation with antibiotic susceptibility is challenging
        - » Most reliable for macrolides and amikacin
    - Mycobacterium abscessus complex
      - Sub-speciation not always done
      - Antibiotic susceptibility testing not always done
        - » Macrolide susceptibility crucial
          - ERM gene testing
  - Reference labs difficult to access for patients

Laboratory challenges

Acid Fast Smear+Culture
AFB Specimen Processing

	Concentration
Acid Fast Smear	**Positive Abnormal**

2+, 4-36 acid-fast bacilli per 10 fields at 400X magnification, fluorescent smear
Notified Chelse K. 12/08/17 at 1035 (MAB).
Faxed to 301-942-8031.

Acid Fast Culture	**Positive Abnormal**

Acid-fast bacilli have been detected in culture at 1 week; see AFB Organism ID by DNA probe

AFB Organism ID by DNA Probe

M tuberculosis complex	Negative
M avium complex	Negative
M kansasii	Not Indicated
M gordonae	Not Indicated

Other:
Unable to identify by DNA probe. See Organism ID by Sequencing.

Organism ID by Sequencing

	Mycobacterium abscessus Abnormal

Taxonomy of the Mycobacterium abscessus group is currently in flux for the differentiation of M. abscessus (often macrolide resistant) versus M. bolletii (usually macrolide susceptible). This identification is based upon sequencing and macrolide susceptibility testing.

Fungus (Mycology) Culture

Laboratory challenges

Rapid Grower Broth Suscep.

Organism ID

Mycobacterium abscessus Abnormal

Amikacin	4.0 ug/mL	Susceptible
Cefoxitin	32.0 ug/mL	Intermediate
Ciprofloxacin	4.0 ug/mL	Resistant
Clarithromycin	8.0 ug/mL	Resistant

This organism has been evaluated for inducible macrolide resistance.

Doxycycline	>16.0 ug/mL	Resistant
Linezolid	8.0 ug/mL	Susceptible
Minocycline	>8.0 ug/mL	Resistant
Moxifloxacin	8.0 ug/mL	Resistant
Tigecycline	0.25 ug/mL	
Trimethoprim/Sulfa	>8/152 ug/mL	Resistant

Please note:
Results of this test are labeled for research purposes only by the assay's manufacturer. The performance characteristics of this assay have not been established by the manufacturer. The result should not be used for treatment or for diagnostic purposes without confirmation of the diagnosis by another medically established diagnostic product or procedure. The performance characteristics were determined by

Current therapy for NTM lung disease

- Treat the underlying cause if possible
  - Identify and treat causes and co-morbidities
    - CF, immune disorders, A1AT deficiency, bronchiectasis
    - Reflux, aspiration
    - Nutrition, immunizations
    - Other microbial pathogens
- Airway clearance modalities
  - Flutter, expiratory resistance, chest wall oscillation
  - Exercise and pulmonary rehabilitation
- Antibiotics
- Surgery

Airway clearance modalities

Current antibiotic therapies for NTM

- MAC lung disease
  - Nodular bronchiectatic disease
    - Macrolide/ethambutol/rifamycin
    - Thrice weekly regimens effective
    - Cure elusive
      - 70% while on therapy
      - 40-50% relapse/re-infection after therapy completed
        - *Wallace RJ et al. Chest 2014;146:276-282*
        - *Jeong B et al. Am J Respir Crit Care Med 2015;191:96-103*
  - Fibrocavitary Disease
    - Macrolide/ethambutol/rifamycin and aminoglycoside
    - Daily therapy, may need surgery
      - *Griffith DE et al. Am J Respir Crit Care Med 2007;175:367-416*
      - *Haworth CS et al. BMJ Open Respir Res 2017;Oct 19*
- Complicated by lack of adherence to guideline driven therapy
  - *Adjemian J et al. Ann Am Thorac Soc 2014;11:9-16*
  - *Van Ingen J et al. Eur Respir J 2017;49:Feb 15*

New drug for refractory MAC

- Liposomal amikacin, approved 2018
  - LAI 590 mg vs placebo for 84 days, then open label
  - Primary endpoint: reduction in NTM growth
  - Other endpoints:
    - Sputum conversion
    - 6 min walk distance
    - Adverse events
  - Primary endpoint: not achieved
  - Sputum conversion: 32% in treated group
  - 6 min walk distance improved
  - Side effects: hoarseness, bronchospasm

- *Olivier KN et al. Am J Respir Crit Care Med 2016;195:814-823*
- *Griffith DE et al. Am J Respir Crit Care Med 2018;198:1559-1569*

Current therapies for NTM lung disease

- Mycobacterium abscessus subsp abscessus
  - Usually not susceptible to macrolide (ERM gene)
  - Standard regimen includes IV therapies
    - Imipenem or cefoxitin and amikacin
    - Other options:
      - Clofazimine, tigecycline, linezolid, tedizolid
    - Surgery may be considered
    - Microbiologic cure unlikely
      - *Griffith DE et al. Am J Respir Crit Care Med 2007;175:367-416*
      - *Jeon K et al. Am J Respir Crit Care Med 2009;180:896-902*
    - Quality of life can be improved
      - *Czaja CA et al. Ann Am Thorac Soc 2016;13:40-48*

Toxicities of standard treatments

- Toxicities/Allergic reactions
  - Macrolides
    - GI/hepatic
    - Cardiac
    - drug interactions
    - hearing
  - Ethambutol: Ocular
    - 10% discontinuation
      - » *Griffith et al. AJRCCM 2005;172:250*
  - Rifampin: GI/allergic/hematologic
  - Aminoglycoside: auditory/vestibular/renal
    - Older age, may be reversible
      - » *Peloquin et al. Clin Infect Dis 2004;* 38:1538

Challenges with NTM antibiotics

- Patient is unable to tolerate three or more drugs
  - Are two drugs for MAC sufficient?
    - » *Miwa S et al. Ann Am Thorac Soc 2014;11:23-29*
- Patient does not want to take 18-24 months of therapy
  - Is a shorter regimen reasonable?
- Patient has macrolide resistant MAC
  - Mortality similar to MDR TB
    - » *Morimoto K et al. Ann Am Thorac Soc 2016;11 Aug 2016*
    - » *Griffith DE et al. Am J Respir Crit Care Med 2006;174:928-934*
- Patient does not have access to drugs
  - Cost, insurance coverage
  - Home infusion issues
- Physician expertise is limited

Why we need new drugs and new treatment regimens

- Growing patient population
  - May be sicker
    - Older, female population
    - Cystic fibrosis population
  - Possibly increasing mortality
  - Patient and FDA priority
- Paucity of effective, paucity of well tolerated drugs
  - Data from mostly retrospective trials
  - Old drugs/old bugs
  - Adverse effects
  - Current clinical trials
- Broad spectrum of disease

What is in the pipeline? Re-purposed drugs

- Old drugs for old bugs:
  - Linezolid and tedizolid, often used, minimal data
  - Tigecycline
    - GI toxicity
    - New tetracycline drugs?
  - Clofazimine
    - MAC lung disease, 107 patients
    - Combined with macrolide and ethambutol
    - 95% converted to negative on treatment
    - 49% relapsed
      - *Jarand J et al. Chest 2016;149:1285-1293*
    - 112 patients from 2006-2014
      - Safe and well tolerated
        - *Martiniano SL et al. Chest 2017;152:800-809*
  - Fluoroquinolones
    - Probably ineffective

What's in the pipeline?

- Bedaquiline
  - 10 heavily treated patients with NTM (6 MAC/4Mab)
  - Best available companion drugs
  - 60% had microbiologic response
  - Side effects
    - Nausea, arthralgias, anorexia, subjective fevers
      - » *Philley JV et al. Chest 2015;148:499-506*
- Inhaled nitric oxide
  - Case series
    - » *Yaacoby-Bianu K et al. J Cyst Fibrosis 2017;S63-S174*
  - A small, pilot Phase 1/2 clinical trial evaluating the safety and efficacy of Thiolanox inhaled nitric oxide gas in treating nontuberculous mycobacteria (NTM) infection has been approved by Health Canada. ... Nov 7, 2017
- Dry powder nitric oxide
  - » *Vast Therapeutics Press release: QIDP designation 2017*
- B-lactams with avibactam
- Phages

Surgery for NTM lung disease

- A consideration for select patients
  - Localized disease
  - Worst area of disease
  - Good response to antibiotics but with residual disease
  - M. abscessus disease
  - Patient is a good candidate for surgery
  - Surgeon is experienced
    - » *Mitchell JD. Thorac Surg Clin 2019;29:77-83*

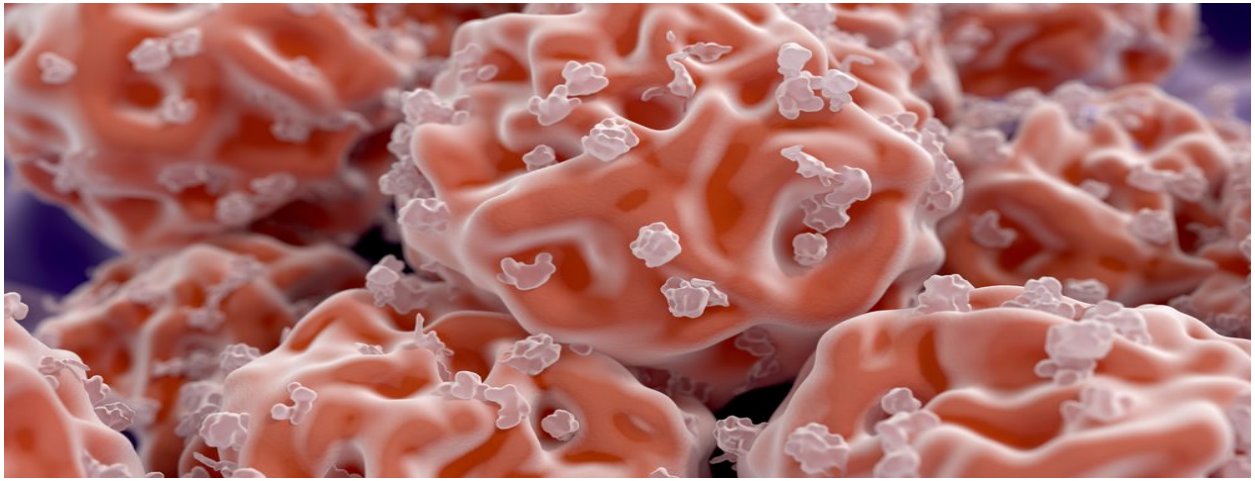
Untested therapies puts patients at risk

Stem Cell Transplants Rejuvenate Chinese Bronchiectasis Patients' Damaged Lungs (February 15, 2018)

BRONCHIECTASIS NEWS TODAY

An article on the pilot clinical trial's results appeared in the journal *Protein & Cell*. It was titled "Regeneration of functional alveoli by adult human SOX9^{+}airway basal cell transplantation."

> With stem cell transplants, "chronic lung diseases could be conquered within five years," Zuo suggested.



Untested therapies: risk

Lung Institute
Breathe Easier.

Treatment options for bronchiectasis

There is no cure for bronchiectasis. It is a progressive condition that may continue to worsen over time. However, there are many treatment options available to help you manage your symptoms, and some treatment options that may help slow the progression of your condition.

While traditional treatments for bronchiectasis include an inhaler, medication and oxygen therapy, regenerative treatments use the cells in a patient's own body to help target and reduce the inflammation in the lungs. Traditional treatments play a very reactive role in treating bronchiectasis; they are only useful when symptoms are occurring. However, regenerative treatment aims to reduce the occurrence of symptoms altogether.

The cellular therapy treatment offered at the Lung Institute is proven effective to help target and reduce inflammation in the lungs. Our treatment has earned a 95 percent patient satisfaction rate*, and 85 percent of our patients^ have reported an improvement in quality of life within three months of receiving our treatment.

If you would like to find out more about our available treatment options available for bronchiectasis and other lung conditions, please contact one of our patient care coordinators today at (888) 510-9356 to schedule a free consultation.

Untested therapies

Advantages of Cellular Therapy (PRP-PC)

The healing properties of our science-based holistic medical treatments are beneficial to patients at any stage of their lung disease. Traditional medical treatments only address the symptoms. Our natural treatments and wellness approach can provide our patients with a more effective way to address chronic inflammatory lung diseases. We are improving lives and helping people breathe easier.

•THE JOINT COMMISSION ACCREDITATION

We have received national accreditation as a top healthcare organization providing safe, high quality care to our patients.

•EFFECTIVE TREATMENT PLANS

Move beyond traditional treatments that only address symptoms. Our integrated wellness approach addresses the root cause.

•NO DOWN TIME

Our outpatient therapy requires no downtime or post-therapy restrictions.

•*95% PATIENT SATISFACTION*

Based on patient surveys following treatment.

•CALMS LUNG INFLAMMATION

Our integrated wellness approach has the potential to calm lung inflammation, and to slow lung disease progression.

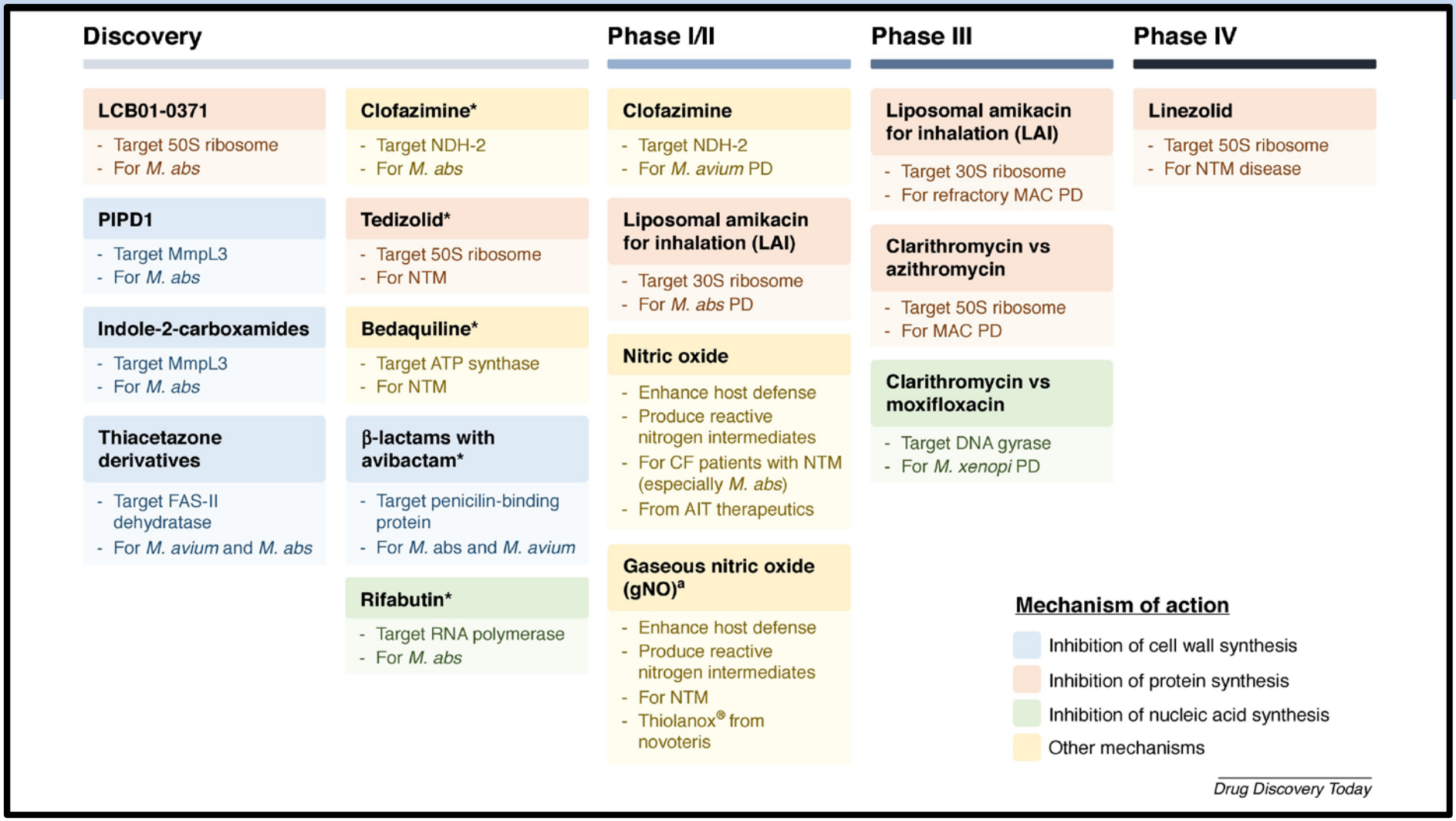
•REGENERATIVE MEDICINE

A new approach to your lung health. Our doctors are board-certified and our clinicians undergo rigorous training.

•85% FIND IMPROVEMENT^

Based on patient surveys, 85% of patients report quality-of-life improvements at three months of treatment.

NTM Drug Discovery: Status, gaps, way forward



Wu M et al. Drug Discovery Today 2018:23:1502-1519

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Patient priorities

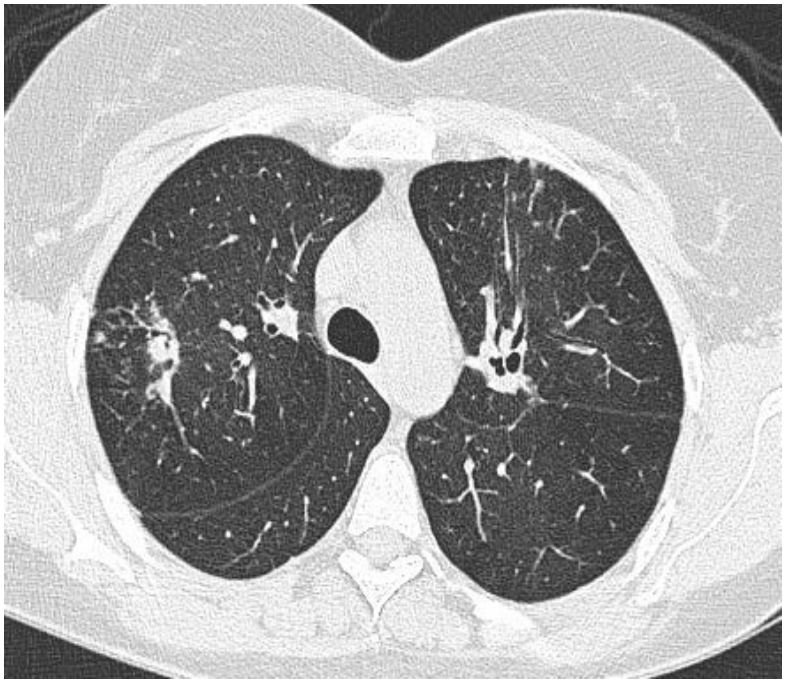
- NTM Research Consortium Workshop
  - Prevention
    - Strengthen the role of patients in preventing re-infection
    - Limit the risk of patient to patient transmission in CF
  - Diagnosis
    - Improve timeliness of diagnosis
    - Develop better laboratory techniques/susceptibility testing
  - Quality of life priorities
  - Treatment priorities
    - Reduce burden of antibiotics
    - Holistic approaches
    - Deciding who needs treatment
  - Outcomes and prognosis

» *Henkle E et al. Ann Am Thorac Soc 2016;13:S379-S384*

Broad spectrum of disease

- Minimal/asymptomatic to severe/life-threatening
- Diagnosis is straightforward
  - If the physician thinks of it/performs proper testing
  - If the laboratory support is adequate
- Prognosis/progression is unpredictable
- Treatment is challenging
  - Drugs/combinations/doses/delivery methods
  - Duration of therapy
  - Adverse effects
  - Inability to “cure”
  - Need for maintenance strategies
- Challenges of new drug development
  - » *Falkinham JO. Front. Microbiol 2018;9:1613*

Patient #1:
chronic disease, no progression



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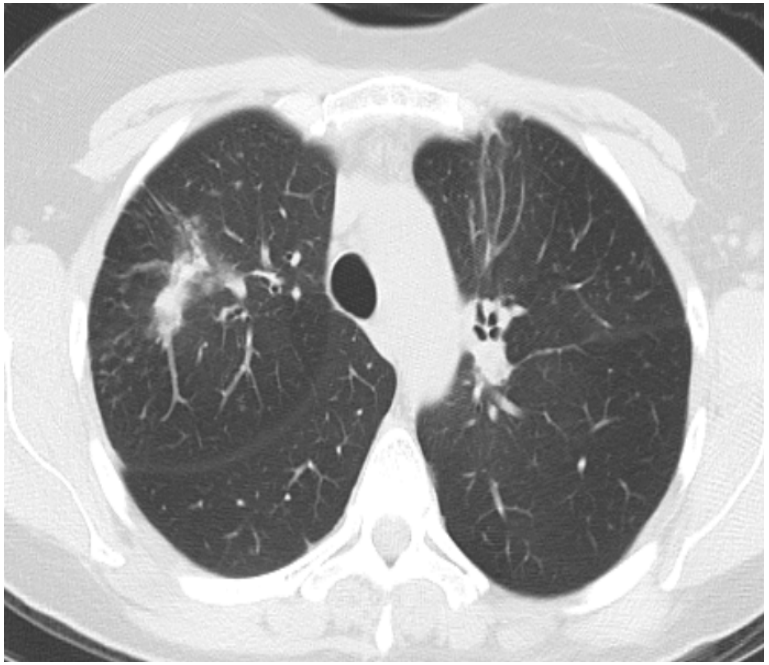

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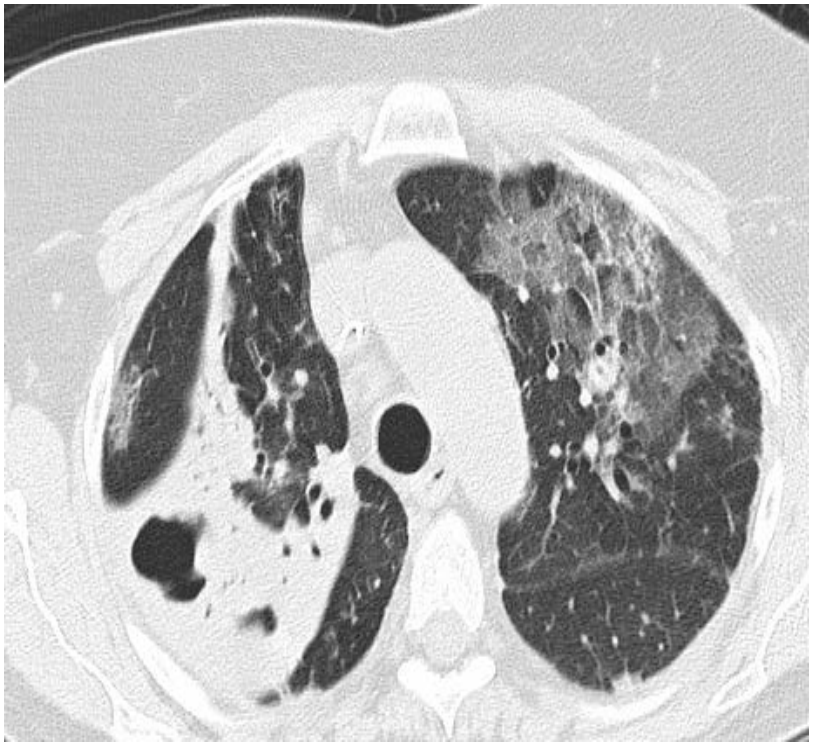
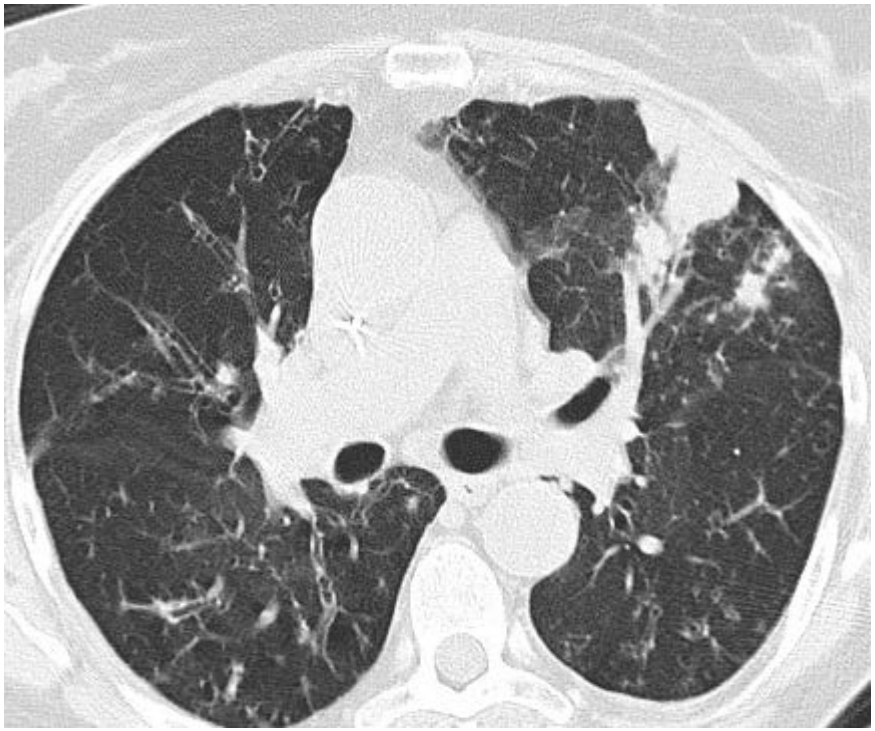
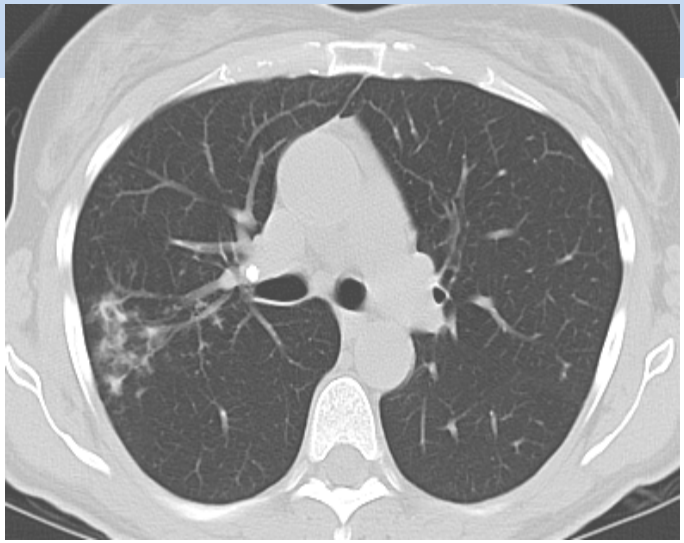
Patient #2:
Severe disease: MAC, M. abscessus, p. aeruginosa





Patient #3:

Progressive then stabilized disease



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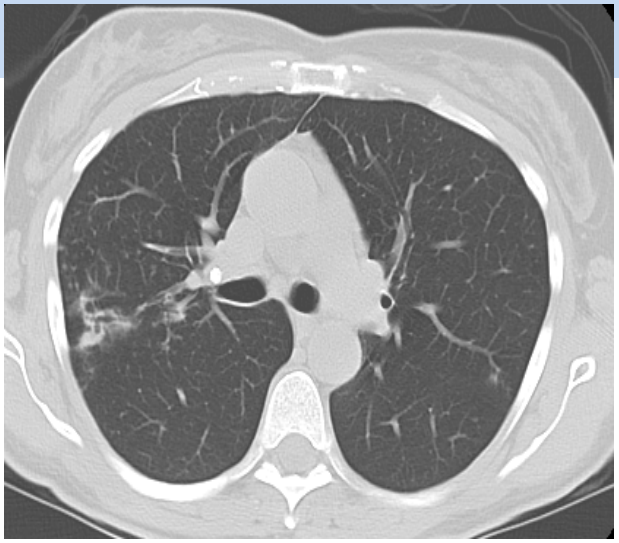

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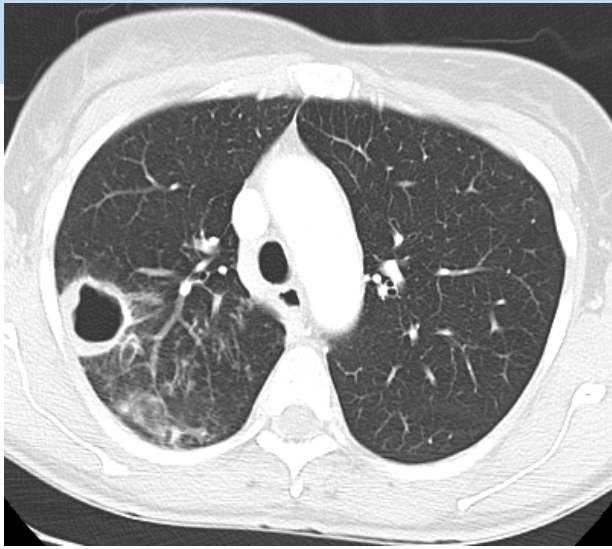

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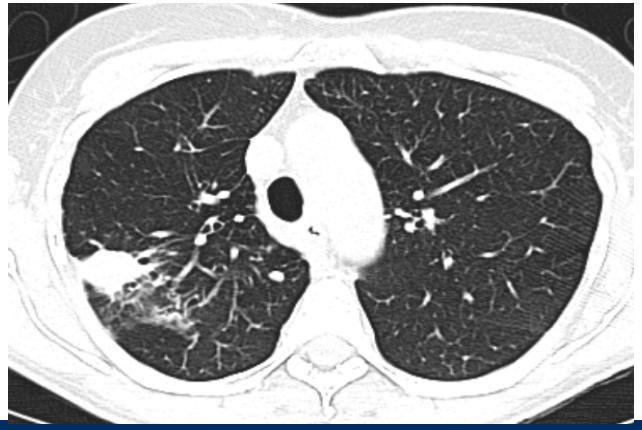

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Urgent unmet needs

- Better understanding of the microbiology
  - Role of susceptibility testing
- Better understanding of the host-bacterial interaction
- Better ability to prognosticate
  - Who needs treatment
  - Who will progress and at what pace
- Better ability to personalize treatment
  - By patient phenotype
  - By antibiotic
  - Ensure patient safety
- What to do with patients intolerant of antibiotics:
  - Need for better companion drugs
  - Need to understand role of inhaled delivery
  - Need to better define duration of therapy