NTM Pulmonary Disease in non-HIV : Spectrum and Challenges in Management

The usual and the unusual

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INTRODUCTION & ACKNOWLEDGEMENT
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www.lsudocs.com www.lsuhsc.edu
http://www.medschool.lsuhsc.edu/tb/
http://ntm.lsuhsc.edu

TEAM MEMBERS
Dr. AZ, JG , BASIC SCIENCE /LAB TEAM
LD , MS, MV (RESEARCH COORDINATORS)

DISCLOSURES

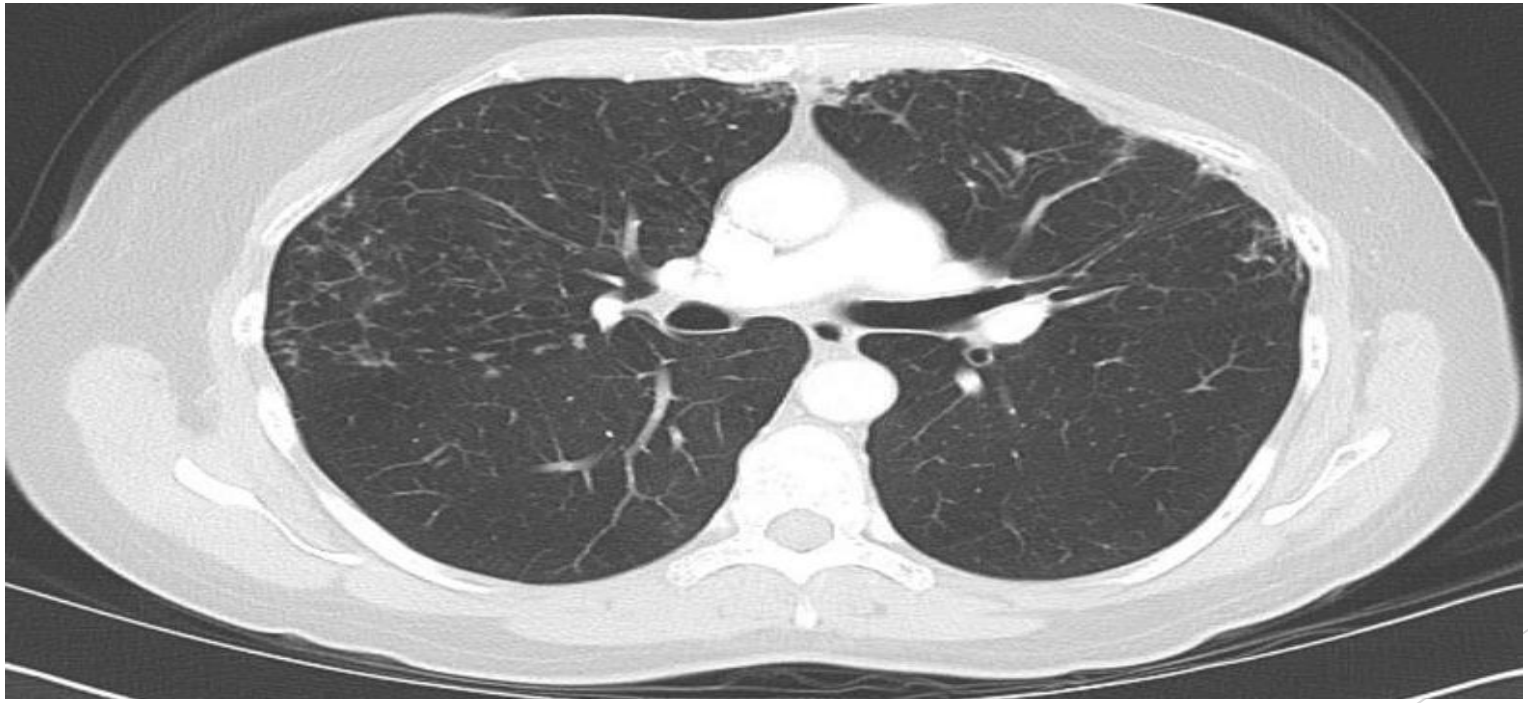
- Consultant / Speaker's Forum : Oxford Immunotec
- Consultant / Advisory Board / Speaker : INSMED

- Study PI /Co-PI: INSMED 212/312 (Inhaled Liposomal Amikacin for refractory MAC) now FDA approved as ARIKAYCE
- Study PI / Co-PI: INSMED Willow Study (Non-CF Bronchiectasis)

- Acknowledgment & Thanks : joint preparation Dr. Nicole Lapinel

CASE 1

A 52-year old Caucasian active woman sought medical attention due to chronic cough. Physical exam was unremarkable. Sputum culture revealed light growth with few colonies of *Mycobacterium avium* complex (MAC). Repeat sputum cultures (1 of 2) later again revealed a few colonies of MAC. The patient was treated symptomatically and followed clinically by serial sputum test (s) and radiographic evaluation. No specific therapy for MAC was initiated and the patient did well



Case 1 continued

- Remained asymptomatic except symptoms of allergic rhinitis and mild GERD
- Infrequent cough
- Repeat CT scan one year later revealed minimal increase in TiB pattern right ML and LUL nodule. " PCP said you may have MAC Lung Disease "
- Repeat Sputum : negative for AFB on culture

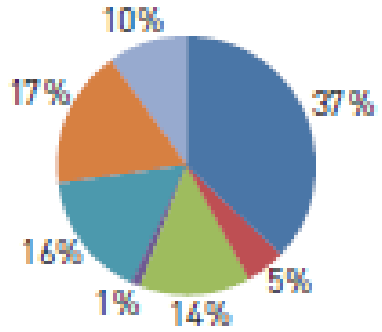
- Patient asked : what does this all mean ?

Case 1 : Discussion/Action item

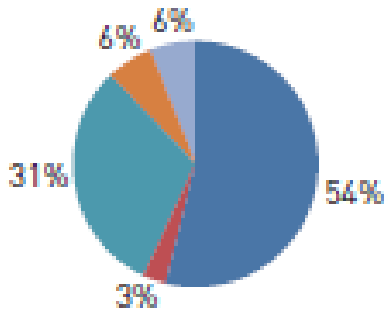
- NTM/ MAC Circus. All NTM are created equal (NL: Our program)
- Reassurance /No Specific Antibiotic Rx
- Risk factors
- Short-term /Long term prognosis
- Worse case scenarios
- ……..

Worldwide NTM Distribution (Respiratory)

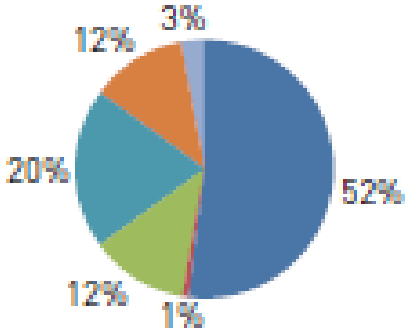
Europe



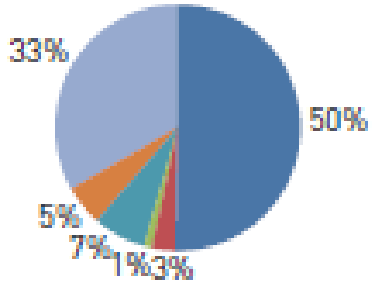
Asia



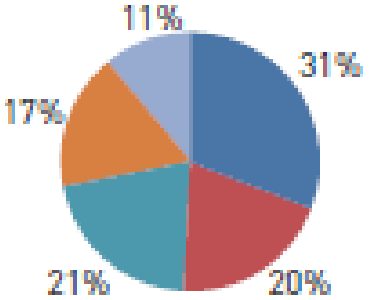
North America



South Africa



South America



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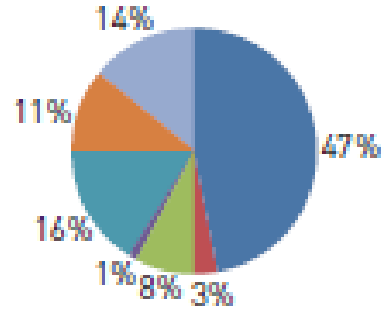


Distribution of NTM

- MAC
- *M. kansasii*
- *M. xenopi*
- *M. malmoense*
- RGM
- *M. gordonae*
- other SGM

Hoefsloot W, van Ingen J, Andrejak C, et al. *Eur Respir J.* 2013;42(6):1604-1613.

NTM Pulmonary Disease in the United States

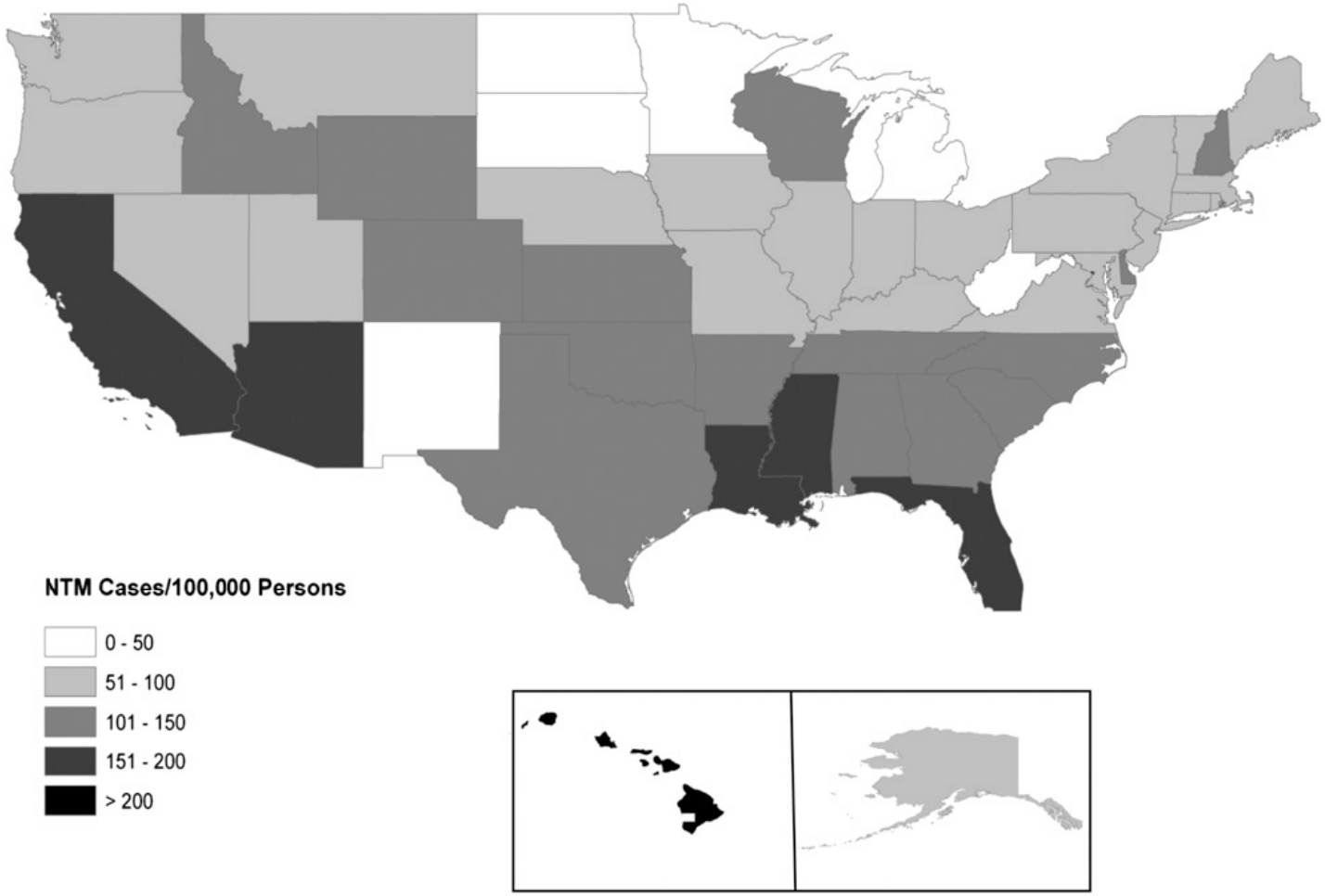


Figure 1. Prevalence of pulmonary nontuberculous mycobacteria cases among a sample of U.S. Medicare Part B enrollees aged 65 and older, 1997 to 2007. NTM = nontuberculous mycobacteria.

Adjemian J, Olivier KN, Seitz AE, Holland SM, Prevots DR. *Am J Respir Crit Care Med*. 2012;185(8):881-886.

TABLE 1. SUMMARY OF ALL SIGNIFICANT CLUSTERS IDENTIFIED BY SaTScan OF PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE AMONG U.S. MEDICARE BENEFICIARIES 65 YEARS OF AGE AND OLDER

Cluster Type	Centroid County and State	No. of Counties (Radius, km)	Relative Risk	*P* Value
High risk	Highlands, FL	24 (159.4)	1.9	<0.0001
	Santa Barbara, CA	18 (344.5)	2.0	<0.0001
	Montgomery, PA	5 (42.2)	2.2	0.0001
	New York, NY	1 (0)	2.7	0.002
	Milwaukee, WI	1 (0)	3.6	<0.0001
	Kalawao, HI	3 (114.8)	3.7	<0.0001
	Plaquemines, LA	3 (70.2)	6.5	<0.0001
Low risk	Washington, RI	16 (106.7)	0.5	0.02
	Iosco, MI	93 (351.4)	0.4	<0.0001
	Roane, WV	208 (268.5)	0.4	<0.0001
	Polk, MN	247 (689.7)	0.4	<0.0001
	Cayuga, NY	95 (289.0)	0.3	<0.0001

7 significant HIGH-risk clusters

- 3 Southern Coastal Parishes identified within the cluster in **Louisiana**:
  - Plaquemines
  - Jefferson
  - St. Bernard

- Previous nationwide study on NTM in CF patients:
  - Orleans Parish = highest NTM prevalence among 21 sites

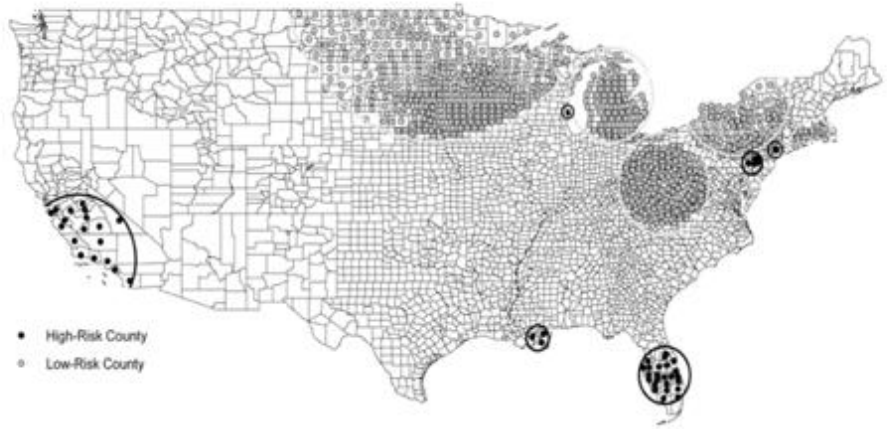


Figure 1. Significant clusters of counties identified by SaTScan as being at either high or low risk for pulmonary nontuberculous mycobacterial (PNTM) disease among U.S. Medicare beneficiaries 65 years of age and older.

**Lung disease due to NTM occurs commonly in structural lung disease, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, CF, pneumoconiosis, prior TB, pulmonary alveolar proteinosis, and esophageal motility disorders

**Abnormal CF genotypes, CFTR Gene mutation and _1-antitrypsin (AAT) phenotypes may predispose some patients to NTM infection

**NTM lung disease also occurs in women without clearly recognized predisposing factors There is also an association between bronchiectasis, nodular pulmonary NTM infections and a particular body habitus, predominantly in postmenopausal women (e.g., pectus excavatum, scoliosis, mitral valve prolapse)
"A mean MAC machine in the thin and lean"

**Bronchiectasis and NTM infection,
usually MAC, often coexist, making causality difficult to determine. These patients may carry multiple MAC strains over time, suggesting either polyclonal infection or recurrent infection with distinct strains). It is unclear whether this problem is due to local abnormalities (e.g., bronchiectasis) or to immune defects

Am J Respir CC M 178; 1066-1074 , 2008 NHLBI

RESULT / SEQUELAE LEADING TO THE MANY FACES OF NTM PULM DISEASE

- Resultant Granuloma formation
- Release of cytolytic and cytotoxic enzymes to form either a cavity, necrotic nodules

  Resulting in PRIMARY BRONCHIECTASIS / F/C disease

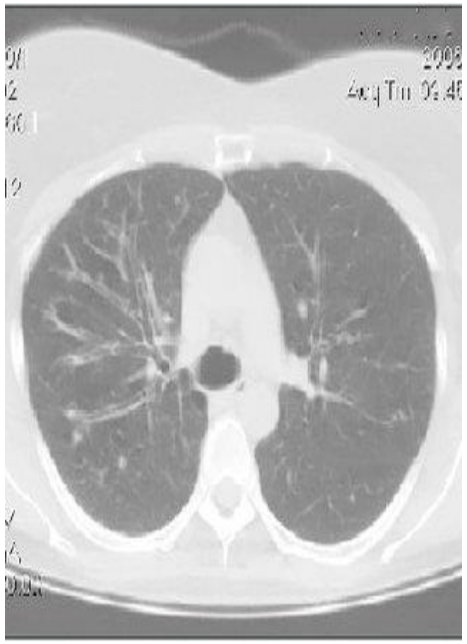
  or F/N disease with traction like cylindrical bronchiectasis

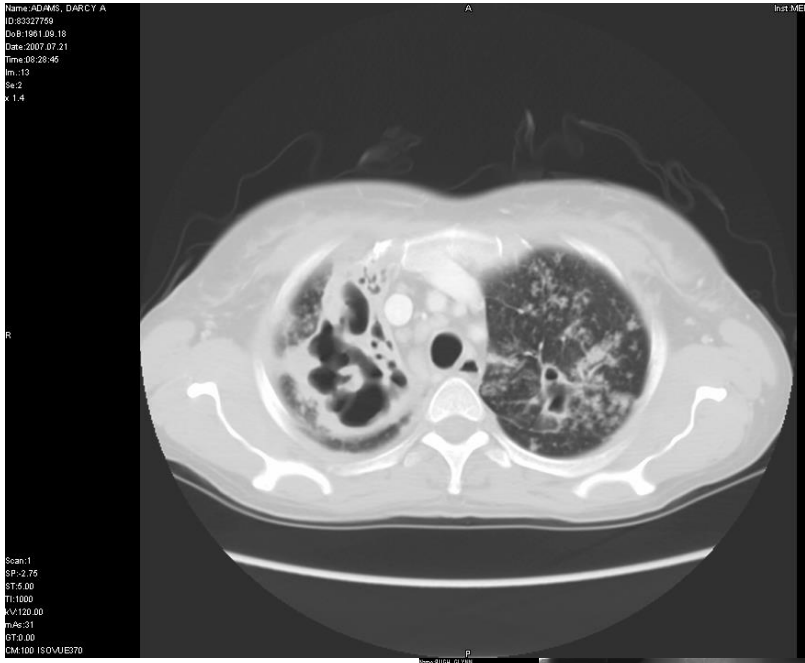
Add to the mix the underlying structural disease:

Type 3-4 Sarcoid/ IPF / COPD /Old TB

With its anatomical distortion

and secondary bronchiectasis

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Manuf:GE MEDICAL SYSTEMS
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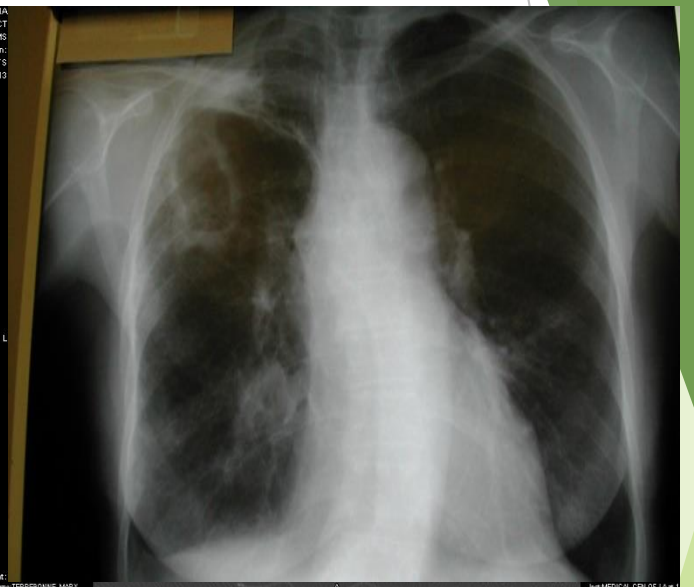
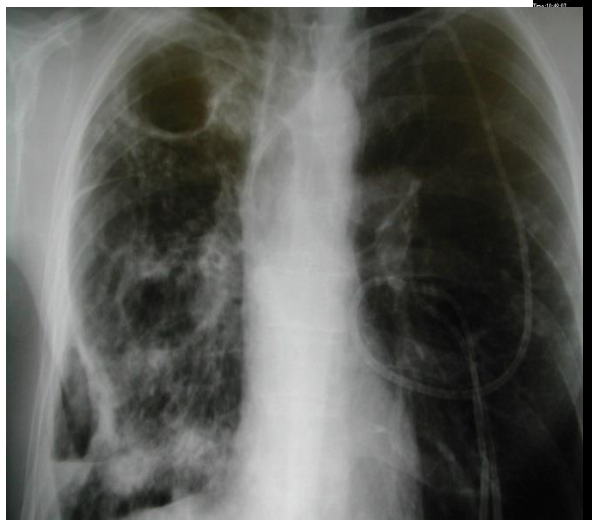
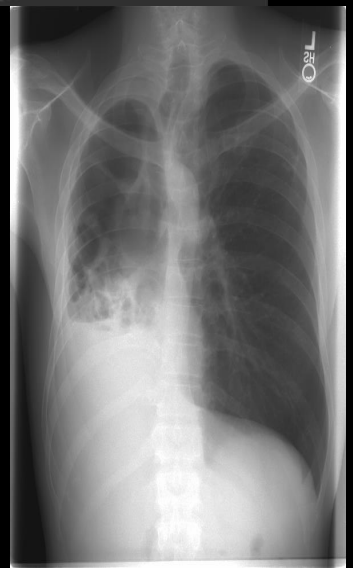
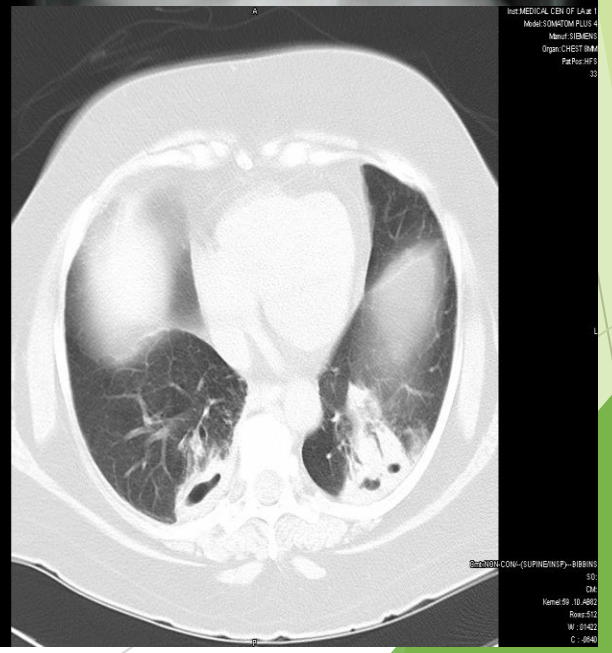








CASE 2

- Chronic cough /repeated Bronchitis/ Very active otherwise
- Diagnosis: classic **"Lady Windermere Syndrome"**

- Recommended Treatment:
  - Rifampin / Ethambutol / Azithromycin three times weekly
  - Albuterol nebulizer 2-3x daily for airway clearance
  - Rhinitis: Flonase/Antihistamine
  - GERD: H2B/PPI

- Challenges:
- Establish cause of the start of this process : Sustained symptoms : ? Chronic /fatigue ?
  - Patient complained of nausea and diarrhea on days she would take her meds preventing her from leaving the house
  - DISCUSSION

Discussion & ACTION PLAN Case 2

- Re-establish Goals and expectations
- Role of ACT
- Discuss Alternatives if no Rx
- Identify Red Flags/Danger points
- Step ladder escalation of therapy
- Modify time of Administration
- ……..

- References: ATS guidelines/Expert Opinion/ Clinical Experience

Chronic cough in a non smoker with a normal CXR

- Upper airway syndrome
- Hyperreactive airways post viral syndrome
- Cough Variant Asthma
- GERD with aspiration
- Drugs/ACE

- Early HF
- Early IPF
- CTD
- Sjogren's plus ……one more

Common CLINICAL challenges RELATED TO BACKGROUND GUIDELINE BASED ANTIMYCOBACTERIAL THERAPY

- Who to treat?
- How long to treat?
- How to convey the goals and seek patient partnership and engagement
- Establish outcome parameters
- Distinguish symptoms and radiology of NTM and underlying diseases and problems
- Which regimen is ideal?
  - Drug intolerance
  - Drug side effects
  - Drug-drug interactions
- How do patients afford their lengthy/complicated medication regimen?
- Are susceptibility data reliable?

UNDER THE CLOUD OF INCIPIENT OR OVERT Bronchiectasis: PRINCIPLES OF Management

- GOALS
  - Reduce symptoms
  - Maintain lung function
  - Prevent exacerbations
  - Watch for red alerts monitoring BSI scores etc

- TREATMENT OPTIONS
  - Antibiotic therapy
  - Airway Clearance / Mucolytics
  - Anti-inflammatory agents with caution
  - Respiratory conditioning/ EXERCISE PROGRAM
  - Surgery in selected cases (localized)

Bronchiectasis Severity Index (BSI)

Severity criteria	0 points	1 point	2 points	3 points	4 points	5 points	6 points
Age	<50		50-69	-	70-79	-	80+
BMI kg/m2	>18.5		<18.5	-	-	-	-
FEV1 % predicted	>80%	50-80%	30-49%	<30%	-	-	-
Hospital admissions in the past 2 years	No					Yes	
Exacerbation frequency in last 12 months	0-2		3 or more				
MRC dyspnea score	1-3		4	5			
Colonization status	Not colonized	Chronic colonization		*P. aeruginosa* colonization			
Radiological severity	<3 lobes involved	3 or more lobes or cystic changes					

PLUS FACED SCORE

- **Interpretation:**
- 0-4: Mild bronchiectasis
  - 1 year outcome: <2.8% mortality rate; <3.4% hospitalization rate
  - 4 year outcome: <5.3% mortality rate; <9.2% hospitalization rate
- 5-8: Moderate bronchiectasis
  - 1 year outcome: 0.8-4.8% mortality rate; 1-7.2% hospitalization rate
  - 4 year outcome: 4-11.3% mortality rate; 9.9-19.4% hospitalization rate
- 9+: Severe bronchiectasis
  - 1 year outcome: 7.6-10.5% mortality rate; 52.6% hospitalization rate
  - 4 year outcome: 9.9-29.2% mortality rate; 41.2-80.4% hospitalization rate

INFECTION, INSULT PLUS IMPAIRED HOST*

Impaired host
1. Defect in host defense**
2. Defect in clearance
3. Defect in airflow (OAD)

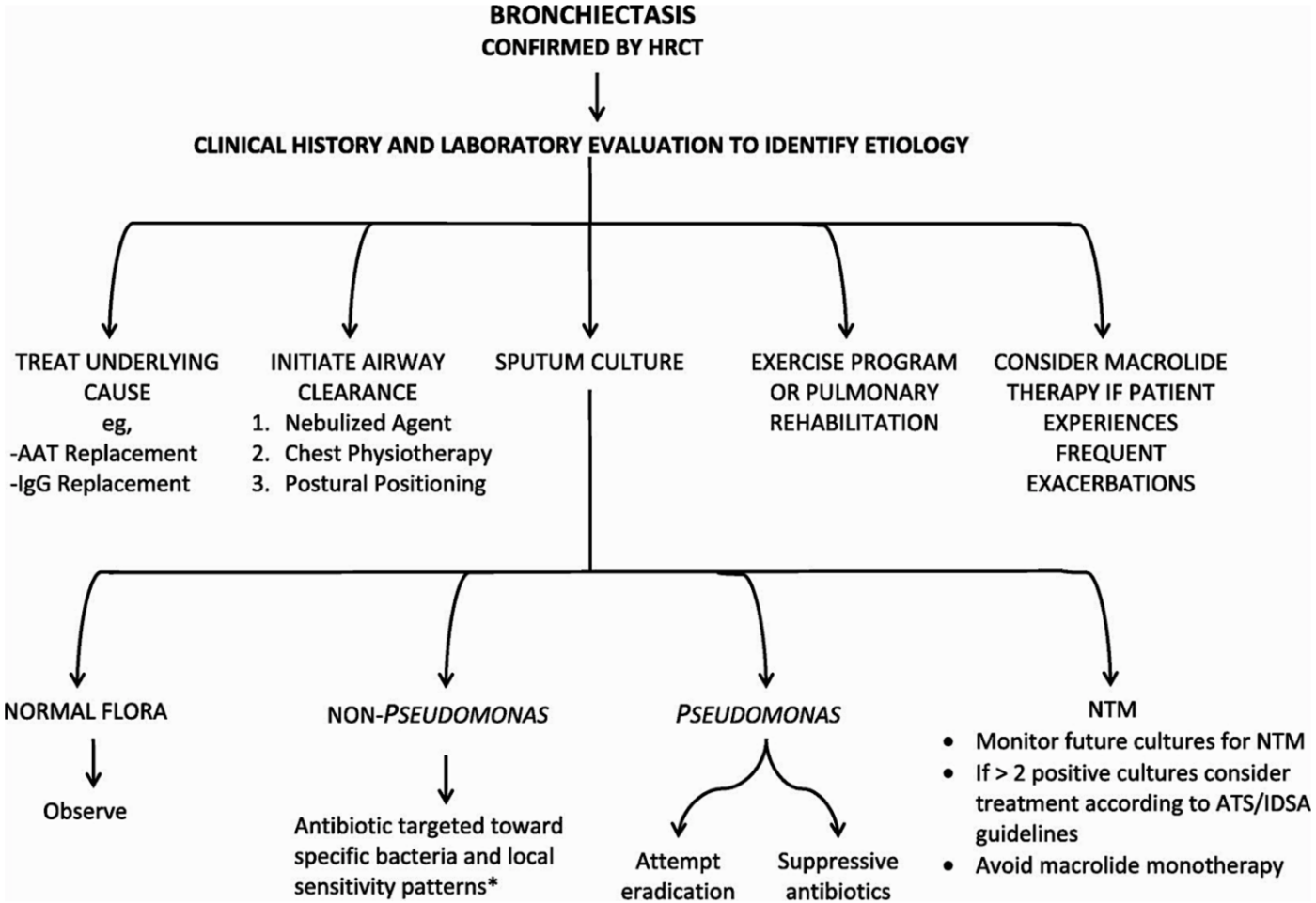
Host response
1. Unopposed Neutrophilic elastase and Neutrophilic serine proteinases activity*
2. Oxygen intermediates
3. Inflammatory cytokines

Blocked by A1AT
Could be blocked by inhibitor agents

In Non CF :
CFTR variants with single mutations
Association with Vit D deficiency

At an anatomic level
inflammation /edema/ulceration/neovascularization
Irreversible bronchiolar dilatation and tissue destruction
At the cytokine level
Increased mucus secretions
Inhibition of mucociliary clearance

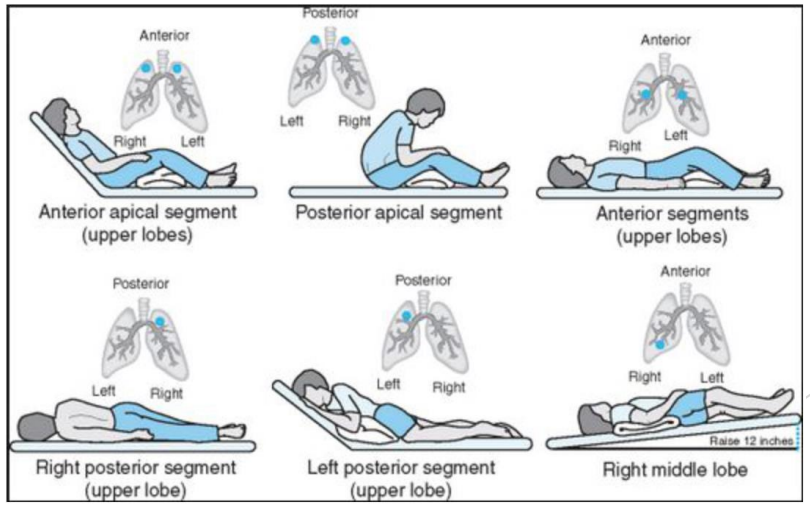
Management of non-CF Bronchiectasis



Am J Respir Crit Care Med 2013 188, 647-656.

Airway clearance

- Options
  - Traditional CPT/postural drainage
  - Oscillatory positive expiratory pressure (PEP) (i.e. Aerobika, Acapella)
  - High frequency chest wall oscillation (The VEST)
  - Autogenic drainage
  - Active cycle breathing with huff coughs



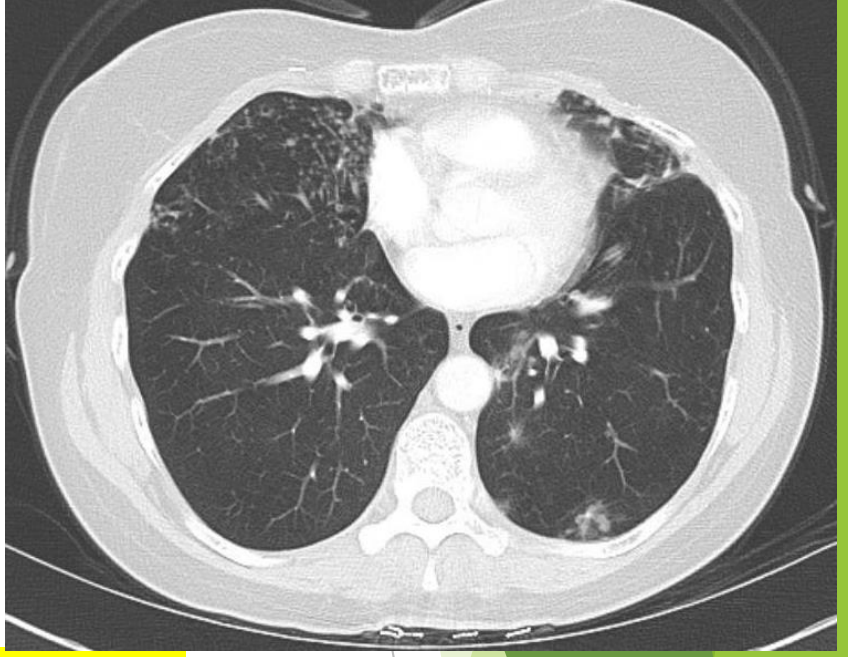
Airway Clearance – Inhaled Therapy

- Mucolytic agents and Airway Hydration:
  - **Nebulized hypertonic saline**
    - Recommended for CF
    - Cochrane review: No firm conclusions for use in non-CF bronchiectasis; unlikely to have benefit over isotonic saline in patients with milder disease.
  - **Nebulized Mannitol**: available evidence does not suggest benefit (CI with underlying asthma)
  - **Acetylcysteine:** no well-designed studies in non-CF (no clear benefit in CF even)
  - **Dornase alpha (DNAase):** NOT effective in non-CF, potentially harmful
- Systemic hydration: no evidence that hydration beyond euvolemia provides benefit

BRONCHIECTASIS

. The paradox of Cough In NTM Bronchiectasis
. Is cough good or a bad ?
ACT:
Efficacy
. Indications
. Contra-indications
. Sustained Adherence

Case #3



- 57 yo Caucasian F ,never smoker with **nonproductive cough** intermittently for “a few years” – worse in Spring/Fall. Had episode of scant **hemoptysis**, spontaneously resolved, but prompted bronchoscopy for further evaluation. Cough somewhat more productive of clear/white sputum since bronch. No shortness of breath. Some postnasal drip. No fever, chills, night sweats, weight loss. No established pulm history but recalls repeated episodes of bronchitis in early adulthood. Hobbies : gardener

Case #3

- **Pulmonary Function Test**
  - FEV1/FVC = 72
  - FEV1 = 2.06 (80%)
  - FEF25-75% = 1.46 (60%)
  - TLC = 104%, RV = 123%
  - DLCO = 69%
  - **No obstruction, gas trapping with mildly reduced DLCO.**

- **Microbiology:** BAL AFB smear 1+, Culture = MAC; all other micro and cytology negative NOTE : Dx by Bronch

CASE # 3

- Recommended Treatment by Specialist :
  - Rifabutin / Ethambutol / Azithromycin THREE times weekly

- Challenges:
  - Adverse rxn to Rifabutin: High fever, N/V/D, 5lb weight loss, arthralgia/myalgias, debilitating fatigue

Discussion

Discussion & Action Plan Case 3

- Re-evaluate Goals and Expectations
- Importance of quantification of infection/colony count
- Sputum vs Bronchoscopy
- Significance of hx of hemoptysis
- Consideration of RBT vs RIF
- Daily vs Thrice weekly
- No RIF Regimen
- Addition of IV aminoglycoside
- Addition of Inhaled AG
- Any other considerations

- References :
- PICORI Trial

Case 4

- 60 year old woman with Hx Severe COPD /chronic cough and frequent mild hemoptysis
- Sputum cultures x 4 all positive for moderate growth of Mycobacterium Avium Complex

Case 4 continued

- Started treatment with Daily GBT with IV Amikacin 3 months ago
- Tolerating Rx well
- Being treated for COPD with ICS /LAMA /LABA and B2 prn
- Rx with BS antibiotics and steroid rescue when having acute exacerbation
- To date doing well

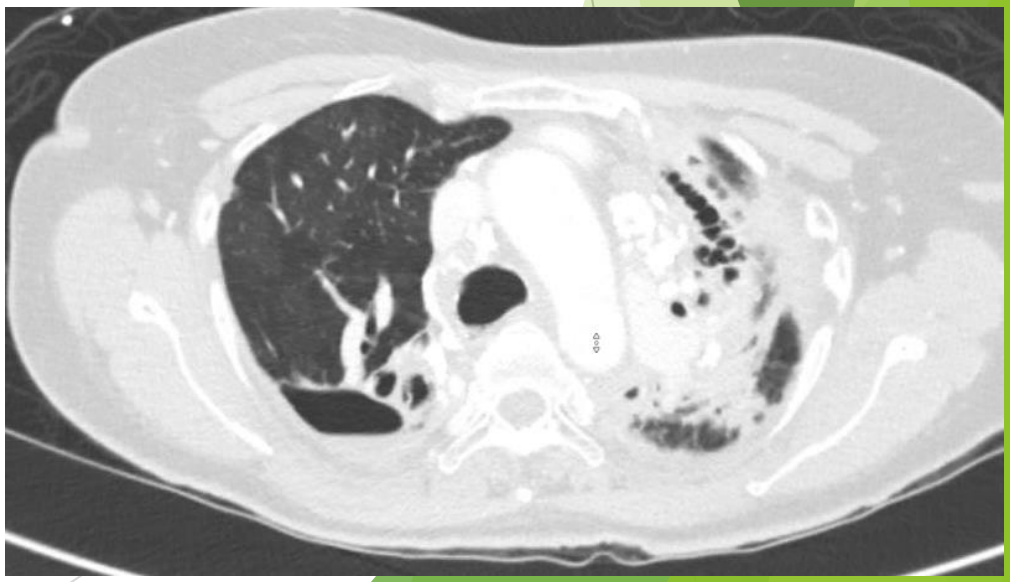
- Discussion

Discussion and Action Plan Case 4

- Stay the course
- Steroids use
- USE of ICS ???
- Hemoptysis “ Red flag ”
- Duration of IV AG
- Role of inhaled later
- Surgery ?
- Any other considerations

CASE # 5

- 63 yo F with progressive **shortness of breath**, **fatigue** and unintentional **weight loss** of 15 lbs. Also complains of intermittent nonproductive cough.
- PMHx: Sarcoidosis (stage V), Pneumothorax, Chronic hypoxemic resp failure, DM, pancreatic& adrenal insufficiency, HTN, Pulm MAC (tx 1990s)
- Social Hx: 10pk/yrs (quit 30yrs ago)
- Meds: Methotrexate, Hydrocortisone, Insulin



CASE # 5

- **Pulmonary Function Test**
  - FEV1/FVC = .53
  - FEV1 = 0.55 (26%)
  - FEF25-75% = 0.26 (13%)
  - TLC = 59%, RV = 91%
  - DLCO = 19%
  - **Very severe obstruction with moderate restrictive lung disease and severely reduced DLCO.**
- **Microbiology**
  - 11/2013: Smear (-), Group IV RGM
  - 7/2017: Smear (-), M. abscessus
  - 8/2017: Smear 1+, MAC
  - 9/2/17: Smear 2+, M. abscessus (1 CFU) + ESBL Klebsiella pneumonia
  - 9/3/17: Smear 2+, M. abscessus (<10 CFU)
  - 9/23/17: Smear (-), negative
  - 5/2018: Smear 2+, M. abscessus (10-50 CFU)

Case # 5

- DIAGNOSIS: **Fibrocavitary disease** due to MAC + M. Abscessus

- Treatment Course & Challenges
  - IV Ertapenem for ESBL Kleb
  - Started on **DAILY Rifampin / Ethambutol / Azithromycin + IV Amikacin/**
  - IV Amikacin discontinued after 2 weeks
  - REA held after 4 months
- Challenges
  - Cellulitis d/t PICC line
  - Weight loss - down 25lbs from baseline
  - Tinnitus; Vision changes –
  - Cholecystitis req surgical intervention

Discussion and Action Items Case 5

-
- ?????
- Limited options/
- Second line drugs ? /
- Suppressive Rx ?
- Addressing Fatigue
- Addressing weight loss

Factors contributing
to the poor response to therapy

included

1. cavitary disease,
2. previous treatment for MAC lung disease,
3 and a history of
chronic obstructive lung disease or bronchiectasis
And 4
macrolide resistance,

Pulmonary Rehab / Exercise

- Eight weeks of exercise (30min moderate intensity, 3x per wk.) improves exercise capacity, dyspnea, fatigue (Newall et al 2008, Mandal et al 2012, Lee et al 2014, Lee et al 2017)
- When combined with airway clearance therapy, improvement in cough-related quality of life is achieved (Mandal et al 2002).
- Increased time to first exacerbation and reduces number of exacerbations at 12 months.

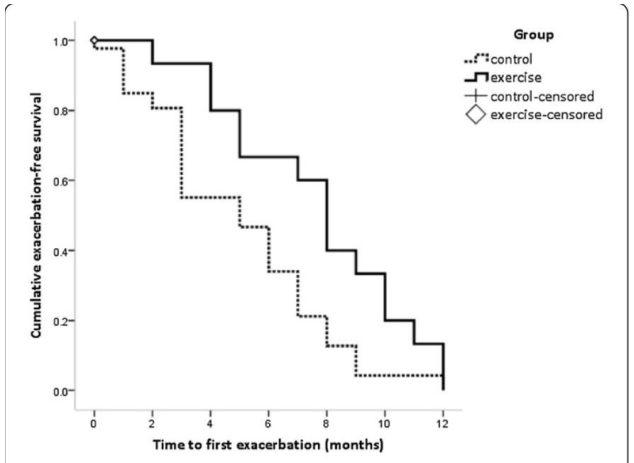


Figure 4 Time to first exacerbation, p = 0.047.

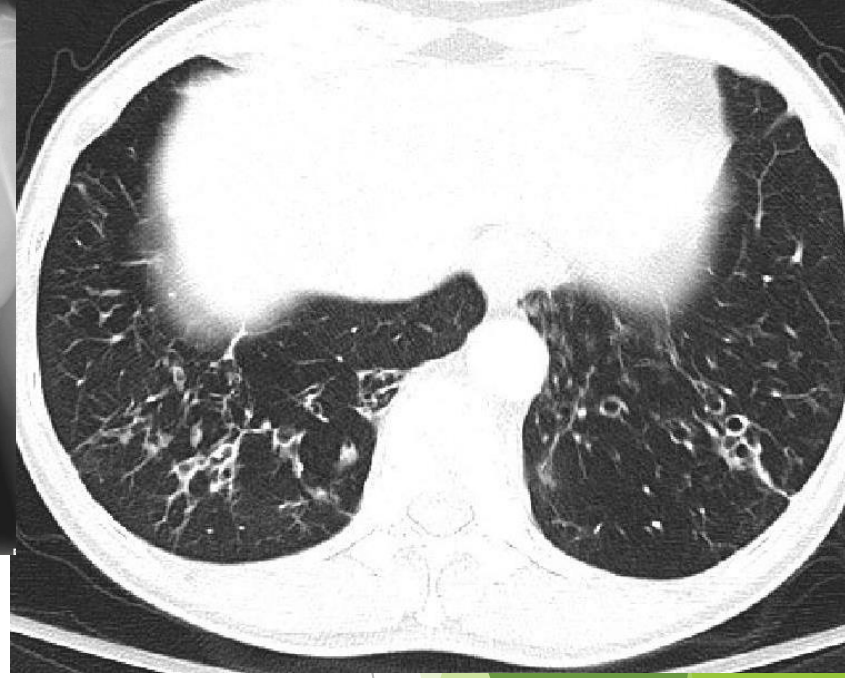
Table 3 Number of exacerbations over 12 months (n = 55)

	Control n = 25	Exercise n = 30	p value
Exacerbations	2 (1 – 3)	1 (0 – 2)	0.012
Exacerbations requiring antibiotics	2 (0 – 4)	1 (0 – 2)	0.061
Exacerbation days	10 (2 – 13)	7 (3 – 11)	0.23
Exacerbation days with antibiotics	11 (2 – 15)	7 (2 – 13)	0.36

Data are median (IQR), p value represents difference between groups.

Respiratory Research 2014, 15:44

Case # 6



- CC: intermittent cough/fever
- 64 yo Asian M presents as a referral for history of NTM & Pseudomonas infection with progressive bronchiectasis. **Intermittent cough** and **fever**. Unintentional **weight loss** of 5 lbs.
- PMHx: **Documented Immunoglobulin deficiency ;** Bronchiectasis (Dx 2002); Multiple NTMs in the past ; Pulmonary MAC + M. Kansasii (s/p tx x 14 mos 2014)
- Social Hx: 5pk/yrs (quit 4yrs ago)
- Meds: monthly IVIG

CASE # 6

- **Pulmonary Function Test:**
  - FEV1/FVC = 64
  - FEV1 = 2.60 (93%)
  - TLC = 116%, RV = 116%
  - DLCO = 103%
  - **Mild obstruction.**
- **Microbiology: Earlier : MAC**
  - 11/2014 x 2: smear 2+; M. kansasii
  - 5/2017 (BAL): 2+; M. abscessus
  - 9/2017 x 2: smear (-); Group IV RGM
  - 11/2017 = smear (-); M. abscessus (>50 CFU)
  - 12/2017 = smear (-); M. abscessus (>50 CFU)

CASE # 6

- DIAGNOSIS: Nodular bronchiectatic disease due to M. abscessus (prior MAC, m. kansasii)

- Treatment Course:
  - 3 month course of DAILY IV Amikacin / Imipenem / Azithromycin
  - ACT: Vest/Acapella/CPT
  - Monthly IVIG
  - To begin NEW regimen: Clofazimine / Linezolid / Azithromycin (did not tolerate Linezolid)

Discussion /Action item Case 6

- Challenges:
  - **Importance and types of immunoglobulin deficiencies**
  - **Variable + DELAYED** identification & susceptibility reporting
  - Intensive regimen requiring IV therapy
  - Polymicrobial infections/ “NTM Migration”
  - **Recurrence vs relapse vs reinfection???**
  - **Action item : Modified treatment / Burden of disease ? What next ?**

Looks like a duck, walks like a duck, but may not be a duck always

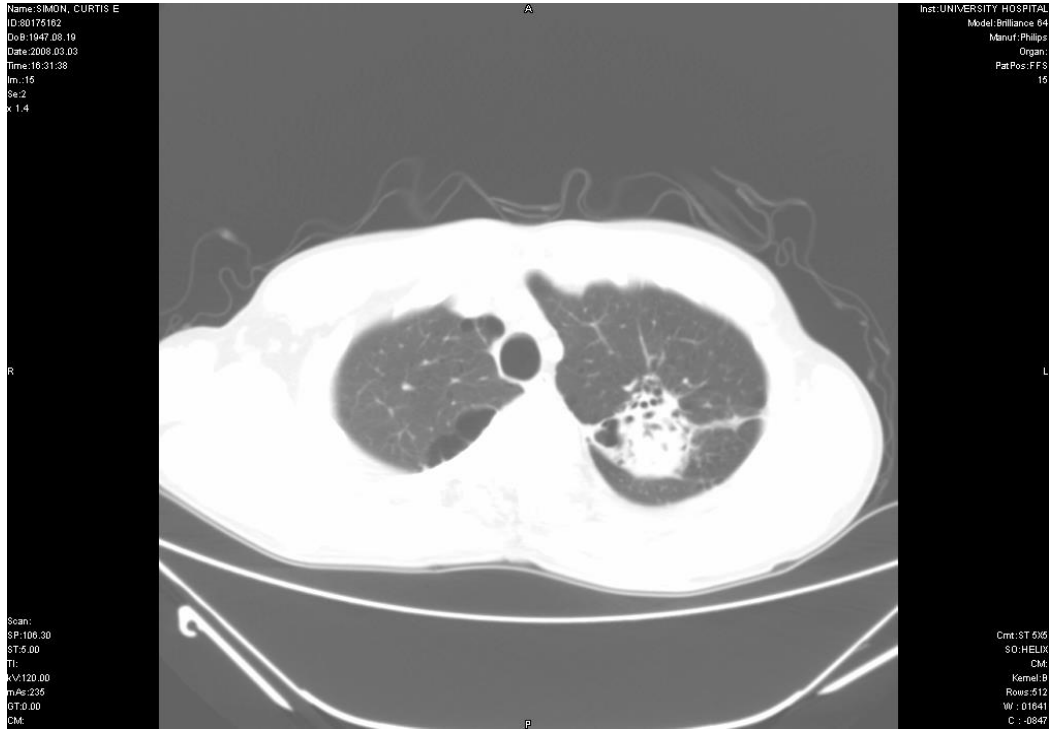
TB? RIPE

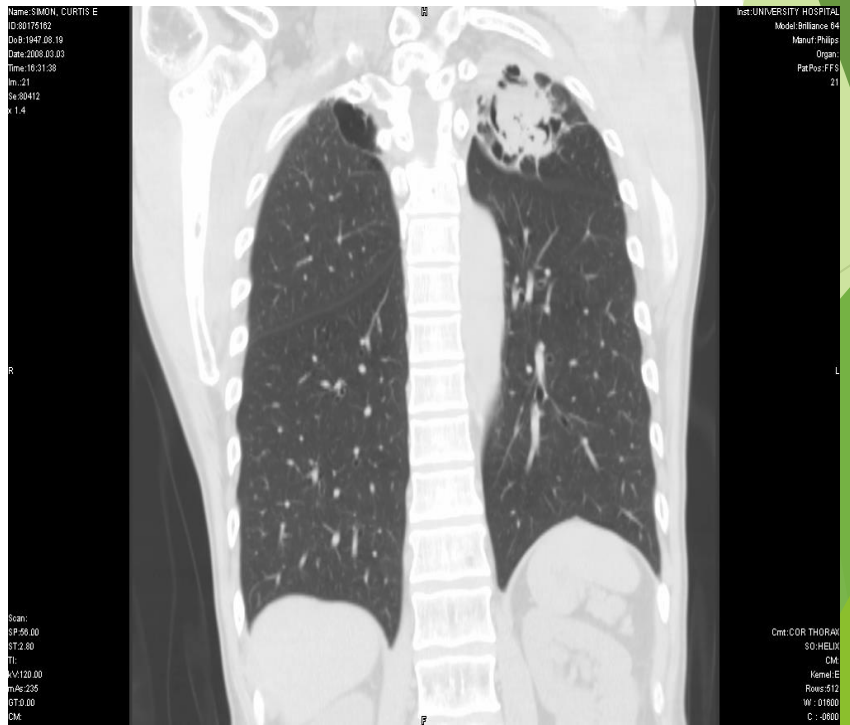
MK

MAC

A

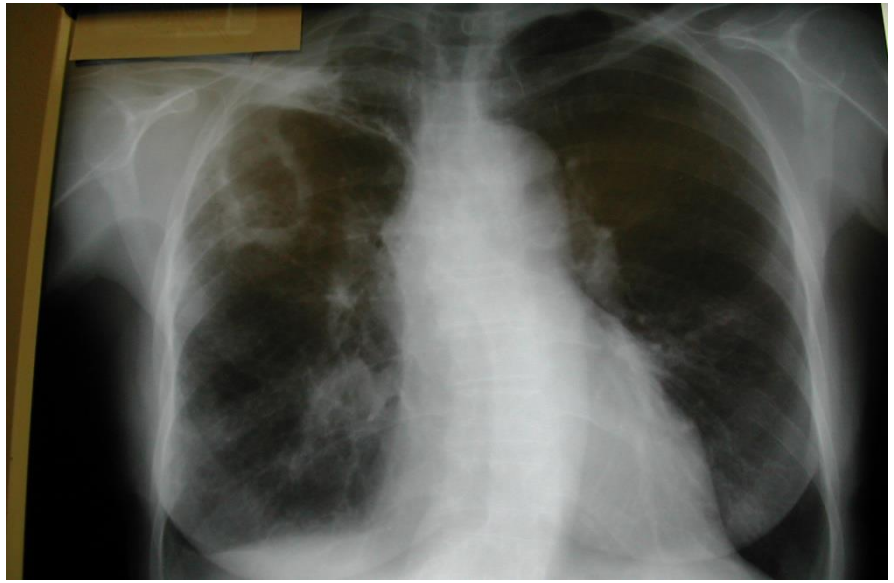
MAN !! The Mycobacterial **F**reeway





Case 7

A 76- year old Caucasian woman, smoker, with past history of TB, treated completely in the 1960's, was seen with chronic cough, fatigue and minimal shortness of breath. Pulmonary function tests revealed moderate obstructive airways dysfunction. Sputum tests revealed moderate growth of *Mycobacterium avium* complex on repeated examinations Offered GBT with IV amikacin ; Patient refused and wanted minimal treatment and was placed on daily treatment with clarithromycin and ethambutol with bronchodilators.



Discussion /Action item Case 7

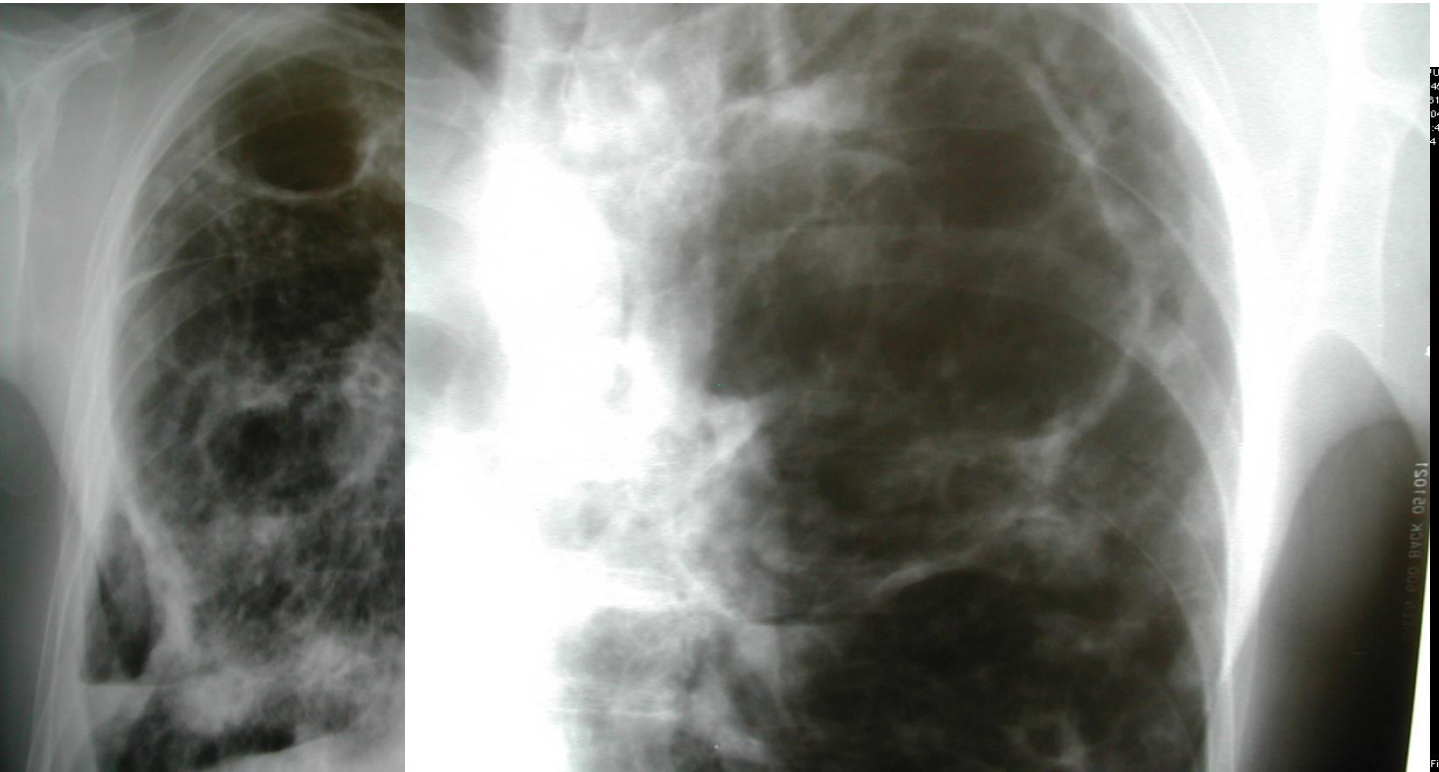
- Approach Right or wrong?
- Cavitary disease and GBT
- Role of Suppressive therapy and pros and cons
- ……..

Case 7 follow up

- She remained stable on this regimen for 4 years of her follow up without any acute exacerbations of NTM related issues. Serial sputum cultures intermittently revealed light growth of *Mycobacterium avium* complex ;She passed away at a later date due to Respiratory failure/COPD

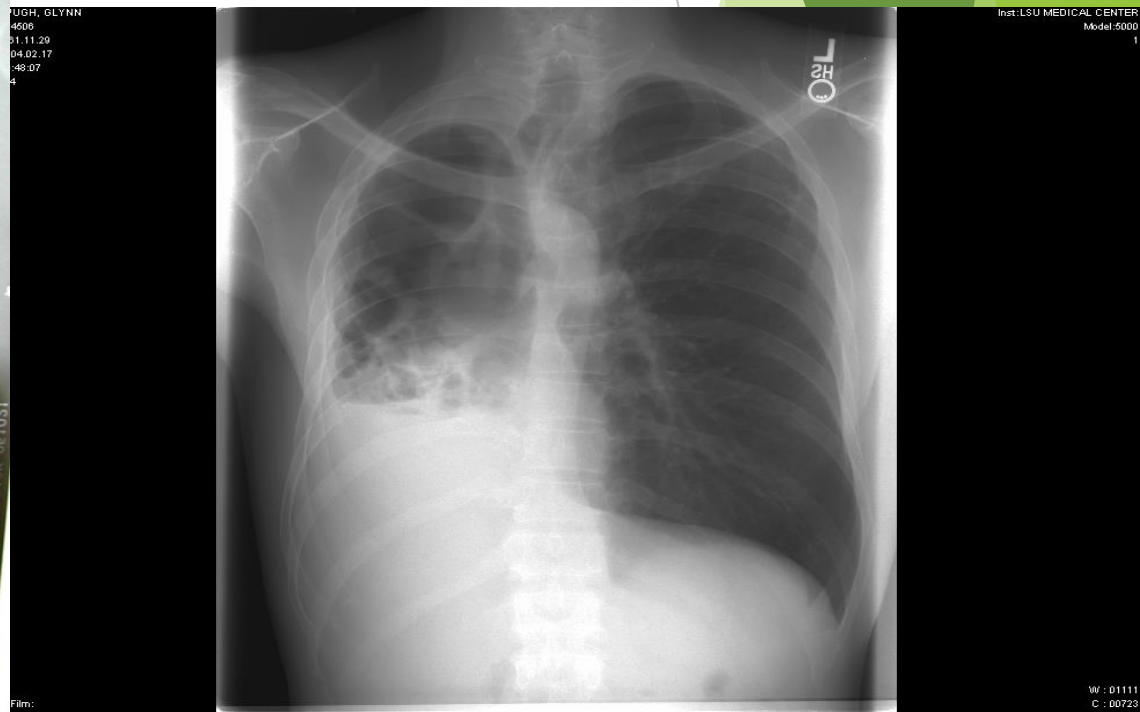
Case 8

A 50-year old man with severe COPD and bronchiectasis was on long term treatment for *Mycobacterium avium* complex pulmonary disease (MAC-PD) initially and later for macrolide-resistant MAC (MRMAC). He was admitted in moderately severe respiratory distress with fever and increasing cough. In addition to the multiple drugs used for the treatment of this patient though the course of his illness, therapeutic trials of thalidomide, interferon gamma and high dose mefloquine were given. Due to progressive bilateral disease and poor pulmonary function, surgery was not considered. (The patient later died of respiratory failure and overwhelming infection.



Case 9

A 42-year old man with history of treated TB in 1980 developed progressive fibro-cavitary MAC infection in 1993. His treatment with ethambutol, rifabutin and clarithromycin was erratic due to non-adherence. No IV or inhaled aminoglycoside was He was admitted to the hospital with increasing cough, night sweats and a ten pound weight loss. No culture and sensitivity data were available. With the history of erratic treatment, His pulmonary function tests revealed a FEV1 of 1.4 L and a split perfusion pulmonary scan showed one percent perfusion of the right lung and 99% of blood flow to the left lung. presumed macrolide resistance and unilateral fibro-cavitary right sided disease, he was evaluated for surgical excision and pneumonectomy. The patient had a complicated operative and perioperative course and died of respiratory failure after a month long stay in the ICU.



SPECIFIC NTM management limitations

- Methods of identification (accuracy, timeliness, availability)
- Not a reportable disease
- Mycobacterial evasion / inefficient treatment options:
  - **Intrinsic** resistance
    - **Macrophage** barrier (intracellular) to Rx
    - **Hydrophobicity** of NTM with drugs being hydrophilic in nature(e.g. more hydrophobic drugs - rifabutin as opposed to rifampin)
    - **Cell wall associated permeability** barrier (e.g. *M. Chelonei ;* hence ethambutol in combination a better choice)
    - **Caseum growth** & nonreplicating state of persistence
    - **Mucus growth** (e.g. M. abscessus undergo phenotypic switch in mucus niche)
    - **Biofilm growth** (NTM in biofilms are ten times less susceptible)
  - Poor correlation between in vitro and therapeutic efficacy
  - Multi strain sero-variance (e.g. AIDS patients; subjects with nodular/bronchiectatic disease pattern AND NTM migration)
  - **Adaptive** resistance due to continual exposure

The SMART Microbe
Why survival and immune evasion?*

- Biofilm formation, Cell wall characteristics blocking vacuolar acidification
- Inhibition of phagosome-lysosome fusion
- Anaerobic intracellular environment
- Induction of NTM related genes that enhance replication
- Inhibition of the host macrophage function and lymphocyte proliferation

The GPL* difference : MICROBE

- Produced by NTM and not MTB
- Impacts colony morphology
- Smooth variants with nsGPL are cleared but rough variants without nsGPL evolve and persists
- The severity and persistence of disease depends upon the transition between smooth and rough variants .The variation and presence or absence of nsGPL and ssGPL dictates intracellular survival
- Serovariable oligosaccharides contribute to species specific pathogenesis.
- This coupled with biofilm formation dictates Immune evasion and thus

survival of NTM

*The Gycopeptolipids

The WEAK HOST
Why survival and immune evasion? 2

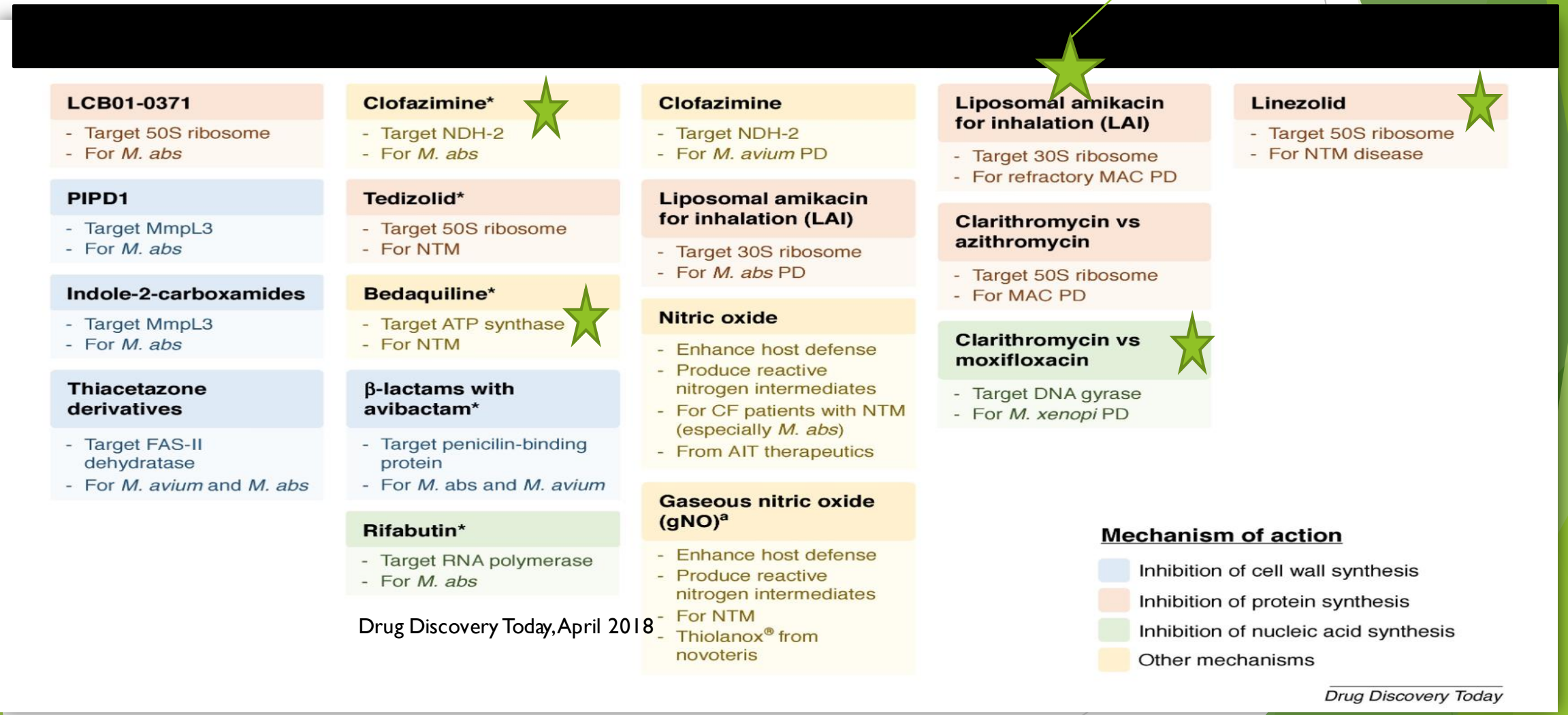
* Induction of macrophage apoptosis by down regulation of Bcl-2 gene

* Absence of or sluggishness of the T helper lymphocyte or NK innate immunity

* Defective clearance *

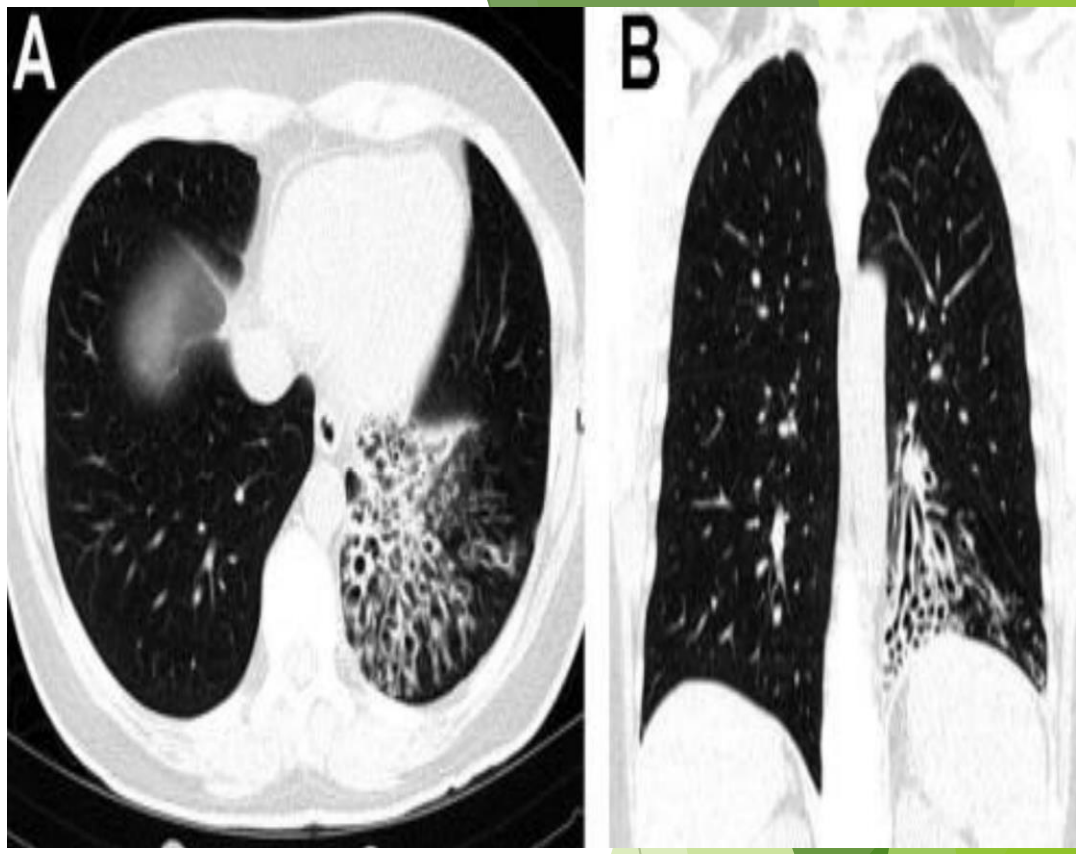
treatment options GBT and/ or

THE NEW KID ON THE BLOCK
DRUG –DELIVERY –ACTION
DATA SUPPORT
PRECAUTIONS



Drug Discovery Today, April 2018

Surgery



- When to consider:
  - Localized disease and failure of treatment
  - Recurrent hemoptysis
- Should be done in specialized centers.
- 171 patients (observational, Univ of Colorado)
  - 212 surgical procedures with 0% mortality
  - Overall complication rate of 8.9% with persistent air leak most common (5.6%)
- 790 Chinese patients followed for mean of 4 yrs., 1.1% mortality at 30d, 75% asymptomatic/improved
- 134 USA patients followed mean 6 yrs., 2% mortality, 89% improved

Ann Thorac Surg 2012;93:1033–1039

Other Therapies

- **Role of LABA/LAMA/ICS ?**
- **NSAIDs:** insufficient data to support use
- **Nutritional supplementation:** requires further study; randomized 30 well-nourished patients in 12wk pulm rehab to high-protein (hydroxy-beta-methyl-butyrate) supplement, this group showed improvement in some parameters of strength/physical function (QOL-B)
- **Statins:** preliminary data do not support a role unless patient has another indication for therapy
- **Immunizations:** limited guidelines, but at least pneumococcal + influenza
- **Sinus Surgery:** 161 patients with rhinosinusitis, nonrandomized endoscopic vs meds alone, improved symptoms, numerical scoring & reduced exacerbations in surgery group BUT WHEN?

Multidisciplinary management approach

- **Specific therapy /phasic protocol** ID/PULM/INFUSION CENTERS
  - Surveillance
  - Suppressive treatment
  - Regular GBT
  - Inhaled AG
  - Regular with Inhaled
  - Intensive with inhaled
  - Intensive with IV
  - Under evaluation

- **Underlying non-pulmonary/pulmonary disease**
  - Autoimmune: Co-mgmt with Immunologist/ Rheumatologist (RGM)
  - Chronic rhinitis / sinusitis: Referral to ENT (MAC)
  - GERD/Esophageal motility d/o: Referral to GI (MG MA)
  - Bronchiectasis/ IPF/COPD/Sarcoidosis/TB/Lung Cancer Pulm (ALL)

Multidisciplinary management approach

- **Laboratory**
  - Speciation / colony count /Susceptibility testing
- **Nutritional support** **Watch weight loss**
- **Respiratory therapy**
  - Education/Goals/Expectation/Practical implementation
  - Airway clearance techniques (Nebulizer / PEP devices / Percussive vests / Postural drainage)
- **Psychological support**
  - Patient outreach /Caregiver support
  - Support groups

Multi-faceted Management principles CHECKLIST

- Immune status & Rx thereof
- Triggers and Associated Confounders : Avoid Steroids /ICS if possible
- Environmental /"Eco check" Yes and No but never hurts
- Contribution of underlying disease and sift out symptoms & causes related to these co morbid states/secondary infection : ABCDEFG
- Evaluation of degree of infection and specific treatment plan including cautious waiting
- Overarching : BRONCHIECTASIS & Management thereof recognizing that non-productive cough is the most difficult to manage.
- Watch for progression and red alert danger signs (Increasing Fatigue/ Respiratory Cachexia Weight loss/Hemoptysis)

In summary…

- Pulmonary disease due to NTM is increasing in prevalence worldwide, particularly among the elderly
- NTM is ubiquitous in the environment with important geographic predilections or “hot spots”
- For NTM disease to progress it requires a complex interplay between host susceptibility, inoculum size/frequency and mycobacterial evasion techniques
- Diagnosis of NTM disease is complex and requires communication and coordination between pulmonologists/ID specialists, radiologists and microbiologists / Auxiliary teams and PATIENTS with set goals and expectations.
- Awareness of “ Red flag Alert Points” (related to disease , underlying conditions and therapy)
- NTM causes various forms of pulmonary disease (i.e. nodular, bronchiectatic, cavitary) inn different settings and requiring different management approaches
- Management of co-morbid conditions and associated pulmonary diagnosis and contributing/associated TRIGGERS (Immune state , naso-sinusitis /GERD/Aspiration/Environmental /Constitutional)
- Treatment options remains limited and are encumbered by long, ill-tolerated multi-drug regimens. Engagement of patients/caregivers/ Goals of Rx / Limitations/ Outcomes well understood
- **THUS : NEED FOR COORDINATED EFFORTS/ REGISTRIES* / STUDIES/PARTNERSHIPS**
- **Thank you. Juzar Ali with *NL/JA prgm**