An Evolving Pulmonary Diseases Troika

1. THE TB, NON-TB MYCOBACTERIAL PULMONARY DISEASE & BRONCHIECTASIS CROSSROADS

2. FROM CLINICAL CARE TO PROGRAMATIC DEVLOPMENT & RESEARCH COLLABORATION

OUR* *JOURNEY THROUGH THE YEARS*

***Patient, Clinician/Physician /HCP, Scientist, Researcher, Industry, HealthCare systems**

Juzar Ali, MD, FRCP(C), FCCP

LSU Alumni Klein Professor of Medicine
Section of Pulmonary/Critical Care at LSU Health Sciences Center , LSU School of Medicine
Director LSUHSC-Wetmore Mycobacterial Disease / NTM- Bronchiectasis Program
Office of Public Health /Region 1 & 2
University Medical Center,
New Orleans, Louisiana

LSU Health NEW ORLEANS
School of Medicine
Department of Medicine
Section of Pulmonary/Critical Care & Allergy/Immunology

Objectives Part 1

- At the end of this presentation , the participants will be able to

- ***1. Recap the history of NTM-Pulm disease as clinicians observed it over the years through the prism of TB/Mycobacterial Disease/Bronchiectasis pathophysiology***
- ***2. Understand the present knowledge base on management of NTM –Pulm disease as per clinical guidelines and expert opinions***
- ***3. Be aware of the new therapeutic options coming down the pike***
- ***4. Appreciate the multi-disciplinary and multifaceted approaches /challenges/opportunities in its management***

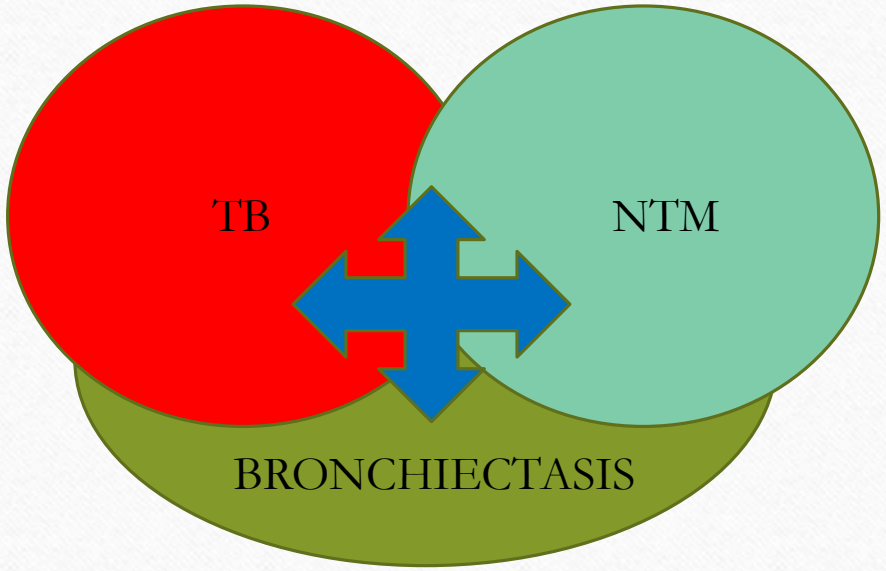
Objectives Part 2

- At the end of the presentation , the participants will

- Know about the journey of this Troika of Diseases (TB /NTM-Bronchiectasis) from Awareness and Recognition to Disease Management
- Understand this evolution from **Clinical Care to Programmatic Development**
- Appreciate the journey moving forward escalating to **Research and Multi-system Care Coordination and Collaboration**

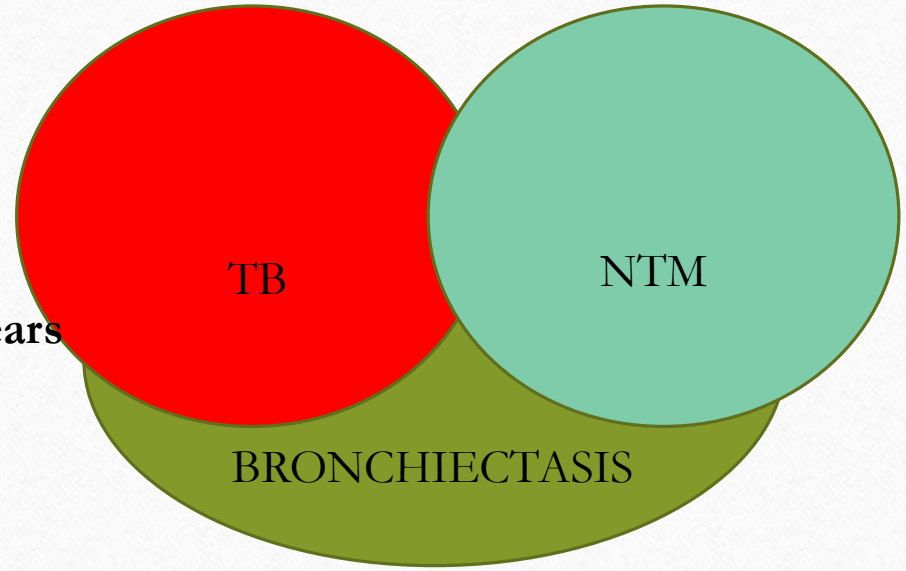
TRIOKA OF DISEASE PROCESSES :

"THE OTHER TB & THE OTHER COPD"



TROIKA : THE COMMONALITY IN CLINICAL IDENTITY & MGM

Chronic Cough
Chronic Resp Symptoms
Prolonged Debility
Enhanced Frailty
Increased Disability adj life years
Radiographic Similarity
Management & Rx Overlap

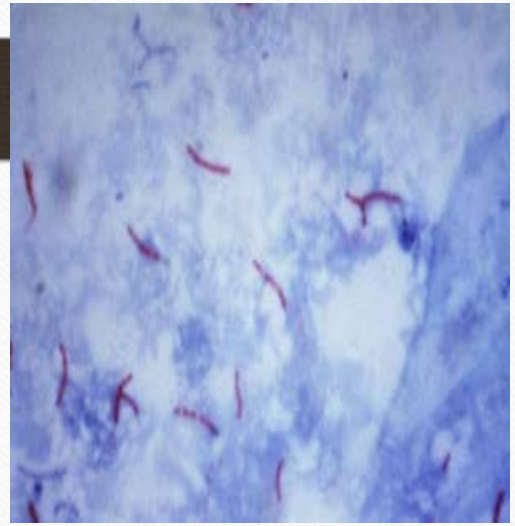


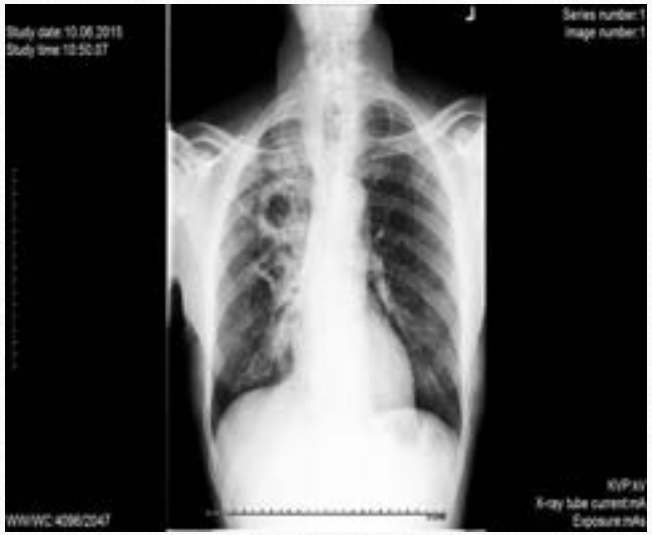
“To Be or Not To Be” and it is not Hamlet

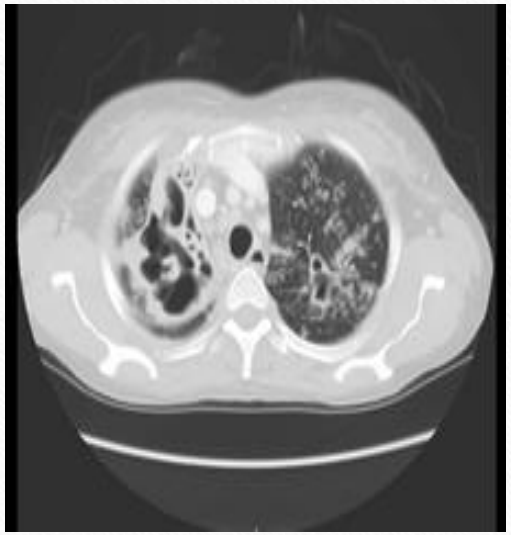
Risk, Signs, Symptoms, IGRA/TST?*:

Micro (Smear, NAAT, Culture, Probe, Final Culture)
Images Tissue Dx

Looks like a duck, walks like a duck, must be…







...But is it?

“The TB Wanabees”
Post TB Lung diseas

*Note Variable Performance in LTBI, Active TB, NTM

Public Health Image Library: ID#5789 Ziehl-Neelsen stain

For TB

General “Standard”: No follow up after culture conversion and completion of anti-TB Rx

Advances in microbiological treatment notwithstanding beyond RIPE

YET

“For many persons with tuberculosis, a microbiological cure is the beginning, not the end of their illness.”

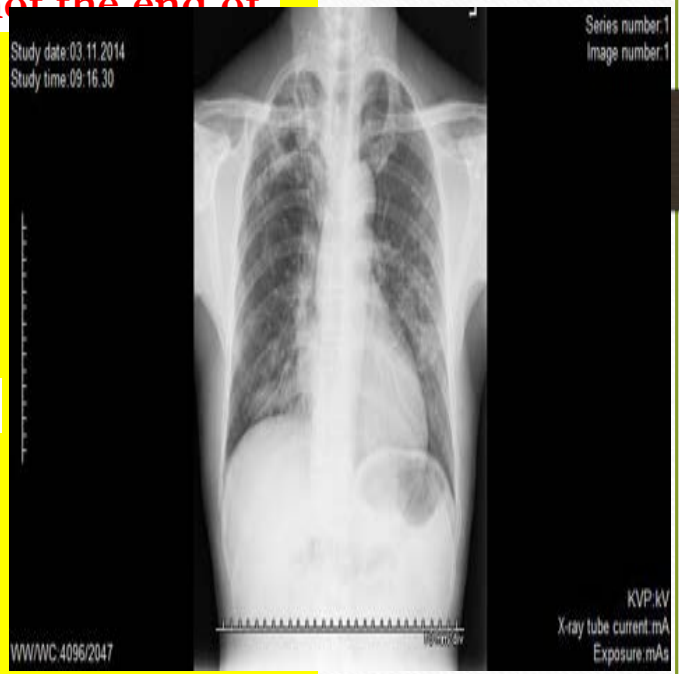
PLUS

TB Care cannot be given in isolation

THUS

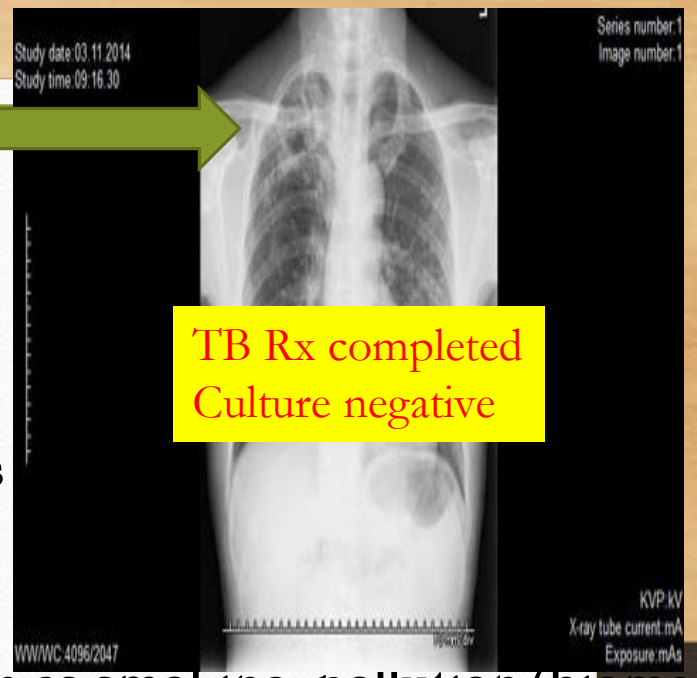
NEED FOR PRIMARY /SPECIALTY CARE COORDINATION POST TB TX COMPLETION

The increasing awareness of Post-TB Lung Disease (PTLD)



Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, Drewyer G, Weis SE. Pulmonary impairment after tuberculosis. Chest. 2007 Jun;131(6):1817-24. doi: 10.1378/chest.06-2949. Epub 2007 Mar 30. PMID: 17400690.

What is PTLD?



-a heterogeneous lung disease
including **BRONCHIECTASIS & BRONCHIECTASIS SICCA**

-airway, parenchymal, pleural, and pulmonary vascular complications

-variable symptoms

-frequently complicated by multiple other respiratory exposures (such as smoking, pollution/biomass, occupational or drug exposures)

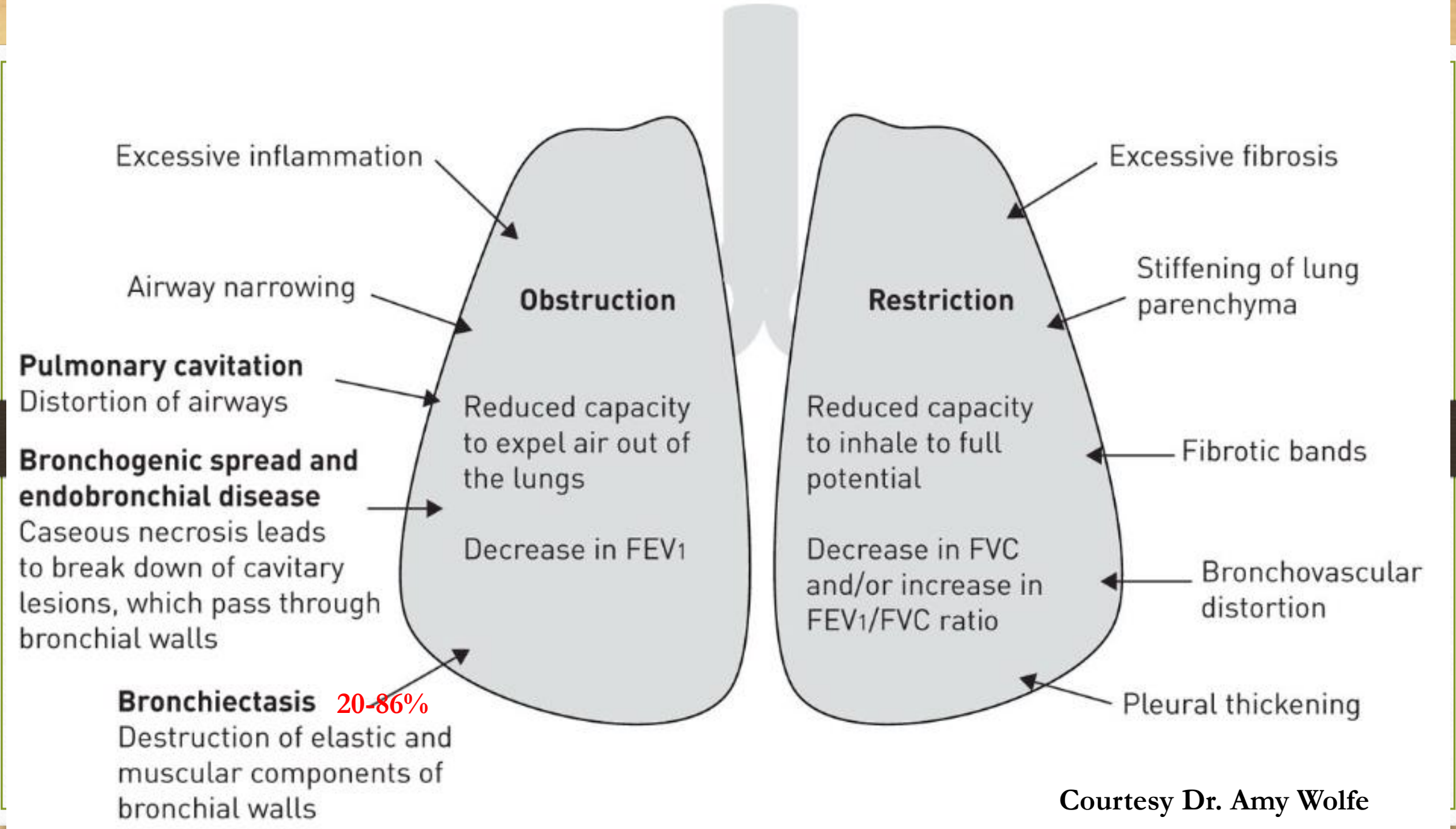
-can increase risk for secondary infections **(NTM, fungal, pseudomonas, etc)**

-shortened life expectancy and increased disability

-increased risk of recurrent **TB / TB NTM Co infection and its co-morbidities**

This lead to start of the ELD –NTM –BE Clinic 2010 at ILH and 2017 at UMC

Courtesy Dr. Amy Wolfe



Courtesy Dr. Amy Wolfe

Tuberculosis and lung damage: from epidemiology to pathophysiology Shruthi Ravimohan, Hardy Kornfeld, Drew Weissman, Gregory P. Bisson European Respiratory Review Mar 2018, 27 (147) 170077; **DOI:** 10.1183/16000617.0077-2017

OPH Region 1 /NOLA Wetmore TB Center

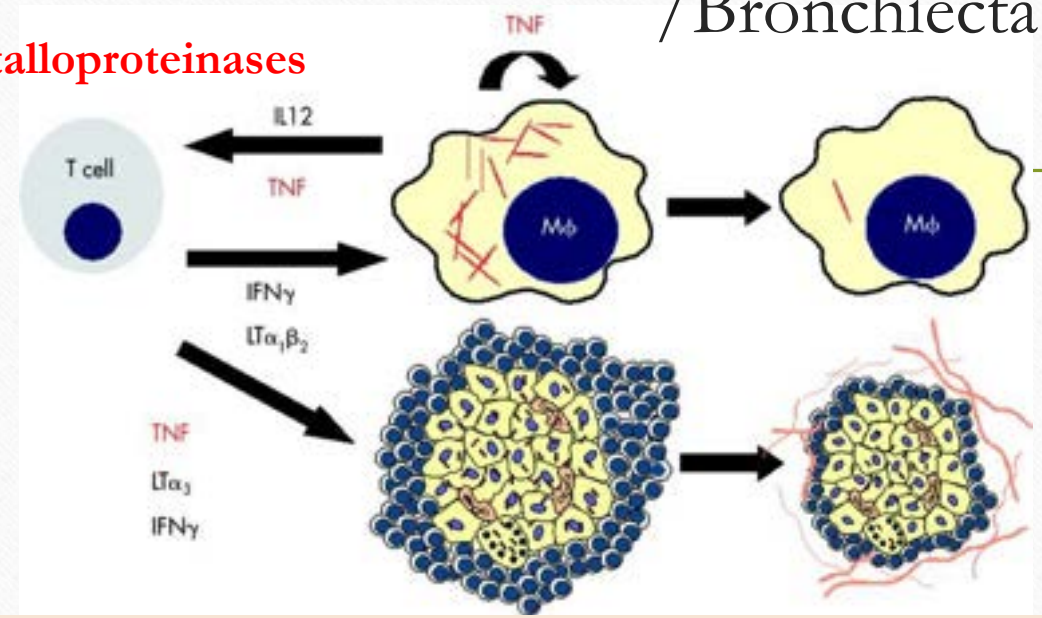
- TB Management with standard of Care pathways
- Public Health Coordination
- Establish on Site Focused Primary Care Venue with specific Goals and pathways for referrals and follow up during TB mgm and post TB management (Immediate Bridge Care/Education/Referrals /Follow up/Other Navigational and Access to Care Help /Medication and DME Assistance
- Establish and develop a Research Consortium for Clinical and other studies and substrate or publications

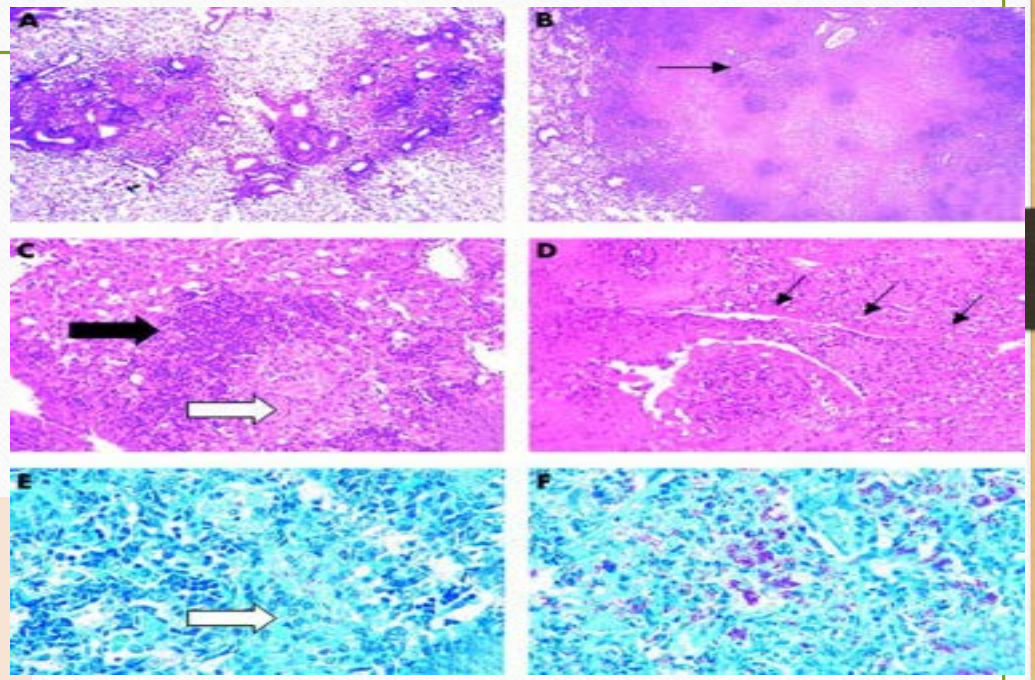
The Cytokine soup

The Pathologic Vortex of the Troika

Th 1 cascade
Th17
IL-12
Matrix Metalloproteinases

Macrophage to Inflammation to Granuloma* to Necrosis /Bronchiectasis to Fibrosis



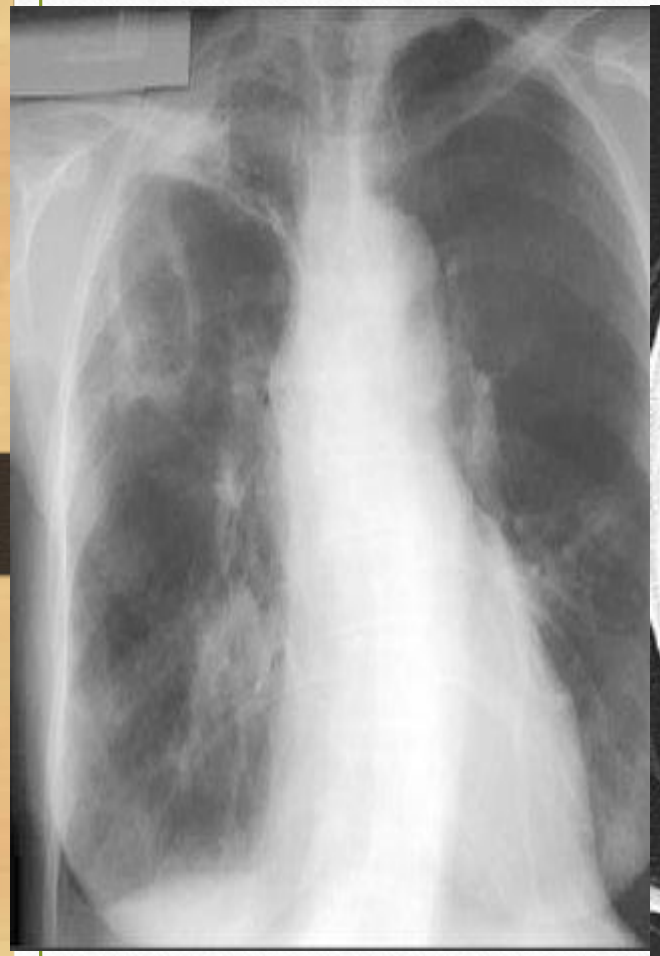


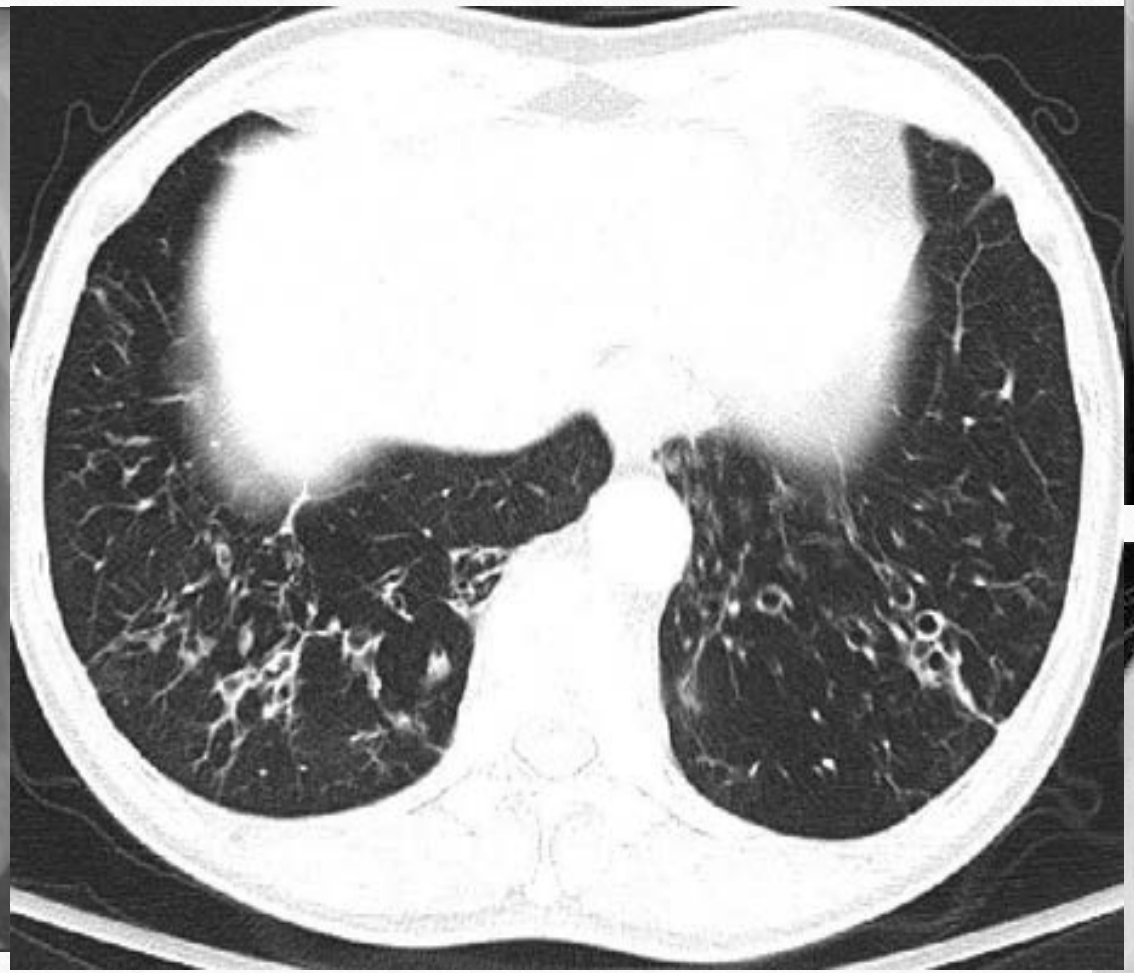
"**TNF** is involved at multiple steps in antibacterial and inflammatory responses to *M tuberculosis* infection. **It is a macrophage activating cytokine and is necessary for the sustained recruitment of inflammatory cells into granulomatous lesions.** It is produced by macrophages and T cells, and it strongly synergises with interferon-γ in containing mycobacterial infection by inducing bacterial killing and granuloma development."

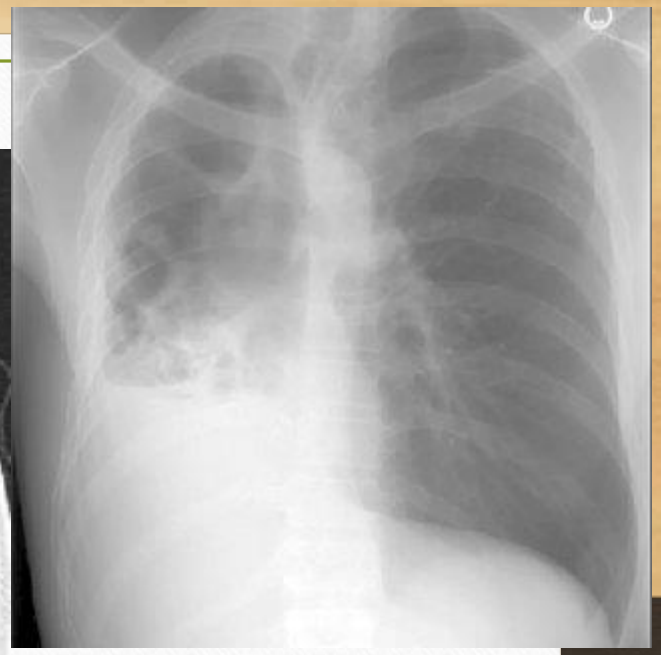
Adapted from : hlers S. Role of tumor necrosis factor (TNF) in host defense against tuberculosis: implications for immunotherapies targeting TNF. *Ann Rheum Dis*. 2003;62(Suppl 2):ii37-ii42.

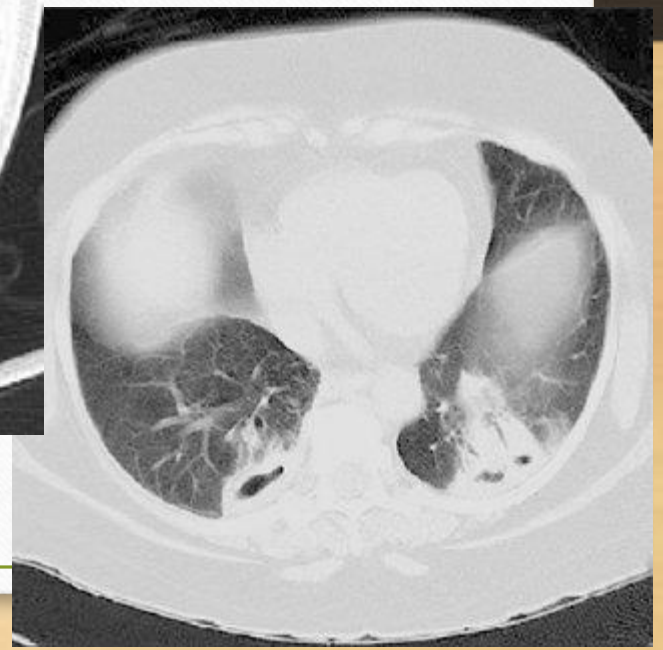
The Radiologic Vortex of the Troika

The many faces of TB/NTM-LD & Bronchiectasis









NTM* Pulmonary Disease in non-HIV :

Past ,Present & **Future** Insights

*

Anonymous
Atypical
Unclassified
Unknown
Tuberculoid
Environmental
Opportunistic
MOTT

Classification of mycobacterial species commonly causing human disease

M. tuberculosis complex
M. tuberculosis
M. bovis
M. africanum
M. microti
M. leprae

Slowly growing mycobacteria
Photochromogens, Runyon* group I
M. kansasii
M. marinum
Scotochromogens, Runyon group II
M. gordonae
M. scrofulaceum
Nonchromogens, Runyon group III
M. avium complex
M. avium
M. intracellulare
M. scrofulaceum
M. terrae complex
M. ulcerans
M. xenopi
M. simiae
M. malmoense
M. szulgai
M. asiaticum
Rapidly growing mycobacteria
Runyon group IV
M. fortuitum
M. chelonae
M. abscessus

The “Staph” of mycobacteria

Some basic differences

TB

- Exposure
- Human to human transmission
- LTBI
- Latent disease
- Paucibacillary?
- Reactivation
- Incidence /Prevalence
- Relapse
- Cure rates 95% plus

NTM

- Environmental
- Ingestion
- No H-H transmission*
- IGRA/TST variability
- Could be Paucibacillary
- Mixed infection
- Indolent / “colonization “
- New Infection
- Cure rate ?

Pulmonary Disease Risk Factors

NTM Risk Factor
Pulmonary conditions
Cystic Fibrosis
COPD / Pulm Fibrosis
Prior TB
Bronchiectasis Primary /Secondary
Silicosis/Fibrosis
Asthma
Lung cancer
GERD
Persons living with HIV/AIDS
Soil exposure
Alcohol abuse
Smoking
Low body weight
Steroid use/Immune deficiency / suppression/ Endogenous and Exogenous

TB Risk Factor	Relative Risk
Persons living with HIV/AIDS	50−170[1]
Transplant recipients	20–74[1]
Silicosis	30[1]
Chronic renal failure/hemodialysis	10–25.3[1]
Recent TB infection (within prior 2 years)	15[2]
Carcinoma of the head and neck	16[2]
Radiographic evidence of prior healed TB	6–19[2]
TNF-alpha blockers	1.7–9.0[2]
Glucocorticoid treatment	4.9[2]
Infants and children < 5 years of age	2.2–5[2]
Diabetes mellitus	2–3.6[2]
Low body weight	2–3[2]
Cigarette smoker (1 pack/day)	2–3[2]
Gastrectomy	2–5[1]
Jejunoileal bypass	27−63[1]
Alcohol abuse	2.0–5.9[3]

US Immunocompromised Population[1]

Condition	Estimated # of US Persons
HIV infection	1.2 million
Rheumatoid arthritis	1.5 million
Inflammatory bowel disease	1.1 million
Systemic lupus erythematosus	320,000
Systemic sclerosis	49,000
Spondyloarthropathies	2.4 million
Vasculitis	1.0 million
End-stage renal disease	0.87 million
Hematologic malignancies	1.0 million
Solid organ transplant candidates	120,000
Total	**10 million**

What is missing ? Diabetes, Exogenous Immunosuppression

1. Redelman-Sidi G, Sepkowitz K. *Am J Respir Crit Care Med*. 2013;188(4):422-431.

PAST OF NTM/MAC Infection

1980's The AIDS era

1. Disseminated MAC in HIV

***Mycobacterium avium* Complex Infection in the Acquired Immunodeficiency Syndrome**

.C. Robert Horsburgh, Jr., M.D.

ORGANISMS of the *Mycobacterium avium* complex have long been recognized as an uncommon cause of pneumonia in persons with chronic lung disease.[1] [2] [3] [4] Organisms of this complex, which comprises two closely related species, *M. avium and M. intracellulare*, appear to have little virulence in the normal host. Before the acquired immunodeficiency syndrome (AIDS) epidemic, disseminated infection with *M. avium* complex was extremely rare; by 1980, only 24 cases had been reported in the medical literature.[5] Beginning in 1982, however, when the infection was recognized in patients with AIDS, the number of cases increased dramatically

Clinical Investigations

Mycobacterium avium Complex Pulmonary Disease Presenting as an Isolated Lingular or Middle Lobe Pattern:

The Lady Windermere Syndrome* (Courtesy : Oscar Wilde)

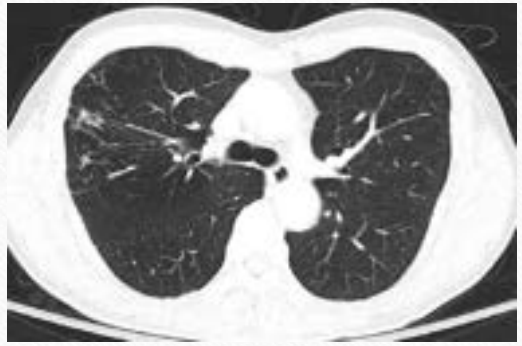
Jerome M.ReichM.D.[a]Richard E.JohnsonPh.D.[a†]

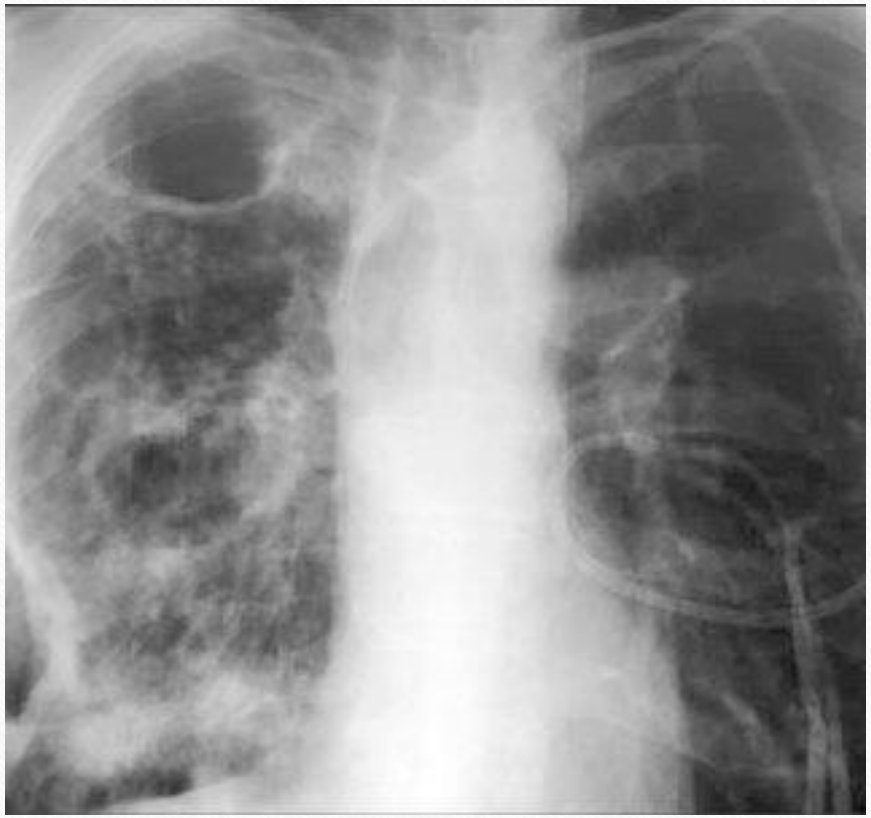
a

Division of Pulmonary Medicine, Bess Kaiser Medical Center, and the Center for Health Research, Kaiser Permanente, Northwest Region, Portland, Oregon

Chest 101 (6) 1992

* Typical Phenotype
* Mild to moderate Nodular Bronchiectasis
*MAC in sputum





LSU Network clinics experience late 1990's onwards

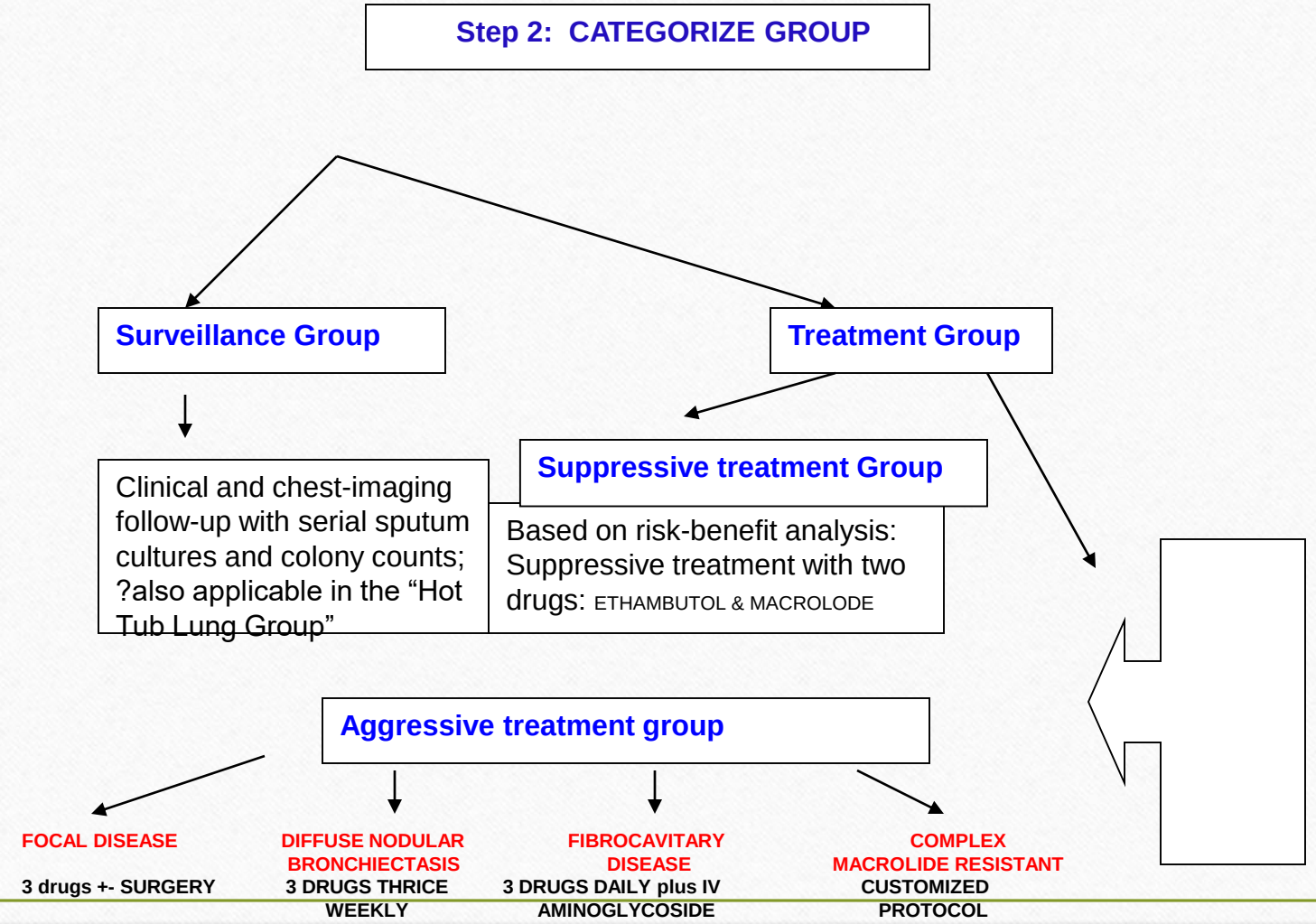
** Chitty S, Ali J. Mycobacterium Avium Complex Pulmonary Disease in immune competent patients. Southern Medical Journal **June 2005**, 98 (6) pp 646-652

Limited Awareness /Limited Rx options

MANAGEMENT OPTIONS

Step 1: Diagnosis & Clinical Classification**

** Ref 9 Chitty S, Ali J. Mycobacterium Avium Complex Pulmonary Disease in immune competent patients. Southern Medical Journal June 2005, 98 (6) pp 646-652 Based on ATS Guidelines



Awareness of prevalence of NTM in Cystic Fibrosis

NTM: Multicenter Prevalence Study in Cystic Fibrosis

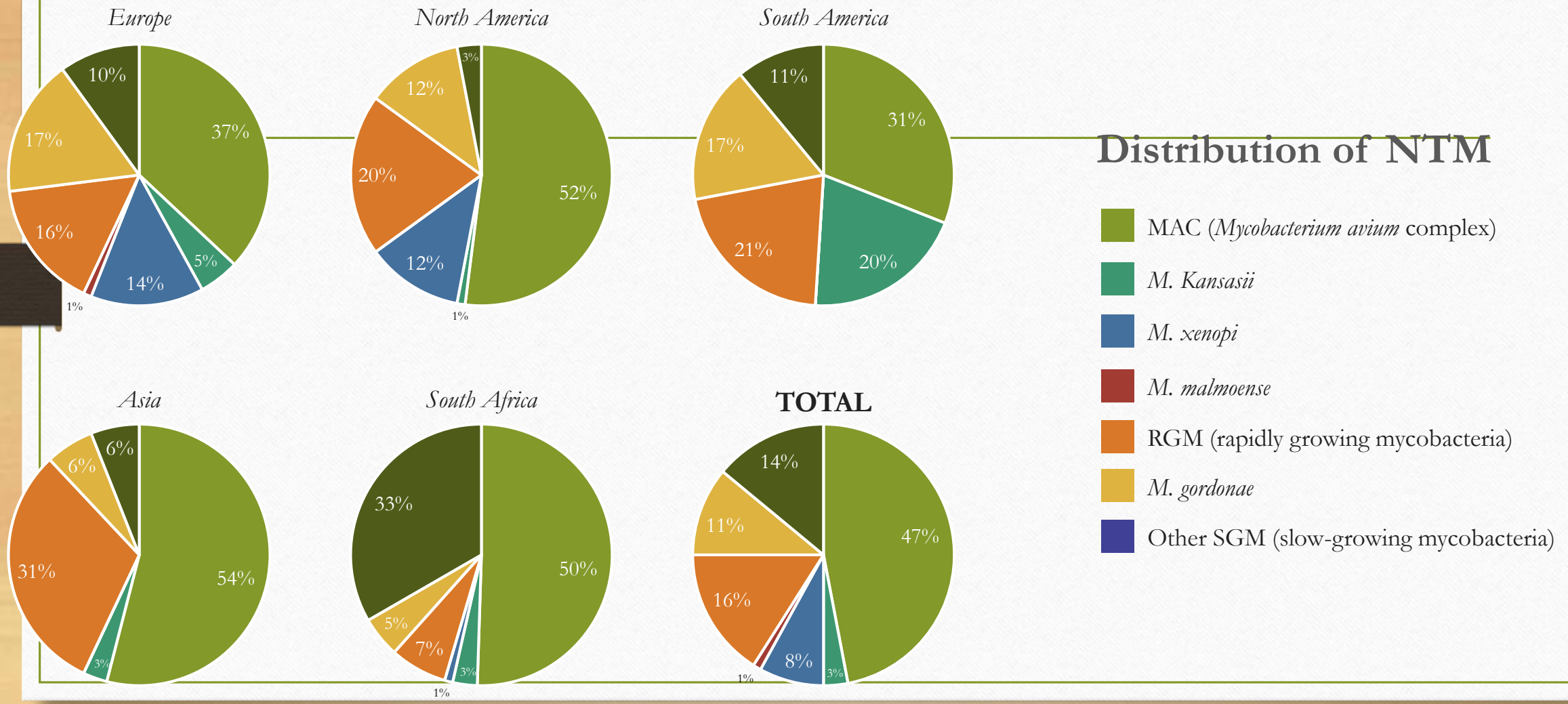
Kenneth N. Olivier , David J. Weber , Richard J. Wallace Jr., Ali R. Faiz , Ji-Hyun Lee , Yansheng Zhang , Barbara A. Brown-Elliot , Allison Handler , Rebecca W. Wilson , Michael S. Schechter , Lloyd J. Edwards ,

Current:
How big a problem is this?

- Based on high prevalence of PPD reactivity to MAC : High
- Based on culture ID in lab specimens : High* increased prevalence from 20 to 47/100K in a10 year period ending 2007; Increased in the western and SE states ; more in Asian Pacific Islanders Still rising
- 40 % more likely to die if associated with co-morbid conditions** ***That is the key***
- Based on reportability : Unknown

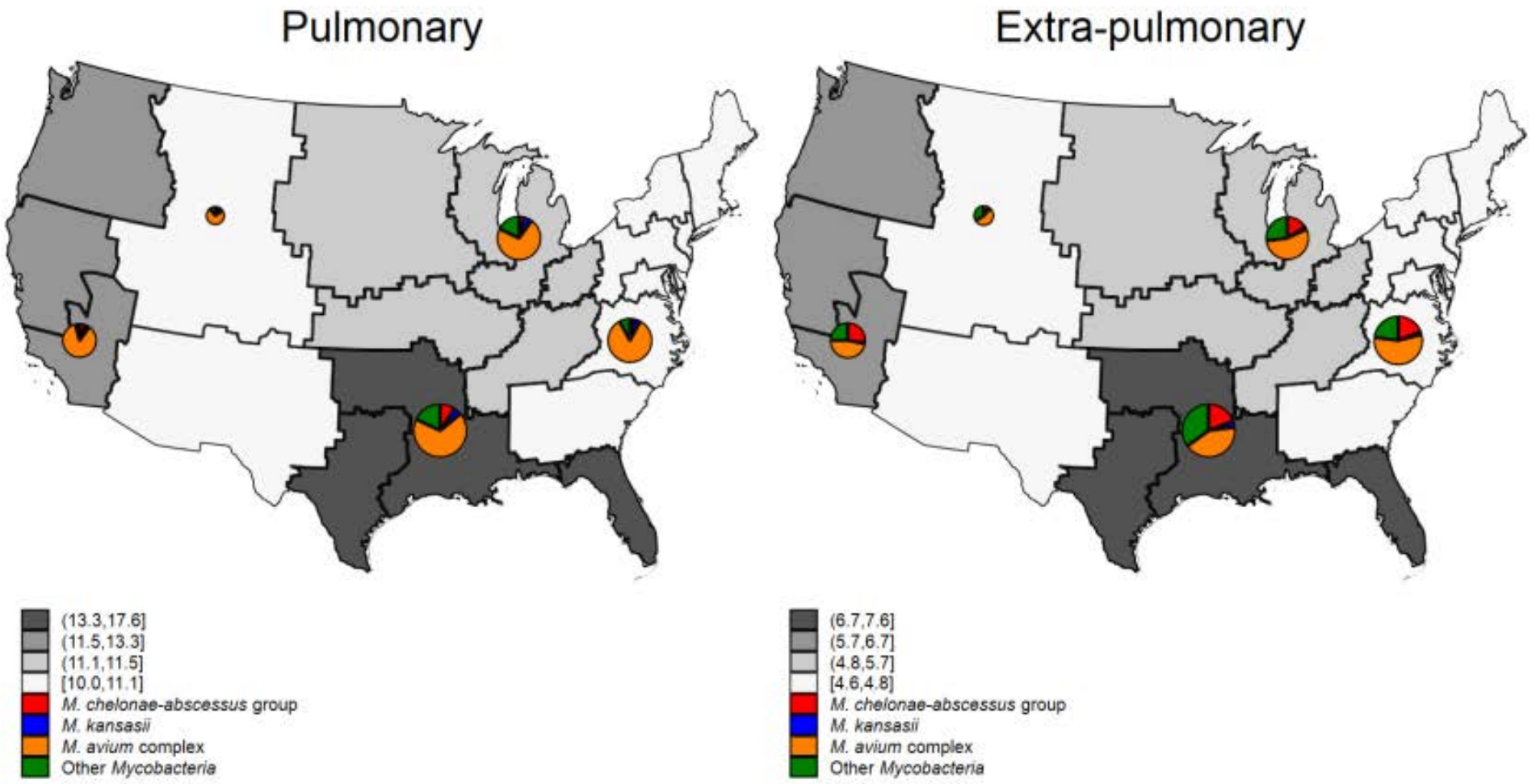
From: "Most will die with it" To "….. 40% may die from it"

Worldwide NTM Distribution (Respiratory)



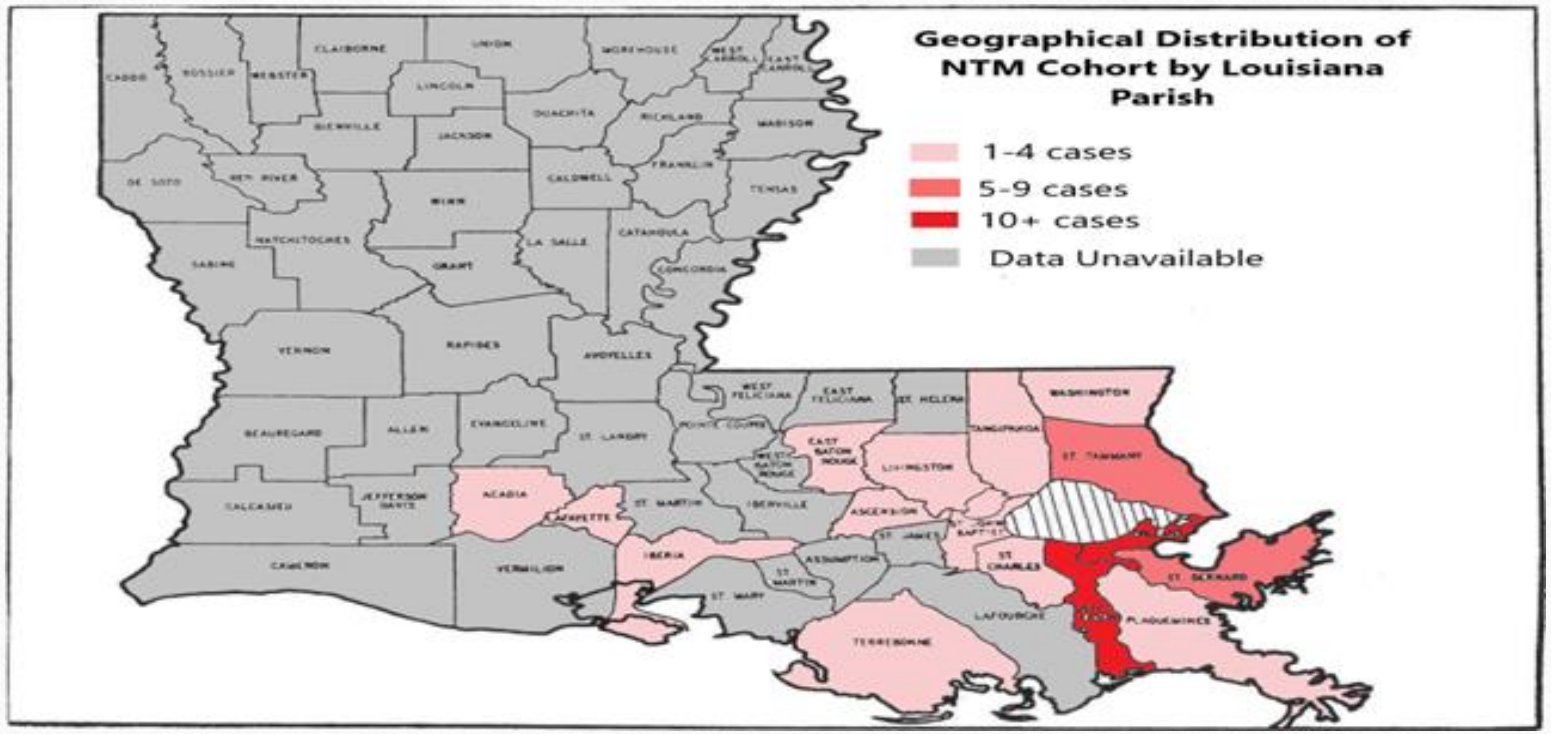
Hoefsloot W, Ingen J van, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J.* 2013;42(6):1604-1613.

Cases per 100k patient-years



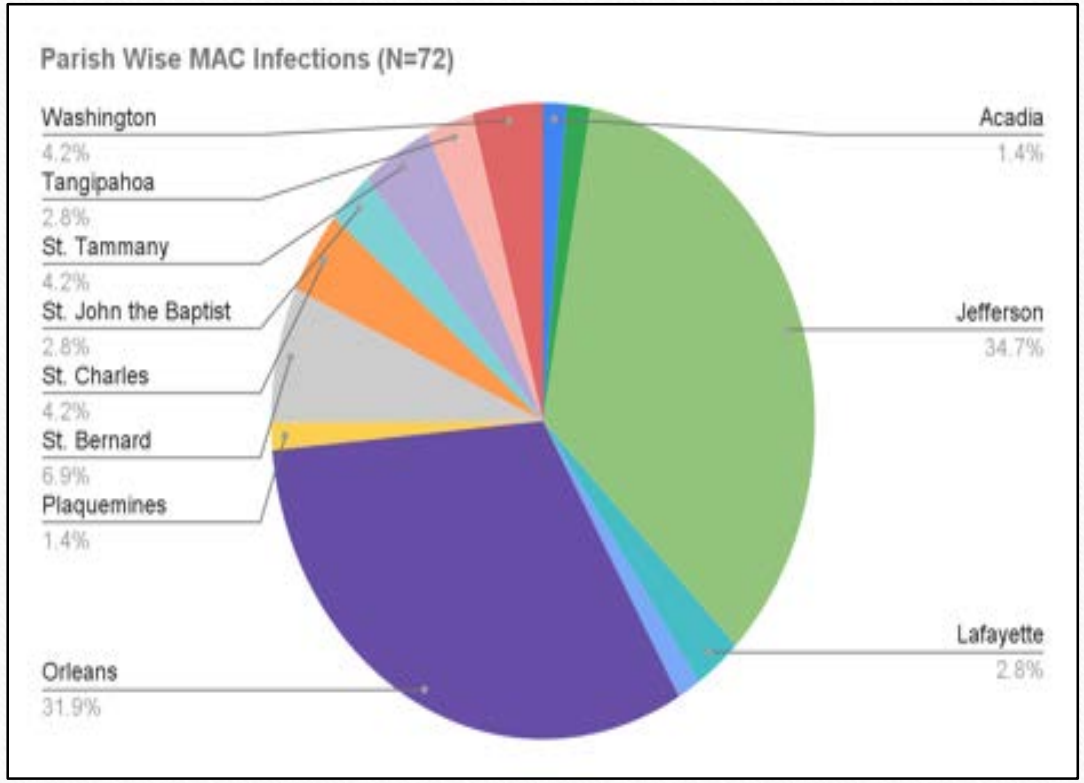
Jones et al *PLoS One* 2018

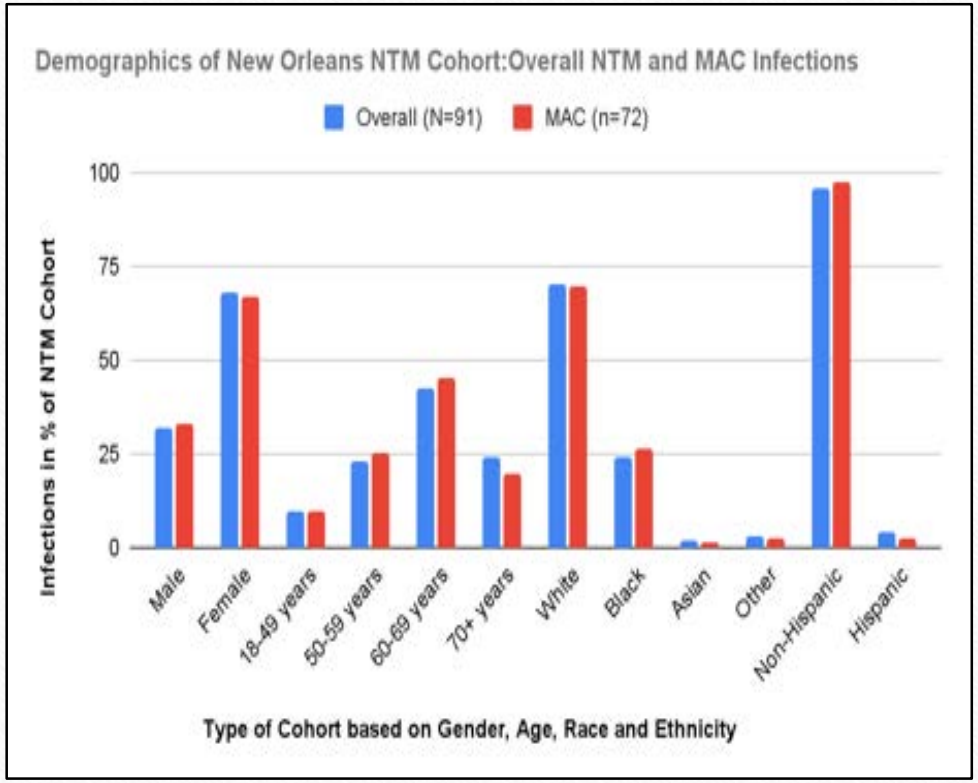
METHODS



In the current study, we assessed the prevalence of different NTM species in the Greater New Orleans area of Louisiana state with a cohort of 91 subjects. The data was captured from 16 parishes and analyzed.

Geographical Distribution And Clinical Characteristics Of Non-tuberculous Mycobacteria Pulmonary Disease In New Orleans





NTM –BE Team at LSUHSC : Acknowledgement to Dr Nicole Lapinel for her tenure 2017-2021

Suggested Management Paradigm
A to I

- **A: Awareness** , recognition , high index of suspicion**

**** The transition from concept of 1. colonization to 2. infection to 3. disease to 4. morbidity /co-morbidities to 5. mortality**

- Recurrent Bronchitis /Hx of repeated "pneumonia" Repeated need of Antibiotics /Chronic cough (let the normal CXR deceive us)
- Underlying Bronchiectasis(primary, secondary, idiopathic)
- Associated with Pulmonary and Non-Pulm co-morbidities
- CF-HIV (not withstanding)
- Exogenous and Endogenous Immune Deficiency syndromes
- **** or lack thereof**: ***Ask the medical students/residents rotating through the clinic***

B: Bronchiectasis

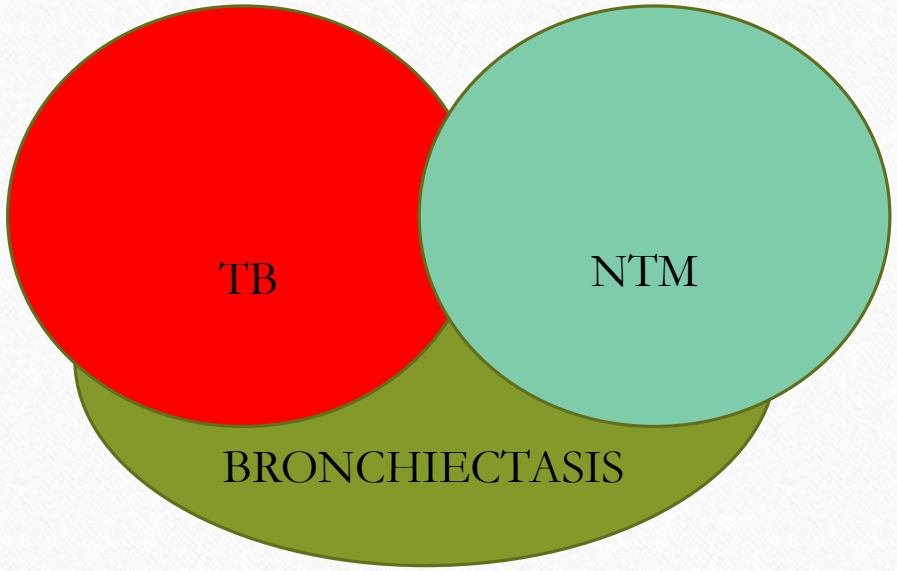
Primary or Secondary: "The chicken or the Egg dilemma"

Underlying Pathology

TROIKA : THE COMMONALITY IN CLINICAL IDENTITY & MGM

Chronic Cough

Chronic Resp Symptoms
Prolonged Debility
Enhanced Frailty
Increased Disability adj life years
Radiographic Similarity
Management & Rx Overlap



Q 1: The Clinical Vortex: Chronic Cough with a normal CXR in a non-smoker

- UACS /RhinoSinus/Allergic & Non Allergic Rhinitis
- Asthma
- Non-Asthma Eosinophilic Bronchitis (NAEB_)
- GERD/LPR/Acid and Non-Acid
- Drugs
- ** Early IPF/CHF/ Sjogren Syndrome or ……*

Fill in the blank ; See next slide for options

Ref: Irwin et al Chest 2018 (153) 1 196-209)

Question 1
Answer choices

- A. TB
- B. Acute Bronchitis
- C. Chronic Bronchitis
- D. Bronchiectasis

Epidemiology - USA

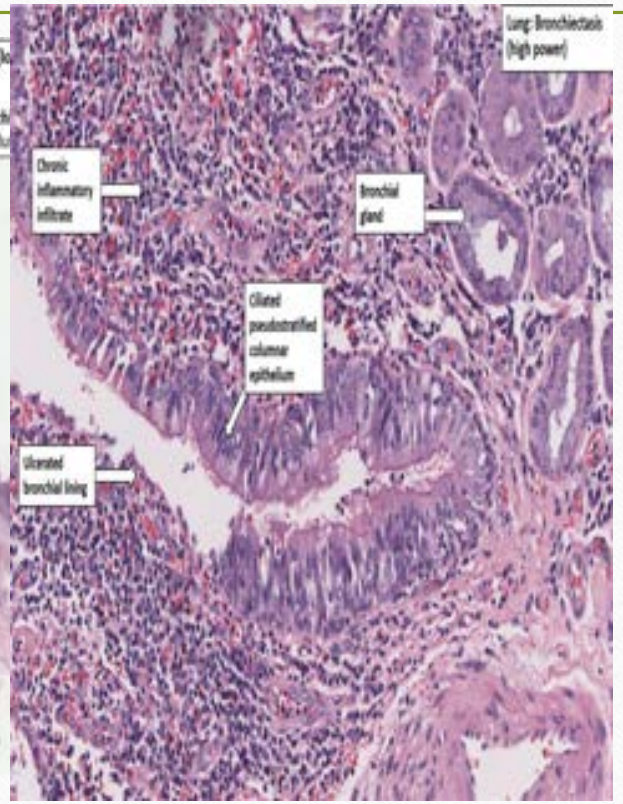
Prevalence of Non-CF BE

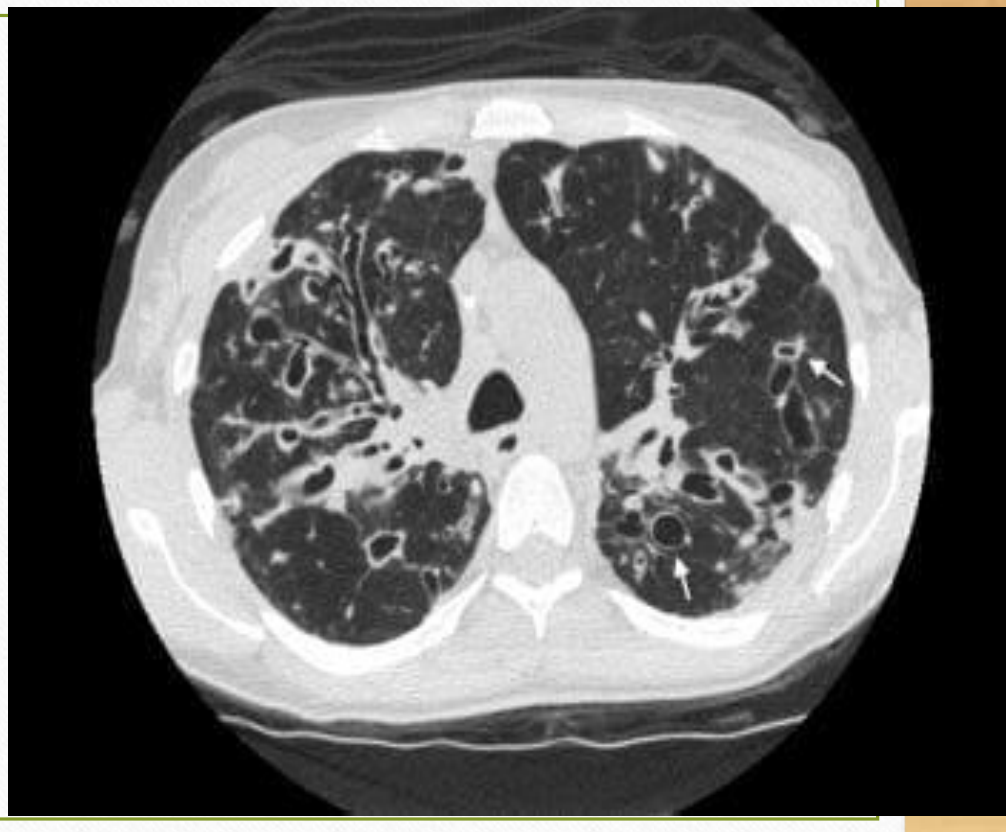
- Estimated 350,000-500,000 adults in the US with bronchiectasis
  - Prevalence increases with age
    - 300-500/100,000 age >40 versus 40-50/100,000 age <40
    - In adults > 65 may be as high as 700/100,000

US Bronchiectasis and NTM Research Registry (BRR)

- 2017 data 63% of patients with non-CF BE had NTM
- 2023 data (not yet published) 58.8% of 2,634 patients with NTM at baseline
  - Probability of acquiring NTM was approximately 4%/year

Bronchiectasis: Histology to Radiology





Reference and Acknowledgement

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

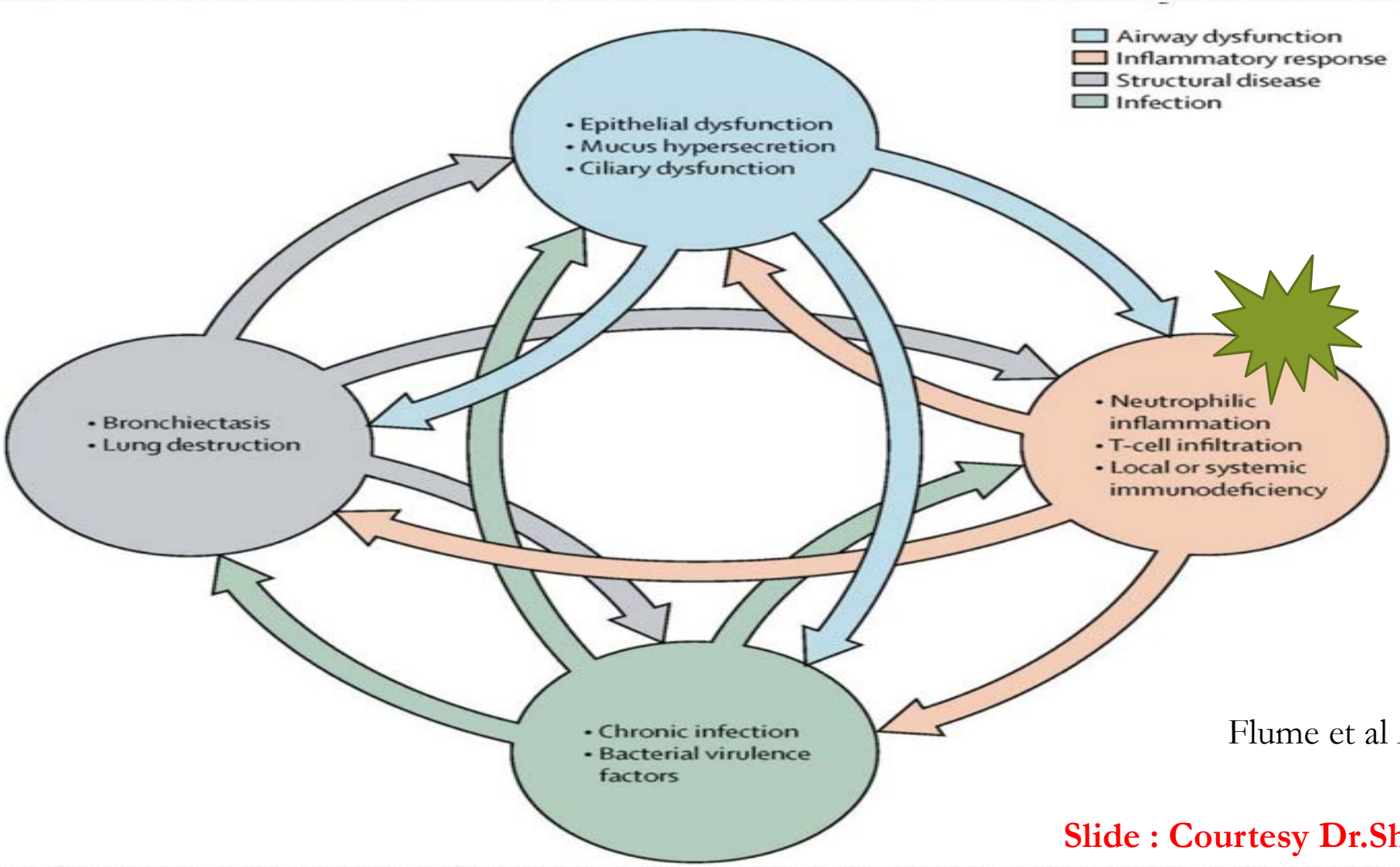
inflammation /edema/ulceration/neovascularization

Irreversible bronchiolar dilatation and tissue destruction

At the cytokine level

Increased mucus secretions

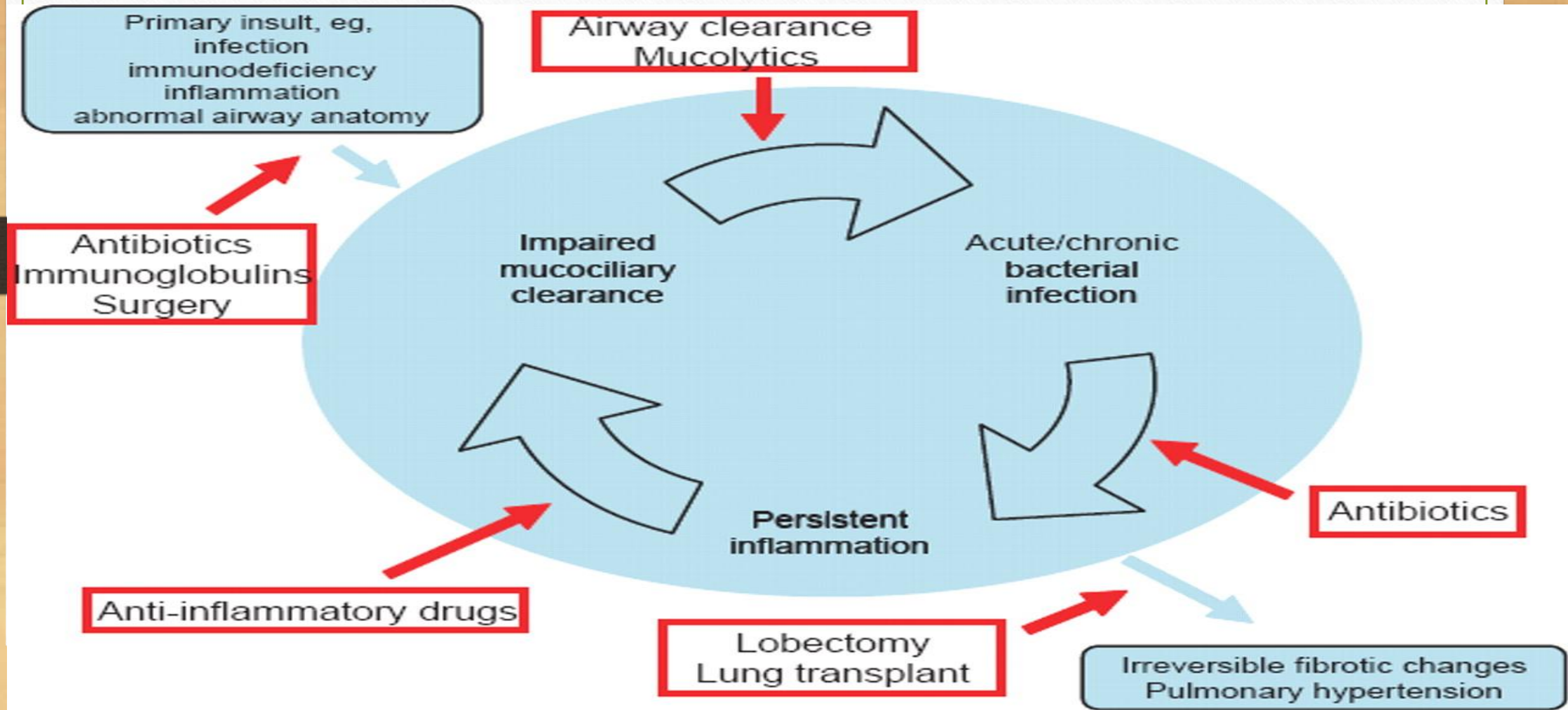
Inhibition of mucociliary clearance



Flume et al *Lancet* 2018

Slide : Courtesy Dr.Shelby MacRae

Targets of Therapy

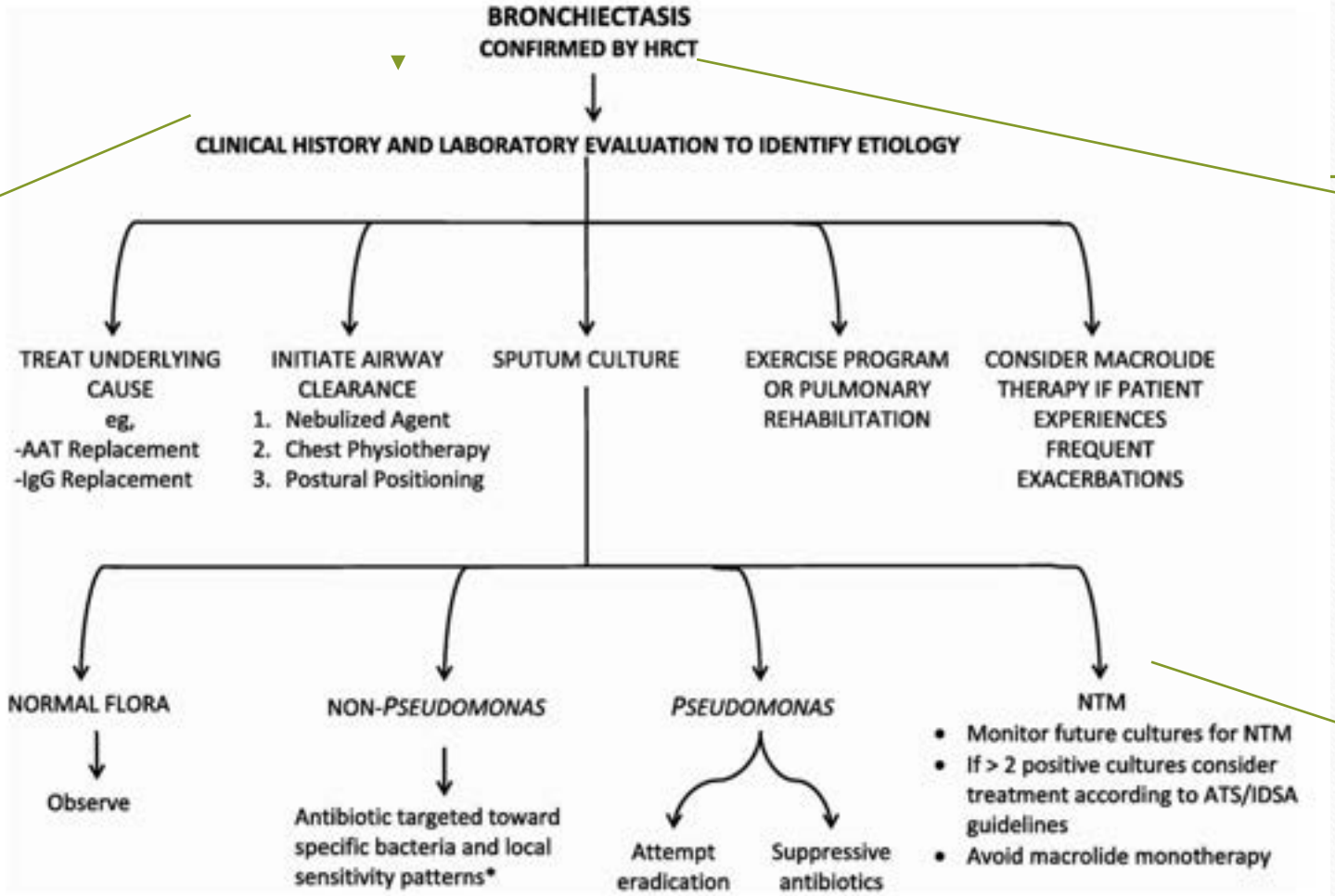


Management of non-CF Bronchiectasis with its complexities

THE CONTROL OF COUGH DILEMMA

* Dry cough
* Wet with Copious sputum

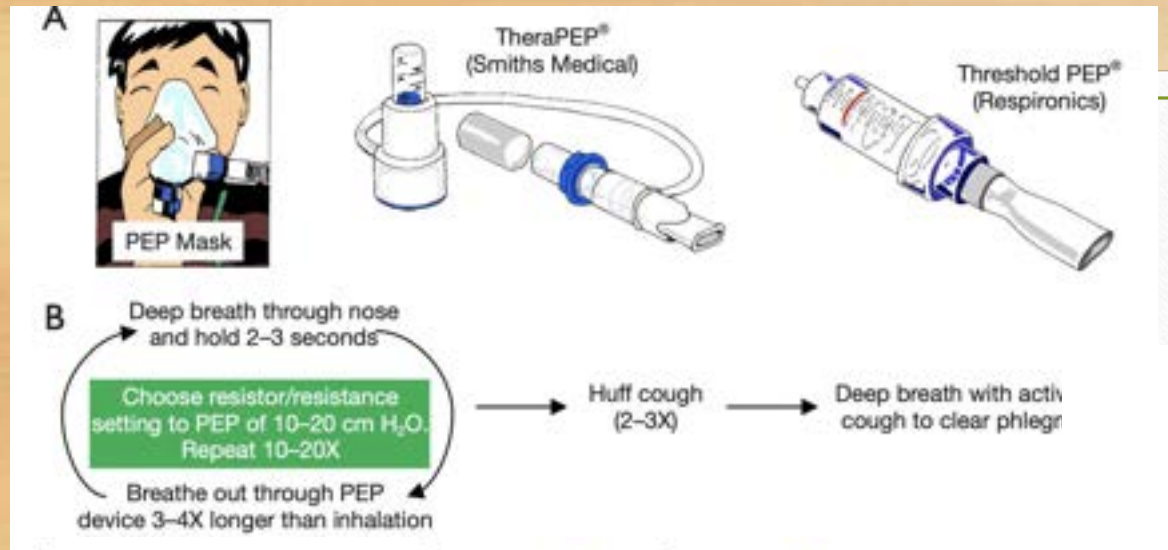
Multi faceted
Nodular,TIB, Tubular
Cystic,Cavitary

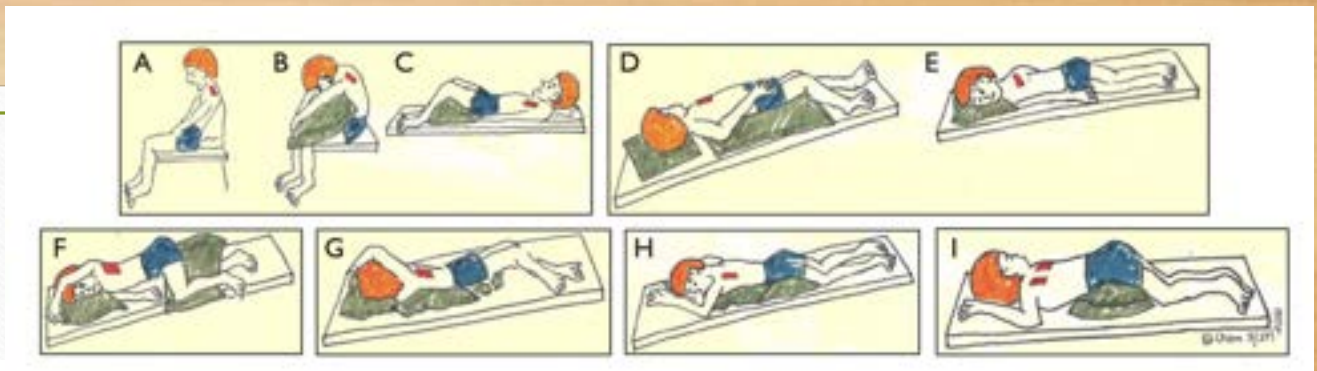


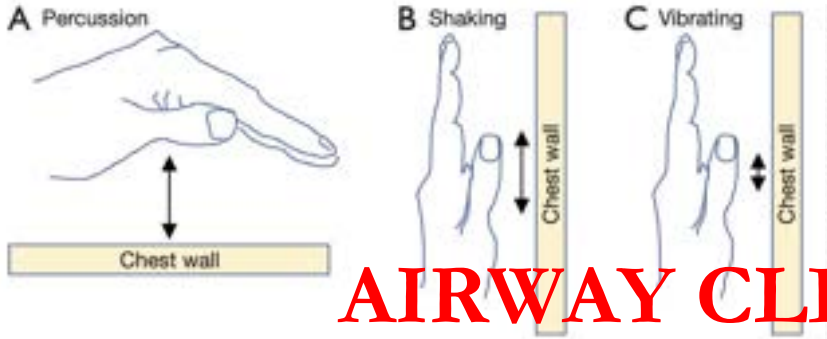
Am J Respir Crit Care Med 2013 188, 647-656.

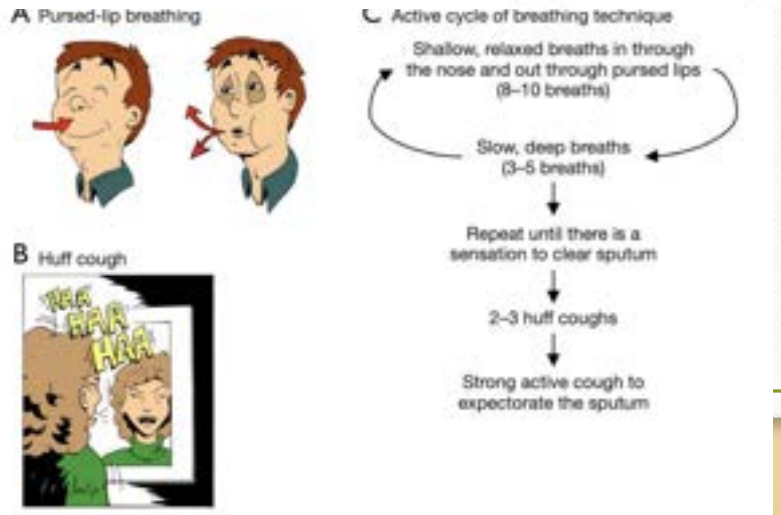
See 2020 Guidelines
For Antimicrobial
Therapy
REA with or without AG

AIRWAY CLEARANCE METHODS & DEVICES









Youssefnia et al *J Thor Dis* 2022

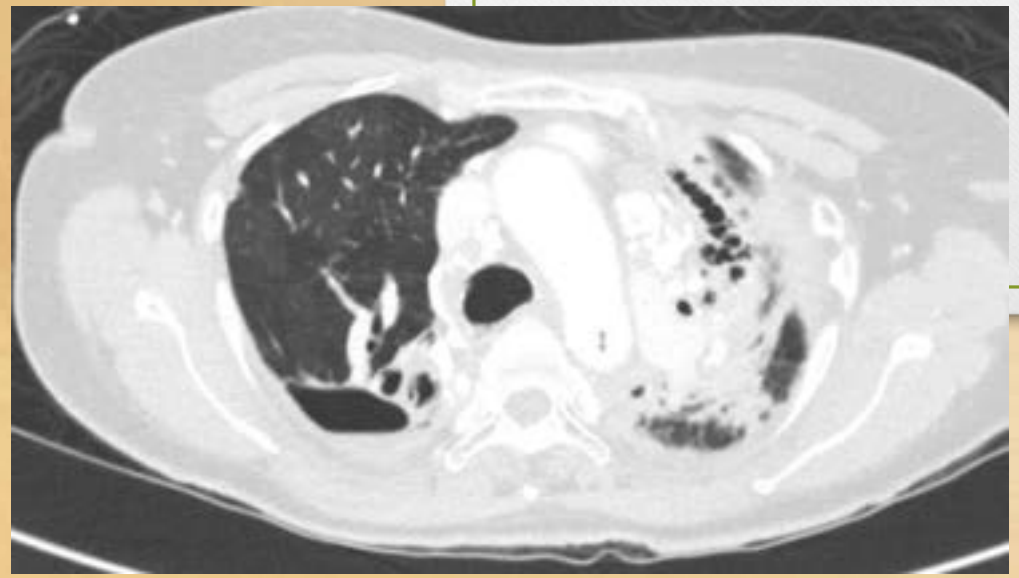
Q 2: Regarding Non-CF Bronchiectasis (NCFBE) which of the following is incorrect

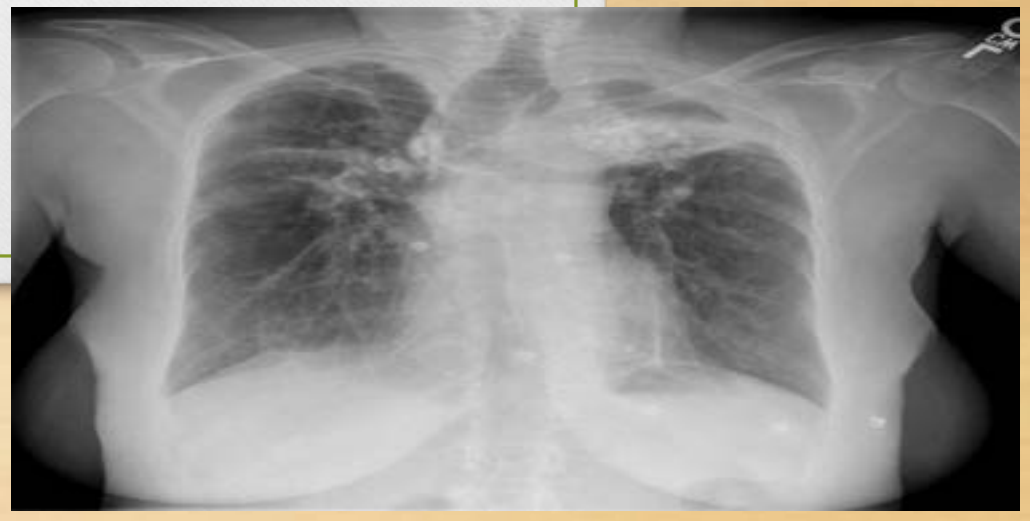
- A. Most diagnosed cases are post-infectious or idiopathic
- B: Affected individuals account for disproportionate healthcare costs
- C: Cases with non –CF BE have a higher mortality
- D: NCFBE exacerbations are caused by a vicious vortex of eosinophilic inflammation

- Ref: Plume et al Lancet 2018

C: Co-morbid Pulmonary diseases

OLD TB /COPD/SARCOID/ IPF /CTD-ILD/ICS /STEROID USE





D: The Disease /NTM itself

More about the Mycobacteria with its heterogenicity and complexities in diagnosis and management

The SMART Microbe
1. 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

2. Why survival and immune evasion?*

Some of the HOST FACTORS

- 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

NTM/MOTT
WHO DAT MAC:
The Mycobacterial Avium Complex: Not a single entity

- Conventional Criteria
- Serotypes
- Multi-locus Enzyme Electrophoresis types
- Phage types
- Large RFLP types with different colony morphology (smooth rough opaque etc)
- Colony variant Types

- & ….then differences in cell wall/envelopes/microbial genetics of mycobacteria and antibiotics

Ref Inferlied et al Clin Micro Review July 1993

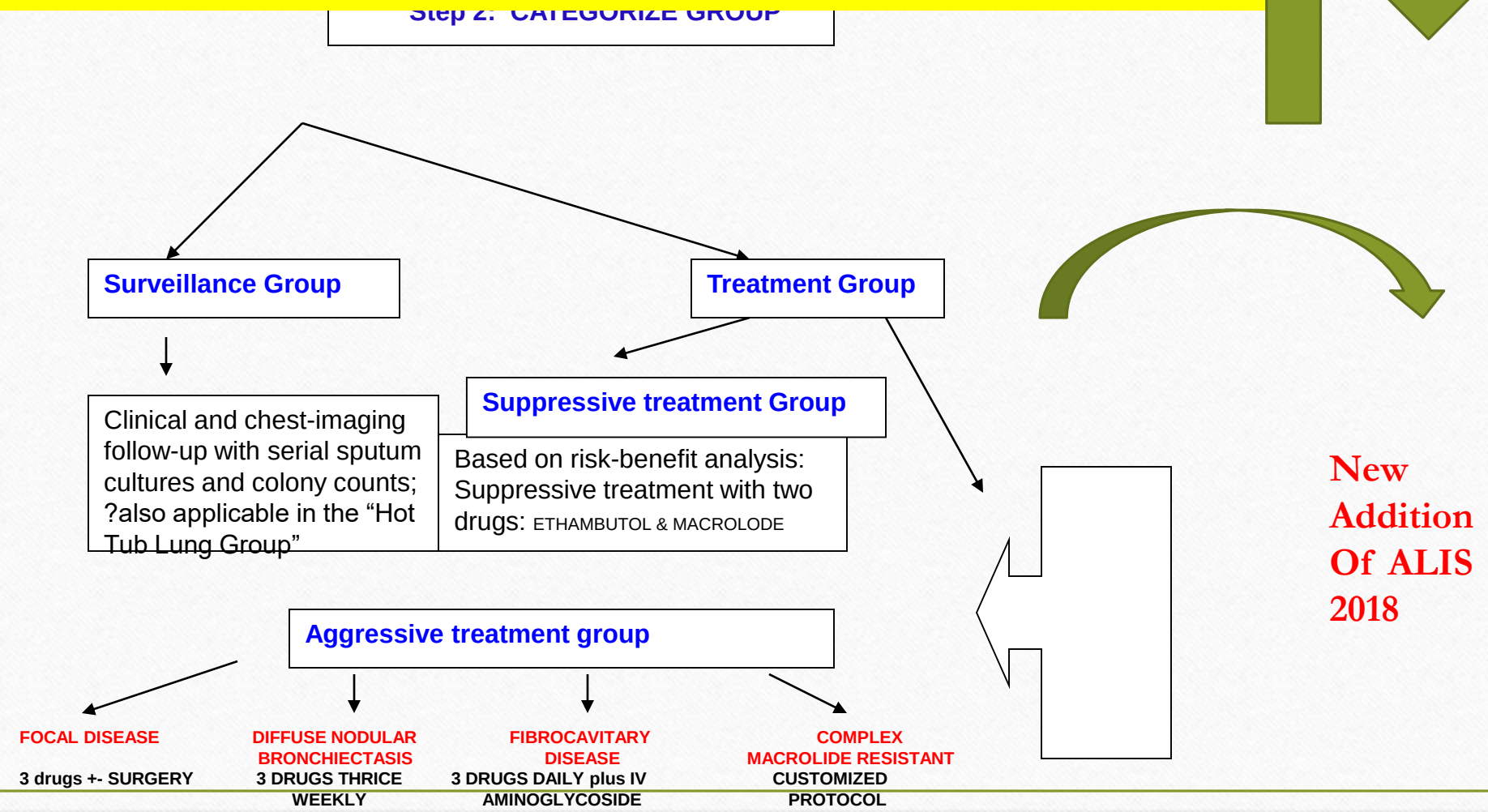
MAC: Not necessarily a single presentation

- Pulmonary/ LWS/TIB/BE/HP/Associated Infection
- Lymphadenitis
- Disseminated
- Skin & Soft tissue
- Occupational
- Device related

MANAGEMENT OPTIONS

Step 1: Diagnosis & Clinical Classification**

**** Ref 9 Chitty S, Ali J. Mycobacterium Avium Complex Pulmonary Disease in immune competent patients. Southern Medical Journal June 2005, 98 (6) pp 646-652**



New Addition Of ALIS 2018

NTM treatment and its specific challenges

Methods of identification (accuracy, timeliness, availability)

- **Not a reportable disease and if so not followed by Public Health**
- **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 (The granuloma debate)**
    - **Mucus growth (e.g. M. abscessus undergo phenotypic switch in mucus niche) /difficult Rx options**
    - **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**

Environmental Considerations Transmission

- **Environment = major source of human NTM infections**
- **Routes of exposure:**
  - 1) Aerosolization and inhalation
  - 2) Swallowing and aspiration
  - 3) Introduction into wounds (injury/surgical)
  - 4) Zoonotic (pigs, birds, cattle)
- Rarely transmitted from patient to patient***

Environmental Sources of NTM
Soils, acidic pine forest or coastal swamp soils
Dusts from agriculture, garden & potting soils
Drainage waters from acidic pine forests or coastal swamps
Natural waters
Drinking water
Water / ice from refrigerators
Water from granular activated charcoal filters
Aerosols from natural & drinking waters
Aerosols from indoor humidifiers
Mist from indoor swimming pools

Proven Routes of NTM Infection

- 1) Matching **pulsed field gel electrophoresis patterns** of M. avium isolates from AIDS patients, Charles River water & drinking water in Boston
- 2) Matching **rep-PCR patterns** of M. avium isolates showerhead
- 3) M. avium infected patients & isolates from their household plumbing
- 4) Identical **16S rRNA sequences** of NTM isolates from patients & their potting soils
- 5) Similarity of **RFLP patterns** among human & porcine isolates indicates close genetic relatedness, suggesting that *M. avium* is transmitted between pigs and humans

Watch Out for “F” Follow up challenges

positive cultures with underlying /occult malignancy

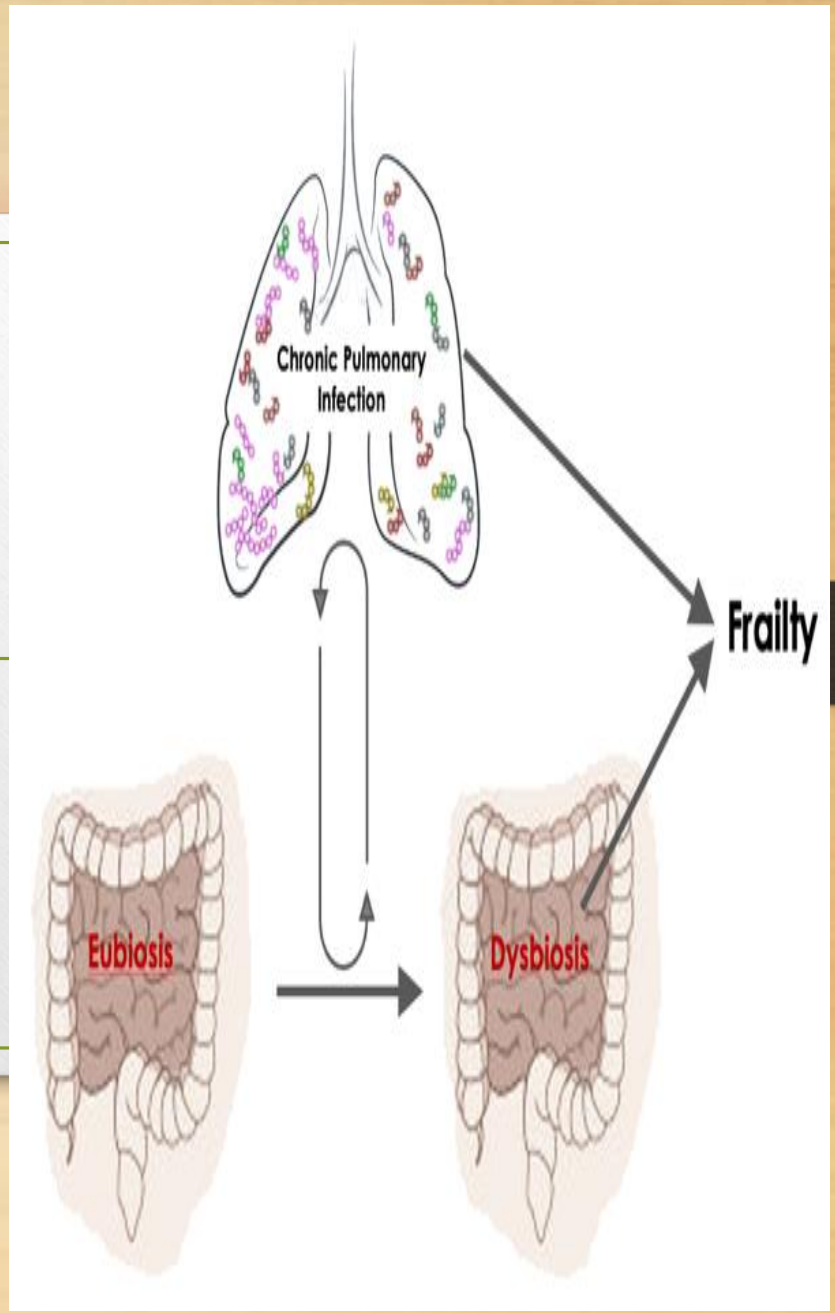
Criteria of response ; Adherence to therapy/Poor Rx tolerance

HIGH DROP OUT RATES

G: Gastric/Reflux /NTM Aspiration/Increase in Cough

Micro Aspiration /Swallowing defects Specially with RGM

The challenges of long term antibiotics Rx and impact on Gut microbiome



Courtesy/ Collaboration

Chronic disease, outcomes are variable
Disease fatigue
Treatment fatigue
Healthcare provider fatigue

H: Holistic Approach

Focus on Psycho-social issues and General Wellbeing in this chronic condition where cough ,weight loss, and fatigue are the most debilitating complaints

ASSESSING FRAILITY * (Wetmore study)

Importance of Exercise Programs

I: The Immune Domains

Exogenous immune deficiencies/ Chronic systemic and inhaled Steroid use/ CFTR traits/ Alpha One Anti-trypsin Def / Primary Ciliary Dysfunction disorders/ Immunoglobulin Deficiencies /Connective Tissue Disorders

Interferon Gamma Deficiencies; Signal Transducer and activator of transcription (STAT1) deficiency; Autoantibody to Interferon Gamma; HIV and Non HIV related CD4 lymphopenia;Risk of use of TNF-alpha inhibitors and Janis Kinase (JAK) inhibitors

Summary : Multidisciplinary management approach

An Oncology Paradigm

- **Antimicrobial therapy**
  - Surveillance only with ACT
  - Suppressive treatment
  - Active treatment /GBT REA with or without AG
- **Underlying non-pulmonary/pulmonary disease**
  - Autoimmune: Co-mgmt with Rheumatology specialist
  - Chronic rhinitis / sinusitis: Referral to ENT
  - GERD/Esophageal motility d/o: Referral to GI
  - Bronchiectasis/ IPF/COPD/Sarcoidosis/TB
- **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

THE ALPHABET A to I MULTI DISCIPLINARY MULTI-SPECIALTY PARADIGM

Multispecialty interaction and coordination of care

	Awareness and early recognition	**B**ronchiectasis and underlying pathology	**C**omorbidities	**D**isease assessment and treatment	**E**nvironmental surveillance	**F**ollow-up measures	**G**astro-esophageal reflux precautions	**H**olistic approach	**I**mmune and genetic testing
THE TEAM	Primary care physician with or without other specialists	Pulmonary and respiratory therapists/ radiologist/CT surgeon/ENT	Pulmonologists and other specialists	Infectious disease specialist/micro-biologist/ radiologist	Infectious disease specialist/ specialized laboratory technicians	Multidisciplinary team	Gastro-enterologist	Nurse/ nutritionist/ OT/psycho-logist/PT/SW	Rheumatologist/ immunologist
THE APPROACH	Consideration of NTM-LD in patients with other pulmonary conditions	Monitor Bronchiectasis Severity Index scores regularly to prevent irreversible loss of lung function	Screening for NTM prior to initiating therapy for lung diseases and distinguishing underlying cause of radiographic pulmonary mass or nodule	Regular multidisciplinary follow-up and use of antibiotic initiation checklist	Discuss methods to reduce risk of reinfection with patient/caregiver	Individualized monitoring plan that continues after culture conversion	Monitoring for and management of GERD to reduce mycobacterial burden	Create a customized and comprehensive plan to increase successful management of NTM-LD	Periodic review with this team may help identify any contributing factors that impede improvement

Ali, J *Expert Rev Resp Med* 2021

Q 3
Which of the following is the most important in the management of Non CF BE with or without NTM/TB

- A: Multi-specialty collaboration
- B: Patient/Caregiver engagement in managing Acute Exacerbation and chronic care management
- C: Prompt initiation of Bronchodilator therapy
- D: Nutritional /PT support
- E. All of the above
- F. A B & D

Ref: 1. New developments in bronchiectasis

- The Lancet Respiratory Medicine Published: August 14, 2023
- 2. Daley et al **An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline**

..And now to the **Future**

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
- Cough/Fatigue and how to handle that
- 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? / Need for broader susceptibility data and beyond MIC

Following the CF Trail

Use of CF transmembrane conductance (CFTR) regulators

Improvement in lung function
Reduction of symptoms
Decreased exacerbations

National Experts: Rx CF trait positive pts (Delta F 508 cohort **with** Trikafta (Lexacaftor, Tezacaftor and Ivacaftor Tablets

Targeted Phase: Validation of NTM MAC and MABC Proteomic Profiles Against Mixed In Vitro Samples					
Sample	Concentration (mg/ml)	ul for 25ug	Detected Strain(s)	Predominant Strain	Actual Strain(s)
1	0.391	64	M. abscessus, M. boletti, M. chimaera, M. intracellulare, M. massiliense	M. abscessus	M. avium + M. intracellulare + M. chimaera + M. abscessus + M. boletti + M. massiliense
2	0.465	54	M. abscessus, M. avium, M. boletti, M. massiliense	M. massiliense	M. abscessus + M. boletti + M. massiliense
3	0.163	153	Not Determined	Not Determined	M.avium + M.intracellulare + M chimaera
4	0.262	95	M. avium	M. avium	M.avium + M. abscessus
5	0.292	86	M. abscessus, M. avium, M. chimaera	All	M.intracellulare + M. abscessus
6	0.388	64	M. abscessus, M. avium, M. boletti, M. chimaera	M. chimaera	M. massiliense + M. abscessus
7	0.259	97	M. abscessus	M. abscessus	M.avium + M.boletti
8	0.295	85	M. avium, M. abscessus, M. massiliense	All	M.abscessus + M.chimaera
9	0.147	170	M. chimaera	M. chimaera	M.avium + M.chimaera
10	0.440	57	M. abscessus, M. avium, M. boletti, M. chimaera, M. massiliense	M. abscessus, M. chimaera	M. avium + M. abscessus + M. massiliense + M. bolletti
11	0.494	51	M. avium, M. massiliense, M. boletti, M. chimaera, M. intracellulare	M. avium	M. intracellulare + M. abscessus + M. massiliense + M. boletti
12	0.428	58	M. abscessus, M. avium, M. chimaera	M. abscessus	M. chimaera + M. abscessus + M. massiliense + M.boletti
13	0.147	170	Not Determined	Not Determined	M. massiliense + M. avium
14	0.150	167	M. chimaera	M. chimaera	M. intracellulare + M. massiliense
15	0.255	98	M. abscessus, M. avium, M. chimaera	M. chimaera	M. chimaera + M. boletti

Diagnostics : Matching strains :Culture/Genetics/ Proteomics track

LSUHSC NTM-BE PROGRAM TEAM BIO-SPECIMEN REDCap REGISTRY PLATFORM

Target regimen profiles for treatment of tuberculosis: a WHO document

Christian Lienhardt[1], Payam Nahid[2], Michael L. Rich[3,4,5], Cathy Bansbach[6], Emily A. Kendall[7], Gavin Churchyard[8,9], Lice González-Angulo[1], Lia D'Ambrosio[10], Giovanni Battista Migliori[10] and Mario Raviglione[1]

Affiliations: [1]Global TB Programme (GTB), World Health Organization, Geneva, Switzerland. [2]Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, San Francisco General Hospital, San Francisco, CA, USA. [3]Division of Global Health Equity, Brigham and Women's Hospital, Boston,

ATTRIBUTE

MINIMUM REQUIREMENT

OPTIMUM GOALS

TABLE 1 Characteristics of the target regimen profile for rifampicin-susceptible (RS) tuberculosis (TB)

	Attribute	Minimum[a]	Optimum[a]
1	Indication	Active against RS *M. tuberculosis* strains	Active against RS *M. tuberculosis* strains including monoresistance to any drug except rifampicin
2	Efficacy and duration of treatment	A regimen of 4 months or less with efficacy not inferior* to the current standard of care 6-month regimen for DS-TB	A regimen of 2 months or less with efficacy not inferior to the current standard of care 6-month regimen for drug-susceptible TB
3	Target population	All age groups, irrespective of HIV status	All age groups, irrespective of HIV status
4	Safety and tolerability	Incidence and severity of adverse events no worse than for standard of care No more than monthly clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, *etc.*)	Incidence and severity of adverse events better than for standard of care No active clinical monitoring and no laboratory monitoring for drug toxicity needed except in special populations (pre-existing liver disease, diabetes, *etc.*)
5	DDI and metabolism	Ability to use safely without active laboratory testing or monitoring with: First-line ART regimen(s) [illegible] (if rifampicin is included in the regimen) Drugs that induce or inhibit P450 liver enzymes Proarrhythmic drugs that prolong QT/QTc interval	No dose adjustment with other medications and ability to use safely without active laboratory testing or monitoring with: First-line ART regimen(s) and co-trimoxazole [illegible] (if rifampicin is included in the regimen) Drugs that induce or inhibit P450 liver enzymes Proarrhythmic drugs that prolong QT/QTc interval
6	Formulation dosage and route of administration	Formulations for the oral for all drugs in regimen, including paediatrics Well tolerated and simple to administer to enhance [illegible]	Exclusively oral delivery (preferably once daily); ideally without the need for weight band adjustments, and suitable for fixed dose combination formulations Parenteral formulations would allow to treat severe cases 3 or fewer pills per day
7	Stability/shelf life	Without cold storage requirements, with shelf lives of at least 3 years for all the drugs comprising the regimen	Without cold storage requirements, with shelf lives of at least 5 years for all the drugs comprising the regimen
8	Special populations	Safe on a wide range of patients (children, pregnant women and patients with comorbidities (HIV, viral hepatitis, diabetes, *etc.*) and low to no drug-drug interactions	For women of child bearing potential and pregnant women, available human data that do not indicate that the component drugs increase the overall risk of structural abnormalities and the drugs are safe with breastfeeding
9	Barrier to emergence of drug resistance (propensity to develop resistance, generation of cross-resistance)	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1 in 10^7 mutations per bacterium per generation New resistance to one or more drugs in the regimen emerges in <1% of treatment courses when taken as prescribed and when no	Each component of the regimen should have no greater mutation rate (in unselected bacterial population) than 1in 10^9 mutations per bacterium per generation Essentially no acquired resistance (<0.01%) when regimen is taken as prescribed and no pre-existing resistance to the drugs in the

Lesson : Develop a TRP for NTM to guide development decisions.

Future treatment options and pathways

- ***Advent of increased use of ALIS (Amikacin Liposomal Inhaled Solution) Convert trials)***
- ***More on inhaled antibiotics***
- ***Focus on Cavitary MAC ??***
- ***Clofazimine back in the limelight (Herman et al Science Direct Oct 2021)***
- ***Bedaquiline in MDR NTM ? (Cholo et al Journal of Antimicrobial Chemo Feb 2017***
- ***Omadacycline (Rizzo et al BMC Nov 22)***
- ***Combination drugs / Combination packaging***
- ***Rx of underlying Bronchiectasis (Brensocatib)***
- ***Understanding Airway clearance options and rationale thereof/Use of Glutathione***
- ***Reduce Biofilm formation …Oils !!!***
- ***Phage therapy / CF trials***

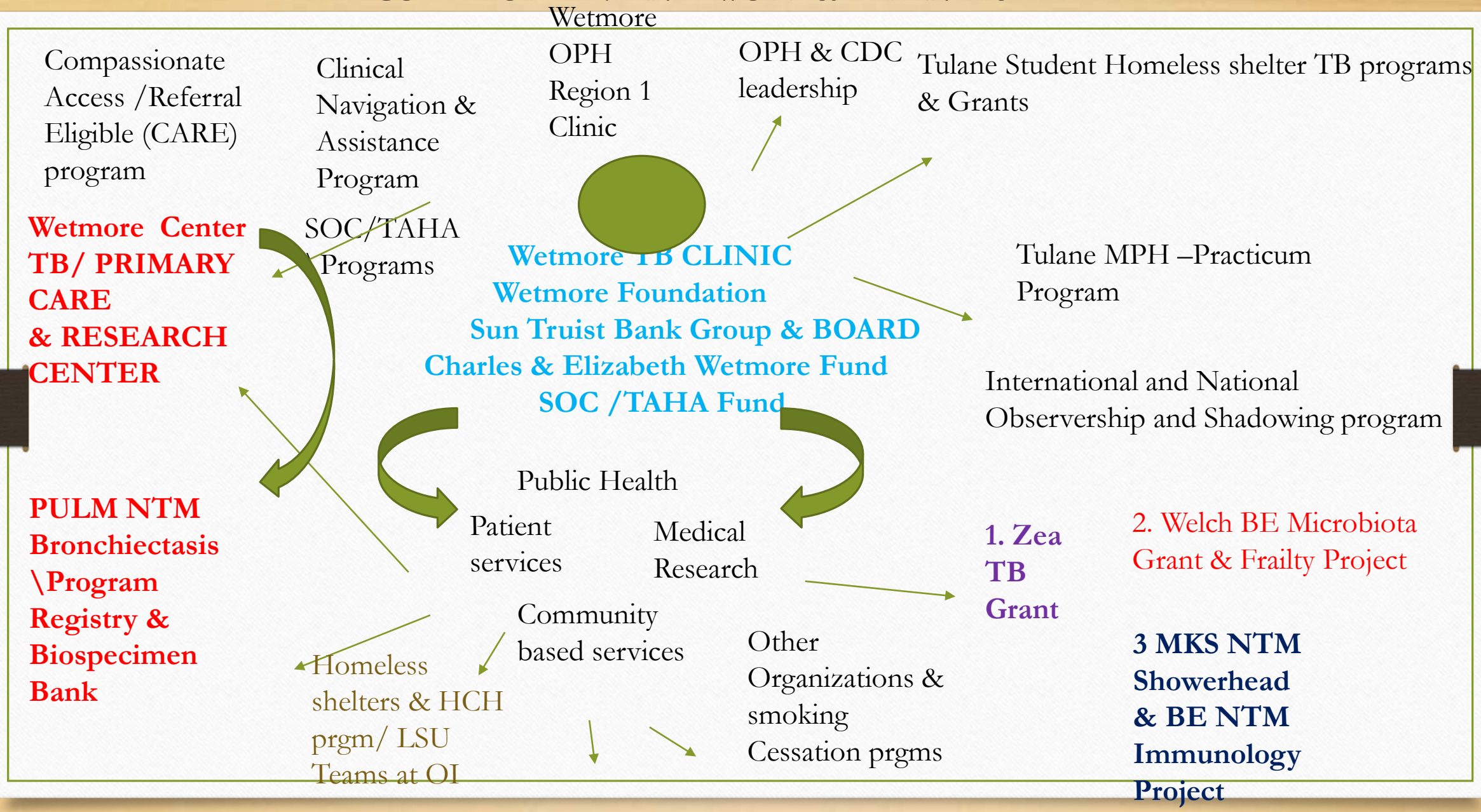
On going Clinical Trials

- 1. Bronchiectasis : Aspen trial Brensocatib
- 2. Arise and Encore Trials : ALIS plus … QOL
- 3. RedHill Multidrug FD combination trial
- 4. BE Research Registry
- 5. Resurrection of Clofazimine beyond Single pt IND and now mono Rx
- 6. PICORI Pragmatic 2 x 3
- 7. Establish sustaining compliance with ALIS (Amikacin Liposomal Inhaled Convert trials data)
- 8 Omadacyclin
- 9. Glutathione
- 10. Epetraborole

Part 2

Towards Program Development and Collaboration

THE COLLABORATIVE NETWORK & PARTNERSHIP



LSUHSC Non-TB Mycobacterial (NTM) - Bronchiectasis (BE) Center

A 7- star Comprehensive Multi-disciplinary Patient Care, Education and Clinical Research Program

2024 Leads
Dr. Shellito
Dr.MacRae
Dr.Wolfe

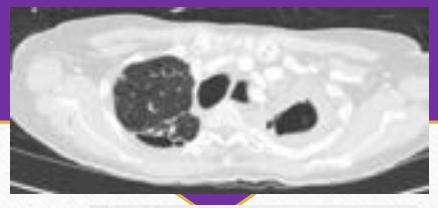
Michelle Koroh Sedgwick MD
Arnold Zea PhD

7. Coordination of care with multiple specialties/REGISTRIES BIOSPECIMEN BANKS /LSUHSC- SOPH/ NIAID and other National Centers Of Excellence and National Societies/ Super Mentors. Dr DW & JS

1. Chronic Care Concierge Patient Centered Comprehensive Programmatic Clinic Through LSU Health

6. Participation in NTM-BE Research Foundation /Bio-specimen Registries

Addressing the need to provide care for the "other COPD and the other TB" patients



2. Easy Access and Availability through Program Hotline with Telehealth Clinics

5. Eligibility in on going clinical trials and Environmental Studies IRB protocols

3. Patient Assistance & Compassionate Care Programs for eligible patients through IRB/IN Pathways

OTHER TEAM MEMBERS

1. Marie Sandi NP
2. P. Lauto
3. P Jadhav PhD
4. Anjel Guitroz
5. Shandrika Seymour

4. Support of Clinical Research and Navigation Team members under the Directorship of Dr. Juzar Ali & NTM-BE team in the section of Pulmonary /Critical Care/Allergy & Immunology.

LSU Health NEW ORLEANS
School of Medicine
Department of Medicine
Section of Pulmonary/Critical Care & Allergy/Immunology

The Troika: Clinical & Program TAKE HOME POINTS

- For the Primary Care Colleagues : **Awareness & Recognition**
- For Specialists dealing with Immune Compromised states: **Close Networking and Liaison**
- For Pulmonologists & ID teams : **Comprehensive Multidisciplinary Programmatic Care**
- For HealthCare System: **NEED TO SUPPORT THIS CONCEPT**
- For Academic Institutions : **Opportunity for Career and Growth & Importance of Front end Investment by Leadership to take Clinical care to Programmatic Development & Research**
- For Industry: **R&D/Education programs / Appreciate Huge Impact of such endeavors**

The work to continue.

Introducing Faculty at LSUHSC

Dr. Amy Wolfe : TB/ Post TB Lung Disease /Bronchiectasis

Dr.Shelby MacRae NTM and Non CF Bronchiectasis & NTM

Dr. Michelle Korah-Sedgwick : Immunology & Hypersensitivity in NTM &BE

Thank you for your kind participation today and ….

…….Thank you for ……..

Juzar Ali