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

The usual and the unusual
INTRODUCTION & ACKNOWLEDGEMENT
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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
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)

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.

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
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.
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
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)

<table>
<thead>
<tr>
<th>Severity criteria</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
<th>4 points</th>
<th>5 points</th>
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<tr>
<td>Age</td>
<td>&lt;50</td>
<td>50-69</td>
<td>-</td>
<td>70-79</td>
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<td>80+</td>
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<tr>
<td>BMI kg/m2</td>
<td>&gt;18.5</td>
<td>&lt;18.5</td>
<td>&lt;18.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>FEV1 % predicted</td>
<td>&gt;80%</td>
<td>50-80%</td>
<td>30-49%</td>
<td>&lt;30%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Hospital admissions in the past 2 years</td>
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<tr>
<td>Exacerbation frequency in last 12 months</td>
<td>0-2</td>
<td>3 or more</td>
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<td>MRC dyspnea score</td>
<td>1-3</td>
<td></td>
<td>4</td>
<td>5</td>
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<tr>
<td>Colonization status</td>
<td>Not colonized</td>
<td>Chronic colonization</td>
<td>P_{aeruginosa} colonization</td>
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<tr>
<td>Radiological severity</td>
<td>&lt;3 lobes involved</td>
<td>3 or more lobes or cystic changes</td>
<td></td>
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**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

PLUS FACED SCORE
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

**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

In Non CF:
- CFTR variants with single mutations
- Association with Vit D deficiency
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
The paradox of Cough In NTM Bronchiectasis

Is cough good or a bad?

ACT:

- Efficacy
- Indications
- Contra-indications
- Sustained Adherence
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/yr (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
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,
4. macrolide resistance,
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.
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

**MAN!! The Mycobacterial Freeway**

TB? RIPE
MK
MAC
A
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 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 given. 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.

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.)
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 persist.
- 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 *
<table>
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<tr>
<th>Treatment Options</th>
<th>GBT and/or</th>
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**LCB01-0371**
- Target 50S ribosome
  - For M. abs

**PIPD1**
- Target MmpL3
  - For M. abs

**Indole-2-carboxamides**
- Target MmpL3
  - For M. abs

**Thiacetazone derivatives**
- Target FAS-II dehydratase
  - For M. avium and M. abs

<table>
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<tr>
<th>Drug</th>
<th>Mechanism of action</th>
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<tr>
<td><strong>Clofazimine</strong></td>
<td>- Inhibition of cell wall synthesis</td>
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<tr>
<td><strong>Liposomal amikacin for inhalation (LAI)</strong></td>
<td>- Target 50S ribosome</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>- Target 50S ribosome</td>
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**Gaseous nitric oxide (gNO)**
- Enhance host defense
  - For NTM
  - Thiolanox® from novoteris

**β-lactams with avibactam**
- Target penicillin-binding protein
  - For M. abs and M. avium

**Nitric oxide**
- Enhance host defense
  - Produce reactive nitrogen intermediates
  - For CF patients with NTM (especially M. abs)
  - From AIT therapeutics

**Tedizolid**
- Target 50S ribosome
  - For NTM

**Bedaquiline**
- Target ATP synthase
  - For NTM

**Rifabutin**
- Target RNA polymerase
  - For M. abs

**Mechanism of action**
- Inhibition of cell wall synthesis
- Inhibition of protein wall synthesis
- Inhibition of nucleic acid synthesis
- Other mechanisms

*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)
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) in 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 remain 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