NYU Langone Health

Division Name

NON-TUBERCULOUS MYCOBACTERIUM: MANAGEMENT

Doreen J. Addrizzo-Harris,MD

Professor of Medicine

Co-Director, NYU Bronchiectasis Program

Associate Director for Education and

Faculty Affairs

Division of Pulmonary, Critical Care and Sleep Medicine

Conflict of Interest

- Principal Investigator for bronchiectasis trials
  - Insmed
  - Aradigm
  - Novartis
  - US Bronchiectasis Research Consortium

NYU Langone Health

NTM Management- First Steps

Non-Pharmacologic Therapy

NYU Langone Health

Bronchopulmonary Hygiene

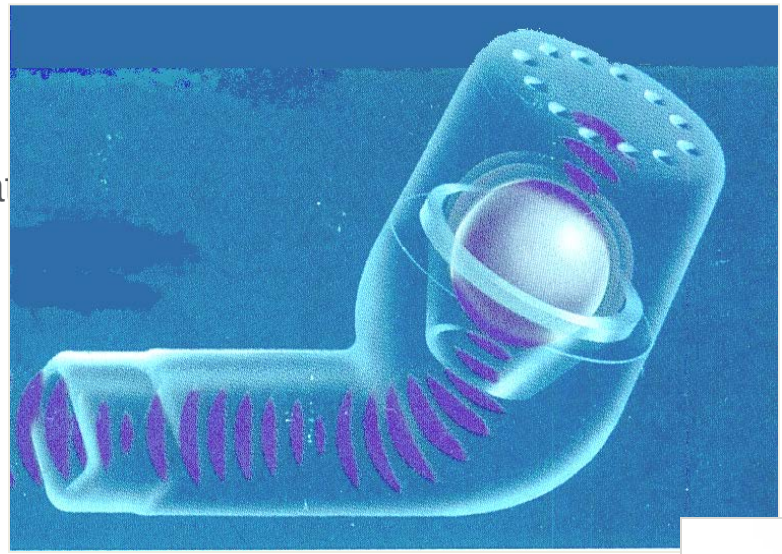
- Airway hygiene techniques
  - Chest percussion and postural drainage
  - Autogenic drainage
  - Positive expiratory pressure (PEP) therapy
  - Airway oscillation valves
  - High frequency chest compression

- Pharmacologic Agents
  - Bronchodilators (e.g., beta-adrenergic)
  - Hypertonic saline 7%, 3%, 0.9% normal saline

Vibratory PEP Devices

- Presenta

Flutter® Device



AerobiKA

High frequency chest compression

Acapella™ Device

- **Nutrition**
  - Accurate assessment of caloric intake
  - Formal nutrition consult

- **Exercise Program**
  - Structured Cadiopulmonary program
  - Cardiopulmonary Assessment with independent exercise program
  - Routine exercise program

Who Should Be Treated with Antibiotics?

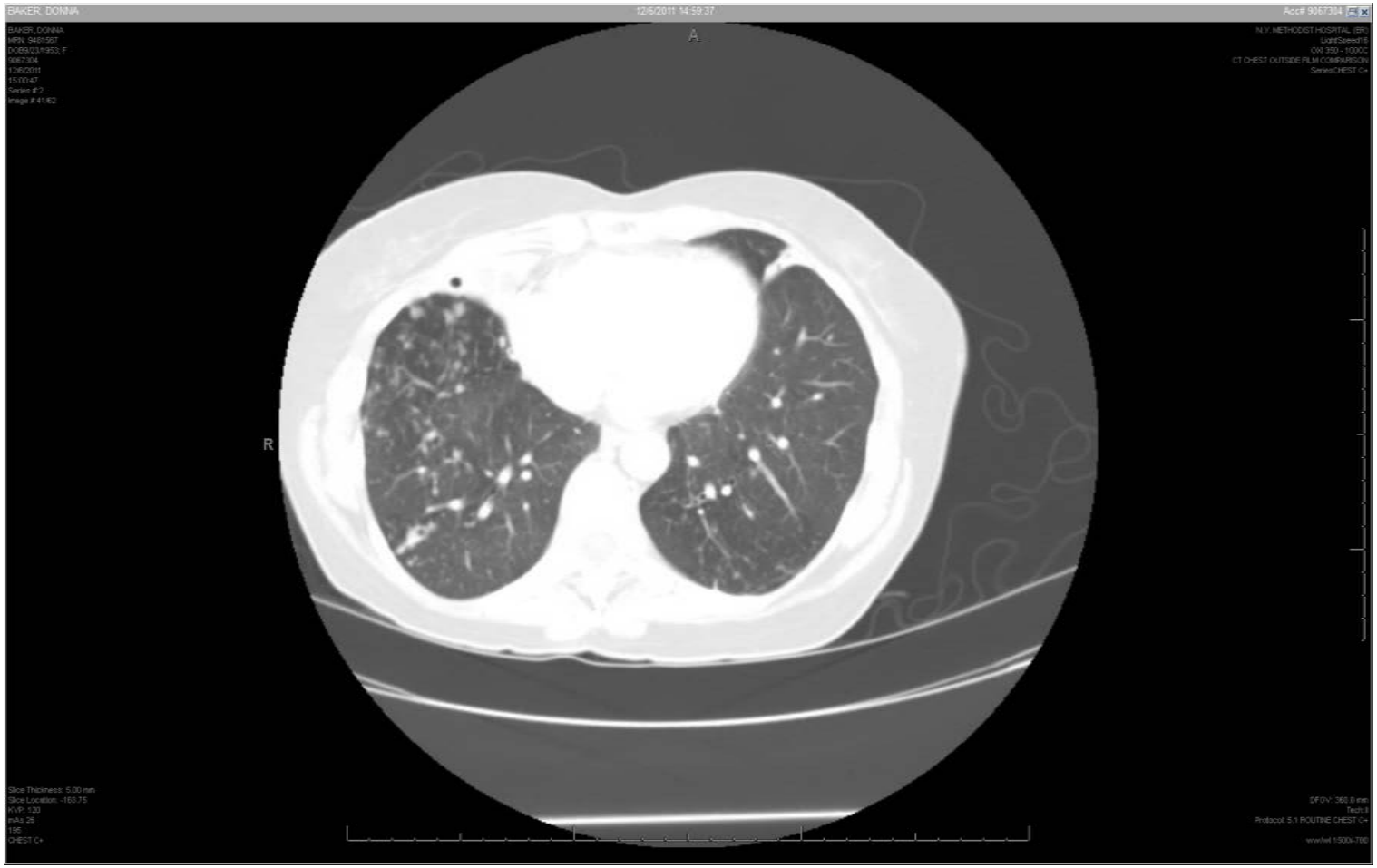
Yes

- Clinical symptoms
  - Pulmonary
  - Constitutional
- Radiographic findings
  - Extent of disease
  - Disease progression
- Other factors
  - Younger Age
  - Co-morbidities
    - Immunosuppression

Probably/maybe no

- Minimal to no symptoms
  - Pulmonary
  - Constitutional
- Minimal radiographic findings
  - ?how often to scan
- Other factors
  - Very advanced age
  - Co-morbidities
- Co-infected with other organisms
  - Bacterial cultures
  - Fungal cultures

MAC fibronodular



MAC Fibronodular Macrolide sensitive

Medication	dosage	frequency
macrolide	Clari 1000 mg OR azithro 500mg	Three days per week
ethambutol	25mg/kg	Three days per week
rifampin	600mg	Three days per week
aminoglycoside	N/A	

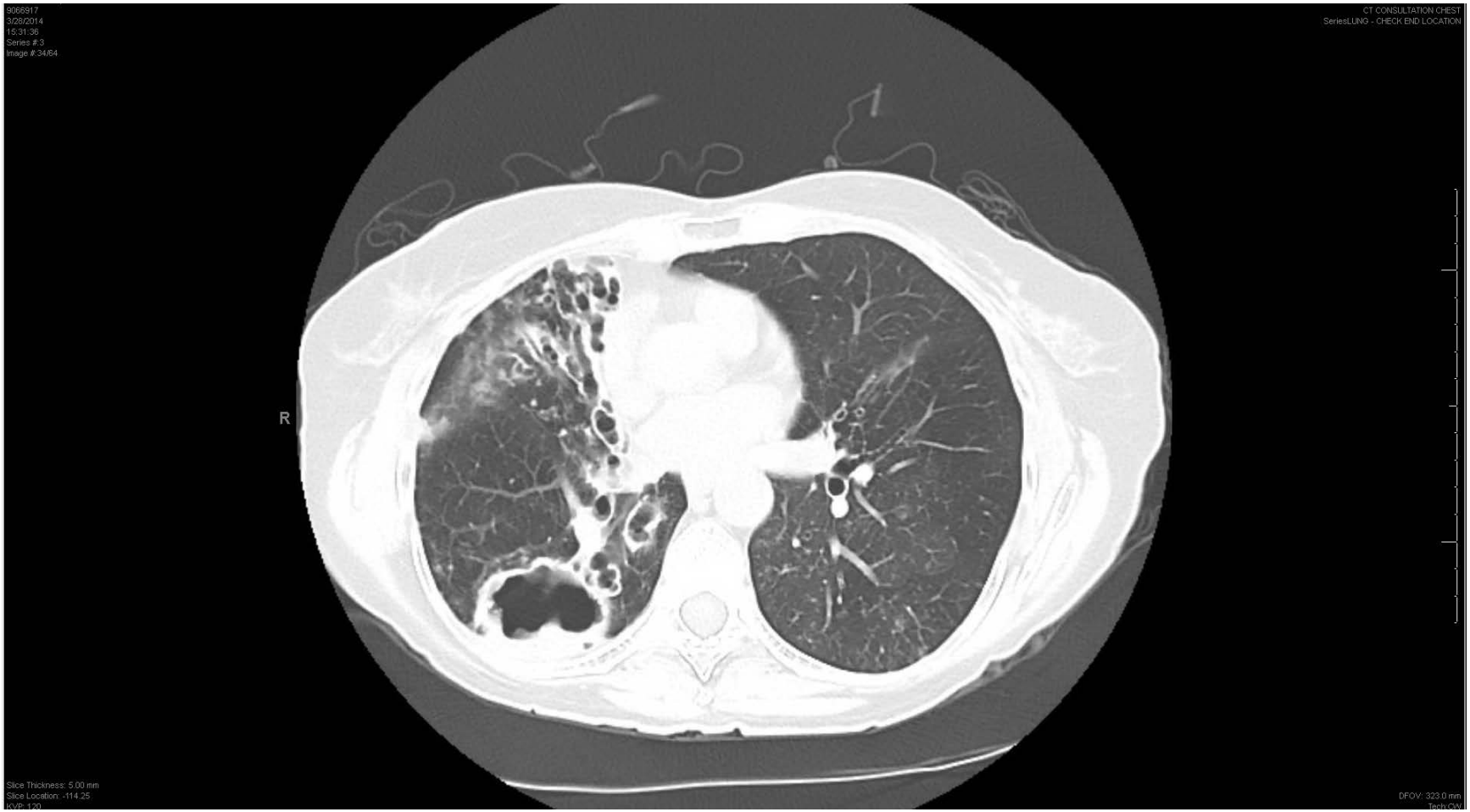
MAC Fibronodular Lung Disease: Treatment

- 180 patients
  - Completed > 12 Months of macrolide/azalide therapy
  - No differences in clarithromycin vs azithromycin
  - Treatment modification increased in daily (80%) vs intermittent (1%)
  - Treatment success achieved in 84% of patients
  - Microbiologic recurrences in 48% after completion of therapy – 75% reinfection isolates/25% true relapse
    - » Wallace RJ, et al Chest 2014 Aug 146:276-82

MAC Fibronodular Lung Disease: Treatment

- **Relapse vs Reinfection of Mycobacterium Avium Complex Pulmonary Disease**
  Patient characteristics and macrolide sensitivity
  Boyle et al, Ann Am Thor Soc 2016
    - 25% suffered a clinical recurrence; 54% relapse/46% reinfection
    - Median time to recurrence was significantly lower in the relapse to reinfection group (210 days vs 671 days, P= .004).
    - MIC for macrolides were significantly more likely to increase in the relapse group vs reinfection group (80% vs 33%, P= .002).
  - Conclusion:
    - True relapse patient with pulmonary NTM recur earlier than reinfection
    - Routine use of pulse- field gel electrophoresis may be beneficial as those with relapse have an increasing macrolide MIC compared to reinfections
    - Need for susceptibility testing in patients with recurrences?

MAC Fibrocavitary



NYU Langone Health

MAC Fibrocavitary

medication	dosage	frequency
macrolide	Clari 500mg/BID Azithro 250 mg	daily
ethambutol	15 mg/kg	daily
rifampin	600 mg	daily
Aminoglycoside Localized	amikacin IV Surgery	uncertain

Additional therapies/treatment

- Inhaled amikacin
- Clofazamine
- Oxazolidinone (linezolid, tedozolid)
- Bedaquiline

Quinolones (moxifloxacin, levofloxacin) – no evidence of in vitro or in vivo efficacy

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

- Phase II, efficacy and safety study of liposomal amikacin for inhalation, double blind placebo controlled
- 89 patients were enrolled; 57 with MAI, 32 with M abscessus (of these 17 also had CF)
- LAI vs placebo was added to multi-drug regimen in patients with persistently positive sputums after a minimum of 6 months of treatment; 81% of patients were on at least 1 year of therapy and 47% were on 2 years or more.
- After 84 days; all patients entered an open label phase of 84 days

NYU Langone Health

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

- Primary endpoint was change from baseline to day 84 on a semi-quantitative mycobacterial growth scale.
  - Other endpoints included sputum conversion, 6-minute walk distance, and adverse events.
- Primary endpoint was not achieved (P=0.072); however, a greater proportion of the LAI group demonstrated ≥1 negative sputum cultures (32% [14/44] vs. 9% [4/45]; P=0.006) and improvement in 6-minute walk test (+20.6 vs. −25.0 meters; P=0.017) at day 84.

- Treatment effect was predominantly in patients with non-CF MAI patients.

NYU Langone Health

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

Adverse events

- The majority (~90%) of patients in both groups experienced at least one treatment-emergent adverse event; most were mild to moderate
- LAI versus placebo
  - dysphonia (43.2% vs. 8.9%)
  - bronchiectasis exacerbation (38.6% vs. 20.0%)
  - cough (31.8% vs.13.3%)
  - oropharyngeal pain (20.5% vs. 2.2%)
  - fatigue (15.9% vs. 8.9%)
  - chest discomfort (11.4% vs. 0%)
  - wheezing (9.1% vs. 2.2%)
  - infective pulmonary exacerbation of cystic fibrosis (9.1% vs. 2.2%)

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

Serious events

- In the double-blind phase, the overall incidence of serious adverse events was higher in the LAI group compared with the placebo group (18.2% vs. 8.9%)
  - bronchiectasis exacerbation (2 LAI; 1 placebo)
  - pneumonia (1 LAI; 2 placebo)

- Renal events – 1 mild event; Audiology - 5 events

NYU Langone Health

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

Conclusions

- This study indicates that in select patients with treatment-refractory non-CF MAI disease, LAI added to guidelines-based therapy can achieve early and sustained negative sputum cultures.
- No patient isolate with a molecularly determined amikacin resistance mutation or a MIC of greater than 64 μg/ml achieved culture conversion.
- Culture conversion in response to treatment with LAI may be associated with improvements in functional capacity;
- Relative to treatment with parenteral amikacin there is limited systemic toxicity.

NYU Langone Health

Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease

Olivier, et al Am J Resp Crit Care Med 2017

- Phase III CONVERT trial closed.
- Demonstrated the addition of liposomal amikacin to guideline based therapy eliminated evidence of NTM lung disease caused by MAC in sputum at month 6 in 29% compared with 9% in the placebo group(P< 0.0001).

NYU Langone Health

Long-term follow up of Mycobacterium Avium Complex lung Disease in Patients Treated With Regimens Including Clofazimine and /or Rifampin. Jarand J, et al. *CHEST* 2016

- Retrospective review of patient with MAC lung disease treated and monitored at least 6 months post treatment.
- Aim was to evaluate clinical and microbiologic response in patients treated with clofazimine and/or rifampin

- 107 patients were included
  - 90 (84%) clofazimine/ethambutol and macrolide
  - 14 (13%) rifampin/ethambutol and macrolide

NYU Langone Health

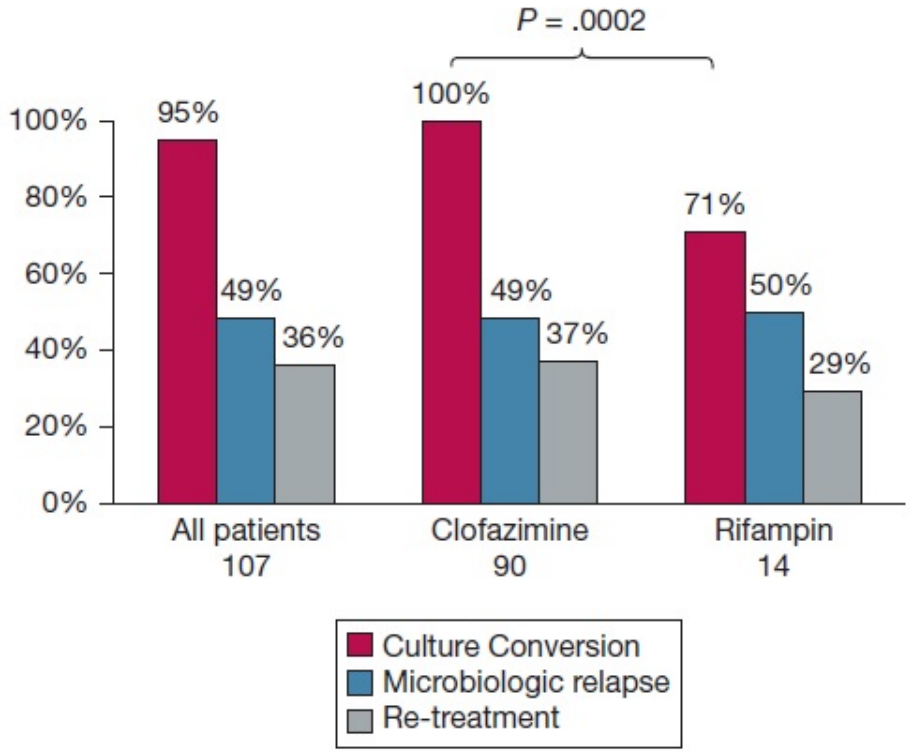


Figure 2 – *Culture conversion, microbiologic relapse, and re-treatment rates.*

Long-term follow up of Mycobacterium Avium Complex lung Disease in Patients Treated With Regimens Including Clofazimine and /or Rifampin. Jarand J, et al. *CHEST* 2016

- Results
  - Ethambutol was the drug most commonly stopped (14 patients) in either arm due to visual changes (12 patients)
  - Of the 93 patients who received clofazimine, 6 (6.5%) stopped due to side effects
  - 5 due to skin darkening or rash; 1 due to hallucinations

- Summary
  - In this cohort, both initial outcomes and re-treatment rates were better or as good in the clofazimine arm vs the rifampin containing regimens.
  - Clofazimine should be considered as an alternative drug for the treatment of MAC lung disease

NYU Langone Health

Safety and Effectiveness of Clofazimine for Primary and Refractory Nontuberculous Mycobacterial Infection

Martinino, et al CHEST 2017

- Observational-cohort study to assess clofazimine safety, tolerability and clinical outcomes in patients treated with clofazimine as part of a multidrug regimen between 2006-2014
- Included pediatric and adult patients with CF and non-CF disease with pulmonary and extra pulmonary NTM infection
- Results
  - 112 patients included; 24 with CF
  - 78% had refractory disease with failure to previous therapy
  - 48% had *M. abscessus;* 37% had *M. avium* complex; 14% mixed
  - Median use of clofazimine was 383 days
  - 50% (41 of 82) of patients with pulmonary disease converted to negative cultures within 12 months

NYU Langone Health

Clofazimine Therapy

Jarand J, et al. CHEST 2016
Martinino, et al CHEST 2017
Yang, et al Antimicrobial Agents and Chemotherapy 2017

- Summary
  - Clofazimine is a safe and reasonable alternative in this cohort, both initial outcomes and re-treatment rates were better or as good in the clofazimine arm vs the rifampin containing regimens.
  - Clofazimine should be considered as an alternative drug for the treatment of MAC lung disease

NYU Langone Health

Treatment duration and monitoring

- Treatment is usually 18-24 months;
- A minimum of 12 months after culture conversion

- Monitor patient closely for response and for side effects; need baseline and serial:
  - Labs
  - EKG
  - Audiometry
  - Ophthalmology exam
  - Physical exam and weights
  - Monthly sputums for AFB
  - Follow up CT scan/ PFTs

M. Abscessuss

- Need speciation
  - *M. Abscessus/Chelonea* (not the same!)
  - *M. Abscessus* subsp *abscessus* (*massiliense* and *bolletii*)
    - Erm gene in 80%
    - Macrolide resistant
  - Often need multiple IV antibiotics
    - Base decisions on treatment on sensitivities
    - Sample regimen
      - Macrolide, IV amikacin, IV tigecyclin, linezolid
    - Can back down to oral and inhaled therapy at times
    - Need to have 12 months of negative cultures

When to consider surgery??

- Refractory to antibiotic treatment/toxicity
- Significant recurrent hemoptysis
- Baseline pulmonary function permits surgical resection
- Localized disease
- Experienced surgeon
- Good follow-up for treatment regimen
  - Pre and post surgery

Treatment and management pearls

- Discuss your options with your physician
- Don’t be afraid to ask questions
- Follow your physicians recommendations; do your airway clearance; exercise; monitor your diet
- Track any changes in symptoms or side effects and contact your physician early
- Seek additional assistance through local patient groups; NTMir; COPD Foundation