Management Challenges in NTM

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Disclosures

- Paid by Insmed to moderate an Advisory board meeting re: Results of recent trial of ALIS (Amikacin liposome inhalation suspension).

Management Challenges in NTM- Outline

- Diagnosis
- Treatment
- Prognosis
- Response to Treatment
- Side Effects of Treatment
- Getting patients on the right Treatment!

NTM Pulmonary Infection- Introduction

- Series of female patients
  - No pre-existing lung disease
  - Lingula and Middle lobe
  - Mean age 65 yrs old
  - Fibronodular disease
- Hypothesis
  - "ladies don't spit"
  - "female patients are more fastidious":
    - Lady Windermere: "How do you do Lord Darlington. No I can't shake hands with you. My hands are all wet with the roses"

Riech J, Johnson R. ***Mycobacterium avium*** **Complex Pulmonary Disease Presenting as an Isolated Lingular or Middle Lobe Pattern*** The lady Windemere Syndrome. Chest 1992

Management Challenges in NTM

How do we diagnose NTM Pulmonary Disease?

NTM Pulmonary Disease Diagnostic Criteria

Clinical
1. Pulmonary symptoms, typical chest imaging (multifocal bronchiectasis, multiple small nodules)
2. Exclusion of other diagnoses
Microbiologic (one of the following)
1. Positive cultures from 2 sputum samples
2. Positive culture from 1 BAL
3. Biopsy with typical histopathology and positive culture- or typical histopathology with positive culture on either sputum or BAL.

Griffith DE, Aksamit T, Brown-Elliott BA, et al. ***An Official ATS/IDSA Statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial diseases****. Am J Respir Crit Care Med 2007*

NTM species

M. avium Complex (MAC)
M. kansasii
M. abscessus
M. chelonae
M. fortuitum
M. genavense
M. gordonae
M. haemophilum
M. immunogenum
M. malmoense
M. marinum
M. mucogenicum
M. nonchromogenicum
M. scrofulaceum
M. simiae
M. smegmatis
M. szulgai
M. terrae complex
M. ulcerans
M. xenopi

NTM Pulmonary Disease Diagnostic Criteria

- >120 identified species of NTM with a wide spectrum of virulence.
- Diagnostic criteria based on experience with the most common pathogens (MAC, M. kansasii, M. abscessus)
- Unrealistic to expect that a single set of Diagnostic criteria would apply to all.

Management Challenges in NTM

When do we treat?

NTM Pulmonary Disease- What Happens?

Yamazaki Y et al. **Markers Indicating Deterioration of Pulmonary MAI Infection**. AJRCCM 1999.

- Retrospective analysis of 57 patients in a hospital in Japan with MAI pulmonary infection between 1994 and 1997.
- None of the patients were started on treatment at the time of diagnosis.
  - All were observed >=12 months.
  - Sputum evaluations (set of 3) Q3months.
  - CT performed at intervals of12 months.
  - Lab data collected at start of observation period.
  - Observed for 28 +/- 13 months.
  - Classified as Deteriorated or Not-deteriorated group
    - (CT and change in sputum culture from negative to positive)
  - All had nodular bronchiectasis.

NTM Pulmonary Disease- What Happens?

Yamazaki Y et al. **Markers Indicating Deterioration of Pulmonary MAI Infection**. AJRCCM 1999.

Deteriorated Group (34/57)- 60%

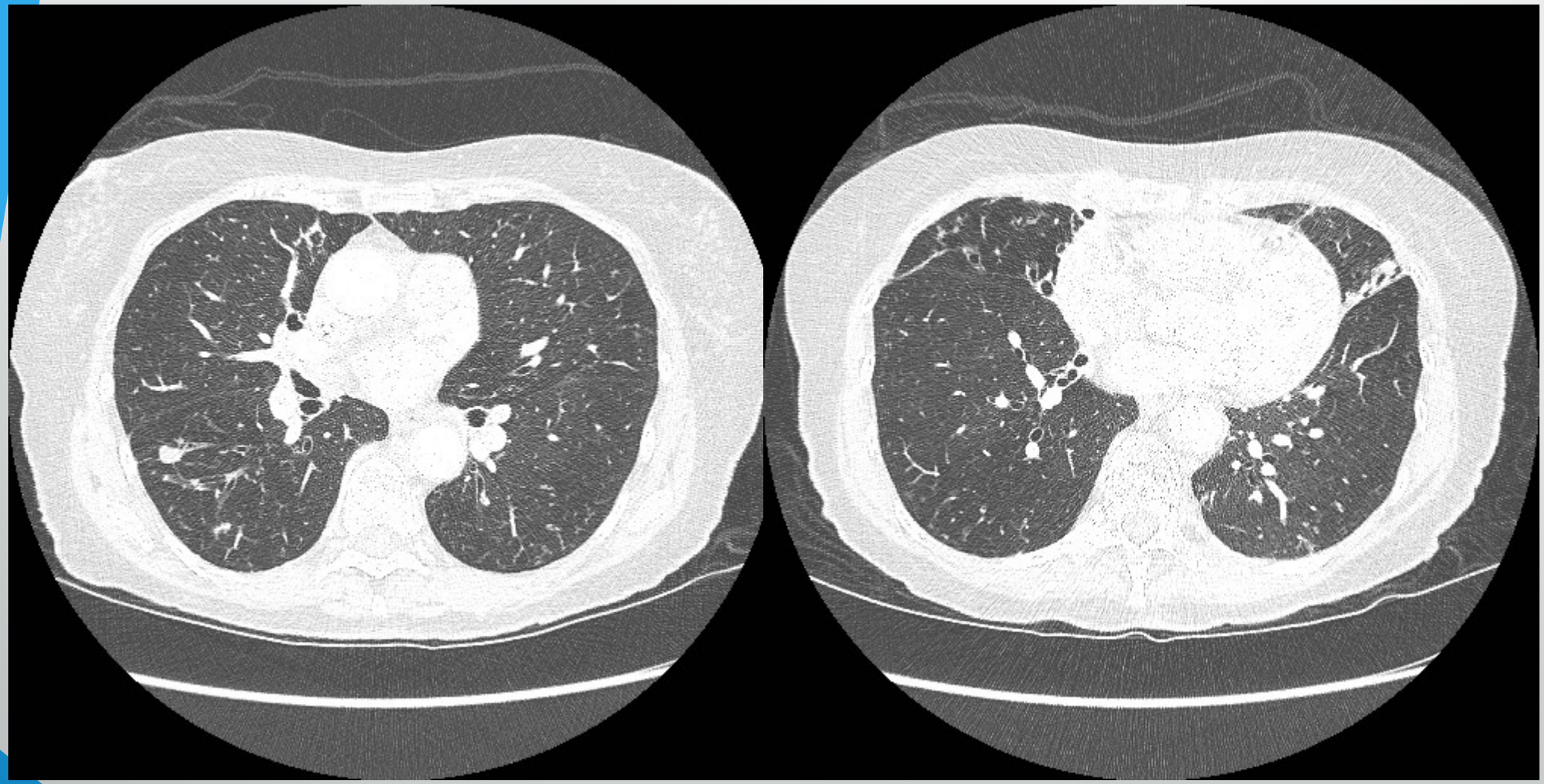
- 31 female
- Mean age 69
- Mean BMI 19.2
- CRP/ESR significantly increased.
- Smear positive
- BAL with higher percentage PMN's.

Not-Deteriorated Group (23/57)- 40%

- 20 female
- Mean age 57
- Mean BMI 21.5

NTM Patient- When do we treat?

- 79 yo Caucasian lady with hx of ovarian cancer.
  - Work up revealed a nodule on CXR Jan. 2009.
  - CT chest



NTM Patient- When do we treat?

- 79 yo Caucasian lady with hx of ovarian cancer.
  - Work up revealed a nodule on CXR Jan. 2009.
  - CT chest
  - BAL 7/09 AFB smear positive. Culture MAC.

NTM Patient- When do we treat?

- Treatment for MAC was never started- minimal clearing of the throat each morning.
- recurrence of ovarian cancer.
  - Underwent another debulking surgery and more chemo in 2011
  - 2015: restarted chemo for increased tumor burden.
- Continued to follow for her MAC PD.
  - Most sputum cultures are positive for MAC.
  - Never started on therapy.
  - Minimal respiratory symptoms and maintained lung function and exercise tolerance.

Management Challenges in NTM

- Clinical Significance and Epidemiologic Analyses of Mycobacterium avium and Mycobacterium intracellulare among Patients without AIDS. Xiang Y. Han1,*, Jeffrey J. Tarrand1, Rosa Infante2, Kalen L. Jacobson2 and Mylene Truong. J Clin Microbiol. 2005.
  - Intracellulare more pathogenic, infects women more

- Isolation of Nontuberculous Mycobacteria (NTM) from Household Water and Shower Aerosols in Patients with Pulmonary Disease Caused by NTM. Rachel Thomson, Carla Tolson, Robyn Carter, Chris Coulter, Flavia Huygens, Megan Hargreaves. J Clin Microbiol. 2013.
  - Avium is caught from the environment.

Management Challenges in NTM

What happens when we treat?

Therapy of MAC Lung Disease- ATS 2007

- Clarithromycin or azithromycin
- Rifampin
- Ethambutol
  - Nodular bronchiectatic disease. 3x/week.
  - Cavitary and severe nodular/bronchiectatic. Daily.
    - Consider IV amikacin or streptomycin 3x/week.
- Continue until culture-negative > 1 year.

Griffith DE, Aksamit T, Brown-Elliott BA, et al. ***An Official ATS/IDSA Statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial diseases****. Am J Respir Crit Care Med 2007*

Therapy of MAC Lung Disease- What to expect

- Wallace et al. Chest 2014.
  - Retrospective single center review of 180 patients with MAC lung disease who completed >12 months of therapy.
    - 95% white, 90% female, 68% lifetime nonsmokers.
    - Mean age at first positive culture for MAC 67 +/- 12.
    - 86% sputum conversion to negative. (3 months in a row)
    - 14% had relapse while on therapy
      - 16/21 were new genotypes (reinfection)
      - 5/21 were identical genotypes (true relapse)
  - Recurrence: 48% (75% reinfection, 25% true relapse)

NTM Pulmonary Disease- Challenges

- High Rates of Adverse events
  - >90% of patients report at least one side effect
    - **Lam PK…. Catanzaro A.** AJRCCM 2006.
  - 29% of patients changed treatment regimens.
    - **Sim YS** et al. Yonsei Med J. 2010.
- Duration of treatment > 14-16months.
- Interaction with other medications.
- Diagnostic criteria: Not all NTM are equal.

Therapy of MAC Lung Disease- Challenges

- No relationship between clinical efficacy and MIC testing has been shown for any drugs:
  - Except Macrolides (Kobashi Y et al. J Infect Chemother 2006).
- Macrolide Resistant MAC Lung Disease.
  - Worse outcomes (Griffith D. AJRCCM 2006):
    - 5% achieved sputum conversion in macrolide-resistant MAC not treated with surgery and IV meds. (macrolide sens 70-80%).
    - One year mortality in those that remain culture positive 34%. (0% for those who converted)
    - Largest risk factor: Macrolide monotherapy.
  - Increasing concern with increased use of macrolides for non-CF bronchiectasis and COPD.

Lack of Adherence to Evidence-based Treatment Guidelines for Nontuberculous Mycobacterial Lung Disease

Jennifer Adjemian[1,2], D. Rebecca Prevots[1], Jack Gallagher[3], Kylee Heap[3], Renu Gupta[4], and David Griffith[5]

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- 582 physicians who treated NTM within the past 12 months were surveyed electronically.
  - Eligible physicians were asked to extract demographic, laboratory, and treatment data from the records of patients with diagnosed PNTM disease under their care.
  - For patients to be eligible:
    - seen by the physician within the previous 12 months.
    - diagnosed with *M. abscessus*– or MAC-associated lung disease.
    - currently under the study physician's care.
    - not been diagnosed with tuberculosis in the previous 12 months.

Lack of Adherence to Evidence-based Treatment Guidelines for Nontuberculous Mycobacterial Lung Disease

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- 81% MAC and 19% M. abscessus.
- Only 13% of regimens prescribed to patients with MAC met the 2007 ATS/IDSA guidelines.
  - The majority of regimens prescribed to patients with MAC (57%) did not include a macrolide at all.
  - 30% of regimens prescribed are associated with an increased risk of developing macrolide resistance.
- Only 7% of regimens met the guidelines for M. abscessus.

Challenges in NTM Lung Disease- summary

- Diagnostic uncertainty
- Wide spectrum of severity of symptoms.
- Indolent disease, uncertain natural history.
- Comorbid conditions.
- Cost of medications.
- Inability to tolerate medications.

Bibliography

- Riech J, Johnson R. ***Mycobacterium avium* Complex Pulmonary Disease Presenting as an Isolated Lingular or Middle Lobe Pattern*** The lady Windemere Syndrome. Chest 1992
- *Griffith DE, Aksamit T, Brown-Elliott BA, et al.* ***An Official ATS/IDSA Statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial diseases****. Am J Respir Crit Care Med 2007*
- Yamazaki Y et al. **Markers Indicating Deterioration of Pulmonary MAI Infection**. AJRCCM 1999.
- Xiang Y et al. **Clinical Significance and Epidemiologic Analyses of Mycobacterium avium and Mycobacterium intracellulare among Patients without AIDS**. J Clin Microbiol. 2005.
- Thomson R et al. **Isolation of Nontuberculous Mycobacteria (NTM) from Household Water and Shower Aerosols in Patients with Pulmonary Disease Caused by NTM**. J Clin Microbiol. 2013.
- Wallace et al. **Macrolide/Azalide Therapy for Nodular/Bronchiectatic *Mycobacterium avium* Complex Lung Disease**. Chest 2014
- *Lam PK et al.* ***Factors Related to Response to Intermittent Treatment of MAC Lung Disease****. AJRCCM 2006*
- Sim YS et al. **Standardized Combination Antibiotic Treatment of *Mycobacterium avium* Complex Lung Disease**. Yonsei Med J. 2010
- *Kobashi Y et al.* ***Relationship between clinical efficacy of treatment of pulmonary Mycobacterium avium complex disease and drug-sensitivity testing of Mycobacterium avium complex isolates****. J Infect Chemother 2006*
- *Griffith DE et al.* ***Clinical and Molecular Analysis of Macrolide Resistance in Mycobacterium avium Complex Lung Disease****. AJRCCM 2006*
- Adjemian J et al. *Lack of Adherence to Evidence-based Treatment Guidelines for Nontuberculous Mycobacterial Lung Disease.* **.** Ann Am Thorac Soc. Jan 2014