

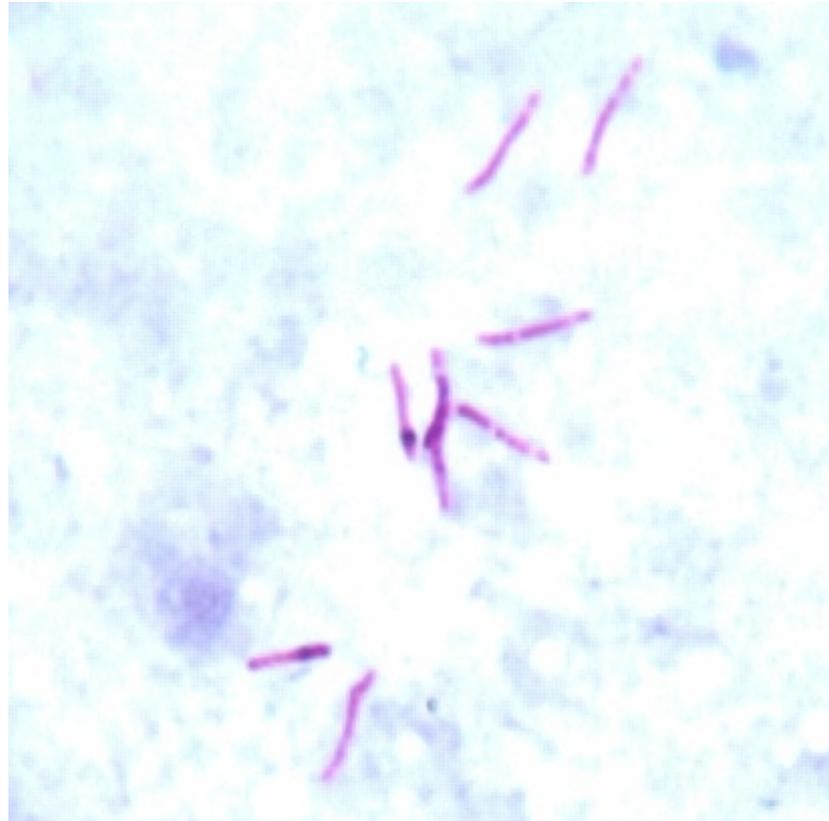
Approach of the Treatment of Nontuberculous Mycobacterial Lung Disease (NTM):What Providers Need To Know

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I have no disclosures.

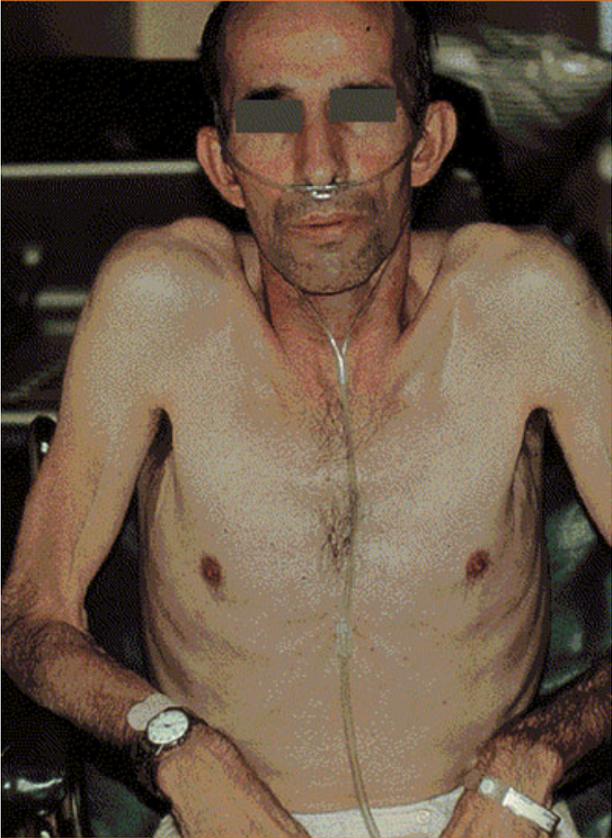


Smear or culture +AFB

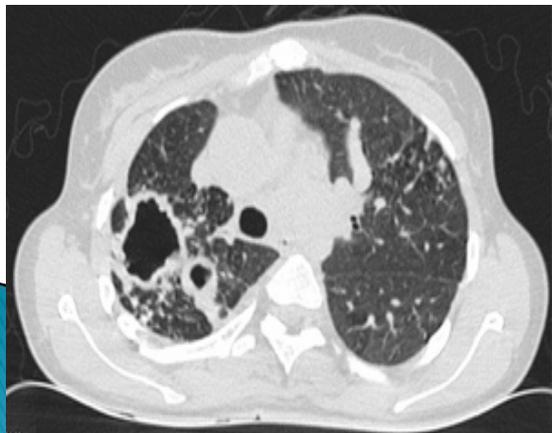


How Do We Get NTM?

- ▶ Direct inhalation of NTM contaminated soils and aerosols
 - ▶ Micro aspirated NTM-contaminated NTM water from the oropharynx into the lungs
 - ▶ GERD
 - ▶ For skin and soft tissue, direct inoculation of NTM containing soils, water or medications
- 



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Epidemiology

1. Prevalence of NTM pulmonary disease is increasing globally, in some countries NTM disease significantly more common than TB
2. Over 150 species of NTM identified
3. The prevalence of NTM pulmonary disease increases with age especially in females
4. ? The most common cause of chronic cough in older women?
5. Different species have different clinical relevance and different ecologic reservoirs: better data needed on environmental distribution and risk factors by species

Who, what, when and where
do we treat NTM?



It can become complicated....



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

(Adjemian, Annals of the American Thoracic Society, et al 2013)

- 1286 physicians randomly selected and contacted to participate
 - 95 % Pulmonary, ID, IM or FP/GP
- All physicians:
 - Actively involved in patient care
 - Sample geographically representative, not based on prior knowledge of PNTM
 - Must have seen ≥ 1 PNTM patient diagnosed in last 12 mo with MAC or *M. abscessus* and currently under physician's care
 - Not diagnosed with TB in past 12 mos

*13% of antibiotic regimens prescribed to MAC patients met the ATS/IDSA Guidelines

*56% did not include a macrolide

*16% were for macrolide monotherapy



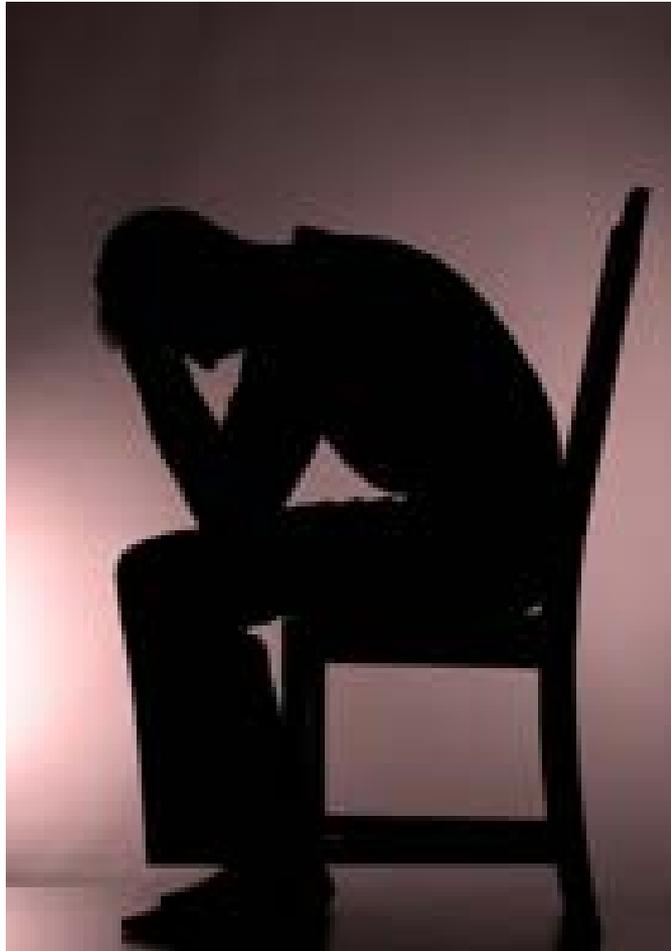
Lack of Adherence to Evidence-based Treatment Guidelines for NTM Lung Disease

(Adjemian et al 2013 in press)

- ▶ Most patients were treated primarily by ID (39%) or pulmonologist (37%)
- ▶ Patients
 - 53% male
 - 49% white, 27% black, 11% Hispanic, 9% Asian/Pacific.

**It is Better to Light a
Candle.....Than to Repeat the
Opinions of Experts.**





NTM Lung Disease

- a) Common species
 - b) Diagnosis
 - c) Treatment
 - d) Future outlooks
- 

NTM cases

In the US: MAC > M. kansasii > abscessus

1. *M. kansasii*
2. *M. fortuitum*
3. Hot tub lung
4. *Mycobacterium avium* complex (MAC)
5. Surgery for focal disease
6. *M. abscessus*

Clinically distinguishing NTM disease from TB

▶ Scenario

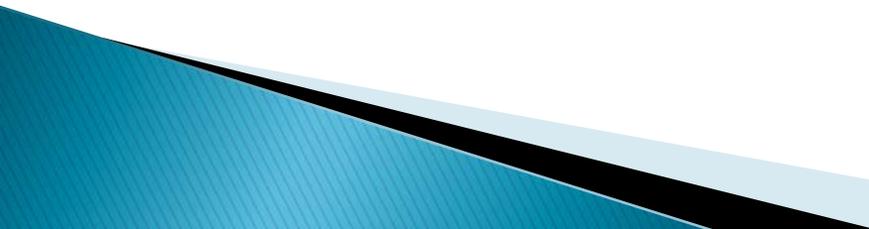
- 35 yo male from Mexico
- History of TB in family
- Several months cough, sweats, weight loss
- (+) PPD
- CXR: apical cavitary consolidation
- 1st sputum AFB culture (+) for MAC

Clinically distinguishing NTM disease from TB

▶ Scenario:

- Pulmonary MAC disease unusual in a 35 yo male
- Multiple risk factors for TB
- Clinical presentation typical for TB
- Patient subsequently grew multiple (+) cultures for *M. tuberculosis*
- Empiric therapy for TB ok in this setting, may occur frequently

Case I

- ▶ 65 yo smoker with COPD seen by his PCP with chronic cough.
 - ▶ Interestingly, a chest CT is available for your review. One sputum had been sent and grew *M. kansasii*.
 - ▶ Does this patient meet criteria for diagnosis of NTM?
 - ▶ Is *M. kansasii* a pathogen?
 - ▶ What do you do?
 - ▶ Do you think this patient can obtain cure?
- 



ATS guidelines for diagnosis of pulmonary NTM

MUST HAVE ALL 3:

1. Clinical – compatible signs/symptoms (cough, fatigue, fever, weight loss, DOE, hemoptysis), documented deterioration in clinical status AND reasonable exclusion of other diseases
2. Radiographic – *CXR*: infiltrates (progressive or persistent), cavitation or multiple nodules or *HRCT*: multiple small nodules and/or multifocal bronchiectasis (if baseline films > 1 yr, should show progression)
3. Microbiologic – At least 2 positive sputums or at least one positive bronchial washing or bronchial lavage or tissue biopsy with pathologic finding consistent with mycobacterial disease (granulomatous inflammation and/or AFB positive)

▶ **Does this patient meet criteria for diagnosis of NTM?**

No. (based on only having one sputum that is positive) Should you bronch him?

▶ **Is *M. kansasii* a pathogen?**

yes, unless there is no clinical evidence to support the diagnosis

▶ **What do you do?**

Obtain more sputum and start him on daily INH 300 mg qd, Rifampin 600 mg qd, Ethambutol 15 mg/kg/d and treat for 12 months from 1st negative sputum. (usually 18–24 months)
Alternatively, MAC therapy can be used.

▶ **Do you think this patient can obtain cure?**

Yes

Case 2– Mrs. P from LA

- ▶ 76 yo with a history of CAD, HTN, osteoporosis, interstitial lung disease, ulcerative colitis, fibromyalgia, GERD, breast cancer s/p chemotherapy (adriamycin) with complaints of abdominal pain which is attributed to kidney stones. Her PCP orders an abd CT and finds one small patchy area of ground glass with several subcentimeter nodules in both lower lobes. She has no respiratory complaints at the time of her visit.
- ▶ Sputum cultures are obtained and 1 / 3 becomes positive for *M. fortuitum*

Which of her above comorbid conditions is highly associated with *M. fortuitum*?

What work-up should be done?

Which of her above comorbid conditions is highly associated with *M. fortuitum*?

GERD/chronic aspiration

What work-up could be done?

Esophagram +/- ph prob, barium swallow

Therapy?

Elevate the HOB, dietary changes, PPI

Case 3 of Mr. T from Miami, FL

48 yo with 6 months h/o chronic cough which began in March 2010. Sought medical attention and was placed on albuterol with minimal relief. An abnormal CXR prompted further evaluation.



ROS: dry cough which is bothersome on a daily basis. Denies fevers, night sweats, nausea, vomiting, joint pains, rashes, dry eyes, dry mouth, chest pain, painful lumps or bumps, conjunctivitis, ulcers, alopecia, weight loss, visual changes, reflux

PMH:
HTN

PSH:
None

FH:
Mother – asthma

Social: smoked 2–3 cigs per day during his freshman year of college only. Married; 2 children, works as an attorney. 1 small poodle, no feather pillows. No recent travel.



- ▶ Ultimately, underwent bronchoscopy with TBBX – inflammatory cell infiltrates in alveoli and interstitial spaces consisting of lymphocytes, plasma cells, activated macrophages and giant cells.

Culture from BAL grew MAC

Diagnosis?

Does this patient meet criteria for diagnosis of NTM?

What do you do?

Hot tub lung

- ▶ **Does this patient meet criteria for diagnosis of NTM?**
close – symptoms but positive culture from BAL plus radiographic changes (no nodular bronchiectasis or fibrocavitary lesions)
- ▶ **What do you do?**
remove the offending source; many would treat as hypersensitivity and not give antibiotics.

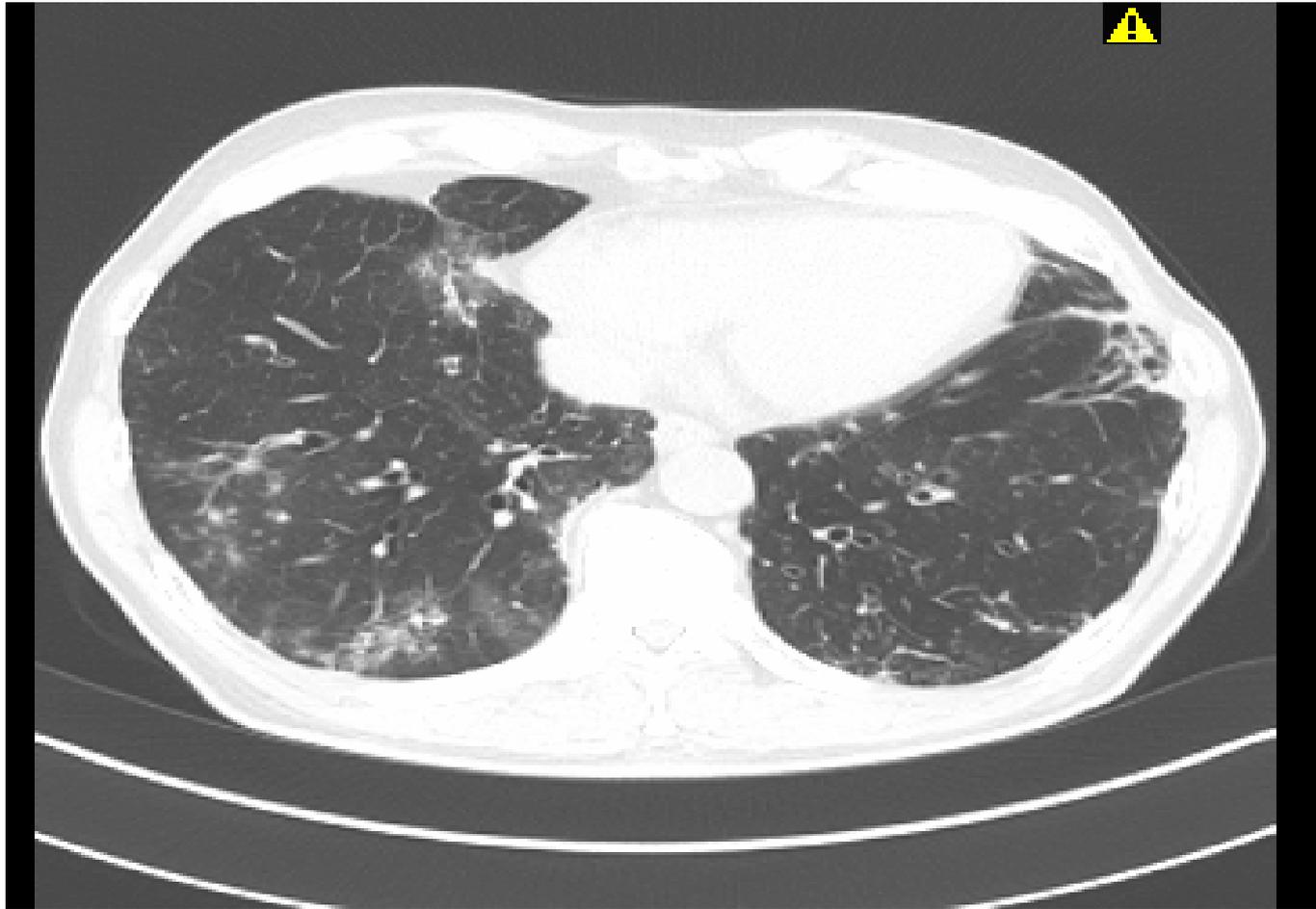
Case 4 – Mr. P from Georgia

- ▶ 82 yo with complaints of a persistent cough diagnosed in July 2010. He had abnormal imaging and was smear positive for MAC.
- ▶ Placed on TIW therapy of azi, eth, rif but developed some dizziness so was switched to clari, eth, rifabutin in December 2010. Continued on this therapy TIW but remained smear positive. (over 8 smear positive sputums)
- ▶ Comes with continued cough, weight loss of 20lb and night sweats
- ▶ On no airway clearance

What is the treatment for MAC?

How do you interpret susceptibility testing?

Mr. P. 82 yo with smear + MAC



Therapy of MAC Lung Disease

ATS NTM Guidelines

- ▶ Cavitory disease: macrolide/EMB/rifamycin ± injectable: DAILY
 - ▶ Nodular/bronchiectatic disease: macrolide/EMB/rifamycin: INTERMITTENT*
 - ▶ Severe or previously treated disease: macrolide/EMB/rifamycin/injectable: DAILY
 - ▶ Duration: 12 months sputum culture negativity while on therapy
- *Not indicated for severe and/or cavitory disease

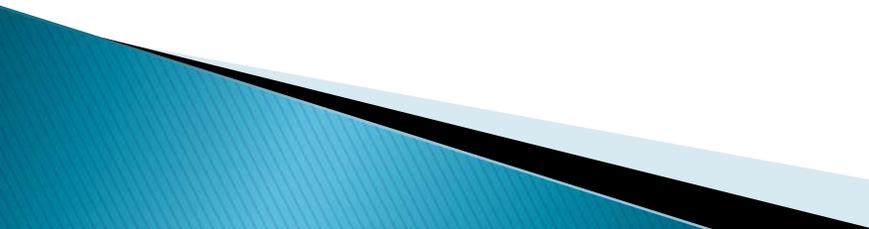
Macrolides for MAC Disease

- Treatment success correlates with in vitro MIC (susceptible $< 8 \mu\text{g/ml}$, intermediate $16 \mu\text{g/ml}$, resistant $> 32 \mu\text{g/ml}$)
- ▶ Disease progression/relapse associated with MIC $> 32 \mu\text{g/ml}$
 - ▶ There are no drugs, other than the macrolides for which there is a correlation between in vitro susceptibility (MIC) and in vivo response for disseminated or pulmonary MAC disease. (*and now amikacin)

Is this disease treatable?



Macrolide/Azalide Therapy for Nodular Bronchiectatic MAC lung disease (Wallace, et. al. Chest, 2014)

- ▶ 180 patients completed >12 of therapy
 - ▶ Sputum conversion occurred in 86% percent of patients (156/180)
 - ▶ No difference between azi and clari patients
 - ▶ Modification of treatment regimen occurred more often in daily vs TIW
 - ▶ No cases of macrolide resistance
- 

Macrolide/Azalide Therapy for Nodular Bronchiectatic MAC lung disease (Wallace, et. al. Chest, 2014)

- ▶ Microbiologic recurrence on therapy – 14%
 - 73% – reinfection
 - 27% – true relapse
- ▶ Overall, treatment success (sputum conversion without microbiologic relapse) achieved in 84%.

Macrolide/Azalide Therapy for Nodular Bronchiectatic MAC lung disease (Wallace, et. al. Chest, 2014)

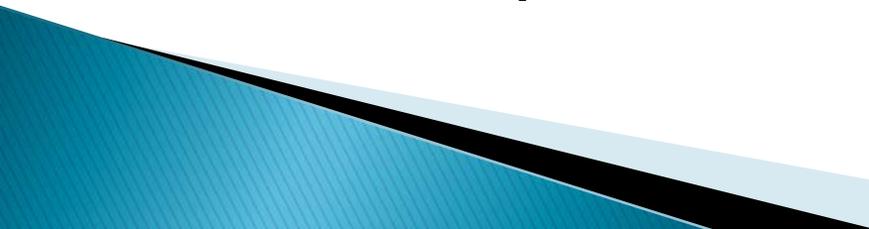
Microbiologic recurrence after therapy– 48%
75% – reinfection
25% – true relapse

Macrolide/Azalide Therapy for Nodular Bronchiectatic MAC lung disease (Wallace, et. al. Chest, 2014)

CONCLUSIONS:

- ▶ Favorable microbiologic outcomes for many patients without promotion of macrolide resistance.
 - ▶ Intermittent therapy is effective and significantly better tolerated than daily therapy.
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Case 5– Mr. M from Las Vegas

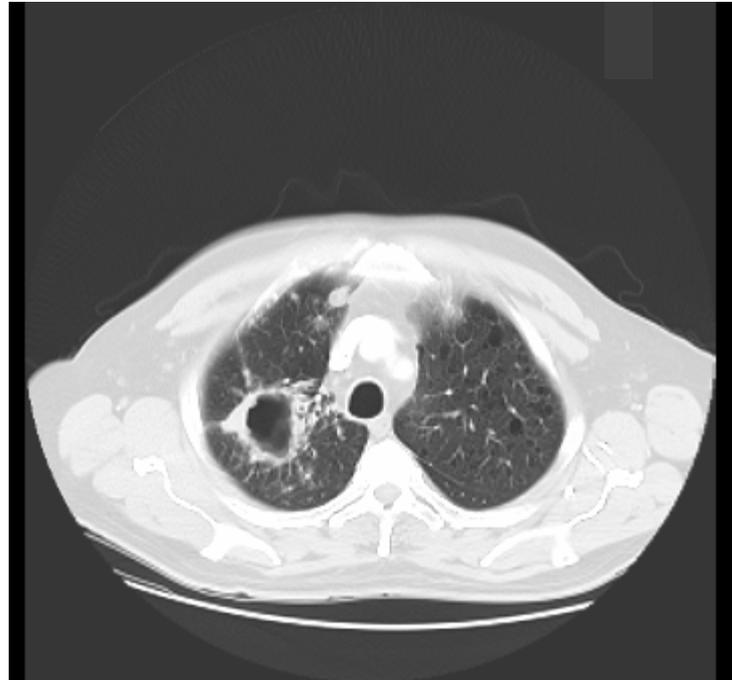
- ▶ 72 yo with a 20 pack year h/o tobacco, quitting in 1980 who in August of 2009, developed wheezing. He was seen by his PCP where an abnormal CXR prompted further work-up.
 - ▶ Diagnosed with MAC in October 2009 by sputum and bronchoscopy culture.
 - ▶ Started 3 drug daily therapy with azithromycin, ethambutol, rifampin
- 

- ▶ In December, developed severe numbness to his toes. His sputums remained positive but his pulmonary symptoms disappeared.

Results from studies

- ▶ Sputum – remained positive for MAC, azi sensitive
- ▶ Alpha-1 WNL
- ▶ Immunoglobulins WNL
- ▶ CF mutations – none
- ▶ CMP, CBC normal
- ▶ B12, TSH, folate, SPEP normal
- ▶ 25-OH D – 16
- ▶ PFTS: FEV1 3.18 L (85% predicted) normal ratio, DLCO 77% predicted
- ▶ Barium swallow normal
- ▶ Esophagram – small hernia
- ▶ Visual acuity – 20/20 both eyes
- ▶ Audiogram – high frequency hearing loss bilaterally

Mr. M



What to do next?



Early surgery better?

- ▶ 22 patients in Japan who received median of 17 months of antibiotics. All received surgical intervention (i.e. lobectomy, segmentectomy, partial lung resection)
- ▶ Post-operatively antibiotics continued for 6–35 months post surgery
- ▶ All patients were alive at 46 months
- ▶ FVC and FEV1 were reduced in both groups but maintained at 89% and 84% of the preop values
- ▶ MAC disappeared from sputum after surgery in all patients. Functional capacity was maintained

Plan for Mr. M....

- ▶ IV amikacin for 2 months prior to surgery and for at least 2 months post-operatively as well. Weekly CMP, CBC, amikacin levels 30 min after each dose with goal 20–25. Monthly audiogram
 - ▶ Continue azithromycin, rifampin daily.
 - ▶ BID acapella
 - ▶ GERD lifestyle changes
- 

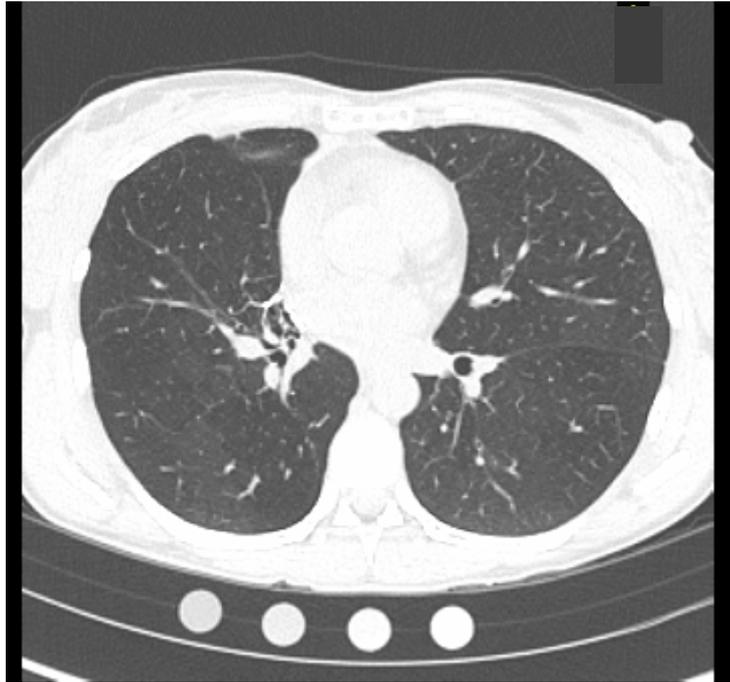
Surgery for NTM

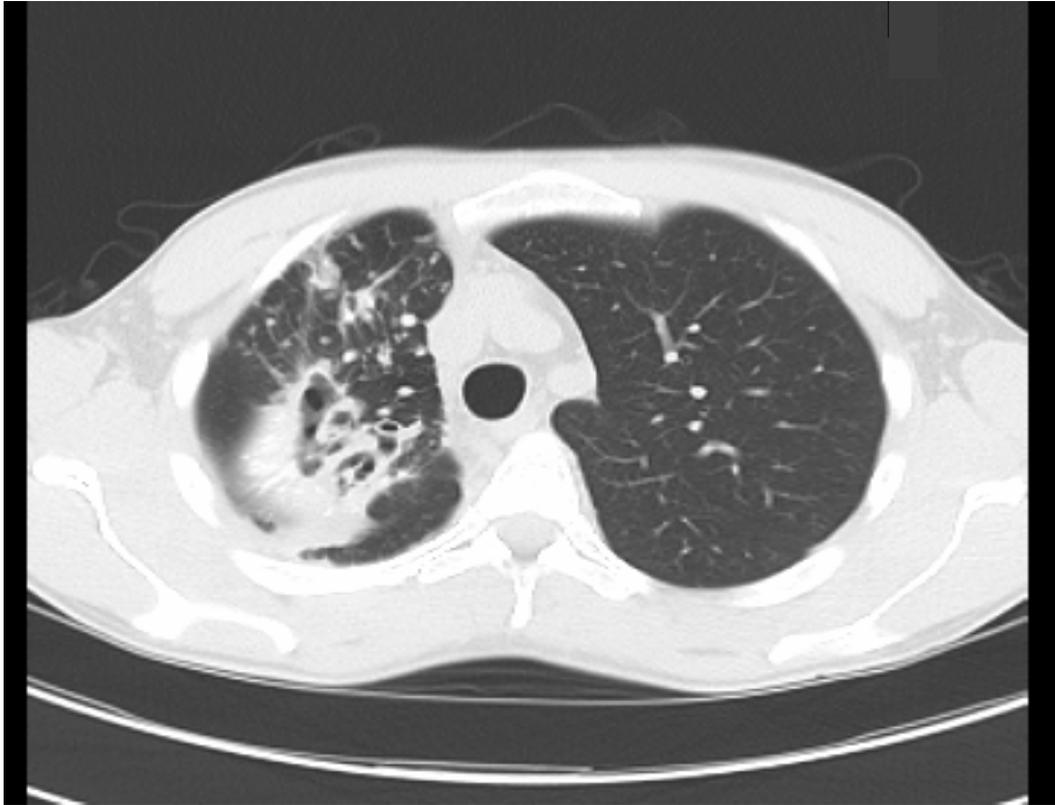
- ▶ Mostly for MAC, *Abscessus*
 - ▶ Usually with localized disease
 - ▶ V/Q scan
 - ▶ Always treat with combination of po and IV antibiotics before surgery (goal of at least 2 months prior)
 - ▶ Maintain adequate nutritional status
 - ▶ Referral to an experienced surgical center
- 

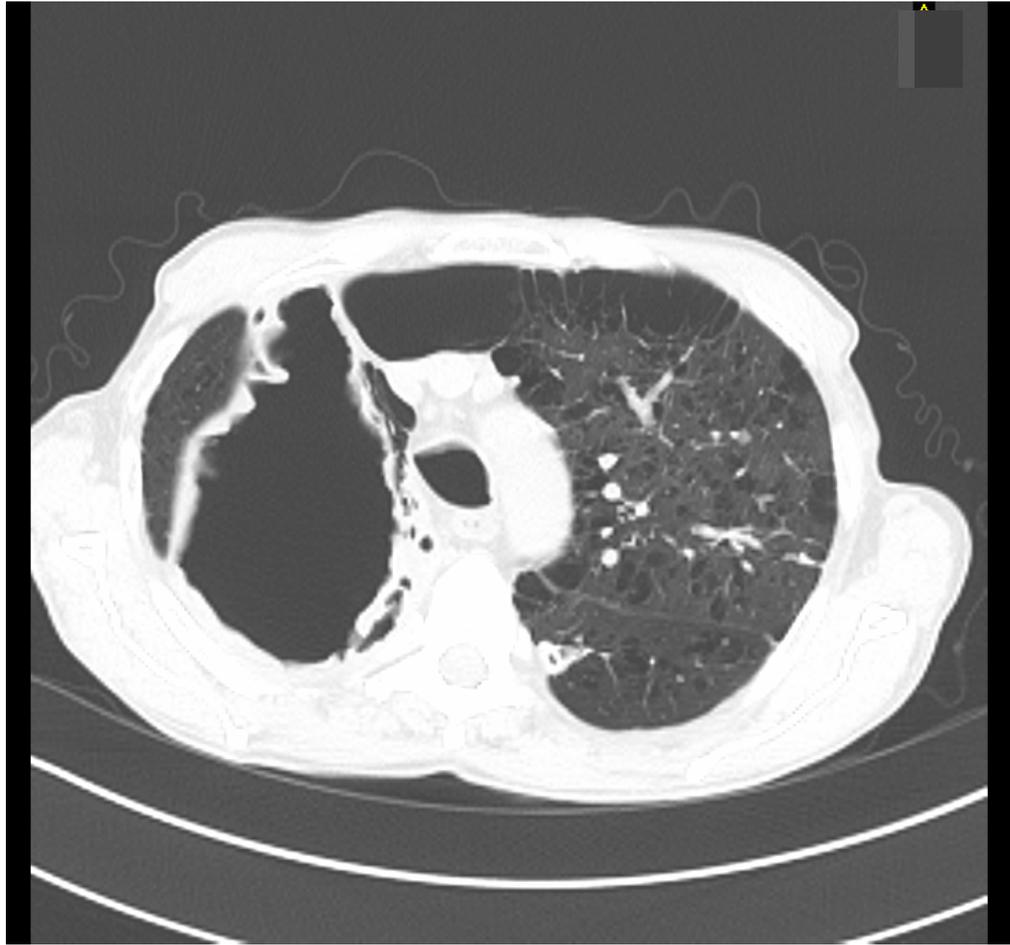
RML Bronchiectasis



Post lobectomy







Case 6

76 yo female with nodular bronchiectasis referred for multiple cultures positive for *M. abscessus*

She has a history of treated MAC lung disease 5 years ago with three drug therapy. She has a “terrible” cough, 5lb weight loss, no hemoptysis. Major fatigue and occasional night sweats.



M. abscessus

There is no predictably or reliably effective medical treatment strategy for *M. abscessus* lung disease.

Treatment of *M. abscessus* Lung Disease

- ▶ Macrolide: value questionable (*erm* gene), may be of value as immune modulator
- ▶ Amikacin 10–15 mg/kg 3–7X/week (we start at 7 mg/kg)
- ▶ Tigecycline 25–50 mg/day
- ▶ Linezolid 300–600 mg/day
- ▶ Alternatives: Imipenem, ceftazidime, clofazimine

Future Outlooks

- ▶ Inhaled amikacin
 - ▶ Bedaquiline?
- 

Nontuberculous Mycobacterial Lung Disease





Thank you

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