Mycobacterium Avium Complex (MAC) Infection: Diagnosis & Treatment

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Objectives

- Overview of Mycobacterium Avium Complex (MAC)
- Diagnosis of Nontuberculous Mycobacteria (NTM)
- Treatment of Mycobacterium Avium Complex (MAC)
- NTM cases

Nontuberculous Mycobacteria(NTM) Are Not A Contraindication to Lung Transplantation

1.All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease.

2.Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and commence treatment before transplant listing.

3.Treatment should be by, or in collaboration with, a physician experienced in the treatment of such patients.

4.Patients with progressive pulmonary or extrapulmonary disease due to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.

Weill D, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the ISHLT. J Heart Lung Transplant. 2015 Jan;34(1):1-15.

Overview of NTM

Over 200 different isolates of NTM have been identified

>80% of isolates in the United States are *Mycobacterium Avium* Complex (MAC)

Mycobacterium Avium Complex (MAC)

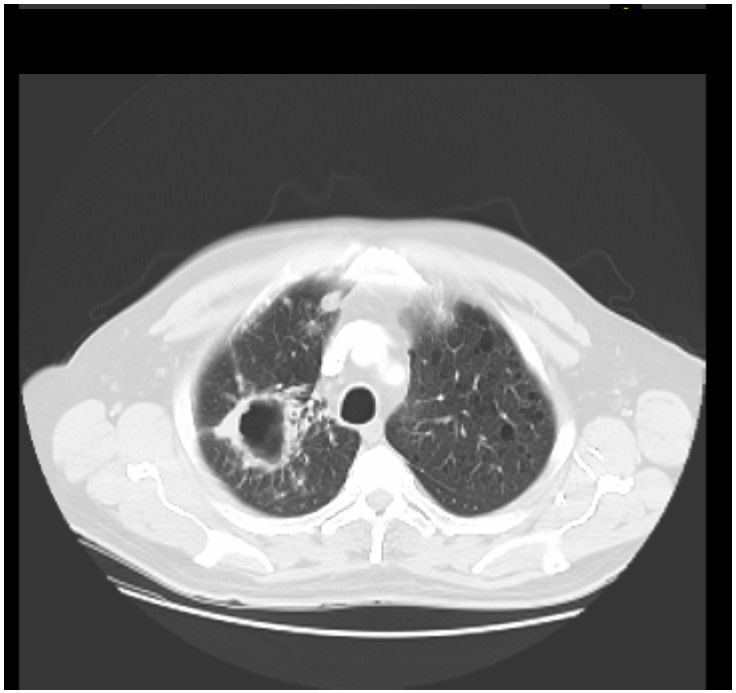
- *M. vulneris*
- *M. colombiense*
- *M. mantenii*
- *M. arosiense*
- *M. timonesne*
- *M. bouchedurhonense*
- *M. avium*
- *M. marseillense*
- *M. paraintracellulare*
- *M. intracellulare*
- *M. yongonense*
- *M. chimaera*

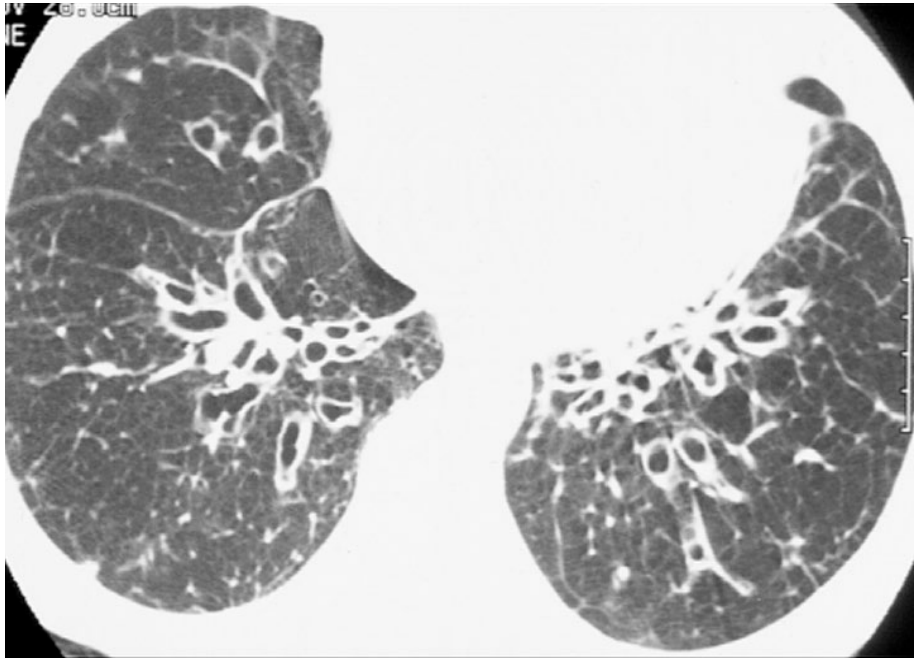
Mycobacterium Avium Complex (MAC)

M. avium and *M. chimaera* – water sources. *M. intracellulare* - ??

May have a higher rate of recurrence but are felt to be less virulent and often present with less advanced disease than *M. intracellulare*

Wallace, et al, J clin micro 2013. 51; 1747
Koh, WJ, et al. CHEST 2012, 142: 1482
Boyles, et al. AJRRCM 2015: 191:1310
Moon, et al. Diag Micro Infec Dise 2016: 86:382

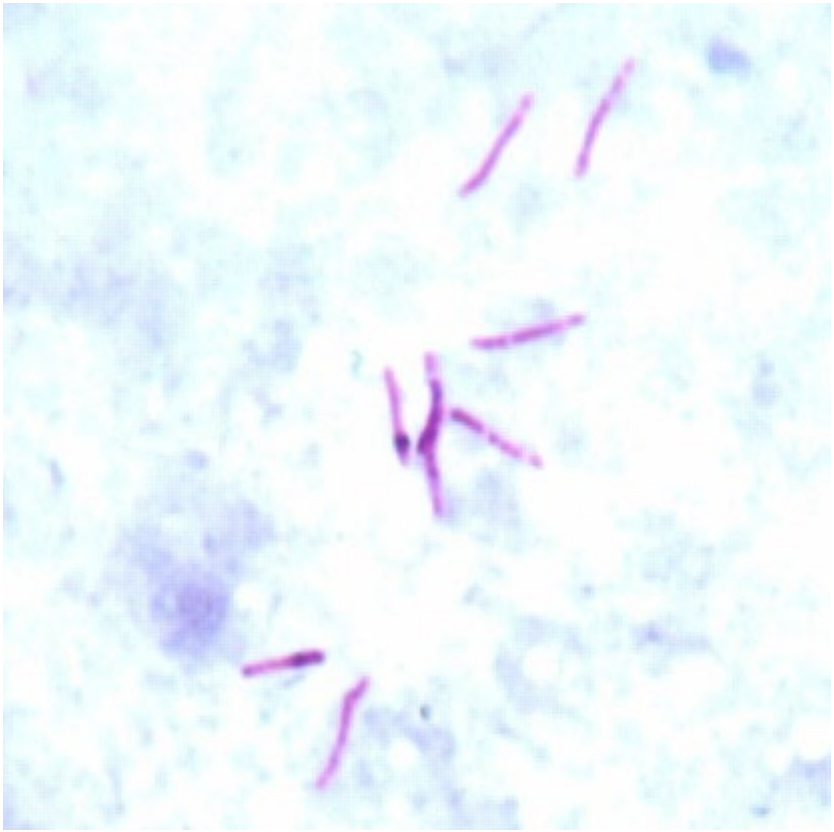




Diagnostic Testing

- Sputum for AFB, gram stain and culture, fungus
- Bronchoscopy (if no mucous production)
- Biopsy (rarely indicated for pulmonary disease diagnosis; often required for skin/soft tissue)

Smear or culture +AFB



It can become complicated….

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

1286 physicians randomly selected:

95 % Pulmonary, ID, IM or FP/GP

All physicians:

- Actively involved in patient care
- Must have seen ≥ 1 PNTM patient diagnosed in last 12 mo with MAC or *M. abscessus*

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

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

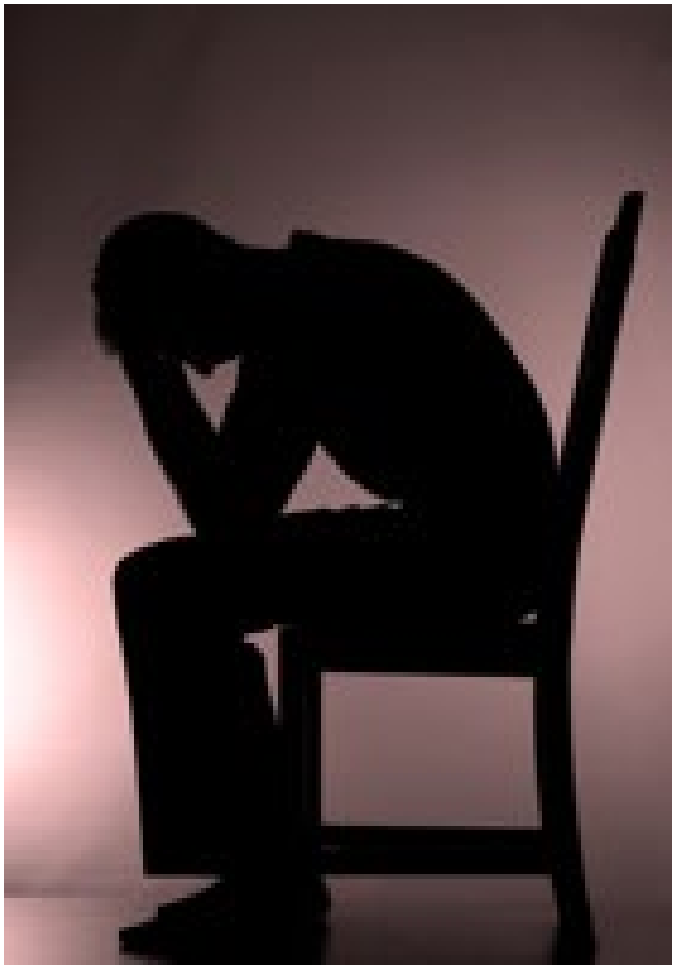
*56% did not include a macrolide

*16% were for macrolide monotherapy

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

(Adjemian et al 2013)

- Most patients were treated primarily by ID (39%) or pulmonologist (37%)



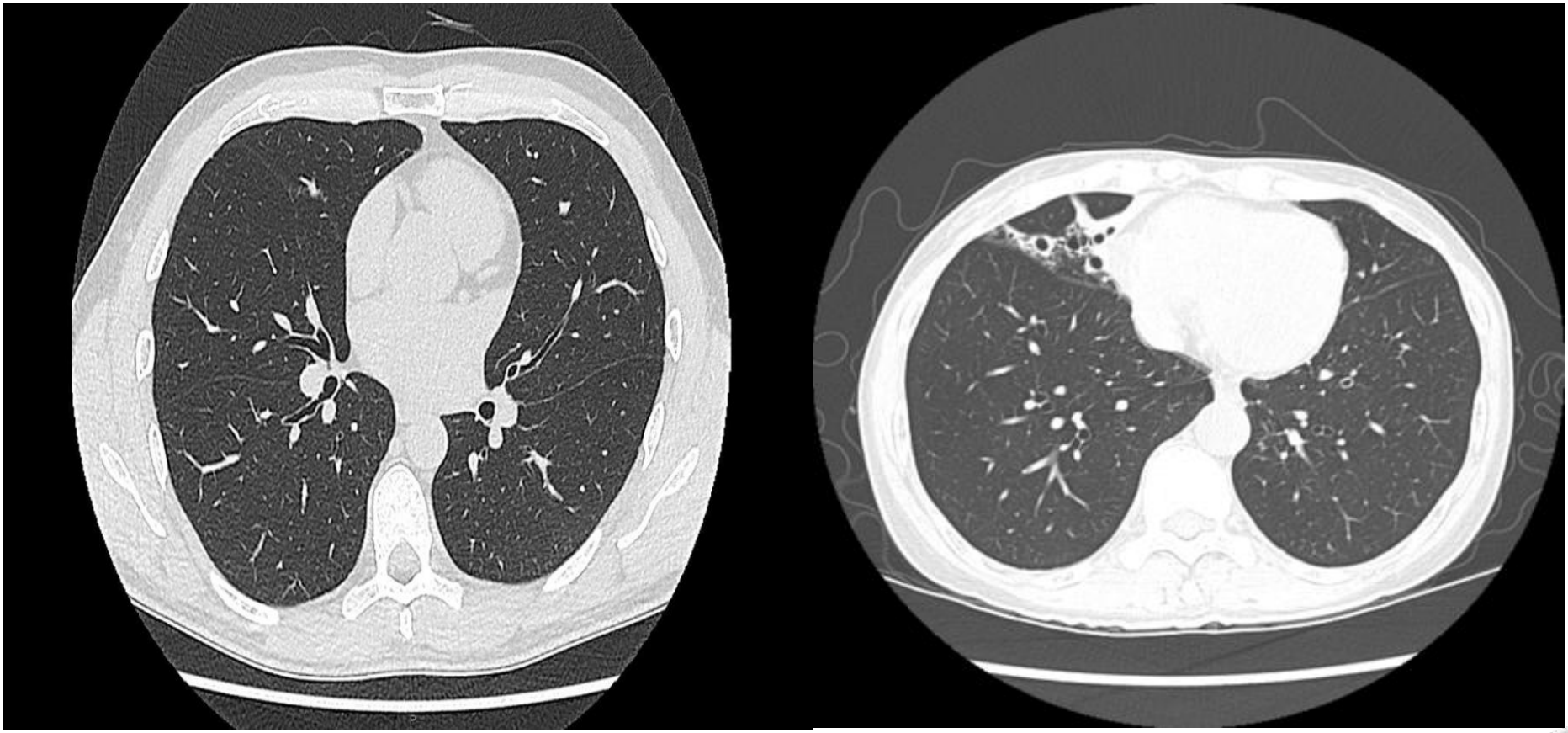
ATS guidelines for diagnosis of pulmonary NTM

MUST HAVE ALL 3:

1. Clinical – compatible symptoms(cough, fatigue, fever, weight loss, DOE, hemoptysis)
2. Radiographic – nodular bronchiectasis and/or fibrocavitary changes
3. Microbiologic – At least 2 positive sputums or at least one positive bronchial washing or bronchial lavage or tissue biopsy

71 yo with dry cough after eating, recently seen by GI and started on PPI with improvement in symptoms. 2 cultures positive for MAC 18 months apart.

71 yo with dry cough having 2 cultures positive for MAC during the last 3 months.



Treatment for MAC

Macrolide (clarithromycin) and amikacin susceptible

↓

Cavitary Disease

NO

Three times weekly:
Azithromycin
Ethambutol
Rifamycin

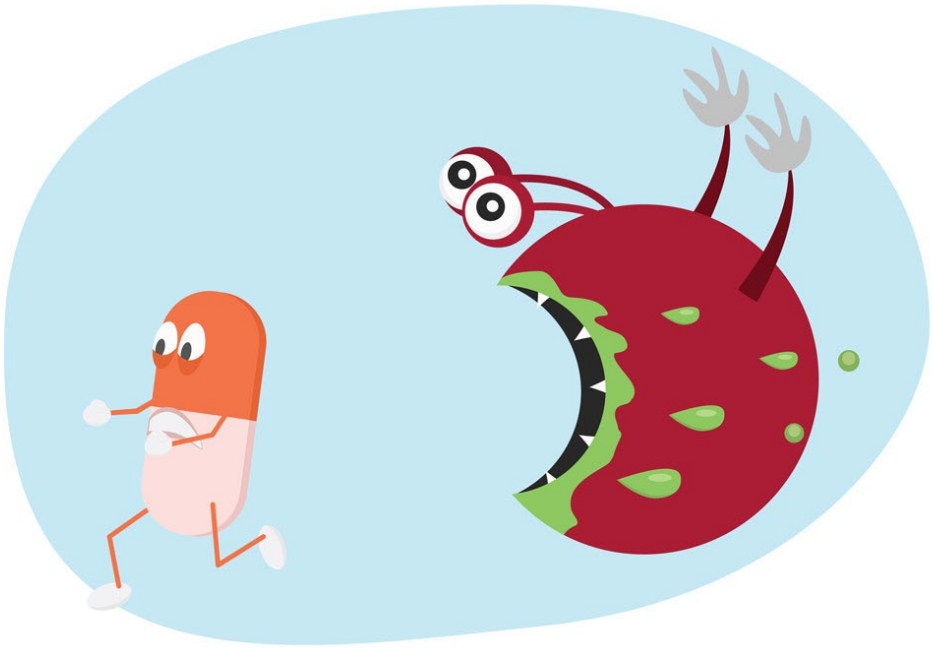
YES

Daily therapy:
Azithromycin
Ethambutol
Rifamycin
Injectable aminoglycoside

How Do I Follow These Patients?

- Clinic follow up every 3 months (minimum)
- CMP, CBC, CRP?, aminoglycoside levels (if appropriate)
- Sputum cultures
- Radiographs
- Eye and hearing tests

Drug Resistant MAC Infections



Treatment for Macrolide Resistant MAC

Macrolide (clarithromycin) Resistant

↓

Daily Therapy:

Rifamycin

Ethambutol

+

Resistant MAC

Macrolide

Mutations in 23S ribosomal RNA gene have been associated with high level resistance and poor outcomes[1]

MIC ≥ 32 mcg/ml: Resistent
MIC 16-32mcg/ml: Intermediate, careful monitoring for emergence of resistance
MIC ≤8mcg/ml: Susceptible

Aminoglycoside

A mutation in 16S ribosomal RNA gene is responsible for high level resistance and poor outcomes [2,3]
MIC >64 mcg/ml: Resistant

[1] Griffith DE, et al. Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med. 2006*; 174(8):928-934.
[2] Prammananan T, et al. A single 16S ribosomal RNA substitution is responsible for resistance to amikacin and othe 2-deoxystreptamine aminoglycosides in Mycobacterium abscessus and Mycobacterium chelonae. *J Infect Dis*. 1998; 177(6):1573-1581.
[3] Olivier KN, et al. Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease. *Am J Respir Crit Care Med.* 2017; 195 (6):814–823.

Other Drugs

- Clofazimine
- Moxifloxacin
- Bedaquiline
- Inhaled amikacin
- IV amikacin
- IM streptomycin

Treatment Duration

12 months of negative sputum cultures

Does any of this work?

Treatment Outcomes for MAC

Macrolides susceptible disease

Noncavitary – around 75-80%

Cavitary – 50-80%

Macrolide Resistant

Aminoglycoside without surgery 5%

Some surgery/aminoglycoside – 15%

Surgery + prolonged aminoglycoside – 80%

Wallace, et al CHEST 2014; 146:276-282
Jeong BH, etal AJRCCM 2015: 191 96-103
Moon, et cal. Antimicob Agents Chemother: 2016. Koh, WJ et al. Eur Resp Journal 2017: 50
Griffith, et al AJRCCM 2006 174: 928
Jeong BH, etal AJRCCM 2015: 191 96-103


UTOPIA
NEXT EXIT

What Do I Do When Patients Remain Positive Despite Therapy?

OPTIONS:

1. Change therapy from intermittent to daily
2. Add another drug – Moxifloxacin, clofazimine, bedaquiline
3. Add inhaled amikacin

*repeat susceptibilities

Koh, WJ. Antimicrob Agents Chemo; 2015; 59; 4994
Koh, WJ; Antimicrob Agents Chemo; 2013; 2281
Martiniano S, et al. CHEST; 2017; 152;800
Philley, etl al. CHEST: 2015; 148
Davis, 2007; Olivier 2014; Yagi 2017; Ihun 2018

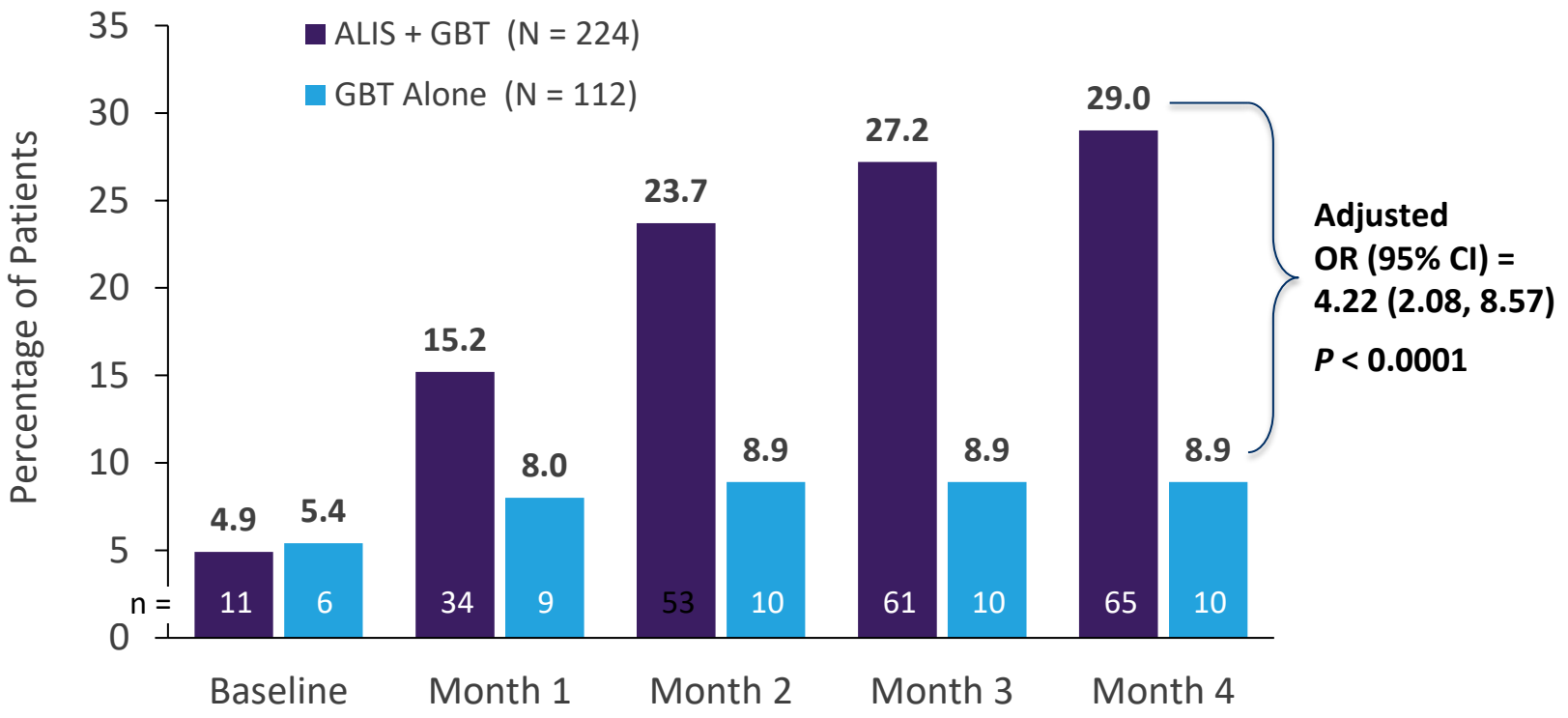
CONVERT STUDY

Objective: Evaluate the efficacy of daily amikacin liposome inhalation suspension (ALIS) added to guideline based therapy in patients with refractory lung disease.

- Enrolled 336 patients (2:1) randomization
- Most had bronchiectasis (62.5%)
- Culture conversion was achieved in 29% (65/224) of the ALIS arm vs 8.9% (10/112)

Griffith DE, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT). Am J Respir Crit Care Med. 2018 Dec 15;198(12):1559-1569.

CONVERT STUDY



Griffith DE, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT). A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med. 2018 Dec 15;198(12):1559-1569.

Most Common TEAEs in CONVERT

Preferred Term	ALIS + GBT N = 223 Patients, n (%)	GBT Alone N = 112 Patients, n (%)
TEAEs occurring in ≥ 10% of patients in either arm		
Dysphonia	102 (45.7)	1 (0.9)
Cough	83 (37.2)	17 (15.2)
Dyspnea	48 (21.5)	10 (8.9)
Hemoptysis	39 (17.5)	15 (13.4)
Fatigue	36 (16.1)	8 (7.1)
Diarrhea	28 (12.6)	5 (4.5)
Nausea	25 (11.2)	4 (3.6)
Oropharyngeal pain	24 (10.8)	2 (1.8)

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; TEAE, treatment-emergent adverse event.

Clinical Cases

Case 1

- 56 yo with a history of CAD, interstitial lung disease on home oxygen, ulcerative colitis, fibromyalgia, GERD, breast cancer s/p chemotherapy (adriamycin) who is undergoing work up for lung transplant evaluation.

- Sputum cultures are obtained and 2/3 becomes positive for *M. fortuitum*

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

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

Transplant candidate?

Case 2

- 82 yo with complaints of a persistent cough diagnosed in July, 2018. He had abnormal imaging and was smear positive for MAC.
- Placed on three time weekly therapy of azithromycin, ethambutol, rifampin December 2018. Continued on this therapy TIW but remained culture positive. (over 8 positive sputums despite 10 months of therapy)
- Comes with continued cough, on/off hemoptysis
- On no airway clearance

How would you treat?

82 yo with smear + MAC

Therapy of MAC Lung Disease
ATS NTM Guidelines

- Cavitary 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 cavitary disease

Treatment

- Airway clearance regimen

- Added amikacin liposomal inhalation suspension (ALIS) 590 mg daily

Change to daily therapy:

Azithromycin

Ethambutol

Rifampin

Macrolide/Azalide Therapy for Nodular Bronchiectatic MAC lung disease

- Microbiologic recurrence on therapy – 14%

  73% - reinfection

  27% -true relapse

- Overall, treatment success (sputum conversion without microbiologic relapse) achieved in 84%.

Wallace, et. al. Chest, 2014

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

Microbiologic recurrence after therapy- 48%

75% - re-infection

25% - true relapse

Case 3

- 72 yo with a 20 pack year h/o tobacco, quitting in 1980 who in August of 2018, developed wheezing. He was seen by his PCP where an abnormal CXR prompted further work-up.

- Diagnosed with MAC in October 2018 by sputum and bronchoscopy culture.

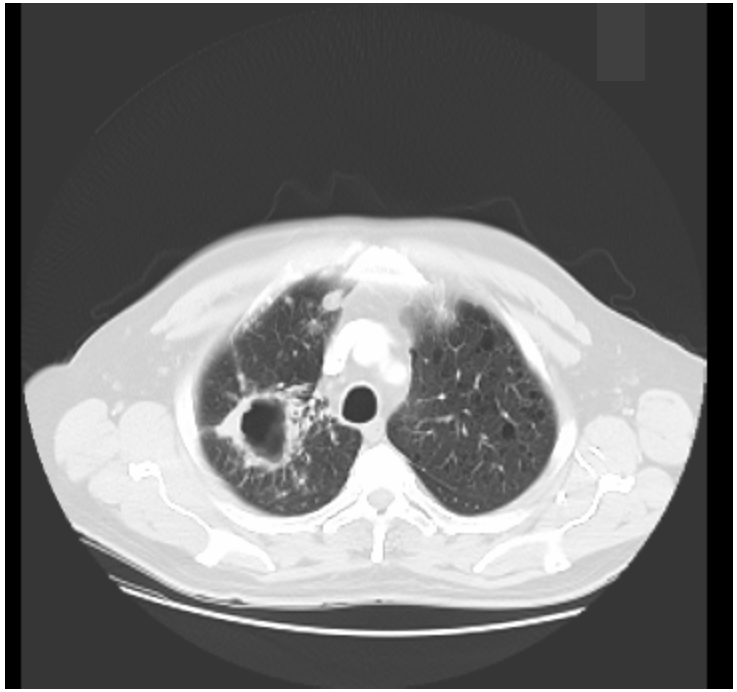
- Started 3 drug daily therapy with azithromycin, ethambutol, rifampin

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, clari sensitive
- Alpha-1 WNL
- Immunoglobulins WNL
- CF mutations – none
- CMP, CBC normal
- B12, TSH, folate, SPEP normal
- 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?

Plan.....

- 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

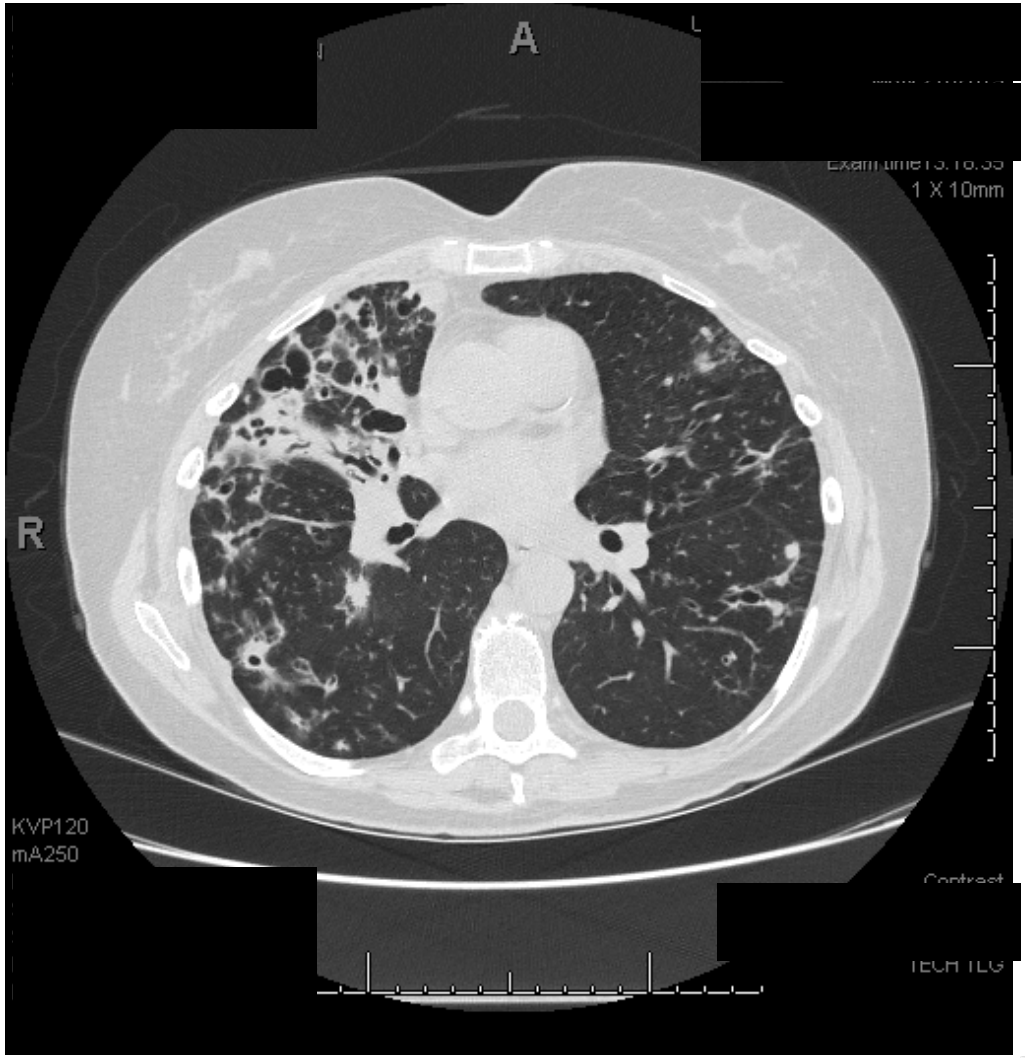
- Usually with localized disease
- V/Q scan
- Treat with combination of po and IV antibiotics before surgery (goal of at least 2-3 months prior)
- Maintain adequate nutritional status
- Referral to an experienced surgical center

Case 4

26 yo female with CF referred for cultures positive for *M. abscessus.* She had been treated with IV amikacin, imipenem and azithromycin for 6 months and was culture for 10 months prior to transplant. Post transplant, she had done very well but began to have cough and wound irritation.

She has a history of treated MAC lung disease 5 years ago with three drug therapy.

Prior to transplant



M. abscessus

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

M. Abscessus in Lung transplantation

- Patients who develop *M. abscessus* lung infection post transplant have been reported to have worse survival.

- Patients with *M. abscessus* lung infection are difficult to manage and require expert consultation.

Hamad Y, et al. Outcomes in Lung Transplant Recipients With Mycobacterium abscessus Infection: A 15-Year Experience From a Large Tertiary Care Center. Transplant Proc. 2019 Jul - Aug;51(6):2035-2042.

Perez AA et al, Management and clinical outcomes after lung transplantation in patients with pre-transplant Mycobacterium abscessus infection: A single center experience. Transpl Infect Dis. 2019 Jun;21(3):e13084.

Shah SK, McAnally KJ, Seoane L, Lombard GA, LaPlace SG, Lick S, Dhillon GS, Valentine VG. Analysis of pulmonary non-tuberculous mycobacterial infections after lung transplantation. Transpl Infect Dis. 2016 Aug;18(4):585-91.

M. Abscessus in Lung transplantation

- No longer a contraindication

"controlled chronic infection pre-operatively and reasonable expectation for adequate control post-operatively"

*Need for pre transplant treatment in CF

Weill D, et al. A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the ISHLT. J Heart Lung Transplant. 2015 Jan;34(1):1-15.

M. abscessus

Bolletti

*inducible resistance to CLR

Abscessus

*10-20% susceptible to CLR via C28 sequevar *erm* (41)

*80-90% inducible resistance to CLR by T28 sequevar of *erm*(41)

Massiliense

*susceptible to CLR

Brown-Elliott, et al, JCM 2015; 53:1211; Mougari F, JAC 2016; 71; Nie, Int J Infect Dis, 2014, Chua, KY; Pathology, 2015
Koh, WJ, etal, Clin Inf Dis, 2017;
Yoshida, S, et al IJTLD 2018; 22., Chew, KL, et al J Med Micro 2017, 66Haworth, CS, Thorax, 2017, 72.

Treatment of *M. abscessus* Lung Disease

"Commercial Lab"

M. Abscessus

Amikacin MIC 16 "S"
Cefoxitin MIC 64 "I"
Cipro MIC 4 "I"
Clarithro MIC 0.5 "S"
Linezolid MIC 32 "R"
TMP/Sulfa "R"

"University Lab"

M. Abscessus

Amikacin "S"
Cefoxitin "I"
Cipro "I"
Clarithro "R"
Linezolid "S"
Tigecycline "NA"

Treatment of *M. abscessus* Lung Disease

- Macrolide: **(*erm* gene, 14 day suscp)**
- Amikacin 7-15 mg/kg 3-7X/week
- Tigecycline 25-50 mg/day, omadacycline?
- Imipenem
- Cefoxitin
- Clofazimine 100 mg
- Linezolid 300-600 mg/day, Tedizolid 200 mg day
- Bedaquiline?
- Minocycline?
- inhaled amikacin?
- ?other treatment modalities

Our Patient:

- Wound debridement/exploration

Treated with:

IV amikacin 15 mg/kg five time weekly

IV imipenem 1 G BID

IV tigecycline 50 mg daily

Clofazimine

The Future

- New drugs
- Nitric Oxide
- GM-CSF
- Bacteriophages
- 2 vs 3 drugs?
- Clofazimine trials
- Roles of inhaled amikacin?