Nontuberculous Mycobacteria in Transplant

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West Coast Transplant ID Conference

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Infectious Disease

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Overview

- Introduction to NTM in Transplant
- Case 1: *Mycobacterium avium complex* in Lung Transplant
- Case 2: *Mycobacterium abscessus* in Lung Transplant
- Case 3: *Mycobacterium immunogenum* in CAR T cell recipient

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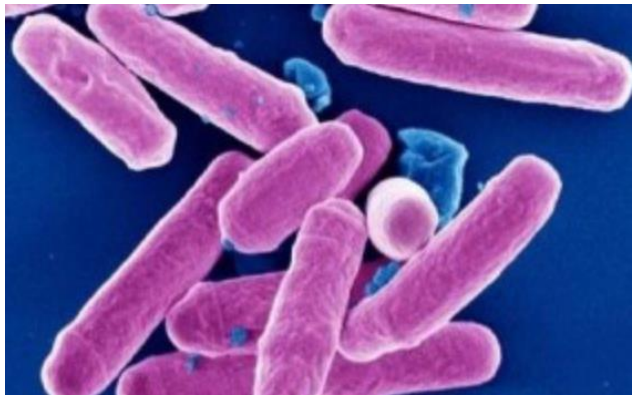
Nontuberculous mycobacteria (NTM)

- Aerobic acid-fast bacilli which stain poorly on gram stain
- Over190 species now described
- Some species pathogenic, others not known to cause disease



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Nontuberculous mycobacteria (NTM)

- Ubiquitous in the environment including household water, potting soil, vegetable matter, animals, and birds
  - Shower head biofilms (28%)
  - Hot tubs
  - Ice Machines
  - Dental units
  - House dust
- Inhalation of water and soil aerosols or contact with water or soil appears to be primary transmission route

Feazel et al PNAS 2009, Mangione EID 2001, Gira, JClin Micro 2004, Gelasse J, Water Health 2003, Schulze-Robbecke, Tub Lug D 1995, Torvinen J Micro Methods 2010

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Classification

Classification of mycobacterial species causing human disease

***Mycobacterium tuberculosis* complex**
M. tuberculosis
M. bovis
M. africanum
M. microti
M. canetti
M. leprae
Rapidly growing nontuberculous mycobacteria
M. fortuitum complex
M. fortuitum
M. peregrinum
M. porcinum
M. chelonae
M. abscessus
M. abscessus subspecies *abscessus*
M. abscessus subspecies *bolletii*
M. abscessus subspecies *massiliense*
M. smegmatis
M. mucogenicum

grow in < 7 days

Slowly growing nontuberculous mycobacteria
Photochromogens
M. kansasii
M. marinum
Scotochromogens
M. gordonae
M. scrofulaceum
Nonchromogens
M. avium complex
M. avium
M. intracellulare
M. chimaera
M. terrae complex
M. ulcerans
M. xenopi
M. simiae
M. malmoense
M. szulgai
M. asiaticum
M. haemophilum

grow in > 7 days, typically 2-4 weeks

www.uptodate.com

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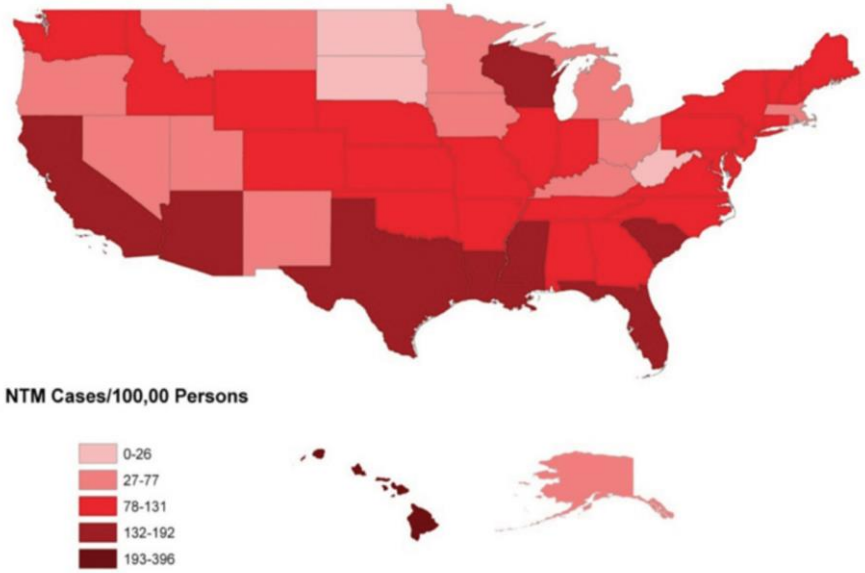
Prevalence of Pulmonary NTM



- increasing in general population ~2.5-8% per year

Adjemian et al. Am J Respir Crit Care Med 2012 185(8):881-886;
Semin Respir Crit Care Med 2018; 39(03): 325-335.

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Incidence in Transplant Populations

Kidney	0.02-0.38%
Liver	0.1%
Heart	0.24-2.8%
Lung	0.46-2.3%
HSCT	0.4-4.9%

- Median time to presentation 10-20 m in SOT, 5 m in HSCT

BM Knoll. Curr Infect Dis Rep 2014 16:421

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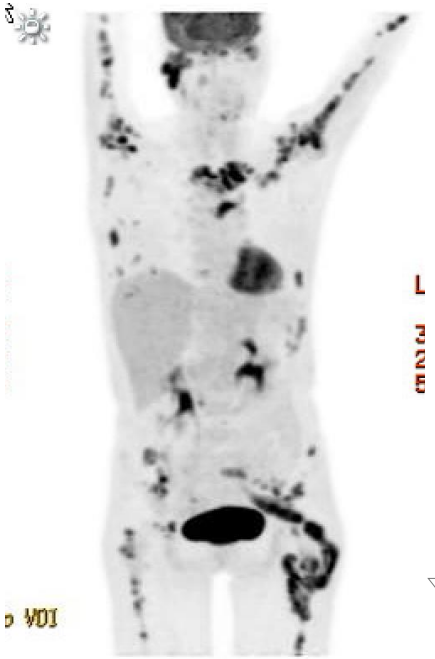
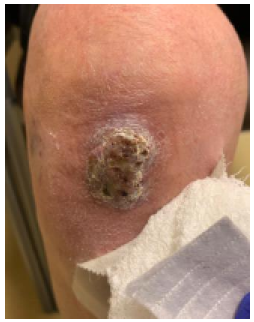
Clinical manifestations

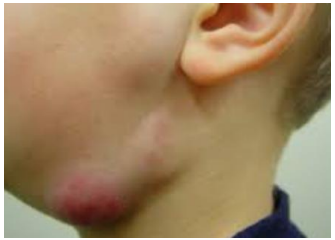


Decreasing immunity

Skin and Soft Tissue
immunocompetent (iatrogenic) or immunocompromised pts

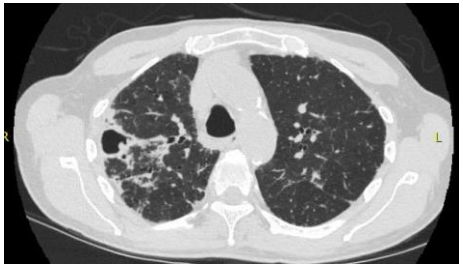


Lymphadenitis
immunocompetent or immunocompromised pts



Line infection
immunocompromised > immunocompetent

Isolated Pulmonary Disease
structural lung disease (CF, GVHD)
Thin immunocompotent* females



Extra pulmonary visceral and disseminated disease
significant immunodeficiency

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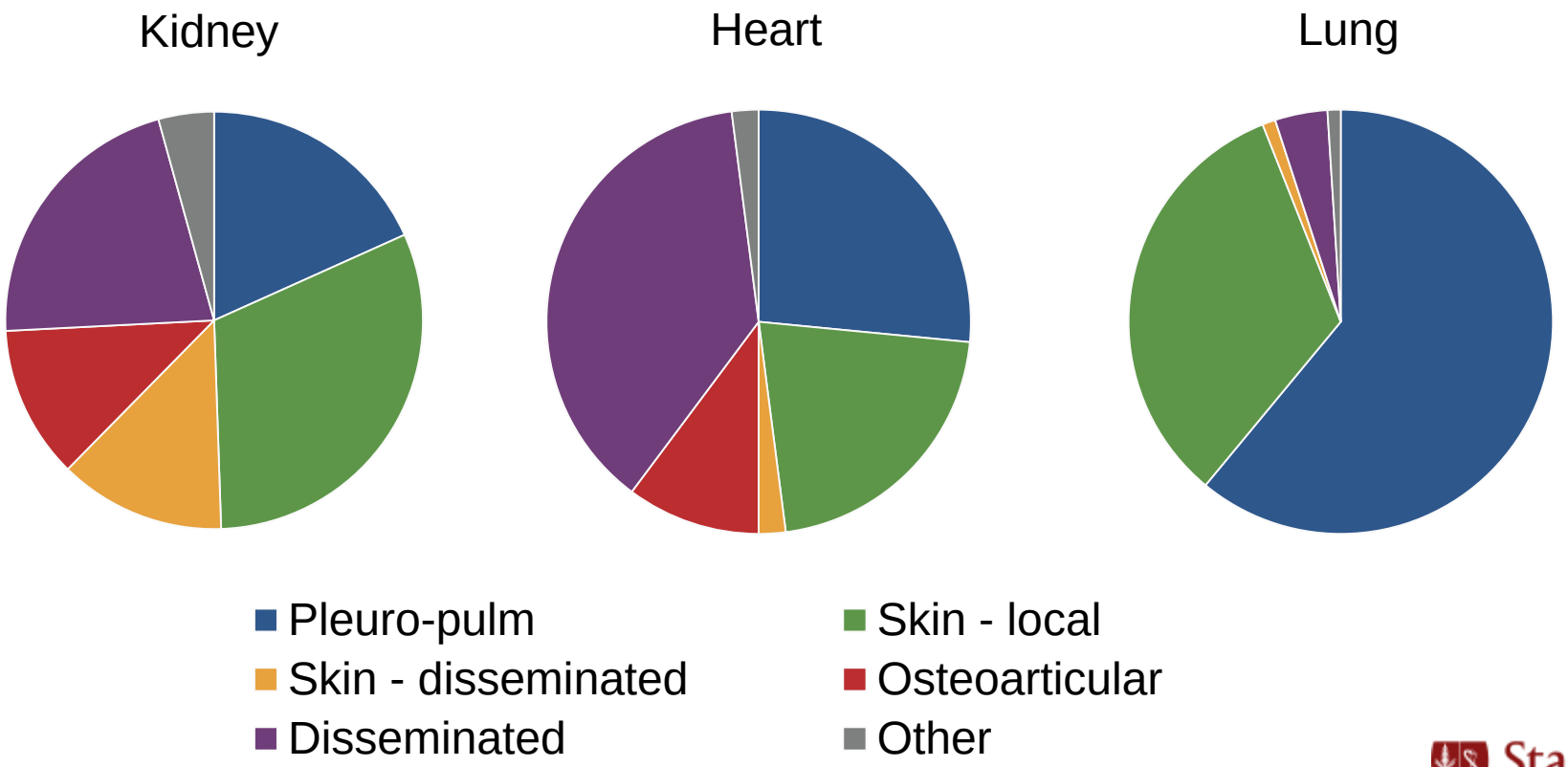
Clinical Manifestations in SOT



BM Knoll. Curr Infect Dis Rep 2014 16:421

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NTM Species in SOT

- **Kidney**
  - M. kansasii (23%)
  - M. chelonae (14%)
  - M. abscessus (10%)
- **Heart**
  - MAC (23%)
  - M. kansasii (21%)
  - M. haemophilum (15%)
- **Lung**
  - M. abscessus (60%)
  - MAC (23%)
  - M. haemophilum (5%)

BM Knoll. Curr Infect Dis Rep 2014 16:421

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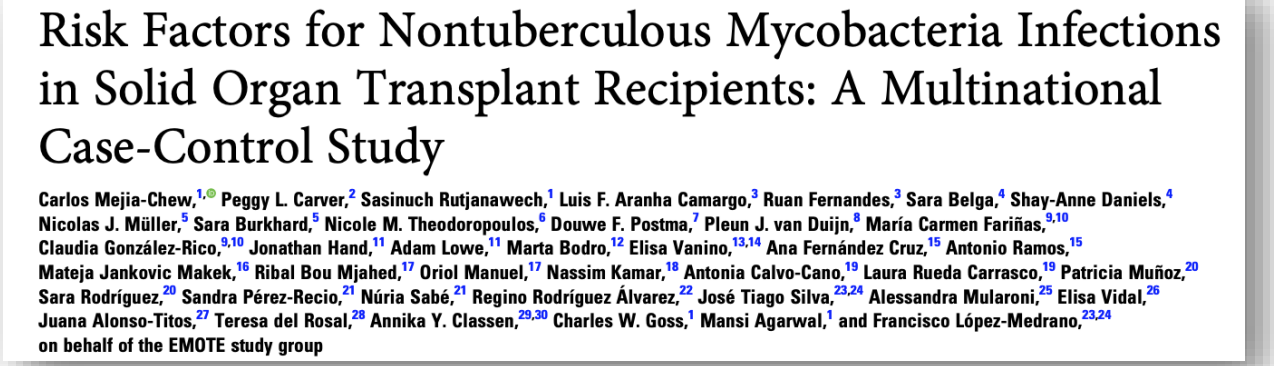

Risk Factors for Nontuberculous Mycobacteria Infections in Solid Organ Transplant Recipients: A Multinational Case-Control Study

Carlos Mejia-Chew,[1] Peggy L. Carver,[2] Sasinuch Rutjanawech,[1] Luis F. Aranha Camargo,[3] Ruan Fernandes,[3] Sara Belga,[4] Shay-Anne Daniels,[4] Nicolas J. Müller,[5] Sara Burkhard,[5] Nicole M. Theodoropoulos,[6] Douwe F. Postma,[7] Pleun J. van Duijn,[8] María Carmen Fariñas,[9,10] Claudia González-Rico,[9,10] Jonathan Hand,[11] Adam Lowe,[11] Marta Bodro,[12] Elisa Vanino,[13,14] Ana Fernández Cruz,[15] Antonio Ramos,[15] Mateja Jankovic Makek,[16] Ribal Bou Mjahed,[17] Oriol Manuel,[17] Nassim Kamar,[18] Antonia Calvo-Cano,[19] Laura Rueda Carrasco,[19] Patricia Muñoz,[20] Sara Rodríguez,[20] Sandra Pérez-Recio,[21] Núria Sabé,[21] Regino Rodríguez Álvarez,[22] José Tiago Silva,[23,24] Alessandra Mularoni,[25] Elisa Vidal,[26] Juana Alonso-Titos,[27] Teresa del Rosal,[28] Annika Y. Classen,[29,30] Charles W. Goss,[1] Mansi Agarwal,[1] and Francisco López-Medrano,[23,24] on behalf of the EMOTE study group

- 85 cases, 169 controls
  - kidney (42%), lung (35%), heart and liver (11%)

- NTM infection associated with:
  - older age at SOT
  - prior hospital admission
  - receipt of antifungals
  - receipt of lymphocyte depleting antibodies

Clin Infect Dis. 2022 Jul 26:ciac608

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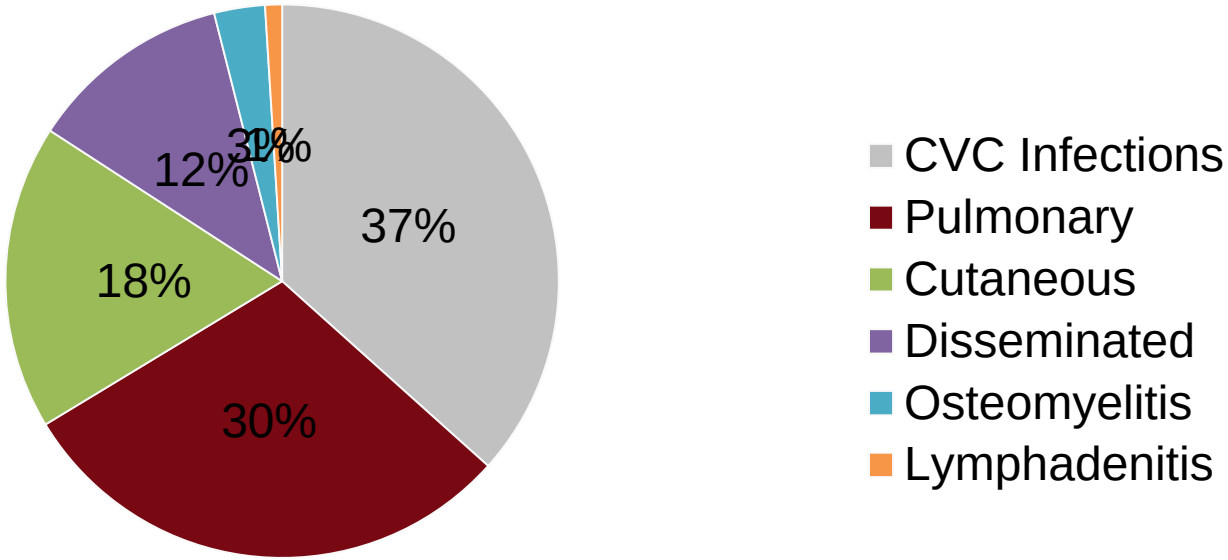
Clinical Manifestations in HSCT



Doucette K. Clin Infect Dis. 2004;38(10):1428-1439.

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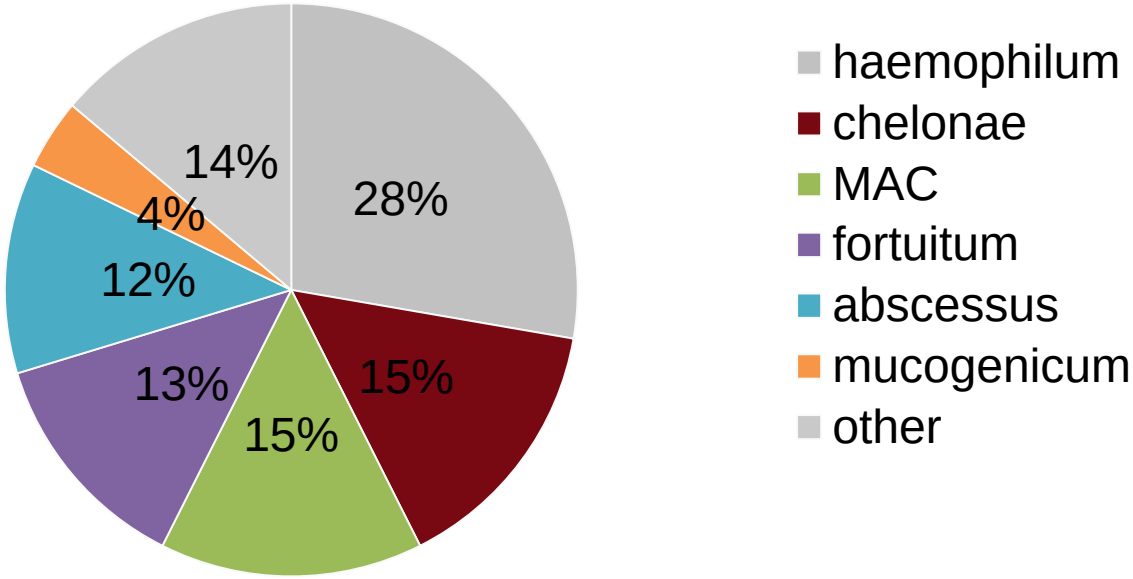
NTM Species in HSCT



BM Knoll. Curr Infect Dis Rep 2014 16:421

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Clinical Manifestations in HSCT

- 1097 Allogeneic HSCT patients from 2001-2013
- 30(2.7%) had clinically significant NTM infection
  - 93.3% isolated pulmonary disease
  - 6.7% disseminated

- Risk factors included:
  - cGVHD (90% had cGVHD, 66% with lung involvement)
  - CMV viremia

Beswick J et al. Biol Blood Marrow Transplant 2018; 24(2):366-372

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Diagnostic Principles

- Isolation of NTM organism from sterile site
  - Granulomatous inflammation on pathology is supportive
- Some species require specialized growth requirements
- Speciation to subspecies level can be important
- In vitro susceptibilities often have poor correlation to clinical outcome

Griffith DE et al, Am J Respir Crit Care Med 2007; 175(4): 367-416.;
Floto RA et al, Thorax 2016; 71 Suppl 1i1-22.

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Diagnosis - Pulmonary disease

Clinical Criteria:
-SOB, cough
-Declining PFTs
-Fatigue, Malaise
-Fever, night sweats
-Weight loss
-(Exclusion of other dx)

Microbiologic Criteria
-Positive cx from at least 2 separate expectorated sputum samples
-Positive cx from one BAL
-Lung biopsy with histopath features & least one positive sputum or BAL cx

Radiographic Criteria:
-bronchonodular
-fibrocavitary

Griffith DE et al, Am J Respir Crit Care Med 2007; 175(4): 367-416.;
Floto RA et al, Thorax 2016; 71 Suppl 1i1-22.

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Cases

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Case 1

- 70-something year old patient with idiopathic pulmonary fibrosis on Ofev being evaluated for lung transplant, in transplant window
- ~2019 developed more productive cough with copious sputum
- Treated for typical bacteria with course of antibiotic therapy with resolution of sputum
- AFB culture completed - 3 out of 3 samples grew MAC, 1 smear pos

Susceptibility

	Mycobacterium avium complex MIC MCG/ML	
Amikacin	32 ug/mL	**Intermediate**
Clarithromycin	4 ug/mL	**Susceptible**
Linezolid	16 ug/mL	**Intermediate** *
Moxifloxacin	8 ug/mL	**Resistant** *

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Case 1

- Referred to ID clinic for pre-transplant evaluation and growth of MAC
- Reported ongoing mild mostly dry cough and progressive shortness of breath
- Using Oxygen at night, limited in activity
- 20 lb weight loss last year, more recently gaining a bit of weight
- No fevers, chills, night sweats

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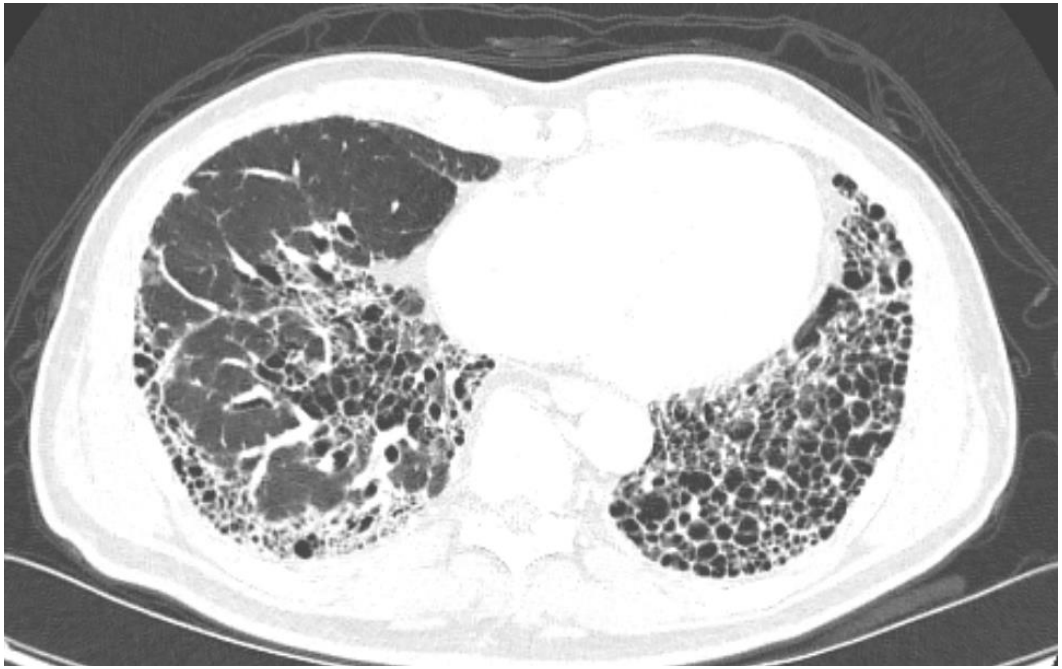
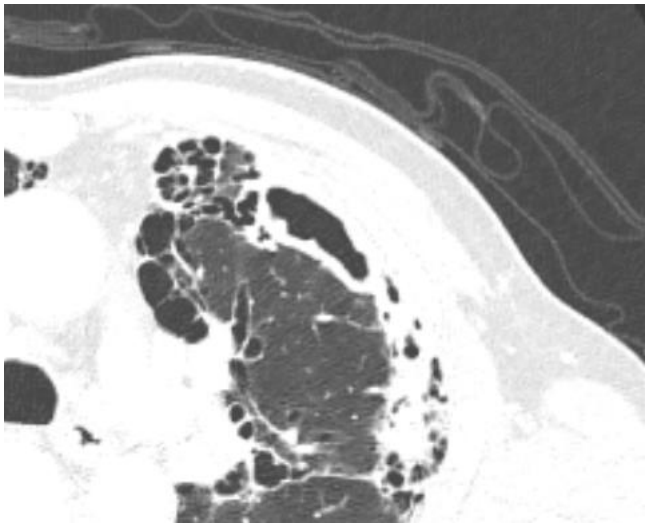
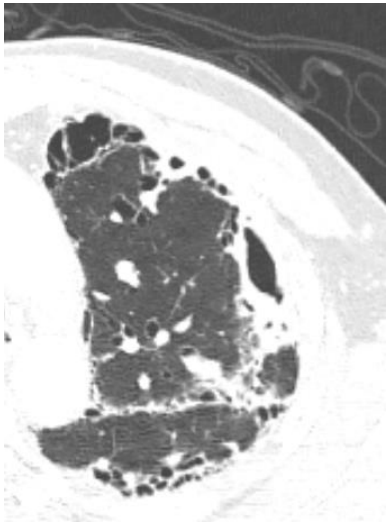
Case 1 - CT imaging







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Case 1 - Smear+ MAC Pre-lung transplant

- **What recommendations for NTM therapy would you make in the pre-transplant setting?**

- A. Daily Azithromycin, Ethambutol, Rifampin
- B. Daily azithromycin, Ethambutol, Rifampin, IV amikacin
- C. Daily Azithromycin, Ethambutol, Arikayce
- D. Daily Azithromycin, Ethambutol
- E. 3x week Azithromycin, Ethambutol, Rifampin
- F. Monitor off therapy
- G. Other

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Case 1 - Smear+ MAC Pre-lung transplant

Organism	No. of Drugs	Preferred Drug Regimen[a]	Dosing Frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	≥3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[c]	≥4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)

Daley et al CID 2020: 71(4): e1-e36.

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Case 1 - Smear+ MAC Pre-lung transplant

- Started on daily Azithromycin and Ethambutol plus IH arikayce 4/2020
  - Rifampin held due to interaction with Ofev
- Follow up Sputum AFB smear 4+, cx + MAC 7/2020

- 9/29/20: bilateral lung transplant
  - Induction with basiliximab
  - Immunosuppression with prednisone, tacrolimus, MMF
  - At the time of transplant, amikacin wash of pleural space
  - Intra-operative AFB smear negative
  - Post-op day 1 BAL AFB smear neg
  - Started on routine post-tx ppx with Valganciclovir, Bactrim, Itraconazole

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Case 1 - Smear+ MAC Pre-lung transplant

- **What recommendations for NTM therapy would you make in the post-transplant setting?**

- A. Daily Azithromycin, Ethambutol, Rifampin
- B. Daily Azithromycin, Ethambutol, Rifabutin
- C. 3x week Azithromycin, Ethambutol, Rifabutin
- D. Daily Azithromycin, Ethambutol, Arikayce
- E. Daily Azithromycin, Ethambutol
- F. Monitor off therapy
- G. Other

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Case 1 - Smear+ MAC Pre-lung transplant

- Started on daily Azithromycin, Ethambutol, Rifabutin
- Tacrolimus levels monitored closely and adjusted
- Itraconazole and Rifabutin level were checked ~1 week into therapy
- Intra-operative and POD1 BAL AFB cx neg

A. LUNG, LEFT, BILATERAL LUNG TRANSPLANT
-- END STAGE CENTRILOBULAR EMPHYSEMA
-- BRONCHIECTASIS AND BRONCHIOLITIS WITH NECROTIZING GRANULOMATOUS INFLAMMATION (SEE COMMENT)
-- SUBPLEURAL FIBROSING INTERSTITIAL LUNG DISEASE WITH USUAL INTERSTITIAL PNEUMONIA PATTERN
-- THREE LYMPH NODES WITH NO HISTOPATHOLOGIC ABNORMALITY (0/3)

B. LUNG, RIGHT, BILATERAL LUNG TRANSPLANT
-- END STAGE CENTRILOBULAR EMPHYSEMA
-- BRONCHIECTASIS AND BRONCHIOLITIS WITH NECROTIZING GRANULOMATOUS INFLAMMATION
-- SUBPLEURAL FIBROSING INTERSTITIAL LUNG DISEASE WITH USUAL INTERSTITIAL PNEUMONIA PATTERN
-- THREE LYMPH NODES WITH NO HISTOPATHOLOGIC ABNORMALITY (0/3)

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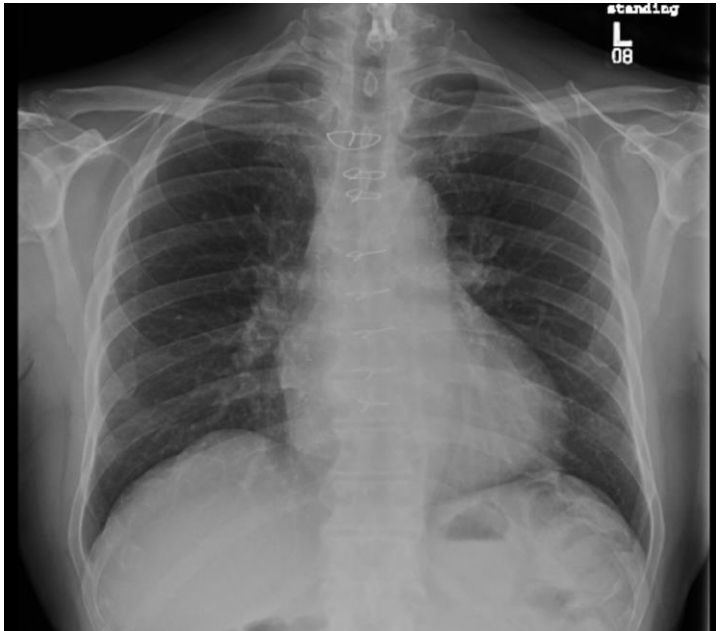
Case 1 - Smear+ MAC Pre-lung transplant

- Recovering well post-transplant, PFTs increasing
- Seen in clinic 7 weeks post transplant
- Mild cough after recent 6 week surveillance bronchoscopy, improving



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Case 1 - Smear+ MAC Pre-lung transplant and negative AFB cultures at time of transplant

- **What duration of NTM therapy post-transplant would you recommend?**

- A. Stop now (~7 weeks post-op)
- B. 3 months
- C. 6 months
- D. 12 months
- E. Other

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Case 1 - Follow up

- MAC therapy continued until recent BAL finalized as negative (total 3 months of therapy)
- Patient did well off therapy with surveillance BAL AFB cx negative

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Case 2

- 40-something year old patient with h/o scleroderma and associated pulmonary fibrosis and ESRD
- s/p bilateral lung transplant and kidney transplant 9/2021
- On tacrolimus and prednisone (cellcept held for leukopenia)
- ppx: valcyte, bactrim, posaconazole
- Post-transplant course c/b:
  - Primary graft failure of kidney requiring ongoing HD
  - Hypoxemic respiratory failure requiring trach, decanulated 12/21/2021

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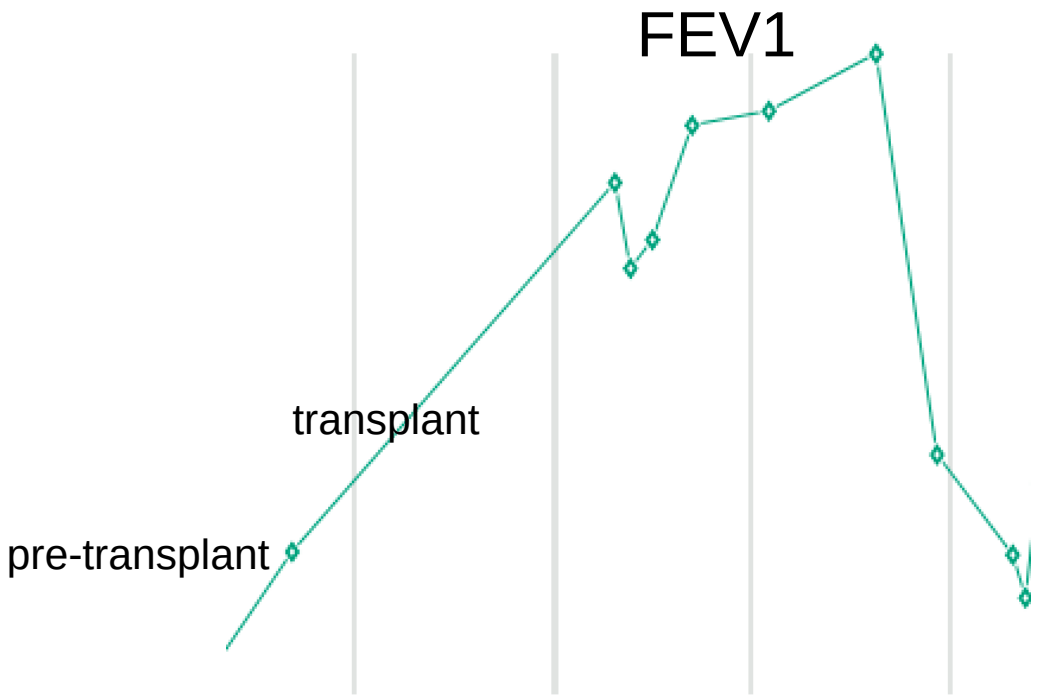
Case 2 - Lung/kidney transplant recipient with MAB

- 9 m post-transplant has decline in PFTs



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Case 2 - Lung/kidney transplant recipient with MAB

- Bronchoscopy shows mild-moderate stenosis of L anastomosis with mild secretions from LLL
- Culture 2+ *Pseudomonas aeruginosa*
- AFB smear neg, cx + *Mycobacterium abscessus* in liquid media

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Case 2 - Lung/kidney transplant recipient with MAB

- New cough, difficulty expectorating sputum
- Fatigue
- No fevers, night sweats. Possible episode of chills
- No change after course of ciprofloxacin

- WBC 3.7, hgb 11.3, plts 266
- Cr 7.66, LFTs WNL

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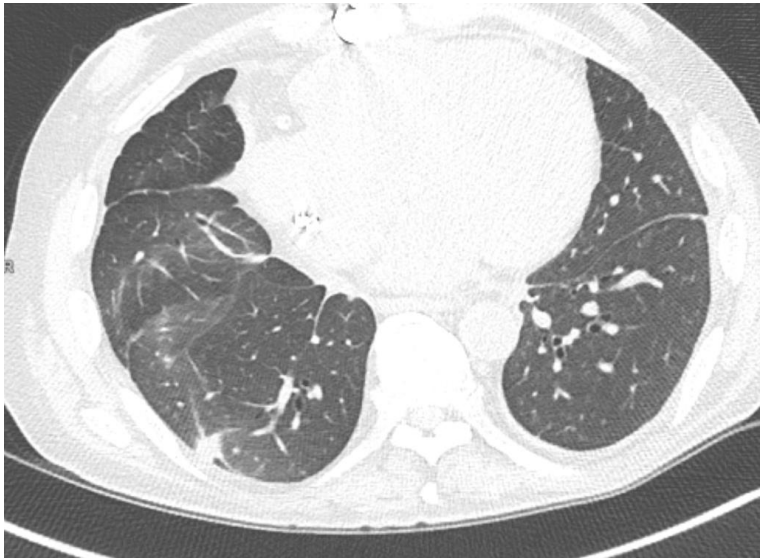
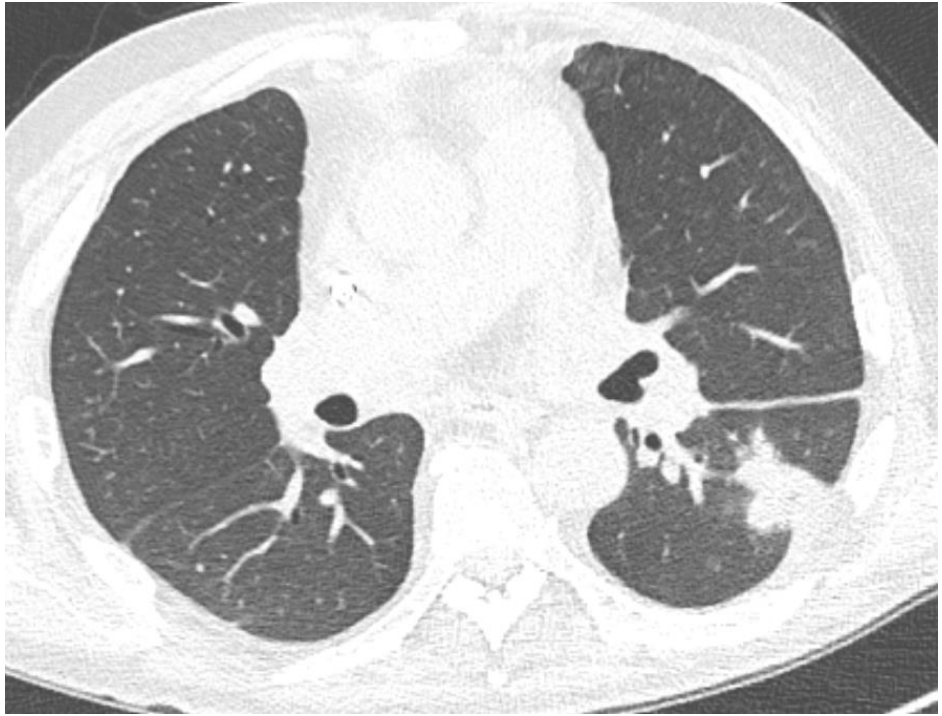
Case 2





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Case 2 - Lung/kidney transplant recipient with MAB

- **In this patient with decline in PFTs, consolidations on CT, growth of *Mycobacterium abscessus* from BAL, what would be your next choice of management?**

  - A. Start NTM therapy with 3 agents (which ones?)
  - B. Start NTM therapy with 4 agents (which ones?)
  - C. Monitor off of antibiotics

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Treatment options *Mycobacterium abscessus*

TABLE 5] Recommended Treatment Regimens for *Mycobacterium abscessus*

Mutational	Inducible	No. of Drugs	Preferred Drugs		Frequency of Dosing
Susceptible	Susceptible	Initial Phase ≥ 3	Parenteral (choose 1-2)[a] Amikacin[b] Imipenem (or cefoxitin) Tigecycline	Oral (choose 2)[c] Azithromycin[d] Clofazimine Omadacycline Linezolid or tedizolid Bedaquiline	Daily (3 times weekly may be used for parenteral aminoglycosides)
		Continuation phase ≥ 2	Oral/inhaled (choose 2-3)[a] Azithromycin[d] Clofazimine Omadacycline Linezolid or tedizolid Inhaled amikacin Bedaquiline		
Susceptible	Resistant	Initial phase ≥ 4	Parenteral (choose 1-2)[a] Amikacin Imipenem (or cefoxitin) Tigecycline	Oral (choose 2)[c] Azithromycin[e] Clofazimine Omadacycline Linezolid or tedizolid Bedaquiline	Daily (3 times weekly may be used for parenteral aminoglycosides)
		Continuation phase ≥ 2	Oral/inhaled (choose 2-3)[a] Azithromycin Clofazimine Omadacycline Linezolid or tedizolid Inhaled amikacin Bedaquiline		
Resistant	Susceptible or resistant		As above: treatment recommendations for macrolide-resistant *M abscesses* are the same regardless of the mechanism of macrolide resistance		
Resistant	Susceptible or resistant	Salvage therapy	Parenteral imipenem with ceftaroline or ceftaroline or ceftazidime; combine with best available oral/inhaled agents		Daily

Griffith DE, Daley CL. Chest Infections 2022 161(1):64-75/

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Case 2 - Lung/kidney transplant recipient with MAB

- Started on:
  - Azithromycin 250 mg PO daily
  - Amikacin IV 3x week
  - Imipenem 250 mg IV BID (renally adjusted)
  - Omadacycline 300 mg daily

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Omadacycline for *M. abscessus* disease

In Vitro Susceptibility Testing of Omadacycline against Nontuberculous Mycobacteria

Barbara A. Brown-Elliott,[a] Richard J. Wallace, Jr.[a]

Organism (*n*)	MIC type	MIC (μg/ml) of:				
		OMC (100% inhibition)	OMC (80% inhibition)	DOX	MIN	TGC
M. abscessus subsp. *abscessus* (20)	Range	0.06–0.5	0.015–0.12	>8	4–>8	≤0.015–1
	50%	0.12	0.06	>8	>8	0.12
	90%	0.25	0.12	>8	>8	0.25
M. abscessus subsp. *massiliense* (3)	Range	0.06–0.25	0.015	>8	4–>8	0.06–0.25
	50%	0.12	0.015	>8	>8	0.25

Antimicrob Agents Chemother 2021; 65(3);

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Omadacycline for *M. abscessus* disease

Omadacycline for the Treatment of *Mycobacterium abscessus* Disease: A Case Series

Jeffrey C. Pearson,[1,2] Brandon Dionne,[1,3] Aaron Richterman,[2] Samuel J. Vidal,[2] Zoe Weiss,[2] Gustavo E. Velásquez,[2,5,6] Francisco M. Marty,[2,4,7] Paul E. Sax,[2,4] and Sigal Yawetz[2,4]

[1]Department of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts, USA, [2]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA, [3]School of Pharmacy, Northeastern University, Boston, Massachusetts, USA, [4]Harvard Medical School, Boston, Massachusetts, USA, [5]Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, USA, [6]Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA, and [7]Division of Infectious Diseases, Dana Farber Cancer Institute, Boston, Massachusetts, USA

Omadacycline in first-line combination therapy for pulmonary *Mycobacterium abscessus* infection: a case series

Marylene Duah [1,*], Melissa Beshay [2]

[1] *Samaritan Medical Center, 830 Washington St, Watertown, NY, United States*
[2] *Emory St. Joseph's Hospital, Sandy Springs, GA, United States*

- 4 patients
- Cure in 3 out of 4
- Other 1 improving
- 1 discontinued after 6 m for nausea

- 3 patients
- Received omadacycline up front with imipenem and amikacin
- Clinical improvement in 3
- Micro cure in 1

OFID 2020; 7(10): ofaa415; Duah et al; Int Journal of Inf Dis 2022; 122: 953-956.

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Case 2 - Lung/kidney transplant recipient with MAB

Susceptibility

	Mycobacterium abscessus group	
	MIC MCG/ML	NUCLEIC ACID TEST
Amikacin	16 ug/mL **Susceptible**	
Cefoxitin	32 ug/mL **Intermediate**	
Ciprofloxacin	4 ug/mL **Resistant**	
Clarithromycin	0.25 ug/mL **Susceptible** [1]	
Clofazimine	0.5 ug/mL **No Interpretation**	
Doxycycline	>8 ug/mL **Resistant**	
ermPCR		**Not Detected** *
Imipenem	8 ug/mL **Intermediate**	
Linezolid	8 ug/mL **Susceptible**	
Moxifloxacin	4 ug/mL **Resistant**	
Tigecycline	0.25 ug/mL **No Interpretation**	
Tobramycin	16 ug/mL **Resistant** *	
Trimethoprim/Sulfamethoxazole.	>4 ug/mL **Resistant** [2]	

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Case 2 - Lung/kidney transplant recipient with MAB

- Omadacycline not approved by insurance

- Continued on:
  - Azithromycin 250 mg PO daily
  - Amikacin 10mg/kg IV 3x week
  - Imipenem 250 mg IV BID (renally adjusted)

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- **Patient tolerates 2-3 months of induction therapy well with up trending FEV1, what is your choice for maintenance therapy?**
  - A. Azithromycin + Imipenem + Linezolid
  - B. Azithromycin + Arikayce + Linezolid
  - C. Azithromycin + Tedizolid
  - D. Azithromycin + Arikayce + clofazimine
  - E. Other

Susceptibility

	Mycobacterium abscessus group	
	MIC MCG/ML	NUCLEIC ACID TEST
Amikacin	16 ug/mL **Susceptible**	
Cefoxitin	32 ug/mL **Intermediate**	
Ciprofloxacin	4 ug/mL **Resistant**	
Clarithromycin	0.25 ug/mL **Susceptible** [1]	
Clofazimine	0.5 ug/mL **No Interpretation**	
Doxycycline	>8 ug/mL **Resistant**	
ermPCR		**Not Detected** *
Imipenem	8 ug/mL **Intermediate**	
Linezolid	8 ug/mL **Susceptible**	
Moxifloxacin	4 ug/mL **Resistant**	
Tigecycline	0.25 ug/mL **No Interpretation**	
Tobramycin	16 ug/mL **Resistant** *	
Trimethoprim/Sulfamethoxazole.	>4 ug/mL **Resistant** [2]	

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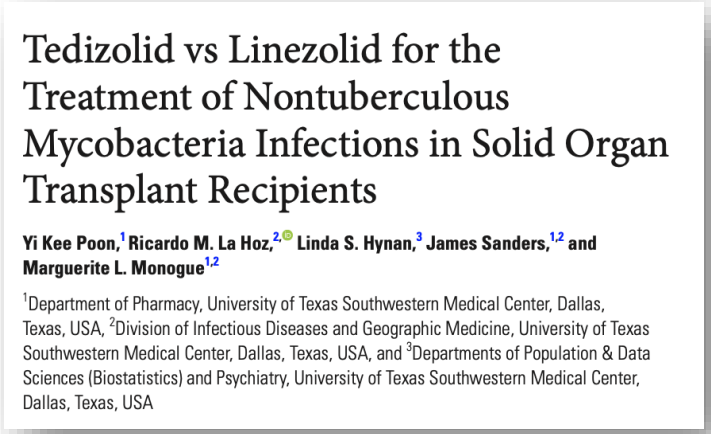

Tedizolid vs Linezolid for the Treatment of Nontuberculous Mycobacteria Infections in Solid Organ Transplant Recipients

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- Single center retrospective cohort
- 24 its included
  - 15 tedizolid
  - 9 linezolid
- No difference in hematologic toxicities between groups

Poon et al, OFID 2021; 8(4): ofab093.

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Case 2

- **If patient had been found to be colonized with *Mycobacterium abscessus* prior to transplant, would they be considered a candidate for transplant at your center?**

- A. Yes
- B. No
- C. Other

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