Updates on the Treatment of Mycobacterium Avium Complex Pulmonary Disease

Andrew Revels, PharmD

PGY-1 Pharmacy Resident

Princeton Baptist Medical Center | Birmingham, AL

Preceptor: Sarah B. Blackwell, PharmD, BCPS, BCCCP,
Clinical Pharmacy Specialist | Princeton Baptist Medical Center

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Learning objectives

At the end of this session, participants should be able to:

1. Recall current guideline recommendations for the treatment of mycobacterium avium complex (MAC) pulmonary disease.

2. Identify antimicrobial pharmacodynamic and pharmacokinetic principles in a regimen for the treatment of MAC pulmonary disease.

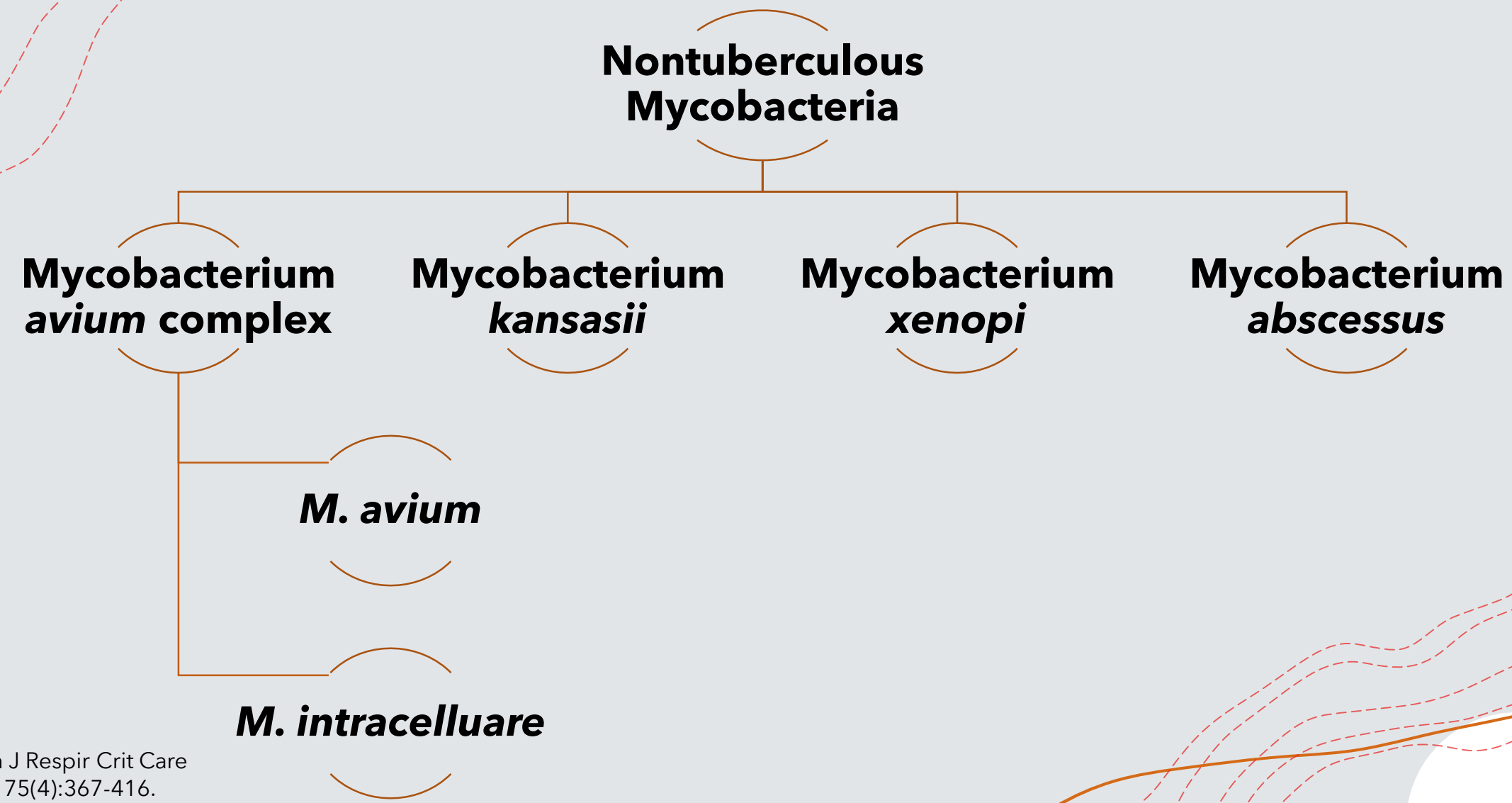
3. Recognize an effective treatment regimen for a patient with MAC pulmonary disease based upon macrolide susceptibility and patient-specific characteristics.

MAC, Mycobacterium avium complex

Abbreviations

- AGs: aminoglycosides
- ALIS, amikacin liposome inhalation suspension
- ATS, American Thoracic Society
- AZM, azithromycin
- BAL, bronchoalveolar lavage
- CAM, clarithromycin
- CI, confidence interval
- CXR, chest radiograph
- EB, ethambutol
- GBT, guideline-based therapy
- HR, hazard ratio
- HRCT, high-resolution computed tomography
- IDSA, Infectious Diseases Society of America
- MAC-LD, Mycobacterium avium complex lung disease
- MAC-PD, mycobacterium avium complex pulmonary disease
- MAC, Mycobacterium avium complex
- MIC, minimal inhibitory concentrations
- MR-MAC, macrolide-resistant mycobacterium avium complex
- NB, nodular bronchiectatic
- NS, not significant
- NTM, nontuberculous mycobacterium
- OR, odds ratio
- RFB, rifabutin
- RFP, rifampin
- RIF, rifamycin
- SM, streptomycin
- TEAE, treatment-emergent adverse event
- TIW, three-times-weekly

Taxonomy



Sources: Am J Respir Crit Care Med. 2007;175(4):367-416.

Epidemiology

Southeastern United States

Environmental sources

Water and Soil

Animals

Natural water sources

Indoor water systems

Pools

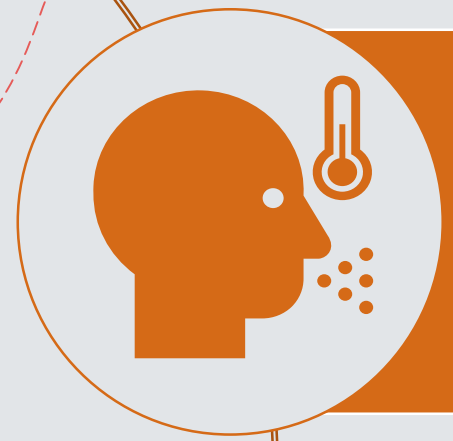
Hot tubs

Sources: Am J Respir Crit Care Med. 2007;175(4):367-416.

Pathogenesis

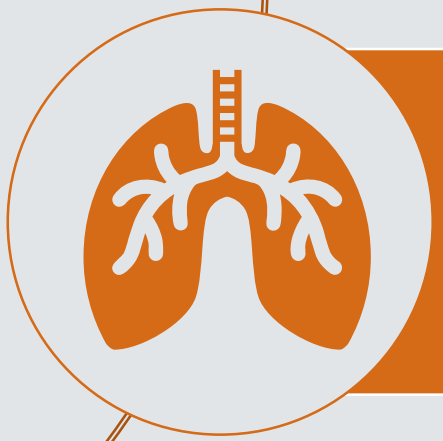
Sources: Am J Respir Crit Care Med. 2007;175(4):367-416.

Clinical Presentation



Variable and nonspecific symptoms

- Chronic or recurring cough
- Sputum production, dyspnea, hemoptysis
- Fatigue, fever, chest pain, weight loss



Nonspecific physical findings

- Chest auscultation: rhonchi, crackles, wheezes, squeaks

Sources: Am J Respir Crit Care Med. 2007;175(4):367-416.

Diagnostic Criteria

Clinical

Pulmonary symptoms

or

Systemic symptoms

Radiologic

CXR: Nodular or cavitary opacities

or

HRCT: Bronchiectasis with multiple small nodules

Microbiologic

2 separate positive sputum cultures

or

1 positive bronchial wash/lavage culture

or

Transbronchial lung biopsy with mycobacterial histologic features + positive culture for NTM

CXR, chest radiograph; HRCT, high-resolution computed tomography; NTM, nontuberculous mycobacterium

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

2007 ATS/IDSA NTM Diseases Guidelines

Initial Therapy for Nodular/Bronchiectatic Disease	Clarithromycin or azithromycin **+** ethambutol **+** rifampin
Initial Therapy for Cavitary Disease	Clarithromycin or azithromycin **+** ethambutol **+** rifampin **+/-** streptomycin or amikacin
Advanced (Severe) or Previously Treated Disease	Clarithromycin or azithromycin **+** ethambutol **+** rifabutin or rifampin **+** streptomycin or amikacin

Sources: Am J Respir Crit Care Med. 2007;175(4):367-416.

ATS, American Thoracic Society; IDSA, Infectious Diseases Society of America; NTM, Nontuberculous mycobacterial

Treatment of NTM Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline (2020)

Recommendations for Specific PICO Questions

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Should patients with macrolide-susceptible MAC pulmonary disease be treated with or without a macrolide?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Relationship between clinical efficacy of treatment of pulmonary MAC disease and drug-sensitivity testing of MAC isolates (2006)

Inclusion: Satisfied ATS diagnostic criteria for NTM infection, availability for treatment and follow-up for over 12 months
Exclusion: Positive serological findings for HIV type 1 or type 2

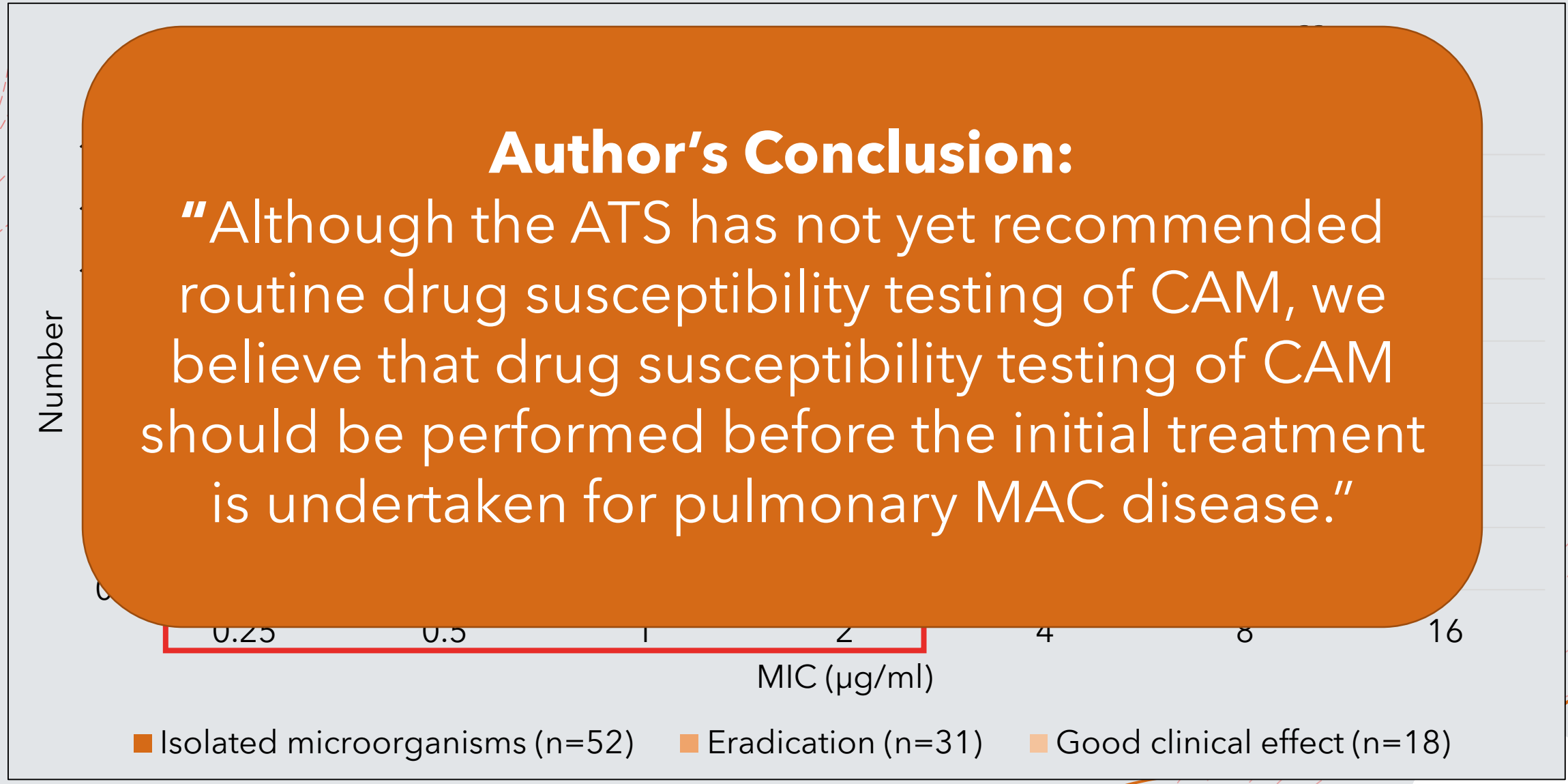
Primary outcome	Secondary outcomes
Sputum eradication rate	Clinical improvement Relationship between clinical efficacy and MICs for antimycobacterial drugs

CAM PO 600mg/day + RFP PO 450mg/day + EB PO 400mg/day + SM IM 1 g three times a week for the initial 2 to 3 months of treatment

Sources: J Infect Chemother 2006; 12:195–202.

RFP, rifampicin; EB, ethambutol; SM, streptomycin; CAM, clarithromycin; MIC, minimal inhibitory concentrations

Relationship between clinical efficacy of treatment of pulmonary MAC disease and drug-sensitivity testing of MAC isolates (2006)



Author's Conclusion:

"Although the ATS has not yet recommended routine drug susceptibility testing of CAM, we believe that drug susceptibility testing of CAM should be performed before the initial treatment is undertaken for pulmonary MAC disease."

Sources: J Infect Chemother 2006; 12:195-202.

The clinical efficacy of a CAM-based regimen for MAC disease: A nationwide post-marketing study (2017)

Inclusion: Symptoms of MAC lung disease, radiographic findings excluding preexisting lung diseases, positive culture results from at least two separate sputum samples or one BAL fluid sample
Exclusion: CAM treatment < 30 days, CAM doses other than 800 mg/day

Primary outcome	Secondary outcomes
Bacilli negative conversion rate	Improvement on chest imaging Comprehensive clinical improvement rate Bacteriological relapse rate

CAM-based regimen until culture negative for 1 year
CAM + EB + RFP: 201 (74.2%)
CAM + EB + RFP + AG: 23 (8.5%)

Sources: J Infect Chemother 2017; 23:293–300.

BAL, bronchoalveolar lavage; CAM, clarithromycin

The clinical efficacy of a CAM-based regimen for MAC disease: A nationwide post-marketing study (2017)

Author's Conclusion:

"This study demonstrated that a clarithromycin-based daily regimen can yield a high bacteriological conversion rate in MAC disease."

Bacteriological relapse rate	5/100 (5.0)	---

Sources: J Infect Chemother 2017; 23:293–300. CAM, clarithromycin; RFP, rifampin; EB, ethambutol; AGs: aminoglycosides

Should patients with macrolide-susceptible MAC pulmonary disease be treated with or without a macrolide?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should azithromycin or clarithromycin be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Macrolide Comparison

	Azithromycin	Clarithromycin
Microbiological efficacy	+++	+++
Tolerability	+++	++
QTc prolongation potential	+++	+++
Drug-drug interaction potential	+	+++
Pill burden	+	++
Cost	++	++

+++, high; ++, intermediate; +, low

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

In patients with newly diagnosed macrolide-susceptible MAC pulmonary disease, should azithromycin or clarithromycin be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Assessment Question 1

AB is newly diagnosed with MAC pulmonary disease, which of the following are advantages of an azithromycin-based regimen over a clarithromycin-based regimen?

a. Drug interaction profile
b. Dosing frequency
c. Risk of QTc prolongation
d. Tolerance profile
e. A & C
f. A, B, & D

Assessment Question 1

AB is newly diagnosed with MAC pulmonary disease, which of the following are advantages of an azithromycin-based regimen over a clarithromycin-based regimen?

a. Drug interaction profile
b. Dosing frequency
c. Risk of QTc prolongation
d. Tolerance profile
e. A & C
f. A, B, & D

In patients with macrolide-susceptible MAC pulmonary disease, should a 2- or 3-drug regimen be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

In patients with macrolide-susceptible MAC pulmonary disease, should a 2- or 3-drug regimen be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

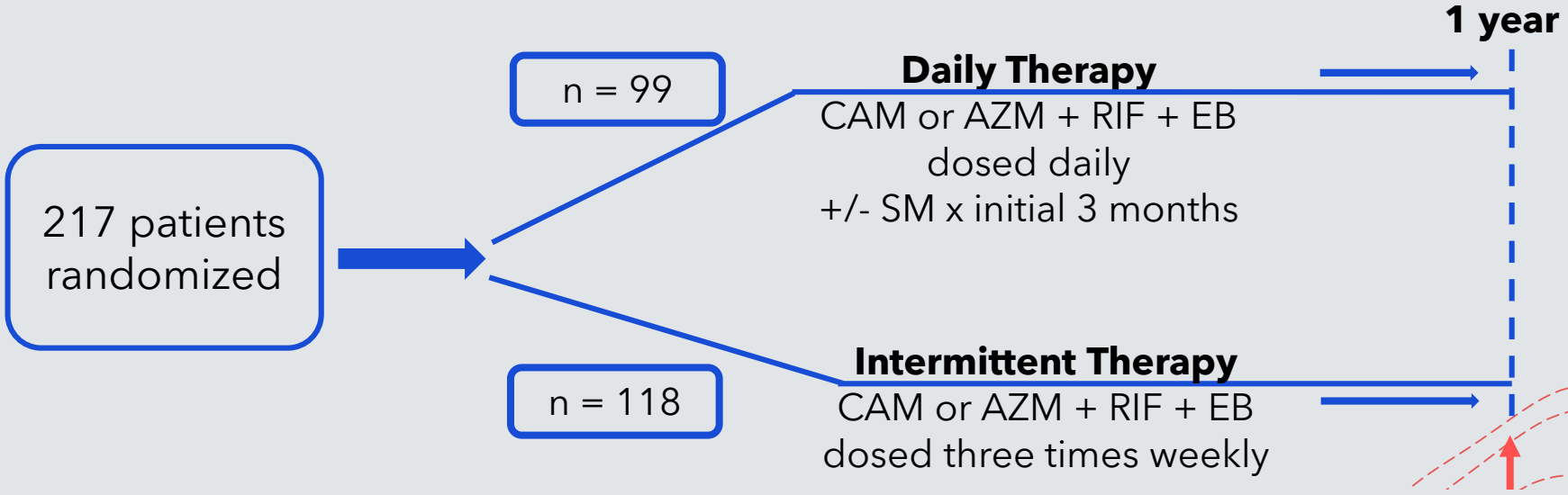
In patients with macrolide-susceptible MAC pulmonary disease, should a daily or 3-times weekly regimen be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Intermittent Antibiotic Therapy for NB MAC-LD (2015)

Inclusion: Meet the diagnostic criteria for NTM lung disease, NB MAC-LD based on HRCT findings
Exclusion: Cavitation on HRCT, previous macrolide treatment, intermediate to higher-level resistance to CAM

Primary outcome	Secondary outcomes
Sputum culture conversion	Improvement of symptoms Improvement of HRCT Development of CAM resistance



Sources: Am J Respir Crit Care Med 2015; 191:96–103.

NB, nodular bronchiectatic; HRCT; high-resolution computed tomography; CAM, clarithromycin; AZM, azithromycin; RIF, rifampin; EB, ethambutol

Intermittent Antibiotic Therapy for Nodular Bronchiectatic MAC Lung Disease (2015)

Author's Conclusion:

"These results suggest that patients with noncavitary nodular bronchiectatic MAC lung disease receiving TIW intermittent therapy are better able to tolerate long-term multidrug antibiotic treatment and had similar clinical response rates compared with patients receiving daily therapy."

Mo			
Early discontinuation of antibiotic treatment, n (%)	15 (15)	13 (11)	0.366
Discontinuation of EB, n (%)	24 (24)	1 (1)	<0.001

Sources: Am J Respir Crit Care Med 2015; 191:96–103.

Factors Related to Response to Intermittent Treatment of MAC Lung Disease (2006)

Inclusion: Moderate to severe MAC-PD, evidence of positive sputum culture, persistent/recurrent radiographic abnormalities, symptoms of MAC-PD
Exclusion: HIV infection, extrapulmonary MAC, cystic fibrosis, malignancies, intolerance/resistance to macrolides

Primary outcome	Secondary outcomes
Culture conversion rate	Culture improvement HRCT improvement Symptom improvement

Oral TIW regimen
CAM or AZM + EB + RFP or RFB

Sources: Am J Respir Crit Care Med 2006; 173:1283–9.

TIW, three-times-weekly; MAC-PD, Mycobacterium avium complex pulmonary disease; CAM, clarithromycin; AZM, azithromycin; EB, ethambutol; RFP, rifampin; RFB, rifabutin

Factors Related to Response to Intermittent Treatment of MAC Lung Disease (2006)

Author's Conclusion:

"TIW therapy was less effective for MAC-PD patients with cavitary disease and a history of chronic obstructive pulmonary disease, bronchiectasis, or previous treatment for MAC-PD."

Culture co			
Culture im			
HRCT impr			
Symptom improvement, n (%)	26 (53.7)	22 (51.3)	1.000

		P-value
		0.001
Noncavitary disease (vs. cavitary)	4.93 (1.88-12.96)	0.001

Sources: Am J Respir Crit Care Med 2006; 173:1283–9.

HR, hazard ratio

In patients with macrolide-susceptible MAC pulmonary disease, should a daily or 3-times weekly regimen be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Assessment Question 2

CD has newly diagnosed cavitary MAC pulmonary disease. How often should he take his treatment regimen?

a. Daily
b. Three-times weekly

Assessment Question 2

CD has newly diagnosed cavitary MAC pulmonary disease. How often should he take his treatment regimen?

a. Daily

b. Three-times weekly

Should patients with MAC pulmonary disease be treated with or without a parenteral aminoglycoside-containing regimen?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary MAC disease (2007)

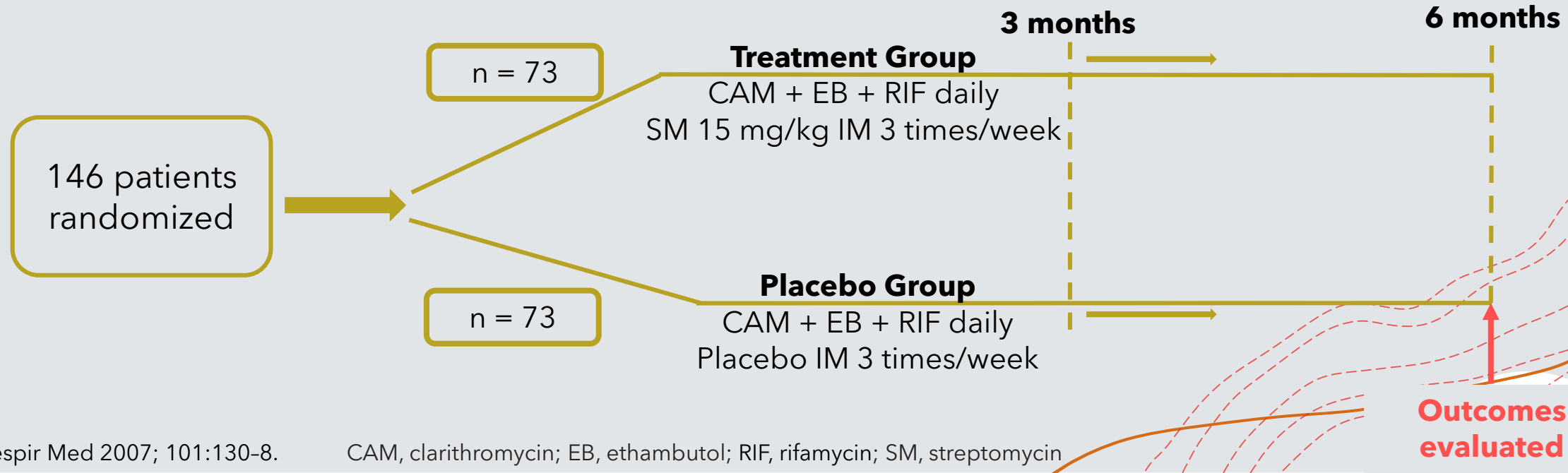
Inclusion: Satisfy the ATS diagnostic criteria for NTM infection, negative serological findings for HIV, positive sputum cultures for MAC
Exclusion: Inability to undergo treatment for > 24 months after culture negative conversion

Primary outcome

Sputum conversion rate for pulmonary MAC disease within 6 months of treatment

Secondary outcomes

Sputum relapse rate
Clinical improvement rate
Adverse reactions



Sources: Respir Med 2007; 101:130–8.

CAM, clarithromycin; EB, ethambutol; RIF, rifamycin; SM, streptomycin

A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary MAC disease (2007)

Ba

			P-value
Age, years			<0.05
Male, n (			NS
Characteristic f			NS
Bronchiectasis, n (%)			
Cavitary lesion(s), n (%)	39 (53.4)	42 (57.5)	

Adverse reactions	18 (24.7)	15 (20.5)	NS

*Findings expressed as n (%)

Author's Conclusion:

"This study provides evidence to support the addition of parenteral SM in patients with pulmonary MAC disease who are without HIV infection as there were no irreversible major side effects seen w/ short-term SM therapy."

Sources: Respir Med 2007; 101:130–8.

NS, not significant

MR-MAC Lung Disease: Analysis of 102 Consecutive Cases

St

Risk fa
macrc

ment

Factors re
prognosis for MR-MAC

- Combination of aminoglycoside + surgery
  - Best treatment outcome (P = 0.02)

Author's Conclusion:

"Drug sensitivity testing should be performed at diagnosis to identify macrolide resistance and patients who may benefit from additional therapy such as a parenteral AG."

Sources: Ann Am Thorac Soc 2016; 13:1904–11.

MR-MAC, macrolide-resistant mycobacterium avium complex

Should patients with MAC pulmonary disease be treated with or without a parenteral aminoglycoside-containing regimen?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

In patients with macrolide-susceptible MAC pulmonary disease, should inhaled amikacin be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

CONVERT

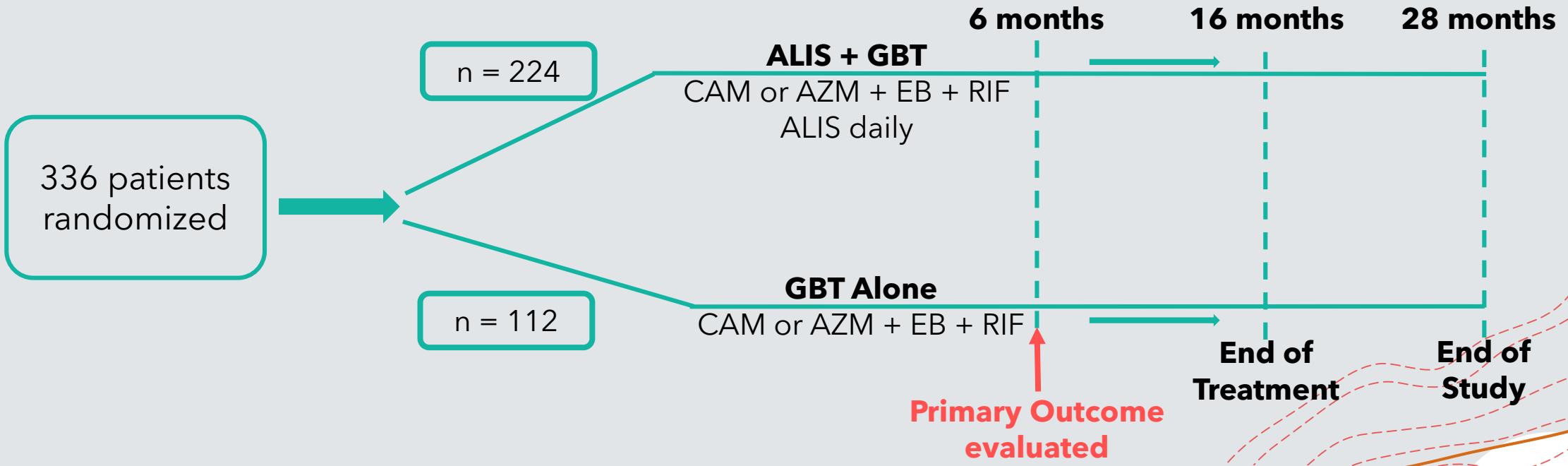
Inclusion: Active MAC-LD, MAC-positive while on stable GBT for at least 6 months and were either on GBT or had stopped GBT less than 12 months before screening
Exclusion: Cystic fibrosis, tuberculosis, MAC isolates with amikacin resistance on culture

Primary outcome

Culture conversion by month 6

Secondary outcomes

Postbaseline amikacin resistance
Adverse events



ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy; MAC-LD = Mycobacterium avium complex lung disease

Sources: Am J Respir Crit Care Med 2018; 198:1559–69.

CONVERT

Author's Conclusion:

"Addition of ALIS to GBT for treatment-refractory MAC lung disease achieved significantly greater culture conversion by Month 6 than GBT alone, with comparable rates of serious adverse events."

				GBT Alone (n = 112)
Sputum culture conversion by month 6, n (%)				102 (91.1)
				---
				1 (0.9)
				0 (0.0)
Postbaseline amikacin resistance, n (%)	23 (10.3)	3 (2.7)	---	---

Dysphonia, n (%)	102 (45.7)	1 (0.9)
Cough, n (%)	83 (37.2)	17 (15.2)

CI = confidence interval; OR = odds ratio; GBT = guideline-based therapy; TEAE = treatment-emergent adverse event

Sources: Am J Respir Crit Care Med 2018; 198:1559–69.

In patients with macrolide-susceptible MAC pulmonary disease, should inhaled amikacin be used?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy

Assessment Question 3

EF has been on GBT for MAC pulmonary disease for the last 6 months and has remained culture positive. Which of the following would be the most appropriate to initiate at this time?

a. Streptomycin IM
b. Isoniazid
c. ALIS
d. Ethambutol

ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy

Assessment Question 3

EF has been on GBT for MAC pulmonary disease for the last 6 months and has remained culture positive. Which of the following would be the most appropriate to initiate at this time?

a. Streptomycin IM
b. Isoniazid
c. ALIS
d. Ethambutol

ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy

In patients with macrolide-susceptible MAC pulmonary disease, should patients be treated for <12 months or ≥12 months after culture negativity?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Microbiologic Outcome of Interventions Against MAC Pulmonary Disease

Stud

Inclu

Results

- Triple therapy was continued for at least 1 year
- Treatment success
  - 65.7% (95% CI, 53.3%-77.4%)

Author's Conclusion:

"Long-term treatments with ATS-recommended regimens for patients who are macrolide susceptible are superior to other macrolide-based therapies."

MAC-PD, mycobacterium avium complex pulmonary disease

Sources: Chest 2018; 153:888–921.

Macrolide Therapy for Nodular/Bronchiectatic MAC Lung Disease

Stud

- Single center
- (n=207)

Treatm

- onths
- months

Sputum Conversion

- <12 months: 6 (22%)
- ≥12 months: 154 (86%)
- P≤0.001

Author's Conclusion:

"Current guidelines for macrolide-based therapies for NB MAC lung disease result in favorable microbiologic outcomes for most patients without promotion of macrolide resistance."

Sources: Chest 2014; 146:276-82.

In patients with macrolide-susceptible MAC pulmonary disease, should patients be treated for <12 months or ≥12 months after culture negativity?

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

Assessment Question 4

GH is newly diagnosed with MAC pulmonary disease. She would like to know how long she will need to receive treatment. What is your response?

a. 6 months after culture negativity
b. 12 months after culture negativity
c. 18 months after culture negativity
d. 24 months after culture negativity

Assessment Question 4

GH is newly diagnosed with MAC pulmonary disease. She would like to know how long she will need to receive treatment. What is your response?

a. 6 months after culture negativity

b. 12 months after culture negativity

c. 18 months after culture negativity

d. 24 months after culture negativity

Treatment Summary

Macrolide-susceptible MAC pulmonary disease	Macrolide-based regimen (CAM/AZM + EB + RFP/RFB) dosed three-times weekly
Cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC-PD	Macrolide-based regimen dosed daily + parenteral aminoglycoside for first ≥2–3 months of treatment
Sputum cultures have not converted to negative after 6 months of GBT	Add-on ALIS as part of the continuation treatment regimen
Treatment duration	≥12 months after culture conversion

Sources: Clin Infect Dis. 2020;71(4): e1-e36.

MAC-PD, mycobacterium avium complex pulmonary disease; GBT; guideline-based therapy; CAM, clarithromycin; AZM, azithromycin; EB, ethambutol; RFP, rifampin; RFB, rifabutin; ALIS, amikacin liposome inhalation suspension

Resources

- Daley CL, Iaccarino JM, Lange C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline [published correction appears in Clin Infect Dis. 2020 Dec 31;71(11):3023]. *Clin Infect Dis*. 2020;71(4):e1-e36.
- Wallace RJ Jr, Brown-Elliott BA, McNulty S, et al. Macrolide/Azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. *Chest*. 2014;146(2):276-282.
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- Diel R, Nienhaus A, Ringshausen FC, et al. Microbiologic Outcome of Interventions Against Mycobacterium avium Complex Pulmonary Disease: A Systematic Review. *Chest*. 2018;153(4):888-921.
- Griffith DE, Eagle G, Thomson R, 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;198(12):1559-1569.
- Kadota JI, Kurashima A, Suzuki K. The clinical efficacy of a clarithromycin-based regimen for Mycobacterium avium complex disease: A nationwide post-marketing study. *J Infect Chemother*. 2017;23(5):293-300.
- Kobashi Y, Matsushima T, Oka M. A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary Mycobacterium avium complex disease. *Respir Med*. 2007;101(1):130-138.

Thank you!

Andrew Revels, PharmD

PGY-1 Pharmacy Resident | Princeton Baptist Medical Center

Andrew.Revels@BHSALA.com