Nontuberculous Mycobacterial Infections
Who, How, When and Why to Treat

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Conflict of Interest Disclosures

- Research Grant:
  - Insmed
- Advisory Board:
  - Insmed
  - Johnson and Johnson
  - Spero Pharmaceuticals
  - Horizon Pharmaceuticals
  - Paratek

Nontuberculous Mycobacterial Infections

Who, How, When and Why to Treat

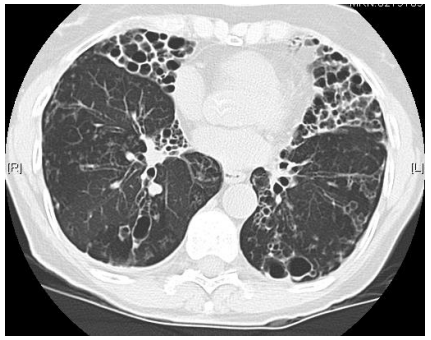
WHO to Treat?

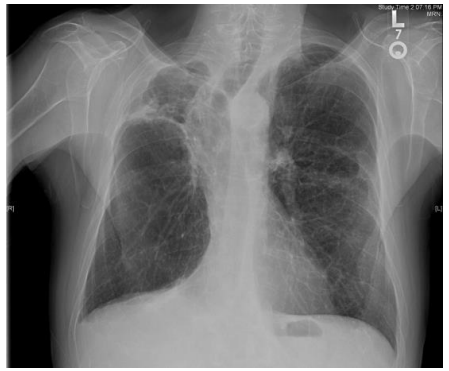
ATS/IDSA Diagnostic Criteria For NTM Lung Disease

Clinical

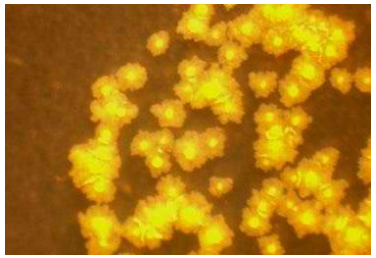
Cough
Fatigue
Weight Loss

Radiographs





Bacteriology



≥ 2 positive
sputum cultures
or
1 positive
bronch culture

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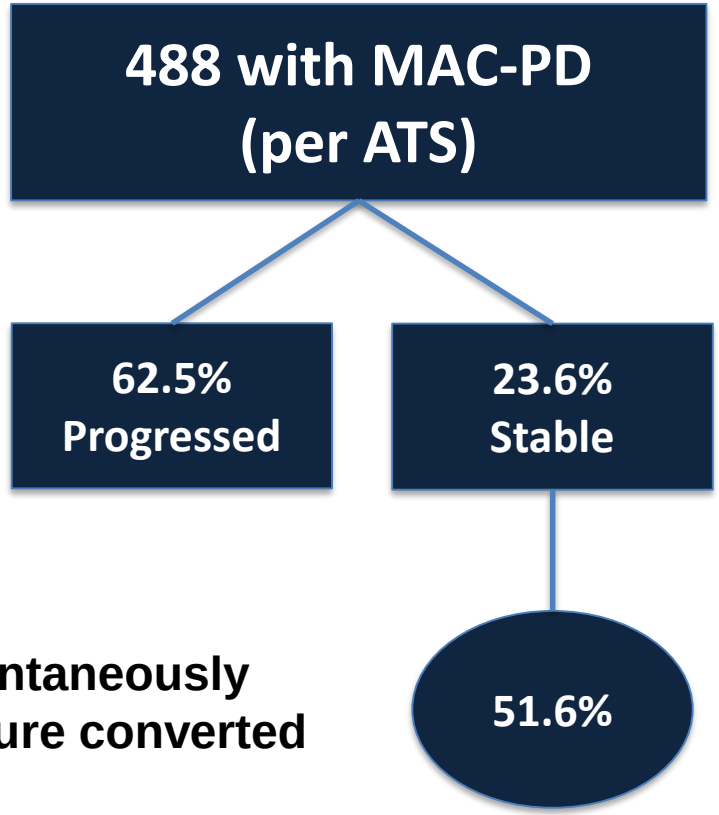
ATS/IDSA AJRCCM 2007;175:367

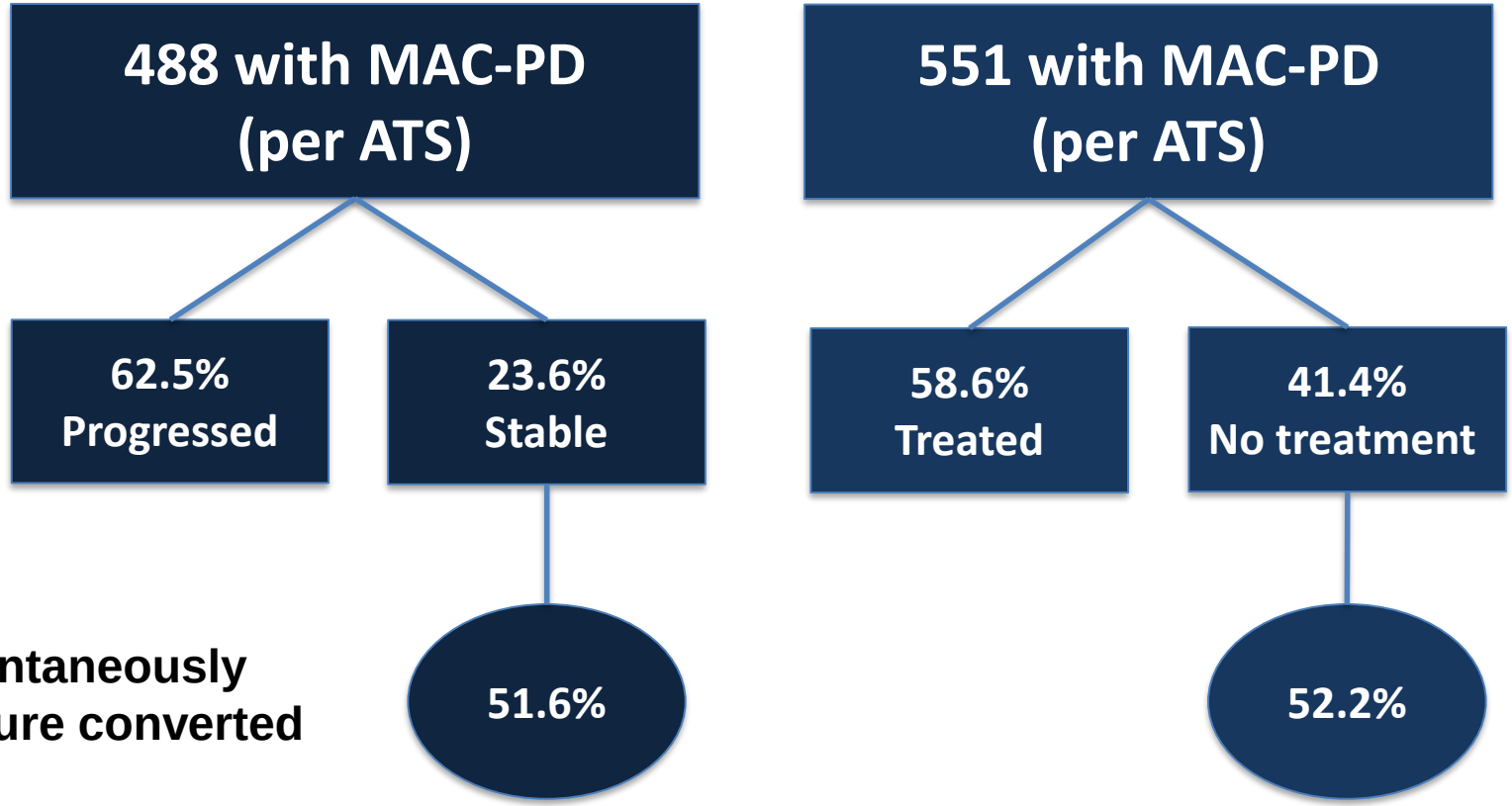
Progression of NTM Pulmonary Disease in Those Who Meet ATS/IDSA Diagnostic Criteria



Hwang JA, et al.

Eur Respir J 2017;49:1600537

Progression of NTM Pulmonary Disease in Those Who Meet ATS/IDSA Diagnostic Criteria

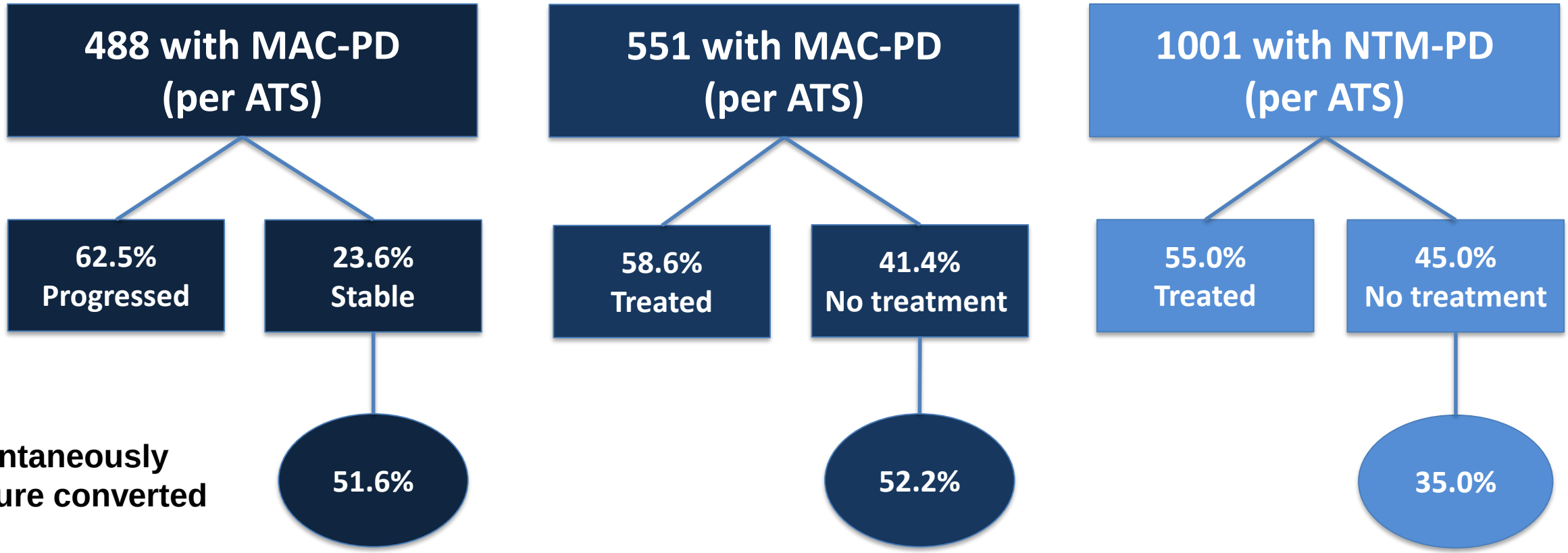


Spontaneously culture converted

Hwang JA, et al.
Eur Respir J 2017;49:1600537

Byoung, et al.
Resp Med 2019;150:45-50

Progression of NTM Pulmonary Disease in Those Who Meet ATS/IDSA Diagnostic Criteria



Hwang JA, et al.
Eur Respir J 2017;49:1600537

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Resp Med 2019;150:45-50

Moon SM, et al.
Resp Med 2019;151:1-7.

WHO to Treat?

Risk Factors Associated with Progression

Host/Demographic Factors	Laboratory Factors	Radiographic Factors	Microbial Factors
• Male gender • Older age • Presence of co-morbidities • Low body mass index	• Elevated inflammatory indices (ESR, CRP) • Anemia • Hypoalbuminemia	• Fibrocavitary • Extent of disease	• Bacterial load • Species

Hwang JA, et al. Eur Respir J 2017;49:1600537
Byoung, et al. Resp Med 2019;150:45-50
Moon SM, et al. Resp Med 2019;151:1-7.

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WHO to Treat?

Characteristics
Age
Symptoms
Radiograph
Progression
Co-morbidities
Drug intolerances
Organism

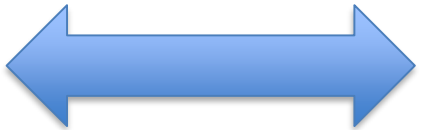
WHO to Treat?

Characteristics	Definitely Treat
Age	Young
Symptoms	Symptomatic
Radiograph	Cavitary, extensive
Progression	Progressing
Co-morbidities	None
Drug intolerances	None
Organism	Pathogenic

WHO to Treat?

Characteristics	Definitely Treat	Possibly Treat	Definitely Not Treat
Age	Young		Elderly
Symptoms	Symptomatic		Asymptomatic
Radiograph	Cavitary, extensive		Non-cavitary, mild
Progression	Progressing		Stable
Co-morbidities	None		Many
Drug intolerances	None		Many
Organism	Pathogenic		Less pathogenic

WHO to Treat?

Characteristics	Definitely Treat	Possibly Treat	Definitely Not Treat
Age	Young		Elderly
Symptoms	Symptomatic	?	Asymptomatic
Radiograph	Cavitary, extensive		Non-cavitary, mild
Progression	Progressing		Stable
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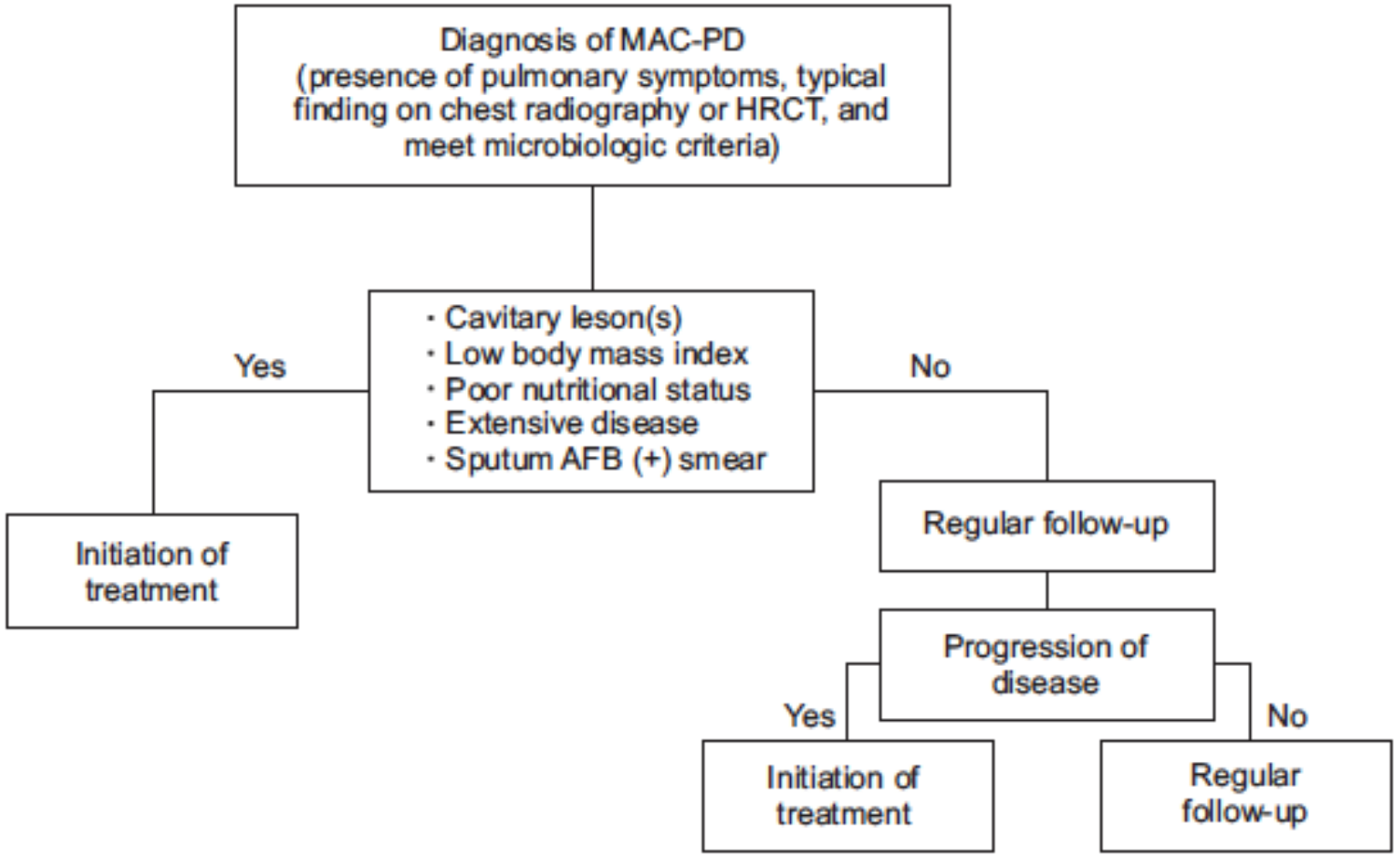
WHO to Treat?

Treatment Initiation Algorithm



Kwon, YS, et al. Tuberc Resp Dis 2019;82:15-26

Nontuberculous Mycobacterial Infections

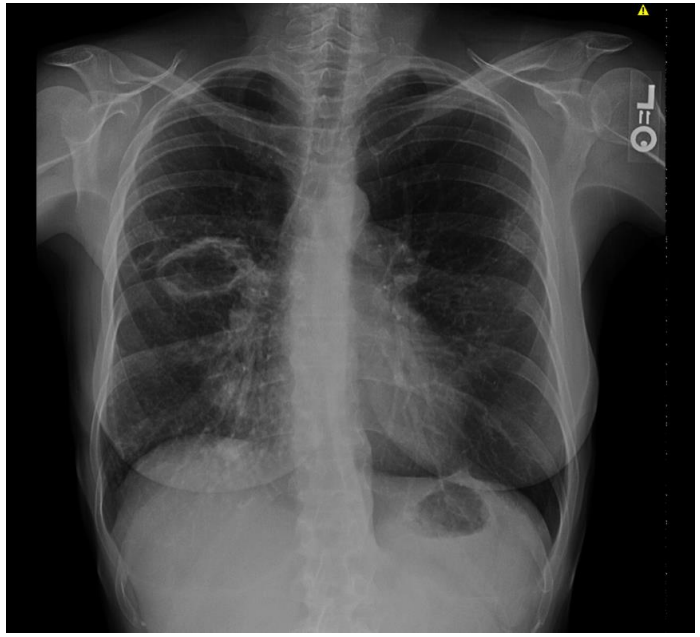
Who, How, When and Why to Treat

HOW to Treat

Treatment of MAC

- 65 year old Caucasian woman treated for *Mycobacterium avium* complex on two previous occasions with macrolide, rifampin, and ethambutol

- Now with AFB smear positive sputum specimen and culture positive for *M. intracellulare*



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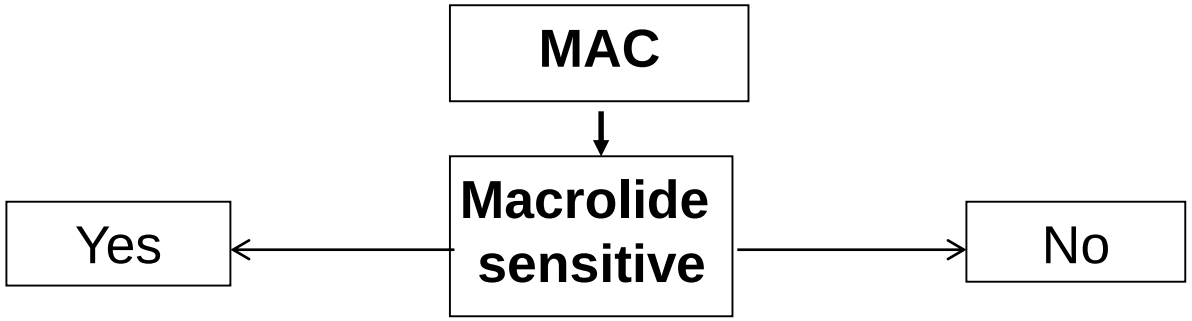
Treatment of Pulmonary *M. avium* complex



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ATS/IDSA AJRCCM 2007;175:367

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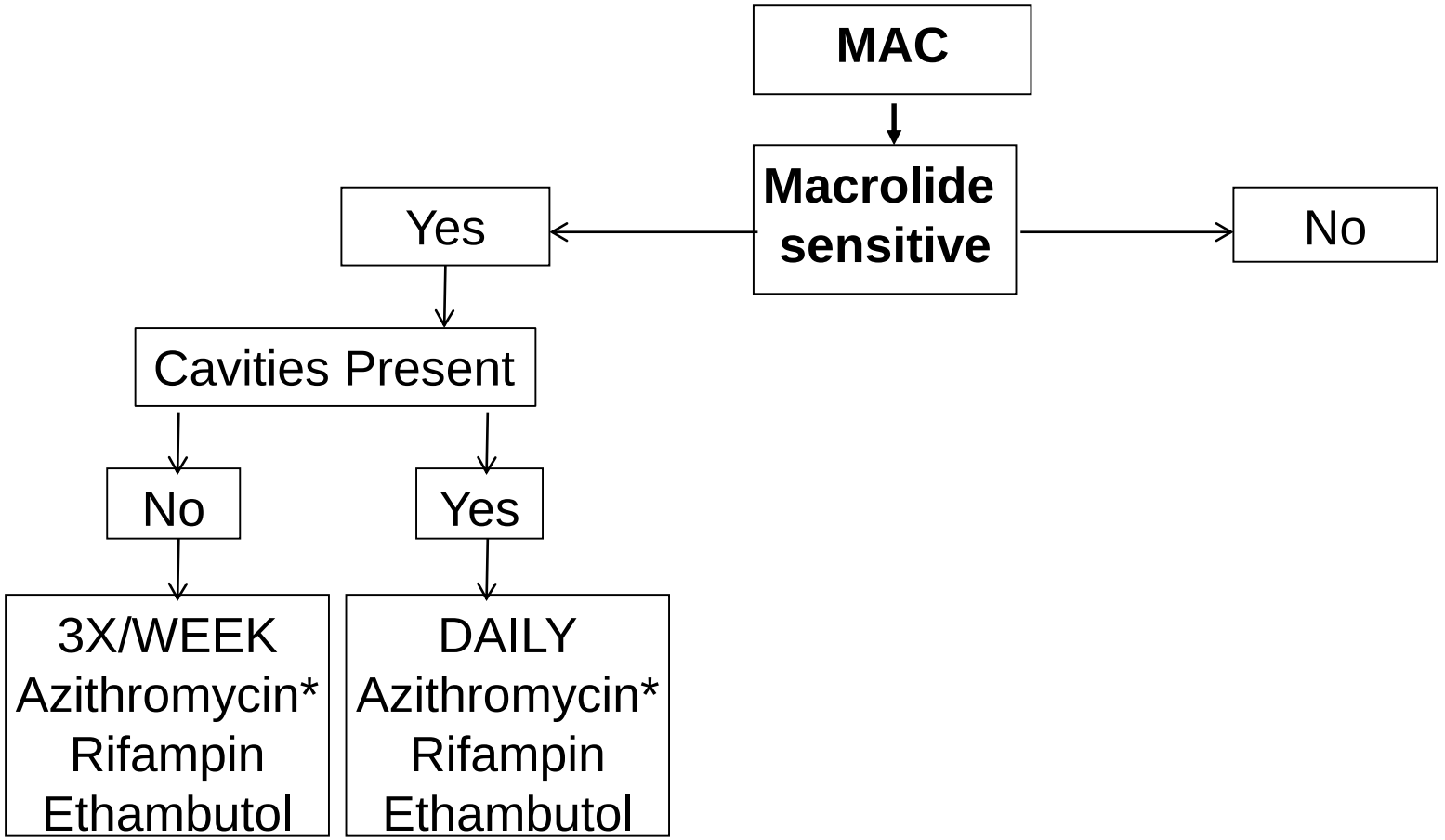

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* Clarithromycin is alternative

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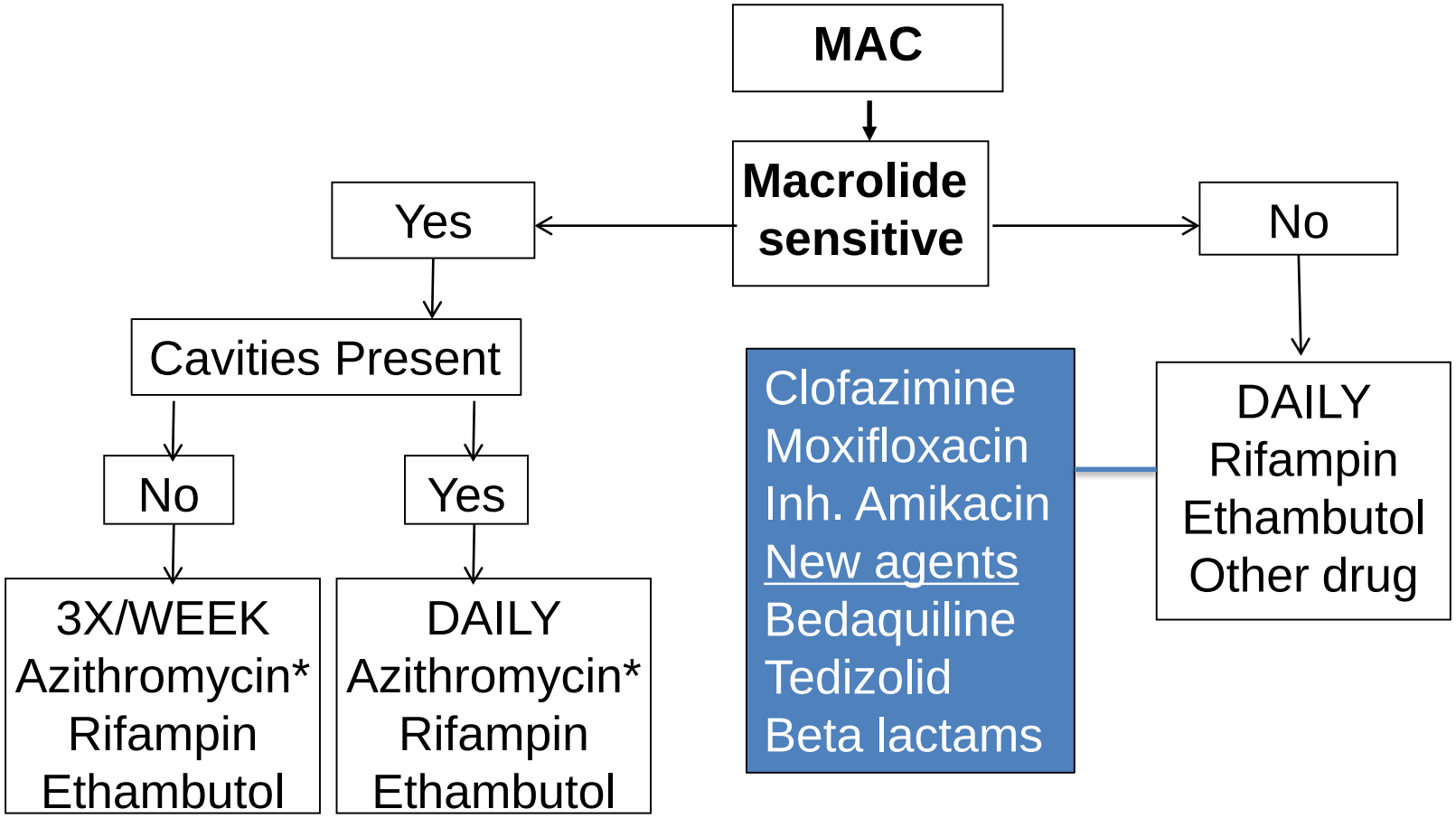
Treatment of Pulmonary *M. avium* complex



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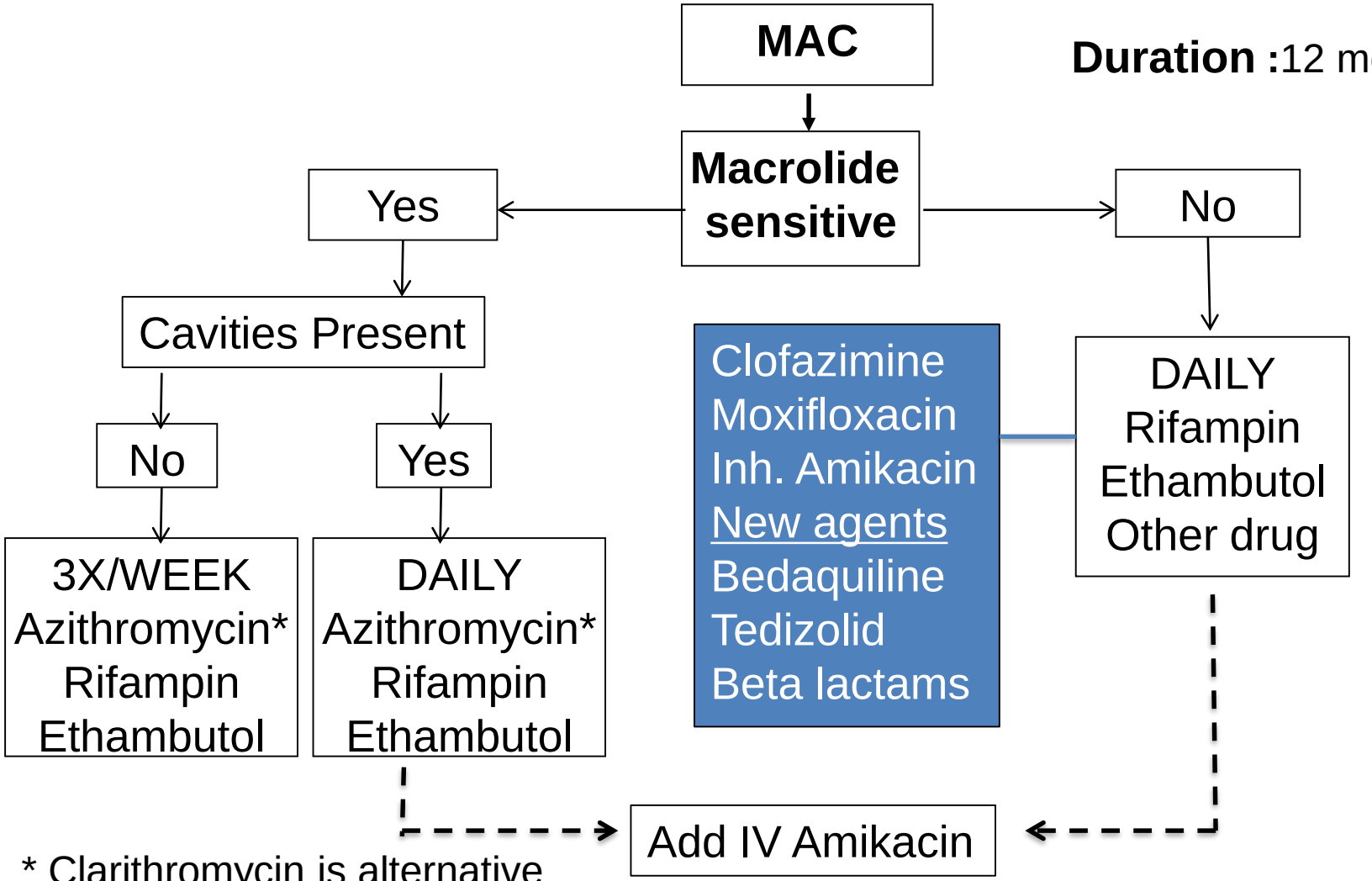

Duration :12 mos culture negativity

* Clarithromycin is alternative

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Treatment Outcomes of Macrolide Susceptible *M. avium* complex

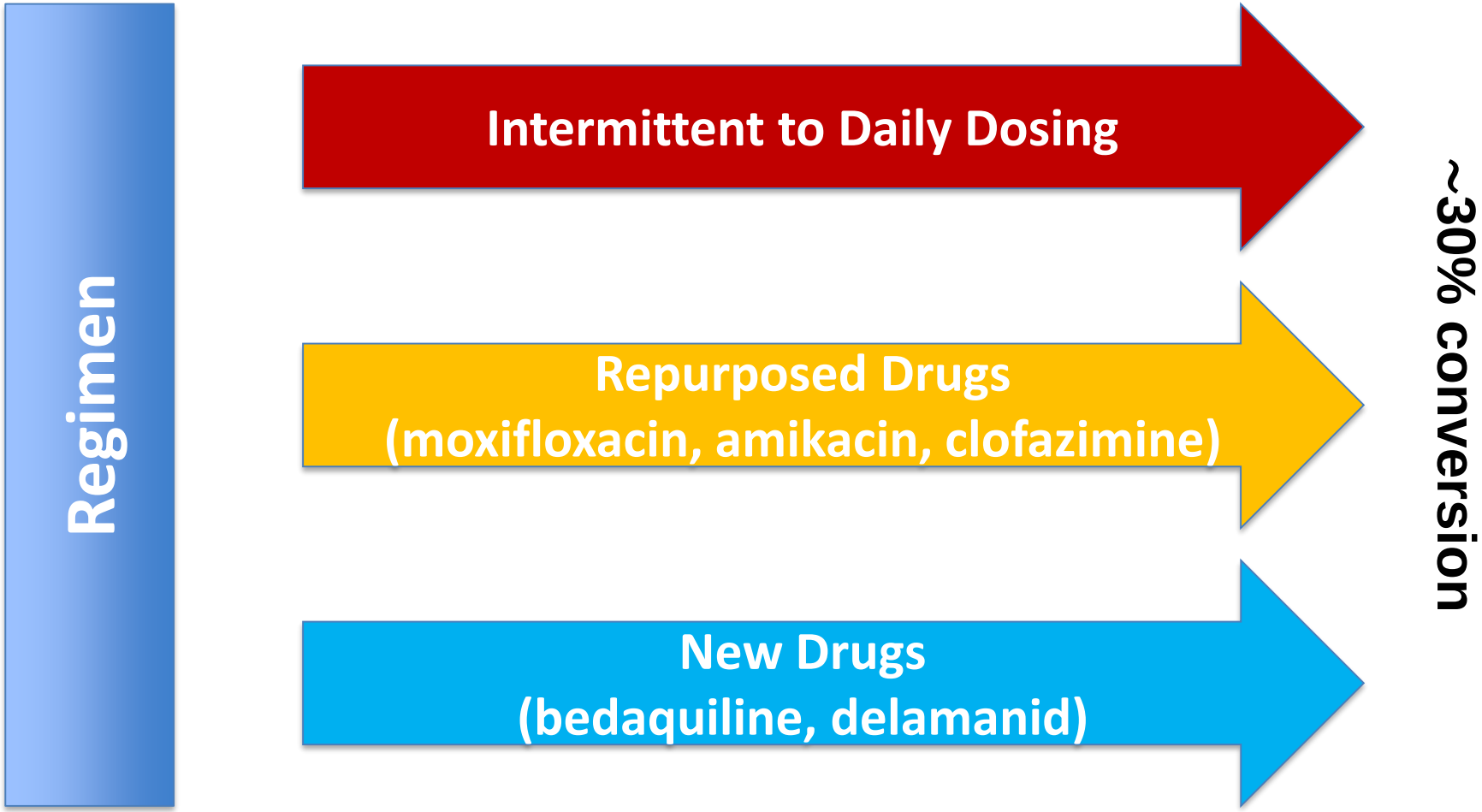
Systematic Review and Meta-analysis

- 42 studies (2,748 patients)
  - 18 retrospective, 18 prospective, 6 randomized
- Treatment success
  - sputum culture conversions – posttreatment microbiologic recurrence
- Treatment success
  - Overall for macrolide containing regimen – 52.8%
  - 3-drug ATS regimen – 61.4%
  - Above taken for at least a year – 65.7%

Diel R, et al. Chest 2018;153:888-921

Treatment Failures

Strengthen the Treatment Regimen



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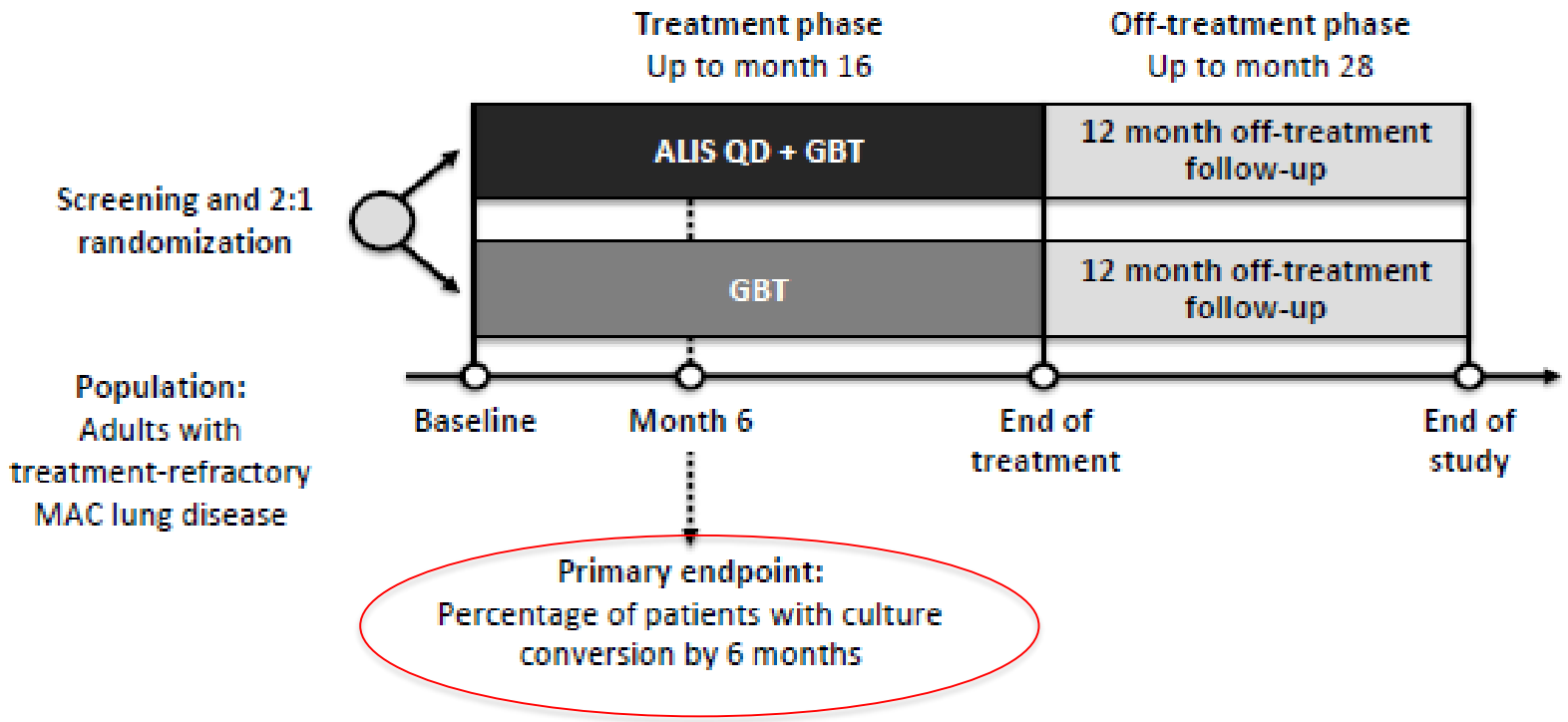
CONVERT STUDY

Phase 3 Randomized, Controlled Trial of Amikacin Liposome Inhalation Suspension (ALIS) + GBT vs GBT alone in treatment refractory MAC lung disease



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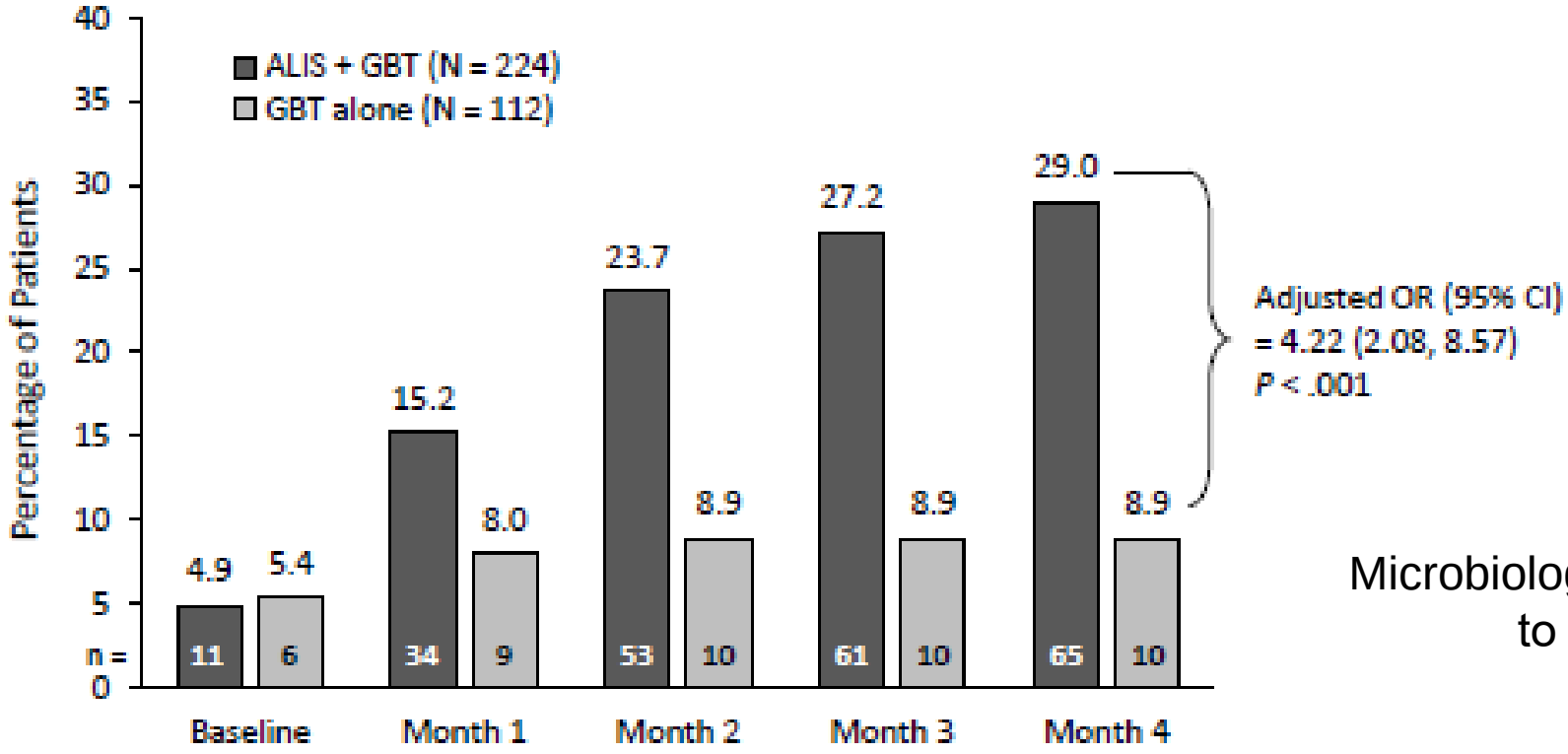
Griffith D, et al. AJRCCM 2018 epub

CONVERT STUDY

Proportion of Patients With Negative Sputum Cultures for NTM



Microbiologic response up to MIC ≤64

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Griffith D, et al. AJRCCM, 2018.

CONVERT STUDY

Treatment Emergent Adverse Events (TEAE)

Adverse Event	GBT + ALIS	GBT
Respiratory-related AEs		
Dysphonia	45.7%	0.9%
Cough	37.2%	15.2%
Dyspnea	21.5%	8.9%)
Hemoptysis	17.5%	13.4%
Oropharyngeal pain	10.8%	1.8%
Audiological AEs		
Tinnitus	7.6%	0.9%
Dizziness	6.3%	2.7%
Hearing loss	4.5%	6.3%
Serious adverse events	20.2%	17.9%
Discontinuation of ALIS	17.5%	–

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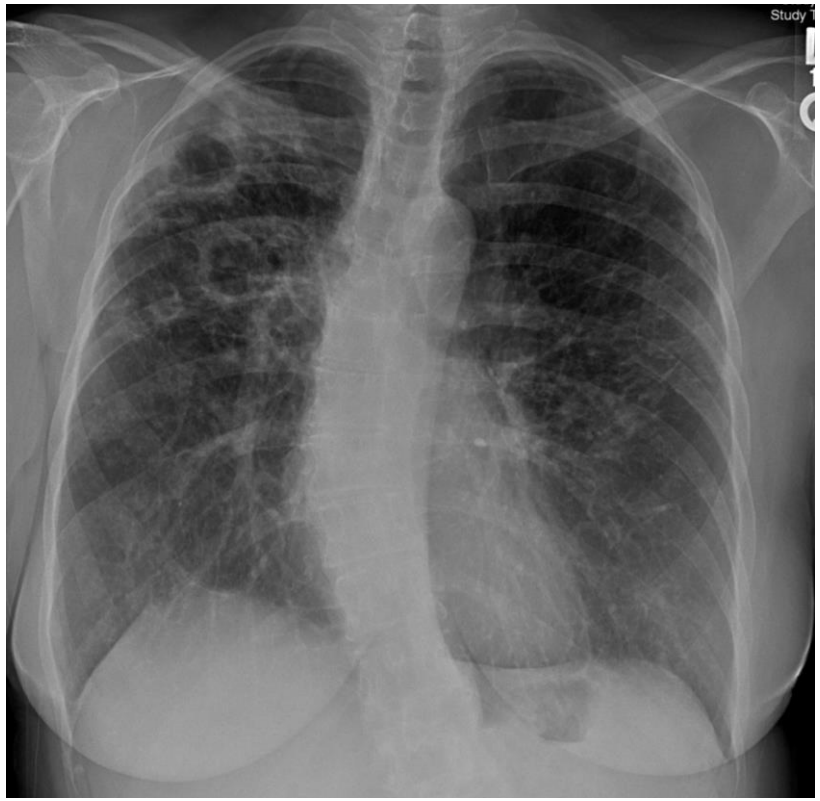
Griffith D, et al. AJRCCM, 2018.

HOW to Treat

Treatment of *M. abscessus*

- 68 year old woman with chronic cough and fatigue



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Macrolide Resistance: Implications for Treatment

Clarithromycin susceptibility results					
Days 3-5	Day 14	Genetics	Subspecies	Susceptibility Phenotype	Use Macrolide
Susceptible	Susceptible	Dysfunctional *erm*(41) gene	*M. massiliense*	Susceptible	Yes

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Haworth C. et al Thorax 2017;72ii1-ii64

Macrolide Resistance: Implications for Treatment

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Susceptible	Susceptible	Dysfunctional *erm*(41) gene	*M. massiliense*	Susceptible	Yes
Susceptible	Resistant	Functional *erm(*41) gene	*M. abscessus** *M. bolletii*	Inducible resistance	Possibly but don't count as active

* 15% have nonfunctional *erm*(41) gene due T to C substitution at position 28

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Macrolide Resistance: Implications for Treatment

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Susceptible	Susceptible	Dysfunctional *erm*(41) gene	*M. massiliense*	Susceptible	Yes
Susceptible	Resistant	Functional *erm(*41) gene	*M. abscessus** *M. bolletii*	Inducible resistance	Possibly but don't count as active
Resistant	Resistant	23S rRNA point mutation	Any	Constitutive resistance	Only for anti-inflam purposes

* 10-15% have nonfunctional *erm*(41) gene due T to C substitution at position 28

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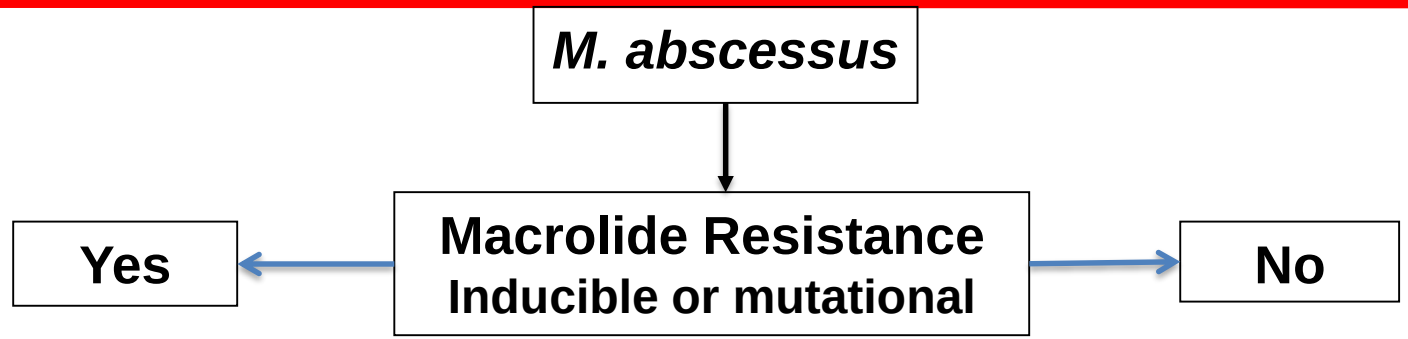
Haworth C. et al Thorax 2017;72ii1-ii64

Treatment of *M. abscessus* complex



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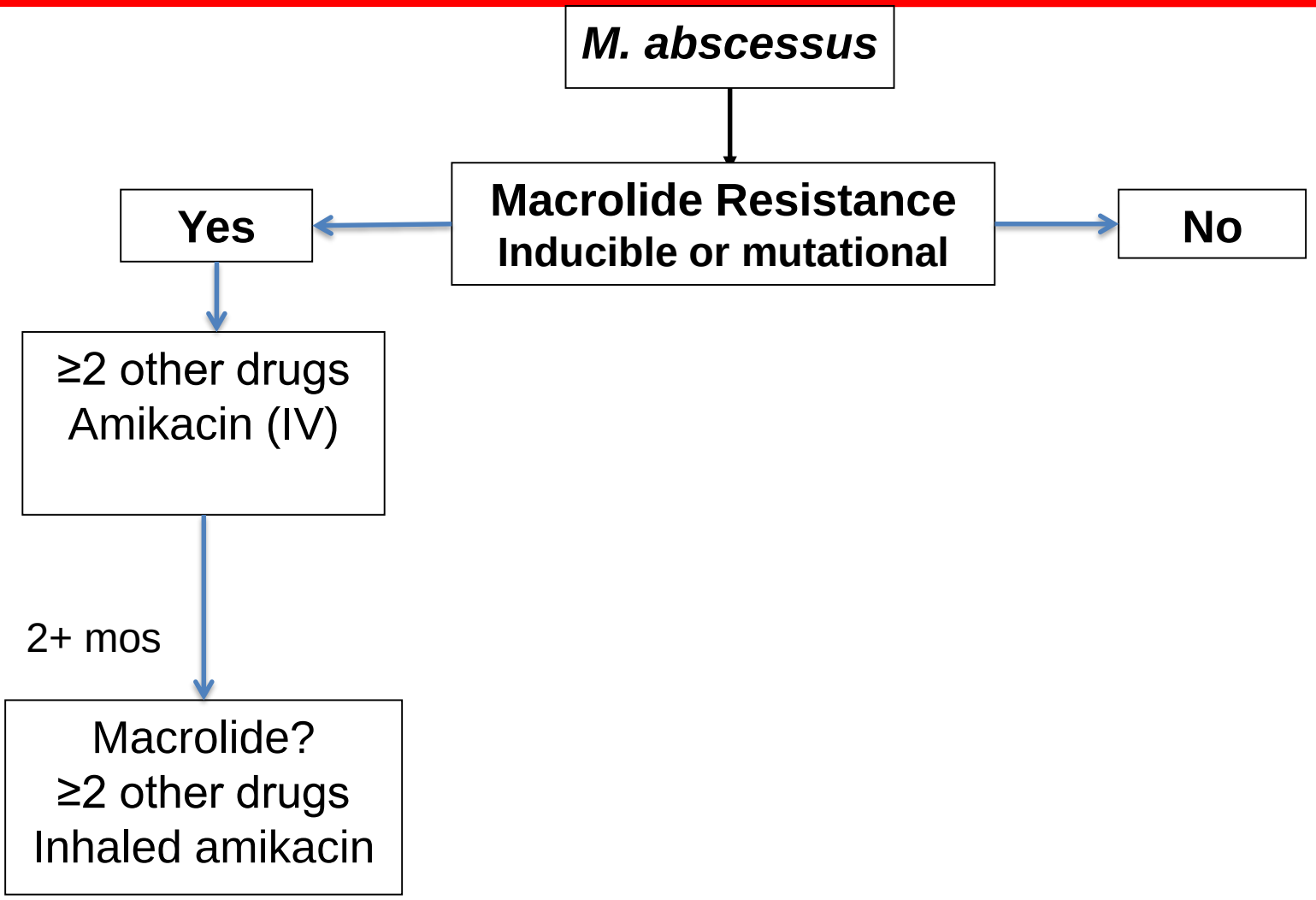

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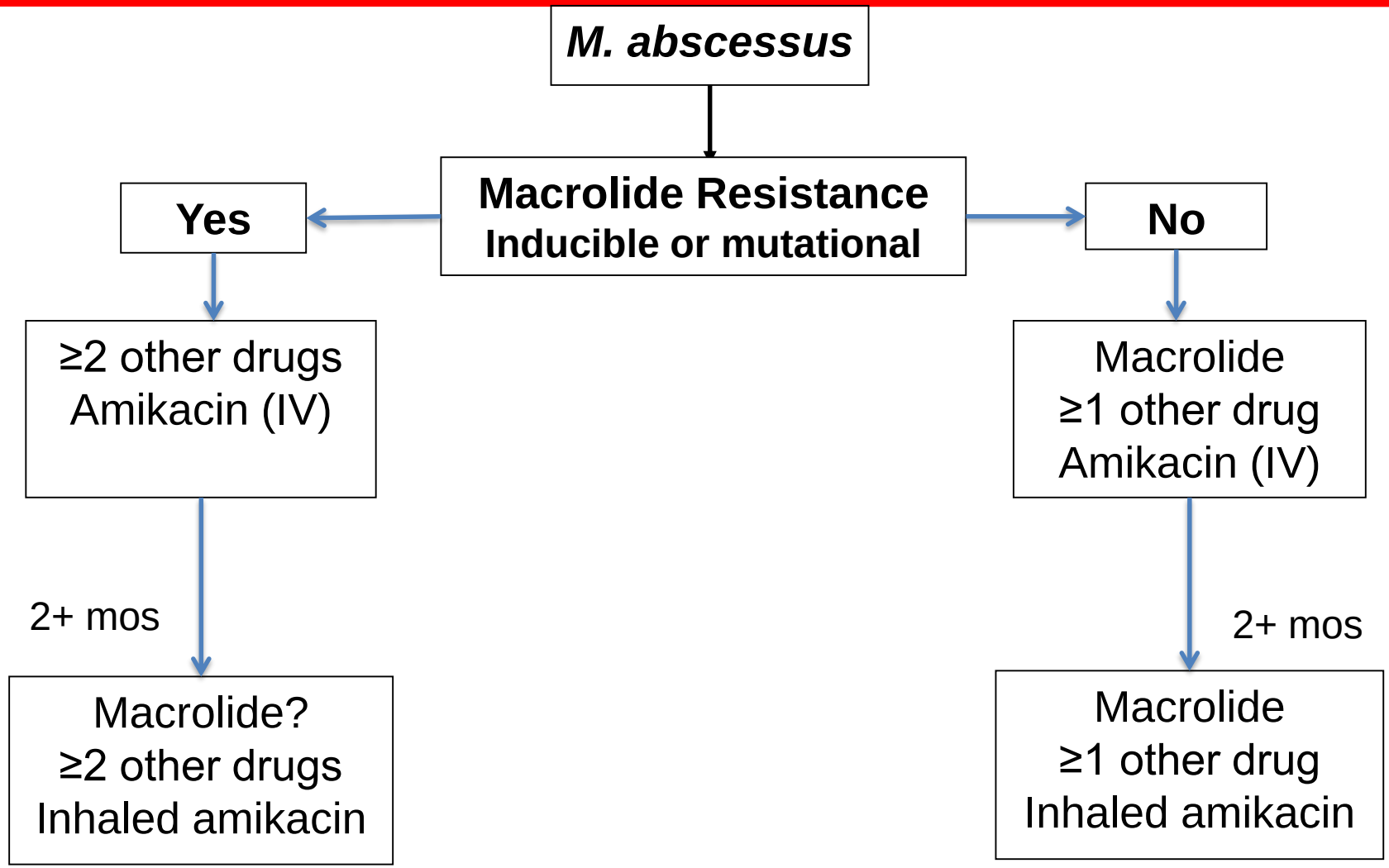

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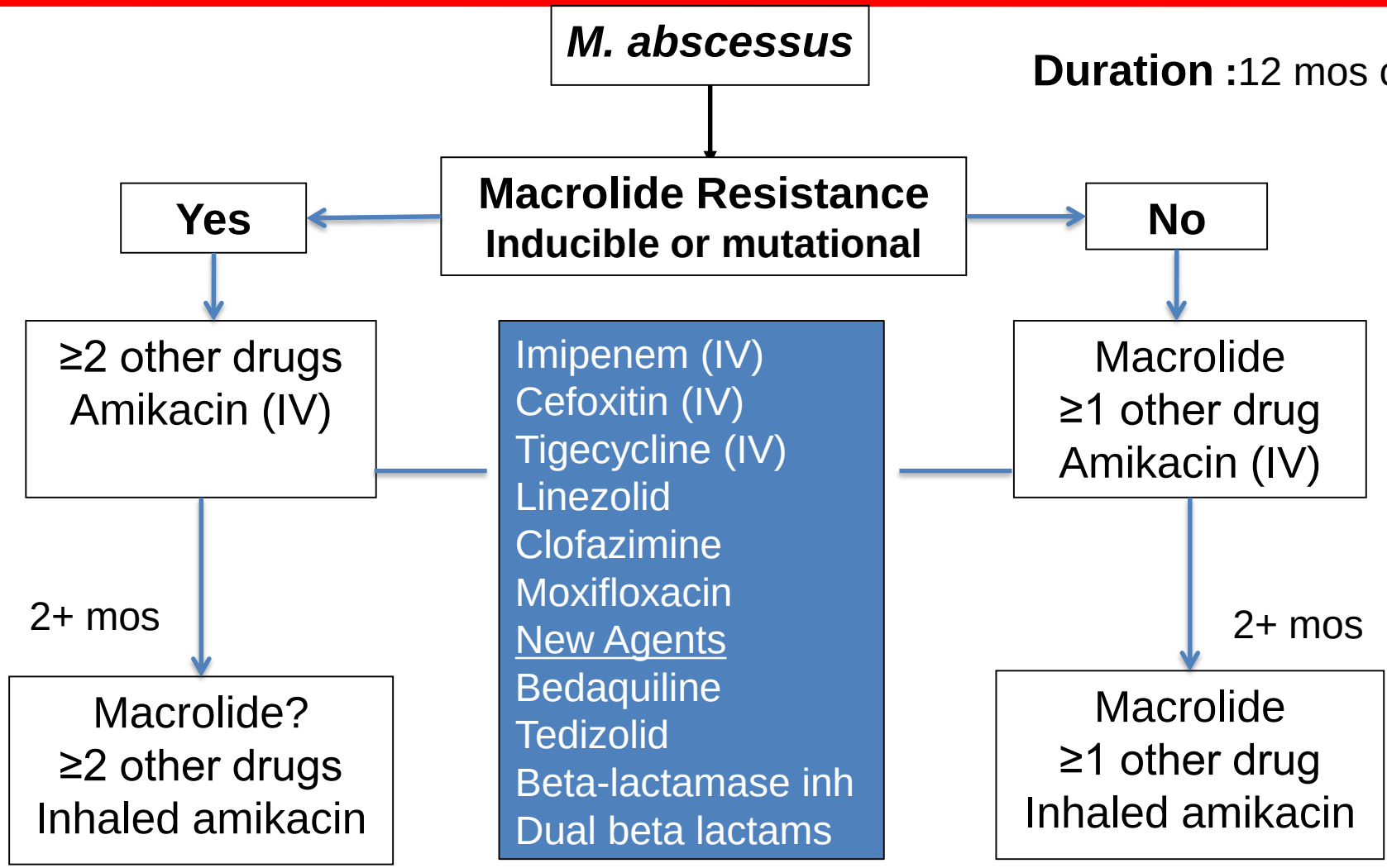
Treatment of *M. abscessus* complex



Duration :12 mos culture negativity?

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Treatment Outcomes for *M. abscessus vs. M. massiliense*

Study	Population	Treatment	N	Sputum conversion	Failure to convert	Relapse
Koh, 2011	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	24 33	25% **88%**	58% **3%**	17% **9%**
Lyu, 2014	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	26 22	42% **96%**	27% **0%**	31% **5%**
Roux, 2015	Cystic Fibrosis	*M. abscessus* *M. massiliense*	12 7	25% **86%**	- -	- -
Park, 2017	Non Cystic Fibrosis	*M. abscessus* *M. massiliense*	19 17	**26%** **82%**	74% **18%**	55% **0%**

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Koh WJ, et al. Am J Respir Crit Care Med 2011;183:405-10
Choi H, et al. Antimicrob Agents Chemother 2016 epub
Park J, et al. CID 2017;64:301-8

Treatment Outcomes with *M. abscessus*
Systematic Review and Meta-analysis

- 14 studies identified (8 provided individual patient data, 303 patients)
- Treatment success
  - culture conversion for ≥ 12 months while on treatment *or* sustained culture conversion without relapse until the end of treatment
- Treatment success
  - Overall – 45.6%
  - *M. abscessus* subspecies *abscessus* – 33.0%
  - *M. abscessus* subspecies *massiliense* – 56.7%
- Imipenem, azithromycin, or parenteral amikacin associated with success in *M. abscessus* subspecies *abscessus*

Kwak N, et al. ERJ 2019 epub

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