OSPEDALE CANNIZZARO
CATANIA
AZIENDA OSPEDALIERA PER L'EMERGENZA

CARMELO IACOBELLO

UOC MALATTIE INFETTIVE

AOE CANNIZZARO

CATANIA

SITA | 13° CONGRESSO NAZIONALE

PADOVA | 23-24 novembre 2023

Presidente SITA
Prof. Matteo Bassetti
Comitato Organizzatore
Prof.ssa Anna Maria Cattelan

Sessione 6 | Mixed Topic

Moderatori: *P.A. Grossi (Varese), R. Luzzati (Trieste)*

11:20 - 11:40 **La neutropenia febbrile: nuovi paradigmi di prevenzione e terapia** *L. Pagano (Roma)*

11:40 - 12:00 **Diagnostica e terapia dell'aspergillosi invasiva nel paziente ematologico** - *M. Mikulska (Genova)*

12:00 - 12:20 **Le terapie antibatteriche soppressive croniche: quando e perché?** *S. Corcione (Torino)*

12:20 - 12:40 **Micobatteriosi atipiche: quando e come trattarle** - *C. Iacobello (Catania)*

12:40 - 13:00 **Diagnostica e terapia della candidemia e candidiasi invasiva** *I. Gentile (Napoli)*

Dichiarazione sul Conflitto di Interessi

Il sottoscrittoCARMELO IACOBELLO in qualità di:

□ moderatore □ docente x□ relatore

Dichiara

che negli ultimi due anni ha avuto rapporti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

- MSD
- ASTRA ZENECA
- GILEAD
- ANGELINI

Table I. Common non-tuberculous mycobacteria (NTM) species causing human diseases

SLOWLY GROWING NTM (growth < 7 days in subculture)

- Photocromogen (M. Kansasii; M. marinum)
- Scotocromogen (M. scrofulaceum)
- Non Cromogens (M. avium complex; M. avium; M. Intracellulare; M. chimaera; M. ulcerans; M. xenopi; M. simiae; M. malmoense; M. szulgai; M. haemophilus)

RAPIDLY GROWING NTM (growth < 7 days on subculture)

- M. Abscessus subsp abscessus
- M. abscessus subsp bolletii
- M. abscessus subsp massiliense
- M. fortuitum
- M. chelonae

Indian J Med Res 152, September 2020, pp 185-226

	NTM	MTB
Where they live	**Environment (water, soil)**	**Infected host**
Infection	**Environmental exposure / inoculation**	**Infective aerosols**
Spread person to person?	**No**	**Yes**
Pathogenic	**Weakly**	**Strongly**
Diagnosis NTM	**Micro/Clin/Rad**	**Micro (sometimes clinical)**

NTM are characterised by thick, hydrophobic cell walls, an ability to evade host defences through sequestration in and manipulation of macrophages, and an array of antimicrobial resistance mechanisms

Table 2 Considerations and challenges to overcome in developing drugs to treat non-tuberculous mycobacterial pulmonary disease

Challenge	Detailed overview
NTM organism—hydrophobicity and innate resistance	○IDROFOBICITA' PER LA PRESENZA DI LIPIDI DI PARETE ○POMPE DI EFFLUSSO E SISTEMI ENZIMATICI DI RESISTENZA ○POLIMORFISMO GENETICO IN GRADO DI MODIFICARE I TARGET DI LEGAME DEGLI ANTIBIOTICI
Acquired drug resistance	✓MUTAZIONI GENOMICHE IN GRADO DI PRODURRE ALTI LIVELLI DI RESISTENZA IN CORSO DI TRATTAMENTI PROLUNGATI
Correlation between in vitro MIC and clinical outcomes	❖RISPOSTA AGLI ANTIBIOTICI IN VIVO NON RIPRODUCIBILE IN VIVO (BIOFILM)
Intracellular growth and sequestration into phagocytic cells	○PATOGENI INTRACELLULARI ○CAPACITA' DI SFUGGIRE ALLA FAGOCITOSI MACROFAGICA ○CAPACITA' DI BLOCCARE LA AUTOFAGIA DEI MACROFAGI
Mucous and biofilm growth	❑CAPACITA' RIDURRE IL METABOLISMO CELLULARE ANCHE IN CARENZA DI OSSIGENO ❑CAPACITA' INDURRE LA PRODUZIONE DI MUCO CHE RIDUCE LA SUSCETTIBILITA' AGLI AINTIBIOTICI

MIC, minimum inhibitory concentration; NTM, non-tuberculous mycobacteria; NTM-PD, non-tuberculous mycobacterial pulmonary disease. Adapted from [52]

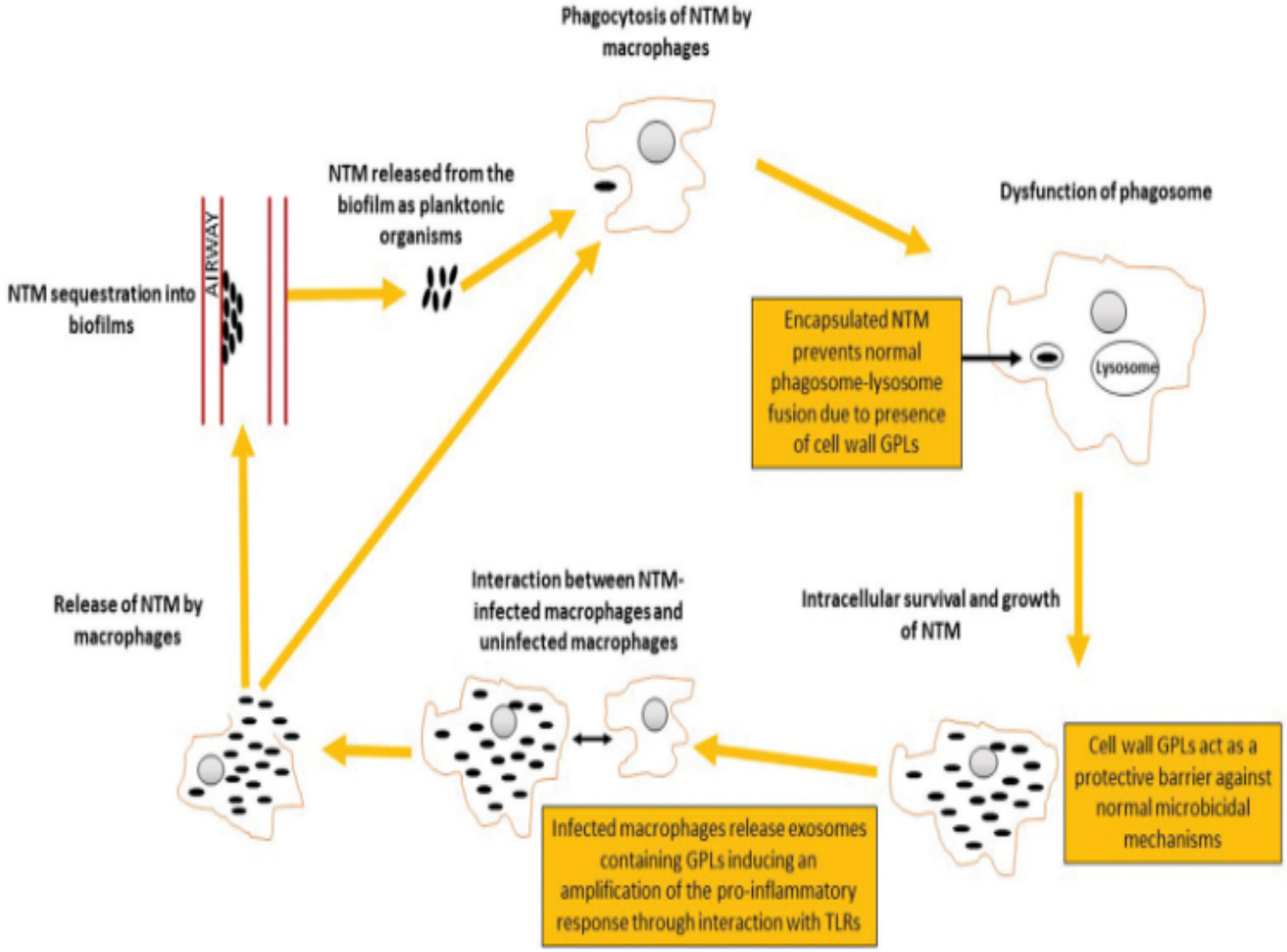

Figure 1. NTM Pathogenesis and Dysfunction of the Phagosome.

Source: Illustration based on Busatto et al. 2019 [9] and Shu et al. 2020 [138]

[a]T helper 1 cell immunity has been suggested as a major protective mechanism against NTM intracellular infection. Diseases and therapies that reduce cell-mediated immunity

FATTORI CHE CONTRIBUISCONO ALL'INCREMENTO DEI CASI DI INFEZIONI DA NTM

- **MUTAZIONI GENETICHE CHE PORTANO ALLA CRESCITE DEL FENOMENO DELLE RESISTENZE.**
- **CAMBIAMENTI CLIMATICI ED AMBIENTALI.**
- **INVECCHIAMENTO E IMMUNODEPRESSIONE DELL'OSPITE.**
- **AUMENTO DELLE MALATTIE DESTRUTTURANTI DEI POLMONI.**
- **MIGLIORAMENTO DELLA DIAGNOSTICA RADIOLOGICA E MICOBATTERIOLOGICA.**
- **MAGGIORE CONSAPEVOLEZZA PRESSO I MEDICI SPECIALISTI DELLE INFEZIONI DA NTM ANCHE PER L'INCREMENTO DELLE PUBBLICAZIONI SULL'ARGOMENTO.**

Surendra K. Sharma & Vishwanath Upadhyay Indian J Med Res 152, September 2020

Guidance for therapy decisions

Available treatment guidelines:

- ATS/IDSA (2007)[3]
- DZK/DGP (2016)[1]
- US CFF/ECFS (2016)[4]
- BTS (2017)[2]


Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

2020

Charles L. Daley,[1,2,3] Jonathan M. Iaccarino,[3] Christoph Lange,[4,5,6,7,8] Emmanuelle Cambau,[9,10] Richard J. Wallace, Jr.,[11,12] Claire Andrejak,[10,13] Erik C. Böttger,[12] Jan Brozek,[14] David E. Griffith,[15] Lorenzo Guglielmetti,[16,17] Gwen A. Huitt,[1,2] Shandra L. Knight,[18] Philip Leitman,[19] Theodore K. Marras,[20] Kenneth N. Olivier,[21] Miguel Santin,[22] Jason E. Stout,[23] Enrico Tortoli,[24] Jakko van Ingen,[25] Dirk Wagner,[26] and Kevin L. Winthrop[27]

Evidence-based approach to treatment of NTM-LD is hampered by a lack of adequately powered randomized clinical trials[5]

ATS, American Thoracic Society; BTS, British Thoracic Society; DGP, German Respiratory Society; DZK, German Central Committee against Tuberculosis; IDSA, Infectious Diseases Society of America; NTM-LD, non-tuberculous mycobacterial lung disease; US CFF/ECFS, US Cystic Fibrosis Foundation (CFF) and European Cystic Fibrosis Society (ECFS).

1. Schoenfeld N, et al. Pneumologie 2016; 70:250-76; 2. Haworth CS, et al. Thorax 2017; 72:ii1-ii64; 3. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 4. Floto RA, et al. Thorax 2016; 71:i1-i22; 67:605-33; 5. Johnson MM, Odell AA. J Thorac Dis 2014; 6;210-20.

Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

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Table 2. Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease[a]

Clinical	Pulmonary or Systemic Symptoms	
Radiologic	Nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows bronchiectasis with multiple small nodules	Both Required
and	Appropriate exclusion of other diagnoses	
Microbiologic[b]	1. Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures **or** 2. Positive culture results from at least one bronchial wash or lavage **or** 3. Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM	

Source: Official ATS/IDSA statement [4].

CLINICAL CRITERIA

IL CORTEO POLISINDROMICO DIPENDE DALLO STADIO DELLA MALATTIA.
TOSSE SECCA O PRODUTTIVA E' IL SINTOMO PIU' FREQUENTE
DISPNEA, ASTENIA, DIMAGRIMENTO E MALESSERE SONO FREQUENTI

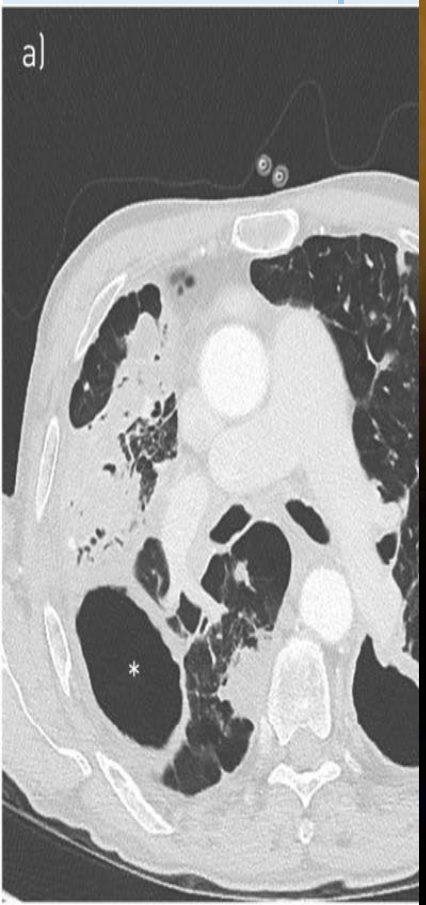
MALATTIA IN PAZIENTE CON PATOLOGIE POLMONARI NOTE
Bronchiectasie croniche da fibrosi cistica
Bpco
Precedente malattia tubercolare
Tabagismo
Patogeni più comuni: M. abscessus e M. Kansasii

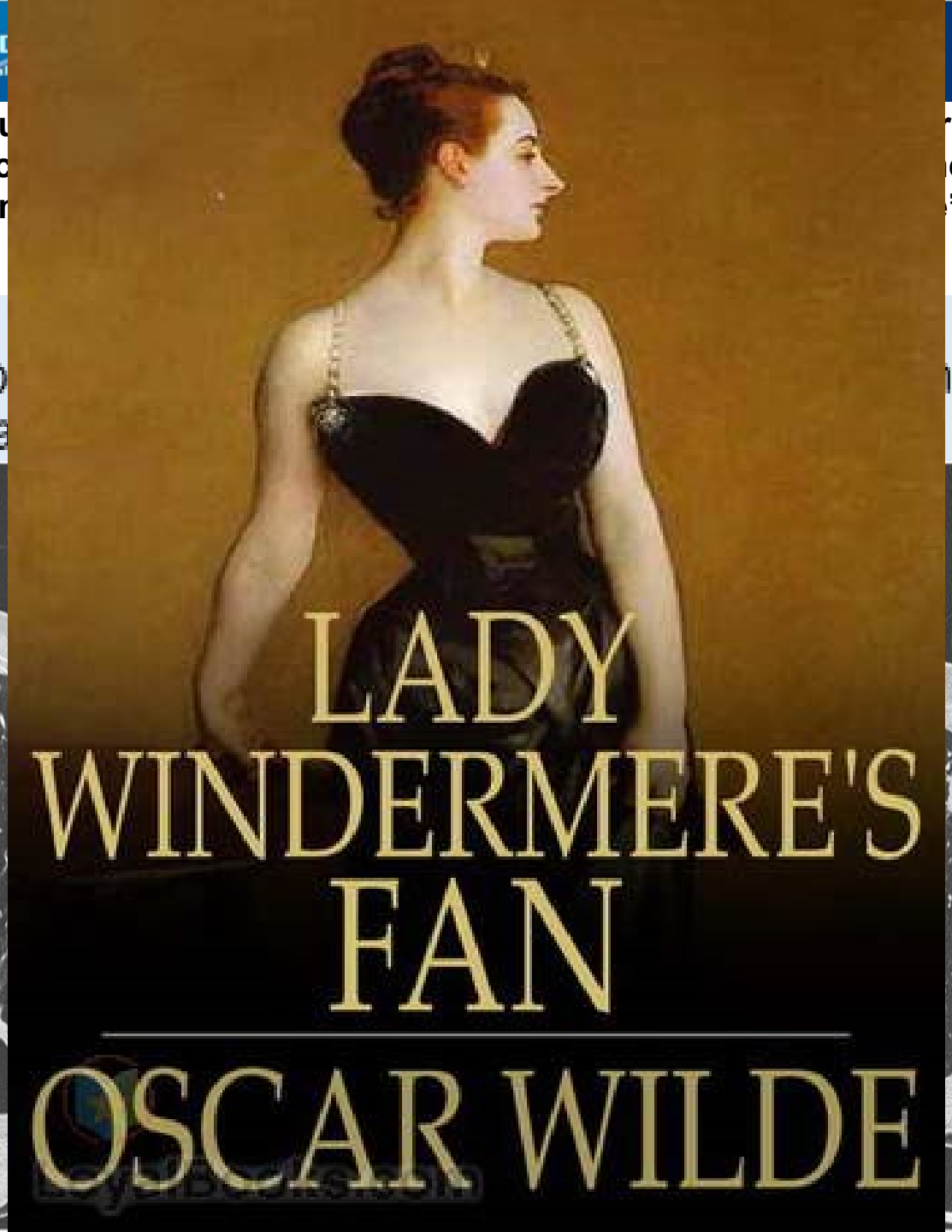
MALATTIA IN PAZIENTE CON PATOLOGIE POLMONARI SCONOSCIUTE
Donne non fumatrice over 50
Bronchiectasie non diagnosticate
Tosse ingravescente e dispnea anche dopo anni
Patogeno più comune: MAC

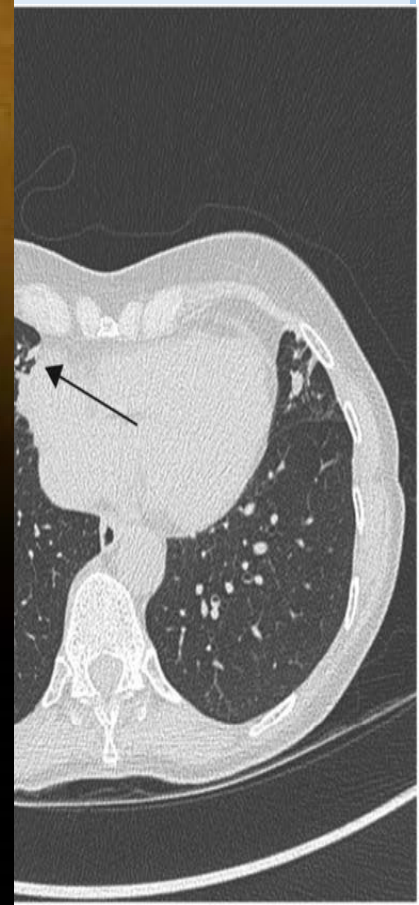
BC Centre for D

The appearance of pu **resolution computed**
tomography: a) fibroc **chiectatic disease in**
the r **" ...**

Radiographic	No tha	n resolution CT scan







MICROBIOLOGICAL CRITERIA

- Colture positive da almeno 2 escreati. Se non diagnostico ripetere Ziehl Neelsen e coltura

Oppure

- Colture positive da almeno un BAL

Oppure

- Biopsia polmonare con aspetti anatomo-patologici di granuloma con cellule giganti di Langhans e crescita di NTM su biopsia

BC Centre for Disease Control
Provincial Health Services Authority

TB Services
655 West 12th Avenue
Vancouver, BC V5Z 4R4
100-237 E Columbia St.
New Westminster, BC
V3L 3W4

METODI MOLECOLARI

- PCR ESEGUITA SU ESCREATRI POSITIVI IDENTIFICANO MAC vs MTB CON UNA SENSIBILITA' PER MAC DELL'87%.

- LA COLTURA RAPPRESENTA IL GOLD STANDARD PER LA DIAGNOSI, IL MONITORAGGIO E PER I TEST DI SUSCETTIBILITA'

Summary for Clinicians: 2020 Clinical Practice Guideline Summary for the Treatment of Nontuberculous Mycobacterial Pulmonary Disease

Sebastian G. Kurz[1], B. Shoshana Zha[2], Derrick D. Herman[3], Michael R. Holt[4], Charles L. Daley[5], Joseph K. Ruminjo[6], and Carey C. Thomson[7,8]

Table 3. First-line antimicrobial agents with clinically established break points*

Antimicrobial Agents	MIC (μg/ml)		
	S	I	R
M. avium complex			
Clarithromycin†	≤8	16	≥32
Amikacin (IV)	≤16	32	≥64
Amikacin (liposomal, inhaled)	≤64	—	≥128
M. kansasii			
Clarithromycin†	≤8	16	≥32
Rifampin	≤1	—	≥2
M. abscessus‡			
Clarithromycin†§	≤2	4	≥8
Amikacin	≤16	32	≥64
Cefoxitin	≤16	32–64	≥128
Imipenem	≤4	8–16	≥32
Linezolid	≤8	16	≥32
Doxycycline	≤1	2–4	≥8
Tigecycline‖	—	—	—
Ciprofloxacin	≤1	2	≥4
Moxifloxacin	≤1	2	≥4

Definition of abbreviations: I = intermediate; IV = intravenous; *M.* = *Mycobacterium*; MIC = minimal inhibitory concentration; R = resistant; S = susceptible.

*Reprinted by permission from Reference 2.

†Clarithromycin is the class drug for macrolides.

‡Clinical outcome data for *M. abscessus* MIC values are available only for macrolides and IV amikacin.

§To detect inducible macrolide resistance, reading for clarithromycin should be at ≥14 days, unless resistance is recognized earlier. Alternatively, sequencing of the *erm*(41) (erythromycin ribosomal methylase causing macrolide resistance of *M. abscessus*) gene should be performed.

‖No clinical break points established; MIC values only should be reported.

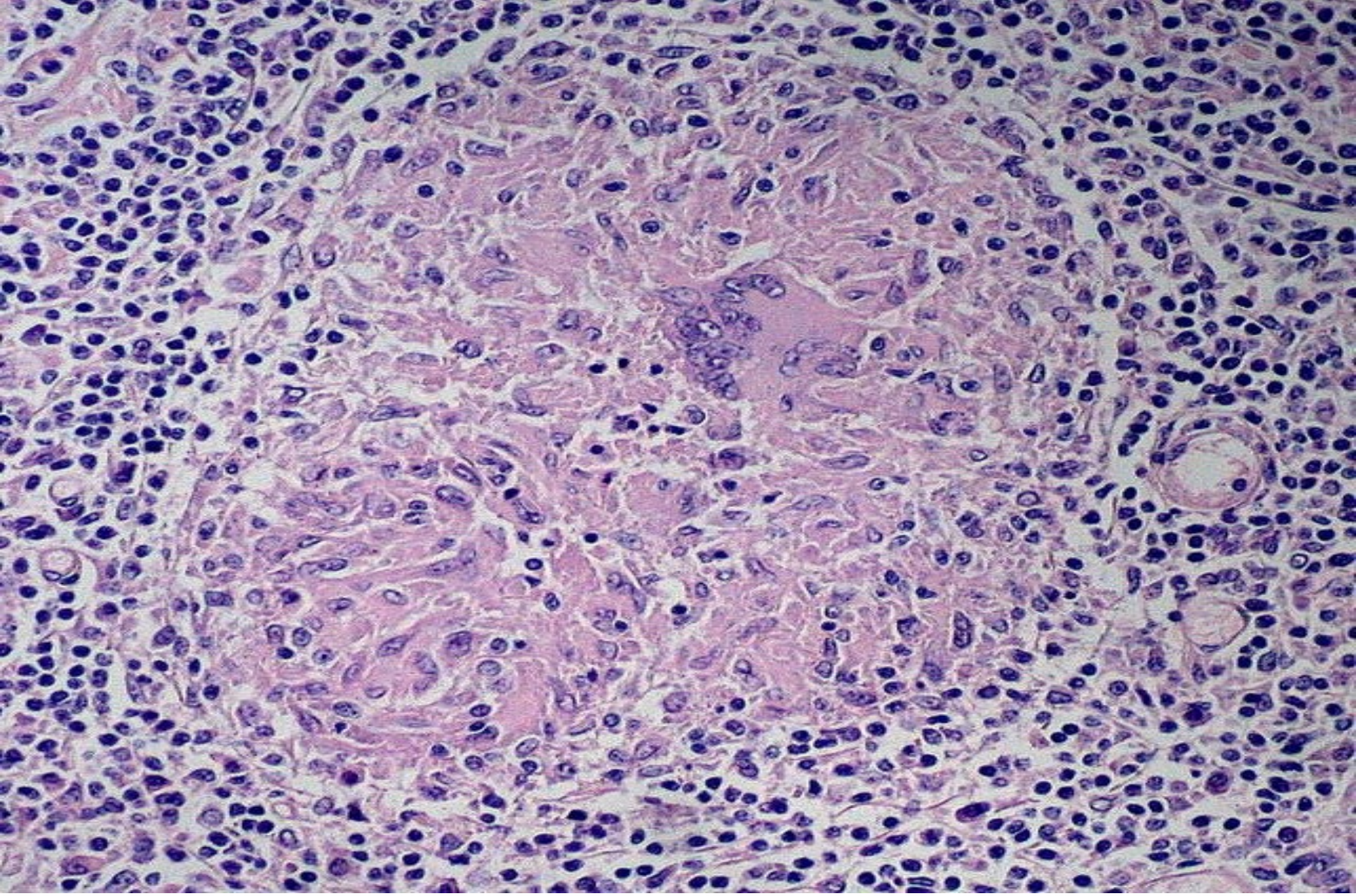
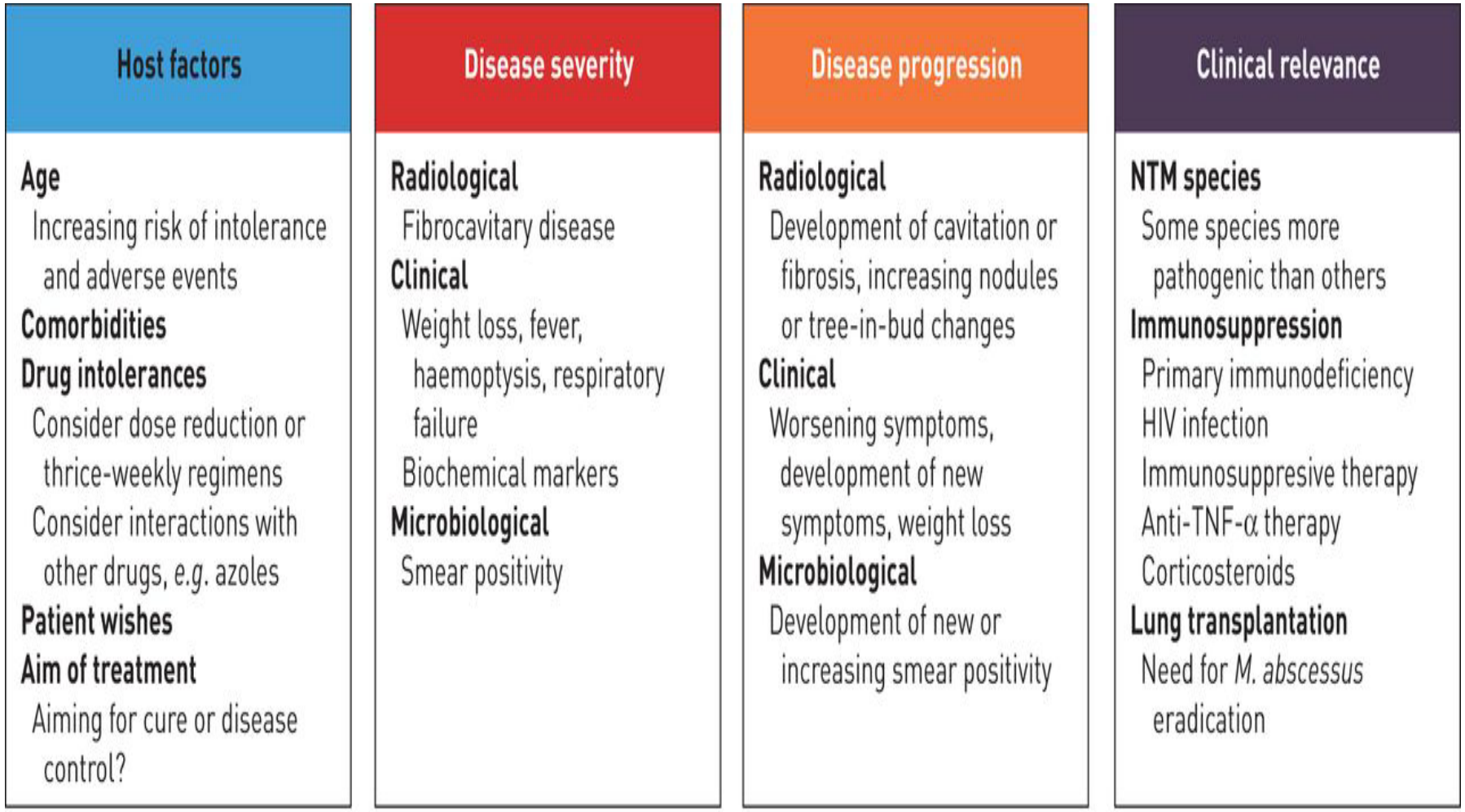


Table 1 Predisposing risk factors for non-tuberculous mycobacterial pulmonary disease [23, 35, 41–44]

Study description	Relative risk, odds ratio or relative prevalence
Bronchiectasis	44.0–187.5
History of TB	178.3
Low bodyweight	9.1[a]
Thoracic skeletal abnormalities	5.4
Lung cancer (neoplasms of larynx, trachea, and bronchus)	3.4
Immunomodulatory drugs/anti-TNF agents	1.3 (undefined) 2.2 (anti-TNF agents)
Chronic obstructive pulmonary disease	2.0–10.0
Steroid use	1.6–8.0
Rheumatoid arthritis	1.5–1.9[b]
Gastroesophageal reflux disease	1.5[a]–5.3[b]

a. Estimated from published data. b. Hazard ratio, fully adjusted for age, sex, income, rurality, and comorbidities for non-tuberculous mycobacteria (HIV, chronic obstructive pulmonary disease and gastroesophageal reflux disease). TB, tuberculosis; TNF, tumour necrosis factor. Adapted from [23]

Factors to consider when deciding on the initiation of treatment for pulmonary nontuberculous mycobacterial (NTM) disease.



Steven Cowman et al. Eur Respir J 2019;54:1900250

If you do not treat

Patients with NTM-PD who are not treated should be followed

Pay attention to comorbid respiratory conditions, especially bronchiectasis

Follow symptoms, micro, (lung function), imaging
- Development of cavities a reason to treat
- Progressive bronchiectasis a reason to treat

Often, when treatment is necessary, the patient knows it

When to Start? Guidelines

Favors observation:

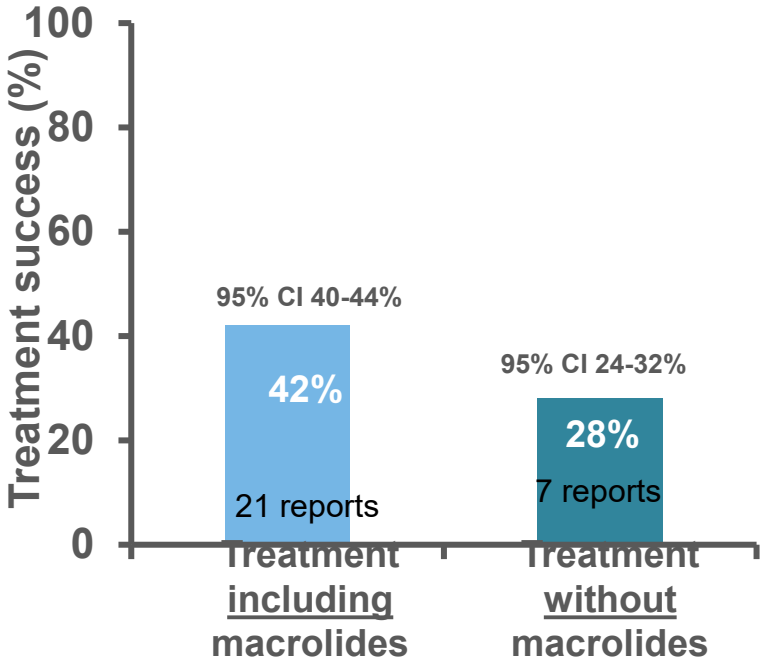
- Mild signs and symptoms.
- Higher potential for medication toxicity/intolerance.
- Organisms less responsive to treatment (e.g., M. abscessus).

Favors treatment:

- Poor prognostic markers (cavitation, low BMI/alb, and elevated inflammatory markers)
- More virulent and/or more treatment responsive species (M. kansasii)
- Immune suppression
- Major symptoms (severe fatigue and marked decrease in quality of life)

Failure of therapy in MAC*-LD – an unmet need

Random-effects meta-analysis of treatment success using different regimens (pooled success estimate) of 21 studies

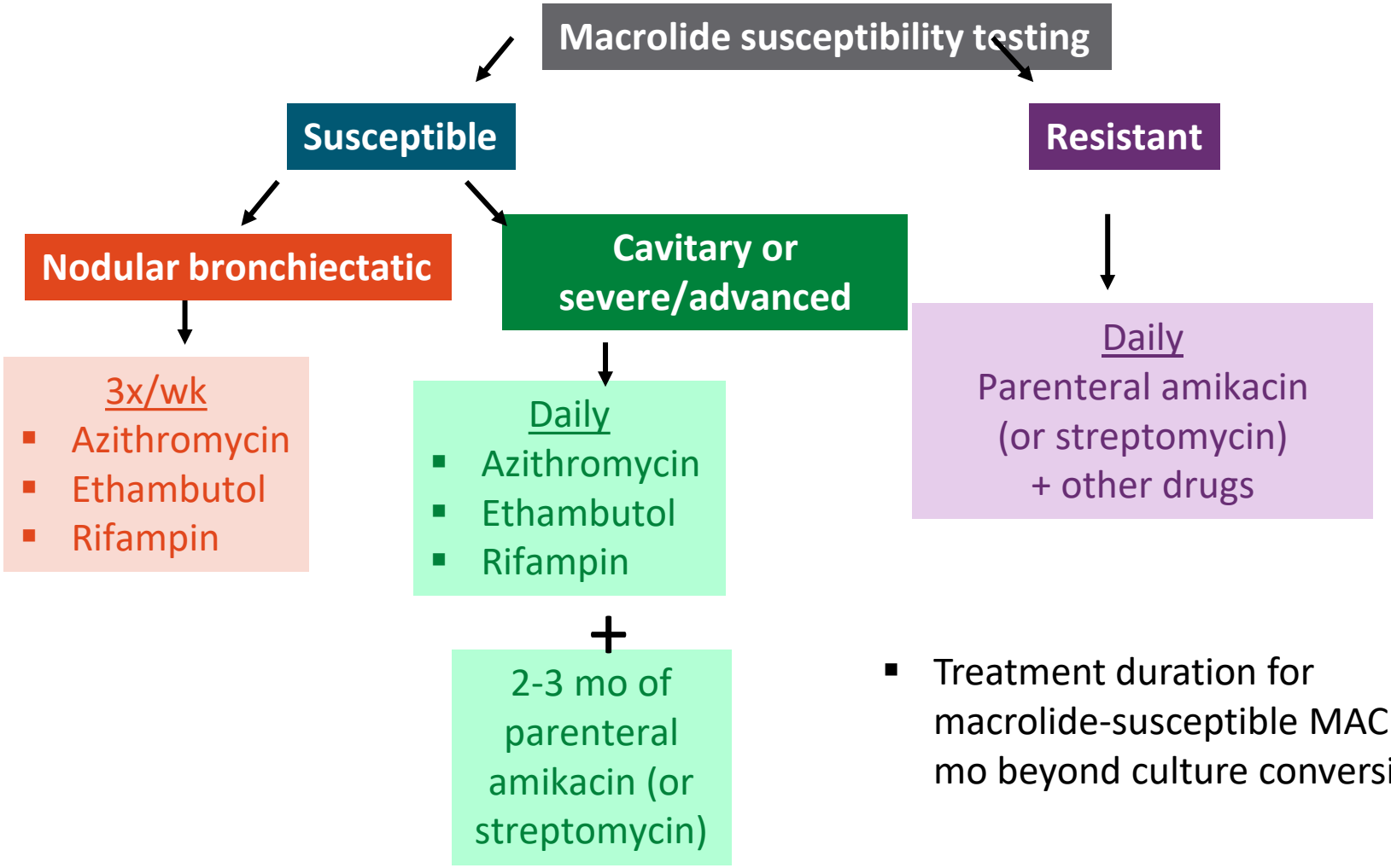


The estimated pooled treatment success rate# for patients with MAC-LD was 39% [95% CI 38–41%]

Although macrolides improve treatment success, many patients with MAC-LD still experience treatment failure

*Most common NTM species. #From all 28 studies included in the meta-analysis.
CI, confidence interval; MAC-LD, *Mycobacterium avium* complex lung disease.
Xu HB, et al. Eur J Clin Microbiol Infect Dis. 2014; 33:347-58.

2020 NTM Guideline: First-line MAC Treatment



- Treatment duration for macrolide-susceptible MAC ≥12 mo beyond culture conversion

Daley. Clin Infect Dis. 2020;71:905.

Refractory MAC*-LD: Antibiotic therapy

Pulmonary MAC with positive sputum cultures after ≥ 6 months of guideline-based therapy

Few choices for effective treatment[1]
(refer to specialized center!)

Potential strategies include:

- **Switching drugs in class[1]**
  - **Azithromycin → clarithromycin**
  - **Rifampin → rifabutin**
- **Switching from intermittent to daily therapy[1]**
- **Parenteral aminoglycoside therapy[2]**
- **Adjunctive surgery[1]**

*Most common NTM species. MAC-LD, *Mycobacterium avium* complex lung disease.

1. Griffith DE, Aksamit TR. Curr Opin Infect Dis. 2012; 25:218-27; 2. Griffith ED, et al. Am J Respir Crit Care Med 2007; 175:367-416; 3. Jo KW, et al. J Infect Chemother. 2014; 20:602-6; 4. Koh WJ, et al. Antimicrob Agents Chemother. 2013;5 7:2281-5.

Summary for Clinicians: 2020 Clinical Practice Guideline Summary for the Treatment of Nontuberculous Mycobacterial Pulmonary Disease

		Fibronodular disease	Extensive/ cavitary disease	Refractory disease
MAC-PD	Azithromycin† Ethambutol Rifampicin‡	**3/weekly** 500 mg 25 mg/kg 600 mg	**Daily** 250 mg 15 mg/kg 450-600 mg‡	**Daily** 250 mg 15 mg/kg 450-600 mg‡
	Amikacin (Streptomycin) iv◊		**3/weekly** 15-25 mk/kg◊	
	Amikacin liposome inhalation suspension Inhaled Amikacin			**Daily** 590 mg 250-500 mg
				Rifampicin resistance
M. kansasii-PD	Azithromycin Ethambutol Rifampicin‡ Isoniazid# Moxifloxacin	**3/weekly or daily** 500 / 250 mg 25 / 15 mg/kg 450-600 mg‡ 300 mg daily#	**Daily** 250 mg 15 mg/kg 450-600 mg‡ 300 mg daily#	**Daily** 250 mg 15 mg/kg 400 mg
M. xenopi-PD	Azithromycin and/or Moxifloxacin, Ethambutol Rifampicin‡	**Daily** 250 mg 400 mg 15 mg/kg 450-600 mg‡	**Daily** 250 mg 400 mg 15 mg/kg 450-600 mg‡	
	Amikacin iv◊		**3/weekly** 15-25 mk/kg◊	

Figure 1. Recommended approach to treatment of slow-growing nontuberculosis mycobacterial PD. Adapted from Reference 1. †For MAC-PD, clarithromycin 500 mg twice daily may be substituted for azithromycin; alternative drugs include clofazimine, moxifloxacin, and linezolid. ‡Rifampicin dosing 10 mg/kg (450 or 600 mg) for daily regimen, 600 mg for 3/weekly regimen. ◊Drug level monitoring: Trough < 5 mg/L, peak 65–80 μg/ml with intermittent dosing. #*M. kansasii*: daily INH, Ethambutol, Rifampicin as alternative for macrolide-based regimen. INH = isoniazid; iv = intravenously; *M.* = *Mycobacterium*; MAC-PD = *M. avium* complex PD; PD = pulmonary disease.

Summary for Clinicians: 2020 Clinical Practice Guideline Summary for the Treatment of Nontuberculous Mycobacterial Pulmonary Disease

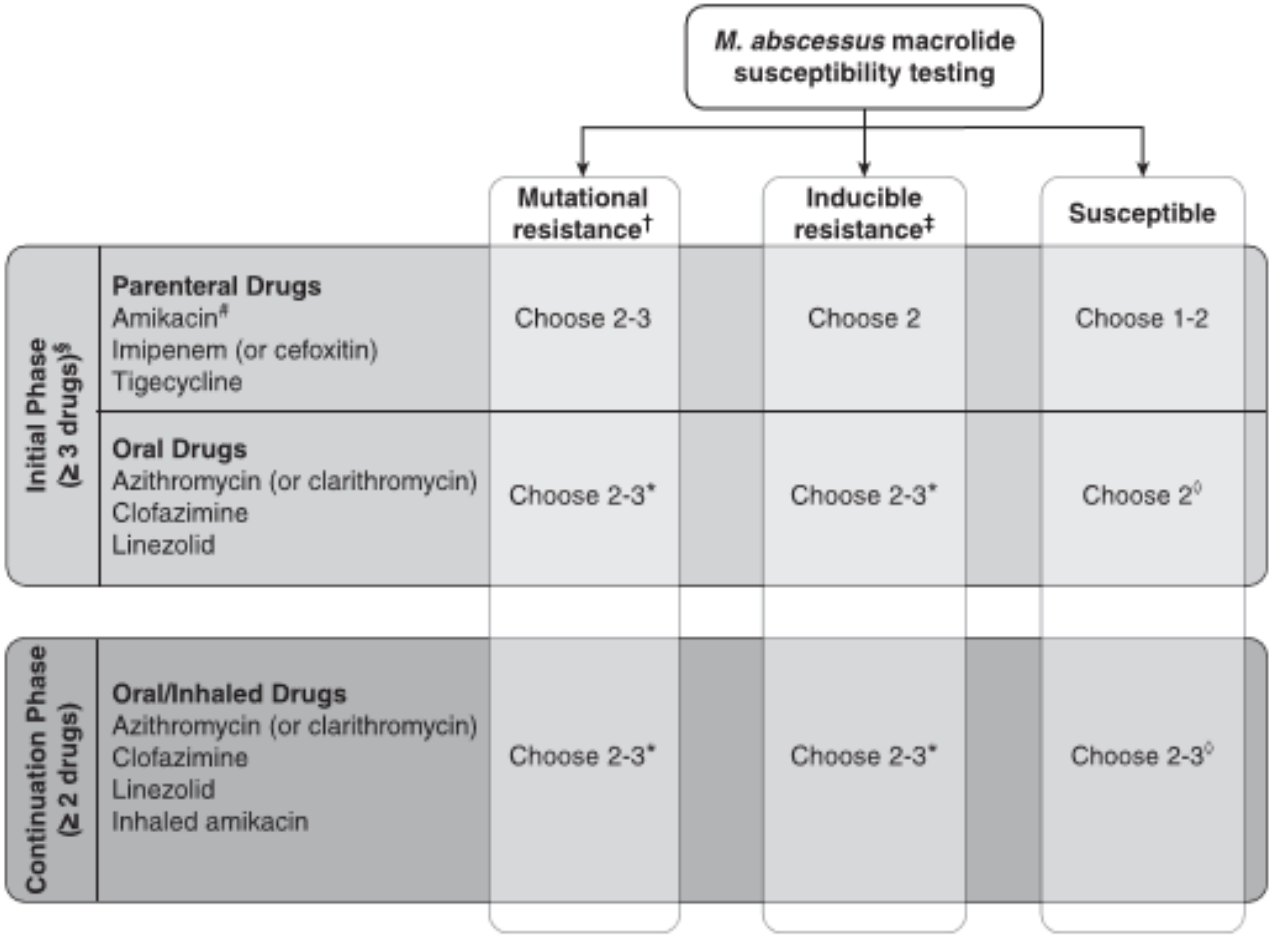


Figure 2. Recommended approach to treatment of *M. abscessus*, according to macrolide susceptibility. Adapted from Reference 1. †Mutational resistance = phenotypic resistance identified at 3-5 days of incubation or *rrl* mutation on sequencing. ‡Inducible resistance = phenotypic resistance identified after 14 days of incubation or functional *erm*(41) on sequencing. §When macrolide resistance is documented, ≥ 4 drugs when possible. #Aminoglycosides may be administered thrice weekly but intermittent dosing is not recommended for other drugs. *Azithromycin and clarithromycin are not counted as active drugs in the setting of mutational or inducible resistance but may be used for their immunomodulatory effects. ◊Azithromycin or clarithromycin should be used whenever possible in the setting of macrolide susceptibility. *erm*(41) = erythromycin ribosomal methylase causing macrolide resistance of *M. abscessus*; *M.* = *Mycobacterium*; *rrl* = 23S ribosomal ribonucleic acid.

Table X. Durations of treatment for different non-tuberculous mycobacteria (NTM) diseases

Site of NTM infection	Treatment duration/adjunct therapies
Pulmonary	Twelve months after sputum culture becomes negative.
Disseminated disease*	Twelve months after blood culture becomes negative. Secondary prophylaxis is required after this till CD4 count is >100 cells/μl for three months.
Lymphadenitis†	Surgery alone may be curative in children with NTM cervical lymphadenitis (*i.e.*, MAC). Combination drug therapy is recommended when surgical debridement is not complete or in the setting of disseminated disease in an immunocompromised host. Duration of treatment is variable. In patients with single peripheral lymph node, surgical excision is the treatment of choice. In patients with disseminated disease, treatment duration is longer.
Skin and soft tissue	Four to six months of combination therapy and adjunctive surgery may be done.
Vertebral disease	Twelve months of drug treatment preferred and adjunctive surgery may be done.
Other bone disease	Six to nine months of drug therapy and adjunctive surgery may be done.
Catheter-associated bloodstream infection	Remove iv catheter, if possible. Treatment should be given 1-3 months depending on the immune status of the individual and NTM species.

*Disseminated disease: Involvement of two or more organs through hematogenous spread. Lung involvement may or may not be present and pulmonary involvement occurs in 2.5-8% of patients with disseminated MAC disease in advanced HIV/AIDS. †In high TB burden countries, *Mtb* is the commonest cause of lymphadenitis. iv, intravenous. *Source*: Reproduced with permission from Ref. 144

Table X. Durations of treatment for different non-tuberculous mycobacteria (NTM) diseases

Site of NTM infection	Treatment duration/adjunct therapies
Pulmonary	Twelve months after sputum culture becomes negative.
Disseminate	months after blood culture bec ry prophylaxis is required afte ce months.
Lymphadeni	alone may be curative in child (MAC). ation drug therapy is recomme plete or in ng of disseminated disease in a reatment is variable. In patients with single periph atment of choice. In patients with disseminated disease, treatment duration is longer.
Skin and soft tissue	Four to six months of combination therapy and adjunctive surgery may be done.
	Twelve months of drug treatment preferred and a
	Six to nine months of drug therapy and adjunctiv
	Rem ul mm ic

[a]Disseminated disease: Involvement of two or . Lung involvement may or may not be present and pulmonary involvement occurs in 2.5-8% e in advanced HIV/AIDS. [b]In high TB burden countries, *Mtb* is the commonest cause of lym uced with permission from Ref. 144

MALATTIA POLMONARE
12 MESI DOPO LA CONVERSIONE

FORMA DISSEMINATA
TIPICA DEL PAZIENTE AIDS
12 MESI DOPO LA EMOMIELOCOLTURA NEGATIVA

MALATTIA CUTANEA
4-6 MESI DI TERAPIA DI COMBINAZIONE

FORMA LINFONODALE
TRATTAMENTO COMBINATO MEDICO E CHIRURGICO

FORMA OSTEOVERTEBRALE
12-18 MESI DI TERAPIA

CONVERSIONE MICOBATTERIOLOGICA

- TRE ESCREATI CONSECUTIVI NEGATIVI PER UN MINIMO DI TRE MESI
- NEI PAZIENTI INCAPACI DI ESPETTORARE NEGATIVITA' AL BAL

RICORRENZA

- DUE ESCREATI POSITIVI PER MYCOBATTERIDOPO LA CONVERSIONE MICOBATTERIOLOGICA
- LA GENOTIPIZZAZIONE PUO' CONSENTIRE DI DISTINGUERE LA RECIDIVA DALLA REINFEZIONE

INFEZIONE REFRATTARIA O RESISTENTE

- PERSISTENZA DI ISOLAMENTO DI NTM DOPO SEI MESI DI TRATTAMENTO

Summary for Clinicians: 2020 Clinical Practice Guideline Summary for the Treatment of Nontuberculous Mycobacterial Pulmonary Disease

Sebastian G. Kurz[1], B. Shoshana Zha[2], Derrick D. Herman[3], Michael R. Holt[4], Charles L. Daley[5], Joseph K. Ruminjo[6], and Carey C. Thomson[7,8]

Indications for surgery are failure of medical therapy, drug-resistant infections, cavitary disease, and complications such as hemoptysis and severe bronchiectasis.

surgery (1). Surgical complications occurred in 7–35% of cases. Operative mortality was 0%, and postoperative mortality was 0–9% (1). Medical therapy before and after surgery was standard, and many experts consider smear conversion be the goal of preoperative treatment. The panel suggests that surgeons be experienced in the surgical management of mycobacterial lung disease.

BC Centre for Disease Control
Provincial Health Services Authority

TB Services
655 West 12th Avenue
Vancouver, BC V5Z 4R4

100-237 E Columbia St.
New Westminster, BC
V3L 3W4

- LA DECISIONE DI CONCLUDERE IL TRATTAMENTO PASSA ATTRAVERSO LA RISOLUZIONE DEI SINTOMI, IL MIGLIORAMENTO STABILE DELLA RADIOGRAFIA E LA CONVERSIONE DELLA COLTURA DOPO UN MINIMO DI 12 MESI.
- PER MAC E ABSCESSUS TRATTARE PER 12 MESI DOPO LA CONVERSIONE
- I PAZIENTI CON MAC E BRONCHIECTASIE HANNO IL 48% DI PROBABILITA' DI AVERE RICORRENZE DOPO IL TRATTAMENTO ED E' BENE INFORMARE IL PAZIENTE

Real-life evaluation of clinical outcomes in patients undergoing treatment for non-tuberculous mycobacteria lung disease: A ten-year cohort study

Stefano Aliberti [a,b,1], Giovanni Sotgiu [c,1], Paola Castellotti [d], Maurizio Ferrarese [d], Lisa Pancini [d], Ana Pasat [a], Nicolò Vanoni [a,b], Maura Spotti [b], Ester Mazzola [e], Andrea Gramegna [a,b], Laura Saderi [c], Carlo Federico Perno [e,f], Jakko van Ingen [g], Luigi Ruffo Co[illegible], Francesco Blasi [a,b,2]

Respiratory Medicine 164 (2020)

170 PAZIENTI ARRUOLATI A MILANO NEGLI ANNI 2007-2017

MAC (71.2%), M. kansasii (9.4%) e M. xenopi (7.1%).

FOLLOW-UP MEDIANO DI 31 MESI AEs 37,6% DEI PAZIENTI.

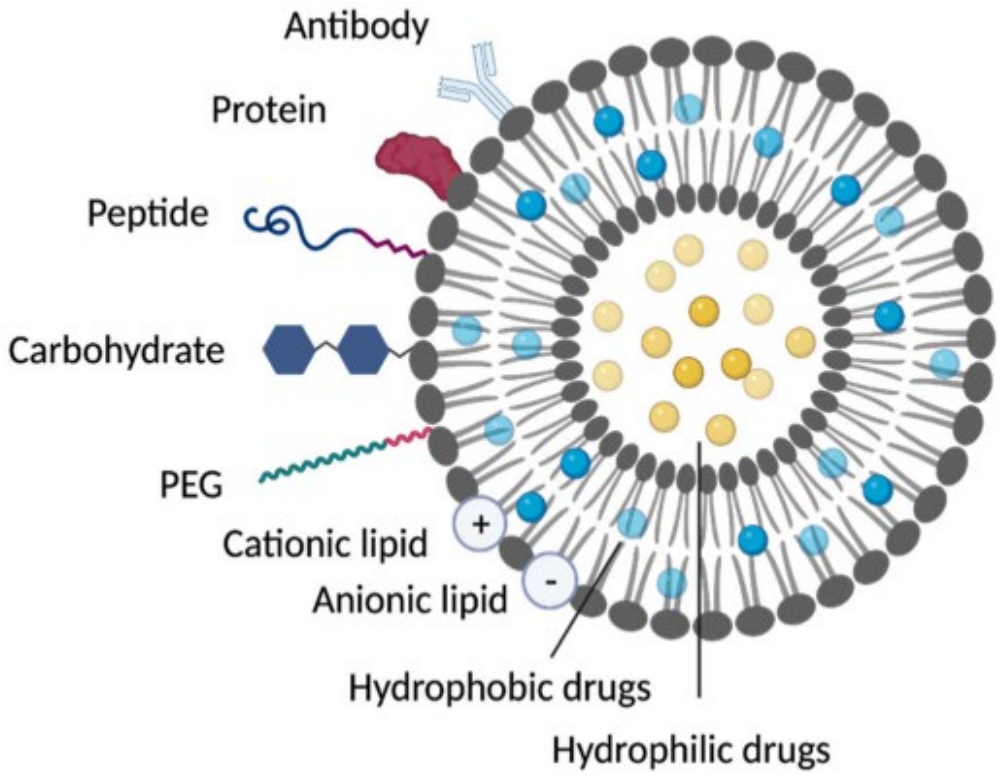
FALLIMENTO DELLA TERAPIA NEL 35,3% DEI PAZIENTI

- RITIRATI PER INTOLLERANZA 13,5%
- RECIDIVE 11,2%
- REINFEZIONI 5,3%
- FALLIMENTO TERAPEUTICO 4,1%

LA MAGGIOR PARTE DEI PAZIENTI RITIRATI ERANO GLI AFFETTI DA INFEZIONI NON MAC (NTM-LD vs MAC-LD 22,4% vs 9,9% p O,O30)

Liposomes as Antibiotic Delivery Systems: A Promising Nanotechnological Strategy against Antimicrobial Resistance

Magda Ferreira [1,2,†], Maria Ogren [1,†], Joana N. R. Dias [1], Marta Silva [1], Solange Gil [1], Luís Tavares [1], Frederico Aires-da-Silva [1], Maria Manuela Gaspar [2,*] and Sandra Isabel Aguiar [1,*]



Advantages
Protection from metabolic breakdown
Controlled and sustained release
Prolonged plasma circulation
Target delivery
Reduced toxicity
Increased bactericidal efficacy

Molecules **2021**, *26*, 2047

CONVERT Study

Randomized, Placebo-controlled Phase 3 Study

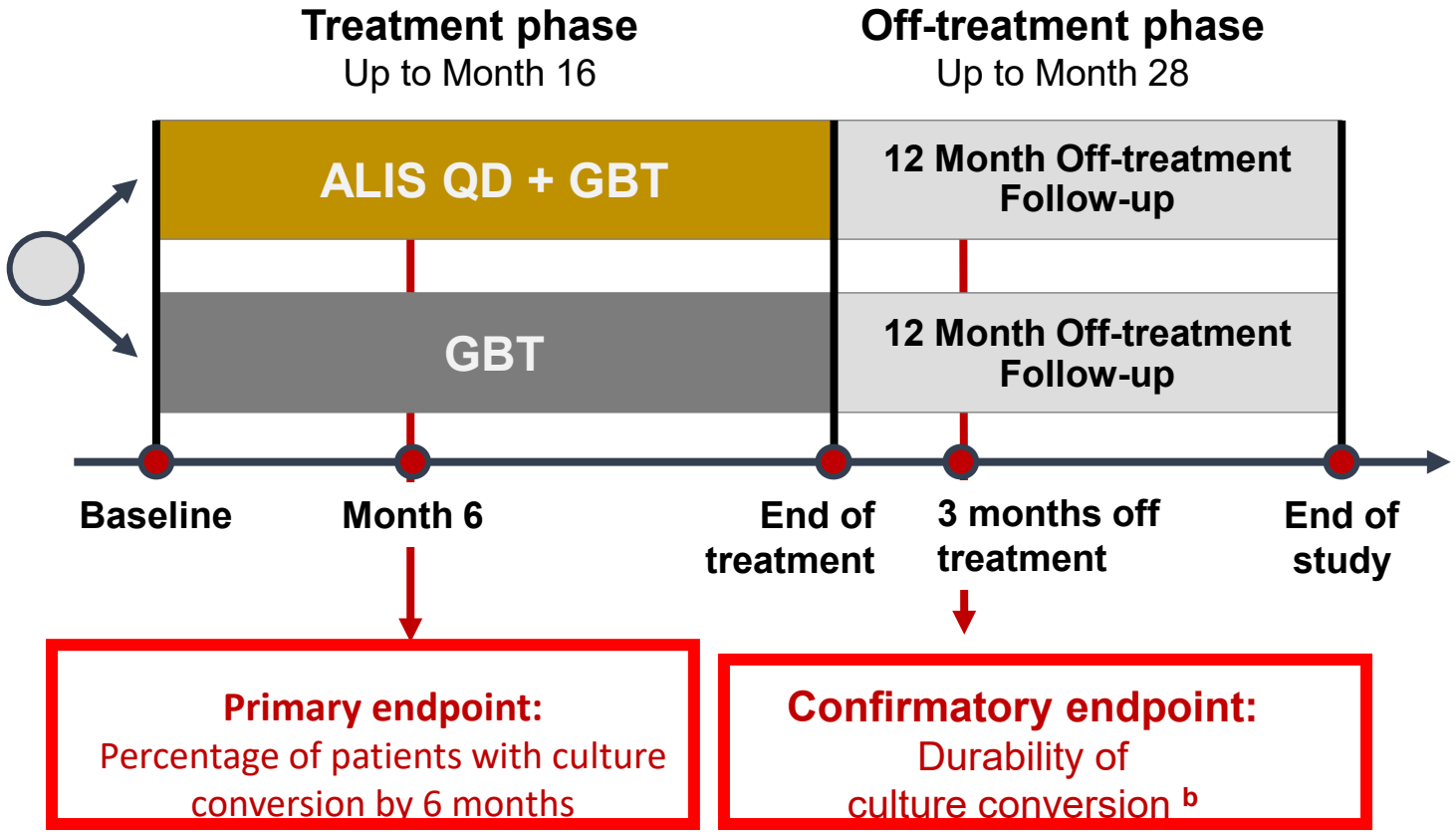
Am J Respir Crit Care Med Vol 198, Iss 12, pp 1559–1569, Dec 15, 2018

Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT)
A Prospective, Open-Label, Randomized Study

David E. Griffith[1], Gina Eagle[2], Rachel Thomson[3], Timothy R. Aksamit[4], Naoki Hasegawa[5], Kozo Morimoto[6], Doreen J. Addrizzo-Harris[7], Anne E. O'Donnell[8], Theodore K. Marras[9], Patrick A. Flume[10], Michael R. Loebinger[11], Lucy Morgan[12], Luigi R. Codecasa[13], Adam T. Hill[14], Stephen J. Ruoss[15], Jae-Joon Yim[16], Felix C. Ringshausen[17], Stephen K. Field[18], Julie V. Philley[1], Richard J. Wallace, Jr.[1], Jakko van Ingen[19], Chris Coulter[20], James Nezamis[2], and Kevin L. Winthrop[21]; for the CONVERT Study Group*

Screening and 2:1 randomization

Population:
Adults with treatment-refractory[a] MAC lung disease



[a] At least 6 months treatment with persistently positive sputum cultures for MAC.

[b] Final analysis at completion of study is durability of culture conversion 3 months off all MAC treatment for patients who complete 12 months of treatment from the first negative culture that defined conversion.

ALIS, amikacin liposome inhalation suspension; GBT, guideline-based therapy; MAC, *Mycobacterium avium* complex.

- Patients who achieved culture conversion by Month 6 and remained culture-negative at Month 6 continued in the trial to complete a total of 12 months of treatment from the first negative culture that defined conversion (up to 16 mo in total).
- After completion of the treatment phase, patients remain in the study for an additional 12 months for follow-up. Patients who did not achieve conversion by Month 6 exited the study at Month 8, and eligible patients were permitted to enroll in an extension study.

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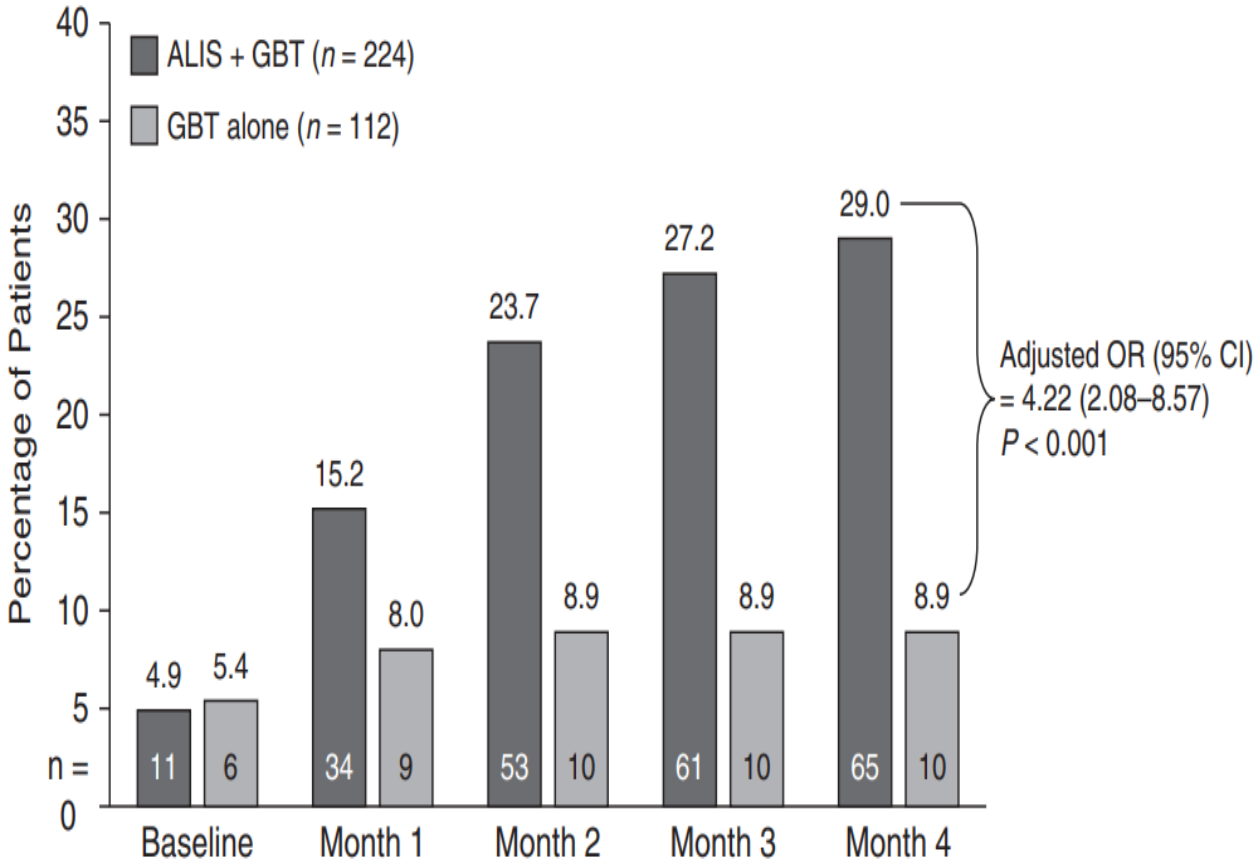
Proportion of patients achieving culture conversion, shown by the first month of conversion: intention-to-treat population.



Am J Respir Crit Care Med Vol 198, Iss 12, pp 1559–1569, Dec 15, 2018

CONVERT Study

Primary Endpoint: Culture Conversion y Month 6[a]

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ITT Population	ALIS + GBT N = 224	GBT Alone N = 112
Converter	65 (29.0%)	10 (8.9%)
Non-Converter	159 (71.0%)	102 (91.1%)
Adjusted Odds Ratio (95% CI)[b]	4.220 (2.078, 8.570)	
P Value	< 0.0001	

[a] Culture conversion defined as 3 consecutive monthly MAC-negative sputum cultures by Month 6

[b] Adjusted Odds ratio and p-value are calculated using Cochran-Mantel-Haenszel test, with stratification factors
of the combination of smoking status and prior GBT as fixed factors..

Sustainability and Durability of Culture Conversion with ALIS

Converter analysis

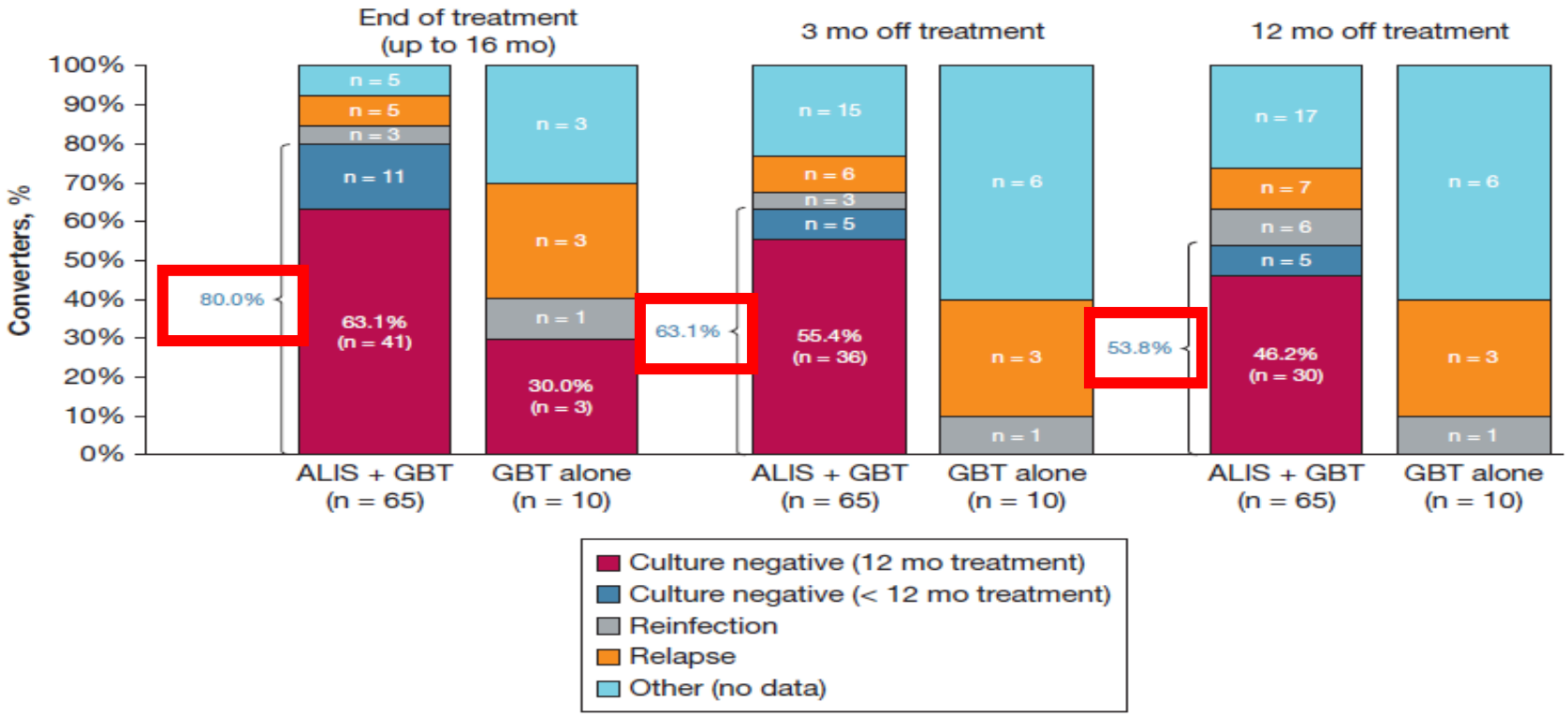


Figure 3 – *Bar graph showing culture status among those who achieved conversion over time. The percentage of patients who met culture conversion criteria by month 6, completed 12 months of postconversion treatment, and showed sustained and durable conversion is shown in red. Eleven patients in the ALIS plus GBT arm completed < 12 months of postconversion treatment and showed negative culture results at the last visit (dark blue). Recurrent samples showing positive results for MAC were genotyped and shown as reinfection (gray) or relapse (orange). Patients in the "other" (light blue) category did not have available sputum culture results (eg, missed visits, missing sputum data, or study discontinuation). All on-treatment relapses occurred in the first 8 months of treatment, and all on-treatment reinfections occurred in the second 8 months of treatment. ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy; MAC = Mycobacterium avium complex.*

Griffith D.; Thomson R.; Flume P. et al. CHEST 2021; 160(3):831-842

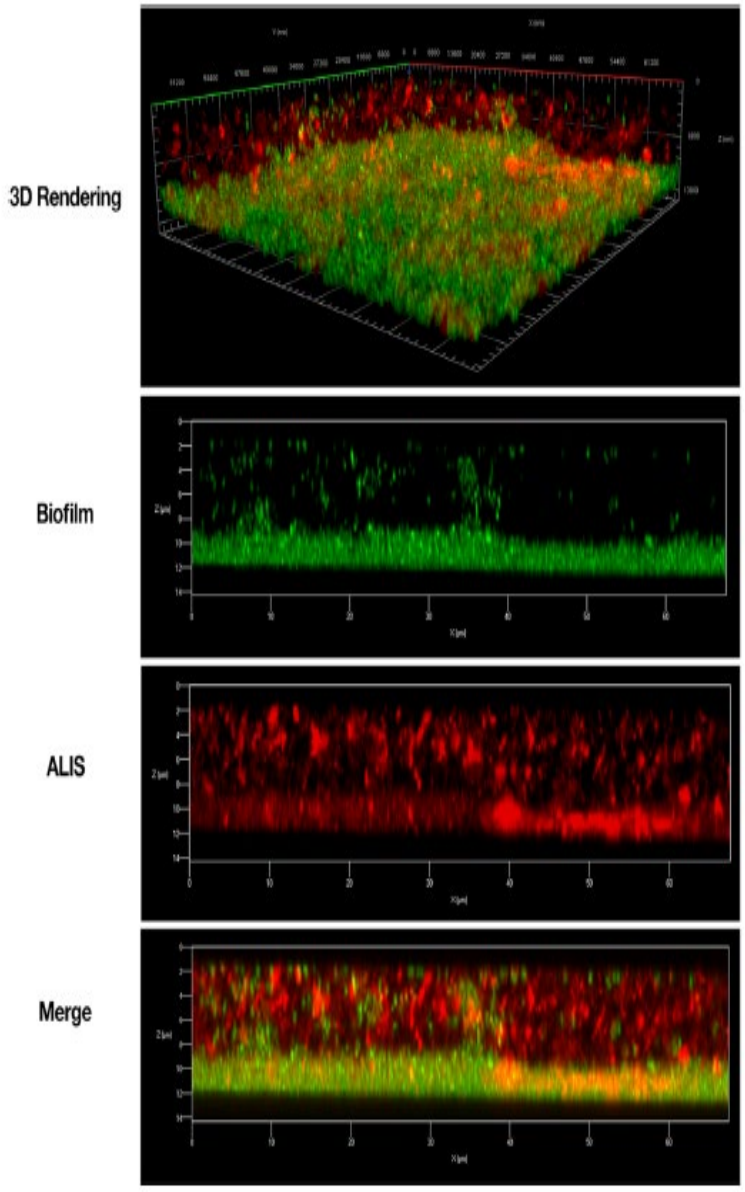
frontiers in Microbiology

ORIGINAL RESEARCH
published: 16 May 2018
doi: 10.3389/fmicb.2018.00915

Amikacin Liposome Inhalation Suspension (ALIS) Penetrates Non-tuberculous Mycobacterial Biofilms and Enhances Amikacin Uptake Into Macrophages

Jimin Zhang[1†], Franziska Leifer[1†], Sasha Rose[1,2], Dung Yu Chun[1], Jill Thaisz[1], Tracey Herr[1], Mary Nashed[1], Jayanthi Joseph[2], Walter R. Perkins[1] and Keith DiPetrillo[1]*

relative to inhaled free amikacin. Compared to intravenous free amikacin, a standard-of-care therapy for refractory and severe NTM lung disease, ALIS increased the mean area under the concentration-time curve in lung tissue, airways, and macrophages by 42-, 69-, and 274-fold. These data demonstrate that ALIS effectively penetrates NTM biofilms, enhances amikacin uptake into macrophages, both *in vitro* and *in vivo*, and retains amikacin within airways and lung tissue. An ongoing Phase III trial, adding ALIS to guideline based therapy, met its primary endpoint of culture conversion by month 6. ALIS represents a promising new treatment approach for patients with refractory NTM lung disease.



Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline

Charles L. Daley,[1,2,a] Jonathan M. Iaccarino,[3] Christoph Lange,[4,5,6,7,a] Emmanuelle Cambau,[8,a] Richard J. Wallace, Jr,[9,a] Claire Andrejak,[10,11] Erik C. Böttger,[12] Jan Brozek,[13] David E. Griffith,[14] Lorenzo Guglielmetti,[8,15] Gwen A. Huitt,[1,2] Shandra L. Knight,[16] Philip Leitman,[17] Theodore K. Marras,[18] Kenneth N. Olivier,[19] Miguel Santin,[20] Jason E. Stout,[21] Enrico Tortoli,[22] Jakko van Ingen,[23] Dirk Wagner,[24] and Kevin L. Winthrop[25]

VI: In patients with macrolide-susceptible MAC pulmonary disease, should a regimen with inhaled amikacin or a regimen without inhaled amikacin be used for treatment?

Recommendations

1. In patients with newly diagnosed MAC pulmonary disease, we suggest neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension (ALIS) be used as part of the initial treatment regimen (conditional recommendation, very low certainty in estimates of effect).
2. In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, we recommend addition of ALIS to the treatment regimen rather than a standard oral regimen, only (strong recommendation, moderate certainty in estimates of effect).

Amikacina per via inalatoria si o no ?

Remarks: Randomized controlled trials have demonstrated the efficacy and safety of ALIS when added to guideline-based therapy for treatment refractory MAC pulmonary disease [19, 20]. ALIS is currently approved by the United States Federal Drug Administration for treatment of refractory MAC pulmonary disease. As noted in question 5, we suggest that parenteral amikacin or streptomycin be included in the initial treatment regimen in patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease.

NEW
Opzioni terapeutiche limitate

2020 NTM Guideline: Refractory MAC Recommendations

Treatment Refractory:

- Pulmonary MAC with **positive sputum cultures** after **≥6 mo** of guideline-based therapy[1]

Recommendation:

- **Amikacin liposome inhalation suspension** should be **added** to a standard oral regimen in patients with refractory MAC[2]

1. Daley. J Infect Dis. 2020;222(suppl 4):S199. 2. Daley. Clin Infect Dis. 2020;71:905.

Activity of Oritavancin and Its Synergy with Other Antibiotics against *Mycobacterium abscessus* Infection In Vitro and In Vivo

Gaoyan Wang [1], Jia Tang [1], Jiajia Feng [1], Wenqi Dong [1], Xinyu Huo [1], Hao Lu [1], Chenchen Wang [1], Wenjia Lu [1], Xiangru Wang [1,2,3], Huanchun Chen [1,2,3] and Chen Tan [1,2,3,*]

- One important factor to consider is that oritavancin is administered intravenously [23].
- This will be a limitation of using oritavancin considering the long clinical therapeutics duration of M. abscessus infections.
- Intravenous administration is a main concern associated with oritavancin, making it difficult to treat chronic diseases.
- In conclusion, this study indicates that oritavancin exhibits activity against M. abscessus in vitro and in vivo, and it does not antagonize other most frequently used antibiotics for treating M. abscessus infections, suggesting the potential of oritavancin as a clinical drug for treating M. abscessus lung disease.

- Bactericidal effect, time and concentration-dependant killing
- Long half-life (393 hours)
- Synergy with clarithromycin, cefoxitin, moxifloxacin, tigecycline, meropenem

Int. J. Mol. Sci. **2021**, 22, 6346.

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Int. J. Mol. Sci. 2021, 22, 6346

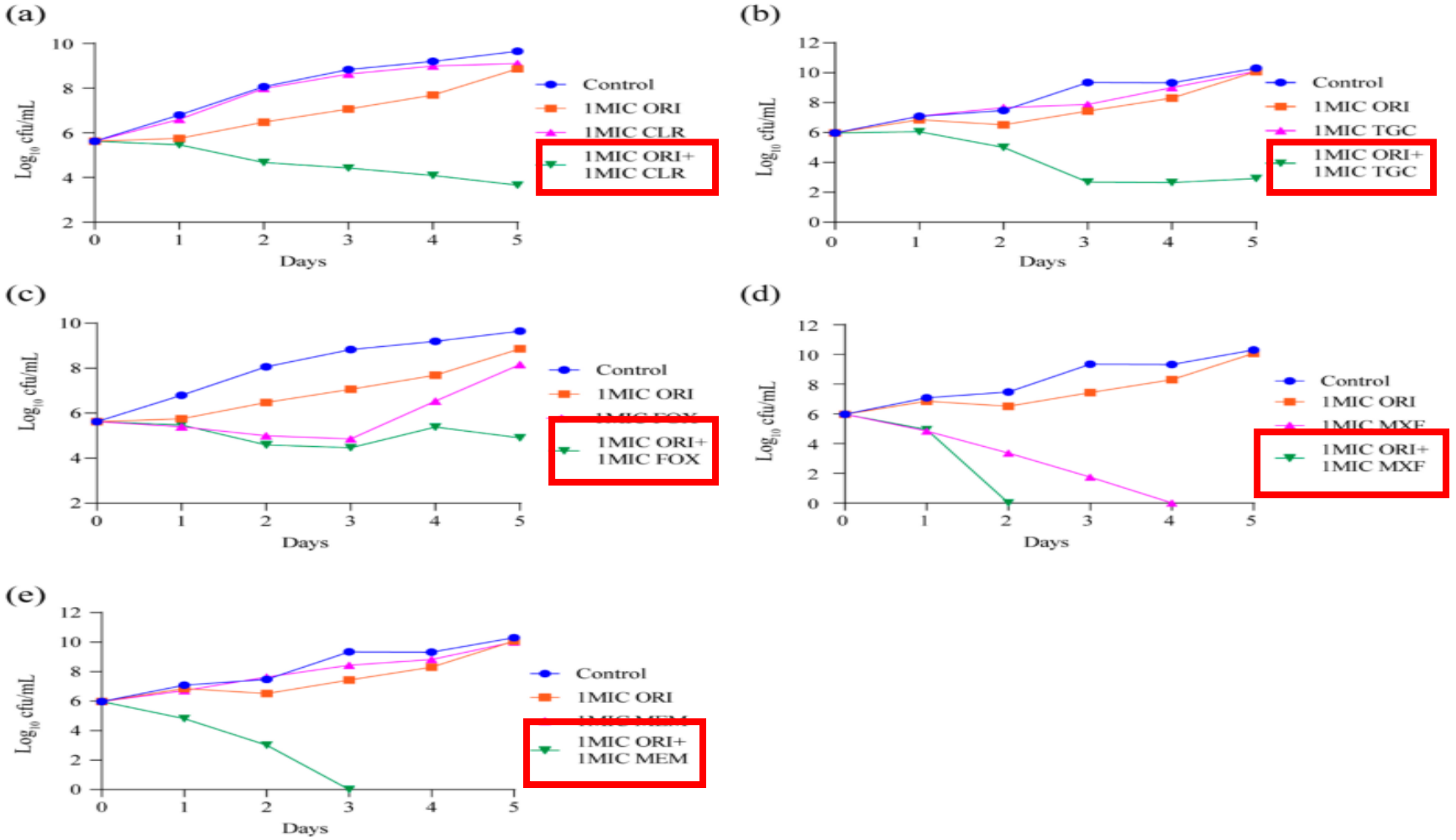


Figure 4. Oritavancin significantly potentiates (**a**) 1 × MIC clarithromycin, (**b**) 1 × MIC tigecycline, (**c**) 1 × MIC cefoxitin, (**d**) 1 × MIC moxifloxacin, and (**e**) 1 × MIC meropenem bactericidal effect against *M. abscessus* in vitro. Data are represented the mean ± standard deviation (SD) of triplicates for each concentration. The error bar is smaller than the symbol size and not showed. ORI, oritavancin; CLR, clarithromycin; TGC, tigecycline; FOX, cefoxitin; MXF, moxifloxacin; MEM, meropenem.

Antimycobacterial Strategies to Evade Antimicrobial Resistance in the Nontuberculous Mycobacteria

Beverley Cherie Millar[1,2,3], John Edmund Moore[1,2,3]

Table 4: Potential synergistic and combination effects with other antimicrobials

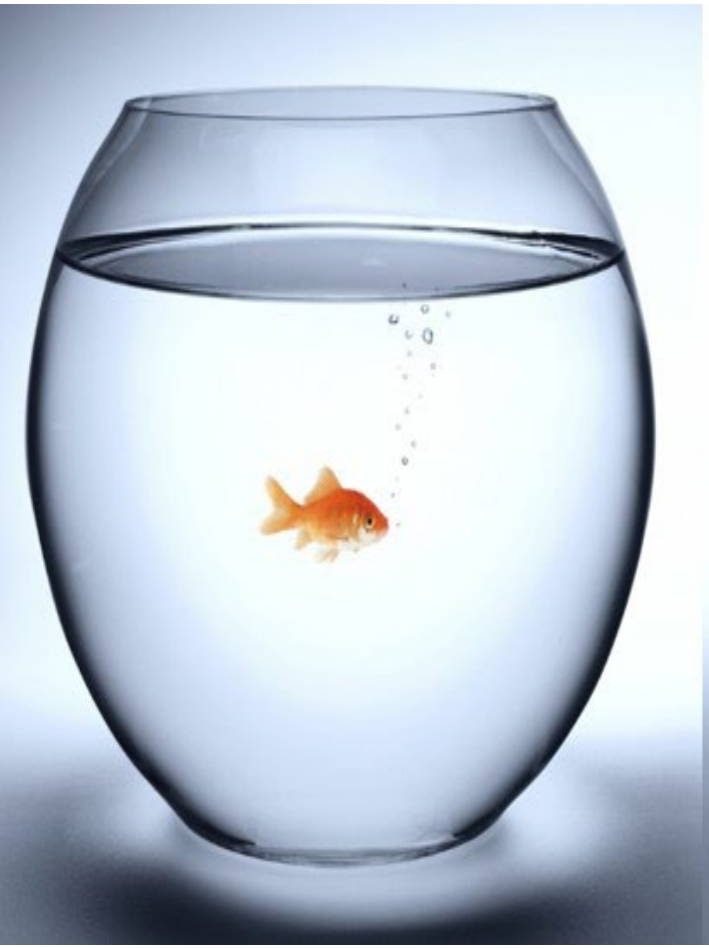
Combinations	Study findings	Species used
Synergistic antibiotic combinations capable of overcoming drug resistance *in vitro*[38]	*In vitro* activity of several antibiotics against a selection of drug-resistant NTM clinical isolates from CF patients and paired combinations of antibiotics against a subset of *M. abscessus* strains Clofazimine and clarithromycin exhibited 100% synergy for all combinations tested, as did AMK, with the exception of one isolate	*M. abscessus* *M. chelonae* MAC
Synergistic effect of LZD with AMK, MOX, CFX and TGC[39]	LZD and AMK most potent synergistic activity Frequent synergism in LZD-AMK and LZD-TGC LZD rarely exhibited *in vitro* synergy with MOX and CFX when tested against MABC LZD-CFX and LZD-MOX combinations antagonistic for half of the isolates	*M. abscessus* *M. massiliense*
Clarithromycin-vancomycin[40]	Strong synergy was found with a FICI score of ≤0.5 and a 4-to10-fold decrease in MIC	MABSC *(subspecies) abscessus, bolletii, massiliense*
Thioridazine/MOX -based combination regimen[41]	Rapid microbial kill could be achieved within 7 days	*M. avium-intracellulare complex*
Ceftazidime/avibactam, rifabutin, TZD and MOX[42]	Kill rates better than standard therapy	*M. avium* subspp. *hominissuis*
Ceftazidime/avibactam[43]	Ceftazidime in combination with the non-β-lactam β-lactamase inhibitor avibactam kills MAC Microbial kill was better than that of standard therapy drugs at currently recommended doses	MAC

Antimycobacterial Strategies to Evade Antimicrobial Resistance in the Nontuberculous Mycobacteria

Beverley Cherie Millar[1,2,3], John Edmund Moore[1,2,3]

Combinations	Study findings	Species used
Avibactam and various carbapenems[44]	The addition of avibactam to various carbapenem antibiotics effectively reduced the MICs of carbapenem-resistant *M. abscessus* isolates to within therapeutically achievable levels *in vitro*	*M. abscessus*
Clarithromycin, rifampin, rifabutin, and ethambutol in combination with ATP[45]	*In vitro* anti-*Mycobacterium* complex activity of combination therapies was expressed in a strain-dependent manner *In vitro* regrowth of drug-treated bacteria was delayed by combined use of ATP	MAC
Synergistic effect of Clarithromycin with LZD, MOX , AMK, and tigecycline[46]	*In vitro*, synergistic activity was noted with clarithromycin and various other drugs	*M. abscessus* *M. massiliense*
Rifampicin with hydroperoxides[47]	Increased membrane permeability owing to the presence of the oxidant, led to higher uptake of the drug Additive effect was noted	*M. bovis* *M. smegmatis* *M. tuberculosis*
Interaction of South Asian spices with conventional antibiotics[48]	Synergetic antimicrobial activity noted *in vitro* between spice extracts and AMK and LZD	*M. abscessus*
Teicoplanin - Tigecycline combination[37]	*In vitro* checkerboard titration assay Synergistic activity observed	*M. abscessus Bamboo* *M. abscessus* subspp. *abscessus, massiliense, bolletii*


One size
does NOT
fit all.



TAKE HOME MESSAGES for NTM TREATMENT

- **LA MALATTIA DA RAPPRESENTA UNA IMPEGNATIVA SFIDA**
- **LA DURATA PROLUNGATA DELLA TERAPIE E LA NECESSITA' DI COMBINAZIONI FARMACOLOGICHE PUO' ESSERE UN PROBLEMA AGGIUNTIVO PER MOLTI PAZIENTI.**
- **ULTERIORI TRIALS CLINICI SONO UGENTI CON UN FOCUS SU TERAPIA PIU' SMART, PIU' BREVI, PIU' EFFICACI E PIU' TOLLERATE**
- **NUOVI APPROCCI TERAPEUTICI BASATI SULL'USI DI VECCHI FARMACI DA ASSOCIARE A PIU' MODERNE FORMULAZIONI E NUOVE TECNOLOGIE POTREBBERO ESSERE DI AIUTO PER IL TRATTAMENTO DELLA PATOLOGIE DA NTM**
- **C'E' ANCORA MOLTA STRADA DA FARE**