NTM: Guidelines and new developments

SBIMC-BVIKM meeting

Brussels / Bruxelles / Brussel 2022

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Center for Infectious Diseases
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NTM/TB program at Radboudumc

- ‘Dekkerswald’ sanatorium

- Multidisciplinary team
  - Pulmonologists
  - Infectious Diseases
  - Pharmacists
  - Radiologists
  - Clinical microbiologists

- Trial site & research lab

The international guidelines

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]

- Evidence-based, GRADE methodology
- Includes a laboratory section

Daley CL, et al. *Eur Respir J* 2020 (ERS/ATS/ESCMID/IDSA guideline)

M. avium complex treatment

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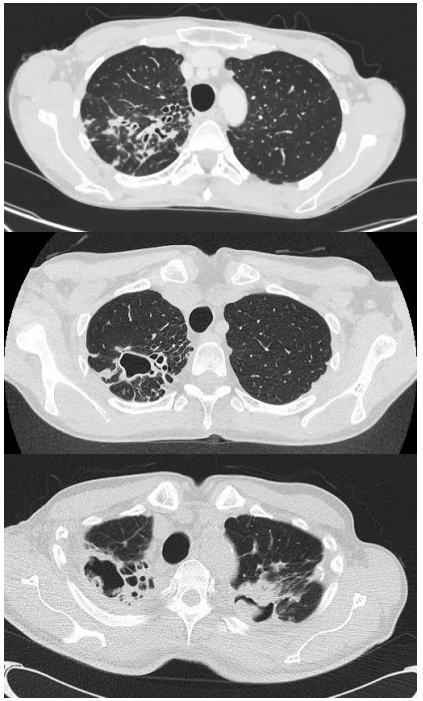
Organism	Number of drugs	Preferred drug regimen#	Dosing frequency
M. avium complex			
Nodular-bronchiectatic	3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol	3 times weekly
Cavitary	⩾3	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin IV (streptomycin)¶	Daily (3 times weekly may be used with aminoglycosides)
Refractory+	⩾4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)¶	Daily (3 times weekly may be used with aminoglycosides)

Daley CL, et al. *Eur Respir J* 2020 (ERS/ATS/ESCMID/IDSA guideline)

M. kansasii and *M. xenopi*

- *M. kansasii*
  - 12 INH-RIF-EMB
  - RIF-EMB-AZI (3x/wk?)

- *M. xenopi*
  - RIF-EMB-AZI
  - RIF-EMB-MOX
  - Severe: RIF-EMB-AZI + AMI (or +MOX?)



M. abscessus treatment

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

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ERS/ATS/IDSA/ESCMID:
Treat with **at least 3 active agents initially**
Options include: amikacin, imipenem, tigecycline, azithromycin, clofazimine, linezolid

Continue with at least 2 active agents (oral/inhal)

TABLE 5 Treatment regimens for *Mycobacterium abscessus* by macrolide susceptibility (mutational and inducible resistance)

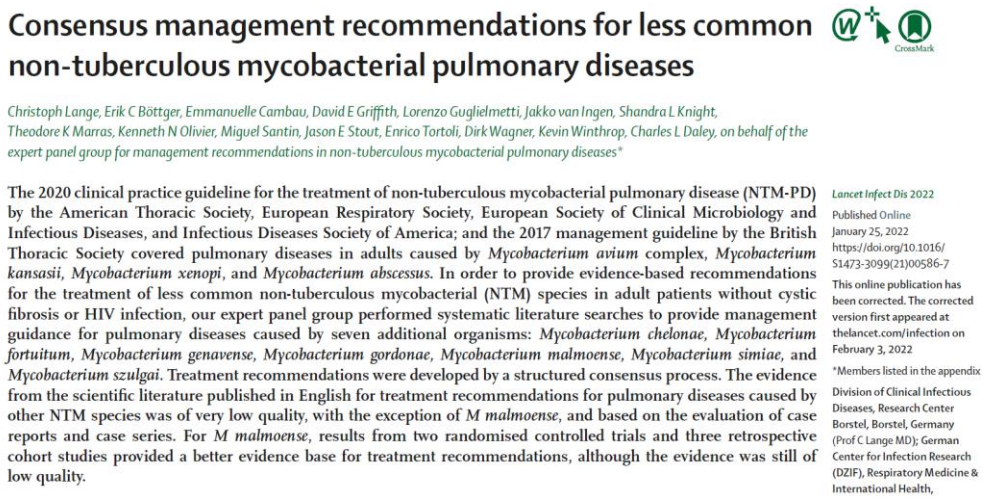
Macrolide susceptibility pattern		Number of drugs*	Preferred drugs	Frequency of dosing
Mutational#	Inducible¶			
Susceptible	Susceptible	Initial phase ⩾3	*Parenteral (choose 1–2)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2)* Azithromycin (clarithromycin)§ Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ⩾2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)§ Clofazimine Linezolid Inhaled amikacin	
Susceptible	Resistant	Initial phase ⩾4	*Parenteral (choose 2–3)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2–3)* Azithromycin (clarithromycin)f Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ⩾2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)f Clofazimine Linezolid Inhaled amikacin	
Resistant	Susceptible or resistant	Initial phase ⩾4	*Parenteral (choose 2–3)* Amikacin Imipenem (or Cefoxitin) Tigecycline *Oral (choose 2–3)* Azithromycin (clarithromycin)f Clofazimine Linezolid	Daily (3 times weekly may be used for aminoglycosides)
		Continuation phase ⩾2	*Oral/inhaled (choose 2–3)* Azithromycin (clarithromycin)f Clofazimine Linezolid Inhaled amikacin	

Daley CL, et al. *Eur Respir J* 2020 (ERS/ATS/ESCMID/IDSA guideline)

New: guidance for rare NTM species

- NTM-PD treatment

- *M. chelonae*
- *M. fortuitum*
- *M. genavense*
- *M. gordonae*
- *M. malmoense*
- *M. simiae*
- *M. szulgai*



Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases

*Christoph Lange, Erik C Böttger, Emmanuelle Cambau, David E Griffith, Lorenzo Guglielmetti, Jakko van Ingen, Shandra L Knight, Theodore K Marras, Kenneth N Olivier, Miguel Santin, Jason E Stout, Enrico Tortoli, Dirk Wagner, Kevin Winthrop, Charles L Daley, on behalf of the expert panel group for management recommendations in non-tuberculous mycobacterial pulmonary diseases**

The 2020 clinical practice guideline for the treatment of non-tuberculous mycobacterial pulmonary disease (NTM-PD) by the American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America; and the 2017 management guideline by the British Thoracic Society covered pulmonary diseases in adults caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium abscessus*. In order to provide evidence-based recommendations for the treatment of less common non-tuberculous mycobacterial (NTM) species in adult patients without cystic fibrosis or HIV infection, our expert panel group performed systematic literature searches to provide management guidance for pulmonary diseases caused by seven additional organisms: *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium genavense*, *Mycobacterium gordonae*, *Mycobacterium malmoense*, *Mycobacterium simiae*, and *Mycobacterium szulgai*. Treatment recommendations were developed by a structured consensus process. The evidence from the scientific literature published in English for treatment recommendations for pulmonary diseases caused by other NTM species was of very low quality, with the exception of *M malmoense*, and based on the evaluation of case reports and case series. For *M malmoense*, results from two randomised controlled trials and three retrospective cohort studies provided a better evidence base for treatment recommendations, although the evidence was still of low quality.

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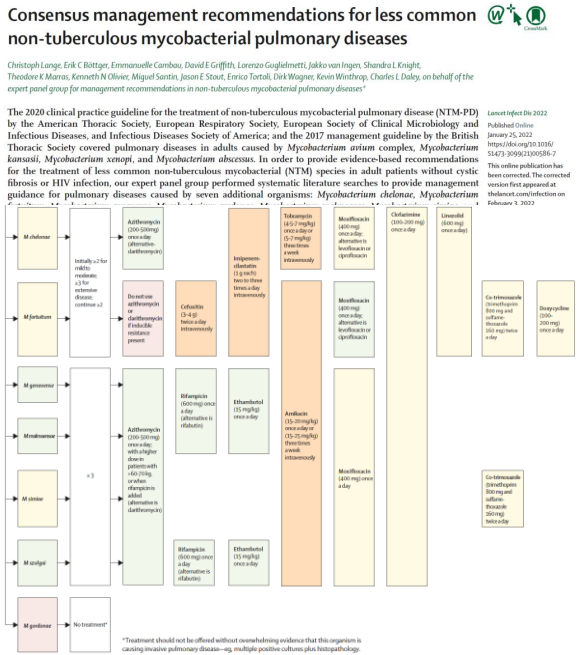
Lange C, et al. Lancet Infect Dis 2022

Regimens for rare NTM species

- NTM-PD treatment

M. chelonae	IMI-TOB-CLO-AZI
M. fortuitum	IMI-AMI-CIP-SXT
M. genavense	RIF-EMB-AZI+/-AMI
M. gordonae	No treatment, unless…
M. malmoense	RIF-EMB-AZI+/-AMI
M. simiae	CLO-AMI-SXT-AZI
M. szulgai	RIF-EMB-AZI+/-AMI



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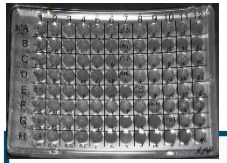
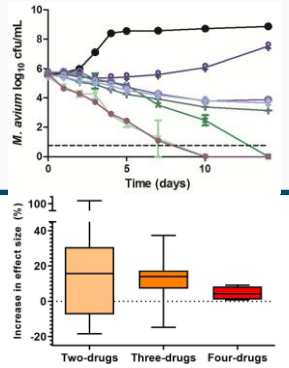
Lange C, et al. Lancet Infect Dis 2022

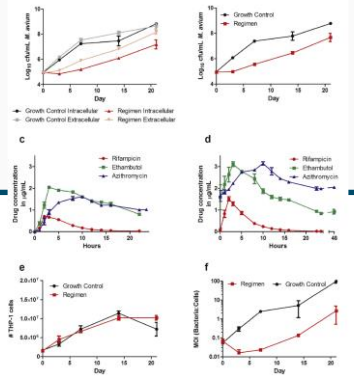
Developments in NTM management

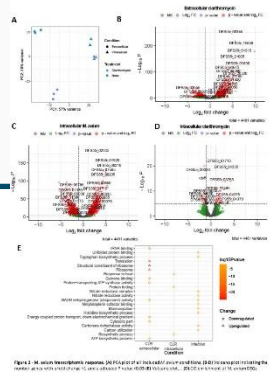
Stratification: more drugs vs smarter choices



MIC = 8 mg/l







Areas of development

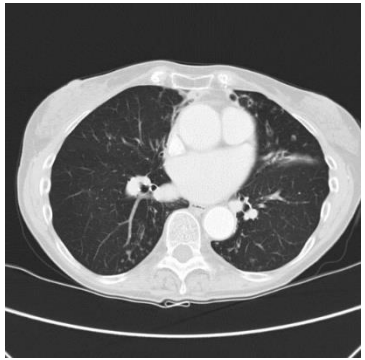
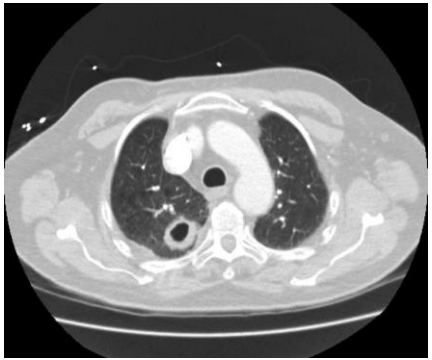
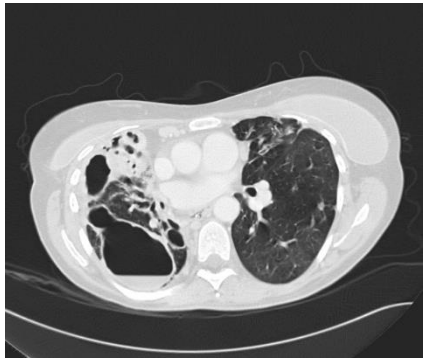
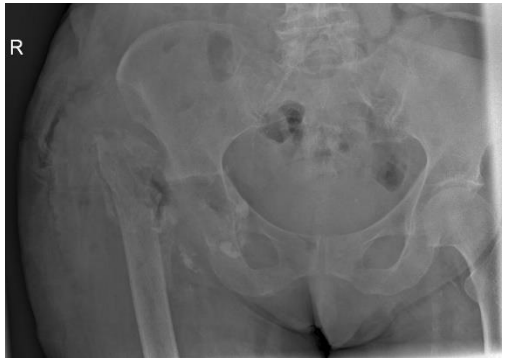
1. Stratified treatment regimens
    1. Stratification on basis of severity / bacterial load / biomarkers
    2. Stratification on basis of treatment history

2. Targeting persisters for eradication

3. Host-directed therapies

Stratification on basis of disease severity

- **2- vs 3- vs 4- vs 5-drug** macrolide-containing regimens

Stratification on basis of disease severity

- **2- vs 3-drug** macrolide-containing regimens for MAC-PD

- HIV/diss-MAC: 3-drug not proven superior (Gordin, 1999)
- Hollow fiber model: equal efficacy, equal macrolide resistance

- Case series: effective in mild non-cavitary MAC-PD (3x/wk!)

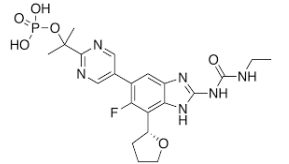
1. Miwa et al. (2014+2020): 60 vs 59 pt, 55% vs 41% culture conversion, no resistance
2. Moon et al. 3/wk (2019): 38 pt, 76% culture conversion, smear pos = failure risk

How to stratify: **Bacterial load** (TTP, smear) and **Radiology** (no cavities)

Stratification on basis of disease severity

- **3-drug** macrolide-ethambutol-containing regimens: which 3rd drug?

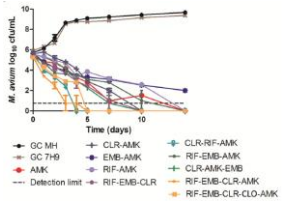
Ongoing clinical trials:
Rifampicin–EMB–AZI *vs* EMB-AZI
Rifampicin–EMB–AZI *vs* **Clofazimine**-EMB-AZI (done!)
SPR720–EMB–AZI *vs* EMB-AZI
ALIS–EMB–AZI *vs* EMB-AZI

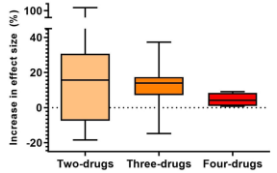


How to stratify? wait for the trial results…
Caveat: trials select for non-cavitary disease

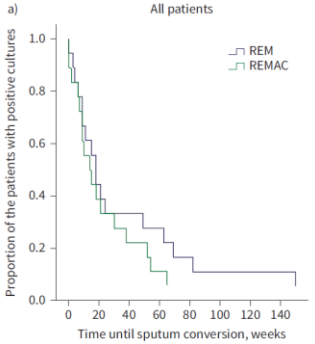
Stratification on basis of disease severity

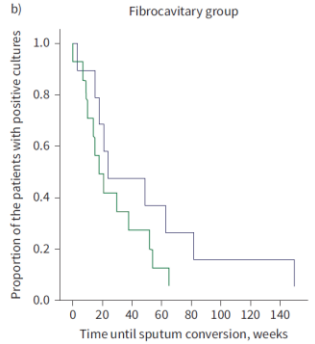
- **3- vs 4/5-drug** macrolide-containing regimens
- ADD amikacin and clofazimine
- *In vitro*: diminishing returns (Sonawane, 2020)





- Retrospective case series (Zweijpfenning, 2021)
  - 44pt, 25 REM vs 19 **REM+AMI+CLO**
  - Microbiological cure 52% vs 74%
  - Time-to-culture conversion: 18 vs 14 weeks



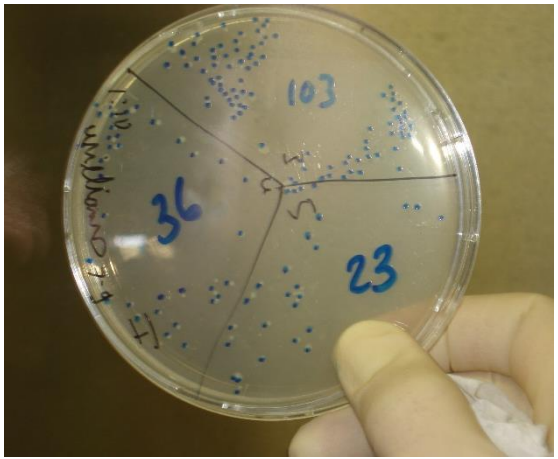


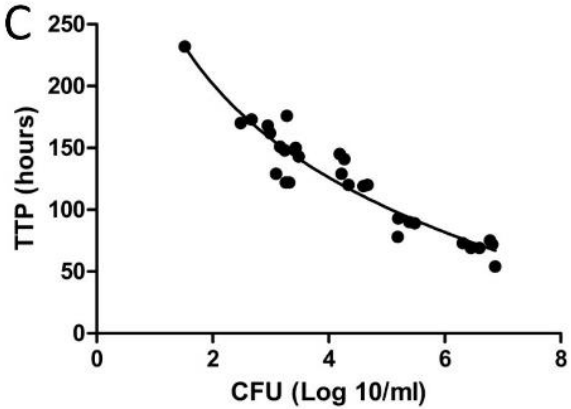
How to stratify: **Bacterial load** (TTP, smear), **Radiology** (cavities), **treatment history**

Raaijmakers J, et al. Exp Op Pharmacother 2021 ; Zweijpfenning S et al., ERJ Open Res 2021

Biomarkers to differentiate between regimens

Quantitative culture, available near you ☺

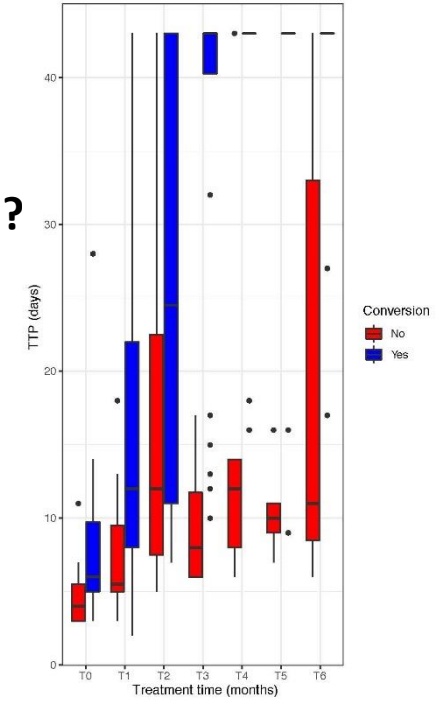




Pennings LJ et al., Diagn Microbiol Infect Dis 2018

Bacterial load made easy: TTP

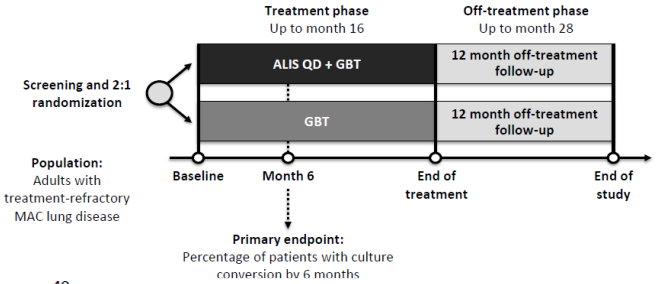
- Two independent observations: load predicts outcome
- Bacterial load drives the outcome: **regimen selection tool?**
- Baseline **MGIT TTP >> in converters** vs non-converters
  - 7.68±4.64 vs. 4.87±2.20 days; p=0.031
- baseline **TTP >7 days associated with culture conversion**
  - Likelihood ratio 6.947, p=0.014
  - ROC curve: sens 41%, spec 93% to predict conversion

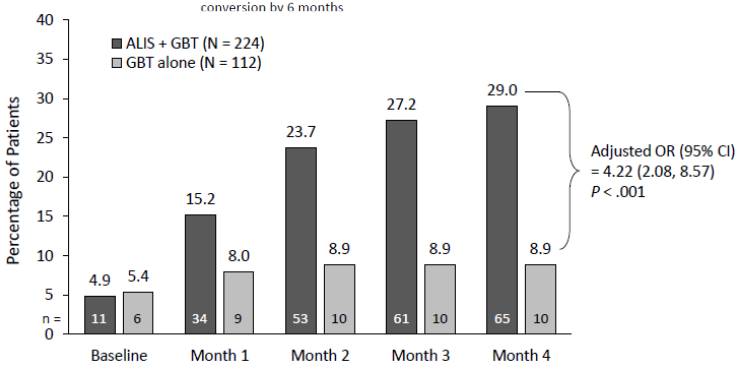


Danho R, et al. Chest 2021 ; Mingora CM et al., BMC ID 2022

Differentiation on basis of history

- Amikacin liposome inhalation solution (ALIS)
- CONVERT: 336 patients with **refractory MAC-PD**
  - 224 GBT+ALIS ; 112 GBT alone
- ALIS+GBT: more **culture conversion**
  - ALIS+GBT 29% vs GBT 9% (p<0.001)
- **Durable** until 3mo after treatment
- Role in first line treatment? ARISE/ENCORE Trials ongoin

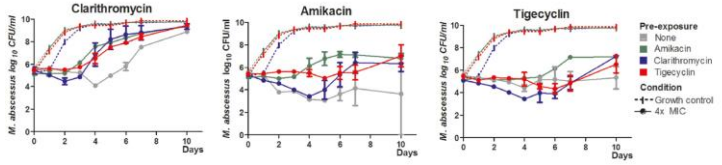


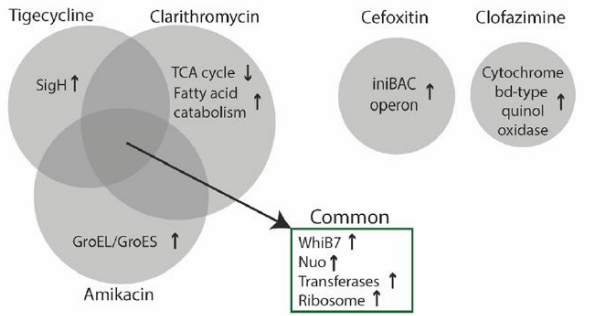


Griffith DE, et al. *Am J Respir Crit Care Med* 2018 ; Winthrop KL, et al. *Ann ATS* 2020

Targeting persisters – the new frontier

- Macrolides and amikacin kill active mycobacteria
- Both induce **metabolic shutdown** in *M. abscessus* and MAC
- The intracellular environment also changes NTM metabolism
- **Who kills the persisters?** *Intracellular* and extracellular
- Options: respiratory chain inhibitors (clofazimine + …?)?





Schildkraut J, et al. Antimicrob Agents Chemother 2021 + unpublished observations

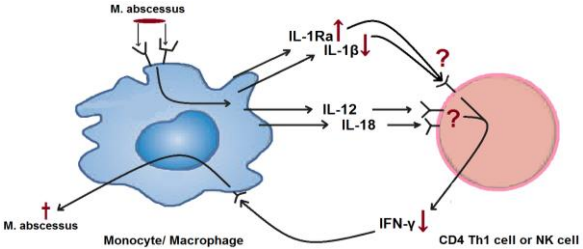
The immunological perspective

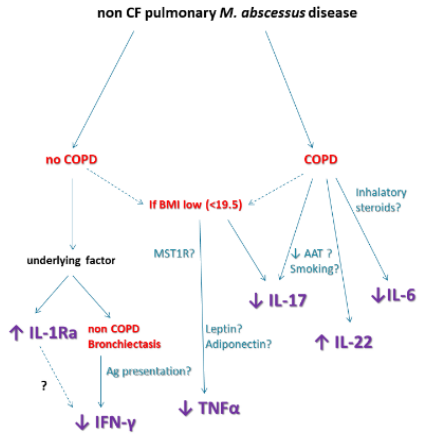
- **2 MAC and *M. abscessus*-PD cohorts**
- **Low IFN-y and IL-17** response to NTM stimuli
- High IL-10 response to NTM stimuli

- Low IL-17 particularly in COPD patients

- Low IFN-y particularly in bronchiectasis patients

- Inroads for **host-direct therapy**?





Schuurbiers M, et al. ERJ Open Res 2020
Bruno M, et al. ERJ Open Res 2020
Delsing CE et al., BMC Infect Dis 2015
Smeekens SP, et al. JICR 2012

Summary: Areas of development

- Stratified treatment regimens
  - Stratification on basis of **severity / bacterial load** / biomarkers
    - 2 vs. 3 vs. 4/5 drugs
  - Stratification on basis of **treatment history**
    - Adjunctive antibiotics treatments
- Targeting **persisters** for eradication
- Host-directed therapies

Radboudumc TB/NTM team

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Cecile Magis


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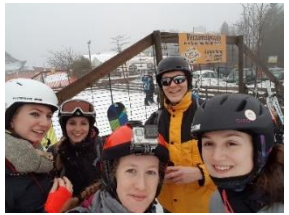
Mycobacteriology teams



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