



## Medical Microbiology

Radboud University Nijmegen  Medical Centre

# Treatment strategy for respiratory NTM infections

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**NTM-net**  
NONTUBERCULOUS MYCOBACTERIA NETWORK EUROPEAN TRIALSGROUP

Medical Microbiology



## Conflict of interest statement

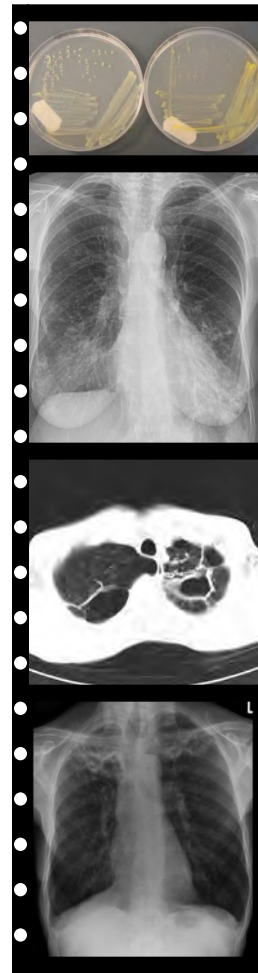
- No conflicts of interest
- No external funding
- Off-label use of quinolones, aminoglycosides and linezolid may be discussed



# What you should know after this session

<i>M. avium</i> complex	18-24 RE(+macrolide) +/- aminoglycoside
<i>M. kansasii</i>	12HRE
Rapid growers	Aminoglycosides, ceftazidime, macrolides, FQ

- Literature: one size fits all
- Clinic: tailor made treatment regimens
- No good quality trials
- In vitro – in vivo discrepancies abound
- PK/PD of current dosing schemes ‘suboptimal’
- In case of doubt, be humble and consult experts



*“Proper management requires greater expertise than is needed for treatment of tuberculosis, first, to decide who needs to be treated and second, to determine which drug regimens to use.”*

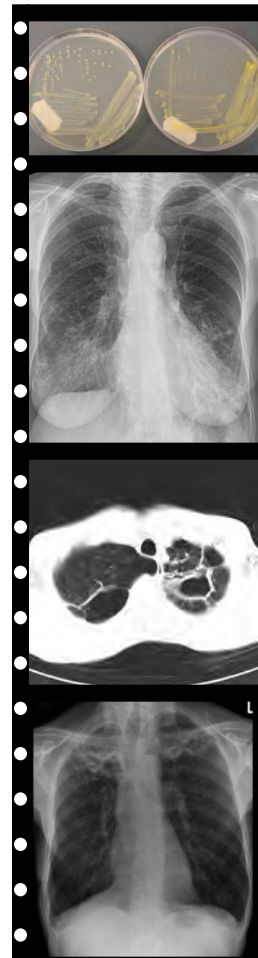
Emanuel Wolinsky

Nontuberculous mycobacteria and associated diseases

*Am Rev Respir Dis* 1979

## Overview

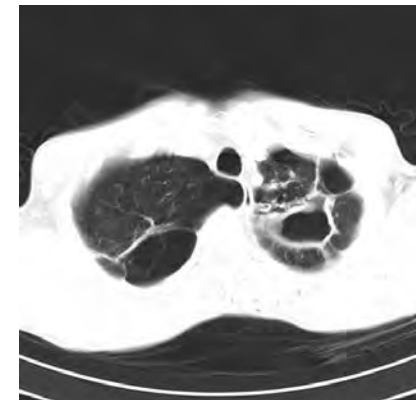
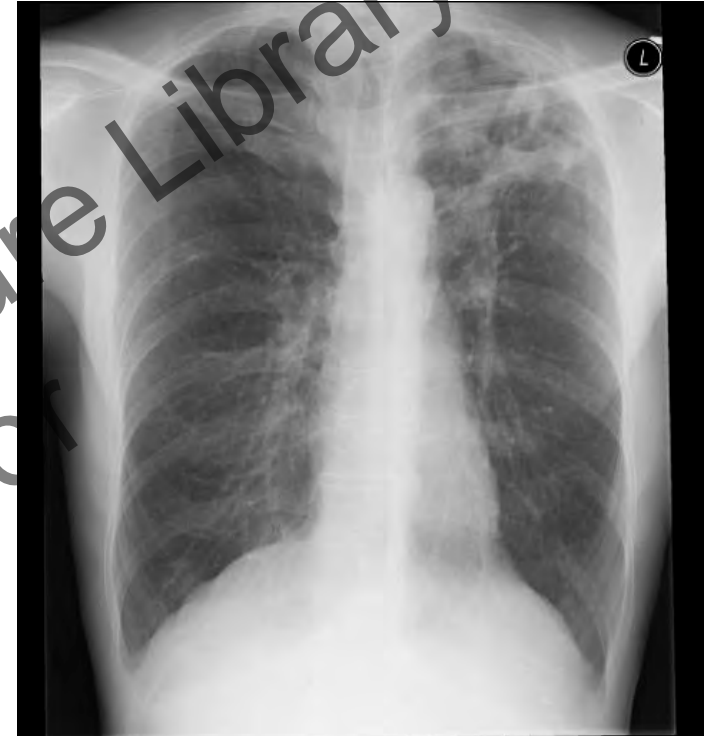
- Local treatment strategy
- Strategic regimen selection
  - Historical data
  - SGM: BTS vs ATS
  - RGM
- Where do we go from here?



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## Case for discussion

- *M. malmoeense* DST
- 58 year old male
- Rifampicin S
- Truck driver S
- Ethambutol R
- Smoker
- Isoniazid R
- COPD (GOLD II) R
- Streptomycin R
- Amikacin, malaise, fatigue
- Cough
- Ciprofloxacin R
- Cavitary lesion LUL
- Moxifloxacin R
- Sputum AFB+ ; BCR *Mtb* negative
- Capreomycin
- Cycloserine S
- => *M. malmoeense*
- Prothionamide S
- Clofazimine S



# Treatment strategy: Who will be treated, how intensively?

*Success estimation*

Patient motivation

Not motivated

NTM species

*M. simiae*?

Cavitary - nodular bronchiectatic?

Previous treatment? Macr

Which regimen?

Daily + AG

Daily

Intermittent

No treatment

Adjunctive surgery?



## NTM-PD treatment, the early days

- *M. kansasii*
- INH-PAS-strepto
  - 2/3 good clinical response
  - 50-60% culture conversion; 90% w/ surgery

Here comes trouble: MAC

- Isoniazid-PAS-streptomycin: 32% cult conv. (92/285)
  - Up to 75% with adjunctive surgery

- *How much better are we today?*

## *Mycobacterium avium* complex

- Outcomes differ by site

- Misconceptions

- Aminoglycosides
- Disease type
- Host factors

- 2 comparative trials

- HRE vs RE
- RE-cip vs RE-cla

Regimen	% "Cure"	REF
>12 REClari (+KM +FQ!)	84% (26/31)	Tanaka '99
>12 REClari (+3 Strepto)	75% (45/60)	Kobashi '12
>12REClari	50% (10/20)	van Ingen'09
24REClari	24% (20/83)	BTS '08
24HRE	34% (13/38)	BTS '01
15CloMinClari	64% (14/22)	Roussel '98
CloE-Clari	67% (20/30)	Field '03

## ***Mycobacterium avium* complex - controversies**

- Nodular-bronchiectatic disease = cavitory disease?
- What is the exact role of the macrolides?
- Adjunctive aminoglycosides?
  - Landmark case series used aminoglycosides\*
  - Kobashi: faster culture conversion only
- Clofazimine-based regimens?

## *Mycobacterium kansasii*

- High cure rates, short regimens
- Ahn (case series, n=40)
  - 12HRE (+3S!)
  - 98% cure, 1 relapse
- Israel (Shitrit D, et al+ case series; n=56)
  - 18-24 RE-Cla
  - 100% cured, no relapses



## *Mycobacterium malmoeense*

- Generally good outcomes; strongly related to COPD
- BTS trials
  - (H)RE: 38-44% alive and cured @ 5yr FU
  - REcip: 20%
  - REcla: 38%
- Hoefsloot (NL, case series, n=40)
  - REcla: 21/30 (70%) cured
- Henry (UK, case series, n= 18): 72% cured

## *Mycobacterium xenopi*

- BTS: outcome poorer than in MAC or *M. malmoeense*  
 24 (H)RE: 10-23% alive and cured @ 5yr FU  
 24 RECipro: 12%  
 24 REClari: 18%
- France (Andrejak, case series): HRE +/-MC/FQ
- 26/122 cured (21%); 69% mortality
- Netherlands (case series): (H)RE +/- Macrolide
- 5/19 cured (26%); 9/19 culture conversion; 4 relapsed
- In vitro: no RIF/EMB synergy
- *Distinct patient category: co-morbidity, co-infections*



van Ingen J et al., Emerg Infect Dis 2008

Andrejak C, et al. Thorax 2009

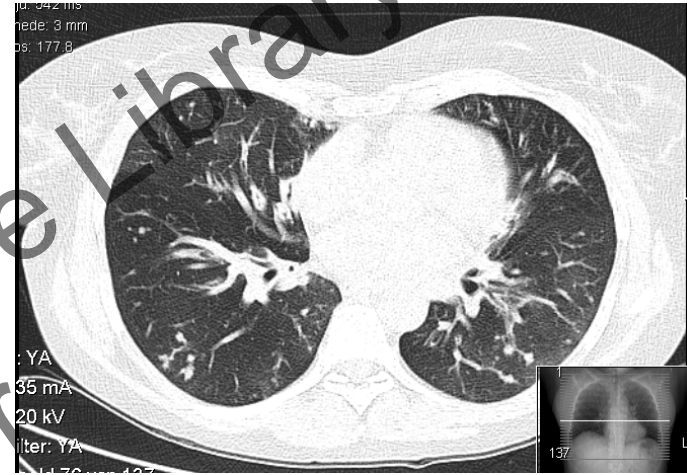
British Thoracic Society, Thorax 2008

## *Mycobacterium simiae*

- Seek expert consultation
- No evidence-based regimen
- Poor outcome of RIF-EMB-macrolide

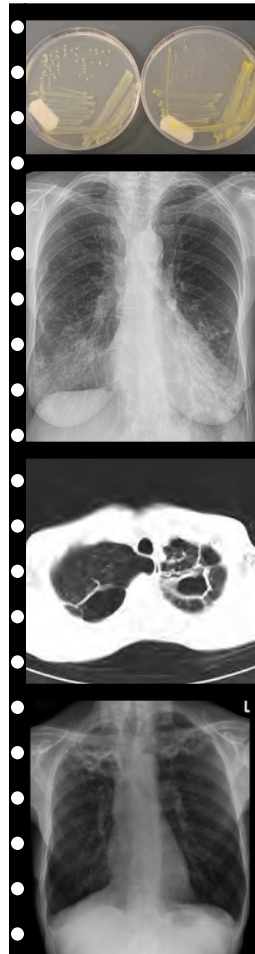
### *In vitro:*

- No rifampicin-ethambutol synergy
- Clofazimine-amikacin synergy



## *Mycobacterium abscessus* group

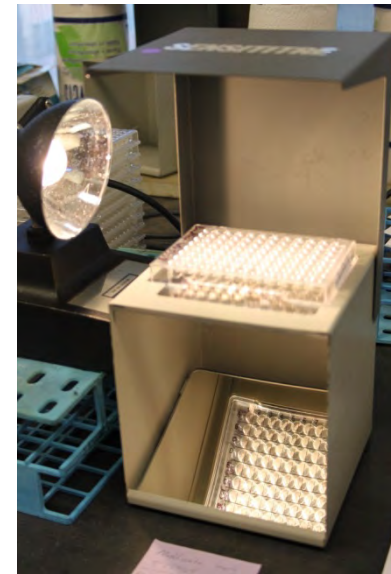
- Seek expert consultation
- Macrolide (?), **amikacin**, AND
  - **Cefoxitin** / imipenem / tigecycline / linezolid
  - Clofazimine?
- Jarand et al.: 48% culture conversion (33/69)
  - Better with adjunctive surgery
- South Korea: Ami+FOX; ClaCipDoxy (n=65)
  - 58% culture conversion
  - best outcomes in '*M. massiliense*'





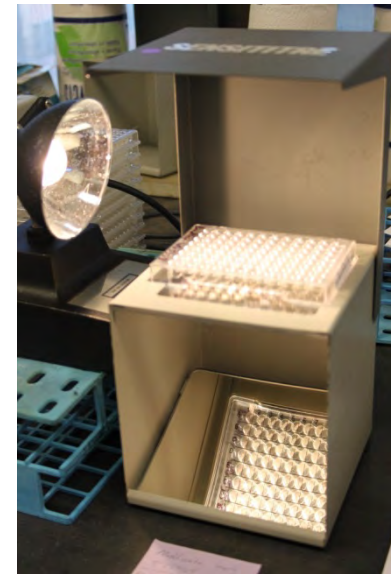
## The role of drug susceptibility testing (1)

- CLSI: broth microdilution in CAMHB
- Broth macrodilution for MAC (BT 460)
- EUCAST does not cover NTM
- Many in-house methods (e.g. E-tests)
  - No proficiency testing
  - No clinical validation of breakpoints
  - Irrelevant drugs
- Know what your (reference) lab does!!



## The role of drug susceptibility testing (2)

- Very limited clinical validation
- MAC: test macrolides only
  - Dubious: moxifloxacin & linezolid
- *M. kansasii*: test rifampicin only
- RGM: Cla, FOX, AGs, FQ, doxy, line, imi
- Inducible macrolide resistance?
  - *erm* gene



Tanaka et al., Am J Respir Crit Care Med 1999  
 Nash K, et al. Antimicrob Agents Chemother 2009  
 van Ingen J, et al., Drug Resistance Updates 2012

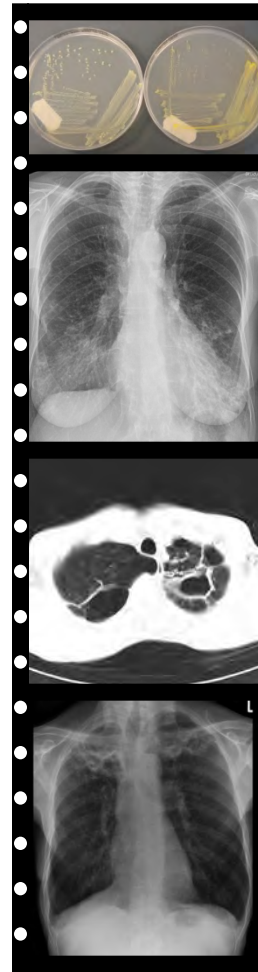
## PK/PD of MAC-LD treatment

- Pharmacodynamic indices not met for the key drugs
  - Rifampicin (AUC/MIC): 20% met target
  - Ethambutol (C<sub>max</sub>/MIC): 57%
  - Clarithromycin: 20-40%
  - Amikacin (C<sub>max</sub>/MIC): 20-40%
- Rifamycins lower macrolide concentration up to 60%
  - Rifampicin > rifabutin
  - Affect clarithromycin > azithromycin

# Conclusions

<i>M. avium</i> complex	18-24 RE(+macrolide) +/- aminoglycoside
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Rapid growers	Aminoglycosides, ceftazidime, macrolides, FQ

- Scant evidence
- No good quality trials
- One size fits all treatment irrespective of bug or host
- In vitro – in vivo discrepancies abound
- PK/PD of current dosing schemes ‘suboptimal’
- In case of doubt, be humble and consult experts



## On the shoulders of giants

- Emanuel Wolinsky
- Richard Wallace Jr.
- David Griffith
- Charles Daley
- Michael Iseman
- Timothy Aksamit



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Questions or comments?

