



Nontuberculous mycobacteria diagnosis and treatment: the clinician's perspective

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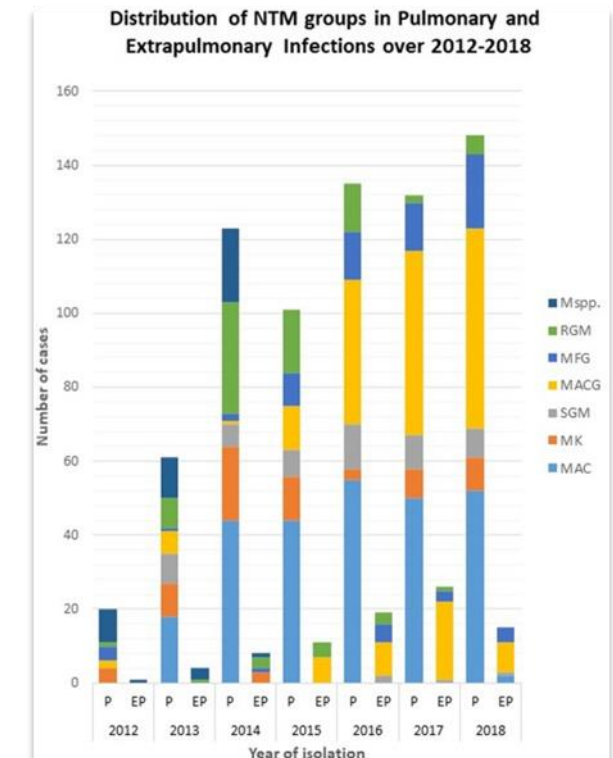
BVIKM symposium, 24 May 2022

Why discuss NTM?

- Omnipresent in soil and aquatic environments
- Opportunistic pathogens
- NTM disease is emerging globally
- Significant burden and economic cost for the health care system

Ahmed et al. Int J Infect Dis 2020

Goring et al. BMC Publ Health Serv Res 2018

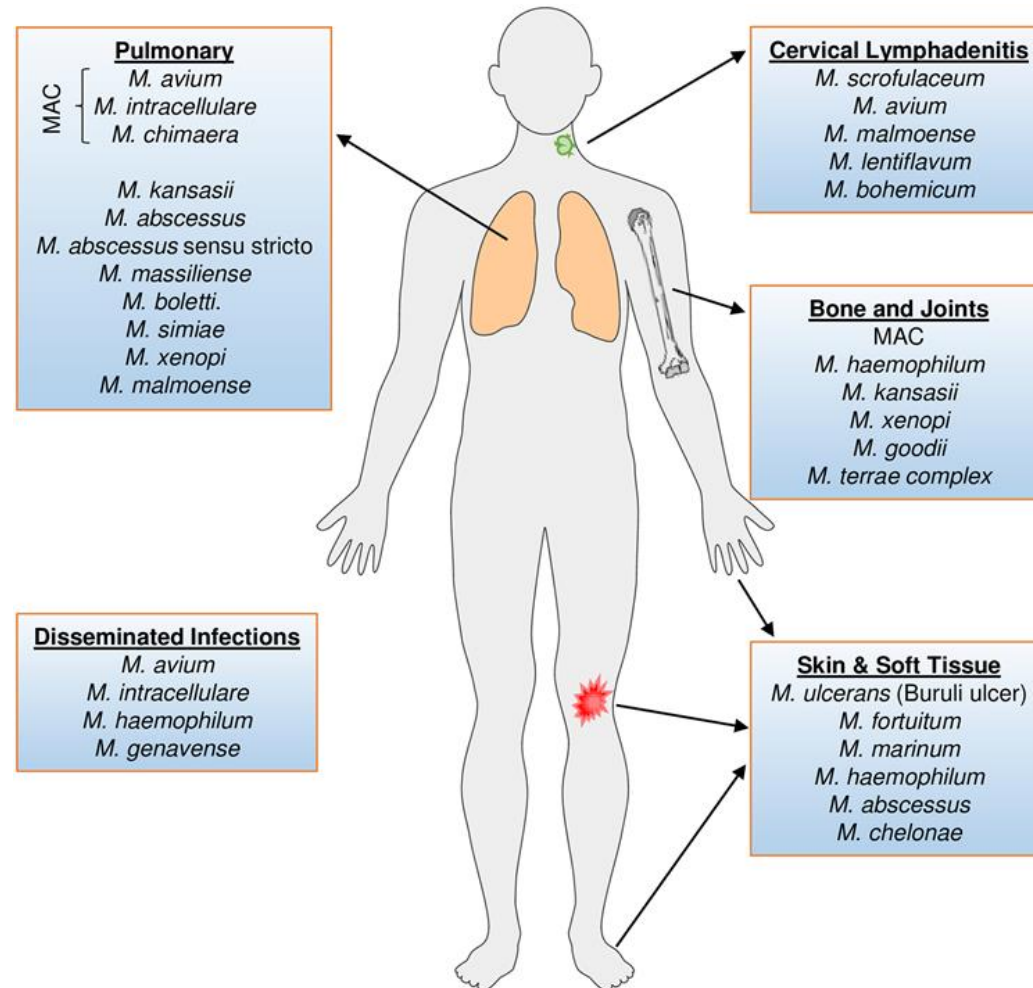


“A neglected disease”

NTM disease entities

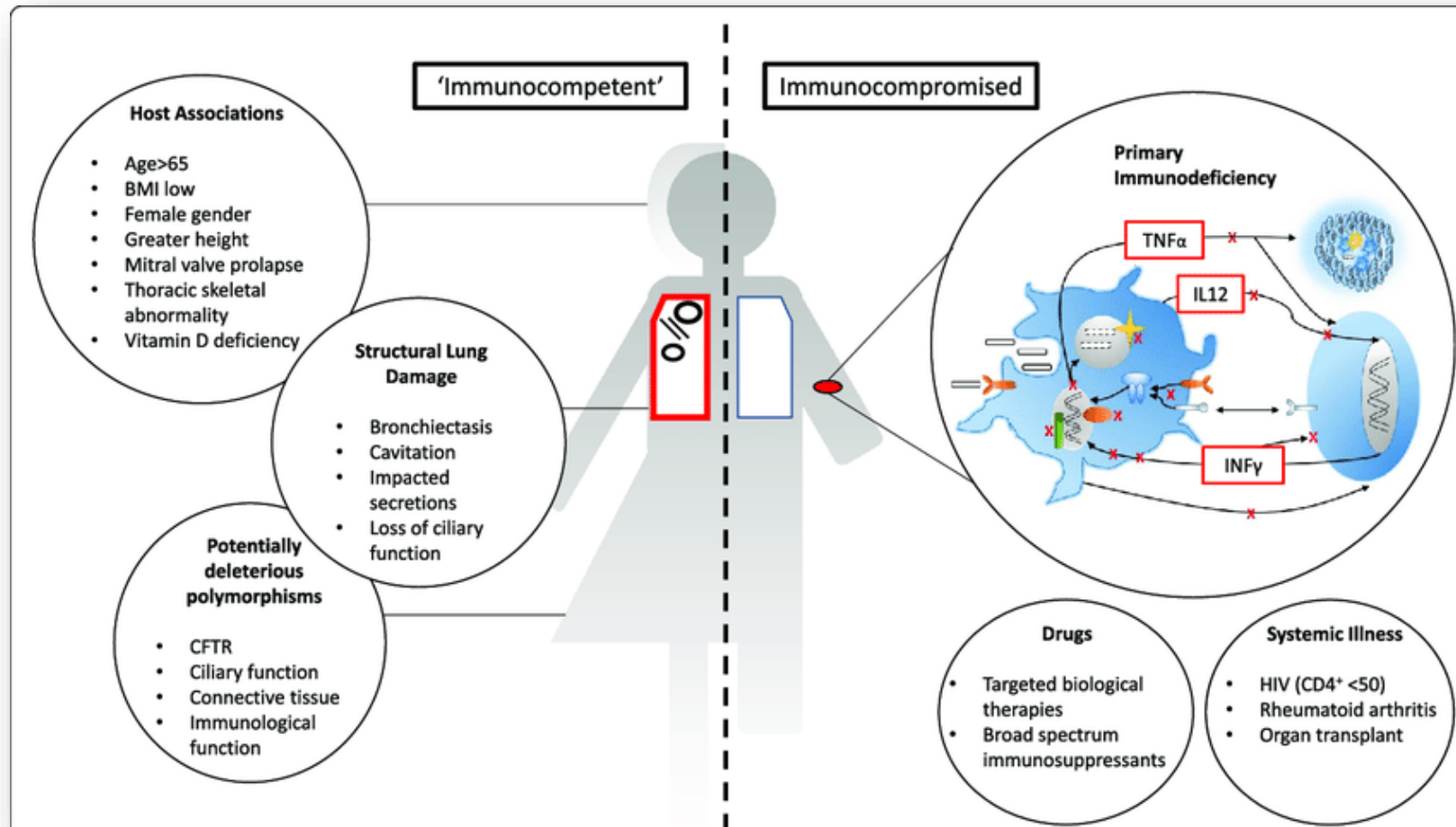
Inhalation/ingestion

Immune suppression



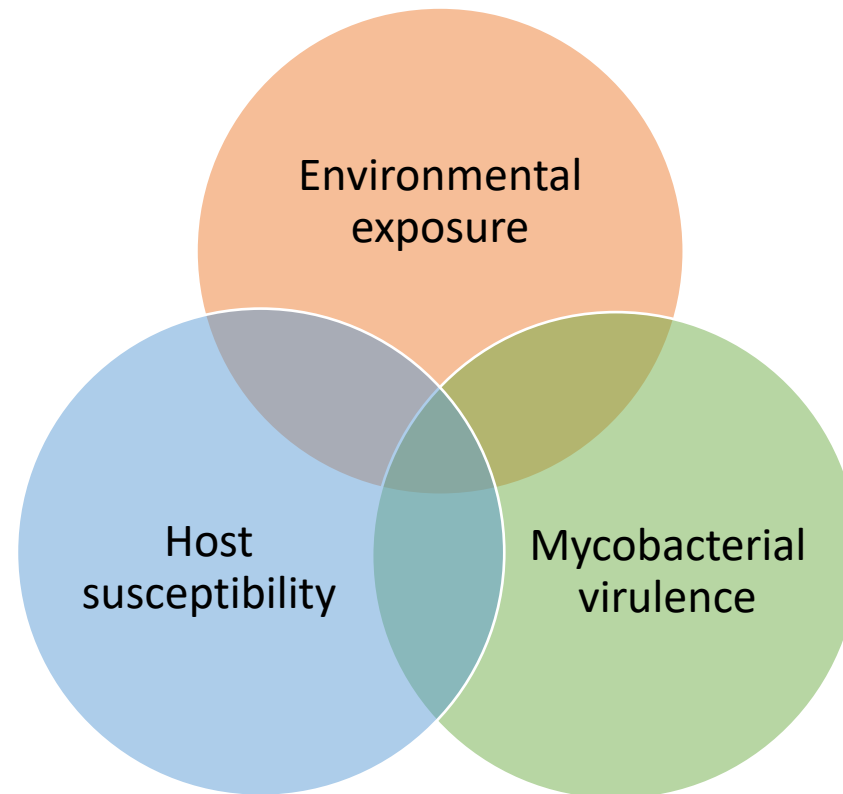
Inoculation

Who is at risk for NTM disease?



Lake et al. BMC Med 2016

Interplay of multiple risk factors can lead to NTM disease



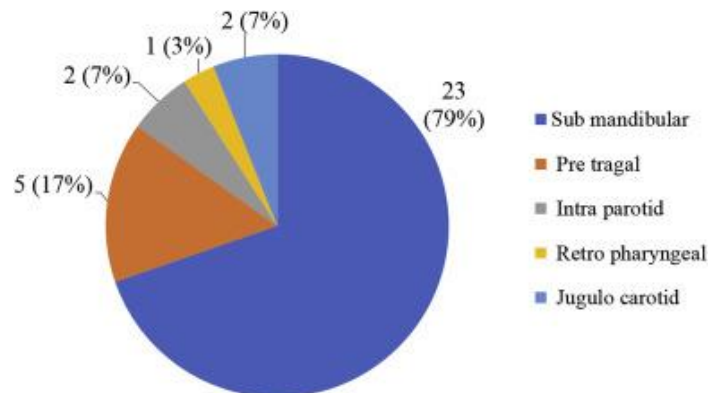
Extrapulmonary NTM disease

Cervicofacial lymphadenitis

1



- Diagnosis: lymph node biopsy
- *M. avium* complex, *M. scrofulaceum*, *M. malmoeense*, *M. haemophilum*
- Management
 - Surgical excision (up to 96% cure rate)²
 - “wait-and-see”^{3,4} - resolution 6-9 months
 - (antibiotic therapy)



¹Gallois et al. Int J Ped Otorhinolaryng 2019

²Lindeboom et al. Clin Infect Dis 2007

³Lindeboom. Clin Infect Dis 2011

⁴Harris et al. Int J Ped Otorhinolaryng 2009

Skin, soft tissue and bone infections

- Nodular skin lesion or ulceration
- Consequence of
 - Direct inoculation (abrasion, surgery, cosmetic procedure,...) in immunocompetent
 - Dissemination in immunocompromised (HIV+, solid organ transplants)
- Diagnosis: recommend surgical biopsy
- Treatment: 2-3 active drugs
 - 4 months for soft tissue infection
 - 6 months for bone infection
 - Consider surgical debridement when tendon/joint involvement and *M. abscessus* infections
 - Removal of foreign material

Fish tank/swimming pool granuloma – *M. marinum*

- Diagnosis: biopsy for AFB and culture
 - Growth at 33°C
- Management
 - Combination of at least 2 active agents
 - Macrolides, ethambutol, rifampicin, trimethopril-sulfamethoxazole, doxy-/tetracyclin
 - 1-2 months following resolution
 - Surgery
 - Failed response to standard R/
 - Tenosynovitis/arthritis

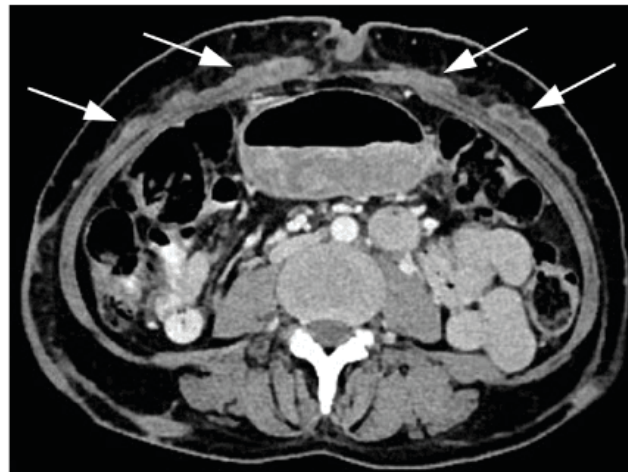


NTM skin/soft tissue infection outbreaks

M. fortuitum nail salon outbreak



M. abscessus ssp abscessus infection following liposuction



Eurosurveillance.org

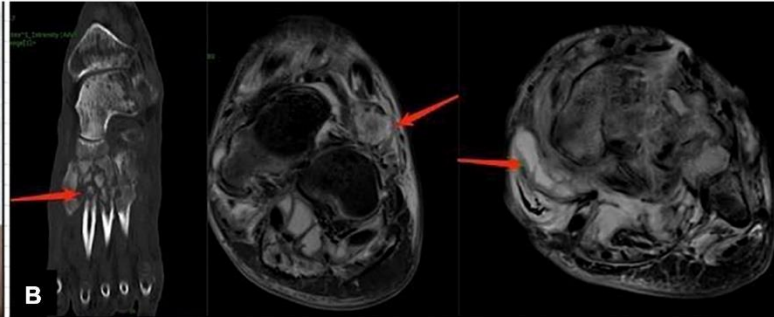
M. chelonae infection following tattoo



Kennedy et al. NEJM 2013

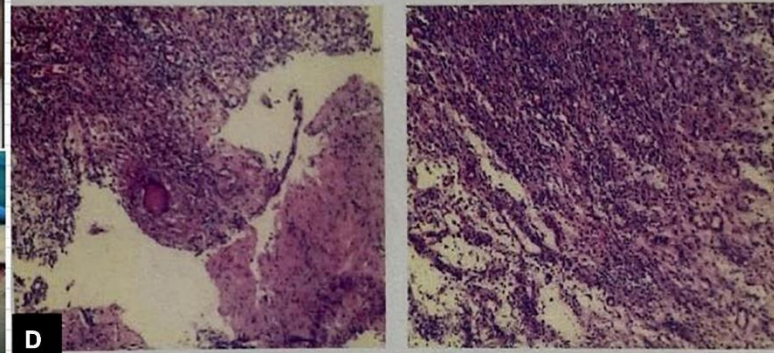
Musculoskeletal infections

Pain, swelling, discharge



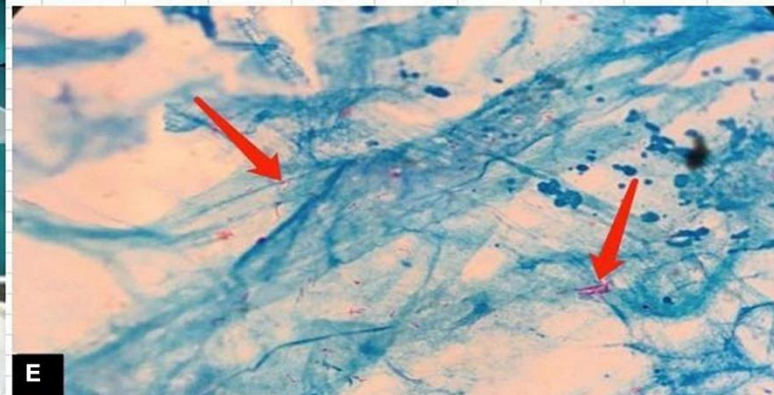
Bone erosion/destruction
Soft tissue swelling

Inflammatory tissue



Granuloma + necrosis

Bone destruction,
granulation tissue



AFB staining of tissue

Prosthetic joint infections

- Most patients >60 yrs old and immunocompetent
- *M. abscessus* complex, *M. fortuitum* > *MAC*, *M. marinum*, *M. goodii*
- Culture of synovial fluid and periprosthetic tissue + granuloma on histology
- Management
 - Removal of prosthesis
 - Plus antibiotic therapy
 - (re-implantation)

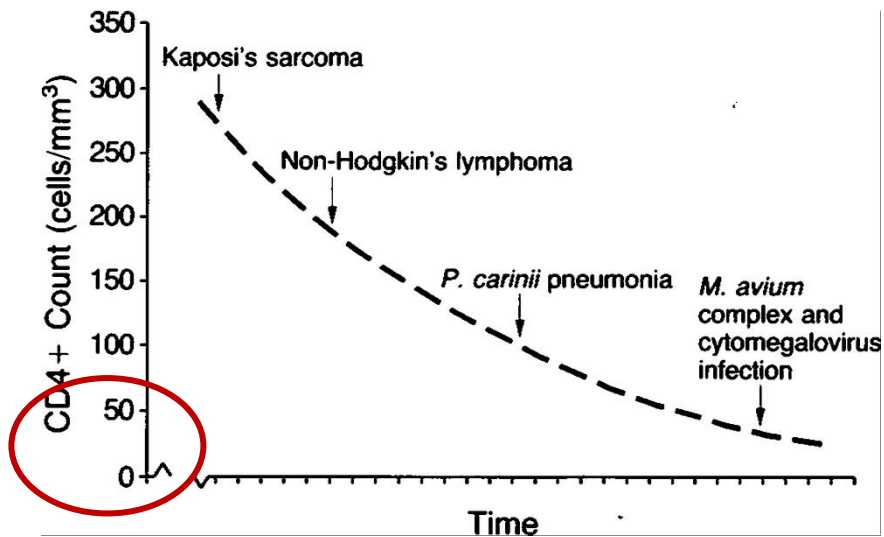


¹Kim et al. The Knee 2017

Goldstein et al. Emerg Infect Dis 2019

Eid et al. Clin Infect Dis 2007

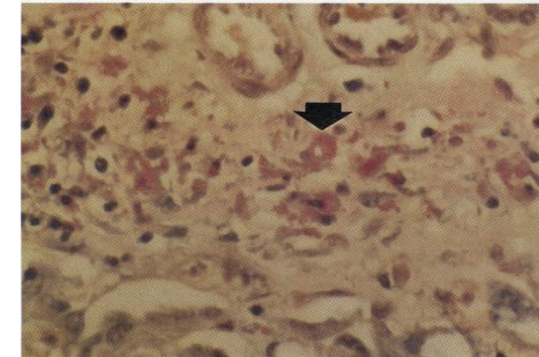
Disseminated disease



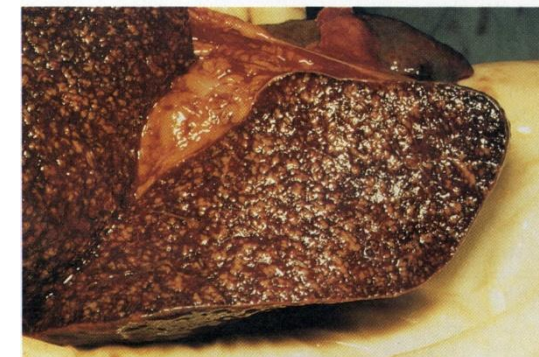
- Via lungs or GI tract
- Clinical presentation
 - Fever, night sweats, **weight loss**, diarrhoea
 - Bacteraemia, elevated alkaline phosphatase, LDH and **anaemia**



A



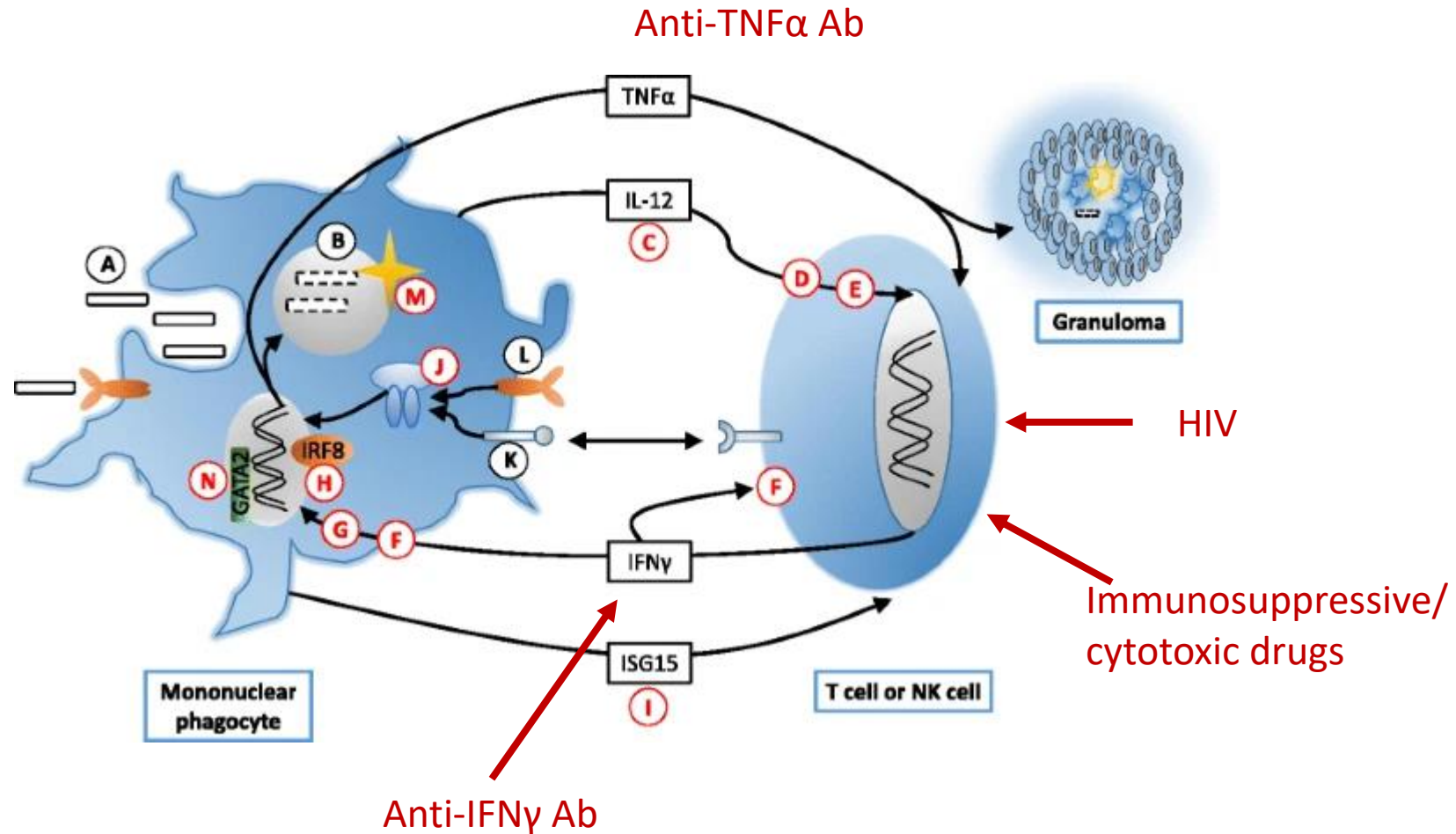
B



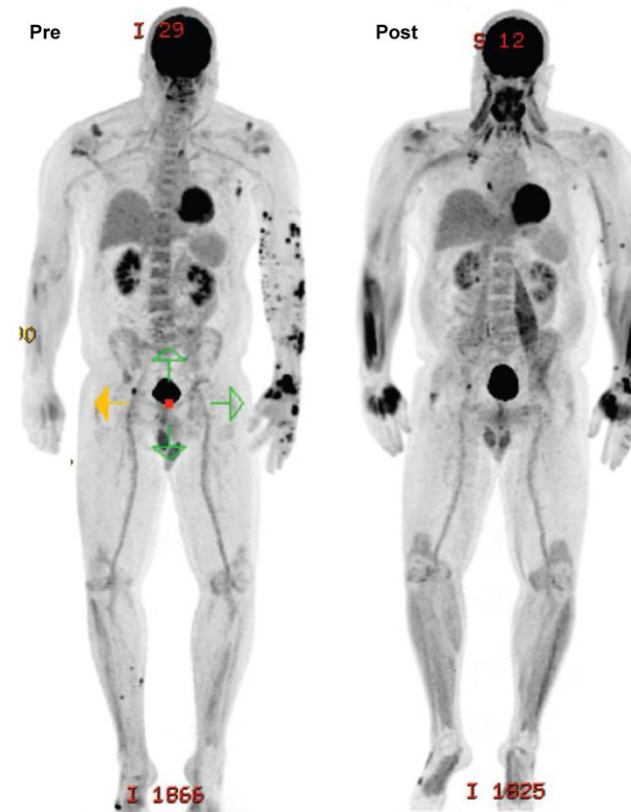
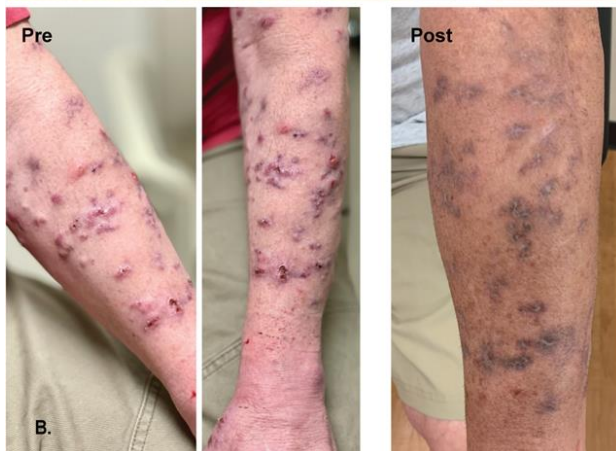
C

Horsburgh. NEJM 1991

Predisposing conditions for disseminated NTM disease



Refractory disseminated cutaneous *M. chelonae* infection in the immunosuppressed



Antibiotic therapy,
surgical debridement
and IV bacteriophage
administration



Prolonged Outbreak of *Mycobacterium chimaera* Infection After Open-Chest Heart Surgery

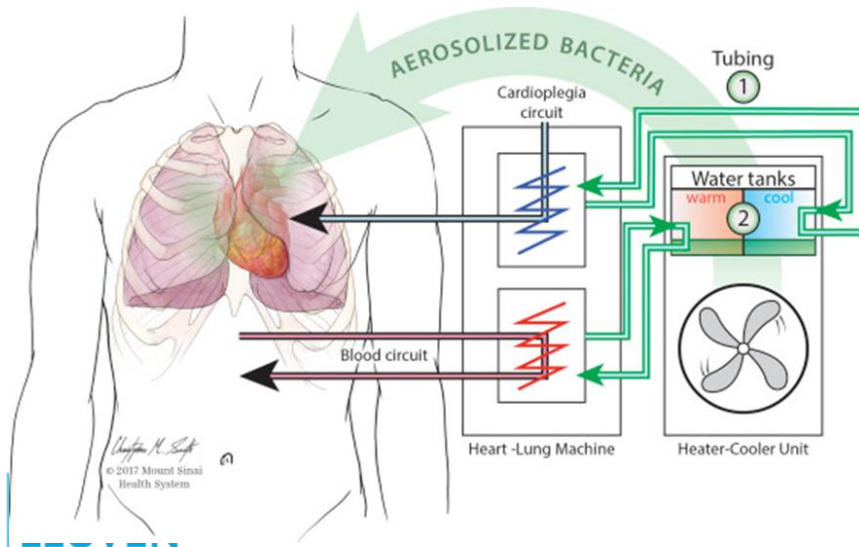
Hugo Sax,^{1,a} Guido Bloemberg,^{2,a} Barbara Hasse,^{1,a} Rami Sommerstein,¹ Philipp Kohler,¹ Yvonne Achermann,¹ Matthias Rössle,³ Volkmar Falk,⁴ Stefan P. Kuster,¹ Erik C. Böttger,^{2,b} and Rainer Weber^{1,b}

¹Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, ²Institute of Medical Microbiology, National Centre for Mycobacteria, University of Zurich, ³Institute of Surgical Pathology, and ⁴Division of Cardiac Surgery, University Hospital Zurich, Switzerland

Background. Invasive *Mycobacterium chimaera* infections were diagnosed in 2012 in 2 heart surgery patients on extracorporeal circulation. We launched an outbreak investigation to identify the source and extent of the potential outbreak and to implement preventive measures.

Long latency between clinical presentation and diagnosis of *M. chimaera* infection

Mortality >50%



Take home messages - extrapulmonary NTM disease

Maintain a high index of suspicion

- Unexplained protracted symptoms
- Immunocompromised
- Post-operative patient (delay!)

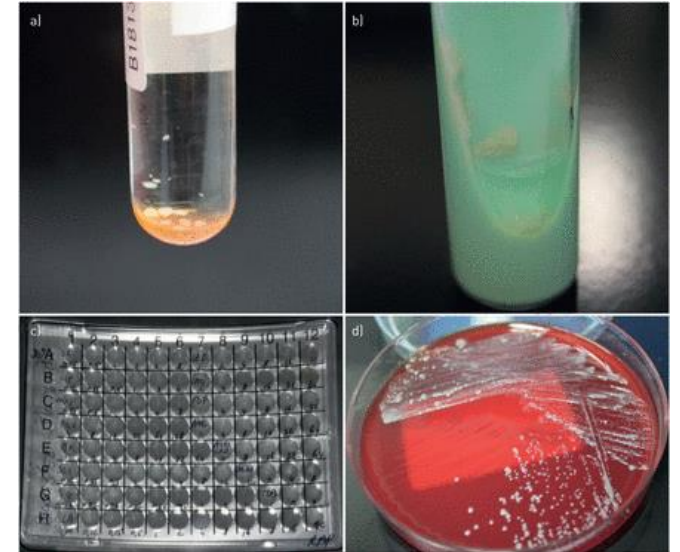


Antibiotic therapy guided by species (and drug susceptibility)

- Lack of consensus guidance
- Treatment duration in months

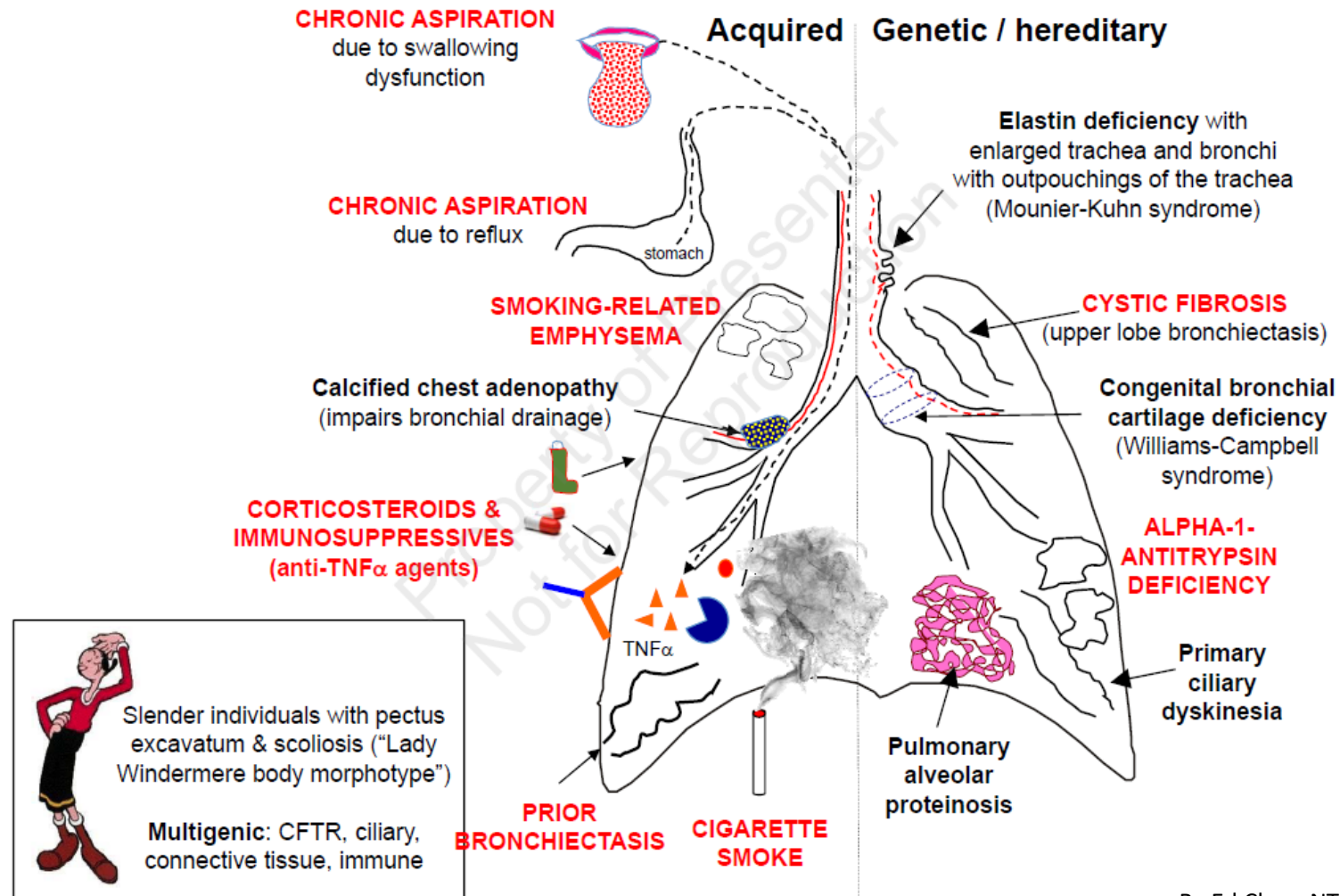
Surgery

- Debridement
- Remove all foreign material



Pulmonary NTM disease

Predisposing conditions for pulmonary NTM disease



By Ed Chan, NTM lecture series, NJH, Sep 2019

ATS/IDSA diagnostic criteria for NTM lung disease

Clinical symptoms



Cough
Fatigue
Weight loss
Fever/night sweats
Dyspnoea
Haemoptysis

New onset/deterioration

ATS/IDSA diagnostic criteria for NTM lung disease

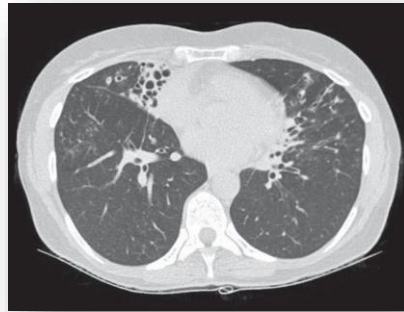
Clinical symptoms

+

Radiology



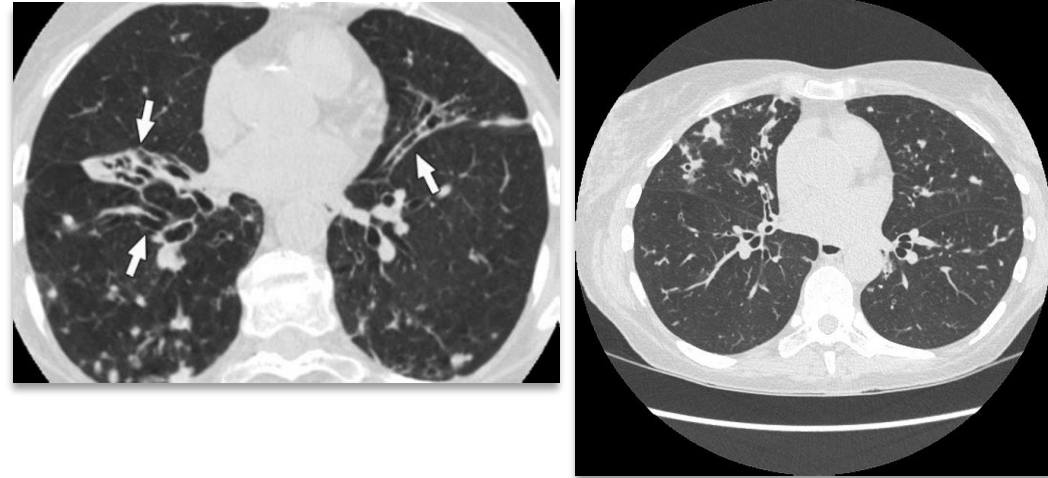
Cough
Fatigue
Weight loss
Fever/night sweats



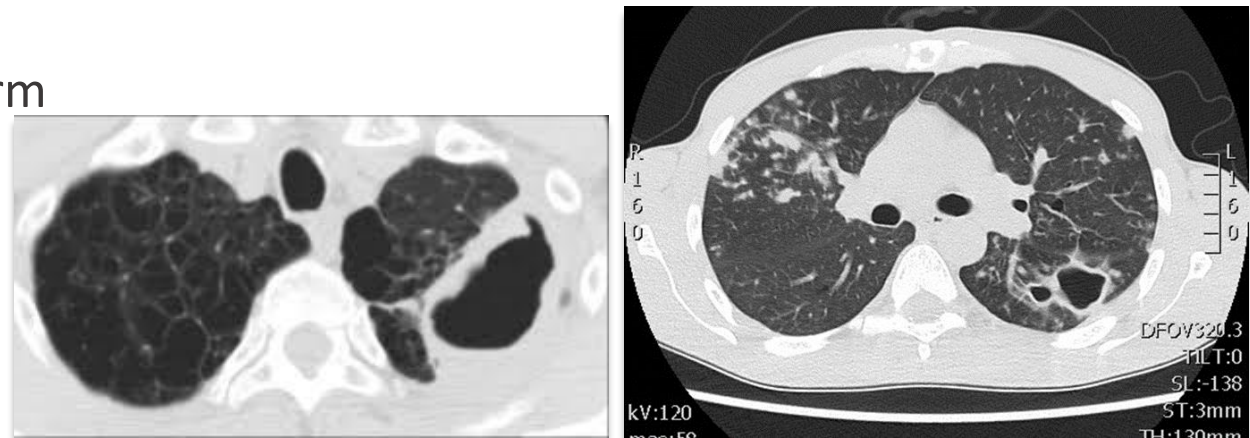
* and appropriate exclusion of other diagnosis

Interpretation of radiographic findings

- Nodular bronchiectatic phenotype



- Cavitory phenotype
 - Fibrocavitary form
 - Cavitory nodular bronchiectatic form



ATS/IDSA diagnostic criteria for NTM lung disease

Clinical symptoms

+

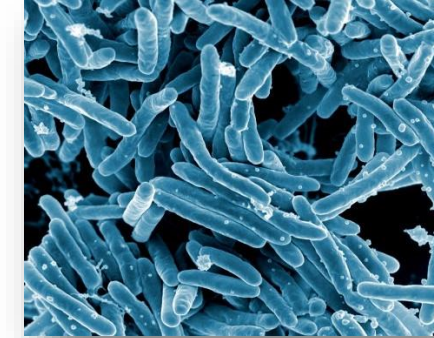
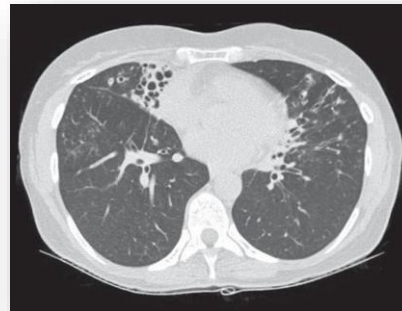
Radiology

+

Microbiology



Cough
Fatigue
Weight loss
Fever/night sweats

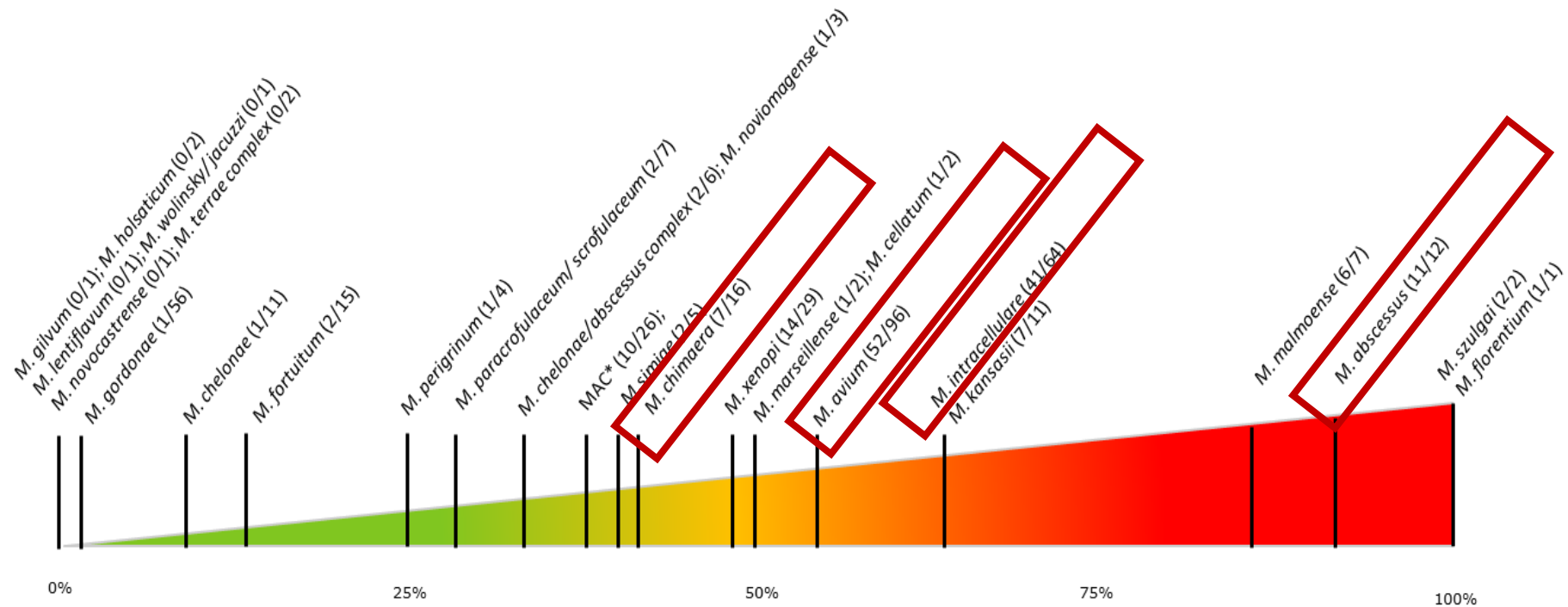


≥2 positive sputum cultures
or
1 positive BAL culture
or
suggestive histology with pos culture

Median time from symptom onset to diagnosis of NTM-PD is 2 years

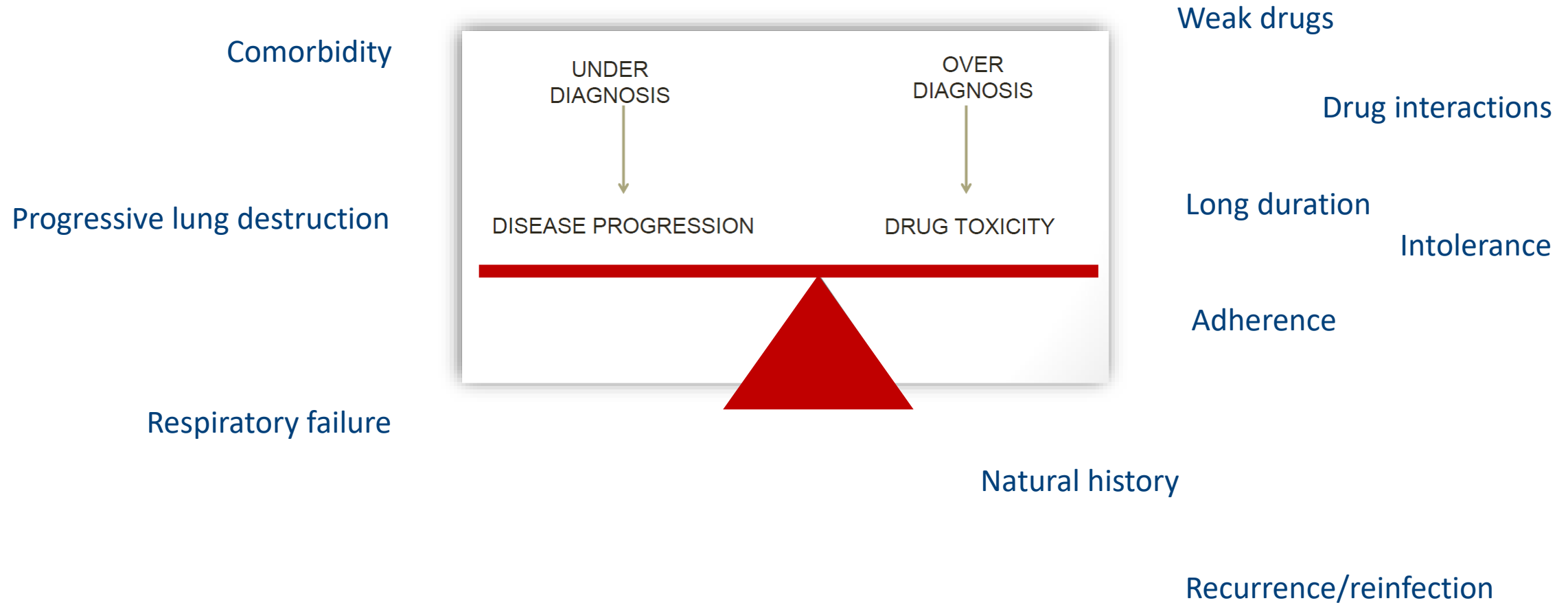
Griffith et al. Am J Respir Crit Care Med 2007

Clinical relevance of respiratory NTM isolates differs by species



Percentage of patients who met diagnostic criteria, per species in 3 reference centres in Belgium

Diagnosis ≠ treatment



Prompt treatment initiation vs 'watchful waiting' approach ?

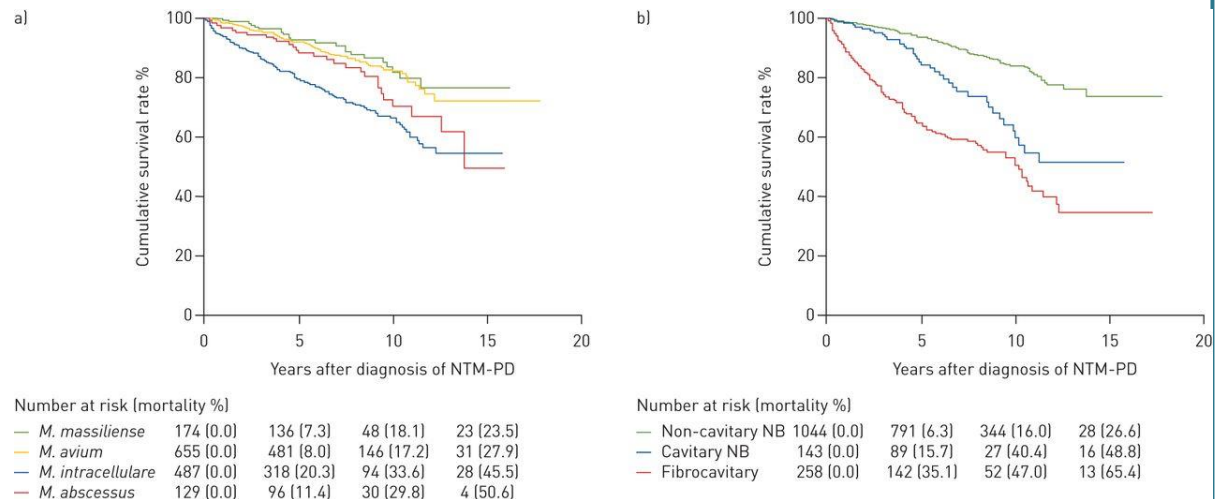
Spontaneous sputum conversion occurs in 15-50% of untreated MAC-PD patients

Unsatisfactory microbiologic treatment success rates (71-85% with guideline-based macrolide-containing regimen)

VS

Elevated morbidity and mortality

Also in non-cavitary disease



Clinical factors to consider prior to starting antimicrobial therapy



Infecting species

- Virulence
- Responsiveness to antibiotic therapy



Individual patient priorities

- Quality of life
- Sign and symptoms of disease
- Adverse effects of therapy
- Benefit of antimicrobial therapy
- Potential for recurrence
- Comorbidities
- Immune suppression



Factors associated with poor prognosis

- Cavitory disease
- High bacillary burden (AFB smear positivity)
- Low BMI
- Young age
- Elevated inflammatory markers

The decision to initiate antimicrobial therapy for NTM lung disease needs to be individualised

Antimicrobial susceptibility testing and NTM lung disease

Drug susceptibility testing of primary isolates and relapse/failure isolates should be performed if the NTM is clinically relevant ^b

CLSI recommends to perform drug susceptibility testing by broth microdilution ^a

M. avium complex

- Clear correlation between macrolide susceptibility of the causative agent and the outcome of treatment with macrolide/ethambutol/rifampin ^{c, d}
- Resistance is defined as a MIC
 - ≥ 32 $\mu\text{g}/\text{mL}$ for clarithromycin
 - ≥ 64 mg/mL for parenteral amikacin
 - ≥ 128 $\mu\text{g}/\text{mL}$ for amikacin liposome inhalation suspension (ALIS)

^a Clinical Laboratory Standards Institute 2018;

^b Daley et al. Clin Infect Dis 2020;

^c Morimoto et al. Ann Am Thorac Soc 2016;

^d Griffith et al. Am J Resp Crit Care Med 2006

Antimicrobial susceptibility testing and NTM disease

M. avium and *M. abscessus* complex

Phenotypic testing (weeks)

Antimicrobial agent	MIC, µg/ml		
	S	I	R
Clarithromycine	≤8	16	≥32
Amikacin (IV)	≤16	32	≥64
Amikacin (liposomal inhaled)	≤64	-	≥128

CLSI Performance standards for susceptibility, 2018

Genotypic testing (hours/days)

rrl mutations (macrolide)

rrs mutations (aminoglycosides)

Inducible macrolide resistance* in *M. abscessus* complex

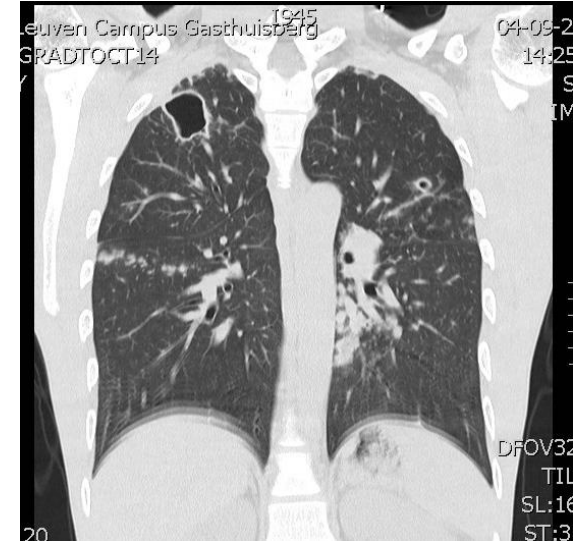
- 14 day incubation
- *erm(41)* gene

Functional *erm(41)* gene confers inducible macrolide resistance

M. kansasii – Rifampicin resistance

M. kansasii pulmonary disease

- “TB light”
- Easy to make treatment decision
 - Cavitory, AFB smear positive disease
- Treatment consists of 12 months REH or REAzi
- Very good treatment outcomes



M. xenopi pulmonary disease

Increasingly common in our region

Difficult to treat – high all-cause mortality

BTS trial RECipro vs REClar = equally ineffective

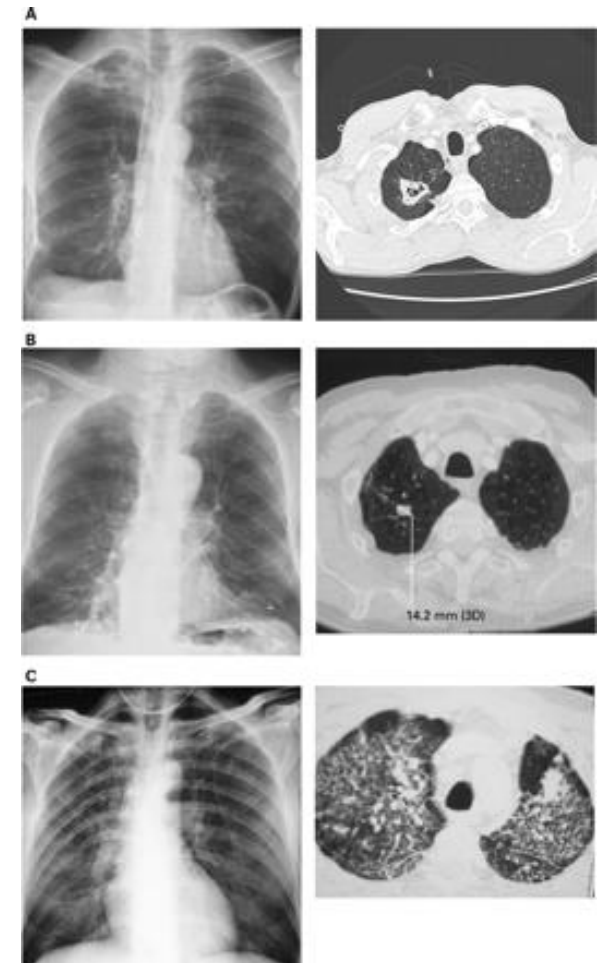
- 12 vs 18% alive and cured after 5 years

Systematic review

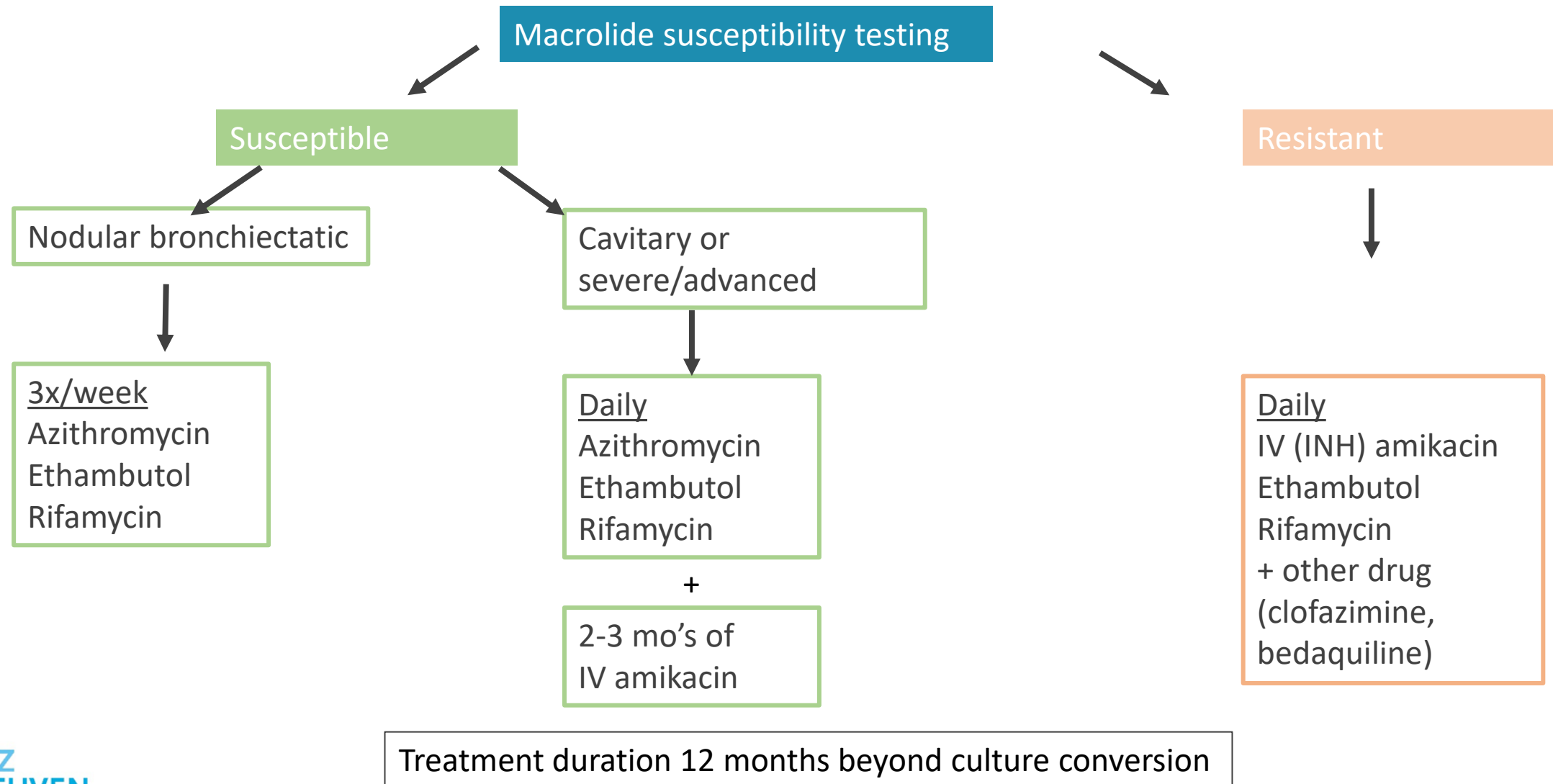
- 65% sustained success rate across different regions

France CaMoMy trial (intermediate results)

- REMox vs REClar = equally performant
- ?? REClar + Mox (4 drugs if severe)



M. avium complex pulmonary disease



M. abscessus complex pulmonary disease

Macrolide susceptibility
? functional *erm(41)* gene
? mutational resistance

M. abscessus ssp *massiliense*

Macrolide susceptible
erm(41) gene non-functional

Macrolide counts as active
drug

M. abscessus ssp *abscessus*
M. abscessus ssp *bolletii*

Inducible macrolide resistance
erm(41) gene functional

Macrolide does NOT count as
active drug

Mutational macrolide resistance
erm(41) functional

Macrolide does NOT count as
active drug

- Initial phase consists of ≥ 3 drugs
- In vitro susceptibility guide inclusion and choice of macrolides and aminoglycosides
- Optimal duration is unclear: recommend expert consultation

Role of surgery in NTM lung disease?

- Adjuvant therapy that may improve outcome
- Carefully selected patients
 - Medication unresponsive (drug resistance, large cavities)
 - Uncontrolled symptoms/hemoptysis
 - Destroyed lung
- Safe but potential complications
 - Mortality rate: 0-6.9%
 - Post-operative complications (5-32%), mainly due to bronchopleural fistula
- Expertise



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

Charles L. Daley,^{1,2a} Jonathan M. Iaccarino, Jr.³ Christoph Lange,^{4,5,6,7a} Emmanuelle Cambau,^{8,a} Richard J. Wallace,^{3,a} Claire Andrejak,^{16,11} Erik C. Böttger,¹² Jan Brozek,¹³ David E. Griffith,¹⁴ Lorenzo Guglielmetti,^{4,15} Gwen A. Huitt,¹² 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. Winthrop²⁵

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Daley et al. Clin Infect Dis 2020;
Daley et al. Eur Resp J 2020

Lange et al. Lancet Infect Dis 2022

Consult the guidelines!

Review

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 goodii*, *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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This online publication has been corrected. The corrected version first appeared at [thelancet.com/infection](https://www.thelancet.com/infection) on February 3, 2022

*Members listed in the appendix
Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany (Prof C Lange MD); German Center for Infection Research (DZIF), Respiratory Medicine & International Health,

Take home messages – pulmonary NTM disease

NTM isolation in respiratory sample \neq lung disease

Think of NTM when unexplained (respiratory) symptoms, predisposing comorbidity

(Sub)species identification is fundamental to guide treatment regimen and response rate

NTM management entails more than just antimicrobial therapy

NTM therapy is complex and can be challenging

Consult the NTM guidelines

Request expert advice

National multidisciplinary NTM consilium

