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Introduction to nontuberculous mycobacteria (NTM)

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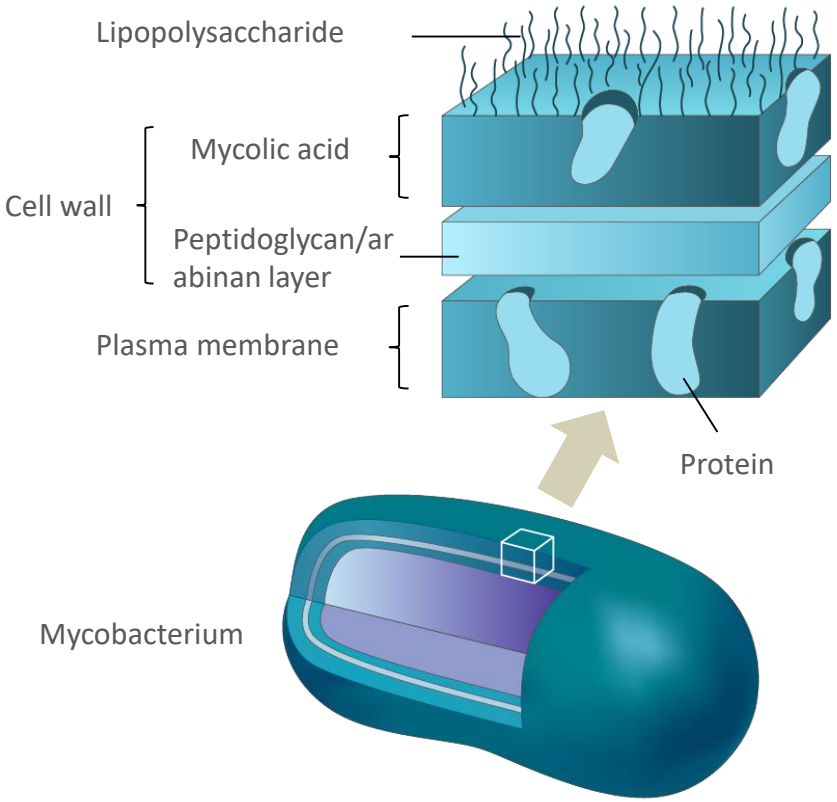
NTM definitions

- ***Nontuberculous mycobacteria*** (NTM): mycobacterial species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*
- Also known as:
  - atypical mycobacteria
  - opportunistic mycobacteria
  - mycobacteria other than tuberculosis (**MOTT**)
  - environmental mycobacteria
- Like MTb they are **acid-fast bacilli** (AFB)

NTM general features (i)

- **Waxy, hydrophobic, triple-layered cell wall** that renders them unusually resistant to varied physical conditions and chemical agents
- Can make use of a **wide variety of carbon and nitrogen sources** and can survive in nutrient-poor environments
- Optimal growth temperatures vary and may influence distribution
  - MAC are often isolated from potable hot-water sources
  - *M. marinum* is found in the cooler water of fish tanks



NTM general features (ii)

- Can be found in the **environment** (soil, dust, and water)
- Can form difficult-to-eliminate **biofilms**
- Opportunistic pathogens of humans and animals (less virulent than *Mtb)*
- As of 2015: >172 different species with distinct virulence features
- Can be classified according to the growth rate in:
  - **RGM**, rapid-growing mycobacteria
  - **SGM**, slow-growing mycobacteria

NTM general features (iii)

NTM	Mycobacterium tuberculosis
Not obligate pathogens – normally live free in the environment	Obligate pathogens: require host
Low virulence: not usually pathogenic in the absence of predisposing conditions	Pathogenic
Human-to-human transmission extremely rare, but some evidence of this in the cystic fibrosis community	Human-to-human transmission
Infection rates increasing, especially in developed countries	Infection rates decreasing, especially in developed countries
Large heterogeneous group of species	Mycobacterium tuberculosis complex contains small group of closely related subspecies

NTM and *Mycobacterium tuberculosis* differ in terms of pathogenicity, infection rates and transmission routes

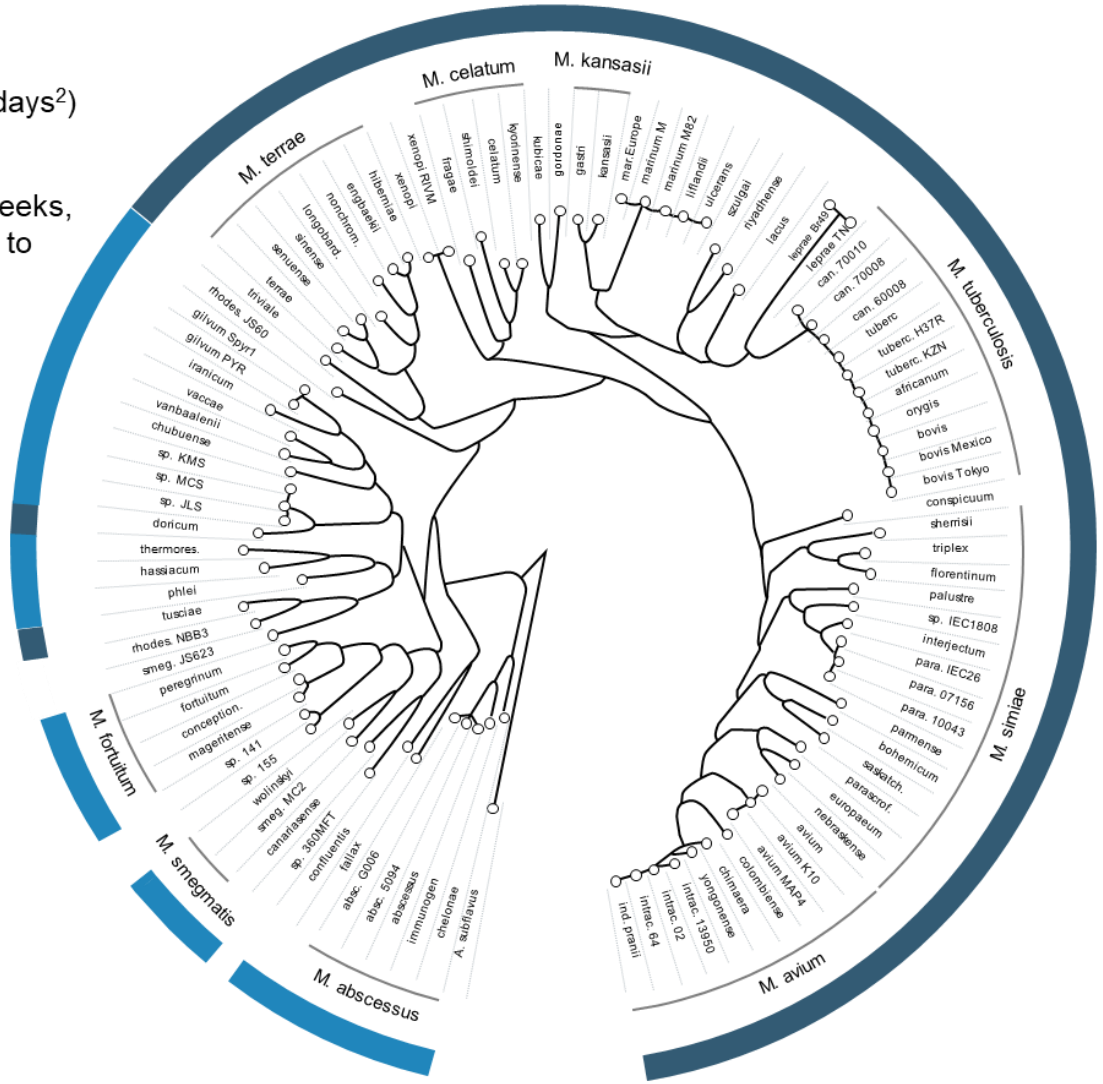
Runyon classification

Rapidly growing nontuberculous mycobacteria (RGM)		*M. fortuitum*
		M. chelonae
		M. abscessus complex (*M. massiliense, M. bolletii*, and *M. abscessus sensu stricto*)
Slowly growing nontuberculous mycobacteria (SGM)	**Photochromogens** (produce a yellow-orange pigment when exposed to light)	*M. kansasii*
		M. marinum
	Scotochromogens (produce a yellow-orange pigment regardless of whether they are grown in the dark or the light)	*M. gordonae*
		M. scrofulaceum
	Nonchromogens (never produce pigment, regardless of culture conditions)	*M. avium* complex *(M. avium, M. intracellulare, M. chimaera)*
		M. terrae complex
		M. ulcerans
		M. xenopi
		M. simiae
		M. malmoense
		M. szulgai

Classification based on genotyping

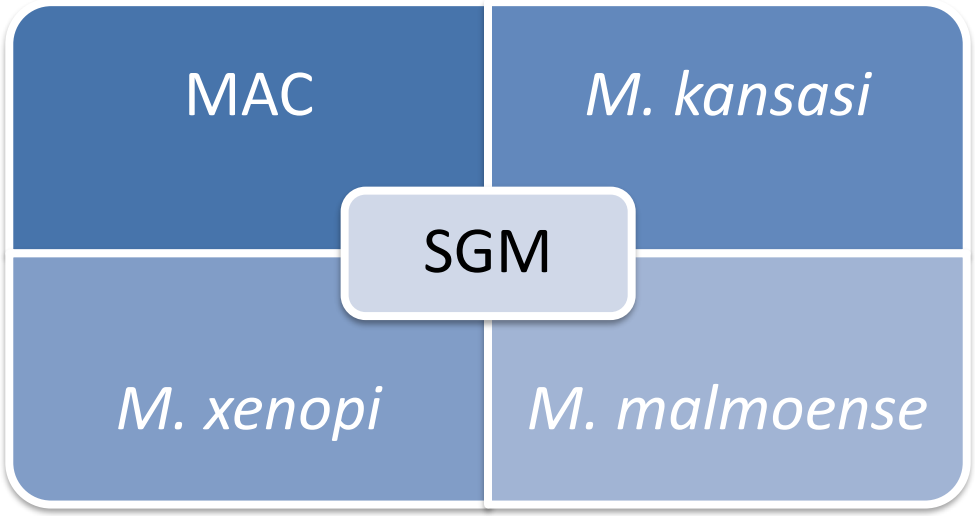
Growth rate

- Rapid (usually 7-10 days[2])
- Slow (usually 1-3 weeks, sometimes up to 8 weeks[2])



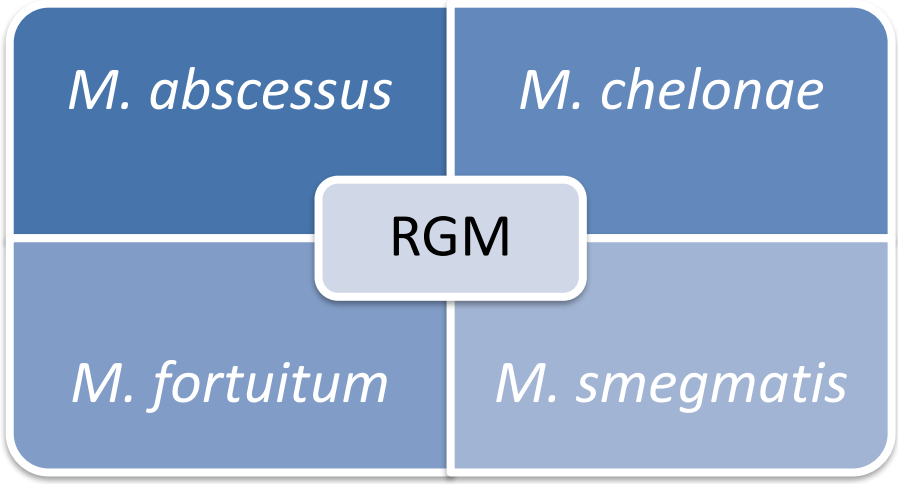
Slow Growing Mycobacteria - SGM

- **Special mycobacterial media** (Lowenstein-Jensen, Middlebrook) are required, usually necessary 2-3 weeks to grow
- **Dosing** schedules for SGM antimicrobial agents can be 3 times/week, commensurate with the long replication times
- Daily dosing for severe disease



Rapid Growing Mycobacteria - RGM

- Can grow on standard microbiologic media (**avg 7 days**)
- **Dosing** schedules for RGM antimicrobial agents are **more frequent**, commensurate with the relatively shorter replication times
- Therapy of the RGM typically involves agents without activity against other mycobacterial pathogens
- RGMs commonly elicit a **weakly granulomatous tissue response** or a frankly dimorphic reaction (a combination of granulomatous and/or pyogenic features)



Epidemiology (i)

- **Asymptomatic infections** with NTM are common in humans and are probably acquired most often from childhood contact with soil, water, and possibly animals (Skin test positive for MAC in 40% of HCWs from the US)
- Since latent infection is not a recognized characteristic of NTM, most symptomatic infections are thought to represent recent exposure
- **Environmental exposures** are assumed to cause most symptomatic infections
- Documented cases related to **nosocomial outbreak and surgical procedures**

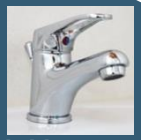
Clinical category	*Mycobacterium avium*	Rapid growers[a]	*Mycobacterium xenopi*	*Mycobacterium kansasii*	*Mycobacterium gordonae*	Other NTM[b]
Disseminated infection in immuno-compromised patients	++					+
Respiratory tract colonization/infection	+	+++	+			
Infections related to hemodialysis		++				
Peritonitis associated with CAPD		++		+	+	+
Injection associated cutaneous and joint infections		++		+		
Intravascular catheter infections	+	++				+
Surgical infections		+++			+	+
Prosthetic valve endocarditis and disseminated disease						

M. chimaera +

Von Reyn et al. *International Journal of Tuberculosis and Lung Disease* 2001
Philips et al. *Clinical Infectious Diseases* 2001
van Ingen et al. *The Lancet Inf Dis* 2017

Epidemiology (ii)

Natural water sources



Drinking water distribution systems (biofilm formation)

Hot tubs and spas

Acidic, brown-water swamps

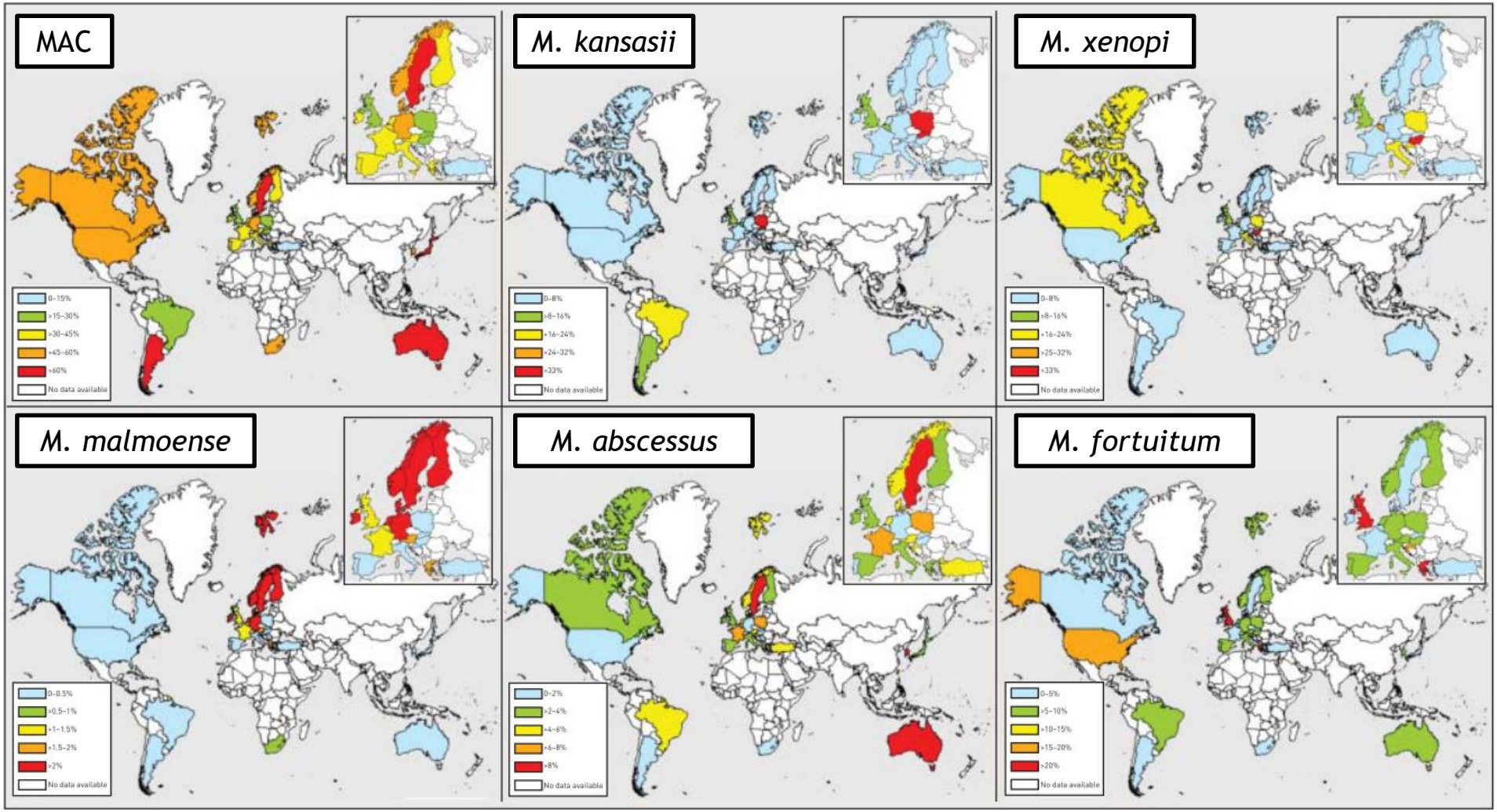
Potting soils

Boreal forest soils and peats

Metal removal fluid systems

NTM habitats are intimately shared with those of humans

Epidemiology (iii)

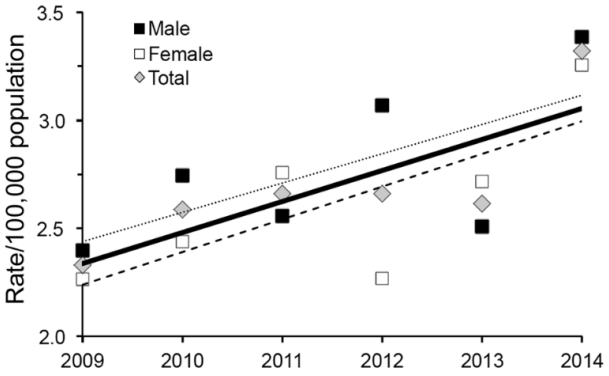


Heofsloot et al. *ERJ* 2013

Increasing prevalence (i)

- **Growing prevalence** of NTM-LD
- In Western countries now more prevalent than *Mtb*

Germany 2014



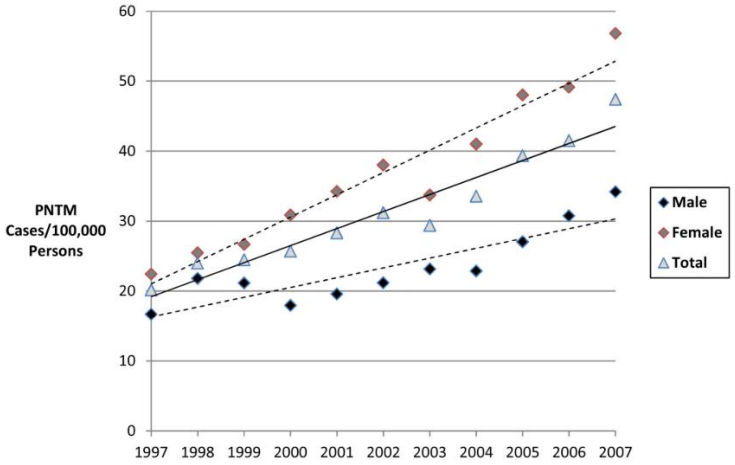
Germany 2016

Estimation	Incidence		
	No. (%)	Rate[a]	Mean age
Coded NTM-PD	50 (0.002)	1.56	66.4
No coded NTM-PD	440 (0.014)	13.77	67.0
Coded and non-coded NTM-PD	490 (0.015)	15.33	67.0

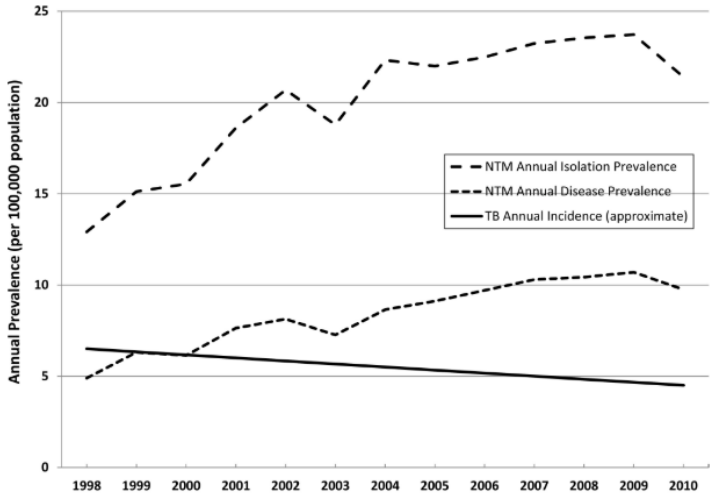
Estimation	Prevalence		
	No. (%)	Rate†	Mean age
Coded NTM-PD	121 (0.004)	3.79	65.8
No coded NTM-PD	488 (0.015)	15.27	67.2
Coded and non-coded NTM-PD	609 (0.019)	19.05	67.0

NTM-PD, nontuberculous mycobacterial pulmonary disease.
[a] Rate per 100,000 population.

US



Canada



Ringshausen et al. *EID* 2016
Ringshausen et al. *IJID* 2021
Prevost & Marras. *Clinics in Chest Medicine* 2015

Increasing prevalence (ii)

- Reasons for increasing prevalence:
  - Increased awareness of the disease
  - Improved diagnostic techniques
  - Ageing population
  - Increasing number of immunosuppressed individuals
  - Decrease of cross protection due to previous *MTb* infections

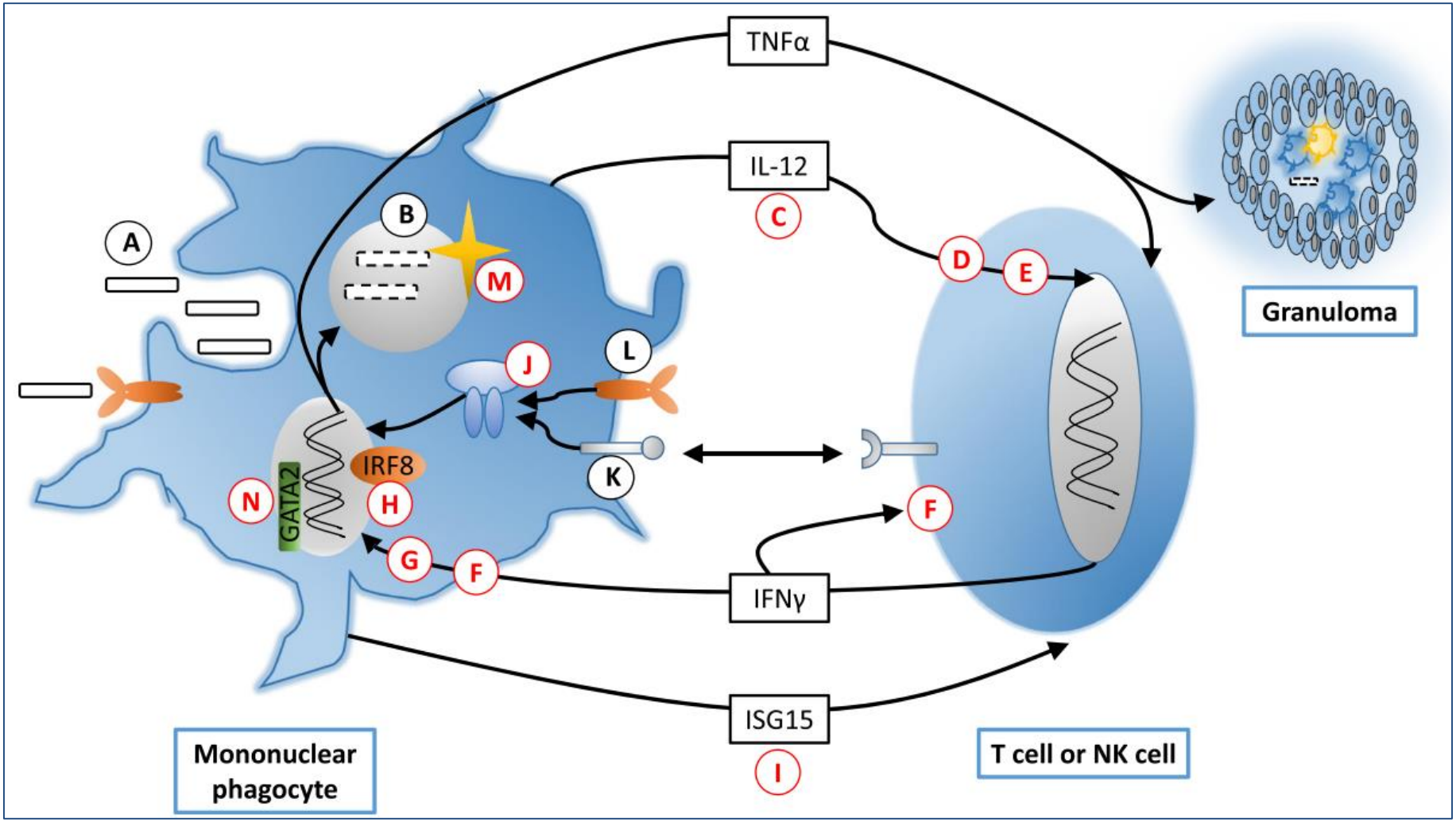
- Nonetheless, NTM infection rates may be **underestimated**

Risk factors (i)

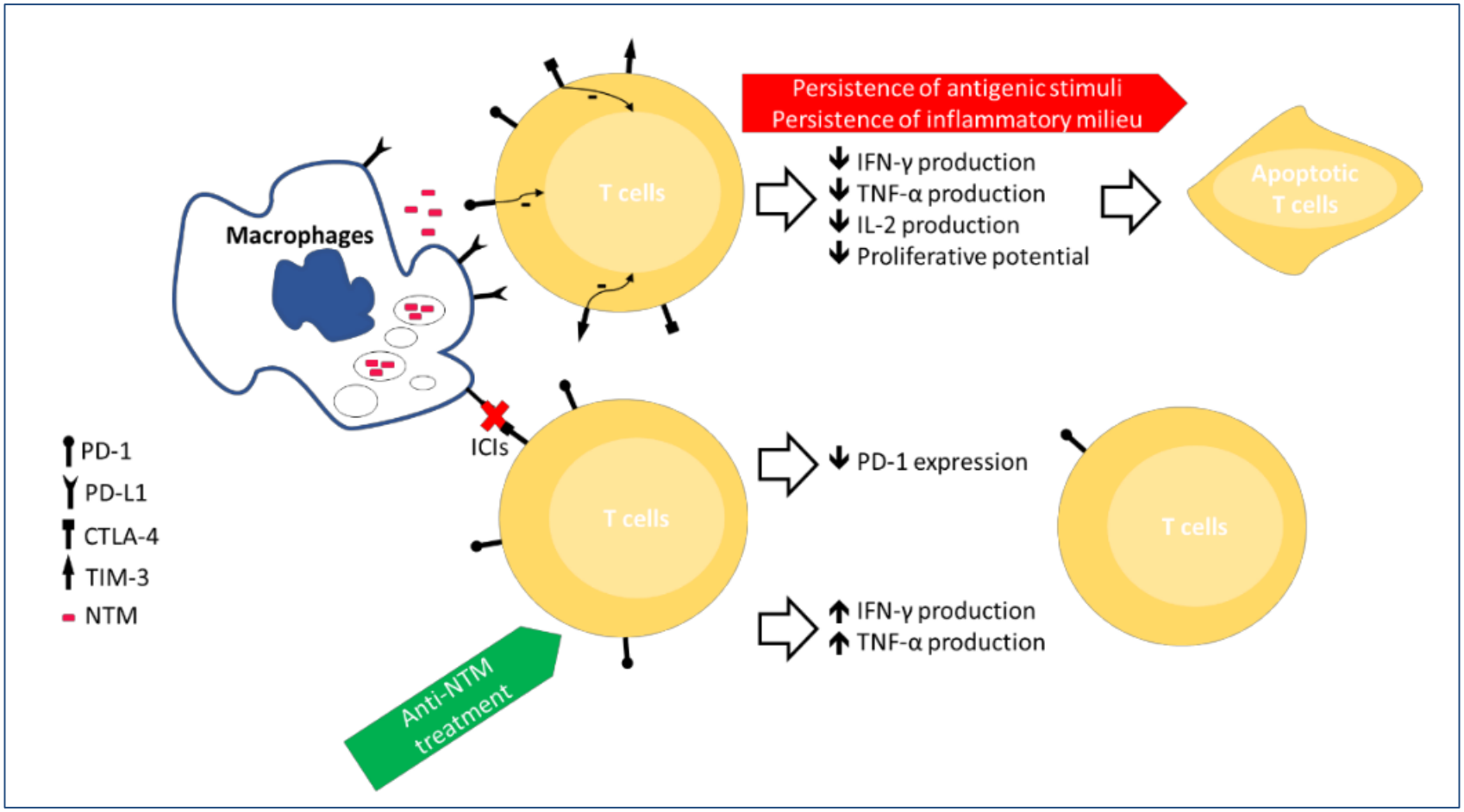
Disease	Tests	Evidence linking to NTMLD
Bronchiectasis, COPD, silicosis, pneumoconiosis, previous TB	HRCT	Cohort studies [24, 30], prevalence studies [22, 23, 26–28], case series [25, 29]
Cystic fibrosis	Sweat chloride, CFTR genotyping	Cohort studies [33], case–control studies [34–39], prevalence studies [40–45]
GORD	24-h pH monitoring (and other diagnostic tests)	Two prevalence studies [46, 47]
Deficiencies in IFN-γR1, IFN-γR2, IL-12, IL-12R	Tests of IFN-γ production in response to mycobacterial antigens, other specialised immunological tests, genotyping	Case reports and series [48–52]; no evidence for isolated lung disease
STAT1 deficiency	Tests of cellular response to exogenous IFN	Case reports [53, 54]; no evidence for isolated lung disease
Chronic granulomatous disease	Tests of neutrophil function (*e.g.* nitroblue tetrazolium)	One case report [55]
HLA types associated with NTM disease	HLA genotyping	One prevalence study [56], one cohort study [57]
SLC11A1 polymorphisms	SLC11A1 genotyping	One case series [58]
CFTR heterozygosity	CFTR genotyping	Prevalence studies [59, 60], one case–control study [61]
α_1-AT deficiency	Serum α_1-AT	No direct evidence
VDR polymorphisms	VDR genotyping	One case series [62]
Vitamin D deficiency	Serum vitamin D	No direct evidence
Coeliac disease	Coeliac autoantibodies and serum IgA	No direct evidence
HIV infection	HIV serology	Cohort studies [63], prevalence studies [64], case series [23, 65–68]
Inhibitory anti-IFN-γ antibodies	Anti-IFN-γ antibodies	One case series [69]

Sexton et al. *ERJ* 2008

Risk factors (ii)



Risk factors (iii)



Clinical manifestations (i)

Pulmonary disease[1,2]

Predisposing lung conditions[1,3]

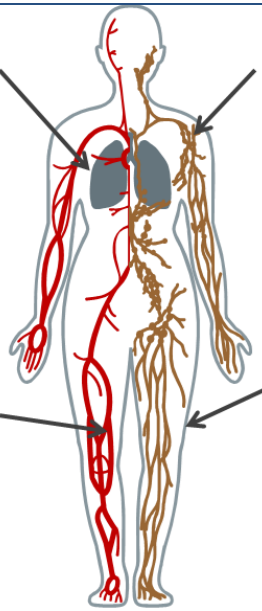
Predisposing genetic factors[4]

Situational (hypersensitivity pneumonitis)[2,3]

The lung is by far the most frequent disease site[1]

Disseminated disease[1,2]

Most commonly seen in association with profound immunosuppression, e.g. HIV infection[2,3]



Lymphatic disease[1,2]

Typically an infantile disease affecting cervical lymph nodes[2]

Also in adults with HIV infection[1]

Skin/soft tissue disease[1,2]

The most common sources include:

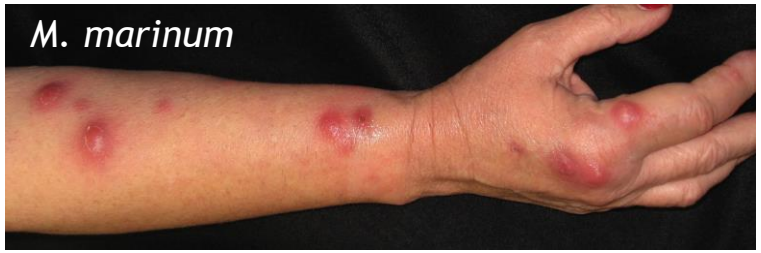
- contact with contaminated water or infected fish[2]
- traumas and surgical wounds[2]

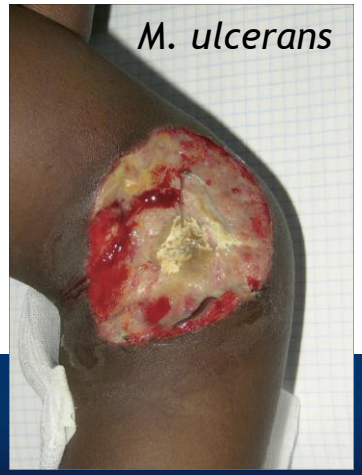
Nosocomial infections have been described[3]

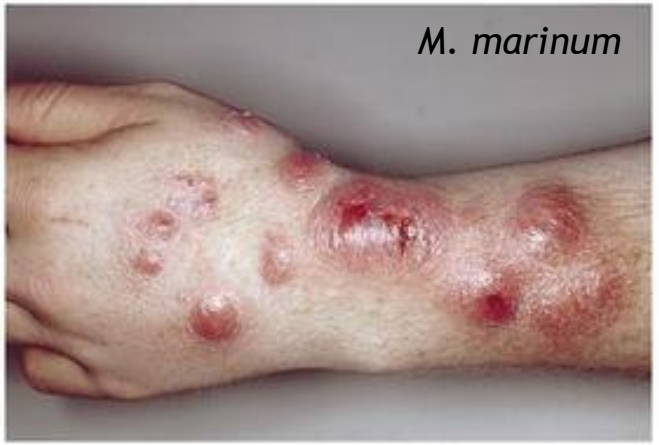
Species	Growth on Solid Media	Environmental Reservoir	Patterns of Disease[a]			
			Cutaneous	Pulmonary	Disseminated	Other
M. avium	Slow	Hot water systems, natural water, soil	–	++	+++	Lymphadenitis
M. intracellulare	Slow	Hot water systems, natural water, soil	–	+++	+	Lymphadenitis
M. kansasii	Slow	Potable and natural water	–	+++	++	–
M. abscessus, *M. chelonae*, *M. fortuitum*	Rapid	Potable and natural water, soil	++	+	–	Sporotrichoid spread
M. marinum	Slow	Fish tanks, salt water	++	–	–	Sporotrichoid spread
M. ulcerans	Slow	Natural water	++	–	–	"Buruli ulcer," osteomyelitis

Clinical manifestations: cutaneous disease

- Can cause a variety of cutaneous disease syndromes when inoculated directly
- Associated with localized or disseminated cutaneous disease in immunosuppressed patients
- ***M. abscessus*, *M. fortuitum*, *M. chelonae*, *M. marinum*,** and ***M. ulcerans*** are the most commonly involved species
- Lesions may be single, or the infection may spread proximally up the lymphatics, producing additional nodules (**sporotrichoid spread**)
- In compromised host possible bacteremic spread
- Clinical suspicion: **chronicity** + **absence of bacterial growth** on routine culture + **failure to respond to standard antibacterial therapy**
- Biopsies**: granuloma formation** + **positive acid-fast stains**



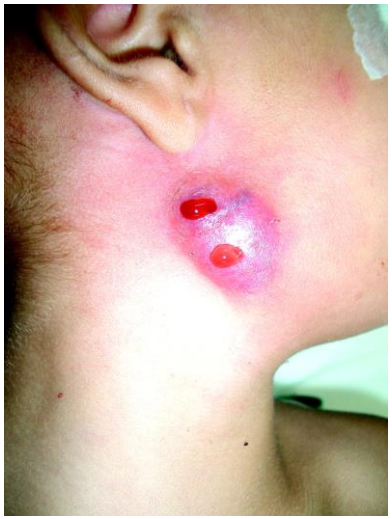


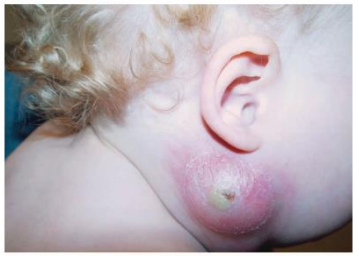


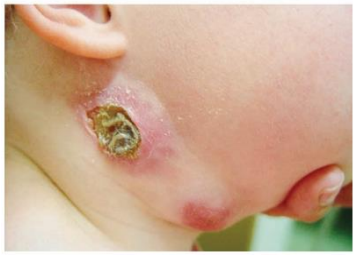
Nguyen. NEJM 2004
Sizaire et al. Lancet ID 2006
Schwendiman et al. Derm Online Journ 2009

Clinical manifestations: lymphatic disease

- **Lymphadenitis** is the most common manifestation of NTM disease in otherwise healthy children
- Mainly caused by MAC or *M. kansasi*
- Usually occurs in immunocompetent children between one and five years of age and involves the **cervicofacial lymph nodes**
- Unilateral, nontender node that slowly enlarges over several weeks, during which fluctuance, violaceous discoloration, thinning of the overlying skin, and sinus drainage may develop
- **Diagnosis**: detection of NTM with culture or PCR assay of fistula drainage, tissue, or caseous material
- Management:
  - Surgical excision without ATB therapy if feasible
  - ATB therapy (AZT, CLT, ETB, RIB, RIF)







Esparcia et al. *Journ Clin Micro* 2008
Lindeboom et al. *CID* 2007

Clinical manifestations: disseminated disease

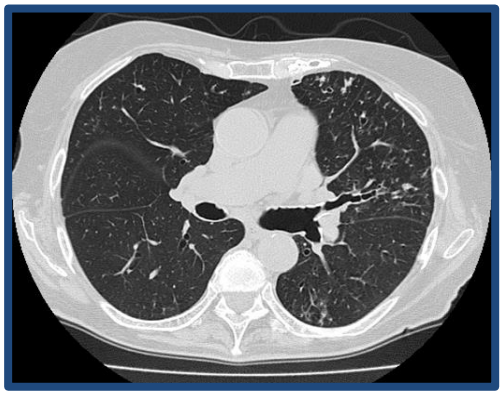
- At risk those immunocompromised:
  - PLWH
  - SOT/HSCT
  - Lymphoma/leukemia
  - Anti-TNF-α therapy
  - IFN-γ deficit
- **Signs/symptoms**:
  - Fever
  - Weight loss
  - Fatigue
  - Hepatosplenomegaly or lymphadenopathy
  - ↑ ALP, anemia

- ***M. avium*** and ***M. kansasii*** are the species most commonly isolated
- Widespread presence of **foamy macrophages with AFB**, which may be demonstrated in biopsy samples of bone marrow, intestine, or liver
- **Granulomas are typically absent** in patients with impaired cellular immunity
- Positive mycobacterial blood-culture

Clinical manifestations: pulmonary disease (i)

- Most frequent manifestation
- Diagnosis hampered by:
  - Variability in clinical and radiologic manifestations
  - Frequent presence of significant prior pulmonary disease
  - Isolation of NTM from the sputum may represent harmless colonization of the lower respiratory tract
- Signs and symptoms:
  - **Chronic cough** with/without sputum
  - Dyspnoea
  - **Fatigue**
  - Fever is unusual
- Heterogenous radiologic pattern

Clinical manifestations: pulmonary disease (i)



Nodular/bronchiectatic

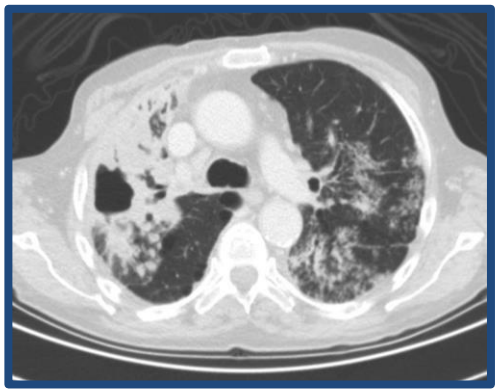
"Lady Windermere syndrome"

Epidemiology
- Postmenopausal females[1]
- Scoliosis, mitral valve prolapse, low BMI[1,2]
- No pre-existing lung disease[2]

Clinical course
- Prolonged cough, fatigue, weight loss[1]

Microbiology (classical)
- Low yield of Ziehl-Neelsen positive sputum culture - should repeat or use BAL[4]

Radiology
- Bronchiectasis with nodules "tree-in-bud" appearance[1]
- Middle lobe and lingula worst affected[1,2]



Fibrocavitary

Epidemiology
- Mostly males[1]
- Middle-aged (late 40s-early 50s)[1]
- Pre-existing COPD, silicosis, fibrosis[3]

Clinical course
- Tuberculosis-like, but slower[4]

Microbiology (classical)
- Often Ziehl-Neelsen positive sputum[4]
- High yield of culture[4]

Radiology
- Fibro-cavitary lesions, upper lobes[3]

Diagnosis: NTM-LD

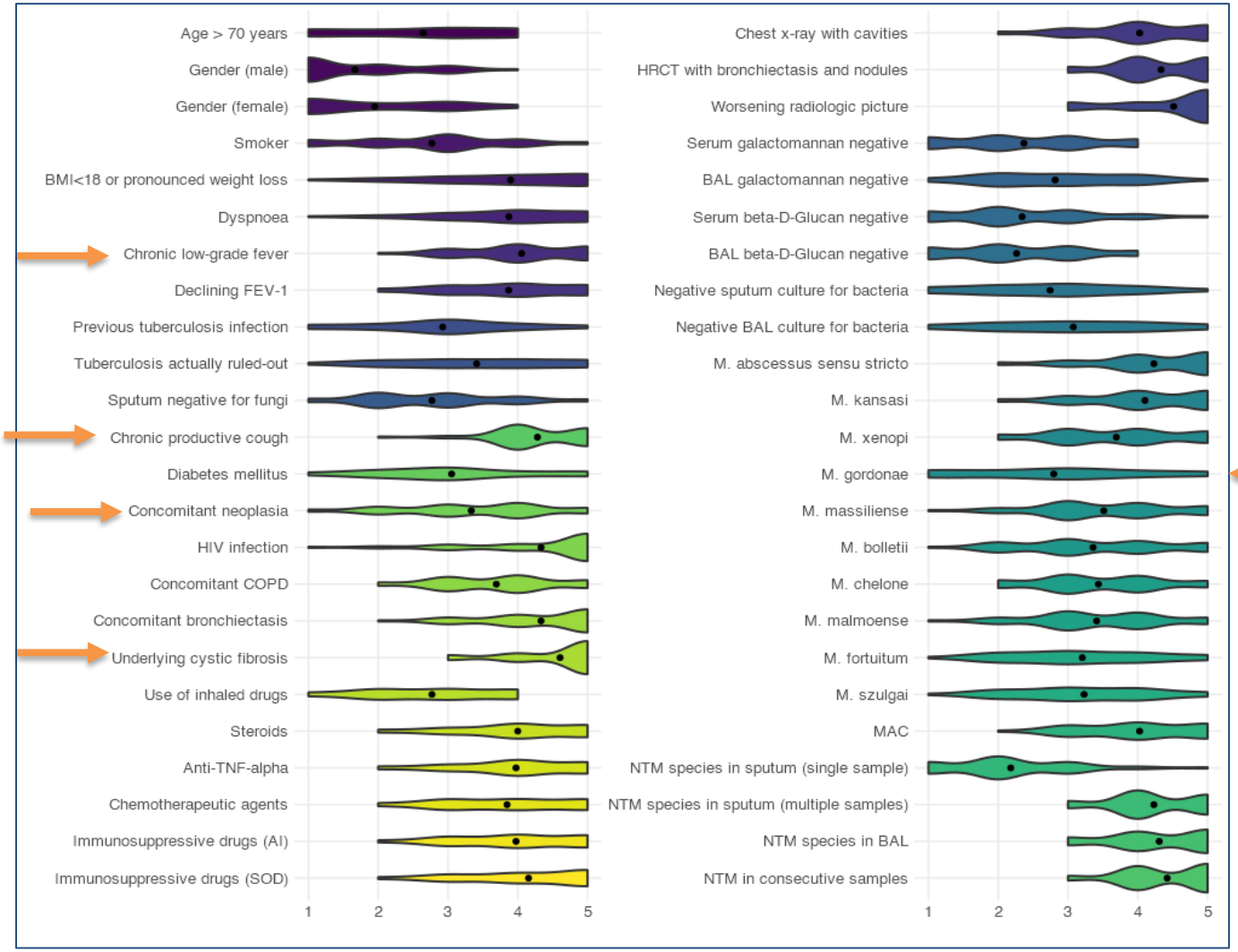
Table 2. Clinical and Microbiologic Criteria for Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease[a]

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	

- Expert consultation should be obtained when NTM are recovered that are either **infrequently encountered** or that usually represent environmental contamination.
- Patients who are suspected of having NTM pulmonary disease but do not meet the diagnostic criteria should be **followed until the diagnosis is firmly established** or excluded.
- Making the diagnosis of NTM pulmonary disease **does not per se, necessitate the institution of therapy**, which is a decision based on the potential risks and benefits of therapy for individual patients.

Dailey et al. *CID* 2020

Diagnosis: NTM-LD (ii)



AST in NTM-LD treatment

Mycobacteria	Susceptibility-based treatment	Breakpoint
MAC	CLT	>= 32 ug/mL
	AMK ev	>= 64 ug/mL
	Lyposomal AMK (ALIS)	>= 128 ug/mL
M. kansasii	RIF	>= 2 ug/mL
	CLT	>= 32 ug/mL
M. abscessus	AMK	>= 64 ug/mL
	AZT*	>= 64 ug/mL
	CLT*	>= 8 ug/mL
	LNZ	>= 32 ug/mL

- For macrolides, a 14-day incubation and/or sequencing of the erm(41) gene is required in order to evaluate for potential inducible macrolide resistance

Daley et al. *CID* 2020

Treatment: MAC-LD

Organism	No. of Drugs	Preferred Drug Regimen[a]	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)[b]	Daily (3 times weekly may be used with aminoglycosides)
Refractory[c]	≥4	Azithromycin (clarithromycin) Rifampicin (rifabutin) Ethambutol Amikacin liposome inhalation suspension or amikacin IV (streptomycin)[b]	Daily (3 times weekly may be used with aminoglycosides)

Drug	Daily Dosing	Thrice Weekly Dosing	Hepatic Impairment	Renal Impairment
Azithromycin (AZT)	250-500 mg	500 mg	N/A	N/A
Clarithromycin (CLT)	500 mg bid	500 mg bid	N/A	50% dose reduction if CrCl<30 mL/min
Ethambutol (ETB)	15 mg/Kg die	25 mg/Kg die	N/A	Increase dosing interval
Amikacin (AMK iv)	10-15 mg/Kg die	15-25 mg/Kg die	N/A	Increase dosing interval or reduce dose
Amikacin (ALIS)	590 mg	N/A	N/A	N/A

Daley et al. *CID* 2020

Treatment: MAb NTM-LD

Macrolide Susceptibility Pattern				
Mutational[a]	Inducible[b]	No. of Drugs[c]	Preferred Drugs	Frequency of Dosing
Susceptible	Susceptible	Initial phase ≥ 3	*Parenteral (choose 1–2)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2)	
			Azithromycin (clarithromycin)[d]	
			Clofazimine	
			Linezolid	
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[d]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	
Susceptible	Resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2–3)	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
		Continuation phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	
Resistant	Susceptible or resistant	Initial phase ≥ 4	*Parenteral (choose 2–3)*	Daily (3 times weekly may be used for aminoglycosides)
			Amikacin	
			Imipenem (or Cefoxitin)	
			Tigecycline	
			Oral (choose 2–3)	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
		Continuation Phase ≥ 2	*Oral/inhaled (choose 2–3)*	
			Azithromycin (clarithromycin)[e]	
			Clofazimine	
			Linezolid	
			Inhaled amikacin	

Daley et al. *CID* 2020

Treatment: "others" NTM-LD (i)

M. kansasii-pulmonary disease	Antibiotic regimen
Rifampicin-sensitive *M. kansasii*-pulmonary disease	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Isoniazid 300 mg (with pyridoxine 10 mg) daily or Azithromycin 250 mg daily or Clarithromycin 500 mg twice daily Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

M. malmoense-pulmonary disease	Antibiotic regimen
Non-severe *M. malmoense*-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Severe *M. malmoense*-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection or severe symptoms/signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

M. xenopi-pulmonary disease	Antibiotic regimen
Non-severe *M. xenopi*-pulmonary disease (ie, AFB smear-negative respiratory tract samples, no radiological evidence of lung cavitation or severe infection, mild-moderate symptoms, no signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or isoniazid 300 mg (+pyridoxine 10 mg) daily Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
Severe *M. xenopi*-pulmonary disease (ie, AFB smear-positive respiratory tract samples, radiological evidence of lung cavitation/severe infection, or severe symptoms/signs of systemic illness)	Rifampicin 600 mg daily and Ethambutol 15 mg/kg daily and Azithromycin 250 mg daily or clarithromycin 500 mg twice daily and Moxifloxacin 400 mg daily or isoniazid 300 mg (+pyridoxine 10 mg) daily and consider intravenous amikacin for up to 3 months or nebulised amikacin Antibiotic treatment should continue for a minimum of 12 months after culture conversion.

Haworth et al. *Thorax* 2017

Treatment: “others” NTM-LD (ii)

	Number of drugs	Drugs*	Duration of therapy	Comments
M genavense	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (moxifloxacin [once a day]); (clofazimine [once a day]); (amikacin IV [once a day])	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results when available; moxifloxacin or amikacin may be used in cases of intolerance or drug resistance to macrolides, rifamycins, or ethambutol
M malmoense	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (amikacin IV [once a day or three times a week]); (moxifloxacin [once a day]); (clofazimine [once a day])	12 months beyond culture conversion	Low level of evidence; drugs should be selected according to DST results, when available; moxifloxacin or clofazimine can be used in case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol; amikacin should be added for cavitary or severe disease; caution patients about aminoglycoside ototoxicity and nephrotoxicity
M szulgai	≥3	Azithromycin (once a day) or (clarithromycin [twice a day]); rifampicin (once a day); ethambutol (once a day); (moxifloxacin [once a day]); (clofazimine [once a day]); (amikacin IV [once a day or three times a week])	12 months or 12 months beyond culture conversion if treatment with a macrolide, a rifamycin, or ethambutol cannot be used.	Very low level of evidence; drugs should be selected according to DST results, when available; fluoroquinolones (moxifloxacin or levofloxacin), clofazimine, or aminoglycosides (streptomycin or amikacin) can be used in case of intolerance or drug resistance to macrolides, rifamycins, or ethambutol; caution patients about ototoxicity and nephrotoxicity of aminoglycosides
M simiae	≥3	Azithromycin or (clarithromycin); moxifloxacin (once a day); co-trimoxazole (twice a day); clofazimine (once a day); (amikacin IV [once a day or three times a week])	12 months beyond culture conversion	Very low level of evidence; drugs should be selected according to DST results, when available; amikacin should be added for cavitary or severe disease; possible combinations include azithromycin, moxifloxacin, and co-trimoxazole; azithromycin, clofazimine, and amikacin; or azithromycin and moxifloxacin in combination with one or two additional drugs based on DST results with clofazimine and amikacin being the most suitable options
M gordonae†	NA	NA	NA	NA

Overall: scarce evidence, therapy based on susceptibility and clinical experience

Conclusions

- NTM are ubiquitous bacteria leading to disease among immunocompromised patients (but incidence among apparently immunocompetent is growing)
- In children mainly lymphatic disease
- Among adults lung is the most frequently affected organ
- Be aware of their existence to perform the right test and don't miss them
- Therapy is long and complex

https://www.registroirene.it/it/osservatorio-nazionale
https://www.amantum.org/