2019台灣胸腔暨重症加護醫學會夏季會
2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

The clinical significance of **subspecies identification** in managing **NTM-lung disease**

潘聖衛

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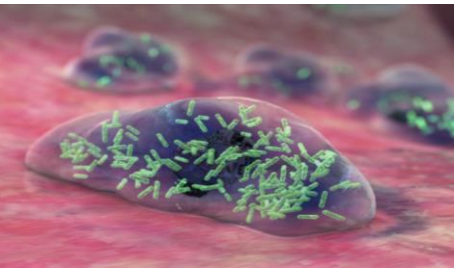


Outline

- NTM history
- NTM lung disease
  - Epidemiology
  - Host and pathogen
- NTM guideline
- Species & subspecies
  - Progression
  - Outcome

- *MAC:*
- *M. avium*
- *M. intracellulare*
- *M. chimaera*

- *MAB:*
- *M. massiliense*
- *M.abscessus*

150 history of NTM

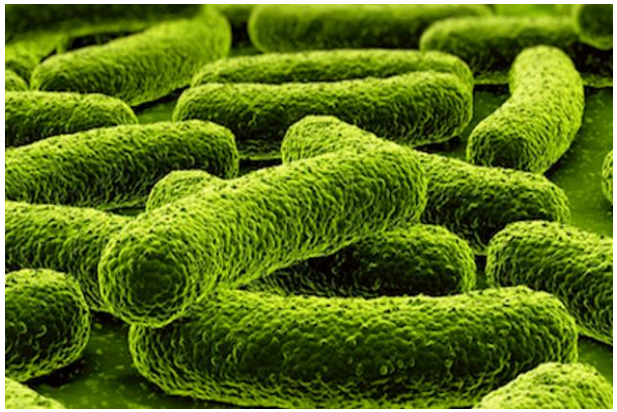
(nontuberculous mycobacterium)

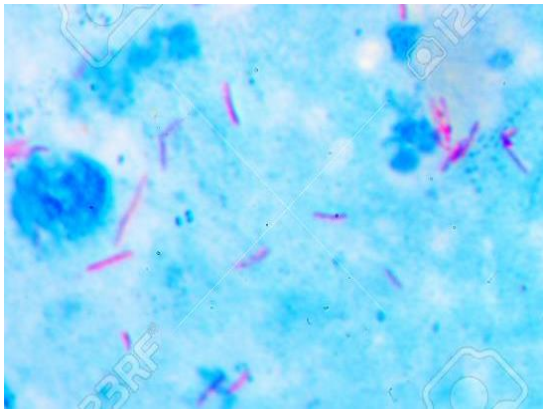
TB in chickens (*M. avium*)	Lab: not Mtb	NTM in human (MAC-lung dz)	US: 1-2% NTM in TB sanatoriums
1868	1890	1930s (1943)	1950s

HIV, ART(-): 20-40% disseminated MAC dz	immuncopentent pt: NTM-lung dz ↗	CF case: *M. abscessus* P-to-Person transmission
1990 report	2000-2010	2016

https://www.nationaljewish.org/conditions/ntm-nontuberculous-mycobacteria/ntm-nontuberculous-mycobacteria-overview/history

Mycobacteria: MTB, NTM





Domain(域/總界): Bacteria
Phylum(間): Actinobacteria
Order(目): Actinomycetales
Family(科): **Mycobacteriaceae**
Genus(屬): ***Mycobacterium***

-M. *tuberculosis* complex
-M. *leprae*

Slowly growing (SGM)

-M. *avium* complex (MAC)
-M. *gordonae* 鳥型分枝桿菌
-M. *kansasii*

Intermediate growth rate

Colony (+) < 7-14 days on agar plate

Rapidly growing(RGM)

-M. *abscessus* group (MAB)
-M. chelonae 膿腫分枝桿菌
-M. fortuitum

Ungrouped

Nontuberculous mycobacteria (NTM)

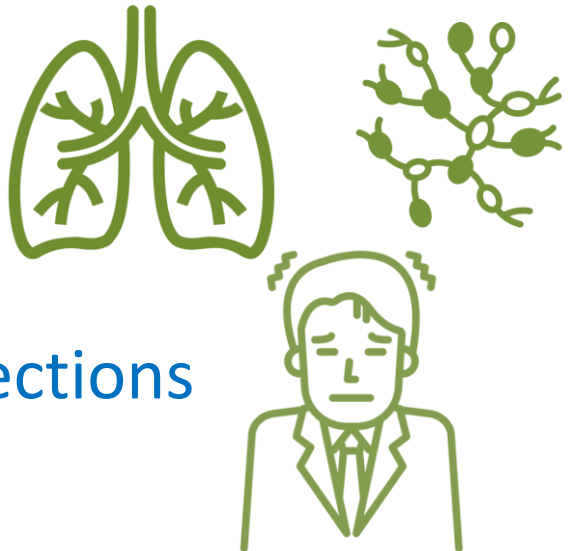
- naturally-occurring organisms,
  - In water & soil, 200 species (differ in pathogenicity)



- NTM are inhaled and cleared from the lungs
  - In most people, do not become ill
  - **In susceptible individuals**

✓Lung, lymph node, SSTI, CNS

✓Catheter-related, disseminated infections



NTM-lung disease (LD)

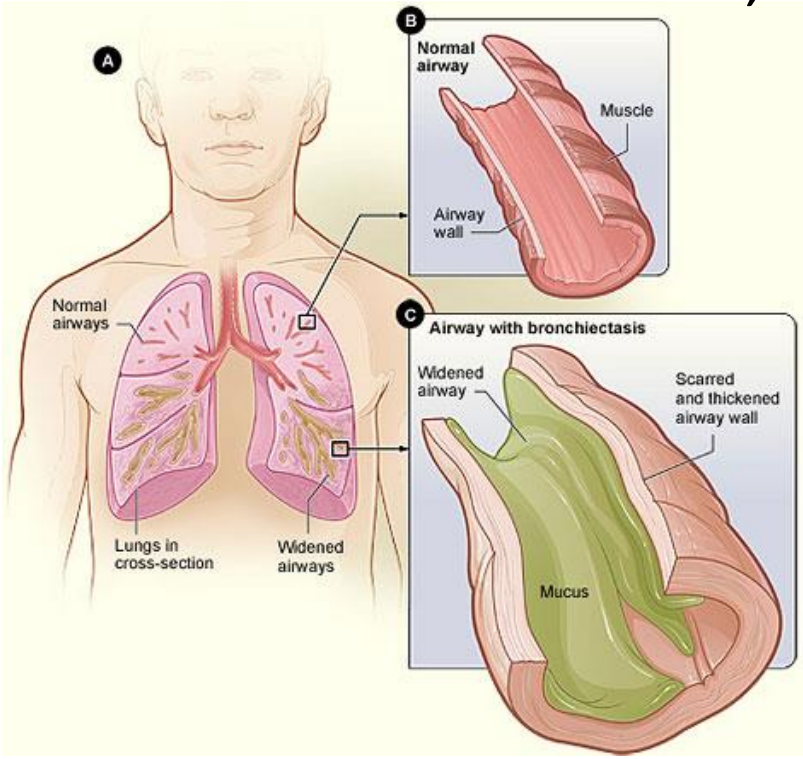
- NTM can cause **progressive inflammatory LD**
  - ✓ structural lung disease, immuno-compromised → NTM-LD
  - ✓ Cough, SOB, hemoptysis, Constitutional symptoms (fatigue/BW loss/ fever/sweats)
  - ✓ M. abscessus or M. malmoense: frequently indicate NTM-LD,

M. *avium* complex (MAC)		**M. *abscessus* group (Mab)**
M. *avium*,		M. *a. abscessus*,
M. *Intracellulare*		M. *a. massiliense*,
M. *chimaera* subspecies		M. *a. bolettii* subspecies

- Also can **transiently, intermittently or permanently** reside within the lungs without causing NTM-PD
  - ✓ asymptomatic infection→ colonization
  - ✓ M. gordonae: contamination or transient colonization

Host susceptibility

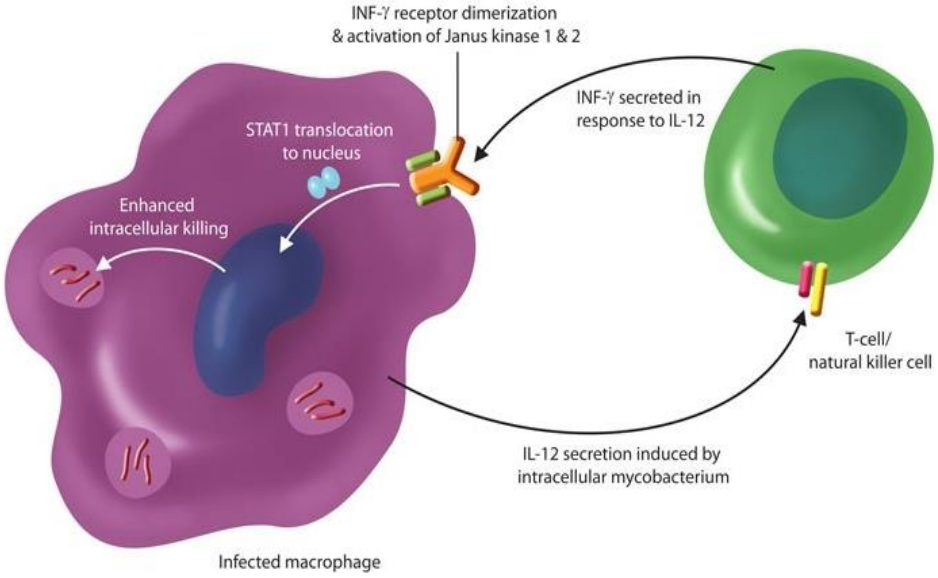
- Pre-existing lung disease
- COPD, cystic fibrosis (CF), non-CF bronchiectasis, ..



✓ Inflammation/impairing mucociliary clearance→ predispose to NTM infection

Chmiel JF, Davis PB - Respir. Res. (2003)

- Immunodeficiency
- low BMI, RA, HIV-AIDS, anti-IFNγ antibodies

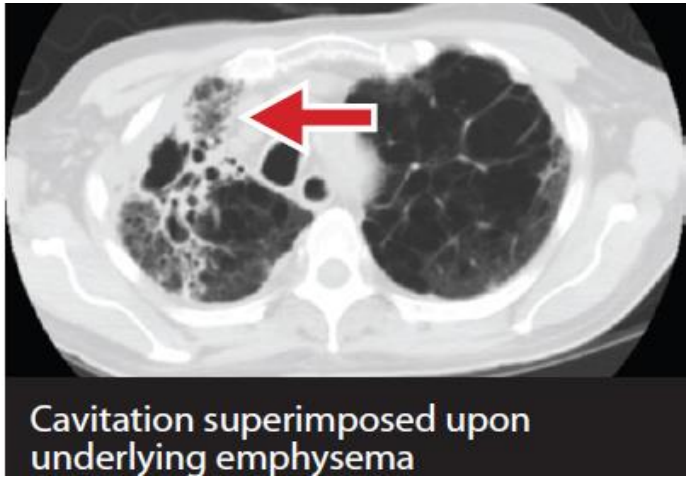


- ICS; anti-TNF α therapy, transplantation, cancer

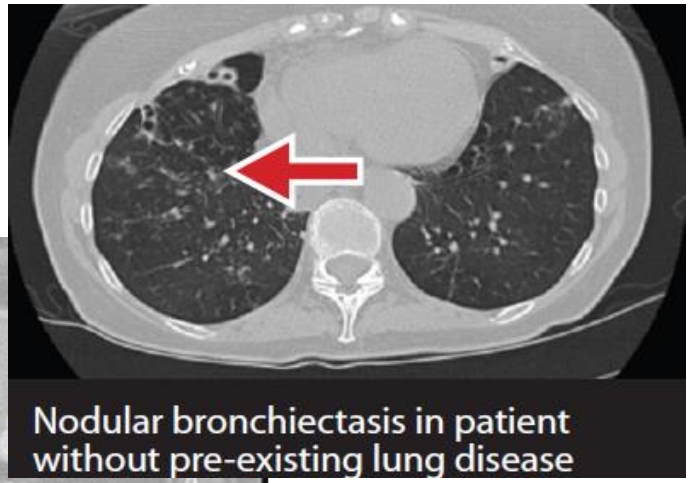
✓ Immune survey if disseminated NTM infection, Recurrent, persistent, severe NTM-PD,

NTM-PD radiographic characteristics

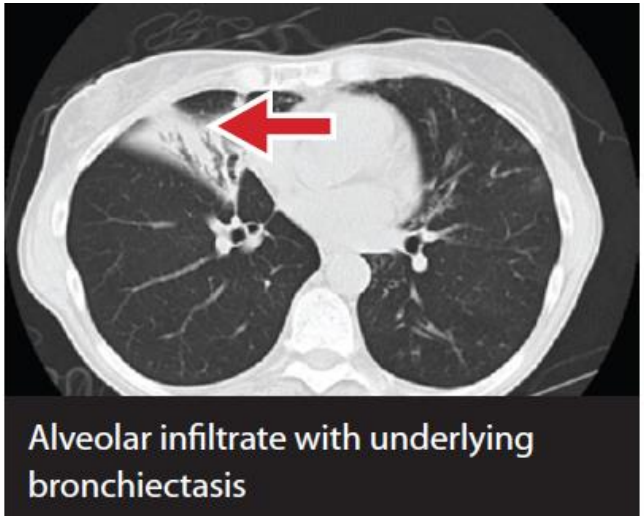
- **Fibro-cavitary (FC)**
  - ✓ commonly mistaken for PTB
  - ✓ often in current/ex-smokers
  - ✓ often smear-positive samples
- **Nodular bronchiectatic (NB)**
  - ✓ often in women without previously lung disease
  - ✓ paucibacillary samples (diagnostic uncertainty)



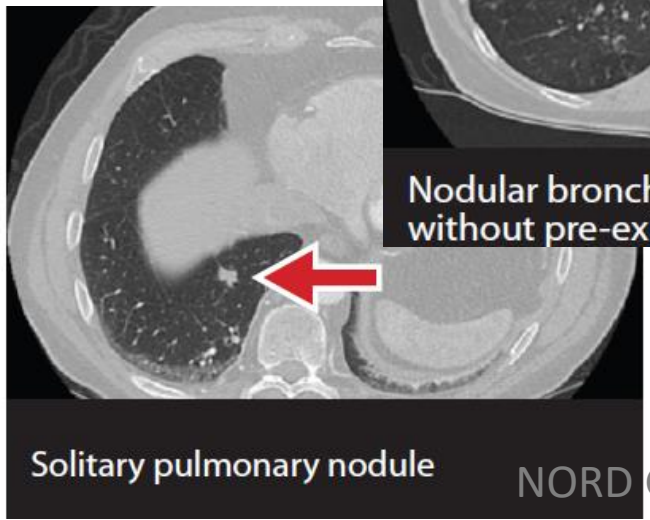
Cavitation superimposed upon underlying emphysema



Nodular bronchiectasis in patient without pre-existing lung disease



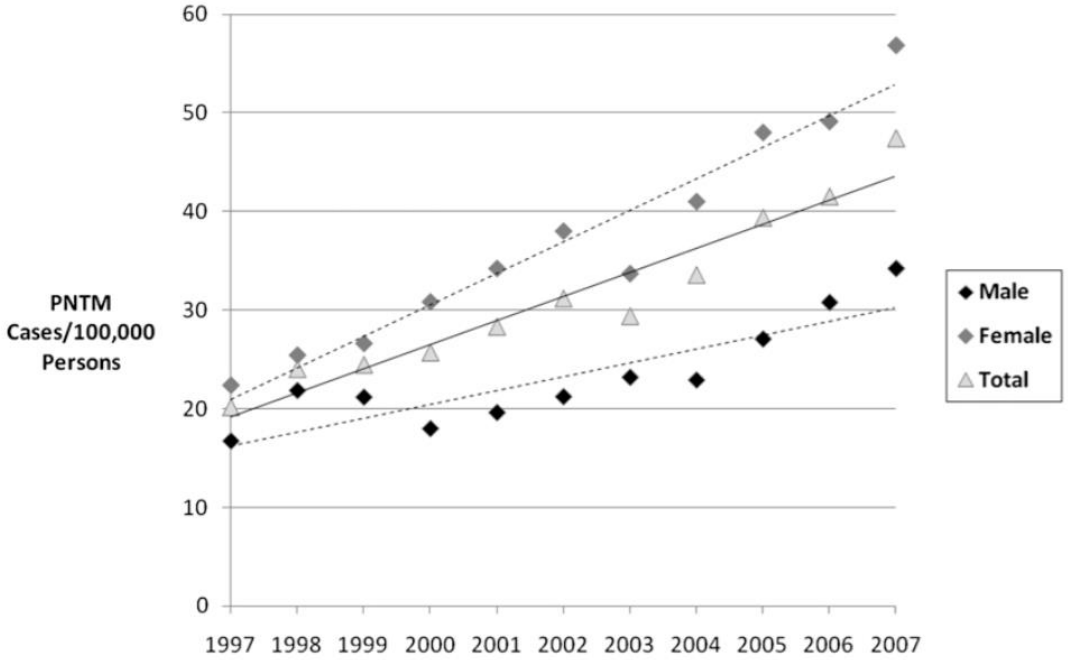
Alveolar infiltrate with underlying bronchiectasis



Solitary pulmonary nodule

NTM epidemiology

- A rise in prevalence over the last four decades.



Prevalence of NTM-PD in USA, 50,000-90,000 people
Older adults: ↗frequency

in USA, NB> FC disease,
NTM-PD females> males
But, in Europe, reversed

✓ improved laboratory methods did not explain this

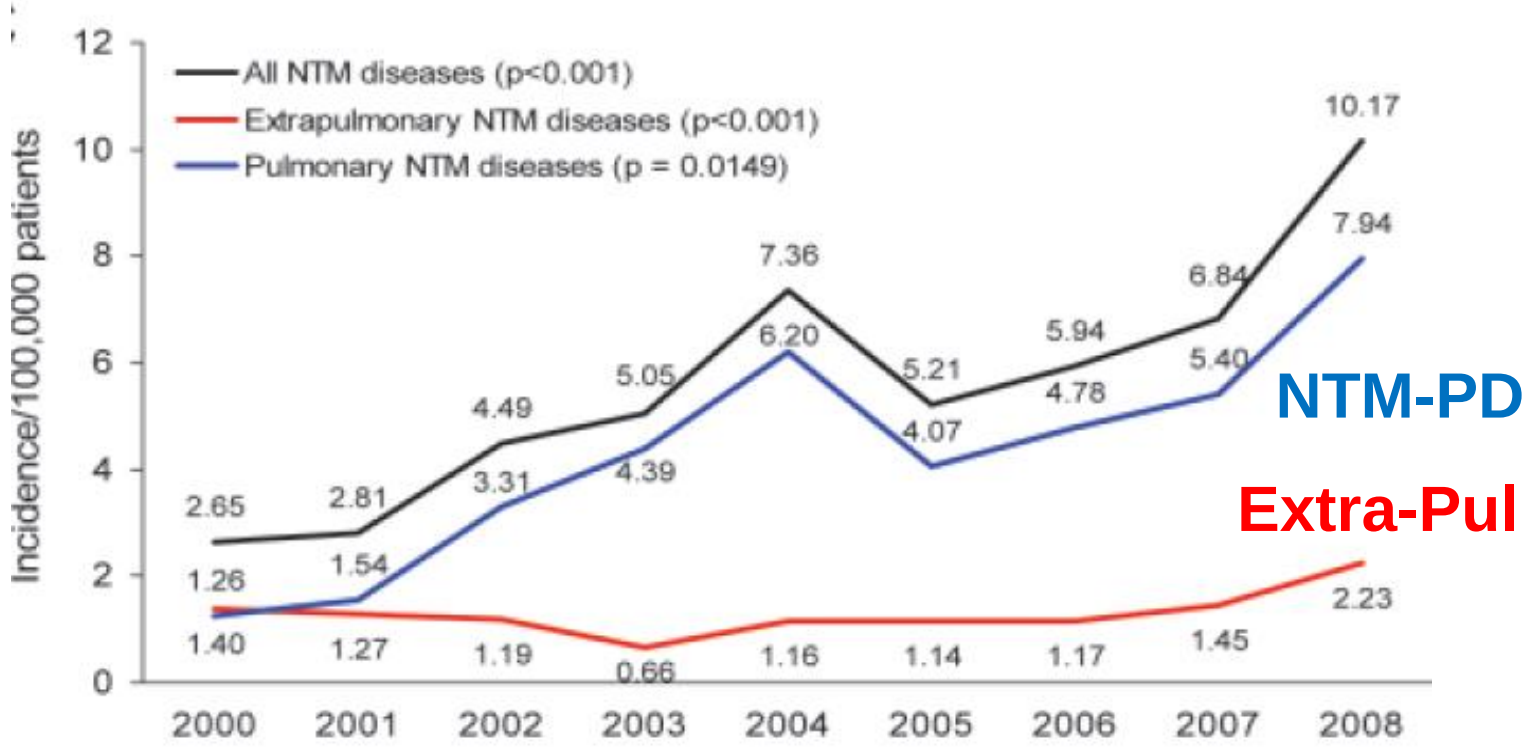
- **UK data: the incidence** of NTM-positive cultures ↗

✓ **4.0**/100,000 in 2007 to **6.1**/100,000 in 2012 (respiratory samples)

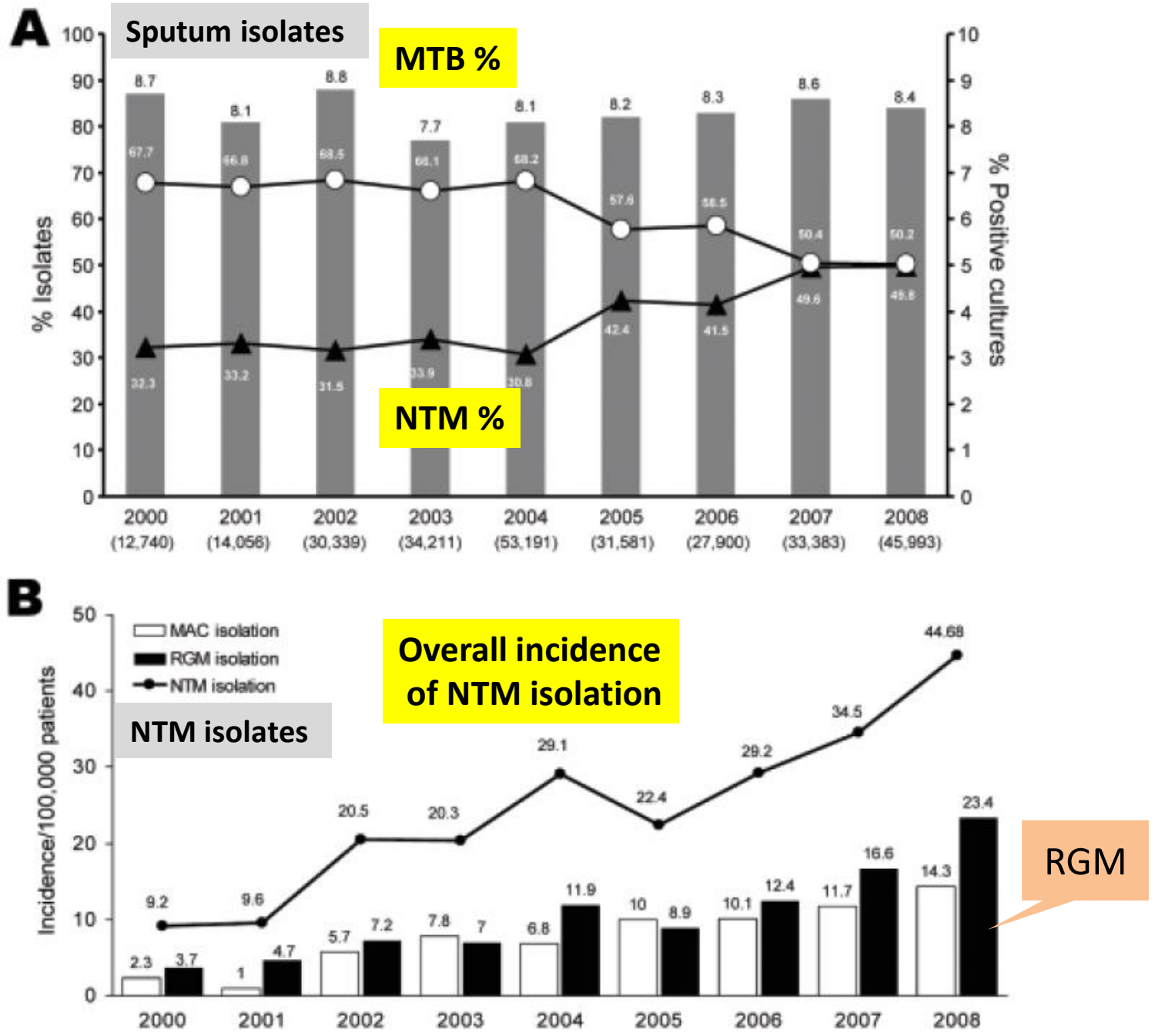
Adjemian AJRCCM 2012

NTM disease in Taiwan

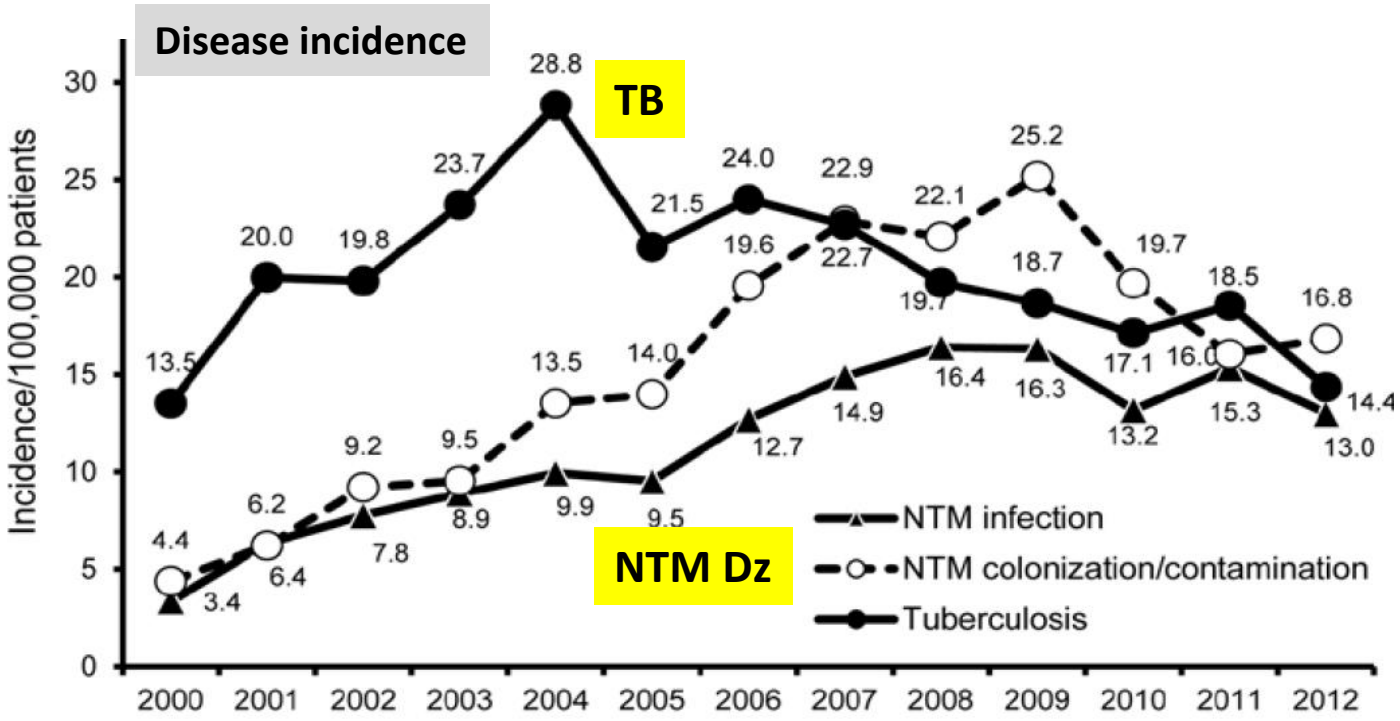
- Pulmonary NTM vs extra-pulmonary= 9:1
- Immunocompromised, Immunocompetent
- Airway colonization✓, NTM-PD incidence↗

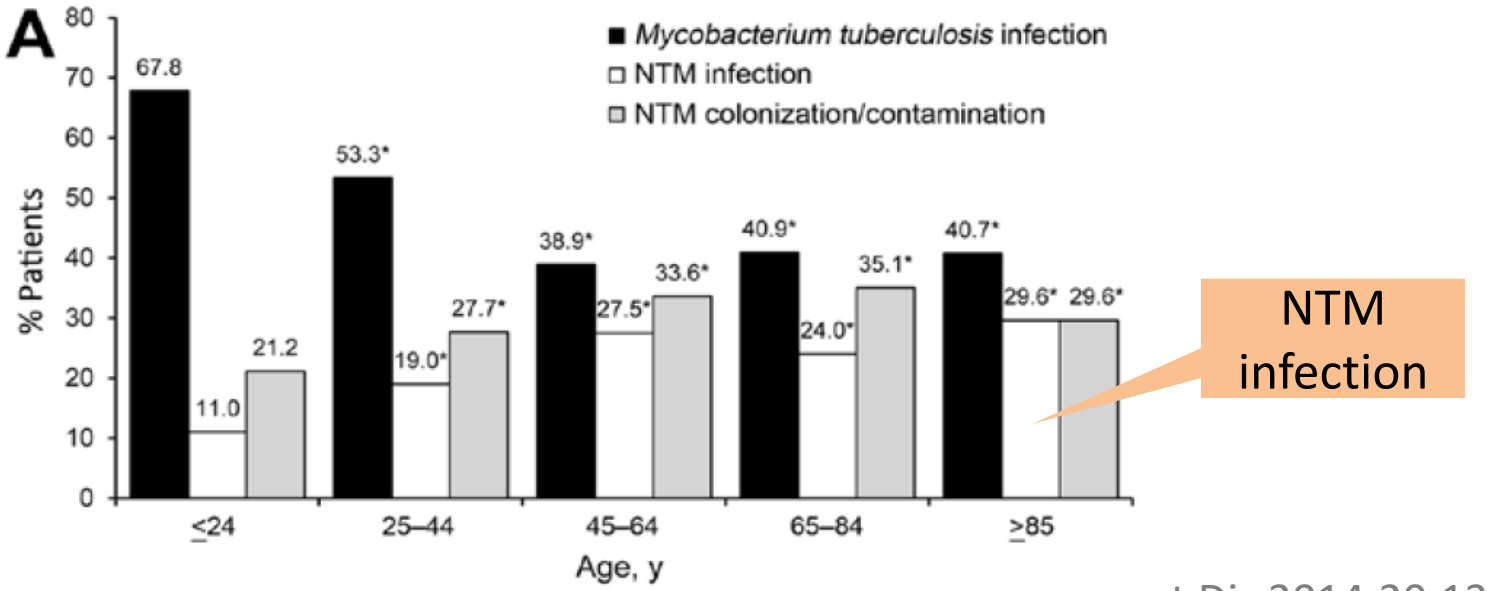


Emerg Infect Dis. 2010;16:294-6



Taiwan, Emerg Infect Dis. 2010;16:294-6



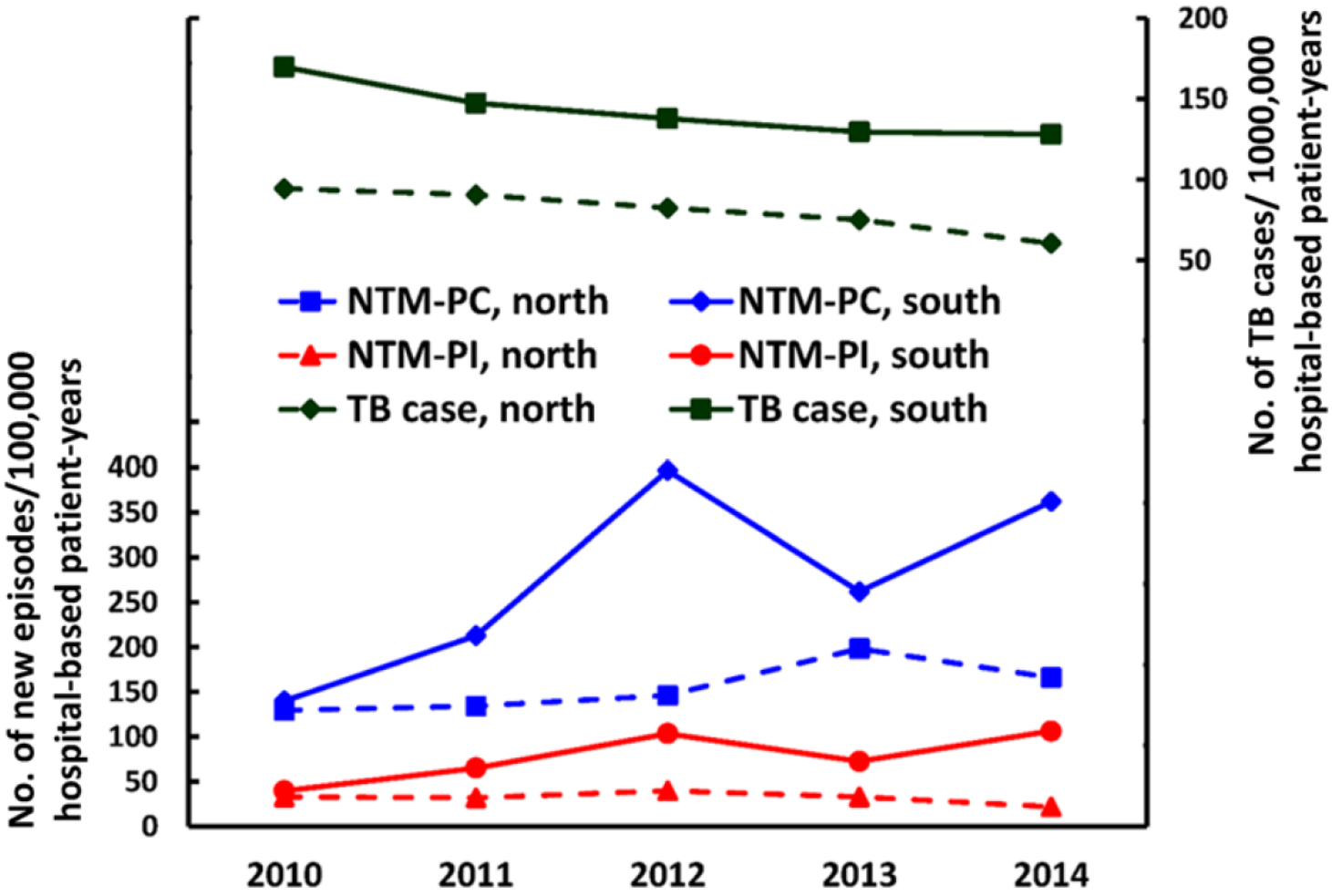


Taiwan, Emerg Infect Dis 2014;20:1382-5.

NTM-LD in Taiwan

- a Retrospective, Five-Year Multicenter Study *(Scientific Reports 2017)*

Hung-Ling Huang, Meng-Hsuan Cheng, Po-Liang Lu, Chin-Chung Shu, Jann-Yuan Wang, et al.



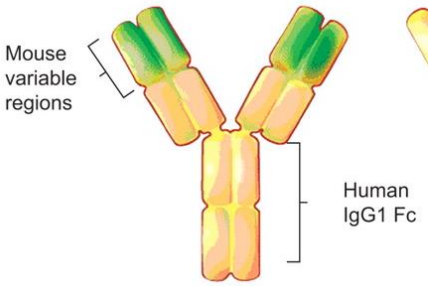
Northern Taiwan, MAC 42.3%

Southern Taiwan, MAB 27.7% and MAC 27.3%

Scientific Reports 7, Article number: 16300 (2017) doi:10.1038/s41598-017-16559-z

A real underlying increase in NTM-PD

- ↗ clinician awareness, detection methods, changing environmental, host factors



✓ **In cystic fibrosis (CF) studies**

- Overtime ↗ in NTM-positive cultures with no change in surveillance intensity or culture methodology

✓ **In NTM skin test studies**

- Overtime ↗ in rates of skin test reactivity to NTM antigens in US population-based studies→ ↗exposure to NTM

BTS guideline on the management of opportunistic mycobacterial infections

2000

British Thoracic Society Guideline for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD)

Charles S Haworth,[1] John Banks,[2] Toby Capstick,[3] Andrew J Fisher,[4]

臨床上(第 1 及 2 點皆必備)

1)呼吸道症狀，影像學在胸腔 X 光有 nodular 或 cavitary opacities，或在電腦斷層有 multifocal bronchiectasis with multiple small nodules 變化。

2)適當地排除了其他可能診斷。

微生物(1 至 3 點中任一成立)

1)至少二套痰培養出 NTM，若需要可重覆驗痰。

2)至少一次支氣管沖洗液培養出 NTM。

3)經氣管或其他肺切片呈現分枝桿菌感染的組織病理變化(有 granulomatous inflammation 或 acid-fast bacilli)加上 (a)切片培養出 NTM 或 (b)至少一套痰或支氣管沖洗液培養出 NTM。

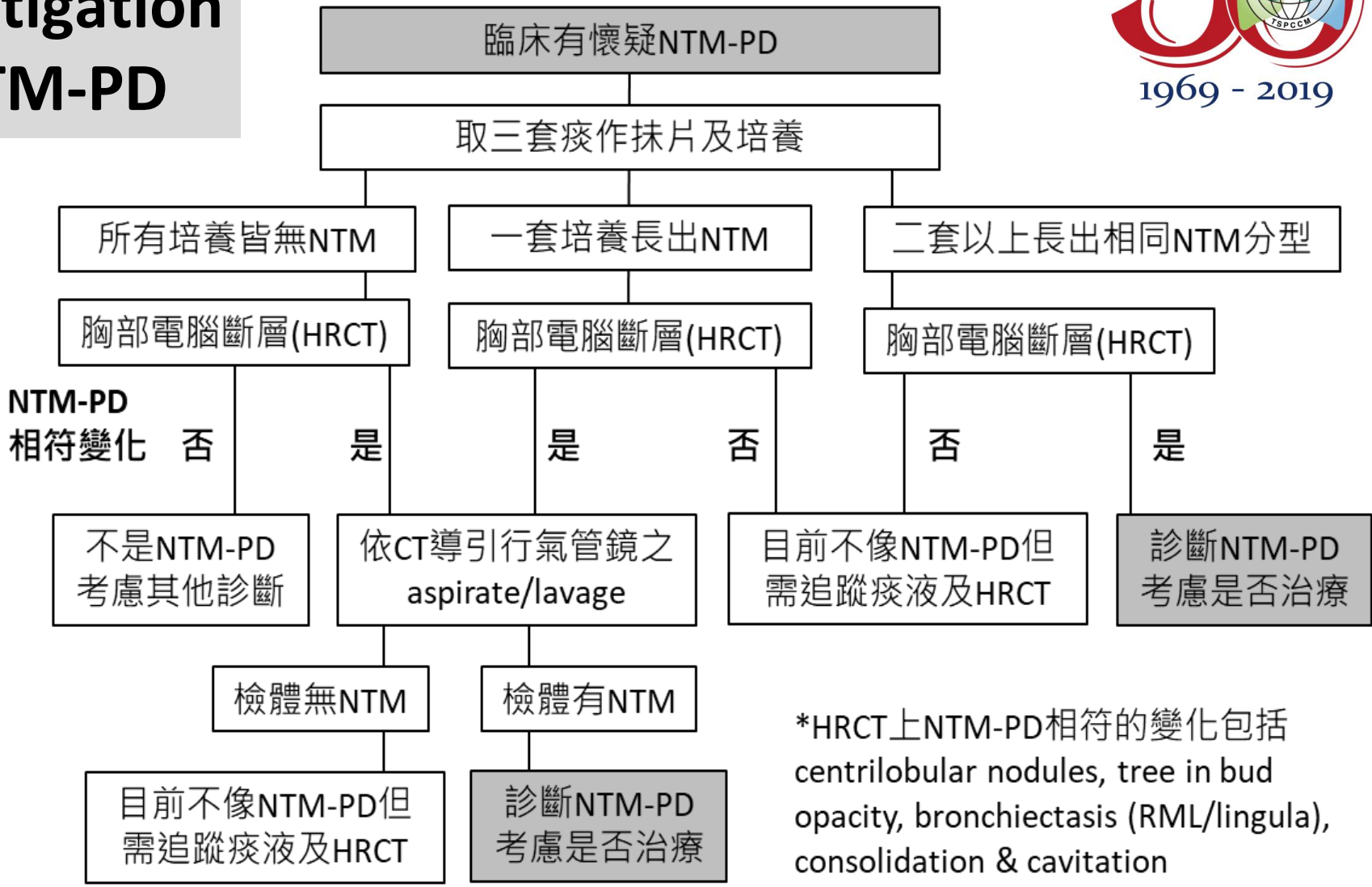
American Th

An Official ATS
Treatment, and
Mycobacterial I

David E. Griffith, Timothy Aksamit, Barbara A. Brown-Elliott, Antonino Catanzaro, Charles Daley, Fred Gordin,

Griffith AJRCCM 2007

Algorithm for investigation of NTM-PD



*HRCT上NTM-PD相符的變化包括 centrilobular nodules, tree in bud opacity, bronchiectasis (RML/lingula), consolidation & cavitation

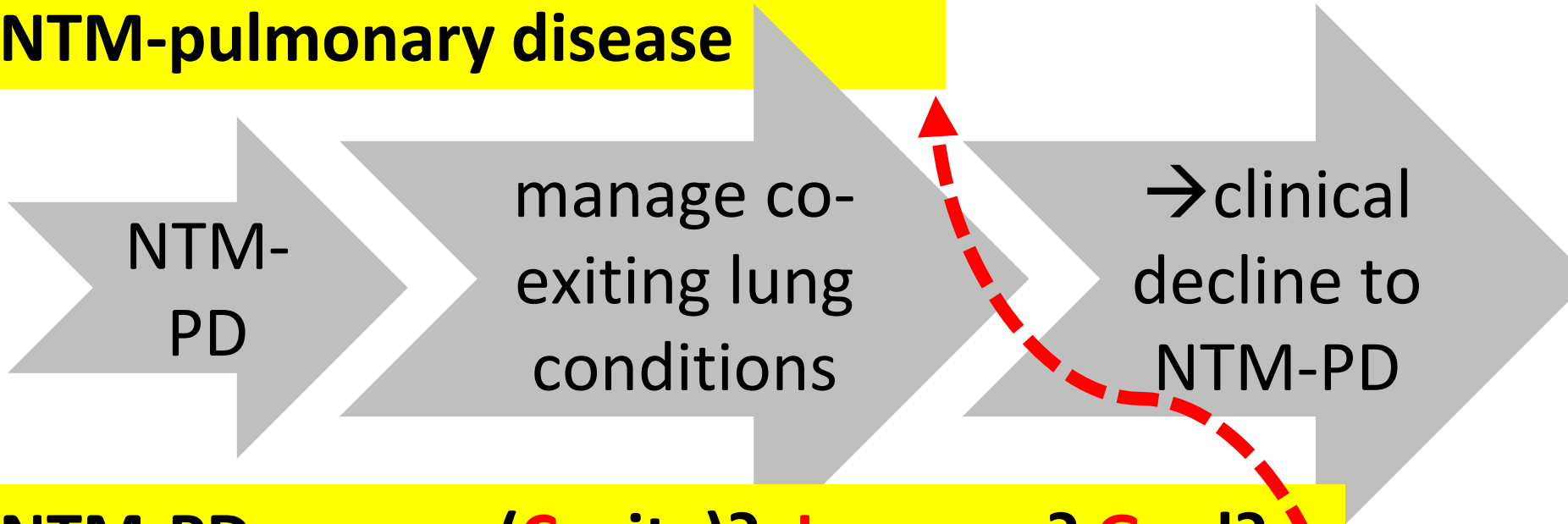
No sputum→sputum induction or BAL

BTS Guidelines 2017

NTM-PD? clinical symptoms due to NTM infection?

NTM-pulmonary colonization

NTM-pulmonary disease

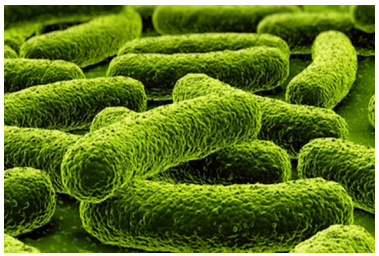


NTM-PD, severe (Cavity)?, Immune? Goal? with Disease progression? (ICD-go)

NTM-PD, start treatment (species, subspecies, DST) observation, spontaneous conversion?

Microbiological sampling to detect NTM-PD, typing

- **Evidence**
  - ✓ NTM serology → not validated for NTM-PD.
  - ✓ **Sputum, bronchial washings or lavage (BAL) samples** and transbronchial biopsies can be used to evaluate NTM-PD



- **Recommendation:**
  - ✓ **All respiratory NTM isolates→ identified to at least species** level using validated molecular or MALDI-TOF MS (Grade A)
  - ✓ **Isolates of M. abscessus →sub-speciated** using appropriate molecular techniques. (Grade C)

identification of **Disease progressive NTM-PD**

Fulfilling the ATS/IDSA NTM-PD criteria does not necessarily imply that treatment should be started (can remain stable without Rx)

Progressive Disease attributable to NTM provides a stronger case for treatment

Immune status, Severity (Cavity, symptoms), Goal of treatment

Microbiological features	**CT features**	**Patient related factors**	**Treatment requirements**
↗ smear positivity, ≥2 positive cultures of the same NTM, particular NTM species	↗ size/number nodules, new or worsening lung cavitation, new foci of consolidation / tree-in-bud opacity and worsening extent and /or severity of bronchiectasis.	severe symptoms, low BMI, lung cavitation and comorbidity	TNFα inhibitors, future lung transplantation (Evidence level 3)

→**Careful longitudinal assessment** → treatment requirements.

→**ICD-goal**

Poor adherence to ATS/IDSA guideline

Survey of NTM Diagnosis and Treatment in the EU

446 physicians, 1012 patients with NTM-PD

- France 206, Germany 211, Italy 210, Spain 230, UK 155
- Pulmonologists 29%, Internal Medicine 21%, GP 30%

- MAC 79%, *M. abscessus* 20%
- **68% received antibiotic treatment**

Proportion of patients with MAC-PD that received
> 6 months of Macrolide/Ethambutol/Rifampicin ?
EU 9% (UK 18%, Spain 8%, France 8%, Germany 4%)

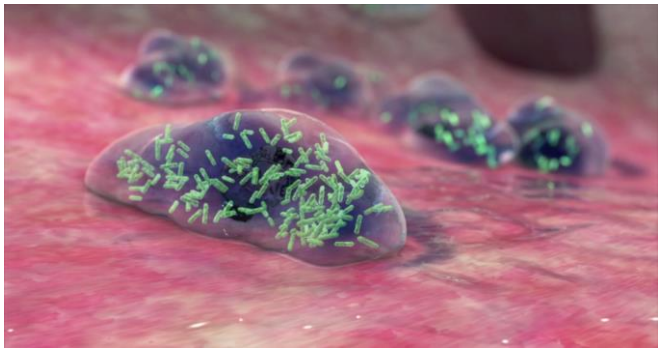
van Ingen Eur Res J 2016

NTM-PD course and outcomes

- Progressive Disease in 1-3 years: 50-75%
- Abx initiation: 20-65%

- Side effect →DC Abx:
  - MAC 20-40% (Macrolide-ER)
  - MAB 60% (Macrolide, IV Amikacine+Imipenen…)
- Cure rate 50-60% (Mab: 58% culture- >12M)

- Recurrence: MAC 1/4, Mab 1/3
- 5-year mortality: 28%



Diagn Microbiol Infect Dis. 2012 Feb;72(2):161-5
Clin Infect Dis. 2017 May 24. doi: 10.1093/cid/cix479

Disease progression and Treatment response?
MAC & MAB-Subspecies

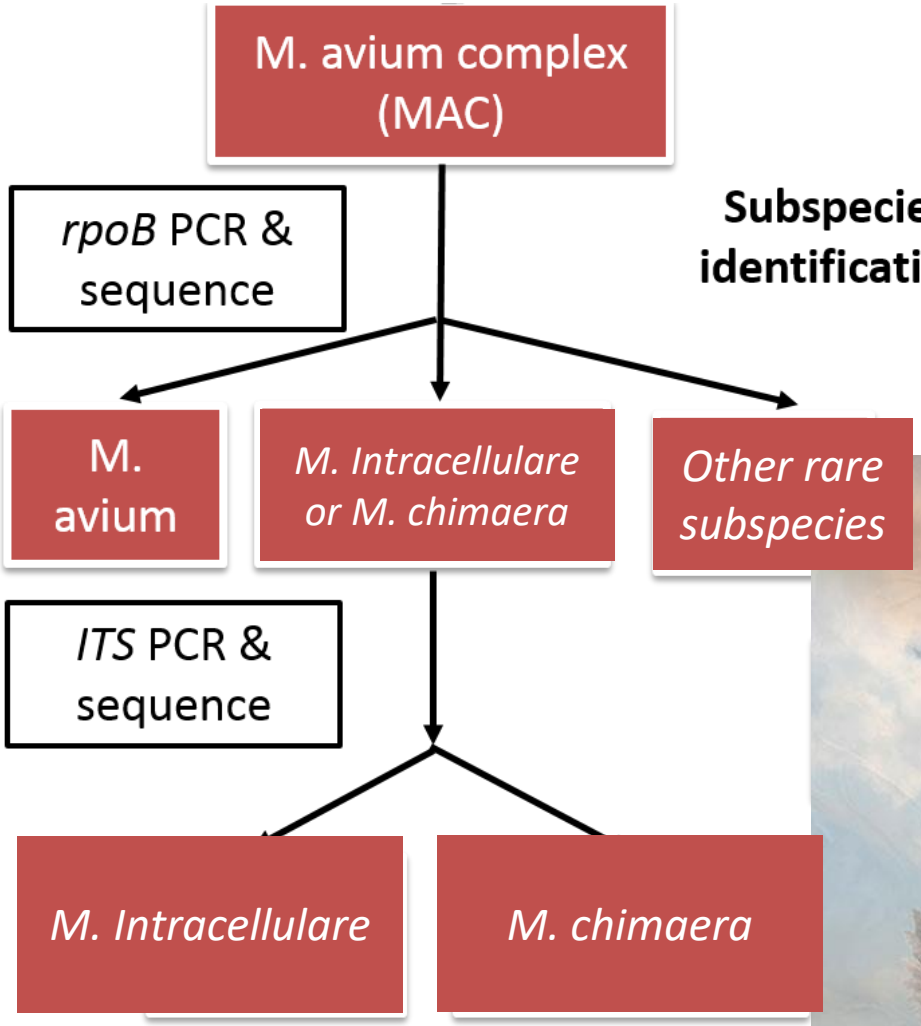
NTM-colonization

NTM-pulmonary disease

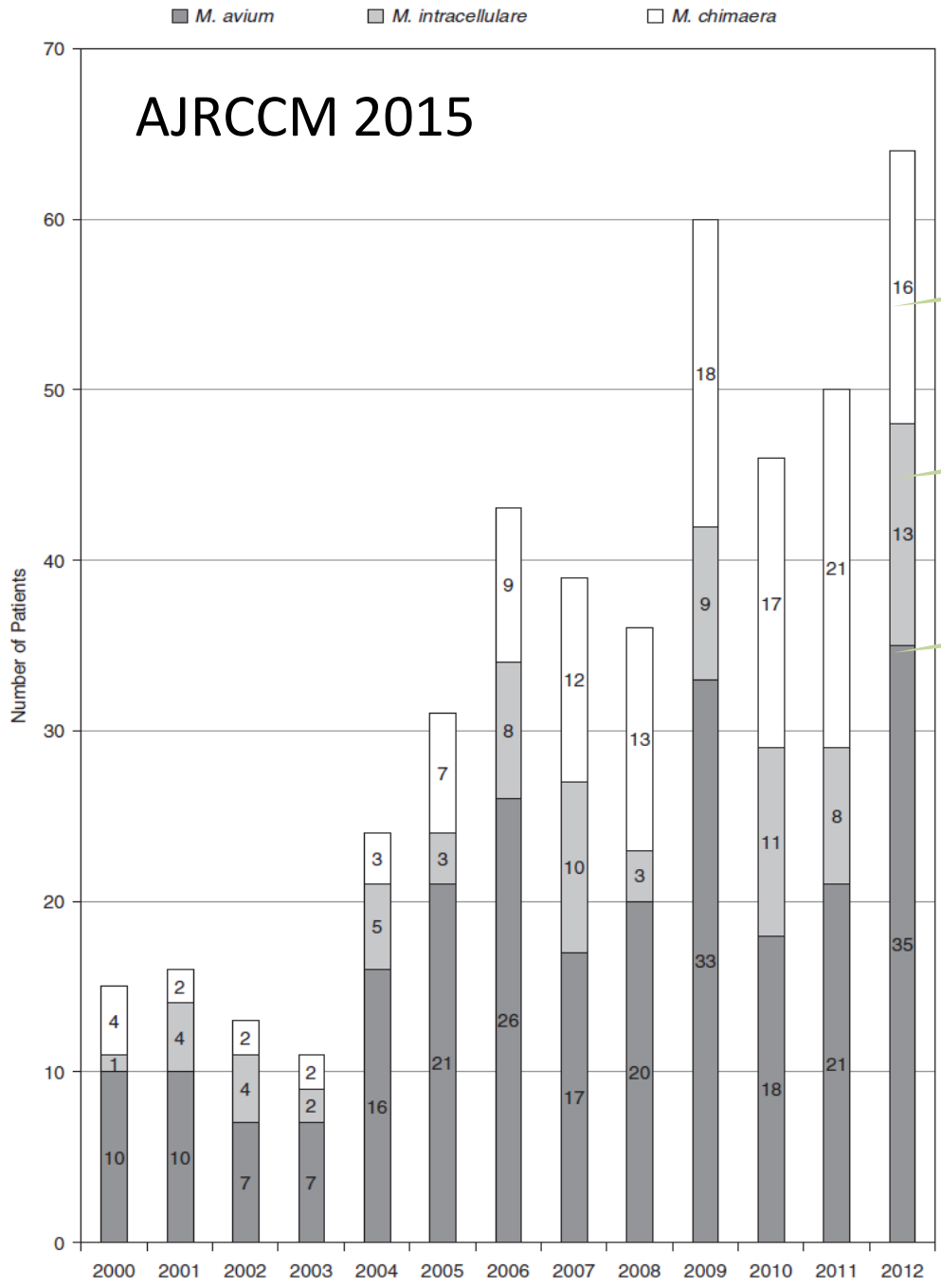
NTM-PD, severe (Cavity)?, Immune? Goal?
with Disease progression? (ICD-go)

NTM-PD, start treatment (species, subspecies, DST)
observation, spontaneous conversion?

MAC or MAB subspecies & NTM-PD disease course



AJRCCM 2015;191(11):1310-7.



MAC subspecies, USA

M. *chimera, 126 (28%)*

M. *Intracellulare 81 (18%)*

M. *avium, 241 (54%)*

5 rare causes of infection in humans (M. colombiense x2, M. marseillense, M. timonense, and M. yongonense)

AJRCCM 2015;191(11):1310-7.

Characteristics	*M. avium* (*n* = 241)	*M. intracellulare* (*n* = 81)	*M. chimaera* (*n* = 126)	*P* Value*
Demographic variables (n = 448)				
n†	241	81	126	
Female, n (%)	140 (58)	66 (82)	73 (58)	<0.001
Age, yr, mean ± SD	62.7 ± 15.9	65.1 ± 12.7	62.1 ± 16.6	0.35
BMI, kg/m^2, mean ± SD	23.2 ± 4.8	22.3 ± 3.8	24.1 ± 7.3	0.09
Laboratory evaluation (n = 448)				
n†	241	81	126	
Smear positive, n (%)	59 (25)	26 (32)	18 (14)	0.009
No. of positive cultures, mean ± SD				0.15
Radiographic findings (n = 439)				
n†				
Cavitary disease, n (%)				0.29
Bilateral lung disease, n (%)				0.002
ATS/IDSA criteria for diagnosis of pulmonary infection (n = 436)				
n†				
Meets criteria, n (%)	142 (61)	56 (70)	53 (43)	<0.001
Started on treatment (n = 392)				
n†	209	76	107	
Yes, n (%)	95 (46)	36 (47)	37 (35)	0.12

MAC-isolate(+)

→ATS criteria 57% (251/436)

M. avium and M. intracellulare:
virulence↗ than *M. chimera*

***M. chimera*: immunosuppressed**

AJRCCM 2015;191(11):1310-7.

Table 2. Univariate and Multivariate Analyses for Meeting American Thoracic Society/ Infectious Diseases Society of America Criteria for *Mycobacterium avium* Complex Pulmonary Infection

Risk factor for MAC-PD vs colonization

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	AOR (95% CI)*	*P* Value
Species compared with *M. chimaera*				
M. avium	2.11 (1.36–3.30)	0.001	2.14 (1.33–3.44)	0.002
M. intracellulare	3.13 (1.72–5.67)	<0.001	3.12 (1.62–5.99)	0.001
Demographics				
Age	1.01 (0.99–1.02)	0.20	1.00 (0.99–1.02)	0.58
Female	2.04 (1.37–3.03)	<0.001	1.83 (1.15–2.91)	0.01
BMI	0.95 (0.92–0.99)	0.009	0.96 (0.92–0.99)	0.04
Ever-smoker	0.66 (0.45–0.97)	0.04	0.69 (0.45–1.05)	0.08
Laboratory values				
Smear positive	2.97 (1.79–4.92)	<0.001	2.46 (1.41–4.30)	0.002
Comorbidities				
COPD	0.62 (0.38–1.03)	0.06	0.66 (0.37–1.17)	0.15
Malignancy	1.26 (0.81–1.93)	0.30		
Transplant	0.71 (0.28–1.82)	0.47		
HIV	0.69 (0.36–1.33)	0.27		
Immunosuppressants†	0.84 (0.49–1.42)	0.51		
Radiographic findings				
Cavitary disease	1.69 (0.97–2.95)	0.07	1.79 (1.04–3.23)	0.04
Bilateral lung disease	2.22 (1.44–3.43)	<0.001	1.65 (1.05–2.82)	0.02

Risk assessment for NTM-PD → progression? → Relapse

Characteristics	*M. avium* (*n* = 142)	*M. intracellulare* (*n* = 56)	*M. chimaera* (*n* = 53)	*P* Value*
Demographic variables (n = 251)				
n†	142	56	53	
Female, n (%)	89 (63)	50 (89)	37 (70)	0.001
Age (yr), mean ± SD	64.3 ± 14.7	65.1 ± 12.8	65.9 ± 15.5	0.69
BMI (kg/m^2), mean ± SD	22.8 ± 4.7	21.9 ± 3.3	22.5 ± 5.0	0.32
Current smoker, n (%)	15 (11)	8 (14)	5 (9)	0.68
Former smoker, n (%)	65 (46)	22 (39)	19 (36)	0.40
Laboratory evaluation (n = 251)				
n†	142	56	53	
Smear positive, n (%)	44 (31)	21 (38)	12 (23)	0.24
No. of positive cultures, mean ± SD	1.47 ± 0.8	1.64 ± 0.9	1.47 ± 0.7	0.26
Comorbidities (n = 244)				
n†	136	56	52	
COPD, n (%)	23 (17)	5 (9)	9 (17)	0.33
Prior TB, n (%)	8 (6)	2 (4)	3 (6)	0.80
CAD, n (%)	29 (21)	7 (13)	13 (25)	0.23
Malignancy, n (%)	42 (31)	17 (30)	18 (34)	0.87
Transplant, n (%)	6 (4)	0 (0)	3 (6)	0.23
Immunosuppressants, n (%)‡	14 (10)	8 (14)	14 (27)	0.02
HIV, n (%)	16 (12)	1 (2)	3 (6)	0.06
DM, n (%)	12 (9)	6 (11)	0 (0)	0.07
Clinical symptoms (n = 220)				
n†	124	50	46	
Weight loss, n (%)	24 (19)	8 (16)	11 (24)	0.61
Hemoptysis, n (%)	19 (15)	7 (14)	2 (4)	0.16
Cough, n (%)	88 (71)	36 (72)	34 (74)	0.93
Hypoxia, n (%)	12 (10)	3 (6)	2 (4)	0.45
Radiographic findings (n = 248)				
n†	140	56	52	
Cavitary disease, n (%)	27 (19)	7 (13)	11 (21)	0.44
Bilateral lung disease, n (%)	108 (77)	52 (93)	38 (73)	0.02
Started on treatment (n = 222)				
n†	128	54	40	
Yes, n (%)	71 (55)	28 (52)	19 (48)	0.66
Clinical relapse/reinfection (n = 190)				
n†	119	34	37	
Yes, n (%)	34 (29)	3 (9)	11 (29)	0.05

MAC-PD cases (ATS criteria)

Started on treatment: 48-55%

***M. avium & chimera:* relapse↗**

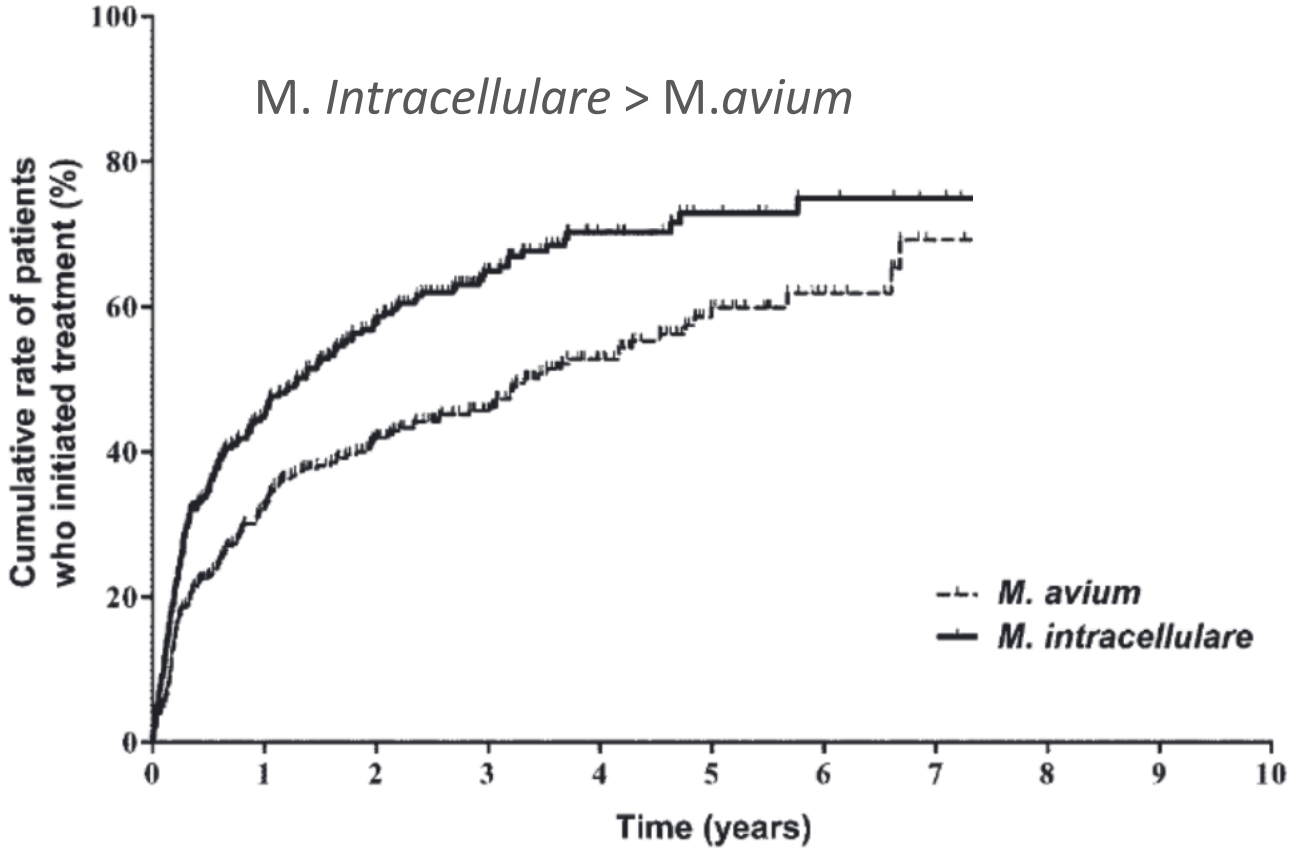
AJRCCM 2015;191(11):1310-7.

Among MAC patient

M. intracellulare exhibited a more severe presentation such as cavitary disease and showed a higher progression rate compared with patients with M. avium

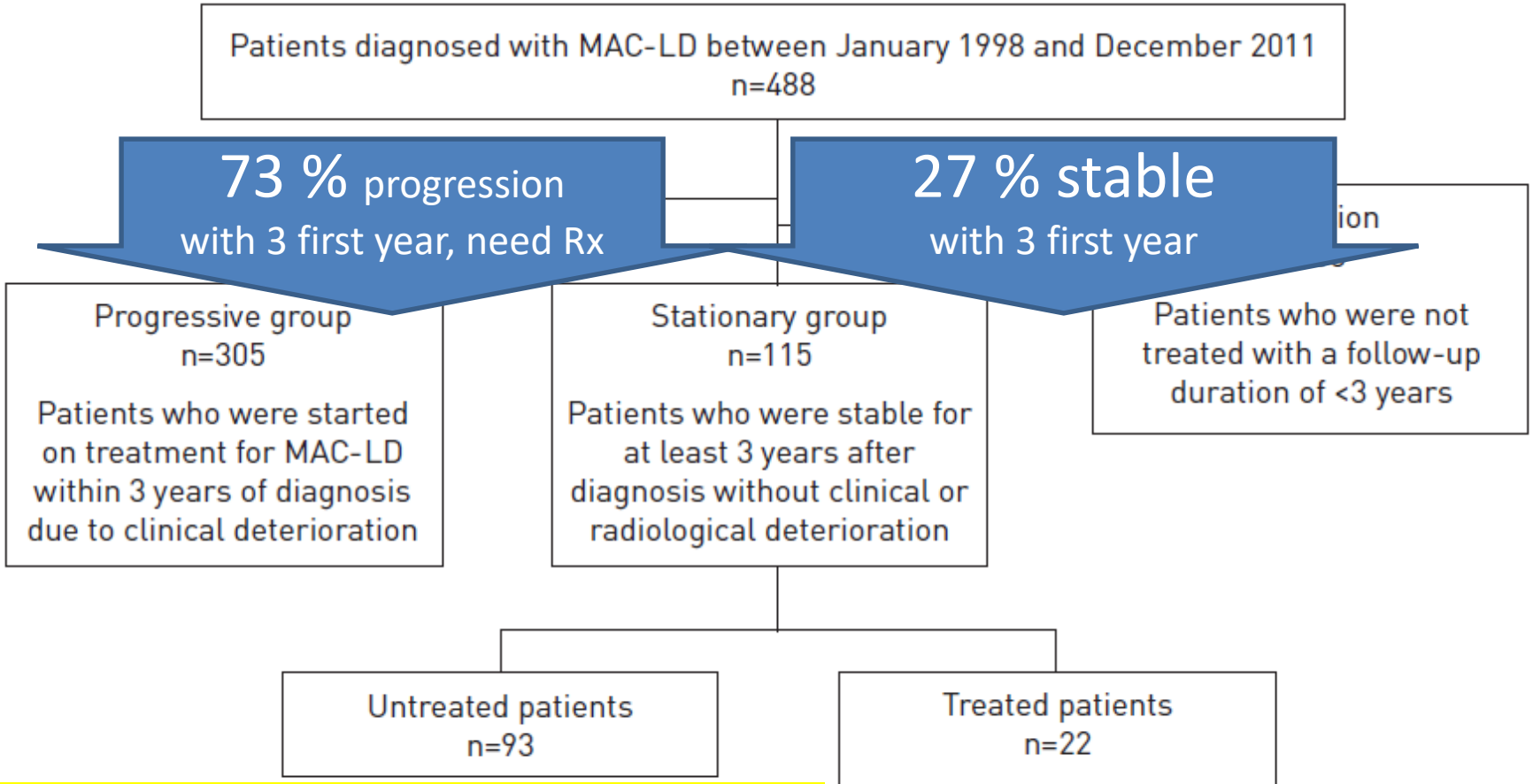
M. *Intracellulare* > M.*avium*

?? M. *chimaera*
(2012 study?
(Korea data?



Won-Jung Koh et al
CHEST 2012; 142(6):1482–1488

MAC-PD can remain stable without treatment, Korea



48% Spontaneous negative conversion

of sputum cultures occurred in 48 (51.6%) patients among the 93 untreated patients in the stationary group.

FIGURE 1 Flow chart of patients diagnosed with *Mycobacterium avium* complex lung disease (MAC-LD) between January 1998 and December 2011.

Ji An Hwang et al, ERJ 2017;49(3). pii: 1600537

Risk assessment for NTM-PD → progression/Rx → Relapse

TABLE 2 Predictors of disease progression resulting in treatment initiation within 3 years of diagnosis of *Mycobacterium avium* complex lung disease (MAC-LD) in a total of 466 patients[#]

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.990 (0.980–1.001)	0.072	0.987 (0.975–0.999)	0.040
Male	0.976 (0.767–1.243)	0.846		
BMI kg·m^{-2}	0.890 (0.856–0.925)	<0.001	0.926 (0.882–0.973)	0.002
Smoker	0.887 (0.695–1.133)	0.337		
Past history of pulmonary TB	1.269 (0.991–1.624)	0.059	0.987 (0.746–1.306)	0.928
Presence of comorbidity[¶]	0.911 (0.714–1.162)	0.452		
Presence of systemic symptom[+]	1.560 (1.191–2.045)	0.001	1.490 (1.095–2.028)	0.011
Positive sputum AFB smear	2.298 (1.795–2.941)	<0.001	1.811 (1.350–2.428)	<0.001
Causative organism		0.001		0.364
Mycobacterium avium	1		1	
Mycobacterium intracellulare	1.512 (1.186–1.928)		0.869 (0.642–1.177)	
Radiological type: fibrocavitary	2.695 (2.099–3.460)	<0.001	2.102 (1.519–2.908)	<0.001
Involved lobes	1.384 (1.260–1.519)	<0.001	1.178 (1.050–1.322)	0.005
FVC % pred	0.991 (0.984–1.998)	0.011	1.001 (0.994–1.009)	0.712

Eur Respir J. 2017 Mar 8;49(3). pii: 1600537

Risk assessment for NTM-PD → progression/Rx → Relapse → spontaneous sputum conversion

TABLE 3 Predictors of spontaneous sputum conversion in the untreated stationary group of 93 patients

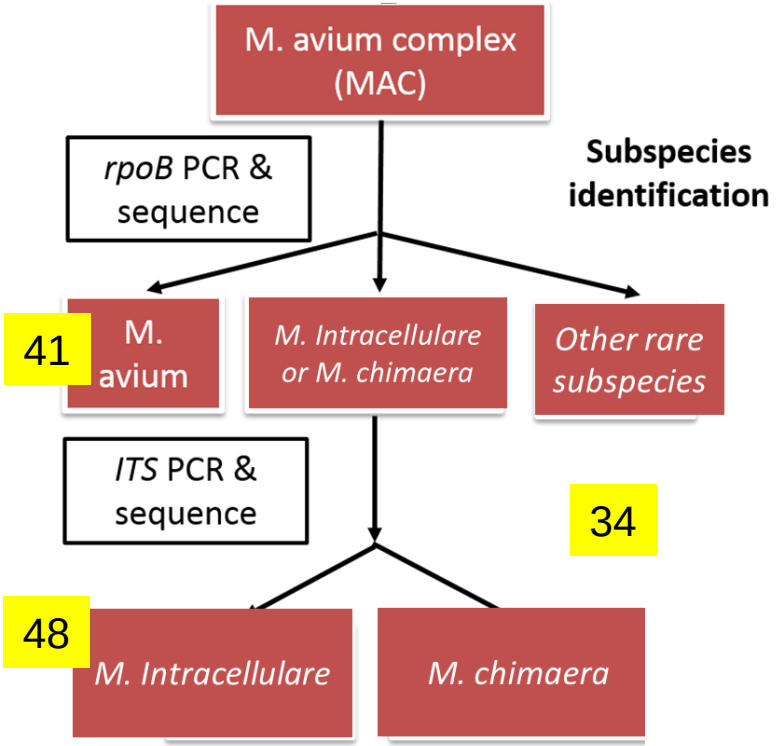
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	0.969 (0.945–0.994)	0.015	0.973 (0.948–0.999)	0.043
Male	1.087 (0.612–1.929)	0.776	0.885 (0.484–1.621)	0.693
BMI kg·m^{-2}	1.108 (1.018–1.205)	0.017	1.101 (1.007–1.205)	0.035
Nonsmoker	0.961 (0.542–1.704)	0.892		
Presence of comorbidity[#]	1.309 (0.730–2.345)	0.366		
Positive sputum AFB smear	0.536 (0.259–1.110)	0.093	0.377 (0.156–0.912)	0.030
Causative organism		0.817		
Mycobacterium avium	1			
Mycobacterium intracellulare	0.932 (0.514–1.691)			
Radiological type: nodular bronchiectatic	1.246 (0.634–2.450)	0.524		
Involved lobes	1.012 (0.770–1.329)	0.934		
FVC % pred <80%	1.165 (0.655–2.072)	0.604		
Transient anti-TB medication (≥1 month)[¶]	2.091 (0.974–4.490)	0.059	3.769 (1.505–9.435)	0.005

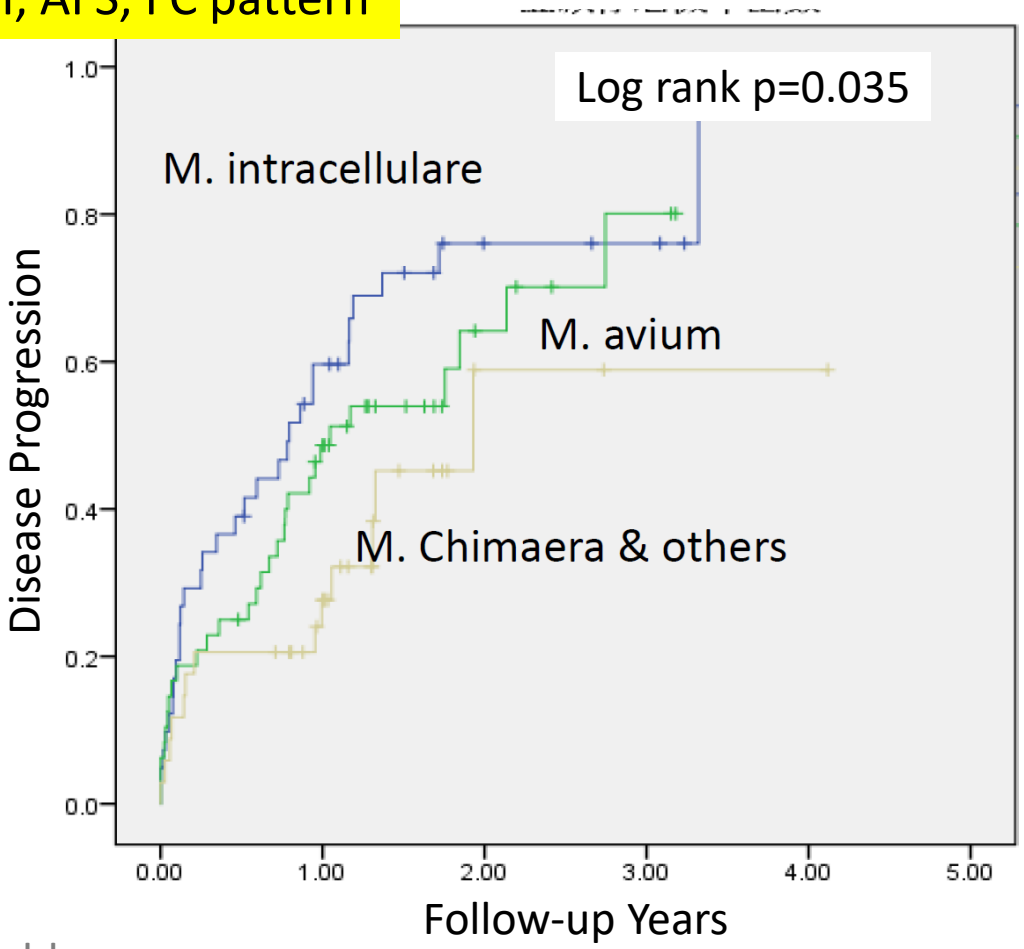
Eur Respir J. 2017 Mar 8;49(3). pii: 1600537

北榮台大兩院合作計畫 2014-2018

- MAC-PD, n=123, risk factor for disease progression
- *M. chimaere+others vs av+in,* aHR:0.51 (0.27-0.97) p=0.039

Other Independent factor: BMI, AFS, FC pattern





Unpublished Data

MAC or MAB-PD w non-cavitary NB pattern, Korea

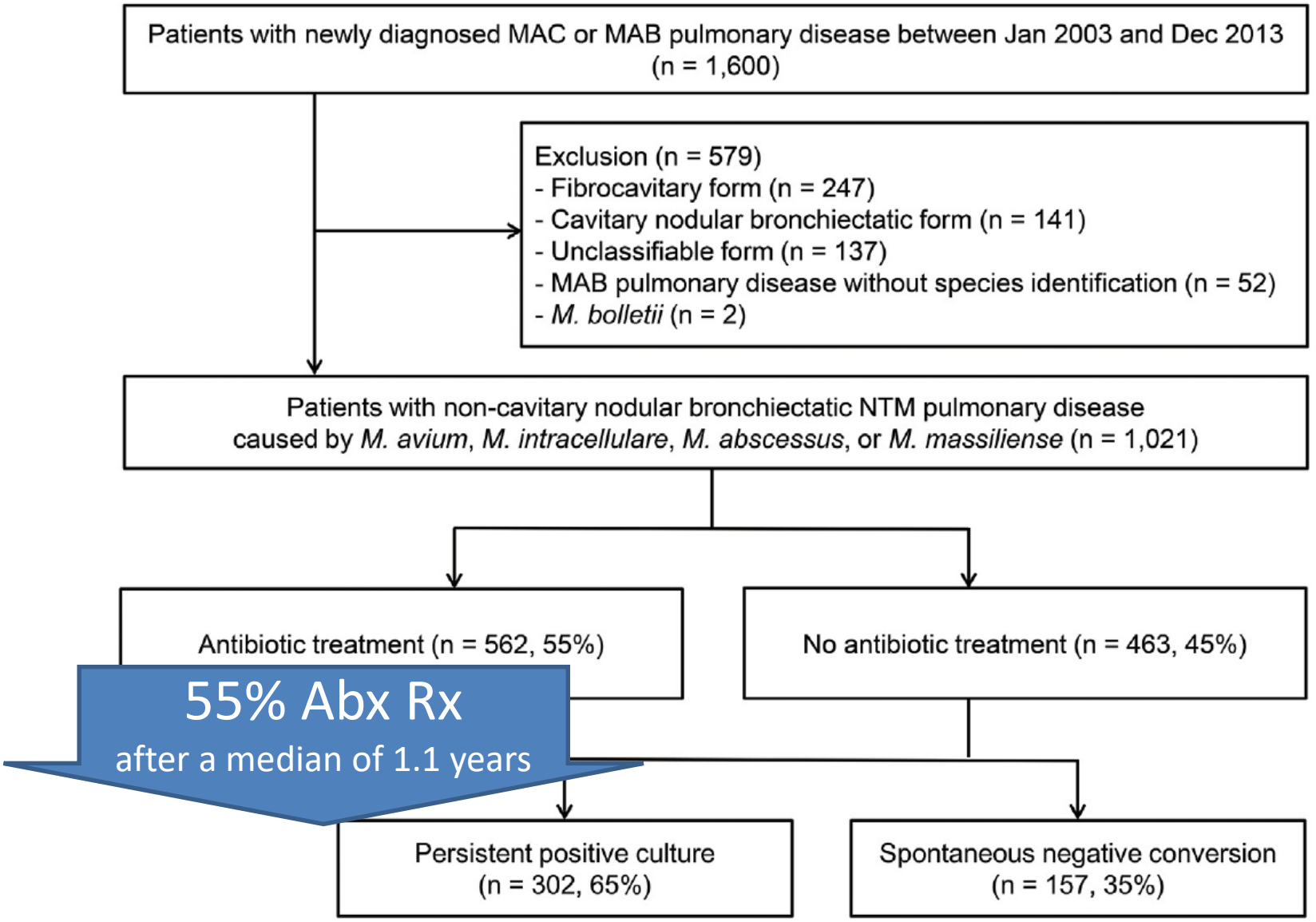
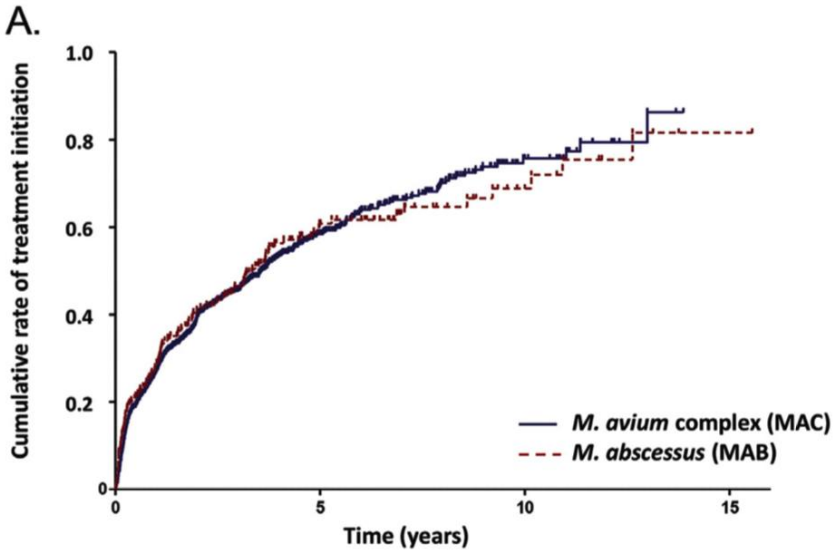


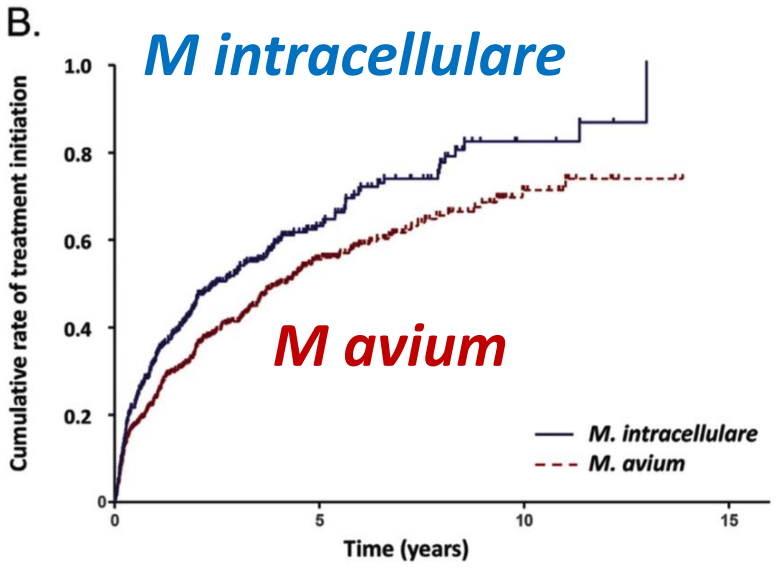
Fig. 1. Study population. MAC: *Mycobacterium avium* complex; MAB: *Mycobacterium abscessus*; NTM: nontuberculous mycobacteria.

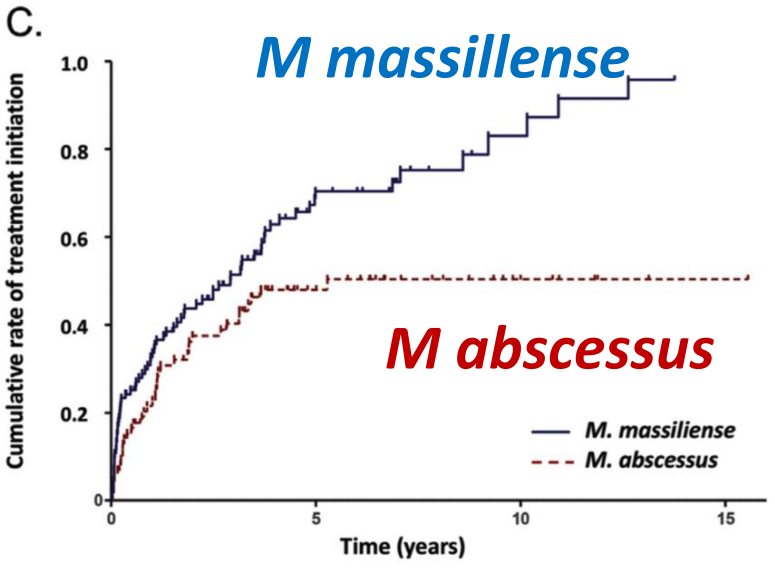
Respir Med. 2019 May;151:1-7.

MAC or MAB-PD non-cavitary NB, Korea, Cumulative rate of treatment initiation



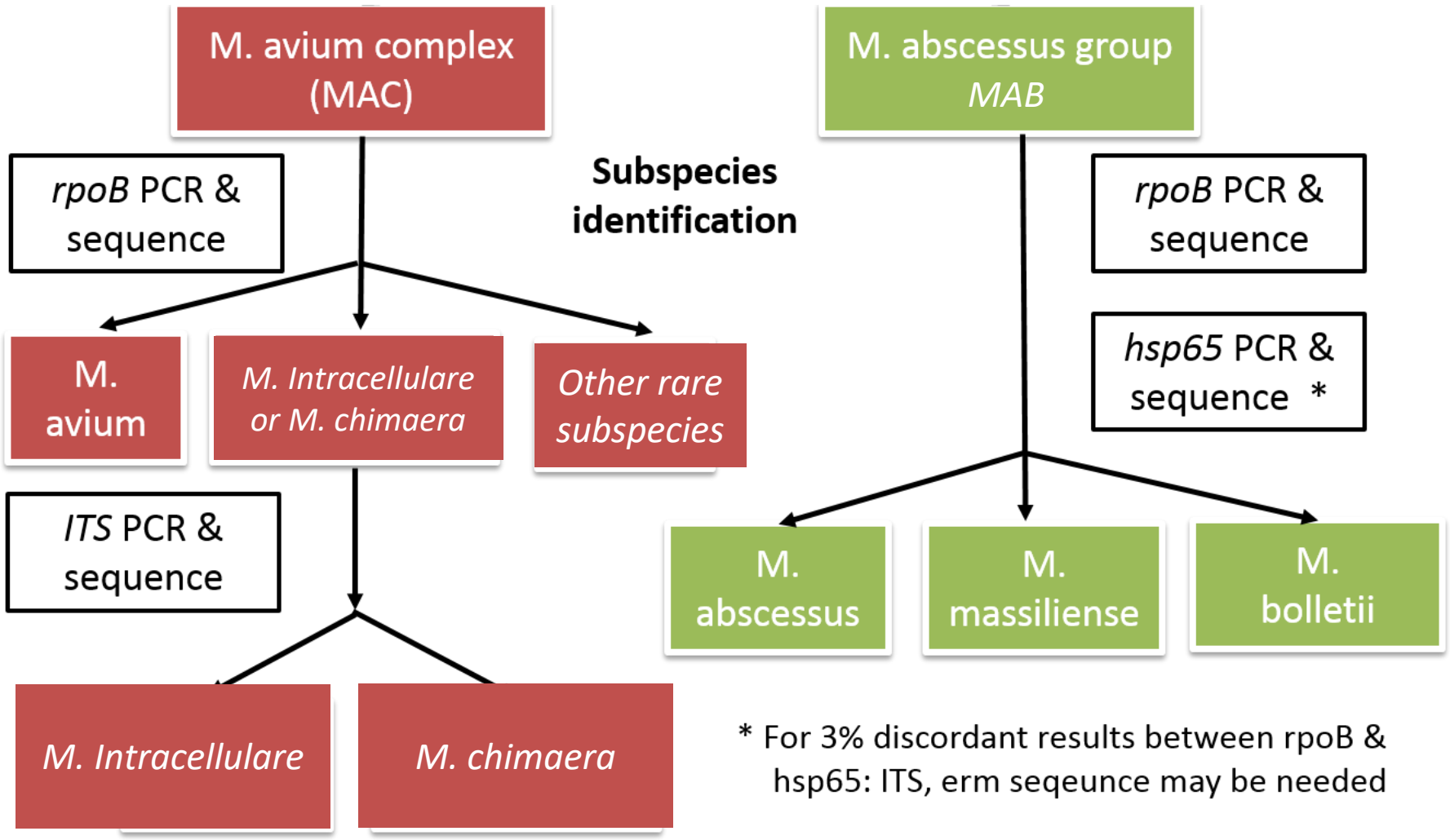
No significant difference between MAC and MAB





Respir Med. 2019 May;151:1-7.

MAC or MAB subspecies & NTM-PD disease course



AJRCCM 2015;191(11):1310-7.

MAB subsp: *M. abscessus vs M massiliense*

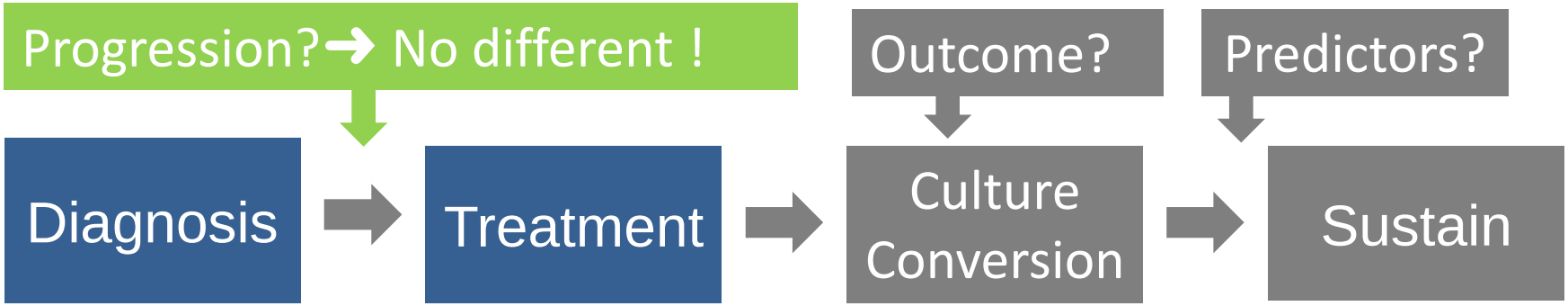
CID 2017;64(3):301–8
Seoul National University Hospital

2006/1~2015/6,
56 M. abscessus-LD
54 M. massiliense-LD

Follow-up period 3.5 years,
disease progression (+Abx)

M. abscessus-LD: 37.5
M. massiliense-LD: 38.9%
(P = .881).

Drug	*M. abscessus* (n = 49)	*M. massiliense* (n = 46)	*P* Value[a]
Clarithromycin			
Susceptible	16 (32.6)	38 (82.6)	<.001
Intermediate	2 (4.1)	0 (0.0)	
Resistant	4 (8.2)	5 (10.9)	
Inducible resistance	27 (55.1)	3 (6.5)	
MIC at day 3, μg/mL, median (IQR)	0.5 (0.5–2.0)	0.5 (0.5–0.5)	.003
MIC at day 14, μg/mL, median (IQR)	64.0 (2.0–64.0)	0.5 (0.5–0.5)	<.001
Amikacin			
Susceptible	40 (81.6)	34 (73.9)	.053
Intermediate	4 (8.2)	11 (23.9)	
Resistant	5 (10.2)	1 (2.2)	
MIC, μg/mL, median (IQR)	16 (16–16)	16 (16–32)	.318



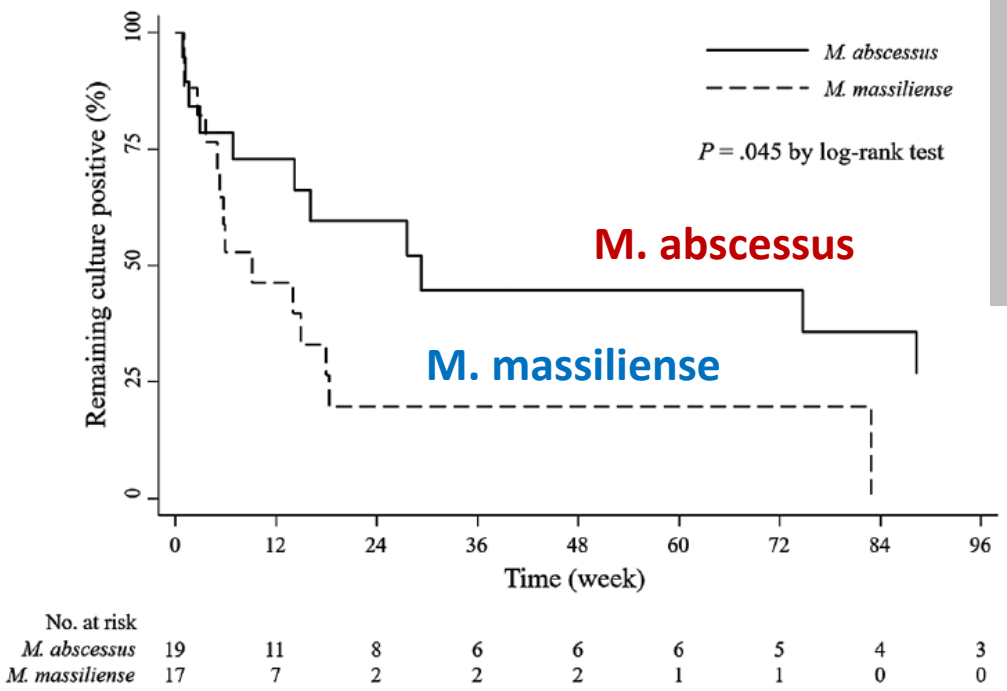
M. *massiliense* vs M. *abscessus*

Progression? → No different !

Diagnosis → Treatment → Culture Conversion → Sustain

Outcome? → Culture Conversion

Predictors? → Sustain



MAB subsp. abscessus → non-conversion (sustain), partly mediated by different susceptibilities to clarithromycin

AZM > Clarithromycin

the superiority of azithromycin in preventing inducible resistance ? some controversy

CID 2017;64(3):301–8

MAB subspecies: macrolide-resistance→ outcomes

- **rrl gene** mutation (23srRNA): constitutional macrolide resistance
- **erm(41) gene,** Erythromycin Ribosomal methyltransferase (erm)
  - ✓ **MAB. *massiliense*:** erm gene, 397-bp deletion→nonfunctional
  - ✓ **MAB. *abscessus***: erm, no deletion, C28→nonfunctional
    T28→inducible macrolide resistance (7-14 days Rx)

表四　Mabs-PD 治療導向之抗藥性分型(phenotype)[1]

	macrolide 無抗藥性	具有誘發性抗藥性	具高度生天抗藥性
Clarithromycin 第 3-5 天藥敏	Susceptible	**Susceptible**	Resistant
Clarithromycin 第 14 天藥敏	Susceptible	**Resistant**	Resistant
可能相符的抗藥基因	erm(41)基因為 dysfunctional	erm(41)基因為 functional	23S ribosomal RNA 點突變
可能相符的菌株分型	*M. a. massiliense*	*M. a. abscessus* 或 *M. a. bolletii*	任何次分型皆可

1.BTS Guidelines 2017

Oral Macrolide Therapy Following Short-term Combination Antibiotic Treatment of Mycobacterium massiliense -PD

Jan 2007 – Sep 2010

Hospitalization for 4 wk
IV amikacin and cefoxitin (or imipenem) + oral macrolide and fluoroquinolone (ciprofloxacin or moxifloxacin)

Oct 2010 – Dec 2012

Hospitalization for 2 wk
IV amikacin and cefoxitin (or imipenem) + oral macrolide

TABLE 3] Treatment Outcomes

Treatment Outcome Data	4-Week IV Group (n = 28)	2-Week IV Group (n = 43)	*P* Value
After 12 mo of treatment, No. (%)			
Symptomatic improvement	25 (89)	43 (100)	.057
HRCT scan improvement	22 (79)	39 (91)	.177
Sputum culture conversion	28 (100)	39 (91)	.148
Sputum culture conversion at the end of treatment, No. (%)	28 (100)	42 (98)	1.000
Follow-up duration after treatment completion, mo	33.8 (12.3-50.3)	14.7 (0.5-29.5)[a]	.006
Microbiologic recurrence, No. (%)	2 of 28 (7)	3 of 42 (7)[a]	1.000

4-wk IV group (n = 28)

2-wk IV group (n = 43)

CHEST 2016; 150:1211-1221

Risk assessment for NTM-PD → progression/Rx → Relapse

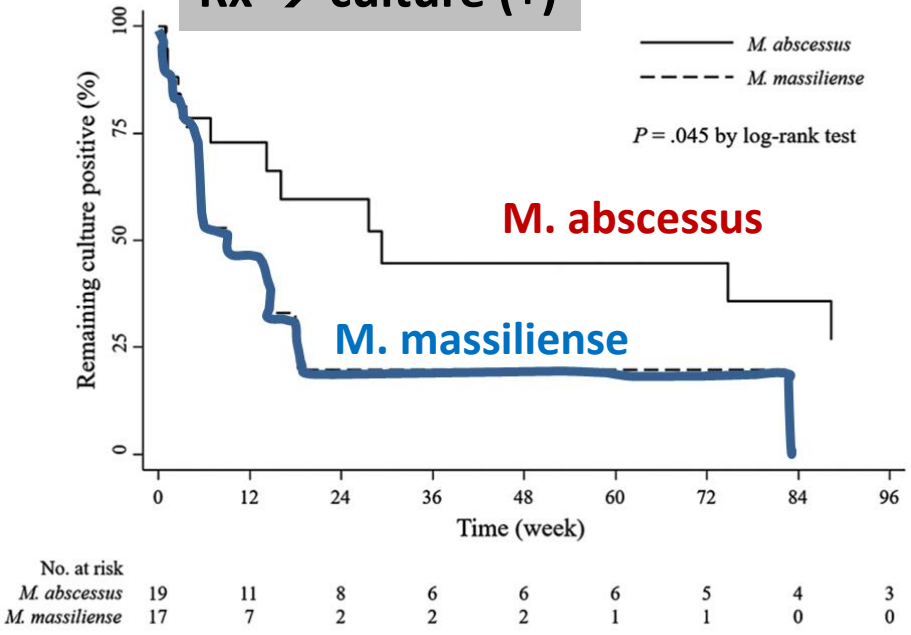
Among MAB patient

Disease progression: MAB. massiliense = MAB. abscessus

Treatment responses : MAB. massiliense > MAB. Abscessus

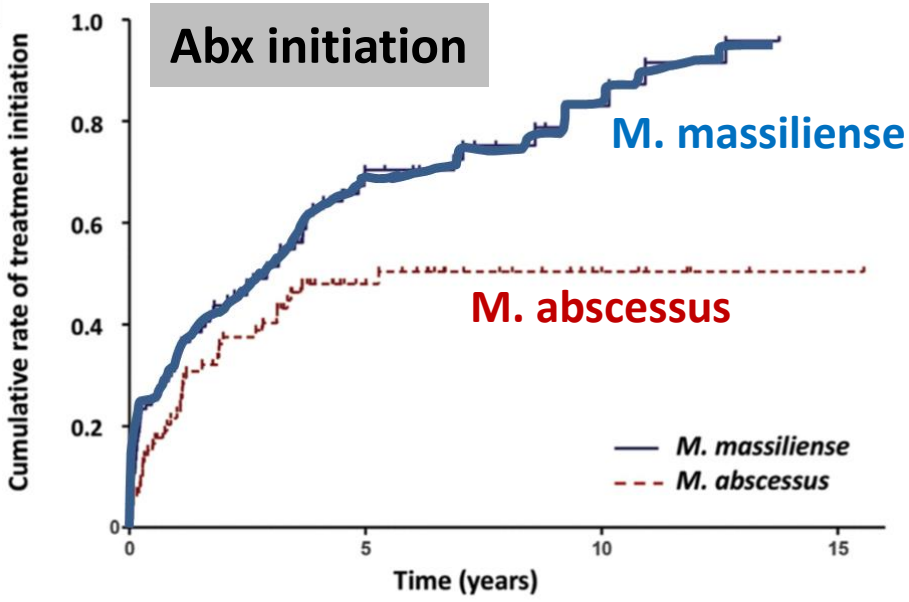
(macrolide resistance)

Rx → culture (+)



CID 2017;64(3):301–8

Abx initiation



Abx ↑? disease progression↑

Respir Med. 2019 May;151:1-7.

Treatment: *MAB*-PD

Non-R or inducible R

Constitutional resistance

2017 … 處方 (Mabs	
在 initial phase (用藥至少一個月†) 每日使用針劑 Amikacin 15 mg/kg (或 15–25 mg/kg tiw ‡) 加針劑 tigecycline 50 mg bid 加針劑 imipenem 1 g bid (若可以適應才使用) 加口服 Azithromycin 250-500 m (或 Clarithromycin 500 mg b 在 continuous phase 吸入型的 amikacin‡ 加口服 Azithromycin 250-500 m (或 Clarithromycin 500 mg b 加以下 1-3 種口服藥(依藥敏及病人適應)：clofazimine 50-100 mg qd，linezolid 600 mg qd or bid，minocycline 100 mg bid，moxifloxacin 400 mg qd，co-trimoxazole 960 mg bid	在 initial phase (用藥至少一個月†) 每日使用針劑 Amikacin 15 mg/kg (或 15–25 mg/kg tiw ‡) 加針劑 tigecycline 50 mg bid 加針劑 imipenem 1 g bid (若 … 才使用) 在 continuous phase 吸入型的 amikacin‡ 加下列 2-4 種口服藥(依藥敏及病人適應)：clofazimine 50-100 mg qd，linezolid 600 mg qd or bid，minocycline 100 mg bid，moxifloxacin 400 mg qd，co-trimoxazole 960 mg bid # 不建議使用 macrolide

IV Amik + Tige, Imipe Oral A/C

IV Amik + Tige, Imipe

2018 年 Kevin Winthrop 回顧 Mabs-PD 診療分類及建議抗生素處方	
一般治療原則	Macrolide 抗藥議題
在 induction phase(用藥至少 4-8 週) 使用 3-4 處方(包含 2 種針劑)，一般至少包含 Imipenem 或 Cefoxitin 加上 Amikacin 使用 4-8 週(Amikaci … mg/kg，於年紀大或長期治療可用 10mg/k… 少毒性)，同時加上 macrolide。 若 Amikacin 或 Imipenem/Cefoxitin 無法使用 … Tigecycline 替代(建議 50mg/day，以降低腸 在 suppressive phase 使用至少 2 種口服或吸性型抗生素。吸入型 … Mabs-PD 效果的相關研究乃在進行中。	用藥建議不明，但指出 Macrolide 抗藥機轉很多，不限於 erm(41)基因。

IV Amikacin + Imipenem or Cefoxitin (or Tigecycine) Oral A/C

14.Semin Respir Crit Care Med. 2018; 39: 362-376.

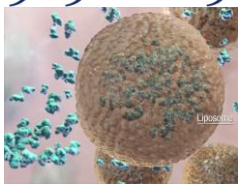
Treatment: *MAC*-PD

表三 MAC-PD 治療分類及處方[1,13]

2017 年 BTS 指引之 MAC-PD 診療分類及建議抗生素處方 (治療需持續至培養陰轉後 12 月)		
Non-severe MAC-PD	Severe MAC-PD (有任一指標因子: acid-fast bacilli (AF… respiratory tra… evidence of lung cavitation /severe infection, or severe symptoms/signs of systemic illness)	Macrolide-resistance MAC-PD
每週三次之 (A/CER TIW) Azithromycin 500mg (或	每日一次之 (A/CER QD) Azithromycin 250mg (或 Cl… 加	每日一次之 (H/MER QD) Isoniazid 300mg (+Pyridoxine 1… 加
加 Rifampicin 600mg	加 Rifampicin 600mg 考慮針劑之 Amikacin 至少三個月或吸入型的 amikacin	加上 Rifampicin 600mg 考慮針劑之 Amikacin 至少三個月或吸入型的 amikacin

2018 年 David E. Giffith 回顧 MAC-PD 診療分類及建議抗生素處方			
Nodular/bronchiectatic disease	Cavitary disease	Severe or previously treated disease	Macrolide-resistance MAC-PD
每週三次 macrolide 加 Ethambutol 加 rifamycin (TIW)(嚴重或開洞病灶不適用)	每日一次 macrolide† 加 Ethambutol 加 rifamycin，考慮使用針劑。大病灶或困難治療可考慮術。	每日一次 macrolide† 加 Ethambutol 加 rifamycin 加針劑如 Amikacin。	每日一次 Ethambutol 加 rifamycin‡加針劑如 Amikacin，並考慮手術。Rifamycin 中雖 Rifabutin 對病人較難適應，但抗菌性優於 Rifampicin。

mg (體重<50kg 用 150mg)或 rifampin 450–



NB pattern **Cavitary** **Severe or prior Rx** **Macrolide resistance**

.BTS Guidelines 2017

13. Semin Respir Crit Care Med. 2018; 39: 351-361

long-term assessment & treatment follow-up

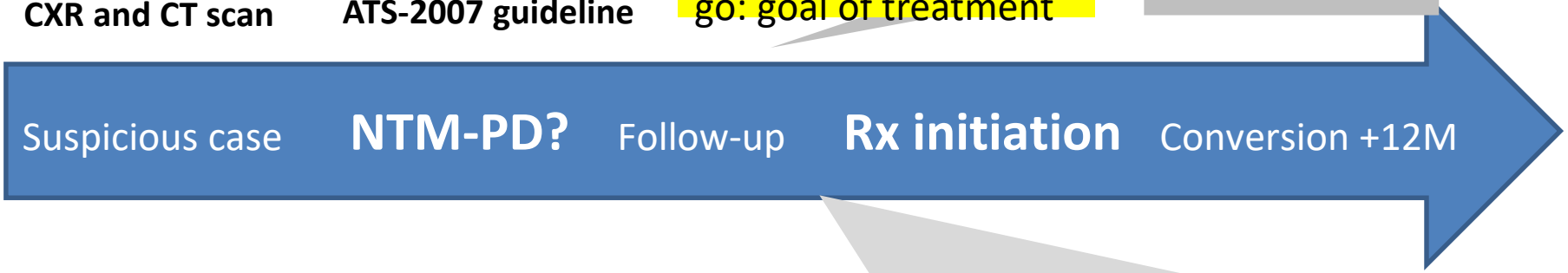
Sent 3 sputum for AFS & culture CXR and CT scan

NTM-ID, DST species/subsp.
M. Intra > M avium

Confirm NTM-PD by ATS-2007 guideline

I: Immunity
C: Cavity, severity
D: Disease progression
go: goal of treatment

✓ **progressive NTM-PD**
AFS (-) → +
CT: new lesion



DST →→

Follow-up

1) Symptoms

2) Microbiology

In vitro resistance	treatment failure in
macrolides and amikacin	MAC infection
rifampicin	M. kansasii infection
macrolides	M. abscessus pulmonary infection

sputum Q3M during Rx and for 12 months after completing Rx;

3) Radiology

→ **CT scan** before starting NTM Rx and at the end of treatment

4) Side effect of anti-NTM Rx

菌株次分型鑑定在NTM-PD的重要性

- **NTM 150 years, NTM-PD ↗**
- **ATS 2007→BTS 2017: Disease Progressive, ICD-go**
- **NTM-species, subspecies (Mab)**

OR/HR	NTM C+	NTM -PD	Disease progression	Spontaneous culture negative	Treatment response	Relapse
M. *avium*		2.1	1		Oral ?IH ?IV	4.5
M. *Intracellulare*		3.1	1.3			1
M. *chimaera*		1	?			5.6
MAB *abscessus*,			++		1	
MAB *massiliense*,			++		17.2 Oral +IV ? IH	

- **Decision to start treatment**
  - ✓**DST (genotyping), Regimen, Risk & Benefit**

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