Bronchiectasis and NTM pulmonary disease

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Contents

1. Prevalence of NTM in BE
2. Prevalence of BE in NTM
3. Pathogenesis
4. Treatment

Nontuberculous Mycobacteria (NTM)

- 200 종류 이상의 마이코박테리아가 환경에서 발견되고 있음 (주로 토양 또는 물)
- 성장 속도에 따른 구별
- Slow Growers (> 7days on solid media)
  - *M. avium complex*
  - *M. avium, M. intracellulare, M. chimaera*
- Rapid Growers (≤ 7days)
  - *M. abscesssus* group
  - Subspecies *abscessus*
  - Subspecies *massiliense*
  - Subspecies *bolletii*
- *Mycobacterium avium* complex 가 가장 흔하고 *M. abscessus, M. kansasii* 가 다음으로 흔하게 폐질환을 일으키고 있음.

Non-tuberculous mycobacteria

Rapidly growing mycobacteria

M. chelonae–abscessus complex
- *M. abscessus* subsp. *abscessus*
- *M. abscessus* subsp. *bolletii*
- *M. abscessus* subsp. *massiliense*
- *M. chelonae*

M. fortuitum

M. smegmatis
M. vaccae

Slowly growing mycobacteria

M. marinum
M. ulcerans

M. avium complex
- *M. avium*
- *M. intracellulare*
- *M. chimaera*

M. haemophilum
M. xenopi
M. kansasii
M. simiae

M. terrae complex
M. gordonae

M. tuberculosis complex

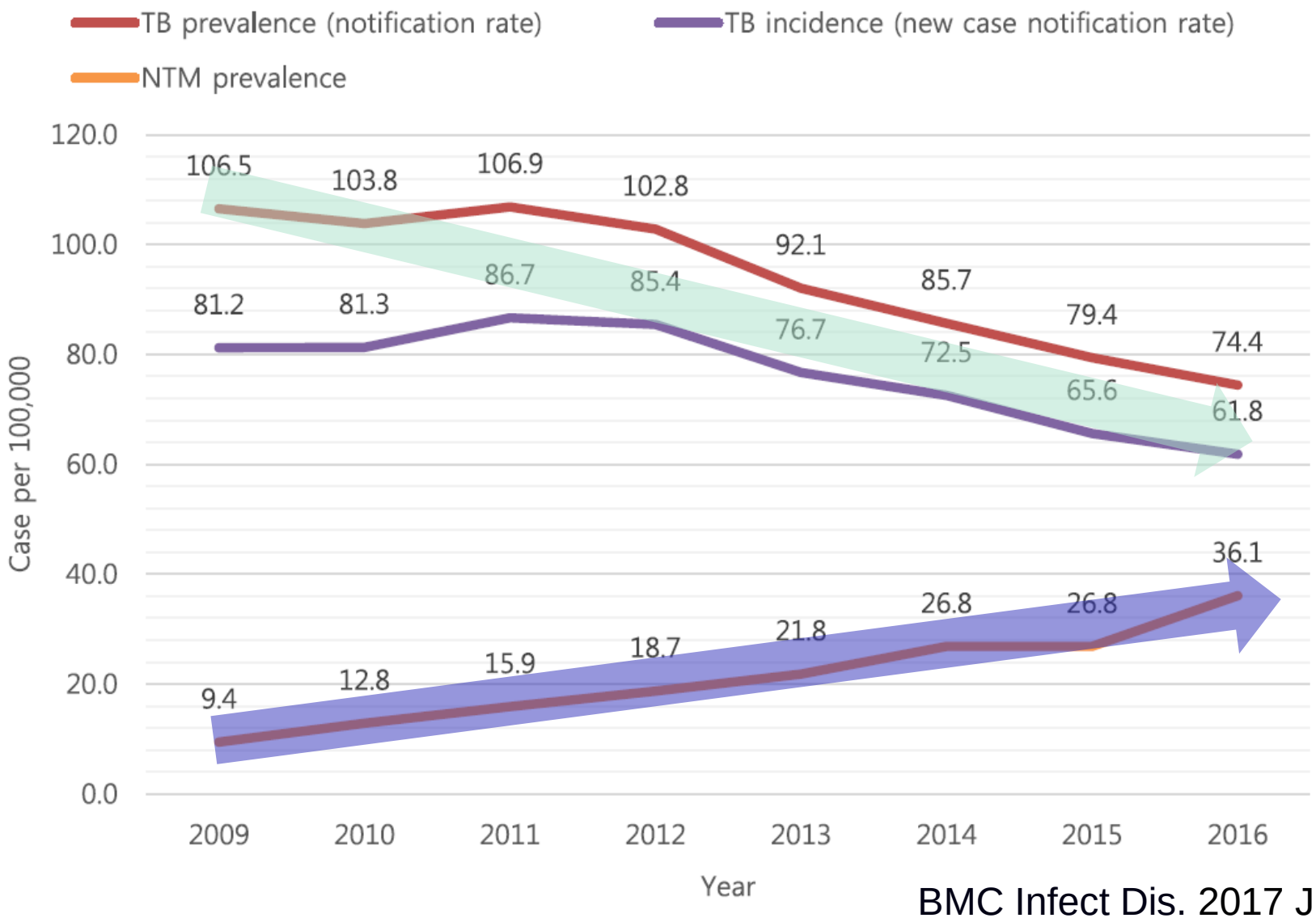
M. leprae

True pathogens
Opportunistic pathogens
Saprophytes*

*can be detected in clinical samples and need retesting to confirm infection

Nature Reviews Microbiology 2020;18: 392

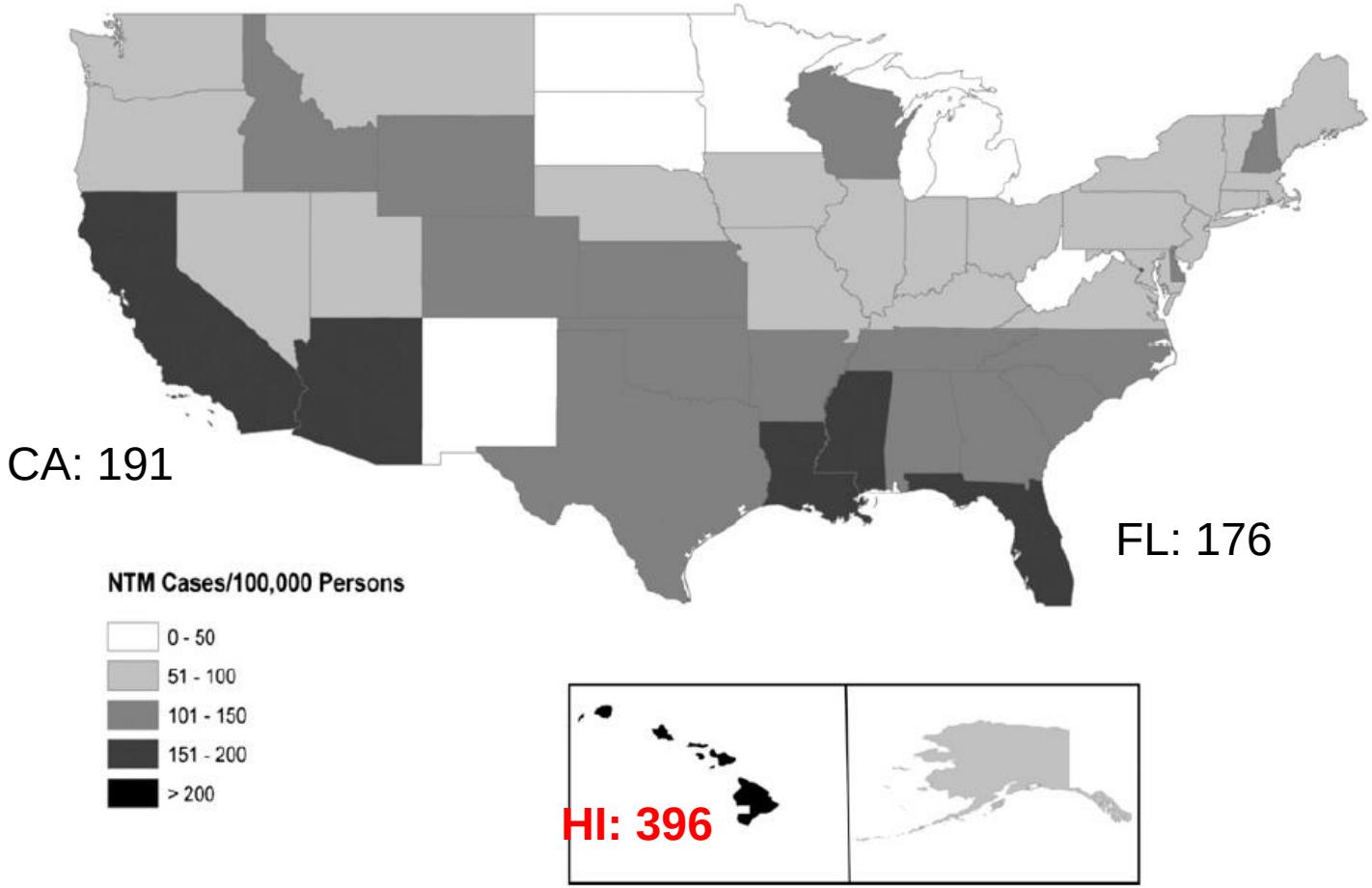
Prevalence and incidence of TB and NTM in Korea



BMC Infect Dis. 2017 Jun 15;17(1):432

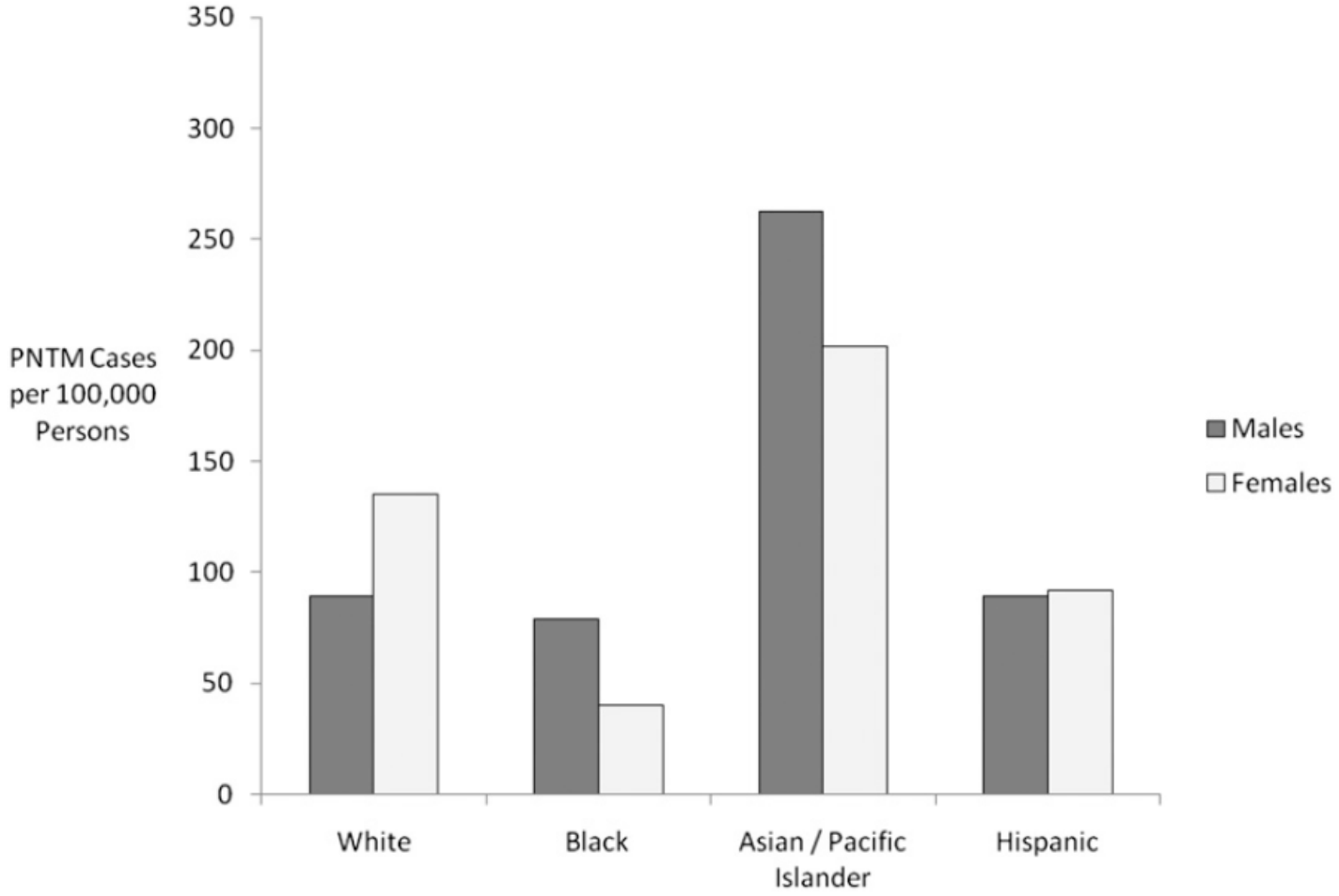
US Medicare Data

US average: 112/100,000



Adjemian J. Am J Respir Crit Care Med. 2012;185:881

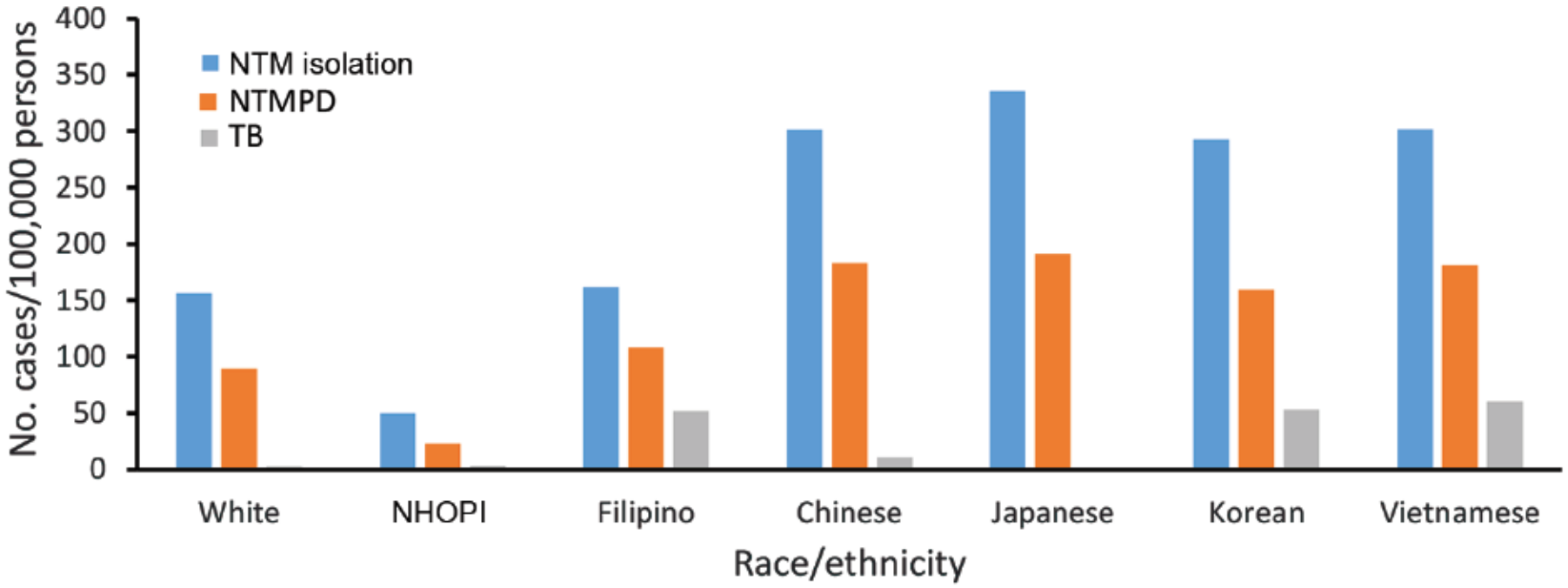
US Medicare Data



Adjemian J. Am J Respir Crit Care Med. 2012;185:881

Prevalence by ethnicity

A cohort of Kaiser Permanente Hawaii patients, Hawaii, 2005–2013.



Adjemian J. Emerg Infect Dis. 2017 Mar;23(3):439-447

Prevalence of NTM

In patients with BE

- Metaanalysis (18 countries, 21 studies)
  - NTM isolate 7.7% (0.6-50%)
  - NTM pulmonary disease 4.1%
    - Respiration 2021;100:1218
- Korea (single center cohort studies)
  - NTM isolation
  - 25% (n=6957) - 서울대병원
  - 44% (n=155) - 분당서울대병원
    - Respir Res. 2019;20:271
    - Respirology. 2016;21:1049

In general population

- Claim data in Korea
  - 6.7/100,000 in 2007 -> 39.6/100,000 in 2016
  - Age≥70, 223/100,000
    - Emerg Infect Dis. 2019;25:569
  - 1.2/100,000 in 2003 -> 33.3/100,000 in 2016
  - Age≥80, 189/100,000
    - BMC Pulm Med. 2019;19:140

NTM in elderly BE

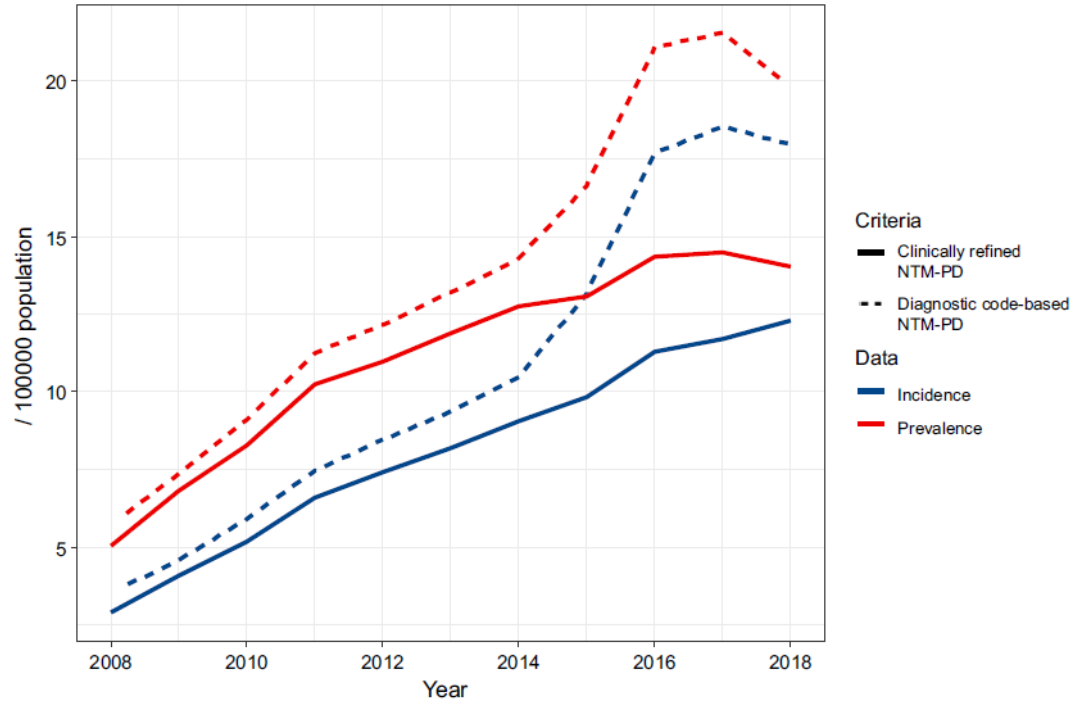
- US Medicare data (> 65 years old with BE between 2006-2014)
- 6% had NTM-PD over 8 years
- 1,950/100,000 person-years (BE > 65) vs.

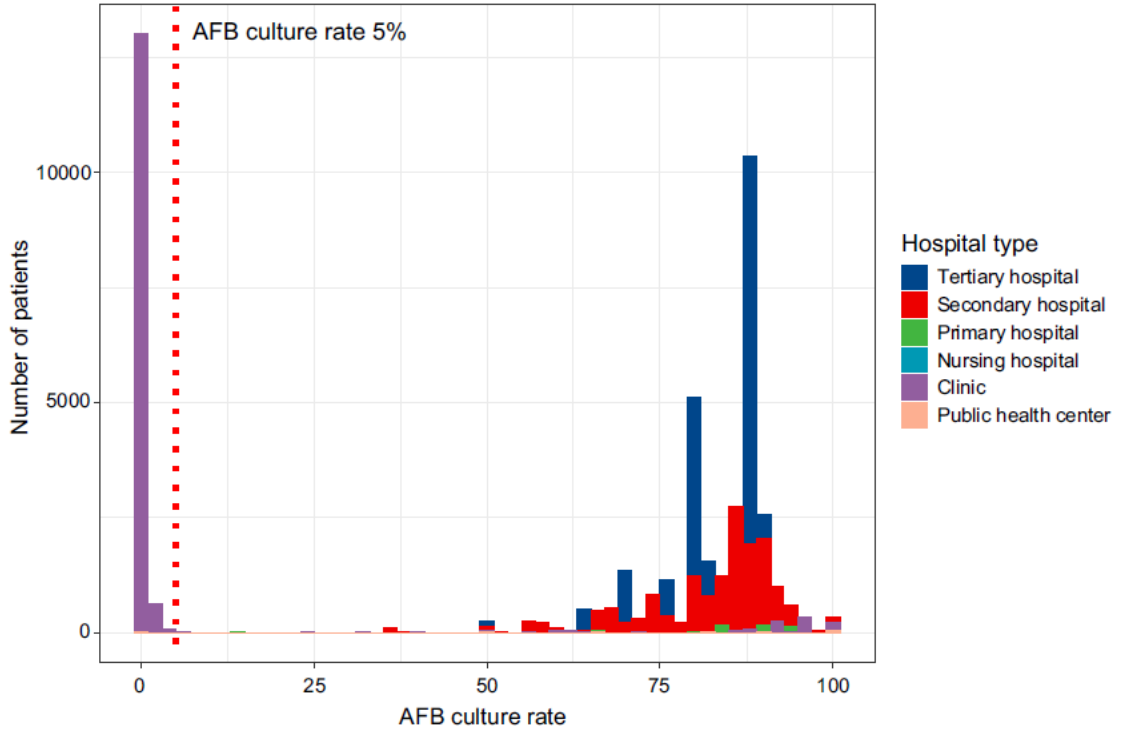
  18/100,000 person-years (General population > 65, claims database,

  Ann Thorac Soc 2020;17:178)
- Higher in older age, women, Asian/Pacific islanders

- Eur Respir J 2022;59:2200018

Overestimate in the claims data

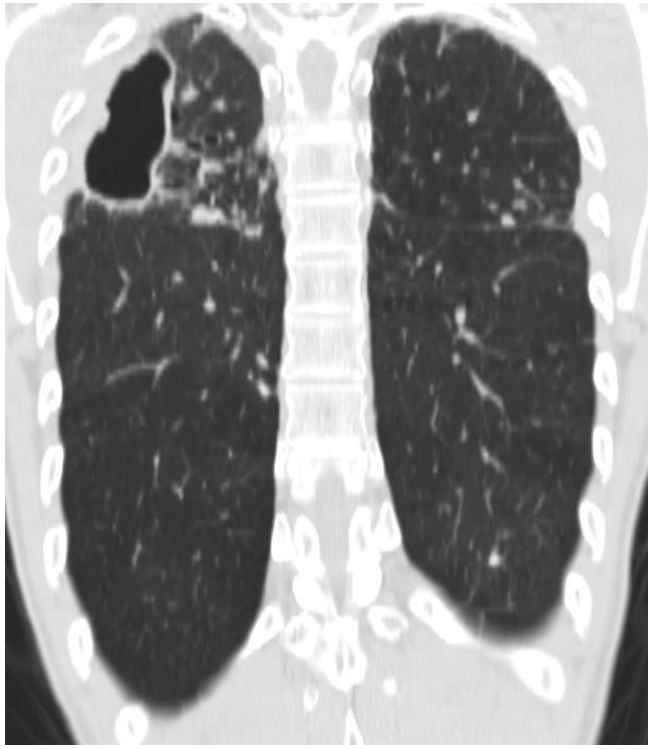


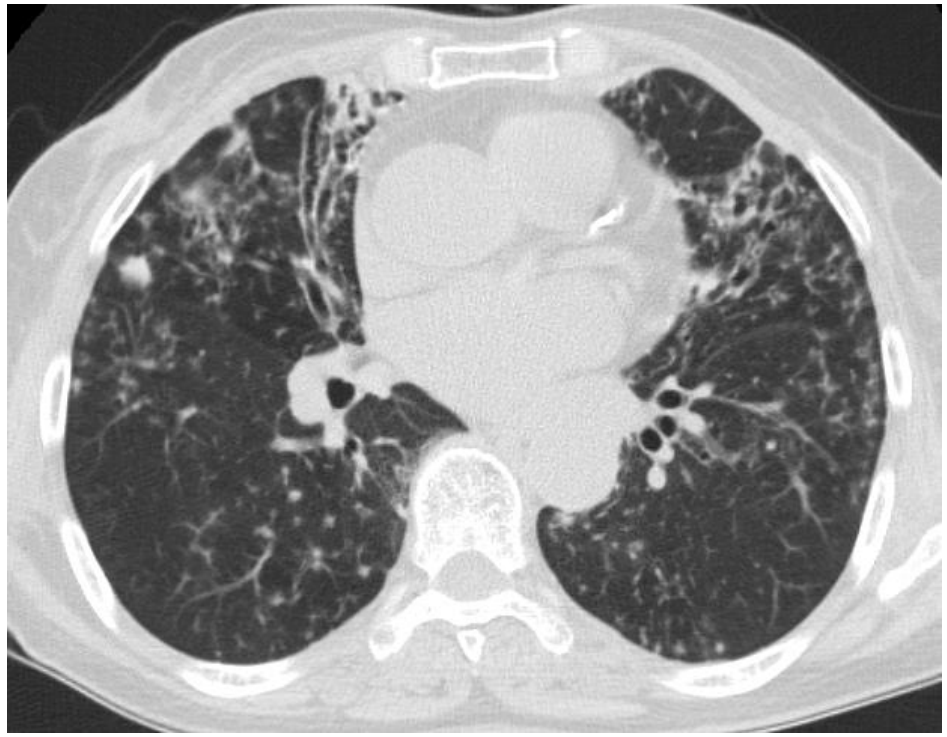


Park et al. BMC Pulmonary Medicine. 2022;22:195

Bronchiectasis in NTM pulmonary disease

- Two major manifestations of NTM-PD



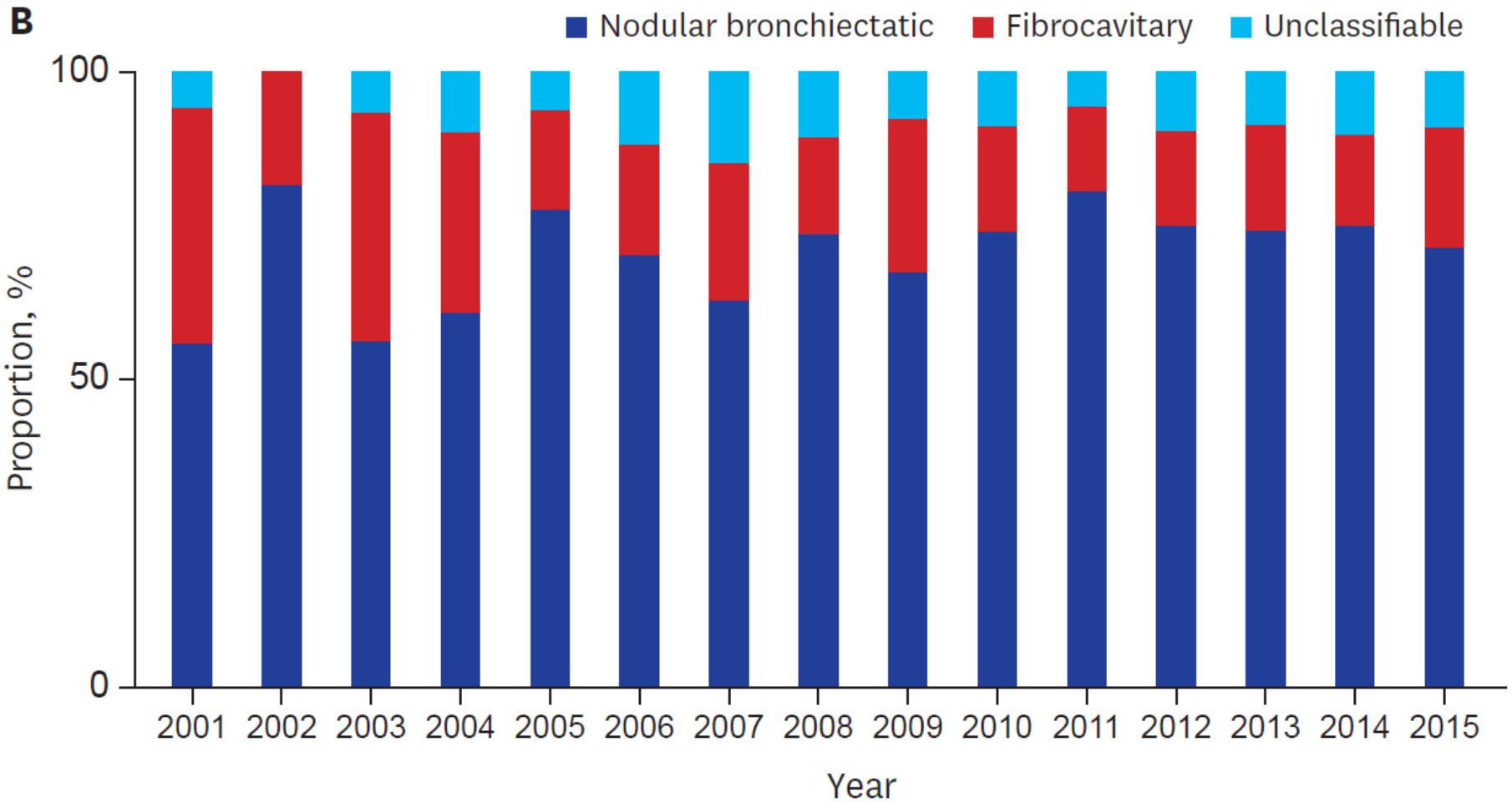


NTM Lung Disease:
Nodular Bronchiectatic Form

- middle-aged or elderly women
- non-smokers
- no previous underlying disorders

- HRCT
  multiple small nodules (< 5 mm) & bronchiectasis
  confined to or most severe in RML and LUL lingular segment

- Indolent course, slow progression of CXR abnormalities



NB form: 56% in 2001 to 72% in 2015

Ko RE. J Korean Med Sci. 2018;33:e65.

NTM infection in pathogenesis of BE

- BE evolves due to underlying genetic risk factors and/or recurrent exposures to environmental mycobacteria.
- Can be
  - A primary cause of BE
  - A secondary infection complicating preexisting BE
- NTM can exacerbate preexisting BE
  - CF, PCD, prior TB, COPD

NTM infection in pathogenesis of BE

- Pathology of MAC pulmonary disease: a single center, n=9

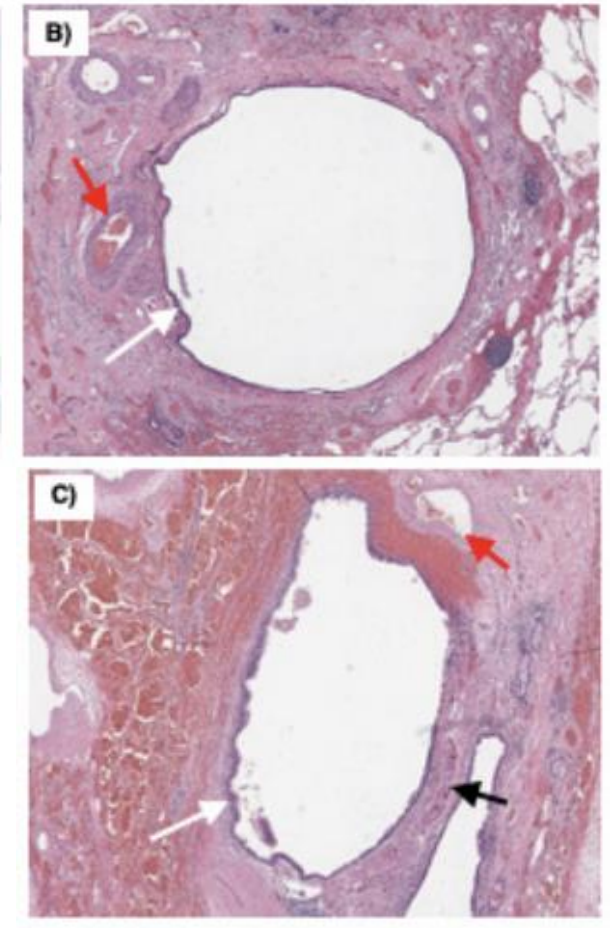
  - ✓ Destruction of bronchial cartilage.
  - ✓ Destruction of smooth muscle layer
  - ✓ Ulceration of bronchial mucosa.
  - ✓ Narrowing of bronchial lumina.
  - ✓ Peribronchial granuloma formation in the large airway.

1. Cartilage and smooth muscle destruction, caused by MAC, could result in bronchiectasis
2. MAC was detected in granuloma of bronchiectasis

Respiratory Medicine. 2003;97:933

NTM infection in pathogenesis of BE

- Pathology of MAC pulmonary disease: a single center, n=999
  - Parenchymal granuloma: 64%
  - Bronchiolitis: 57%
  - Necrotizing granuloma (both airway and parenchymal): 50%
  - Necrotizing parenchymal granuloma: 50%
  - Airway granuloma: 41%
  - Bronchiolectasis: 40%
  - Bronchiectasis: 34%



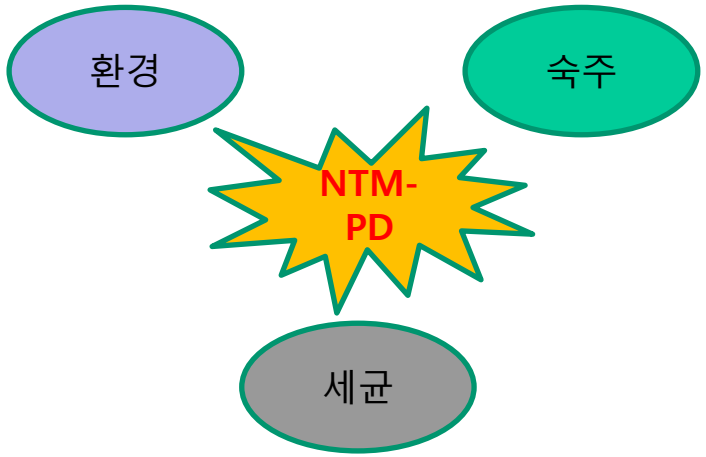
Yale J Bio Med. 2021:94:527

Pathogenesis of NTM infection

비결핵항산균: 토양, 물 등 환경에 존재하는 균

질병발생

- 환경
- 숙주 감수성
- 세균



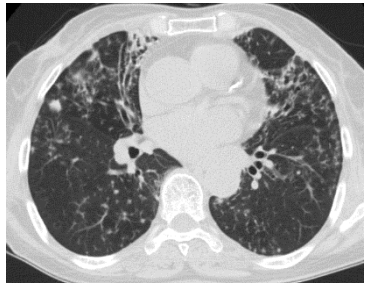
NTM disease according to host immunity

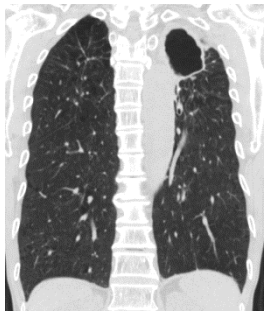
Decreased Immunity

Skin and soft tissue infections: immunocompetent, usually iatrogenic

Arch Aesthetic Plast Surg 2021;27(1):3-11

Isolated pulmonary disease: typical morphotype or structural lung disease





Disseminated: significant immunodeficiency

Susceptibility to pulmonary NTM

Impaired local defenses Bronchiectasis, emphysema, pneumoconiosis, previous cavitary TB, silicosis, COPD	Clinical history, chest imaging, pulmonary function tests
Cystic fibrosis	Sweat chloride test, CFTR genotyping
Primary ciliary dyskinesia	Respiratory epithelia Bx.
Impaired systemic immunity STAT3 deficiency	Total IgE, cardial clinical features & family history, STAT3 genotyping
Immunosuppressant use Tumor necrosis factor-a blockers	Drug history
Idiopathic bronchiectasis (Lady Windermere syndrome)	Clinical history with exclusion of the above conditions, special body morphotypic features

Wu. Lancet Infect Dis. 2015;15:968

Potential endotypes for patients with idiopathic BE with NTM-PD

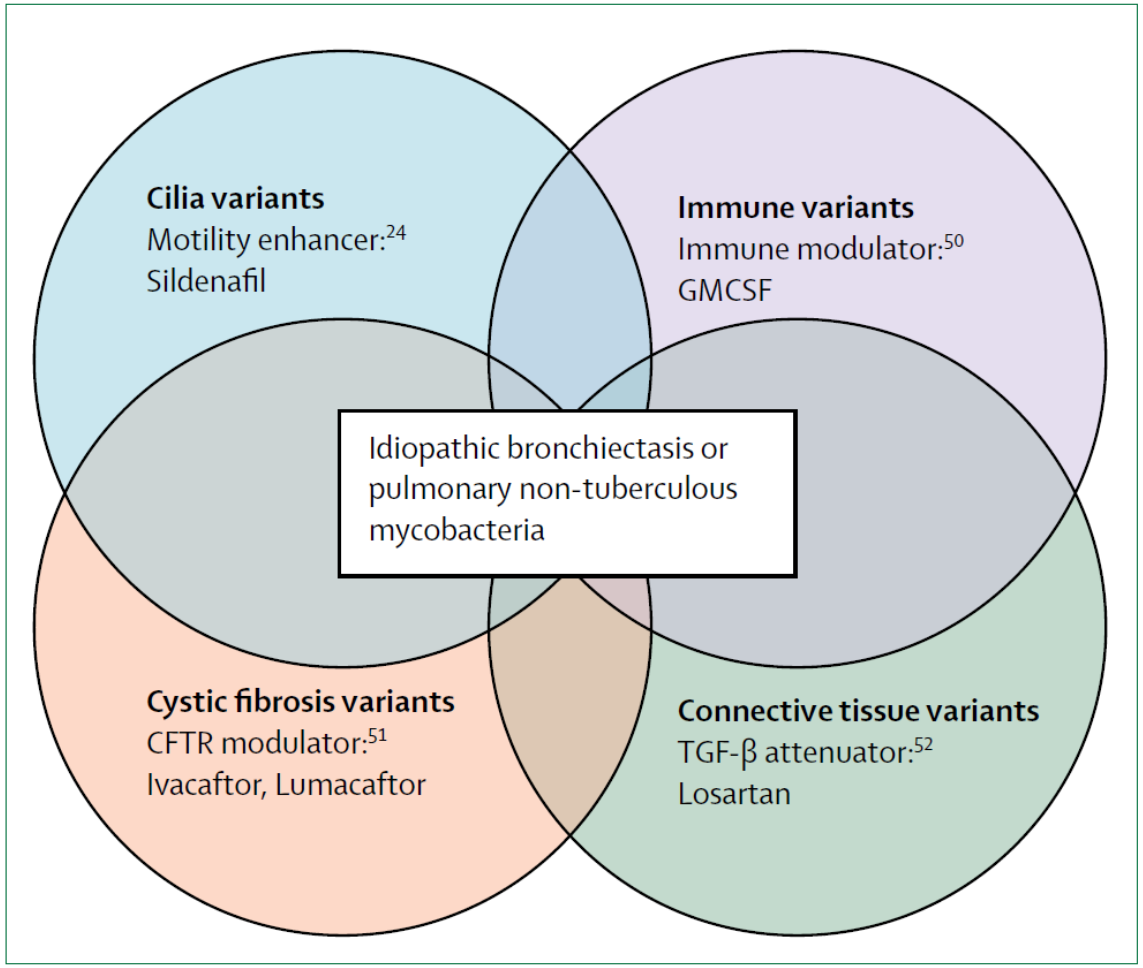


Figure 4: **Potential endotypes for patients with idiopathic bronchiectasis with pulmonary non-tuberculous mycobacteria infections**

Flume PA et al. Lancet 2018; 392: 880

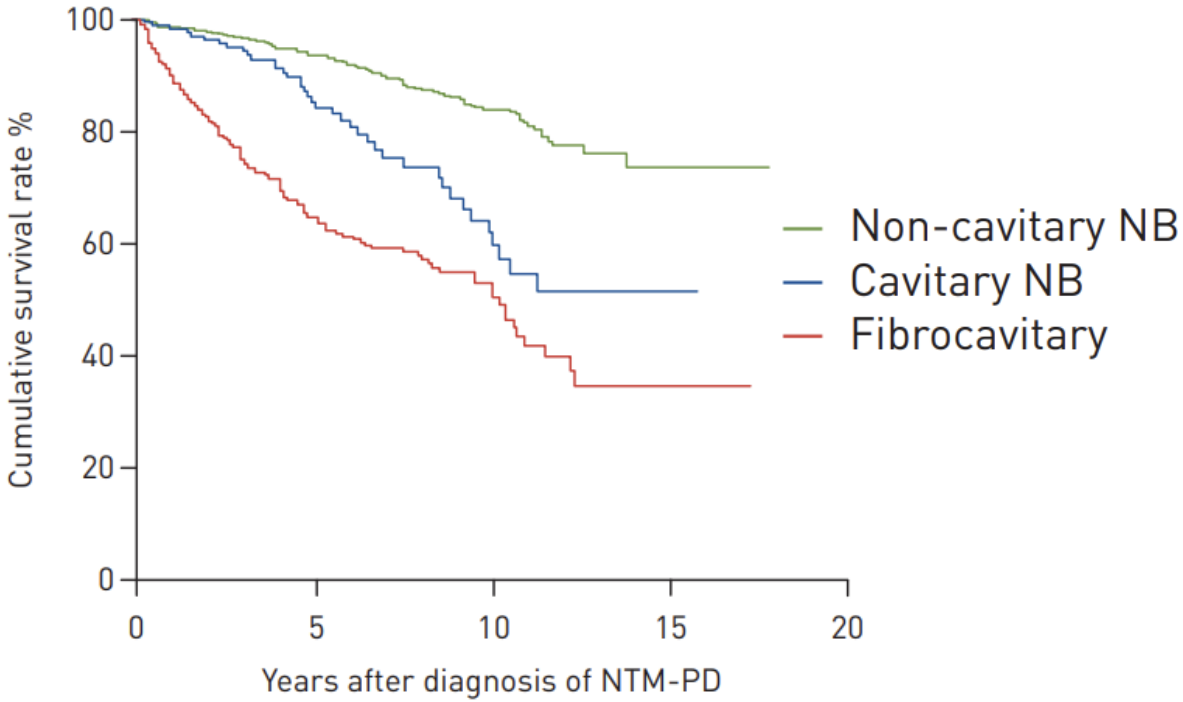
Natural course of NB NTM

- A single center cohort study (n=551)
- Progression within 3 years (received treatment within 3 years): 59%
- No progression: 41%
- Spontaneous culture conversion: 52%
- Predictors of receiving treatment
  - Age ≤ 60, AFB +, systemic Sx., BMI > 18.5, lung involvement ≥ 4 lobes.

- Respir Med 2019;150:45

Natural course of NB NTM

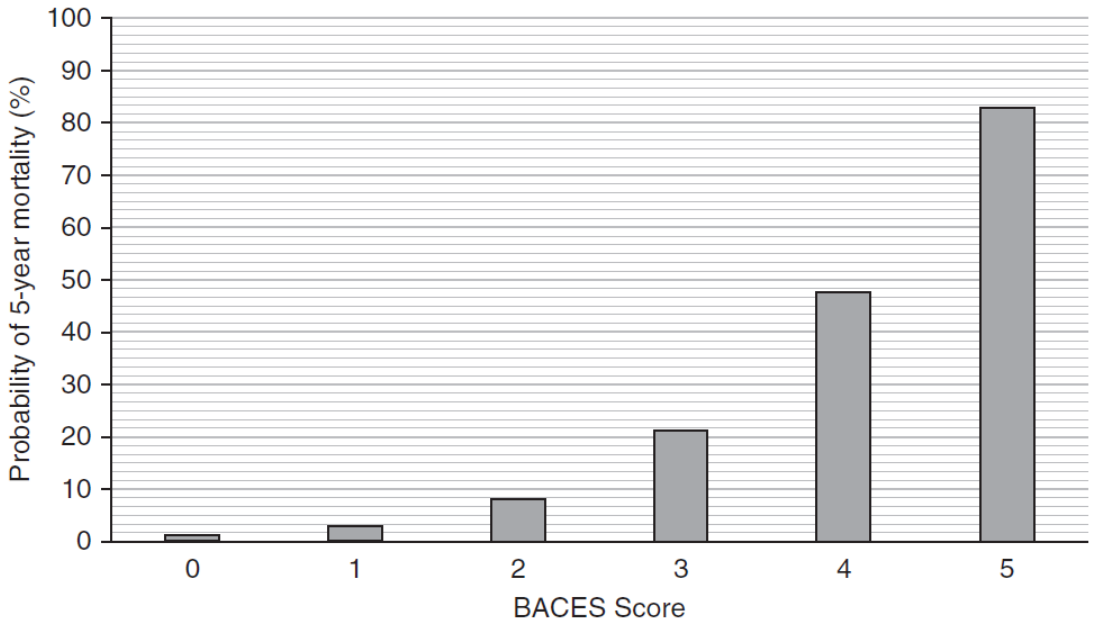
- A single center cohort study (n=1445)
- Factor associated mortality
  - Old age
  - Male
  - Low BMI
  - Chronic pulmonary aspergillosis
  - Malignancy
  - Chronic heart or liver disease
  - ESR
- Species associated mortality
  - *M. intracellulare, M. abscessus*



Eur Respir J 2020;55:1900798

Base score

- **Predictors of mortality**
- **B**MI <18.5 kg/m2
- **A**ge >65 years
- Presence of **C**avitary lung disease
- Elevated **E**SR
- Male **S**ex (BACES score).



Am J Respir Crit Care Med 2021; 203: 230

Macrolide resistant MAC-PD

Author, year	Country	N	Culture conversion	Mortality	Previous Tx.	Recommended Tx.
Griffith, 2006	US	51	25%	1 year: 25%	Macrolide monotherapy Macrolide plus quinolone Macrolide plus RIF	Surgery plus aminoglycosides
Kadota, 2016	Japan	33	36%	NA	CLR plus two drugs CLR monotherapy CLR plus one drug	No regimens improved treatment outcomes
Morimoto, 2016	Japan	102	11%	5 year: 29%	CLR monotherapy CLR plus RIF CLR plus fluoroquinolone	Surgery plus aminoglycosides
Moon, 2016	Korea	34	15%	1 year: 9% 5 year: 47%	Macrolide plus two drugs Macrolide plus RIF	Surgery

Macrolide susceptible	Culture conversion
Non cavitary	80%
Cavitary	50-80%

Kwon YS. Expert Rev Respir Med. 2019;8:1

Treatment outcome: systematic review

Treatment Naive				
Subspecies	N	Sustained culture conversion	Sustained culture conversion without relapse	Recurrence rate
M. abscessus	233	77/233 (34%)	52/223 (23%)	40%
M. massiliense	141	117/141 (83%)	118/141 (84%)	7%

Antimicrob Agents Chemother 2017; Oct 24;61(11).

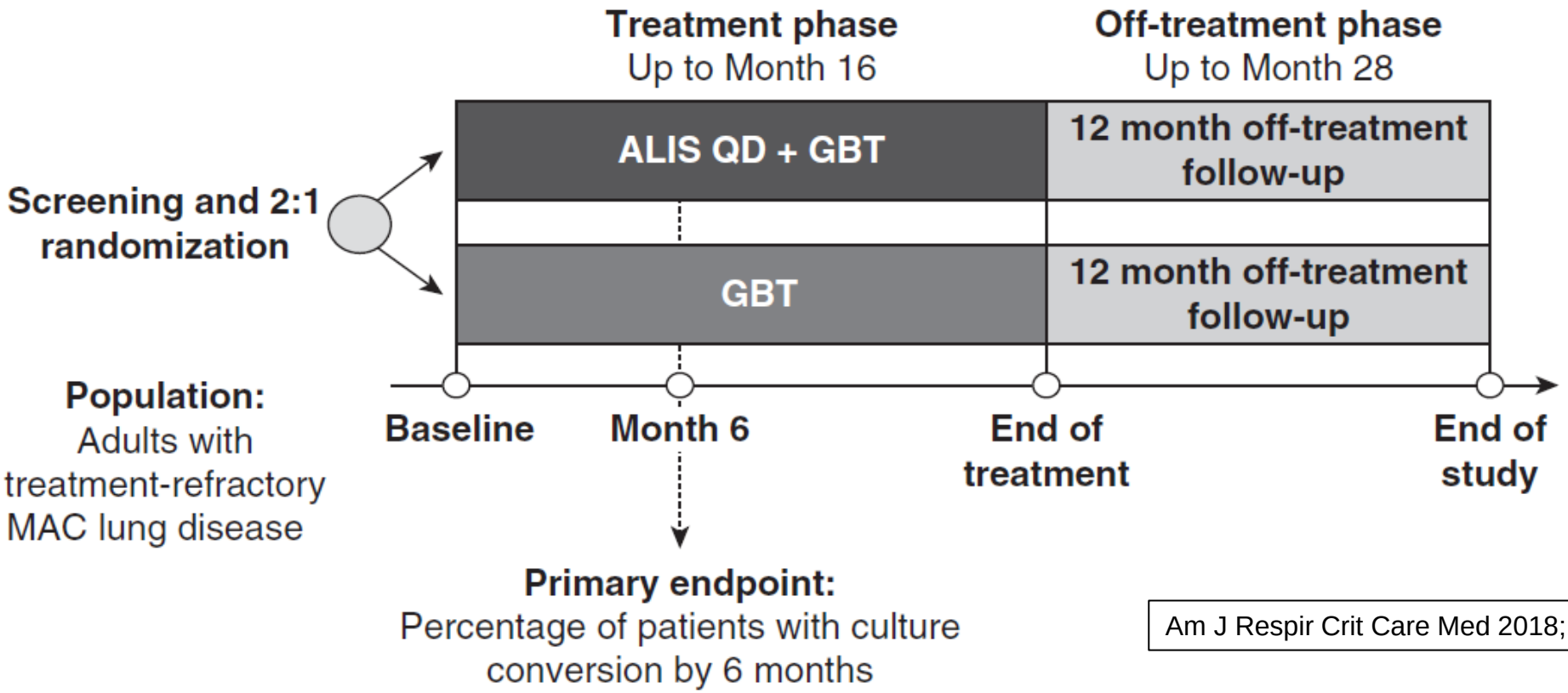
MAC recurrences after completion of therapy

	University of Texas	Northwestern, Chicago	Samsung medical center, Seoul
Number of patients	155	190	402
Microbiologic recurrence	48%	25%	29%
New infection	75%	46%	74%

Wallece R, et al. Chest 2014;146:276
Boyle DP, et al. Ann Am Thorac Soc 2016
Koh WJ et al. Eur Respir J 2017;50:1602503

CONVERT STUDY

Phase 3 Randomized, Controlled Trial of Amikacin Liposome Inhalation Suspension (ALIS) + GBT vs GBT alone



Am J Respir Crit Care Med 2018;198:1559

Table 1. Baseline Demographic and Disease Characteristics: ITT Population

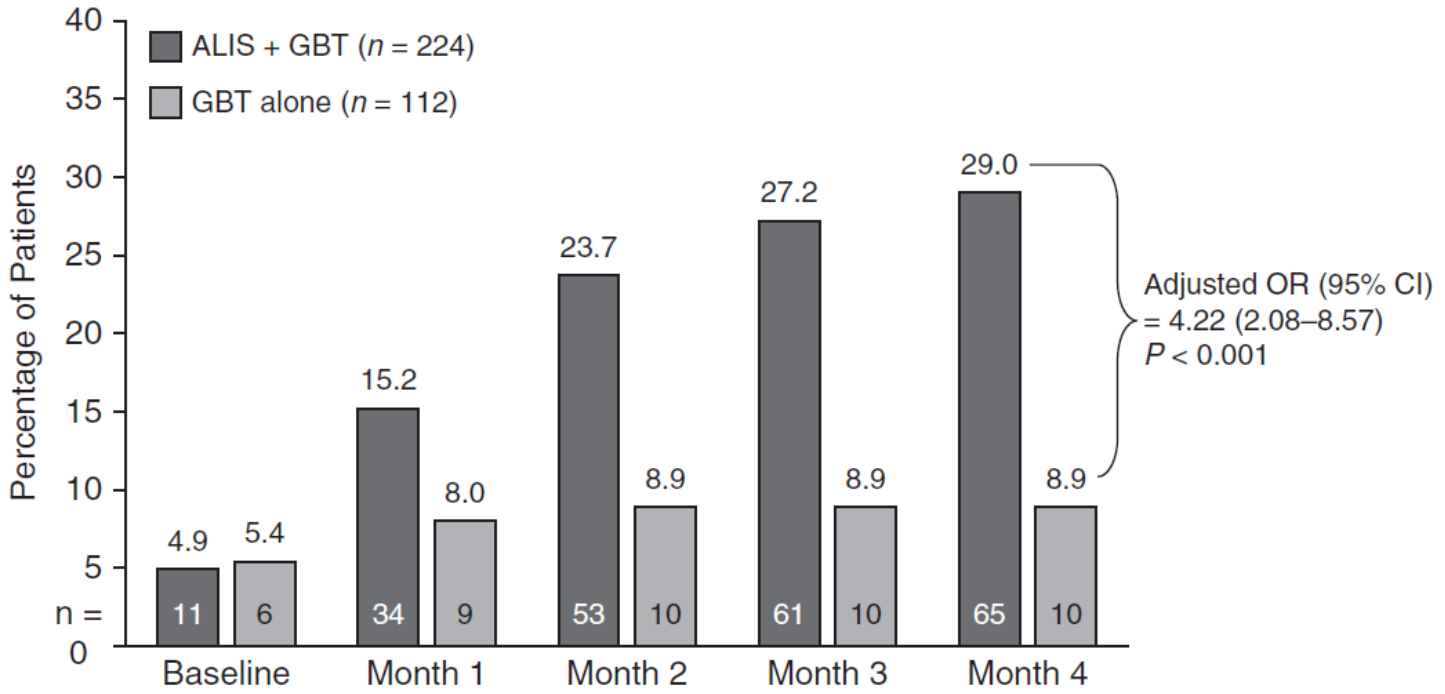
Parameter	ALIS + GBT (*n* = *224*)	GBT Alone (*n* = *112*)	Overall (*n* = *336*)
Age, yr, mean (SD)	64.6 (9.6)	64.9 (10.2)	64.7 (9.8)
Female, *n* (%)	165 (73.7)	68 (60.7)	233 (69.3)
Body mass index, kg/m^2, mean (SD)	21.3 (3.9)	20.9 (3.8)	21.2 (3.9)
Race, *n* (%)			
White	158 (70.5)	77 (68.8)	235 (69.9)
Black/African American	3 (1.3)	3 (2.7)	6 (1.8)
Asian: Japanese	35 (15.6)	15 (13.4)	50 (14.9)
Asian: other	23 (10.3)	10 (8.9)	33 (9.8)
Other/not reported	5 (2.2)	7 (6.3)	12 (3.6)
Underlying lung disease, *n* (%)			
Bronchiectasis only	146 (65.2)	64 (57.1)	210 (62.5)
COPD* only	29 (12.9)	19 (17.0)	48 (14.3)
COPD* and bronchiectasis	22 (9.8)	18 (16.1)	40 (11.9)
Clarithromycin-resistant MAC (MIC ⩾32 μg/ml), *n* (%)	51 (22.9)	22 (19.6)	73 (21.8)
Current smoker, *n* (%)	26 (11.6)	10 (8.9)	36 (10.7)
Receiving GBT at enrollment, *n* (%)	201 (89.7)	101 (90.2)	302 (89.9)

Definition of abbreviations: ALIS = amikacin liposome inhalation suspension; COPD = chronic obstructive pulmonary disease; GBT = guideline-based therapy; ITT = intention-to-treat; MAC = *Mycobacterium avium* complex; MIC = minimum inhibitory concentration.
*COPD diagnosis was derived from medical history.

Am J Respir Crit Care Med 2018;198:1559

CONVERT STUDY

Proportion of Patients with Negative Sputum Cultures for NTM



Am J Respir Crit Care Med 2018;198:1559

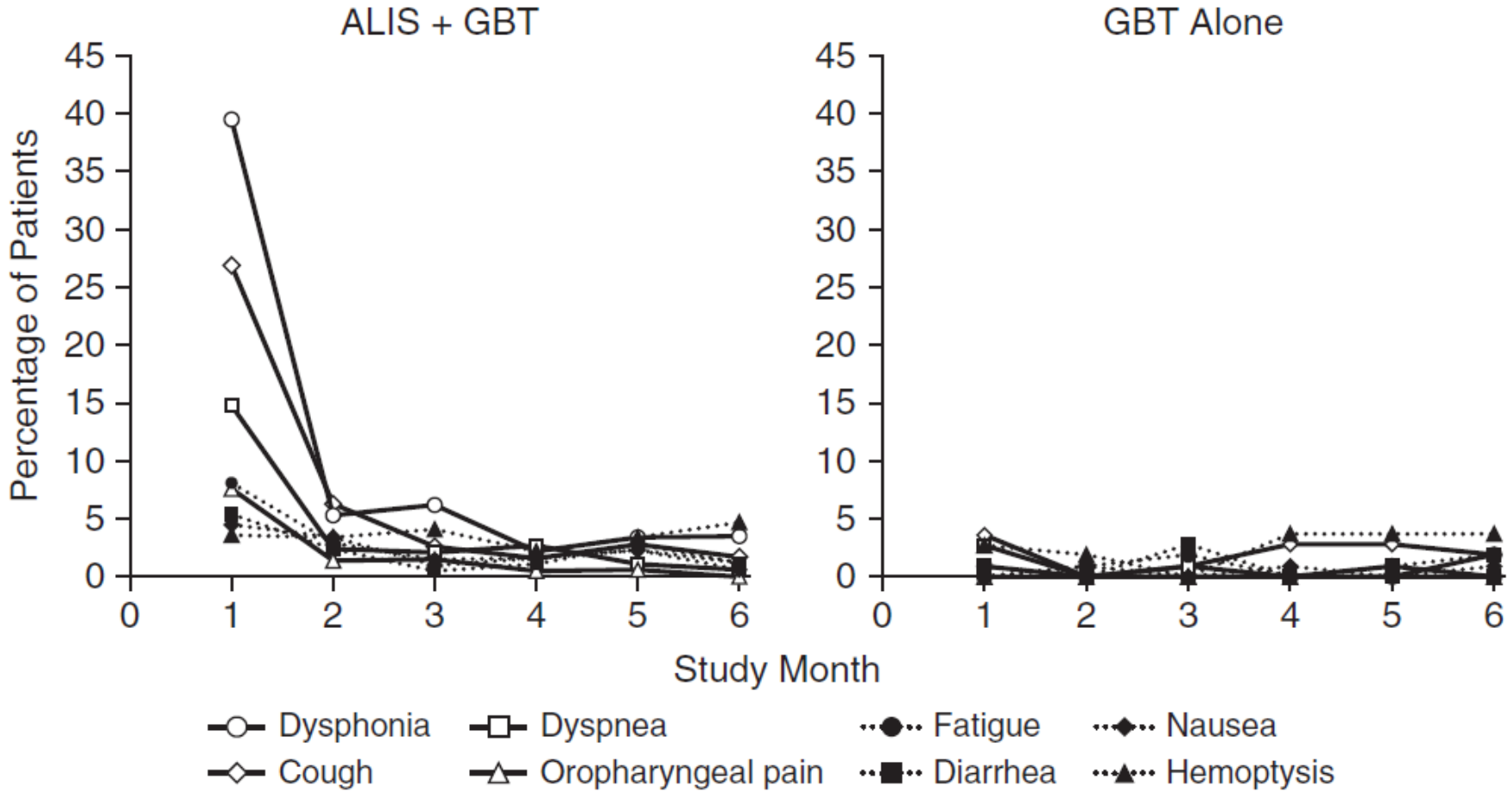
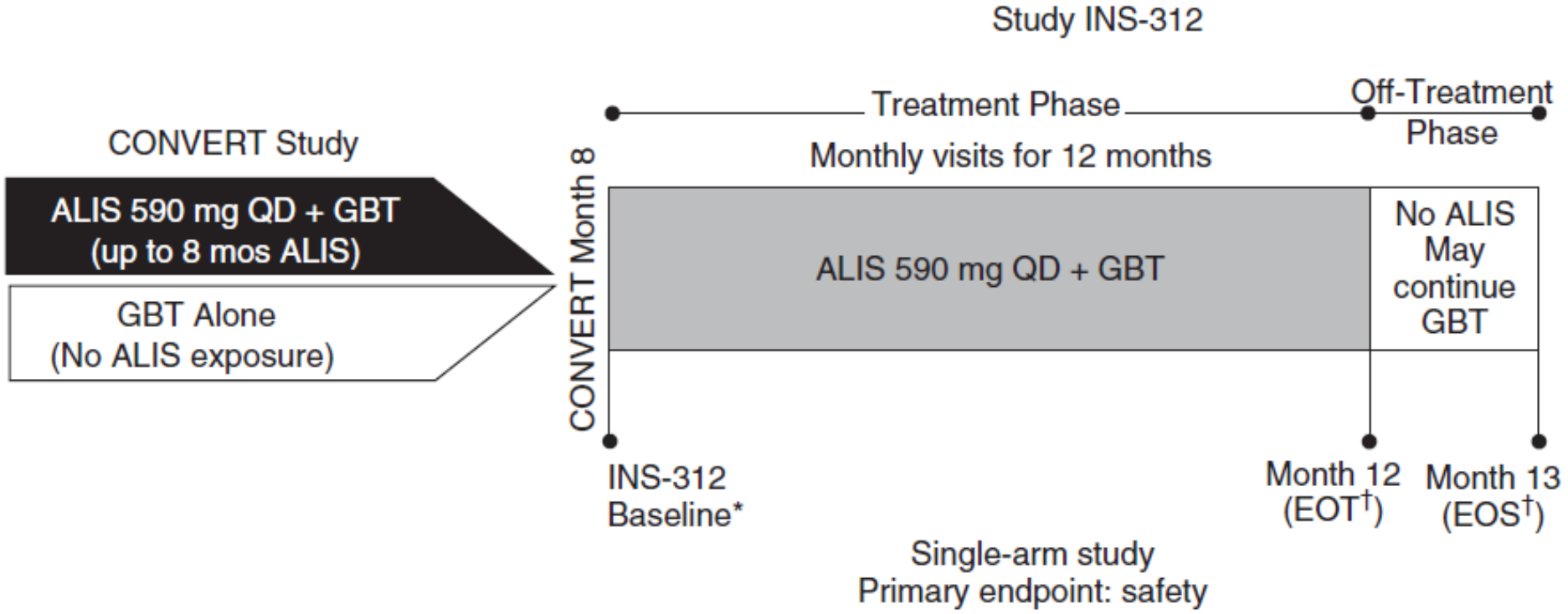


Figure 5. Onset of the most frequent adverse events over time: safety population. Time courses of the onset of the most frequent treatment-emergent adverse events (occurring in ⩾10% of patients in either arm) are shown by treatment arm and study month. Data indicate the month at which the events were first reported after initiation of therapy. ALIS = amikacin liposome inhalation suspension; GBT = guideline-based therapy.

Amikacin Liposome Inhalation Suspension for *Mycobacterium avium* Complex Lung Disease

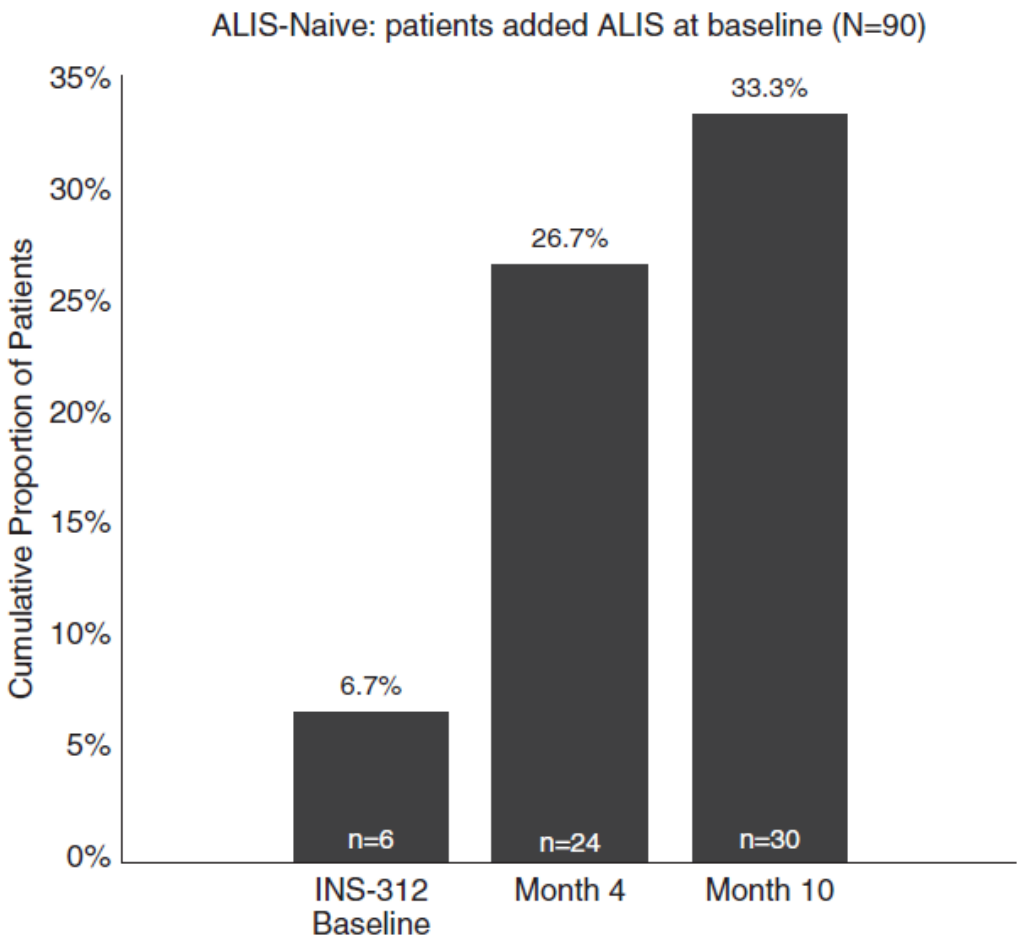
A 12-Month Open-Label Extension Clinical Trial

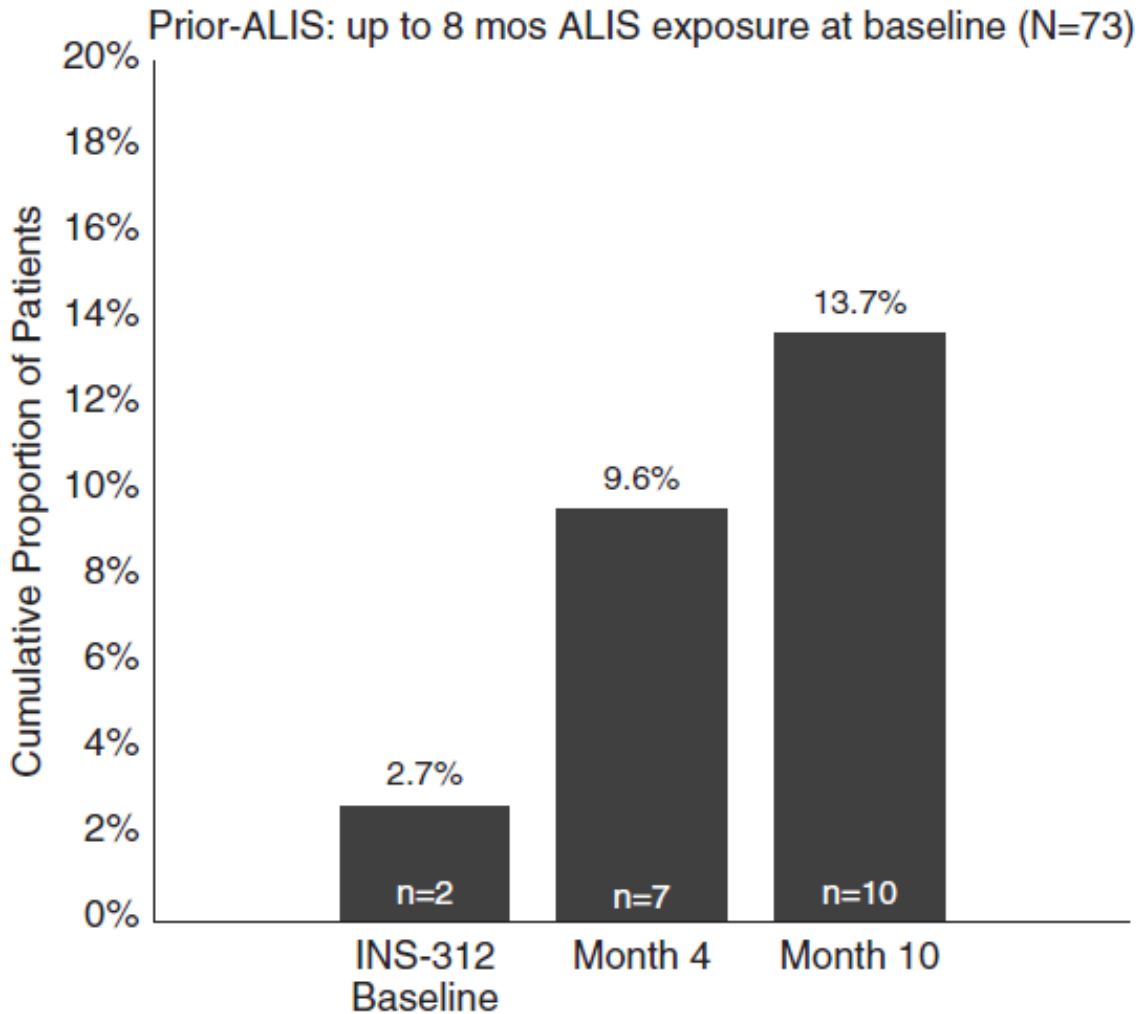
Kevin L. Winthrop[1], Patrick A. Flume[2], Rachel Thomson[3], Kevin C. Mange[4], Dayton W. Yuen[4], Monika Ciesielska[4], Kozo Morimoto[5], Stephen J. Ruoss[6], Luigi R. Codecasa[7], Jae-Joon Yim[8], Theodore K. Marras[9], Jakko van Ingen[10], Richard J. Wallace, Jr[11], Barbara A. Brown-Elliott[11], Chris Coulter[12], and David E. Griffith[11]*; for the INS-312 Study Group



Results are presented by treatment received in CONVERT

- ALIS-Naive Cohort: first ALIS dose received in INS-312
- Prior-ALIS Cohort: received ALIS up to 8 months at INS-312 BL


ALIS-Naive: patients added ALIS at baseline (N=90)
Cumulative Proportion of Patients
35%
30%
25%
20%
15%
10%
5%
0%
6.7%
26.7%
33.3%
n=6
n=24
n=30
INS-312 Baseline
Month 4
Month 10


Prior-ALIS: up to 8 mos ALIS exposure at baseline (N=73)
Cumulative Proportion of Patients
20%
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
2.7%
9.6%
13.7%
n=2
n=7
n=10
INS-312 Baseline
Month 4
Month 10

Coinfection of NTM and Other Pathogens in BE

- *Pseudomonas aeruginosa*: 27-52%

- A single center cohort study
  - *Pseudomonas aeruginosa*
    - ✓ 52% at the time of first isolation of NTM (n=25)
    - ✓ 16%: chronic isolate (two or more Pseudomonas culture)
  - Other organisms
    - ✓ *S. aureus* (28%)
    - ✓ *Haemophilus influenzae* (12%)
    - ✓ *Aspergillus fumigatus* (4%)
    - ✓ *Candida albicans* (8%)
    - ✓ *Stenotrophomonas maltophilia* (4%)

- Biomed Res Int. 2015:197950
- Thorax. 2005;60:1045

Non-pharmacologic therapy: behavioral changes

- Inhalation of aerosolized droplets containing NTM
  - ✓ Natural surface water
  - ✓ Hot water systems
  - ✓ Ingestion with subsequent aspiration.
- Decrease occupational or recreational exposure to NTM
  - ✓ Water: swimming
  - ✓ Soils: gardening, mining, coal working, agriculture, landscaping, construction, tunnel work
  - ✓ Aerosols: showering, hot tubs

ERJ Open Res 2021; 7: 00574

Dual beta-lactam synergy

MIC (ug/ml)

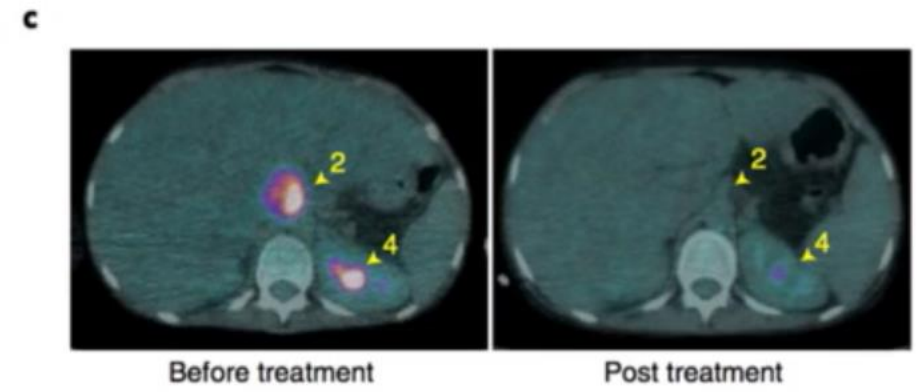
Strain	Species	CAZ+AVI4	CFT	CFT+CAZ10	CFT+CAZ50	CFT+CAZ100	CFT+ CAZ100+AVI4
ATCC 1977	*M. abscessus*	512	32	0.25	0.125	0.125	<0.25
51412	*M. abscessus*	356	8	0.5	0.5	0.5	1
51403	*M. abscessus*	128	8	1	0.25	0.125	0.25

CAZ: ceftazidime CFT: ceftaroline AVI: avibactam

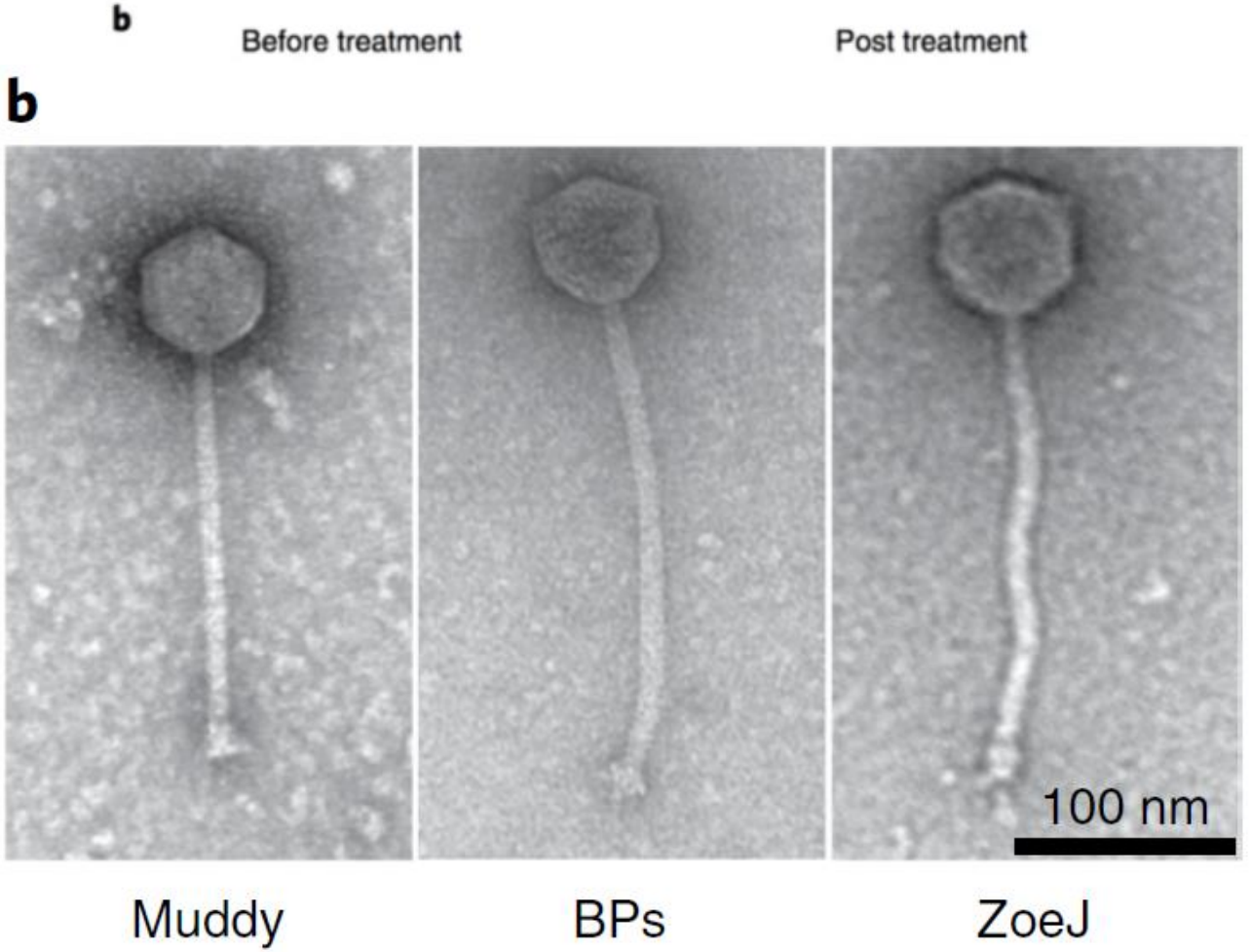
MBio. 2019 Feb 12;10(1)

Engineered Phage Therapy

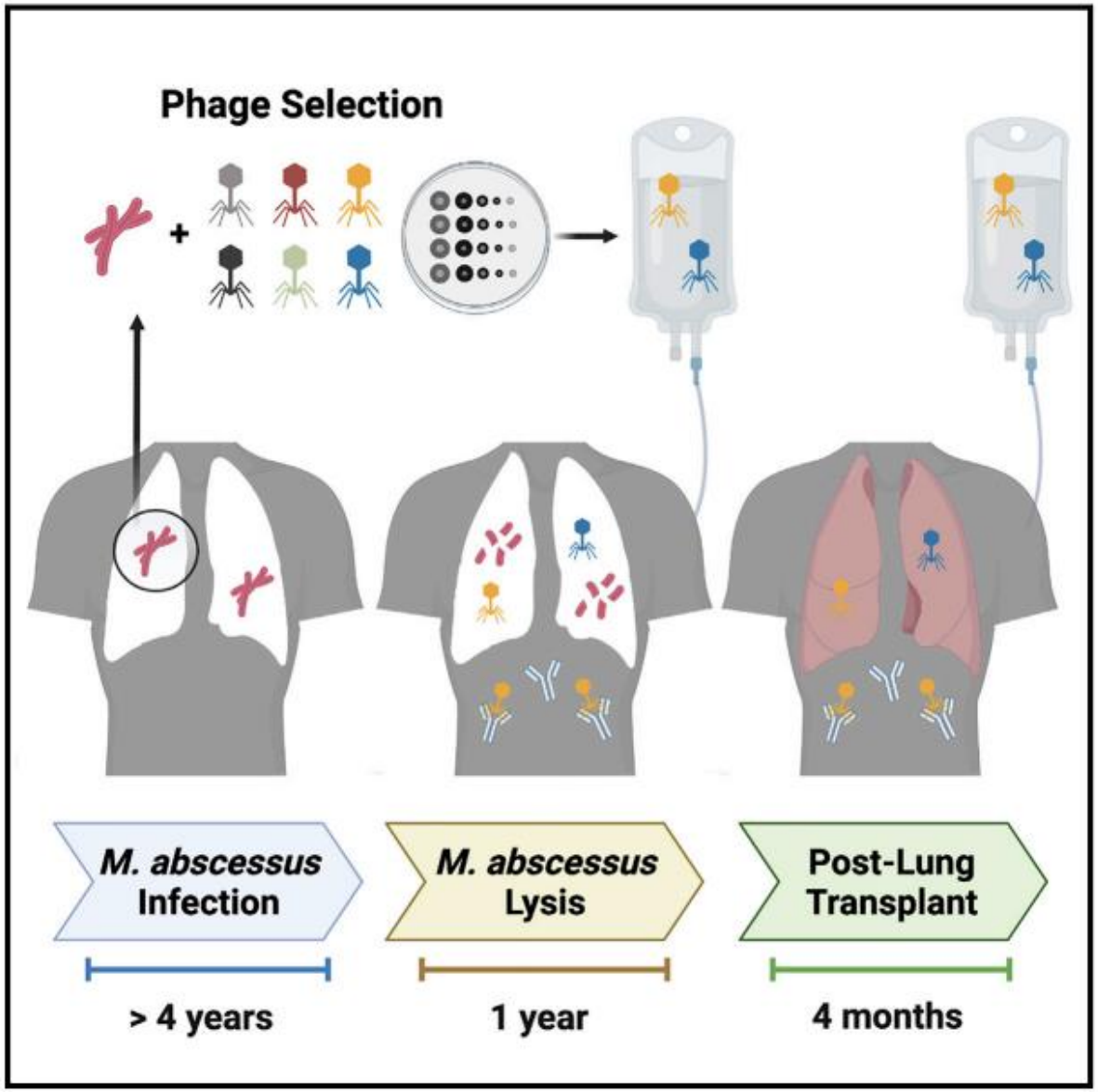
- 15 yo female with disseminated *M. abscessus* post lung transplant
- NTM treatment for 8 years prior to transplant



Whole-body (b) and cross-section (c) PET-CT sc



Dedrick, R. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus. *Nature Medicine*. 2019 May;25(5):730-733



Highlights

- Treatment-refractory *M. abscessus* pulmonary infection was eradicated in a person with CF
- Specific mycobacteriophages lysed the bacteria over the course of a year
- *M. abscessus* did not acquire resistance to the phages
- *M. abscessus* eradication occurred despite a partial anti-phage antibody response

Nick et al., 2022, Cell 185, 1860–1874

Summary

- NTM-PD is increasing.
- NTM infection is common in patients with BE
- NTM infection can make BE
- Pathogenesis of NTM in idiopathic BE is largely unknown.
- Host susceptibility might have role in the development of NTM-PD.
- NB form NTM-PD could have a slow progression.
- New drugs or treatments are needed for refractory NTM diseases.