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Clinical Interplay Between TB, NTM, and Bronchiectasis

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- Diagnostics: how to differentiate the three
- Management: how to co-manage - focus on the host

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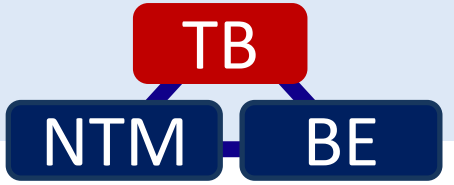
Pathophysiology

Tuberculosis and its Aftermath



- People affected by tuberculosis (TB) face high burden of sequelae after treatment completion.

- The “Post-TB lung disease”
  - “Evidence of chronic respiratory abnormality with or without symptoms attributable at least in part to previous tuberculosis”

- People who recover from TB have decreased lung function (FEV_1>FVC).

Allwood BW et al. Int J Tuberc Lung Dis 2020
Meghji J et al. Lancet Respir Med 2025
Ratnakumar S et al. Lancet Glob Health 2025

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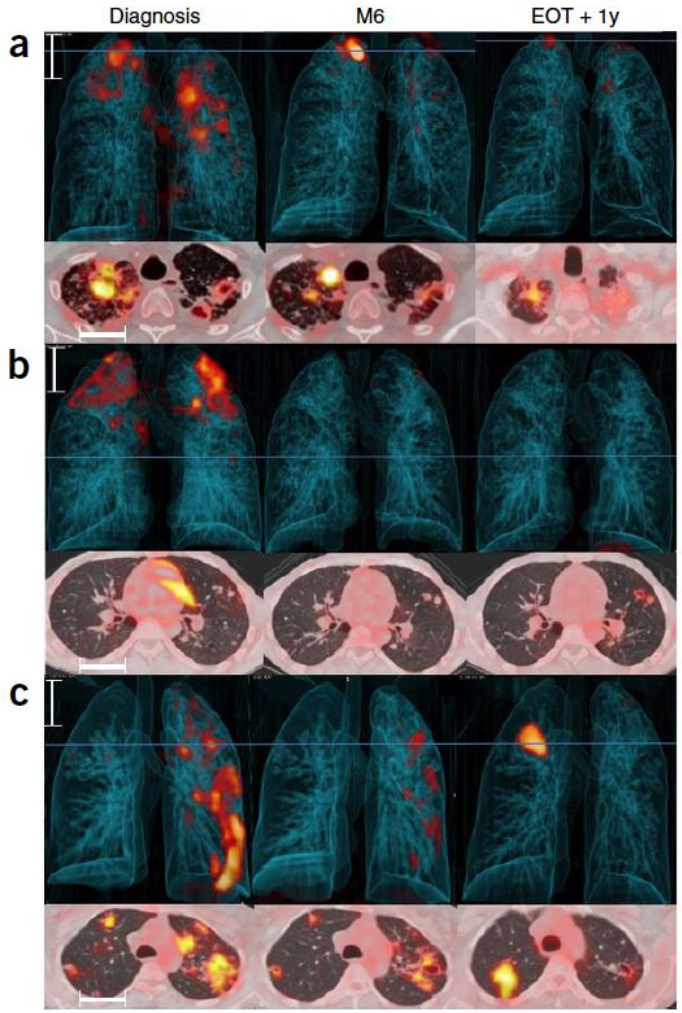
Prolonging TB-Host Interactions after Cure

TB
NTM BE

- Cohort study
  - Patients diagnosed with pulmonary TB (N=113)
  - PET-CT scans performed multiple times
    - Dx, M1, M6, EOT+1y

- Main finding
  - Only 1/3 of the EOT+1y PET-CT scans completely resolved lesions.



➔ ***Host-pathogen interactions may persist after treatment completion***

Malherbe ST et al., Nat Med 2016

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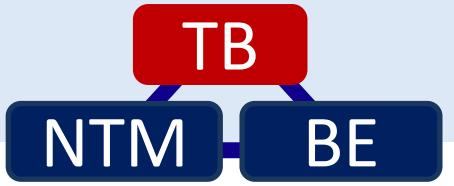
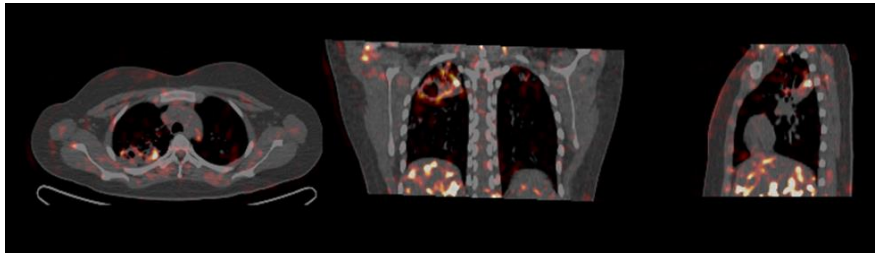
Structural Host Injuries by TB



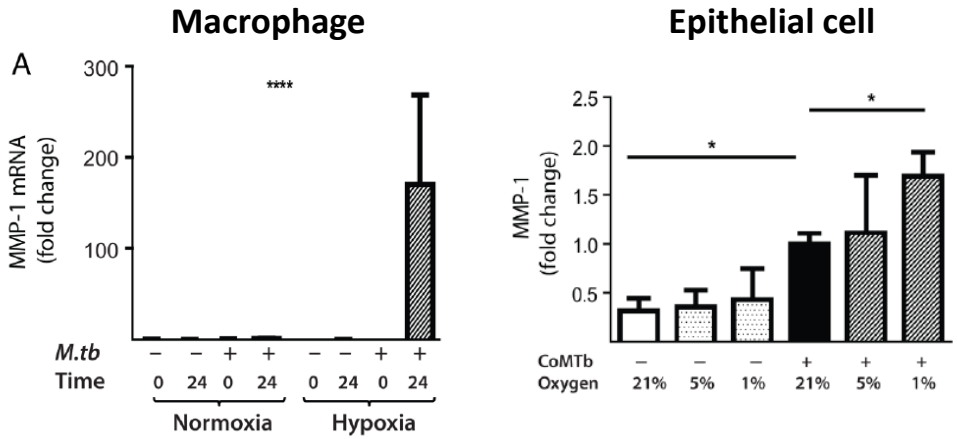
- Hypoxic lesions due to TB lesions
  - Consolidation
  - Regions surrounding pulmonary cavities

[18F]FMISO PET-CT
Indicating hypoxia



- TB + Hypoxia → MMP-1⇧
  - Muman macrophages
  - Human respiratory epithelial cells

MMP-1 expression



- ***TB lesions are hypoxic.***
- ***TB + hypoxia leads to expression of MMP-1 (potentially destructing the lung).***

Belton M et al., Thorax 2016

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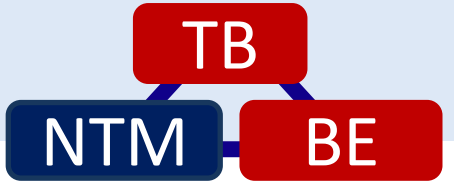
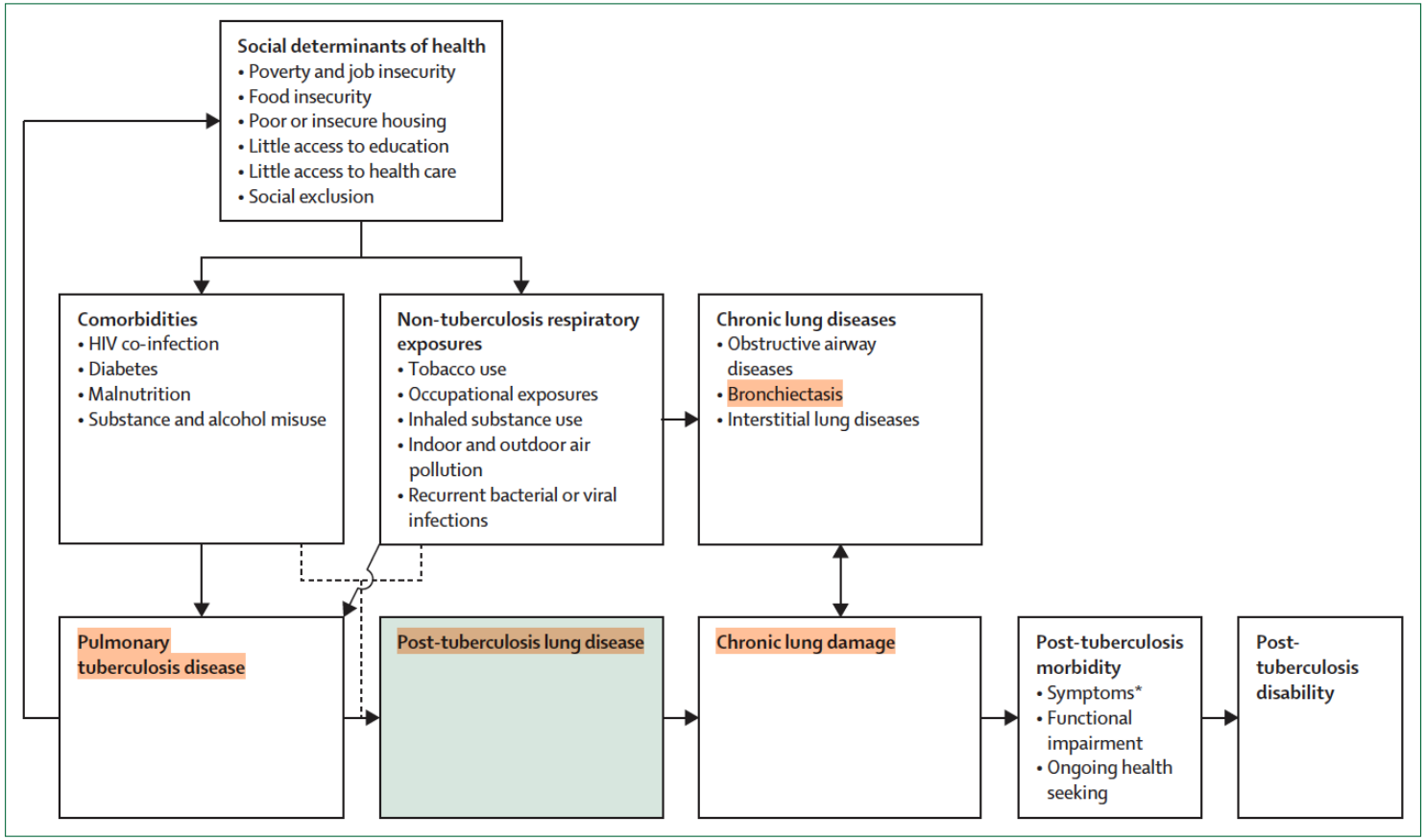
From TB to Bronchiectasis



- Residual imaging abnormalities are common after TB.
- Bronchiectasis observed in 35~86% of TB survivors.



Meghji J et al. Lancet Respir Med 2025

Meghji J et al. PLoS One 2016

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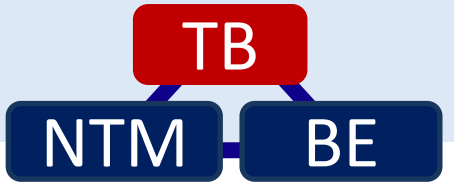
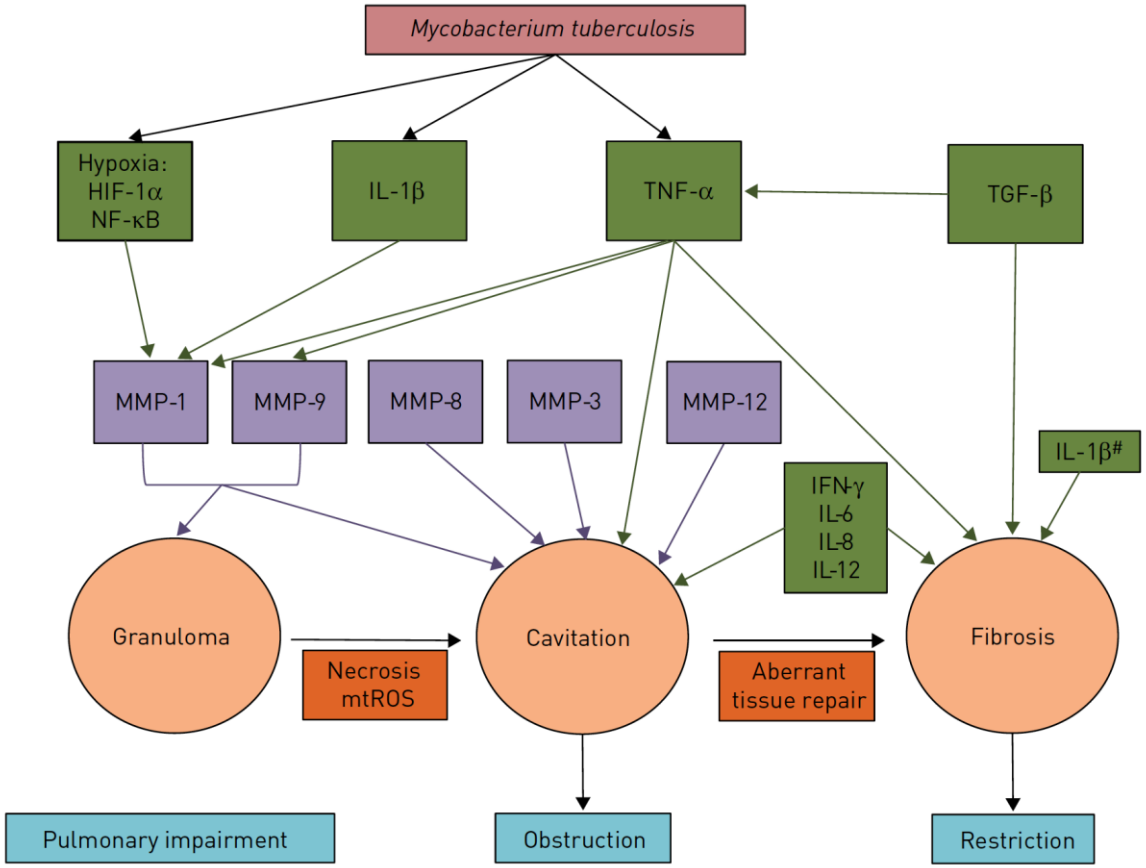
TB Leads to Other Pulmonary Sequelae



- Restrictive / Obstructive lung disease other than bronchiectasis
- Fibrosis, cavitation, etc.



Ravimohan S et al. Eur Respir Rev 2018

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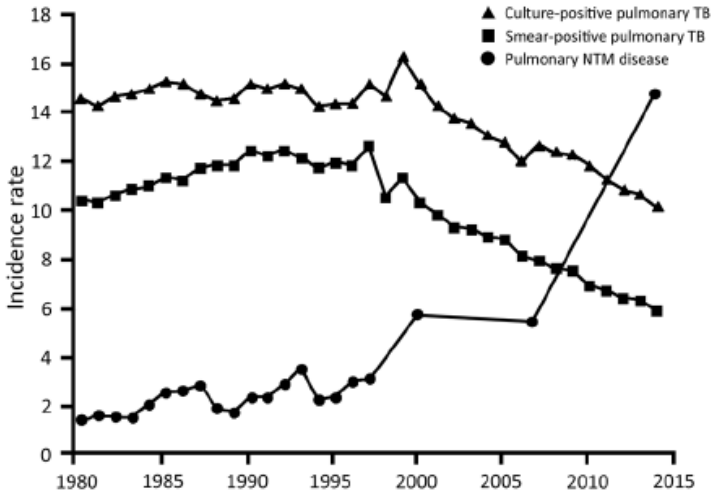
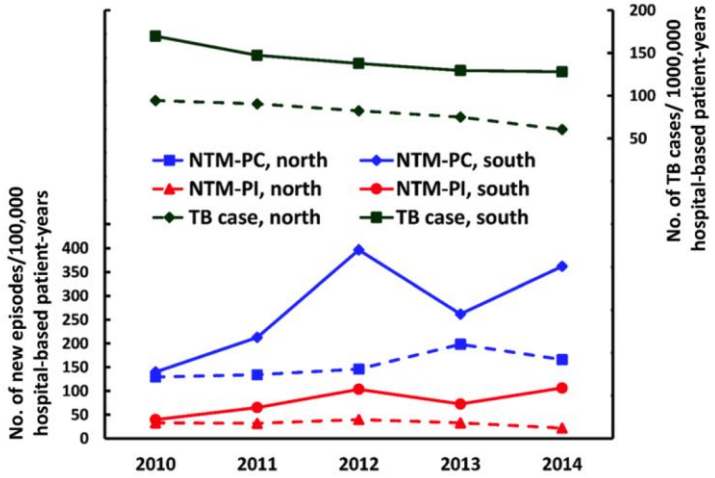
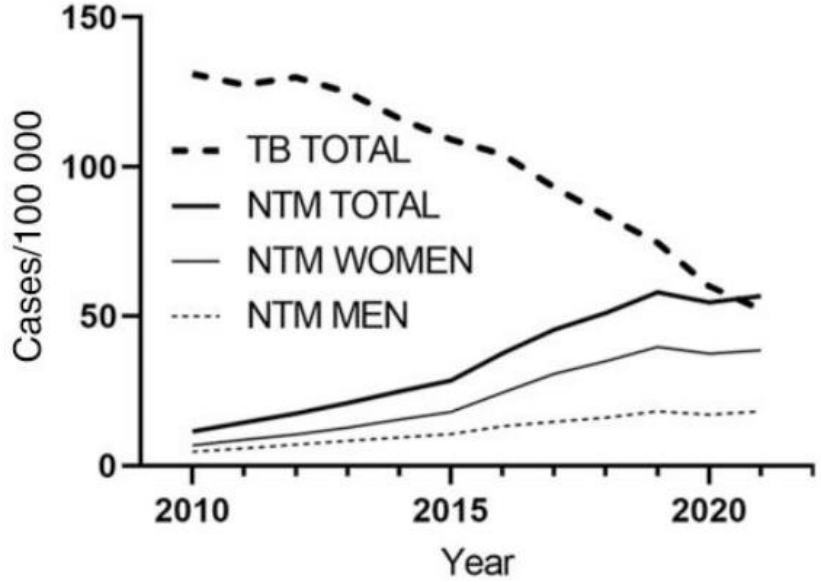
NTM-PD Beyond TB: Coincidence?



Japan



Taiwan

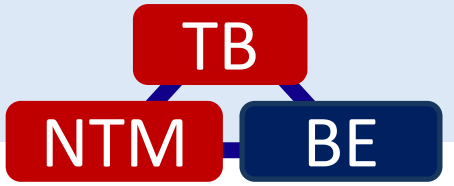


South Korea

➔ ***Trends towards increase of NTM-PD after decreasing incidence of TB***

Namkoong H et al., Emerg Infect Dis. 2016
Huang HL et al., Sci Rep 2017
Kim JY et al., Open Forum Infect Dis. 2022

Direct Link Between TB and NTM-PD?



- Multicenter retrospective study, Taiwan
  - NTM-PD (n=1,674) vs. colonization (n=7,016)
  - Six hospitals, 5-year longitudinal study

Multivariate analysis (Independent risk factor)

Characteristics	Odds Ratio (95% CI)	*p*-value
Location (southern vs. northern Taiwan)	1.73 (1.54–1.94)	<0.001
Age between 25~45 (yes vs. no)	0.36 (0.19–0.67)	0.001
Age between 45~65 (yes vs. no)	0.66 (0.54–0.82)	<0.001
Previous history of tuberculosis (yes vs. no)	1.31 (1.15–1.49)	<0.001
Chronic obstructive pulmonary disease (yes vs. no)	1.17 (1.01–1.34)	0.032
Bronchiectasis (yes vs. no)	2.14 (1.80–2.54)	<0.001
Autoimmune (yes vs. no)	1.79 (1.30–2.46)	0.001
Acquired immunodeficiency syndrome (yes vs. no)	1.51 (1.06–2.16)	0.022
M. avium-intracellulare complex (yes vs. no)	2.34 (2.03–2.70)	<0.001
M. abscessus (yes vs. no)	2.92 (2.50–3.42)	<0.001
M. kansasii (yes vs. no)	3.41 (2.78–4.19)	<0.001

➔ ***History of tuberculosis may be linked to NTM-PD regardless of bronchiectasis.***

Huang HL et al., Sci Rep 2017

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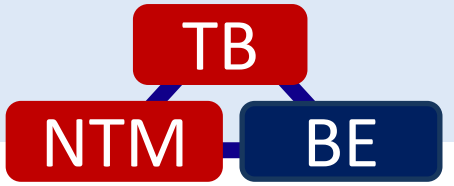
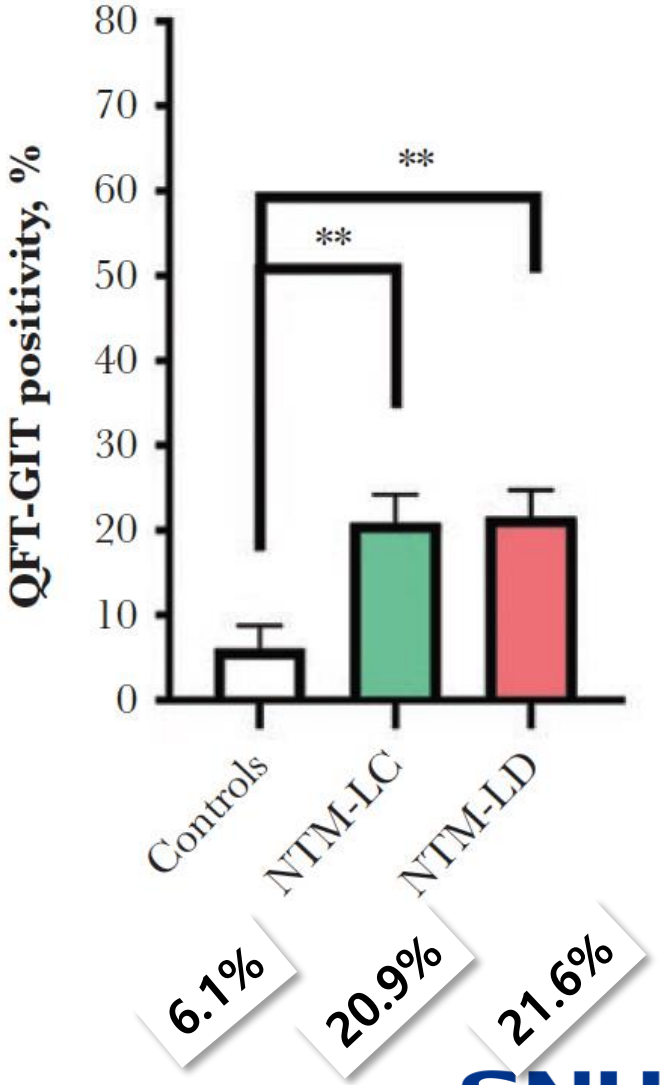
Association Between Latent TB and NTM



- Prospective cohort study
  - Taiwan, single center (N=406)
  - Patients: those having NTM(+) sputum cultures (2011 ~ 2019)
  - Controls: NTM(-) controls from clinics

- Main findings
  - Prevalence of LTBI was higher from NTM positive groups.
  - Old age and pulmonary cavitary lesions were associated with LTBI.



➔ ***Latent TB infection is associated with NTM infection.***

Lee HS et al. Open Forum Infect Dis 2022

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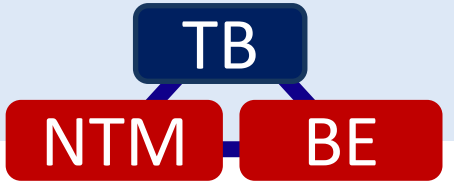
From Bronchiectasis to NTM-PD (1/2)



- Prospective cohort study (N=221)
  - South Korea, single-center
  - Patients with bronchiectasis, no NTM-PD
- Main findings
  - 14.0% of patients developed NTM-PD during median 37 months of follow-up.
  - Radiographic severity worsened after development of NTM-PD.

Table 4 Changes in CT score of 31 patients between the time of entry into the non-NTM bronchiectasis cohort and the time at the diagnosis of NTM-PD

Mean (SD)	Entry of non-NTM BE cohort	Diagnosis of NTM-PD	*P*-value
Bronchiectasis	3.3 (1.7)	4.0 (1.5)	0.010
Severity	1.5 (0.8)	1.7 (0.7)	0.035
Extent	1.3 (0.6)	1.5 (0.6)	0.059
Mucus plugging	0.6 (0.7)	0.8 (0.8)	0.033
Cellular bronchiolitis	3.5 (1.5)	4.1 (1.1)	0.005
Severity	2.0 (0.8)	2.3 (0.6)	0.007
Extent	1.5 (0.8)	1.8 (0.7)	0.039
Cavity	0.3 (1.3)	0.3 (1.3)	> 0.999
Diameter	0.1 (0.6)	0.1 (0.6)	> 0.999
Wall thickness	0.1 (0.5)	0.1 (0.5)	> 0.999
Extent	0.1 (0.3)	0.1 (0.3)	> 0.999
Nodules	0.3 (0.5)	0.5 (0.5)	0.034
Consolidation	0.2 (0.4)	0.2 (0.4)	> 0.999
Total score	7.6 (2.9)	9.1 (2.4)	0.002

NTM-PD nontuberculous mycobacterial pulmonary disease, *SD* standard devation

Kwak N et al. BMC Pulm Med 2020

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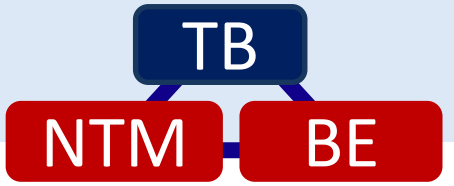
From Bronchiectasis to NTM-PD (2/2)



- National claims data, Korea
  - 1:4 matching for age and sex
    - NTM-naïve bronchiectasis (n=16,967)
    - NTM-naïve control (n=67,868)
  - Followed until development of NTM-PD or death

- NTM-PD incidence
  - ***Bronchiectasis: 109.1/100,000 person-years***
  - Controls: 5.6/100,000 person-years

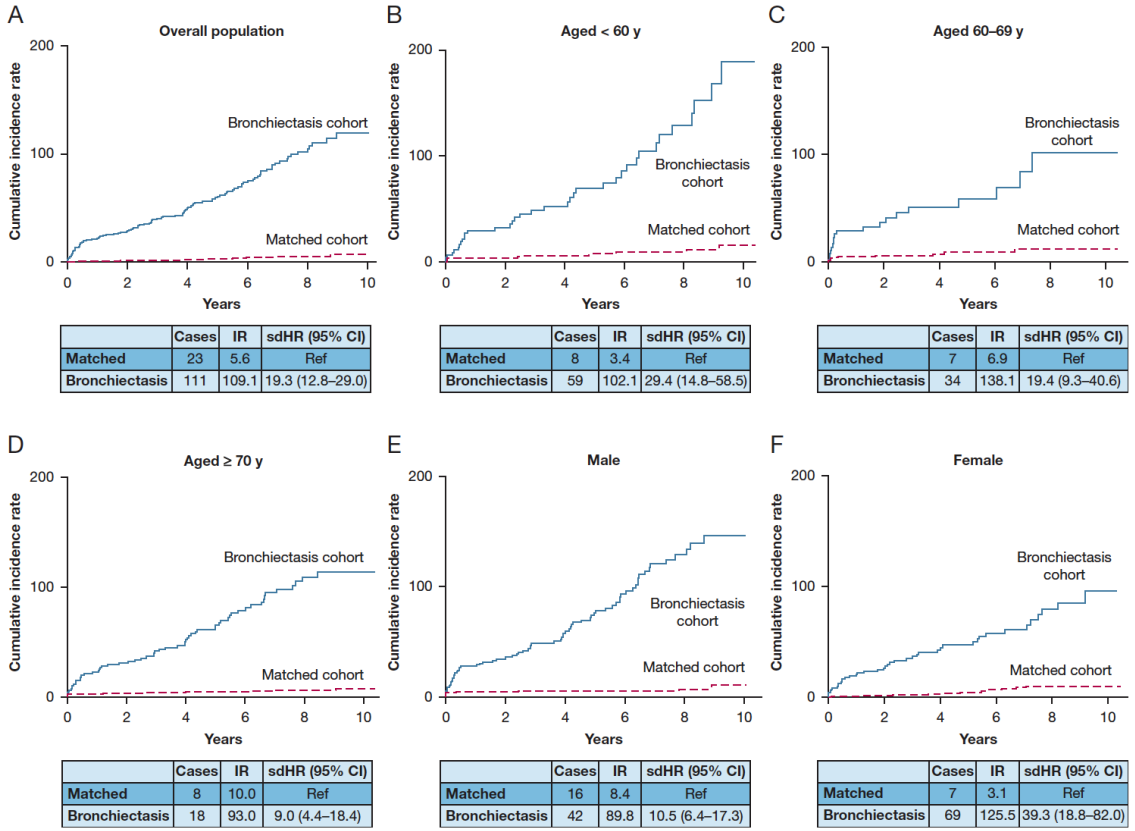


Figure 1 – *Cumulative incidence rates and subdistribution hazard ratios for nontuberculous mycobacterial pulmonary disease (/100,000 person-years) in the bronchiectasis cohort and matched cohort. A, Overall population, B, aged < 60 y, C, aged 60-69 y, D, aged ≥ 70 y, E, male, and F, female. The start of the X-axis indicates the first year of follow-up after a 1-y washout period. IR = incidence rate; Ref = reference; sdHR = subdistribution hazard ratio.*

Yang B et al., Chest 2021

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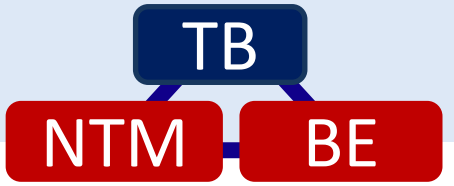
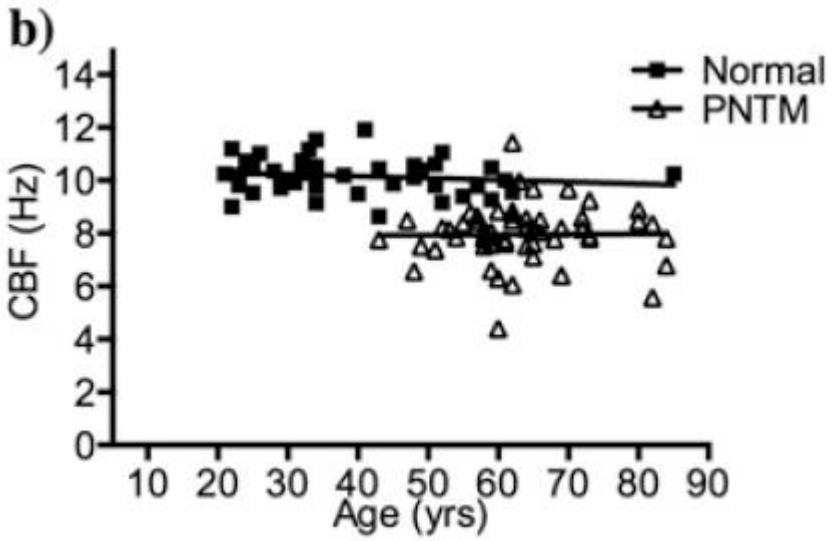
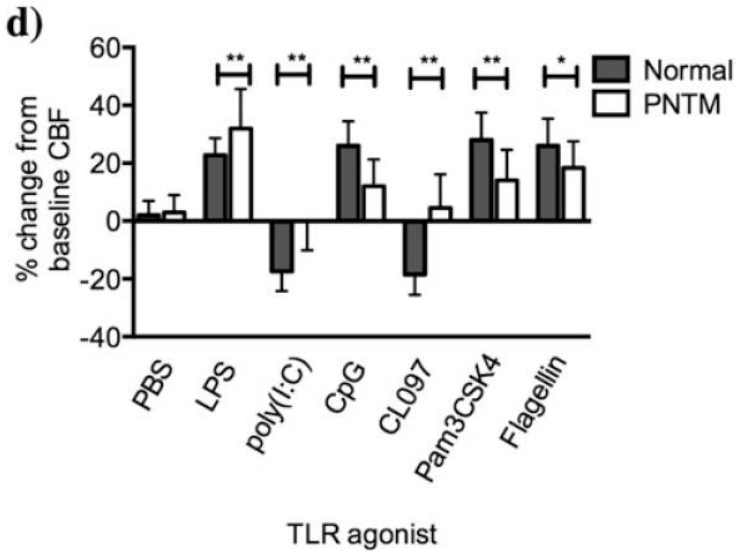
Decreased Ciliary Beat Frequency in NTM-PD Patients



- *ex vivo* study with primary human respiratory epithelial cells
  - NTM patients (n=58) *vs.* control (n=40)
- Ciliary beat frequency (CBF) measured in the absence of inflammation by visual inspection
- Epithelial cells stimulated with TLR agonist



Decreased CBF on the day of collection



Decreased CBF response to TLR agonists

Fowler CJ et al., Am J Respir Crit Care Med 2013

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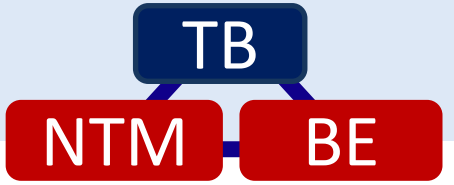
From NTM-PD to Bronchiectasis



- South Korea, single center retrospective study (n=96)
- Suspected NTM-PD without initial bronchiectasis/cavity
  - NTM-PD in 43 patients: more bronchiectasis and cavity during follow-up (vs. controls)

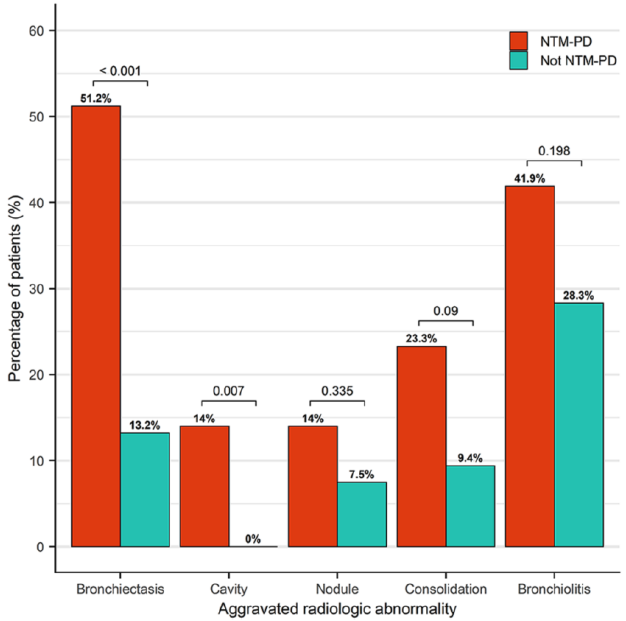


Fig. 3 Percentage of patients with aggravated radiological abnormality

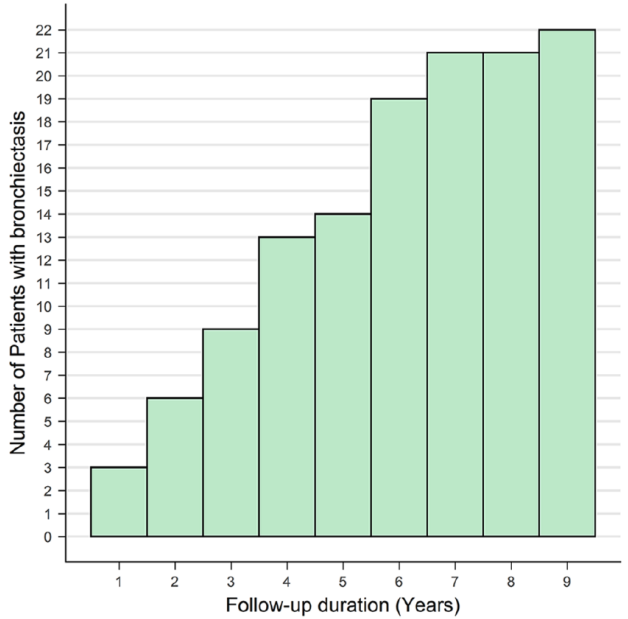
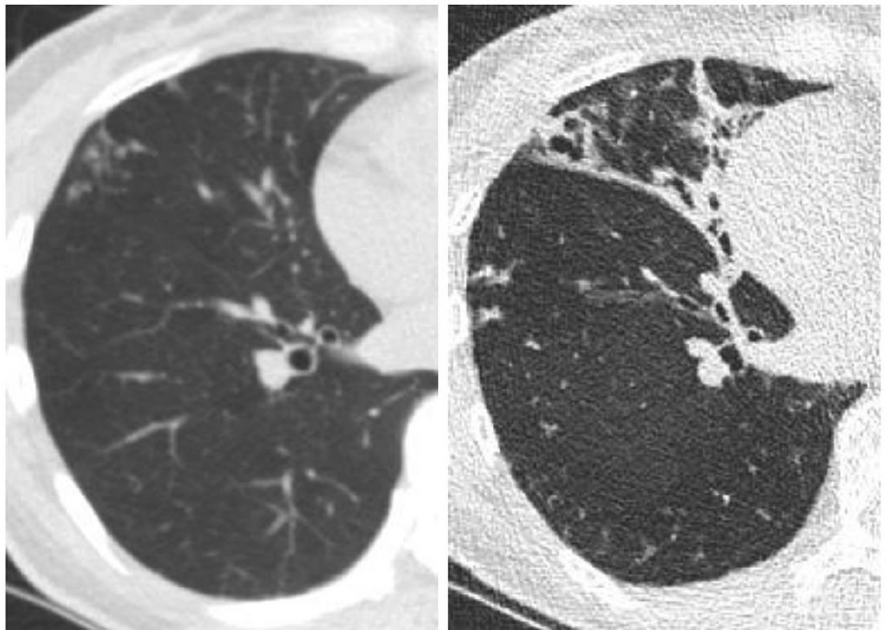


Fig. 4 Cumulative incidence of bronchiectasis in patients with NTM-PD. NTM-PD, nontuberculous mycobacterial pulmonary disease



➔ ***For patients diagnosed with NTM-PD, incidence of bronchiectasis increased over time (51%).***

Yoon SH et al. BMC Pulm Med 2024

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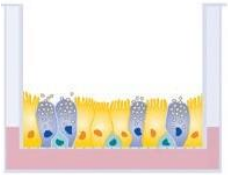
NTM Decrease Ciliation Rate on Epithelium

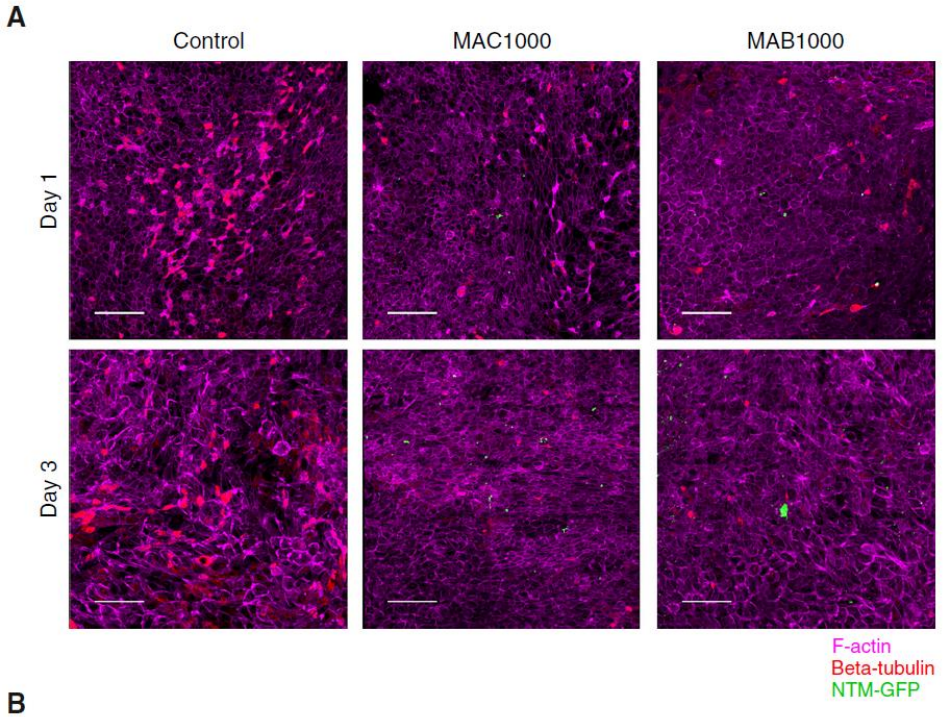
TB
NTM BE

- Air-liquid interface infected with *M. avium* or *M. abscessus*



- The percentage of ciliated cells decreased in NTM-infected respiratory epithelium

- RNA sequencing revealed down-regulation of ciliary genes after infection with NTM.



➔ ***NTM impairs ciliary function of respiratory epithelium.***

Matsuyama M et al., Am J Respir Cell Mol Biol 2018

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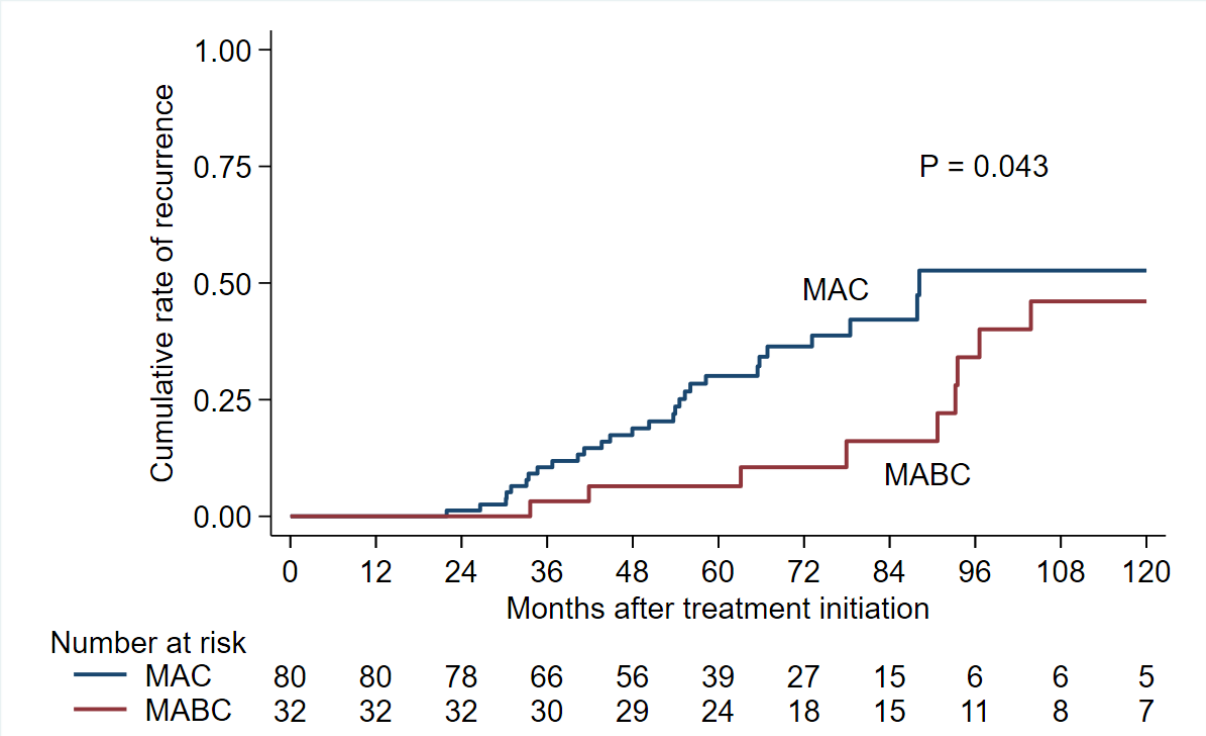
Host Factors Remain, NTM Comes Back



- 125 patients (90 MAC + 35 M. abscessus), antibiotics + surgery
  - Previous TB 46%
  - Nodular BE form 66%
- 112 microbiological cure (80 MAC + 32 M. abscessus)
- Recurrence in 37/112 (33%)
  - 18/37 (49%) were by different species

➔ ***Most recurrences of NTM-PD are due to reinfection, rather than persistence.***

Kang N and Jhun BW, Open Forum Infect Dis. 2024

Pathophysiology: Summary

- TB leads to structural lung damage, leading to bronchiectasis and NTM-PD.
- Bronchiectasis and NTM-PD are predisposing factors for each other.
- Even after cure, remaining host factors lead to frequent reinfection of NTM-PD.

Diagnostics

67-Year-old Male

Patient Case

- Chief complaint: massive hematemesis (onset: 6 hours ago)

- Present illness
  - Has chronic weight loss and general fatigue
  - Living alone without previous medical history or hospital visits

- Initial evaluation
  - BMI 16.54 kg/m^2
  - Hb 3.5 g/dL
  - CRP 1.23 mg/dL
  - Gastroscope findings revealed peptic ulcer with evidence of recent bleeding

- Initial plan
  - Hospitalized to the gastroenterology department
  - Management of peptic ulcer

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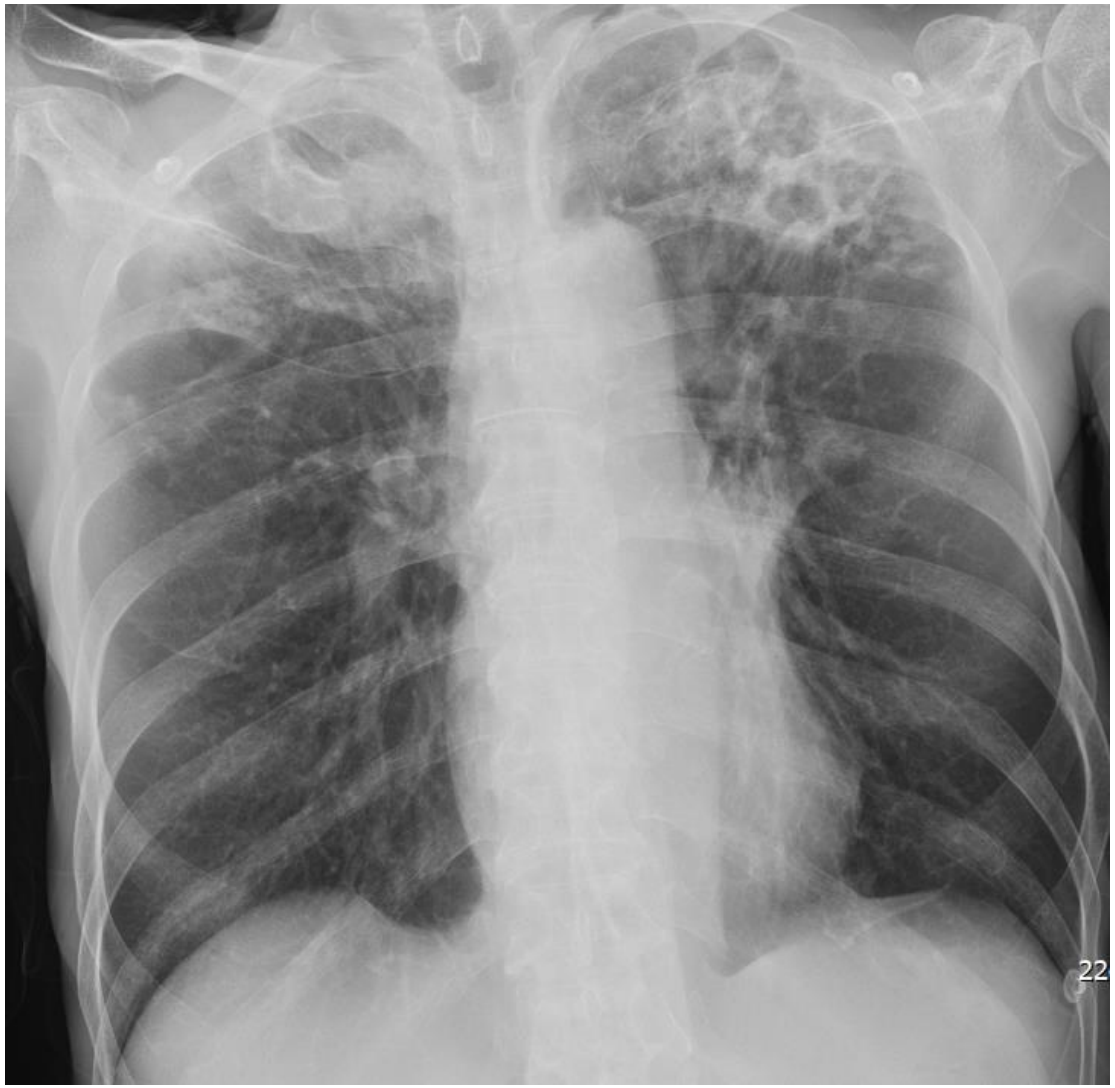
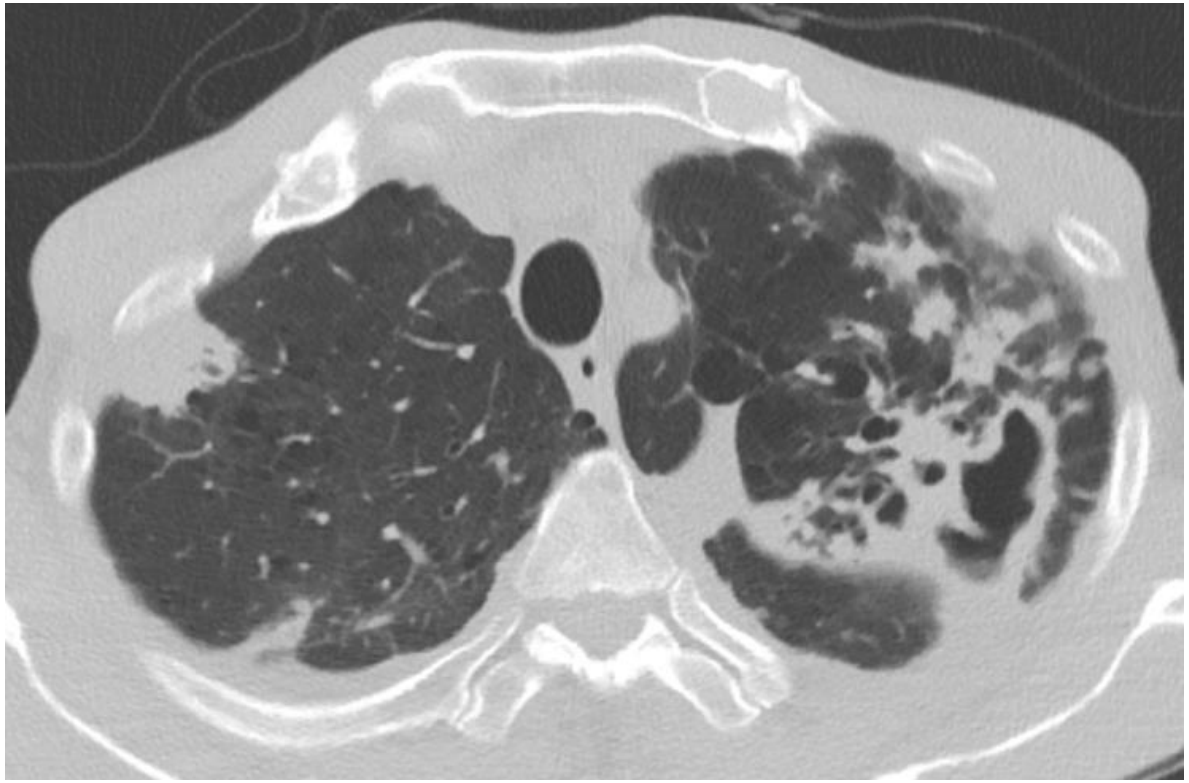
Radiographic Findings





Hospital Course and Microbial Findings

- HD #1
  - Sputum AFB smear 4+

  → Diagnosed as TB, started HREZ, transferred to respiratory department

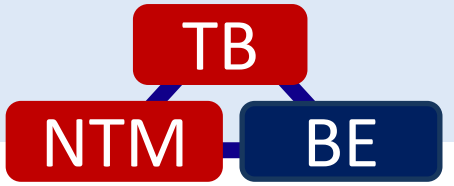
- HD #5
  - Xpert MTB/RIF PCR negative

  → Effect of HREZ???

- HD #15
  - Sputum AFB culture: NTM(+)

  →Stopped HREZ, evaluated as NTM-PD

Clinical Differentiation Between TB vs. NTM-PD



- Retrospective single center study (N=142)
  - Patients: AFB smear negative / culture positive / with cavities
  - Grouped into: TB and NTM-PD

Table 1 Comparison of clinical characteristics in PTB and NTM patients with lung cavities

Characteristics	PTB (n = 112) n (%)	NTM (n = 30) n (%)	P value*
Median age [IQR]	49 [41–61]	62 [50–72]	0.001
Age ⩾65 years	25 (22.3)	14 (46.7)	0.008
Male sex	86 (76.8)	18 (60.0)	0.065
Previous anti-tuberculosis treatment	34 (30.6)	19 (63.3)	0.001
Smoking	62 (55.4)	12 (40.0)	0.135
DM	30 (26.8)	8 (26.7)	0.99
Malignancy	5 (4.5)	1 (3.3)	> 0.99
COPD	7 (6.2)	4 (13.3)	0.245
Pneumoconiosis	8 (7.1)	0 (0.0)	0.203
Immunosuppression	5 (4.5)	0 (0.0)	0.584
Cough	94 (83.9)	26 (86.7)	> 0.99
Sputum	78 (69.6)	23 (76.7)	0.451
Haemoptysis	13 (11.9)	9 (30.0)	0.022
Dyspnoea	28 (25.0)	6 (20.0)	0.569
Fever	37 (33.0)	8 (26.7)	0.505
Weight loss	29 (26.6)	3 (10.0)	0.056

Table 2 Comparison of radiological findings in PTB and NTM patients with lung cavities

Characteristics	PTB (n = 112) n (%)	NTM (n = 30) n (%)	P value*
Cavity location			
Upper	90 (80.4)	26 (86.7)	0.427
Middle/lower	22 (19.6)	4 (13.3)	
Consolidation	98 (87.5)	20 (66.7)	0.007
Distribution			
Upper	82 (73.2)	24 (80.0)	
Lower	25 (22.3)	3 (10.0)	0.196
Both	5 (4.5)	3 (10.0)	
Laterality			
Unilateral	58 (51.8)	15 (50.0)	0.862
Bilateral	54 (48.2)	15 (50.0)	
Pleural effusion	13 (11.6)	4 (13.3)	0.758
Nodular bronchiectatic form on CT, n/N (%)	44/92 (47.8)	7/19 (36.8)	0.382

* χ^2 test or Fisher's exact test.
PTB = pulmonary tuberculosis; NTM = non-tuberculous mycobacteria; CT = computed tomography.

➔ ***TB/NTM patients were mostly similar, except:***
NTM-PD patients were older and had more history of tuberculosis.

Kim YK et al., Int J Tuberc Lung Dis 2014

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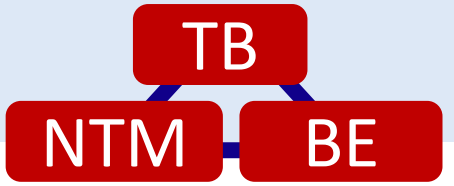
Radiographic Differentiation



- Inter-observer agreement study
  - Two board-certified pulmonologists + two radiologists
  - CT scans of NTM-PD (n=66), Tbc (n=33), non-CF BE (n=33)

	Sensitivity, % (95 % CI[§])	Specificity, % (95 % CI)	PPV, % (95 % CI)	NPV, % (95 % CI)
NTM-LD	56.4 (149/264) (47.9–64.7)	80.3 (212/264) (73.1–86.0)	66.4 (149/201) (55.9–75.4)	58.2 (212/327) (48.9–67.0)
Pulmonary TB	72.0 (95/132) (60.0–81.5)	87.1 (345/396) (81.6–91.2)	52.8 (95/146) (40.1–65.0)	85.7 (345/382) (78.3–90.8)
Bronchiectasis	81.8 (108/132) (71.8–88.8)	81.6 (323/396) (75.0–86.7)	49.3 (108/181) (37.6–61.0)	89.3 (323/347) (82.6–93.7)

[§] Confidence interval

PPV positive predictive value, *NPV* negative predictive value

➔ ***Radiographic differentiation between NTM/TB/BE is difficult.***

Kwak N et al., Eur Radiol 2016

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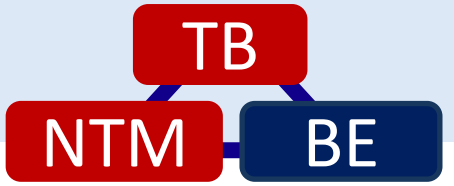
Microbiological Differentiation



- Bronchoscopy for diagnosis of NTM-PD
  - South Korean prospective cohort: 20% diagnosed by bronchoscopy
  - Japanese retrospective study: diagnostic yield 50% for those who could not expectorate sputum

- Post-bronchoscopy sputum for NTM-PD
  - Post-bronchoscopy sputum cultures can offer **3.5%** additional diagnostic benefit

Table 2. Yield of AFB smear and bronchial washing and PBS culture for the diagnosis of NTM pulmonary disease

Variables	AFB smear		NTM culture	
	Positivity	Exclusive positivity	Positivity	Exclusive positivity
Total patients (n = 141)				
Bronchial washing or PBS	19 (13.5)	-	59 (41.8)	-
Bronchial washing	10 (7.1)	3 (2.1)	54 (38.3)	13 (9.2)
PBS	16 (11.3)	9 (6.4)	46 (32.6)	5 (3.5)

Kim HJ et al. BMC Infect Dis 2019
Tomishima Y et al., Respir Investig 2022
Gu KM et al. J Korean Med Sci 2021

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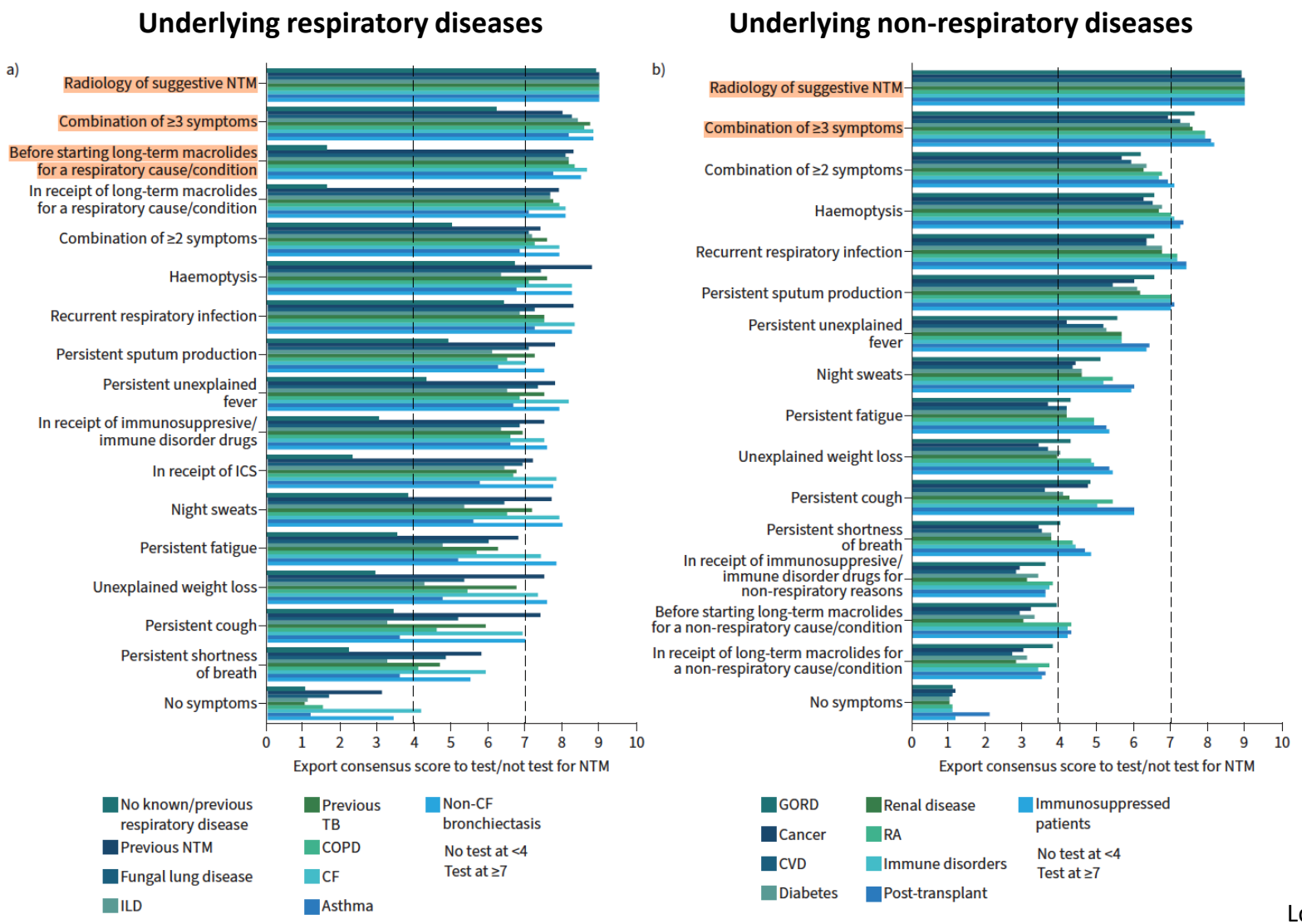
Screening Patients at Risk of NTM-PD

- A Delphi Consensus Study (Europe)



Test for NTM when:

- **Radiologic suspicion**
- **≥3 symptoms***
- **Before starting macrolides**

* Symptoms include cough, weight loss, night sweats, hemoptysis, sputum, fatigue, recurrent respiratory infection, fever, dyspnea

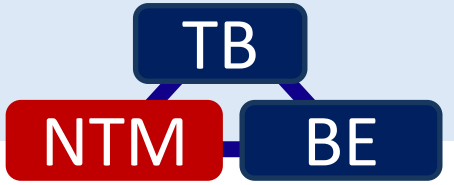
Loebinger MR et al., ERJ Open Res 2024

Diagnostic Pearls: TB/NTM/BE

- Clinical / radiographical differentiation is difficult.
- Use of bronchoscopy or post-bronchoscopy sputum can help differentiating TB *vs.* NTM-PD.
- Indications of judicious work-up for NTM-PD include radiologic suspicion, multiple (≥3) symptoms, and consideration of macrolides.

Management

Time Between Diagnosis and Initiation of Antibiotics



- Single-center registry study, South Korea (N=712)
  - MAC, M. *abscessus*-PD, treated >6 months
  - Analyzed association between waiting duration and treatment outcomes

TABLE 2] Effect of Watchful Waiting Period on 6-Months or 12-Months Culture Conversion in Patients With NTM-PD

Patient Group	Treatment for ≥ 6 mo (n = 712)[a]	Treatment for ≥ 12 mo (n = 676)[a]
Culture conversion	Within 6 mo (n = 479)	Within 12 mo (n = 516)
HR of watchful waiting period for 6- or 12-mo conversion		
Crude HR (95% CI, *P*)	1.00 (1.00-1.00, .412)[b]	1.00 (1.00–1.00, .746)[c]
Model 1, adjusted HR (95% CI, *P*)	1.00 (0.99–1.00, .242)[b]	0.99 (0.99–1.00, .512)[c]
Model 2, adjusted HR (95% CI, *P*)	1.00 (0.99–1.01, .075)[b]	0.99 (0.99–1.00, .213)[c]
Model 3, adjusted HR (95% CI, *P*)	0.99 (0.99–1.00, .074)[b]	0.99 (0.99–1.00, .211)[c]

AFB = acid-fast bacilli; BACES = BMI, age, cavity, erythrocyte sedimentation rate, and sex; HR = hazard ratio; NTM-PD = nontuberculous mycobacterial pulmonary disease.
Model 1: adjusted for smoking, underlying disease, positive sputum AFB smear, BACES severity, etiology, and watchful waiting period.
Model 2: adjusted for BMI (< 18.5), age (≥ 65 years), cavity, erythrocyte sedimentation rate (> 15 mm/h in male and > 20 mm/h in female), and sex (male) instead of BACES in Model 1.
Model 3: adjusted for radiological form (noncavitary nodular bronchiectatic vs cavitary nodular bronchiectatic vs fibrocavitary) instead of cavity in Model 2.
Underlying disease included previous pulmonary TB, obstructive pulmonary disease/asthma, chronic pulmonary aspergillosis, pulmonary malignancy, idiopathic pulmonary fibrosis, extrapulmonary malignancy, diabetes mellitus, chronic heart disease, and chronic liver disease.
[a]These data analyzed patients treated for more than 6 months and 12 months, respectively. An event was defined as a culture conversion within 6[b] months or 12[c] months after starting treatment, respectively. Multivariable analysis results other than "watchful waiting period" in each model are described in

→ Waiting period was not associated with culture conversion.

Im Y et al. Chest 2022

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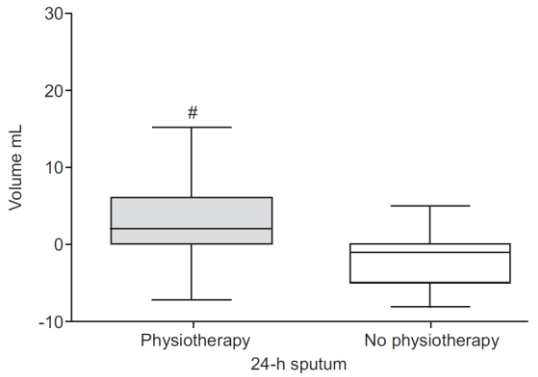
ACT in Bronchiectasis

- Randomized crossover study
- Non-cystic fibrosis bronchiectasis (n = 20)
- OPEP (Acapella) (bid, 3mon) vs. Control



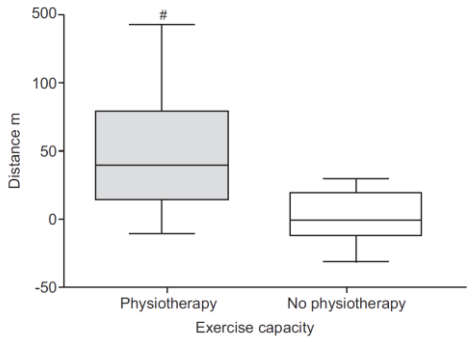


TABLE 3 Treatment differences

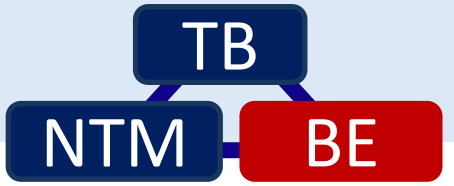
Outcome	Twice daily physiotherapy	No regular physiotherapy	p-value
Total LCQ score improvement	1.3 (-0.17–3.25)	0 (-1.5–0.5)	0.002
24-h sputum volume mL	2 (0–6)	-1 (-5–0)	0.02
FEV_1 L	-0.01 (-0.06–0.08)	-0.01 (-0.1–0.11)	0.7
FVC L	-0.01 (-0.09–0.28)	0.06 (-0.08–0.21)	0.9
$FEF_{25–75\%}$ $L \cdot s^{-1}$	-0.02 (-0.17–0.16)	0.04 (-0.1–0.34)	0.6
MIP cmH_2O	-1 (-9–7)	5.5 (-10–12.5)	0.7
MEP cmH_2O	5 (-11–25)	8.5 (-3.7–19.7)	0.7
Exercise capacity m	40 (15–80)	0 (-10–20)	0.001
Sputum bacterial load cfu·mL^{-1}	-1×10^3 (-2.78×10^6–1.74×10^7)	1×10^3 (-6.5×10^7–6.4×10^6)	0.72
Total SGRQ score improvement	7.8 (-0.99–14.5)	-0.7 (-2.3–0.05)	0.005
Exacerbations n	5	7	0.48

Data are presented as median (interquartile range), unless otherwise stated. LCQ: Leicester Cough Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75}$: forced expiratory flow at 25–75% of FVC; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; SGRQ: St George's Respiratory Questionnaire.

➔ With OPEP:
- Cough ↓
- Exercise capacity ↑
- Sputum ↑

Murray MP et al., Eur Respir J 2009

Pulmonary Rehabilitation in BE



- Randomized controlled trial
- Patients
  - Non-CF bronchiectasis (N=85)
- Intervention
  - Supervised exercise training
  - Review of ACT
- Outcome
  - Exercise capacity
  - HRQOL

➔ With Rehab:
- Exacerbation ↓

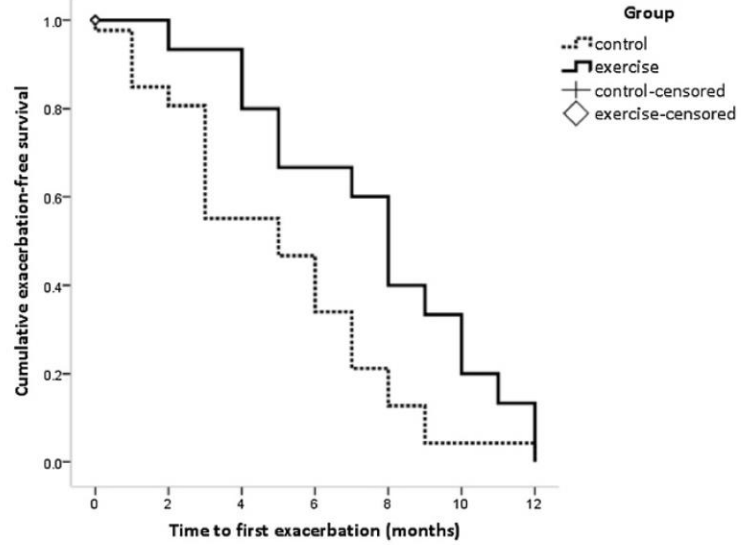


Figure 4 Time to first exacerbation, p = 0.047.

Table 3 Number of exacerbations over 12 months (n = 55)

	Control n = 25	Exercise n = 30	p value
Exacerbations	2 (1 – 3)	1 (0 – 2)	0.012
Exacerbations requiring antibiotics	2 (0 – 4)	1 (0 – 2)	0.061
Exacerbation days	10 (2 – 13)	7 (3 – 11)	0.23
Exacerbation days with antibiotics	11 (2 – 15)	7 (2 – 13)	0.36

Data are median (IQR), p value represents difference between groups.

Lee AL et al., Respir Res. 2014

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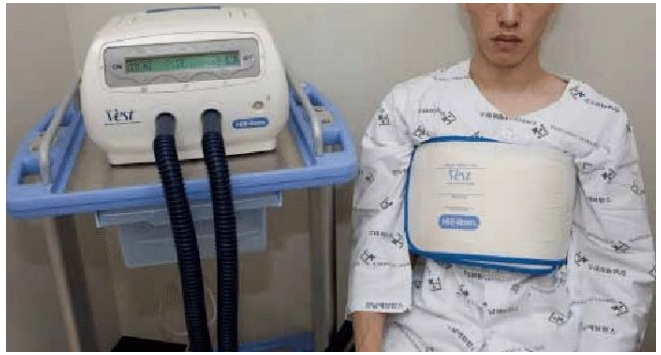
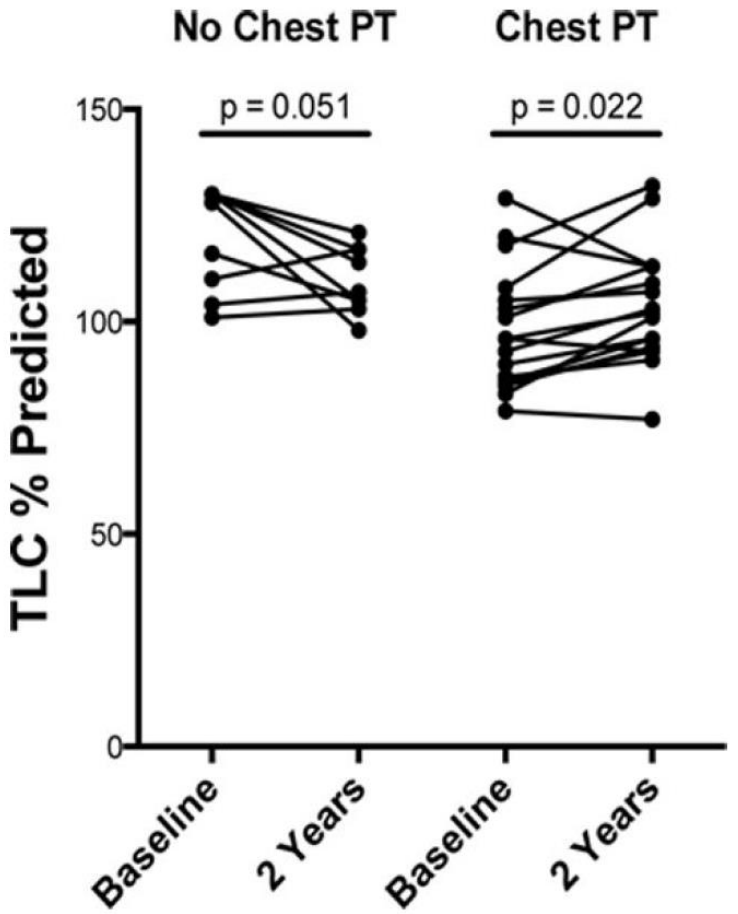
Airway Clearance Techniques in NTM-PD

- Retrospective review of patients with NTM-PD (n = 77)
- OPEP or HFCWO (VEST) vs. Control
- ACT was associated with improvement of:
  - Cough
  - Sputum production
  - Total lung capacity

OPEP



HFCWO



Basavaraj A, et al. Int J Respir Pulm Med 2017

Take Home Messages

- TB, NTM-PD, and bronchiectasis reinforce one another.
- Perfect clinical/radiographic differentiation is difficult: use aggressive microbiological assessment if necessary.
- During microbiological evaluation or watchful waiting period, try to treat the host.

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