

# Overlapping Respiratory Disease BE and NTM-PD

충북의대  
양범희

# M/67

- 지속적인 가래 및 객혈을 주소로 내원
  - 결핵 치료력 : 무
  - 백일해/홍역 (-/-)
  - 소아기 잦은 중이염 및 부비동염, 폐렴 (-)
  - Ex-smoker
  - 병력 : COPD, OA

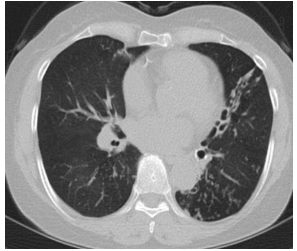
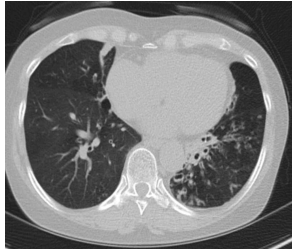
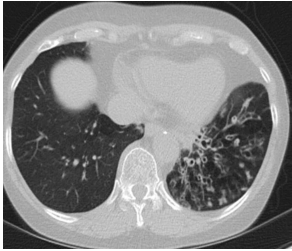


## [Vote] 진단은?

1. 기관지확장증
2. NTM-PD
3. COPD
4. ILD

# F/64

- 지속적인 기침 가래를 주소로 내원
  - 결핵 치료력 : 무
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## [Vote] 진단은?

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# 목차

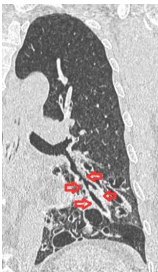
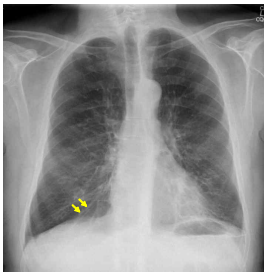
- Definition
- Approach of Bronchiectasis
- Assessment of Bronchiectasis
- Management of Bronchiectasis
- Summary

# 목차

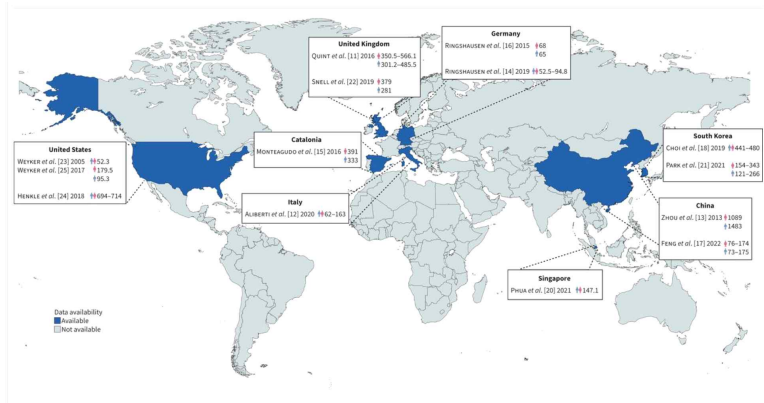
- **Definition**
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# Bronchiectasis

- **Bronchiectasis** is a chronic lung disease in which the **bronchi are permanently dilated**, causing chronic respiratory symptoms and repeated infections.



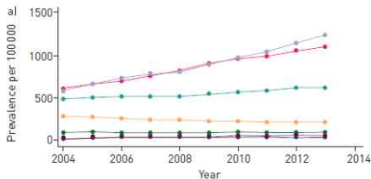
# Prevalence of BE in the general population



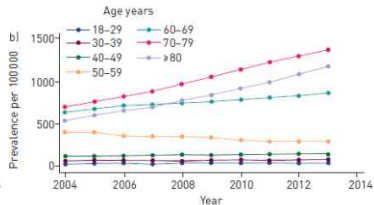


# Bronchiectasis Prevalence

- Bronchiectasis prevalence in UK 



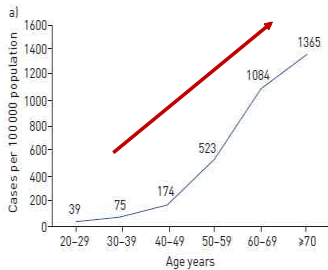
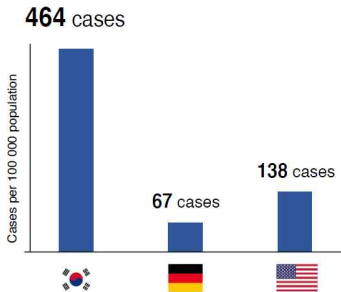
**301.2 (2004) → 485.5 (2013) in Men**



**350.5 (2004) → 566.1 (2013) in Women**

# Bronchiectasis Prevalence in Korea

- HIRA-NPS 2012-2017 data

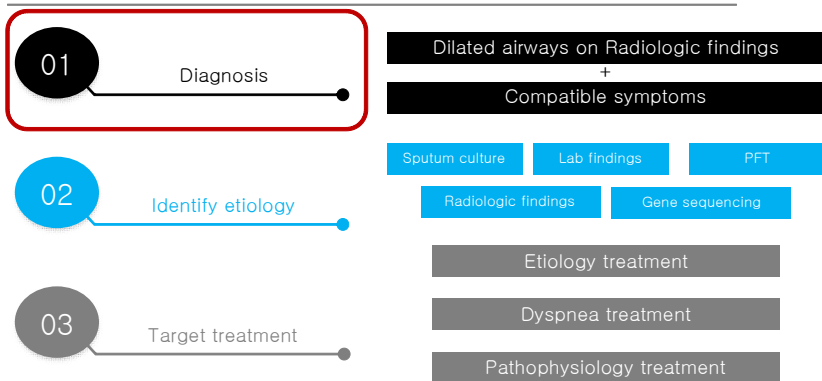


# 목차

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- Approach of Bronchiectasis
- Assessment of Bronchiectasis
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# Approach to patient

Patients with bronchiectasis are **heterogeneous** and thus, their treatment must be **individualized**.



# Diagnosis

The diagnosis usually is based on presentation with a persistent chronic cough and sputum production accompanied by consistent radiographic features.

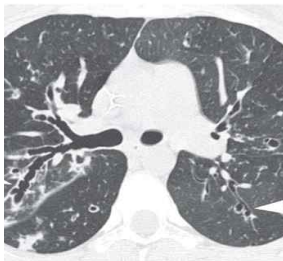
## Chest X-ray

Non-specific.  
Lack sensitivity.



## HRCT

More specific.



# Diagnosis

## HRCT : Golden standard

Signet-ring sign

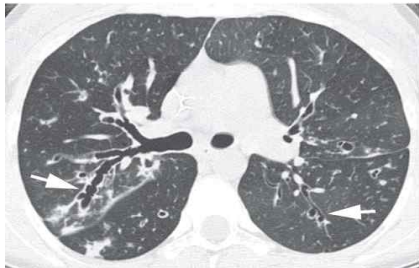
bronchoarterial ratio  $> 1.5$

Tram-track sign

parallel-dilated bronchial wall

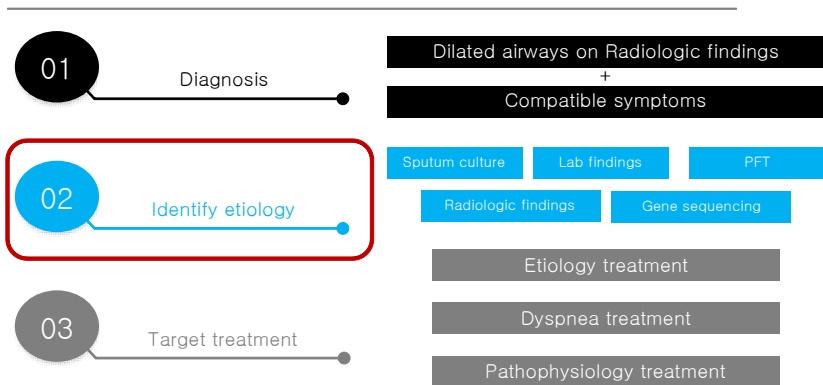
Visible airway within 1 cm of pleural space

bronchial wall thickening & lack of tapering

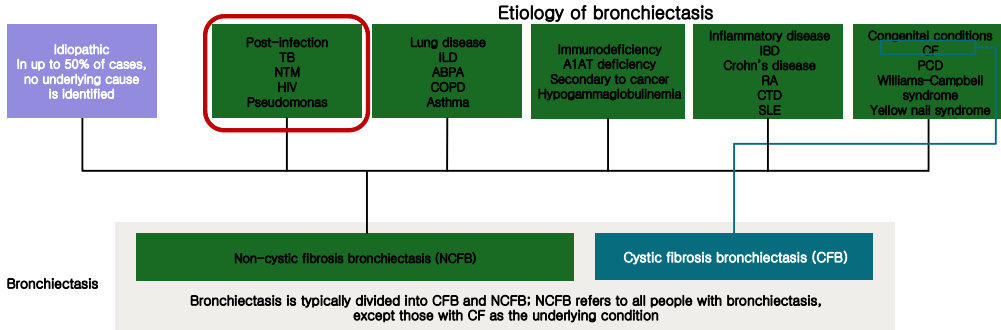


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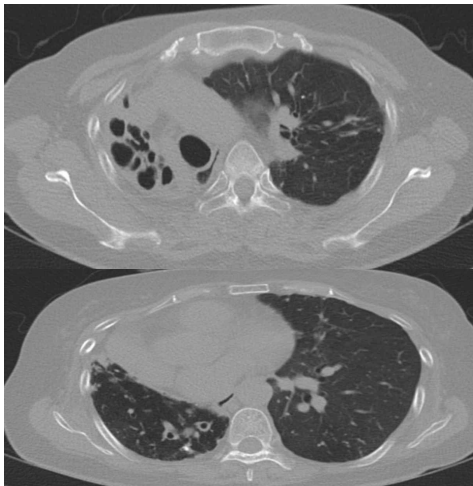
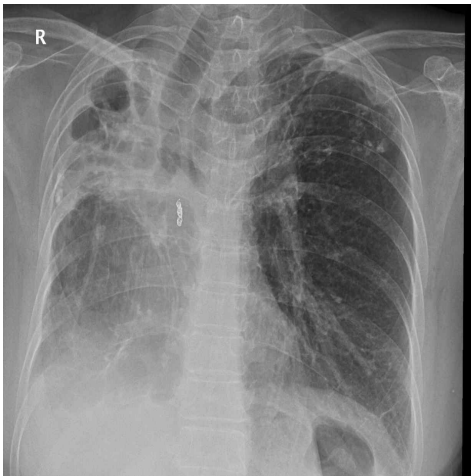


# Etiology



# F/64

- Massive hemoptysis 로 응급실 내원
  - 결핵 치료력 : 유
  - 백일해/홍역 (-/-)
  - 소아기 잦은 중이염 및 부비동염, 폐렴 (-)
  - Never-smoker
  - 병력 : 없음



[Vote] 환자의 기관지확장증 발생 추정 원인은?

1. COPD
2. TB
3. Idiopathic
4. NTM-PD

# Etiology

	Korea	India	China	Japan	Australia	Europe	USA
1 <sup>st</sup>	Idiopathic (41%)	<b>TB (36%)</b>	<b>Post-infective (43%)</b>	NTM (39%)	<b>Idiopathic (29%)</b>	<b>Idiopathic (38%)</b>	NTM (63%)
2 <sup>nd</sup>	<b>TB (20%)</b>	<b>Post-infective (22%)</b>	Idiopathic (30%)		Post-infective (27%)	Post-infective (21%)	
3 <sup>rd</sup>	<b>Post-infective (20%)</b>	Idiopathic (21%)	<b>TB (12%)</b>		NTM (7%)	COPD (8%)	
4 <sup>th</sup>	Asthma (5%)	ABPA (9%)	COPD (5%)		PCD (4%)	Asthma (7%)	
5 <sup>th</sup>	<b>NTM (4%)</b>	COPD (5%)	Asthma (1.5%)		ABPA (4%)	TB (5%)	

# M/63

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  - 백일해/홍역 (-/+)
  - 소아기 잦은 중이염 및 부비동염, 폐렴 (-/-/+)
  - Ex-smoker
  - 병력 : Gout



Etiology : 소아기 감염

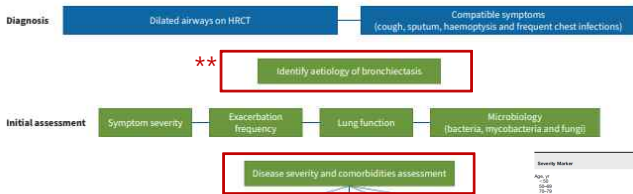
- KMBARC 5-46-0037, 충북대 기관지 확장증- 0022 , low dose azi -0007

#. Gout

# 목차

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- Approach of Bronchiectasis
- **Assessment of Bronchiectasis**
- Management of Bronchiectasis
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# Assessment of BE



## Disease severity assessment

- BE severity index
- E-FACED

- + comorbidities (BE patients = avg 4 comorbidities)
- + extent of Sx
- + underlying cause

Severity Marker	HR (95% CI) for Hospital Admissions during Follow-up	HR (95% CI) for Mortality	Score Points	
Age, yr				
<50	1.0 (reference)	1.0 (reference)	0	
50-64	1.38 (0.72-2.66)	2.21 (0.39-12.5)	2	
75-79	1.50 (0.79-2.83)	8.57 (1.15-63.6)	4	
80+	1.75 (0.88-3.50)	23.16 (2.08-272.7)	6	
FEV <sub>1</sub> , % predicted				
EMR				
<18.5	1.23 (0.73-2.08)	2.28 (1.08-4.87)	2	
18.5-25	1.0 (reference)	1.0 (reference)	0	
26-29	0.80 (0.42-1.53)	0.81 (0.48-1.31)	0	
30 or more	1.14 (0.70-1.79)	1.38 (0.68-2.81)	0	
FEV <sub>1</sub> , % predicted				
<50	1.0 (reference)	1.0 (reference)	0	
50-64	1.37 (0.72-2.66)	3.38 (0.61-20.7)	1	
65-69	1.48 (0.88-2.48)	5.88 (0.73-4.8)	2	
>70	1.82 (1.03-3.24)	4.47 (1.45-13.5)	3	
Hospital admission before study				
No	1.0 (reference)	1.0 (reference)	0	
Yes	13.5 (8.80-19.8)	2.63 (1.38-4.53)	6	
Exacerbations before study				
0	1.0 (reference)	1.0 (reference)	0	
1-2	1.87 (0.78-5.38)	1.78 (0.88-3.98)	0	
>2 or more	2.25 (0.88-5.70)	2.81 (1.02-8.03)	2	
			0	
			1.05 (0.58-2.25)	2
			1.19 (0.65-2.15)	2
			1.0 (reference)	0
			1.08 (0.73-3.34)	0
			1.0 (reference)	0
			1.10 (0.64-2.24)	1
			1.0 (reference)	0
			1.08 (0.52-1.94)	1

Chart 2. E-FACED score: acronym for Exacerbation, FEV<sub>1</sub>, Age, Chronic colonization with *Pseudomonas aeruginosa*, Extent (of CT findings), and Dyspnea.

Variables	Result	Score
Exacerbation	No	Zero
	Yes	2
FEV <sub>1</sub> , % predicted	≥ 50%	Zero
	< 50%	2
Age	< 70 years	Zero
	≥ 70 years	2
Chronic colonization with <i>R. aeruginosa</i>	No	Zero
	Yes	1
Extent of CT findings: number of affected lobes	1-2 lobes	Zero
	> 2 lobes	1
Dyspnea, mMRC scale	0-II	Zero
	III-IV	1
		<b>TOTAL: 0-9 points</b>

Severity: 0-3 points: mild; 4-6 points: moderate; and 7-9 points: severe.  
mMRC: modified Medical Research Council.

# BE severity index

항목	기준	점수
나이	< 50 → 0    50-69 → 2    70-79 → 4    ≥ 80 → 6	0-6
BMI	≥ 18.5 → 0    < 18.5 → 2	0-2
FEV <sub>1</sub> %	≥ 80% → 0    50-79% → 1    30-49% → 2    < 30% → 3	0-3
<b>입원 병력</b>	없음 → 0    있음 → 5	<b>0-5</b>
악화 횟수	0-2회 → 0    ≥ 3회 → 2	0-2
MRC 호흡곤란	1-4단계 → 0    5단계 → 3	0-3
<b>Pseudomonas</b>	없음 → 0    있음 → 3	<b>0-3</b>
다른 균 집락	없음 → 0    있음 → 1	0-1
CT 침범 범위	1-2엽 → 0    > 2엽 → 1	0-1
<b>Total (최대)</b>		<b>0 ~ 26점</b>

## 중증도 판정

Mild

0 ~ 4점

1년 입원율 0.5%  
4년 사망률 2.8%

Moderate

5 ~ 8점

1년 입원율 7.9%  
4년 사망률 9.3%

Severe

≥ 9점

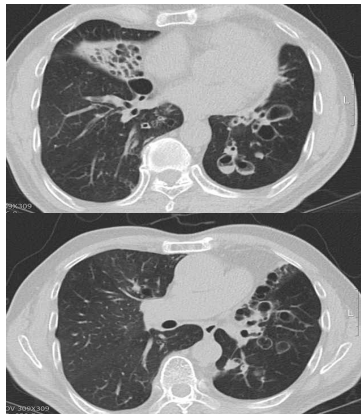
1년 입원율 16.7%  
4년 사망률 29.2%

# M/67

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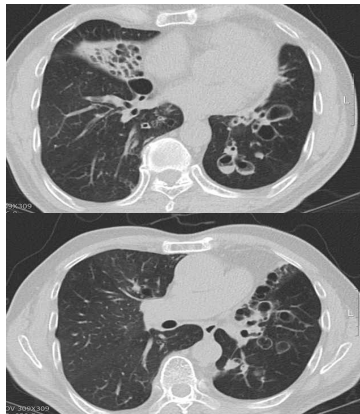
Etiology : Idiopathic



# M/67

- 지속적인 가래 및 객혈을 주소로 내원

- Sputum culture: K. pneumonia
- mMRC : I
- 지난 1년간 입원력 : 없음
- 지난 1년간 악화 횟수: 3번
- FEV1 예측치의 69%
- BMI: 22



## [Vote] 환자에게 해볼 수 있는 치료는?

1. 가래배출 재활치료
2. ACT
3. Low dose AZIT
4. Mucolytic agent
5. 모두 맞다

# BSI score

항목	환자	기준	점수	판정
나이 (Age)	67세	< 70세	0점	
BMI	22	≥ 18.5	0점	
FEV <sub>1</sub> %	69%	50~79%	1점	
입원 병력	없음	없음	0점	
악화 횟수/년	3회	≥ 3회	2점	▲
MRC 호흡곤란	mMRC II	5단계 미만	0점	
Pseudomonas 집락	없음	없음	0점	
다른 균 집락	K. pneumoniae	있음	1점	▲
CT 침범 범위	Bilateral 다엽	> 2엽	1점	▲
합계 (Total)			5점	

Moderate (5~8점) → 1년 입원을 7.9% / 4년 사망률 9.3%

[Vote] 환자에게 악화를 예방하기 위한 가장 중요한 치료는?

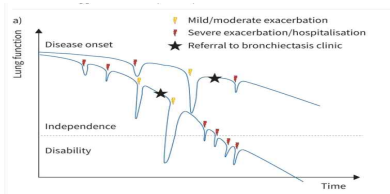
1. 가래배출 재활치료
2. ACT
3. Low dose AZIT
4. Mucolytic agent

# Exacerbations Definition

- 2017 International Consensus definition (for clinical trials):

Deterioration of  $\geq 3$  key symptoms for at least 48h + clinician decision to change treatment

- \*\* Key symptoms: cough, sputum volume/consistency, sputum purulence, breathlessness/exercise intolerance, fatigue/malaise, hemoptysis



Frequent exacerbations  
→ double mortality risk

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# Management

The first step in bronchiectasis management is to identify an etiology that may be treatable or influence management.

---

Treatable etiology

---



Sputum culture

Total IgE

IgA, IgM, IgG

---

Etiology influencing  
management

---



History taking  
Gene sequence

ANA / RF

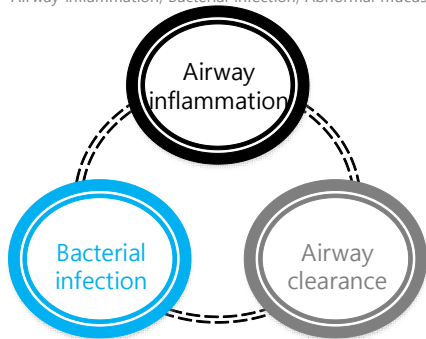
# Management of BE

**Most patients:  
No specific cause /  
no targeted treatment**

- Focus on **treatable traits** of bronchiectasis itself
  1. Abnormal mucus
  2. Chronic infection
  3. Airway inflammation

Target treatable traits in the pathophysiology of bronchiectasis

Airway inflammation, Bacterial infection, Abnormal mucus

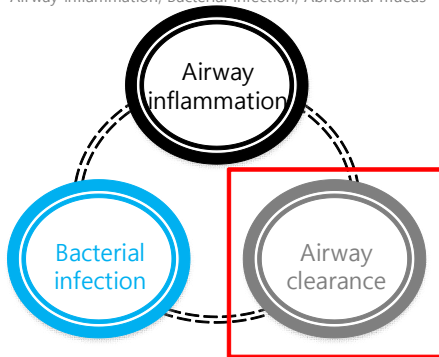


# Airway clearance

Target treatable traits in the pathophysiology of bronchiectasis

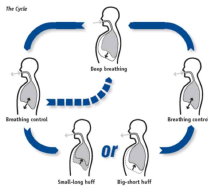
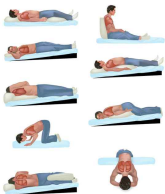
Airway inflammation, Bacterial infection, Abnormal mucus

1. Airway clearance
2. Inhaled hyperosmolar agents & mucolytics
3. Pulmonary rehabilitation & exercise



# Impaired Mucociliary Clearance

## Chest physiotherapy

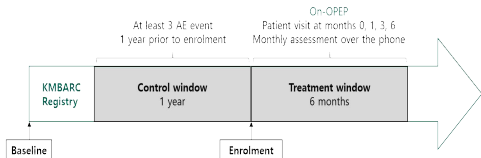


ACBT



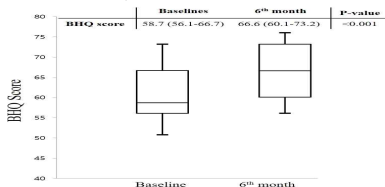
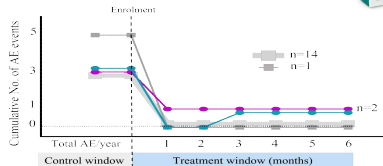
PEP device

# OPEP and bronchiectasis in Korea



Patient visit Months 0, 1, 3, 6
<ul style="list-style-type: none"> <li>Sputum volume</li> <li>Patient questionnaire : mMRC score</li> <li>Patient questionnaire : BHQ score (Baseline, 6 months)</li> <li>Spirometry, laboratory test (Baseline, 6 months)</li> </ul>

Monthly assessment Over the phone
<ul style="list-style-type: none"> <li>Acute exacerbation : incidence of AE</li> <li>Adverse events : pneumothorax, haemoptysis, bronchospasm</li> </ul>



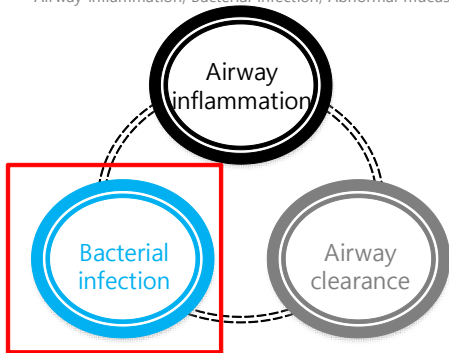
Physiotherapy with an OPEP device in patients with bronchiectasis who have frequent exacerbations may facilitate subjective symptom improvement and AE prevention without severe adverse events.

# Bacterial Infection

Target treatable traits in the pathophysiology of bronchiectasis

Airway inflammation, Bacterial infection, Abnormal mucus

1. Pseudomonas eradication
2. Inhaled antibiotics

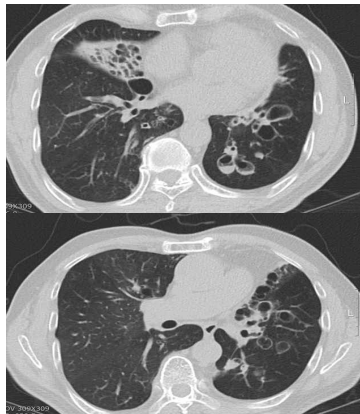


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Etiology : Idiopathic



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합계 (Total)			5점	

+3,  
Severe

Moderate (5~8점) → 1년 입원을 7.9% / 4년 사망률 9.3%

# P. aeruginosa Management

## Pseudomonas Management: Eradication

ERS & BTS guidelines: eradication antibiotics treatment for patients with newly isolated *P. aeruginosa* \*\* European Respiratory Society (ERS); British Thoracic Society (BTS)

- Low evidence (lacking RCTs), but still recommended

Systemic ABX alone (27%) < **systemic ABX + inhaled ABX** (48% success)

Recommended regimen:  
(6 wks. ~ 3 mo.)

↓  
oral fluoroquinolone /  
IV antipseudomonal ABX

with  
/  
followed by

↙  
inhaled ABX

# Inhaled antibiotics

## Long-term, suppressive inhaled antibiotics therapy

- Rationale for using antibiotics:
  - ↓ airway bacterial load → ↓ inflammation & exacerbation risk
- Why inhaled?
  - (+) higher delivery to airway, less systemic side effects
- Long-term use:
  - ABX given for a long period even when patient is stable (not just during AE) = preventive
- **Aim: to reduce bacterial burden & prevent exacerbations**

# Bacterial load & inhaled antibiotics - QoL

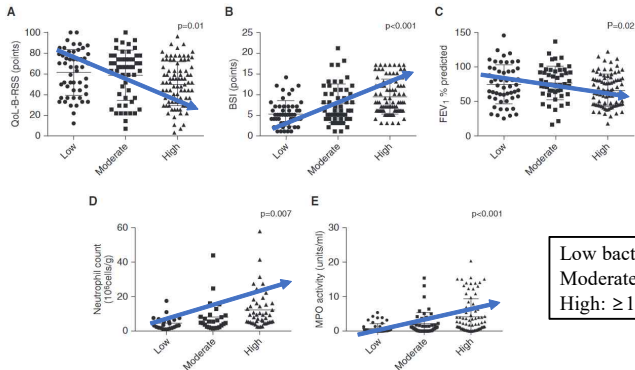
## (Aztreonam Study - AIR-BX1 and AIR-BX2)

AIR-BX1 (n = 181), AIR-BX2 (n = 259)  
 Primary outcome = QoL-B improvement

	AIR-BX1				AIR-BX2			
	AZLI (n=134)	Placebo (n=132)	AZLI-placebo difference, HR (95% CI)	p value	AZLI (n=136)	Placebo (n=138)	AZLI-placebo difference, HR (95% CI)	p value
<b>Change from baseline QOL-B-RSS</b>								
At week 4, adjusted mean (SE)	6.4 (1.4)	5.6 (1.4)	0.8 (-3.1 to 4.7)	0.68*	7.9 (1.3)	3.3 (1.3)	4.6 (1.1 to 8.2)	0.011*
At week 12, adjusted mean (SE)	5.7 (1.6)	4.4 (1.5)	1.3 (-3.0 to 5.6)	0.56*	5.2 (1.4)	4.1 (1.4)	1.1 (-2.7 to 5.0)	0.56*
<b>Time to first protocol-defined exacerbation</b>								
Kaplan-Meier estimates of patients with protocol-defined exacerbation at week 16	0.33	0.26	HR 1.26 (0.79 to 1.99)	0.33†	0.33	0.27	HR 1.23 (0.80 to 1.91)	0.35†
Estimated median days (95% CI)	NE	120 (117 to NE)	..	..	NE	NE	..	..

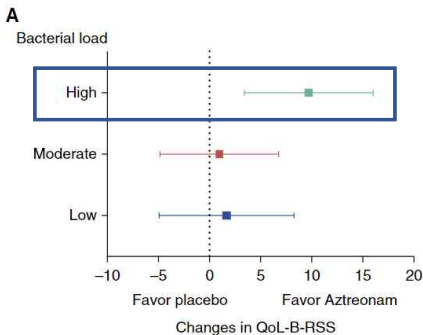
Less than MID – 8.0 point

# Bacterial load – Disease severity & QoL

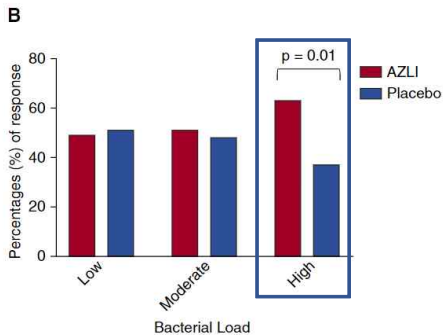


189 clinically stable patients with bronchiectasis

# Bacterial load & inhaled antibiotics - QoL (Aztrenonam Study - AIR-BX1 and AIR-BX2)



More than MID – 8.0 point



# Long-term inhaled Antibiotics vs. macrolide

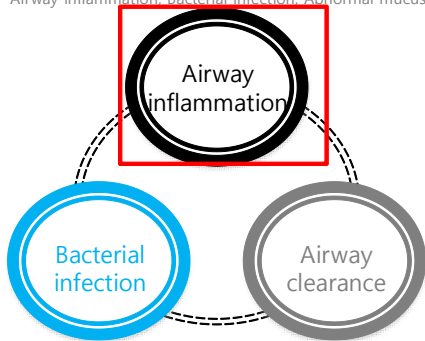
	Inhaled antibiotics	Macrolide
Studies	RESPIRE 1,2 ( $\geq 2$ AE) ORBIT 2-4 ( $\geq 2$ AE) AIR-Bx 1-2 Nebulized tobramycin, ceftazidime, gentamicin, colistin	BAT ( $\geq 3$ AE) – AZIT 250mg QD BLESS ( $\geq 2$ AE) – ETM 400mg BID Daily EMBRACE ( $\geq 1$ AE) – AZIT 500mg TIW
Outcomes		
AE	<b>Improved</b> Rate ratio = <b>0.81(0.67-0.97)</b> Time to first AE (HR) = <b>0.83(0.69-0.99)</b>  Severe AE – Rate ratio = <b>0.43(0.24-0.78)</b>	<b>Improved</b> Adjusted incidence rate ratio = <b>0.49(0.36-0.66)</b> Time to first AE (HR) = <b>0.46(0.34-0.61)</b>  <i>P. Aeruginosa</i> – IRR, <b>0.36(0.18-0.72)</b>
QoL	<b>No effect</b>	<b>Improved</b> QoL measured by the <b>SGRQ (mean improvement 2.93 points [0.03-5.83])</b>
FEV <sub>1</sub>	<b>No improvement</b> (Toward to deterioration) (–2.00 to 0.26%pred)	<b>No improvement</b> (toward to improvement) (67 mL at 1 year, –22-112)

# Airway Inflammation

Target treatable traits in the pathophysiology of bronchiectasis

Airway inflammation, Bacterial infection, Abnormal mucus

1. Tx of neutrophilic inflammation : Macrolide, Brensocatib
2. Tx of eosinophilic inflammation



# Airway Inflammation

Neutrophilic BE

Long-term macrolides

Eosinophilic BE\*\*

Inhaled corticosteroids & anti-TH2 biologics

- Elevated sputum TH2 cytokines
- blood eosinophils  $>300/\mu\text{L}$  / sputum eosinophils  $>3\%$
- Distinct from asthma / ABPA

# Long-term Macrolide

## Macrolides

- Antibiotics, but more than just anti-bacterial
- **Highly effective in reducing exacerbations in BE**
  - Likely due to **anti-inflammatory properties**
  - May also alter microbiome & disrupt quorum sensing in *P.aeruginosa*
    - \*\*Quorum sensing: bacterial communication system that makes a bacteria more chronic, resistant, and virulent (via biofilm production, toxin production...)
    - \*\* Macrolides can interfere with quorum sensing, meaning it can weaken bacterial persistence

ERS & BTS guidelines: long-term macrolide therapy for frequent exacerbators & those with chronic *P. aeruginosa* infection who have not improved with inhaled antibiotics

# Long-term Macrolide

## Evidence for long-term macrolides therapy

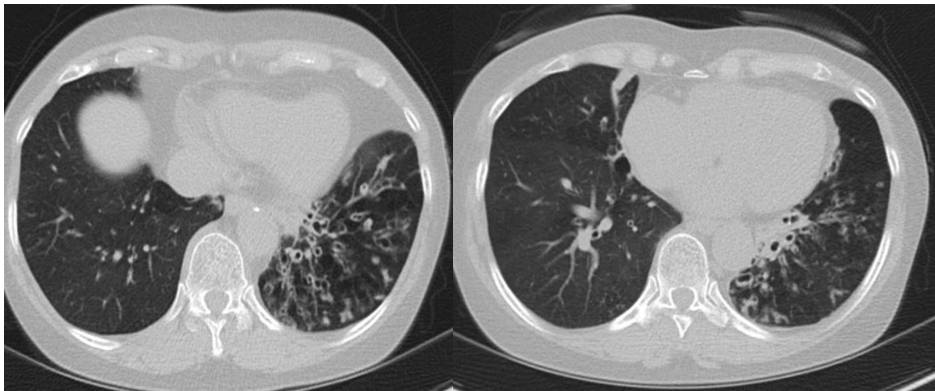
- meta-analysis, n=341
  - ↓ **Exacerbation frequency (IRR 0.49, p<0.001)**
  - ↑ Time to first exacerbation (HR 0.46, p<0.001)
  - Greater benefit in patients with *P. aeruginosa* infection (IRR 0.36, p=0.004)

## Cautions

- Adverse effects
  - **Risk of resistant NTM → baseline sputum AFB culture**

# F/64

- 지속적인 기침 가래를 주소로 내원
  - 결핵 치료력 : 무
  - 백일해/홍역 (-/-)
  - 소아기 잦은 중이염 및 부비동염, 폐렴 (-)
  - Never-smoker
  - 병력 : 없음



# BSI

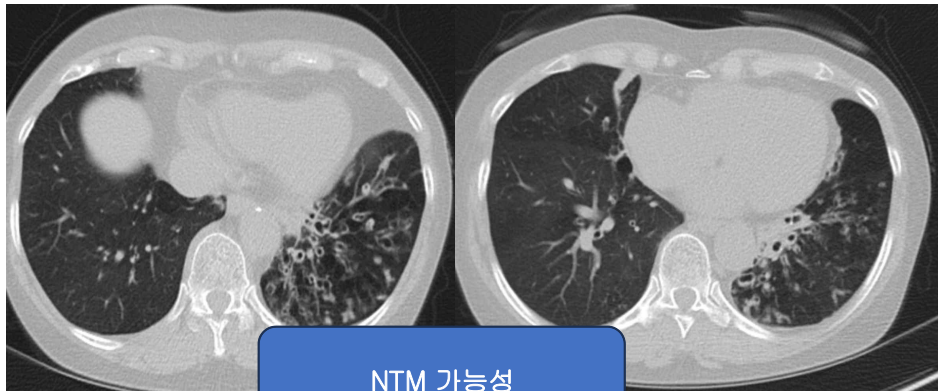
항목	환자	기준	점수	판정
나이 (Age)	63세	< 70세	0점	
BMI	20	≥ 18.5	0점	
FEV <sub>1</sub> %	78%	50~79%	1점	
입원 병력	없음	없음	0점	
악화 횟수/년	≥ 3회	≥ 3회	2점	▲
MRC 호흡곤란	mMRC I	5단계 아님	0점	
Pseudomonas 집락	PA (+) 2024.03	있음	3점	▲
다른 균 집락	PA 단독	PA 해당	0점	
CT 침범 범위	Bilateral 다엽	> 2엽	1점	▲
합계 (Total)			7점	

AZIT?

Moderate (5~8점) → 1년 입원을 7.9% / 4년 사망률 9.3%

[Vote] 악화 예방을 위해 장기Macrolide(Azithromycin) 요법을 고려하고자 할 때, 처방 직전 반드시 확인해야 할 사항은?

1. 24시간 간접흡연 노출 여부
2. 객담 AFB 도말 및 배양 검사 결과 (NTM 동반 여부)
3. 최근 3개월 내 인플루엔자 백신 접종력
4. 폐기능 검사(PFT) 상의 FEV1 수치 변화



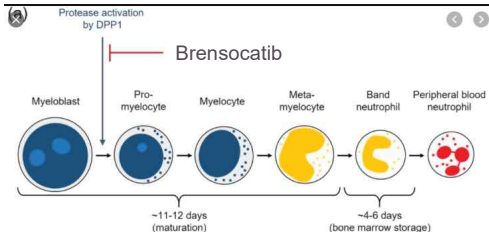
NTM 가능성

2026-01-28 [결핵균검사] [Sputum]	AFB stain	Negative	●
2026-01-28 [결핵균검사] [Sputum]	(고체)AFB Culture and Ide	No AFB isolated in solid culture (8 we	●
2026-01-28 [결핵균검사] [Sputum]	(액체)AFB Culture and Ide	No AFB isolated in broth culture (6 w	●

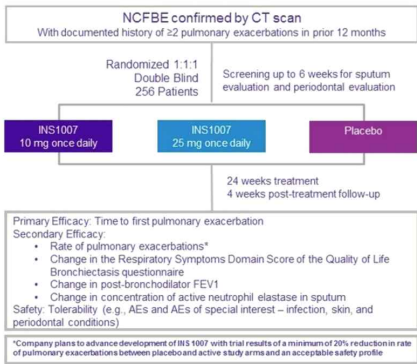
2024-11-12 [일반뇨화학검사] [Spot(Urine	Dysmorphic RBC	Dysmorphic RBC; 86%, G1 cell (acanth
2024-08-26 [외주검사(녹십자)] [Sputum]	(고체)AFB Culture and Ide	[중간보고] 중간결과(4주) - No AFB iso
2024-08-26 [외주검사(녹십자)] [Sputum]	(액체)AFB Culture and Ide	[중간보고] 중간결과(3주) - No AFB iso
2024-08-26 [외주검사(녹십자)] [Sputum]	(고체)AFB Culture and Ide	[중간보고] 중간결과(4주) - No AFB iso
2024-08-26 [외주검사(녹십자)] [Sputum]	(액체)AFB Culture and Ide	[중간보고] 중간결과(3주) - No AFB iso

# Brensocatib

- Brensocatib
  - a small molecule, oral, **reversible inhibitor** of dipeptidyl peptidase I (DPP1), an enzyme responsible for activating neutrophil serine proteases (NSPs), such as **neutrophil elastase**, in neutrophils when they are formed in the bone marrow



# Brensocatib



The WILLOW study met its primary endpoint, with brensocatib significantly prolonging time to first pulmonary exacerbation over the 24-week treatment period versus placebo ( $p=0.027$  for the 10 mg group;  $p=0.044$  for the 25 mg group). **The risk of exacerbation at any time** during the trial was reduced by **42%** for the 10 mg group versus placebo (**HR 0.58,  $p=0.029$** ) and by 38% for the 25 mg group versus placebo (HR 0.62,  $p=0.046$ ).

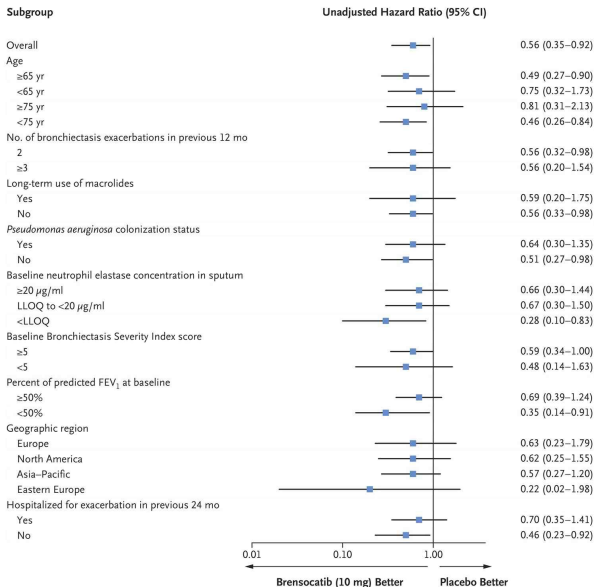
42%

c.f. )Macrolide HR = **0.49 (0.36-0.66)**

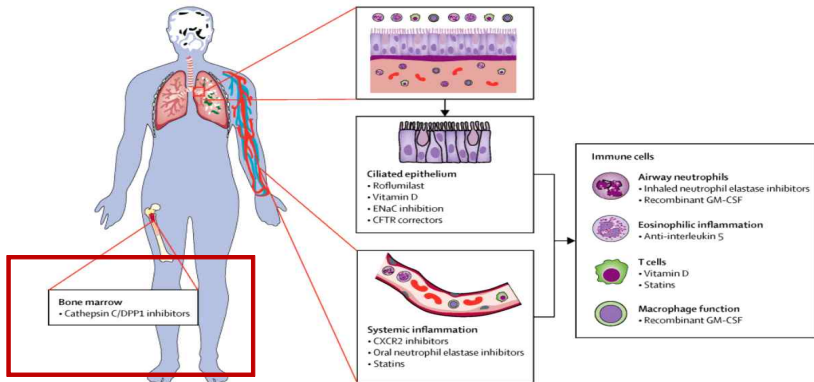
“Sputum neutrophil elastase” below the limit of quantification post-baseline



“72%” lower risk of AE



# Novel treatment approaches

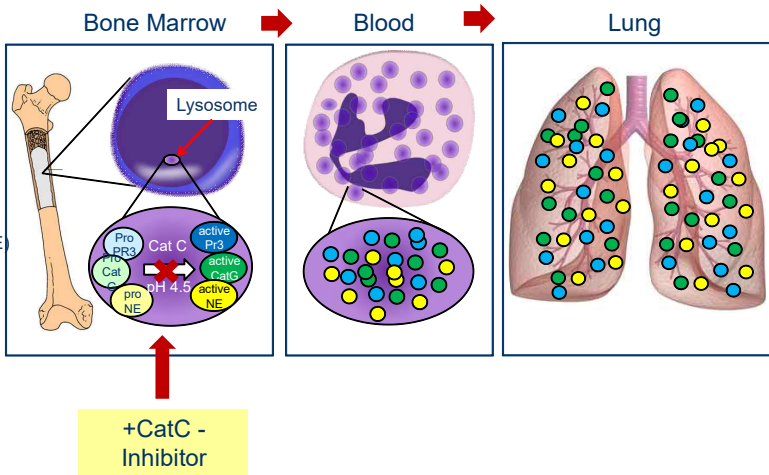


**CathepsinC/DPP1 inhibitors**

# Cathepsin C inhibition

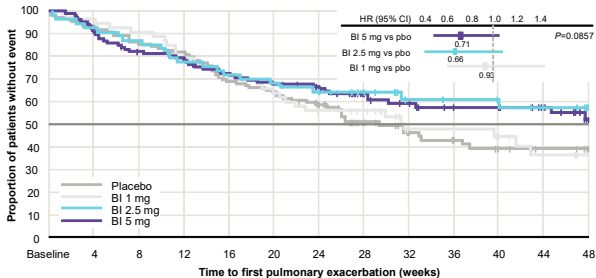
**3 Neutrophil Serine Proteases** are activated by the enzyme Cathepsin C:

- = Neutrophil Elastase (NE)
- = Cathepsin G (CatG)
- = Proteinase 3 (PR3)



# Cathepsin C inhibition

Kaplan–Meier plot of time to first pulmonary exacerbation up to Week 48\*



Placebo	109	100	93	89	74	69	59	39	28	24	19	14	1
BI 1 mg	53	51	47	41	37	33	28	26	15	15	13	9	1
BI 2.5 mg	53	49	46	41	38	36	31	25	18	17	16	12	1
BI 5 mg	107	97	86	82	74	69	63	45	39	34	32	26	1

Patients at risk

Reduction in risk of pulmonary exacerbation up to Week 48:

↓ 5 mg: 29%

↓ 2.5 mg: 34%

↓ 1 mg: 7%

# Summary

- **동반 질환 고려:** 기관지확장증은 환자마다 원인과 증상이 다양하므로, NTM-PD 등 동반 질환 유무를 파악하는 것이 중요
- **적극적 악화 예방:** 빈번한 악화 환자에게 장기 Macrolide(AZIT) 요법은 악화 빈도를 약 50% 낮추는 핵심 전략
- **NTM 배제 필수:** 내성 방지를 위해 AZIT 처방 전 반드시 객담 AFB 배양을 통해 NTM 동반 여부를 확인필요.
- **신약 치료 옵션:** Brensocatib 등 중성구 염증을 타겟으로 하는 신약이 새로운 악화 예방 대안으로 부각되고 있음

**감사합니다**