

Treatable traits of Bronchiectasis

울산대학교병원 | 호흡기내과 | 나승원

부·울·경 호흡기학회 온라인 학술모임

2020.10.22

ULSAN
UNIVERSITY
HOSPITAL



Bronchiectasis – Up to date

강의 순서

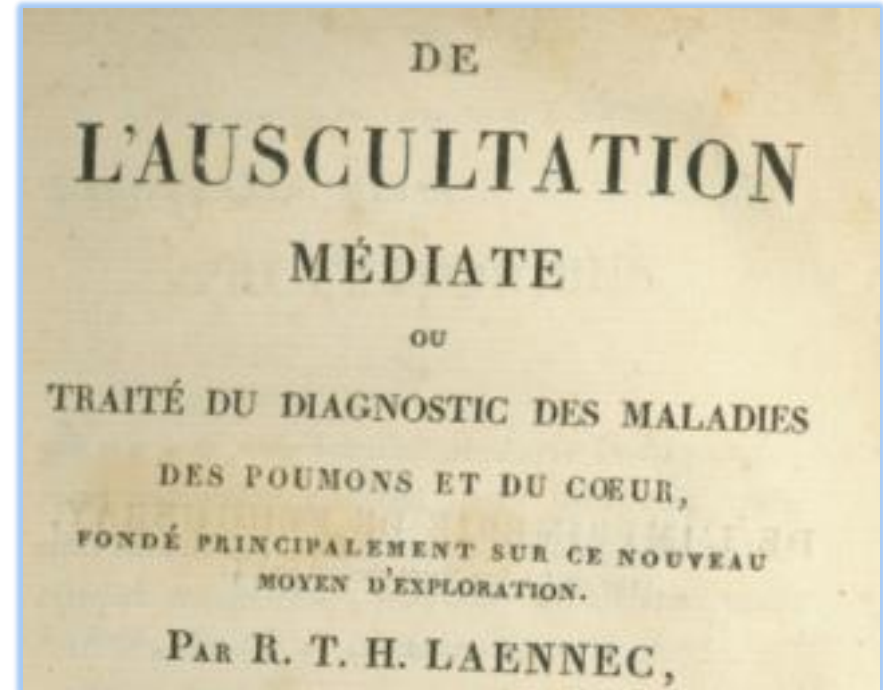
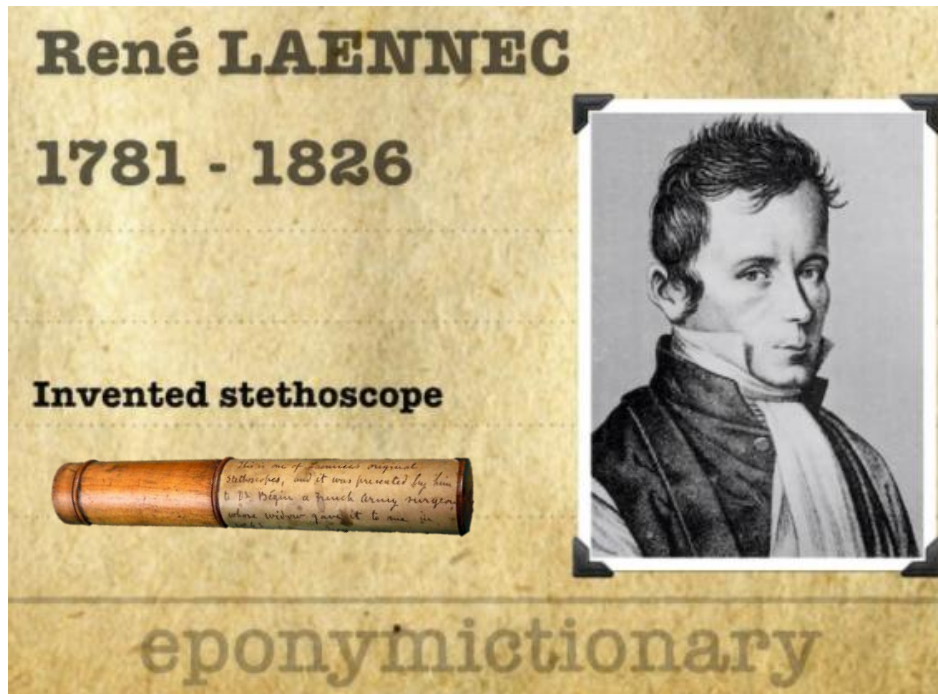
- 정의, epidemiology
- Diagnostic bundle
- Treatment & Treatable traits
- Bronchiectasis exacerbation

Bronchiectasis: definition

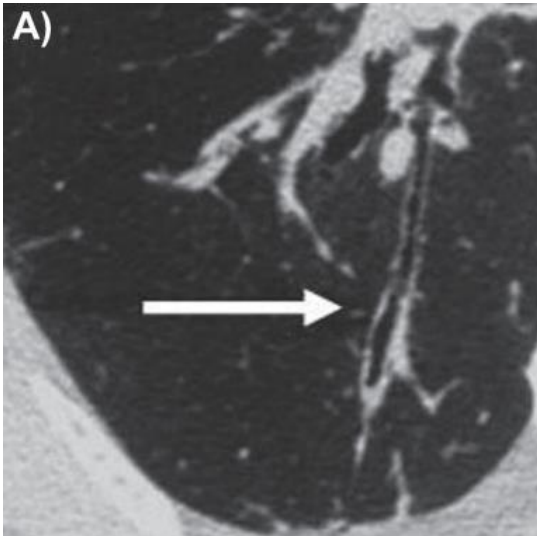
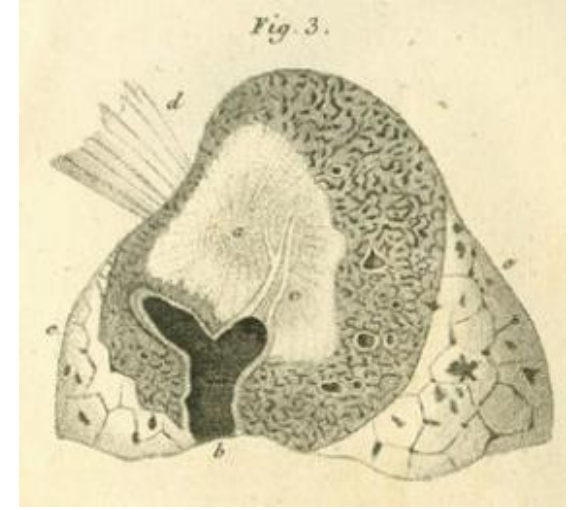
- Abnormal, **usually** permanent, dilatation of the bronchi
- First description by the French physician René Laennec in 1819¹
- In post-antibiotic era, bronchiectasis being described as an orphan or neglected disease.²

1. *Ann. Am. Thorac Soc.* 13, 1667–1670

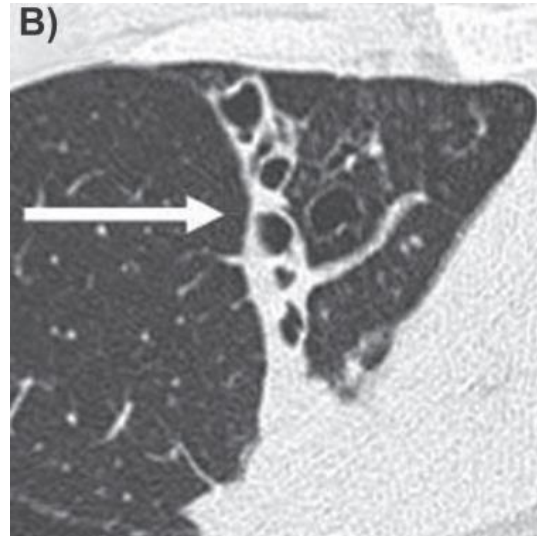
2. *Eur. Respir. J.* 47, 10–13 (2016).



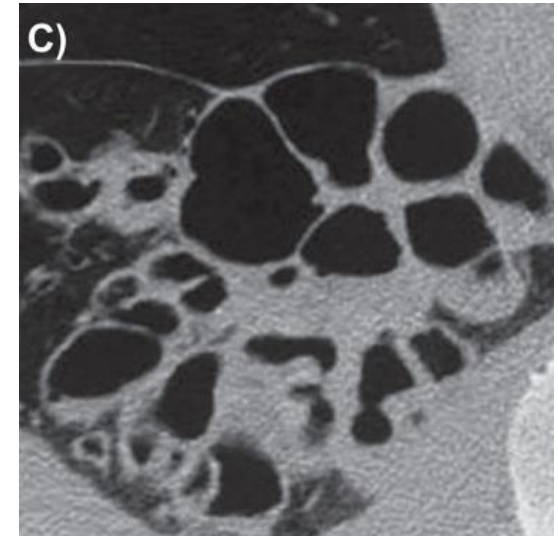
Bronchiectasis: diagnosis



A) Cylindrical



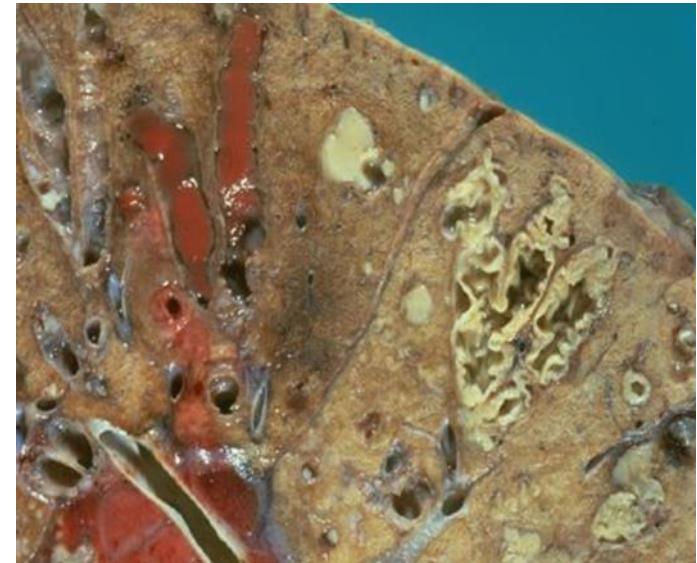
B) Varicose



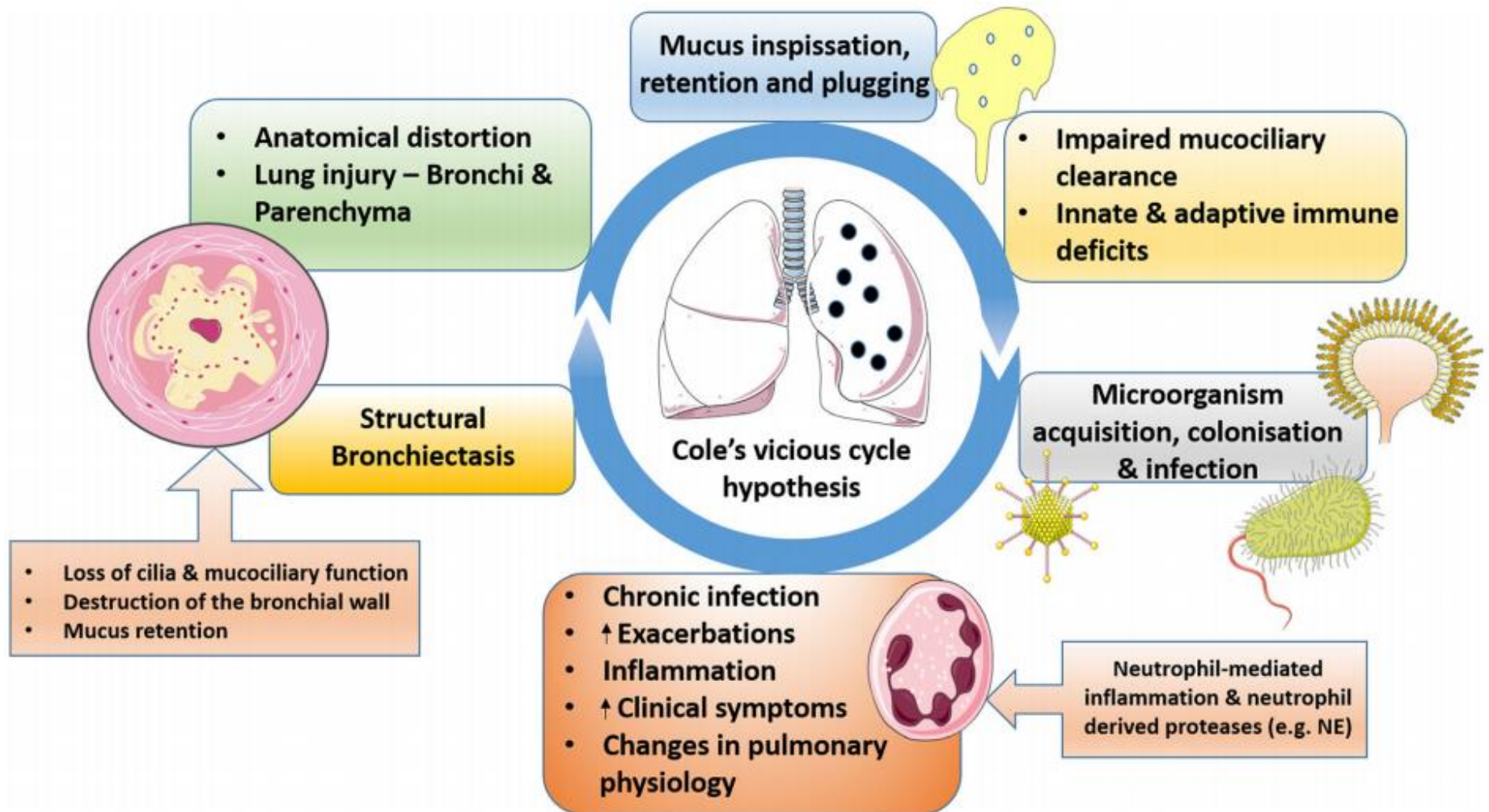
C) Cystic

HR CT diagnosis of Bronchiectasis

1. 기관지 내경과 동반하는 폐동맥의 비 (broncho-arterial ratio, BAR > 1)
2. 기관지 내경의 점진적 감소가 없는 경우 (lack of tapering)
3. 벽측 흉막 1 cm 이내에 기도가 보이거나 또는 종격동 흉막에 기도가 닿는 경우.



Vicious cycle of bronchiectasis

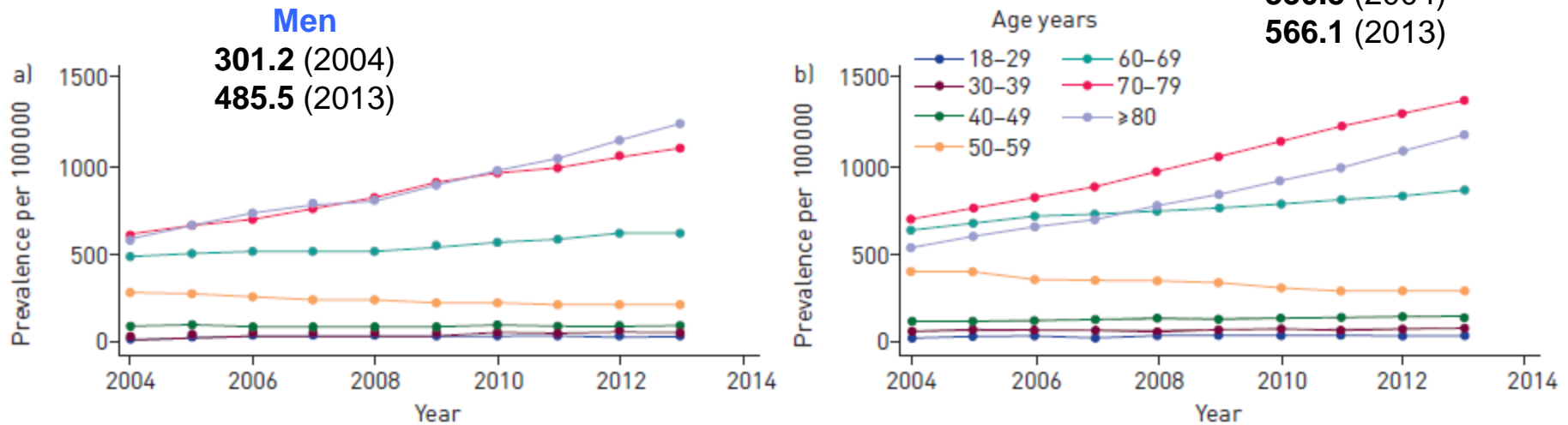


Reversing the vicious cycle of bronchiectasis

- Decreasing infection OR inflammation directly would reduce inflammation leading to improve clinical outcomes.
 - ✓ Airway clearance technique to improve expectoration
 - ✓ Appropriate antibiotics use (14 days for treating exacerbation)
 - ✓ Long-term macrolide for anti-inflammatory effect
 - ✓ Lung resection for the focal bronchiectasis
 - ✓ New drugs with new mechanisms

Prevalence in Europe, USA, and Asia

Bronchiectasis prevalence in UK



- **362** in Spain, **139** in USA, **67** in Germany per 100,000 individuals
- **1,200** in China; **1,470** Central Australian Aboriginal children
- **464** in South Korea (HIRA-NPS 2012–2017 data, **J47** ICD-10 code) per 100,000 individuals

Quint et al. Eur Respir J 2016;47:10

Choi et al. Eur Respir J 2019;54:1900194

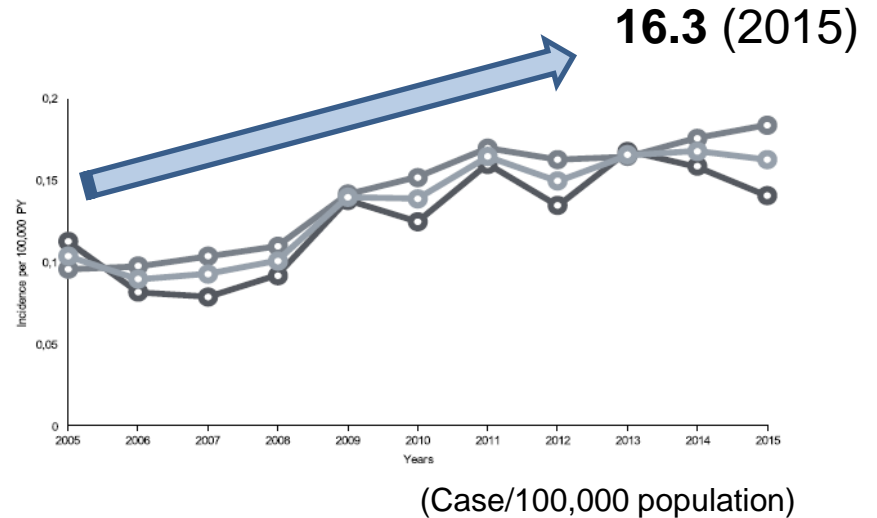
Weycker et al. Chronic Respir Dis 2017;14:377

Ringshausen et al. Eur Respir J 2019;54:1900499

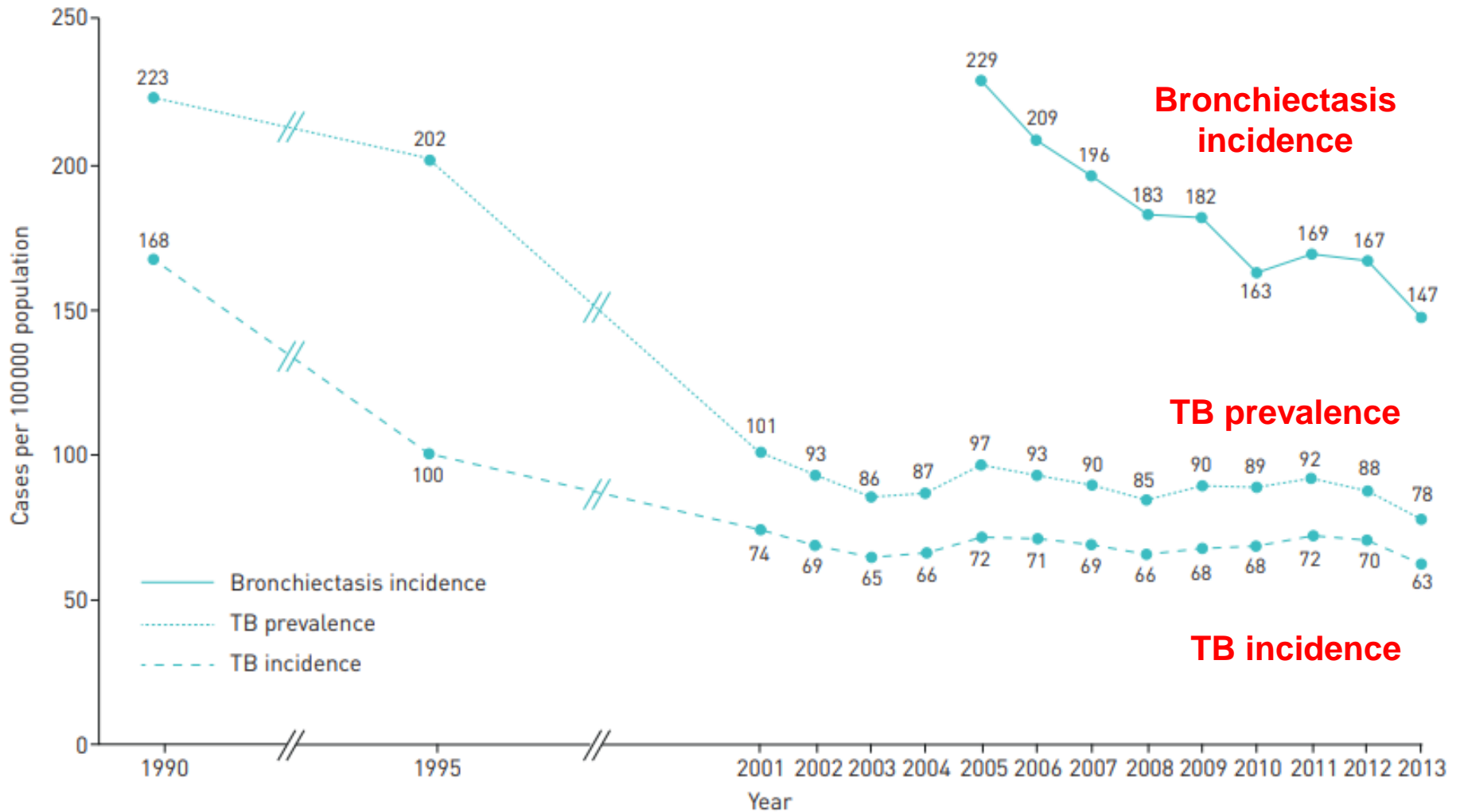
Bronchiectasis Incidence



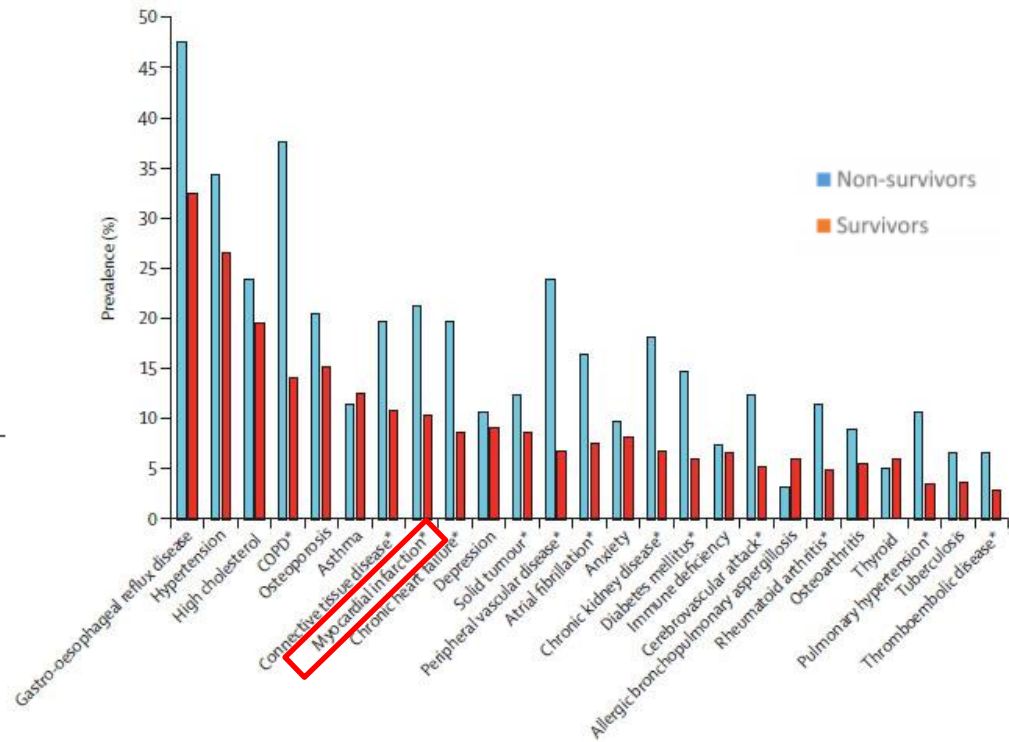
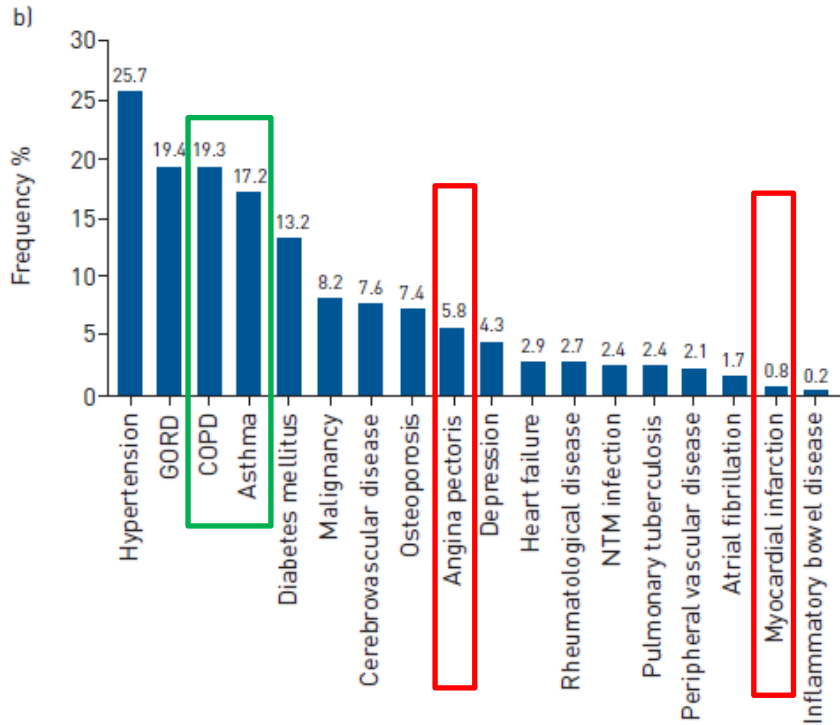
- **18.2** (2004) → **26.9** (2013) in Men
- **21.2** (2004) → **35.2** (2013) in Women
(Case/100,000 population)



Bronchiectasis Incidence Concerning TB epidemiology



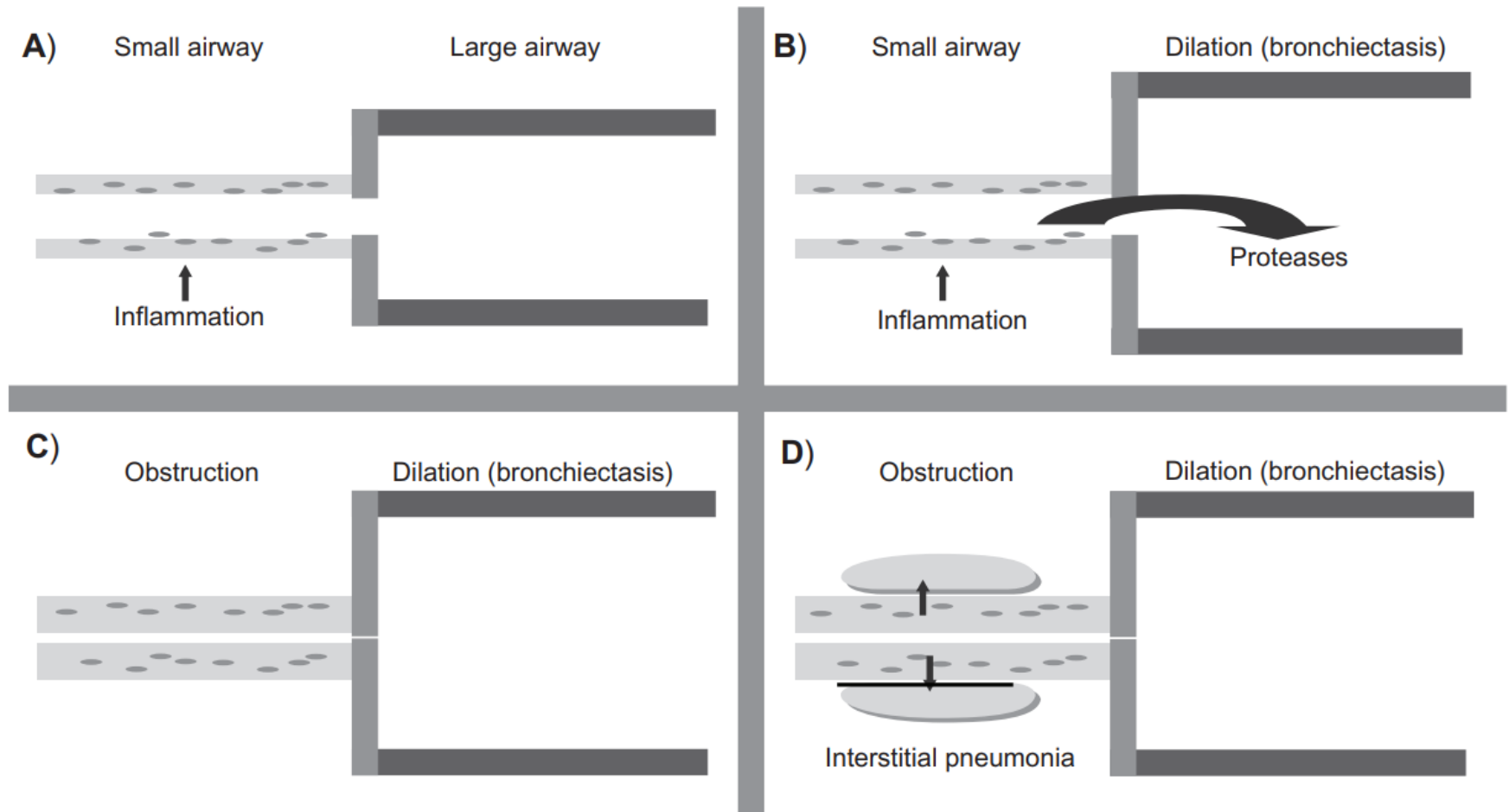
Bronchiectasis: Comorbidities



Choi et al. *Eur Respir J* 2019;54:1900194

McDonnell et al. *Lancet Respir Med* 2016;4:969

Airway obstruction in bronchiectasis



Disease Burden of Bronchiectasis

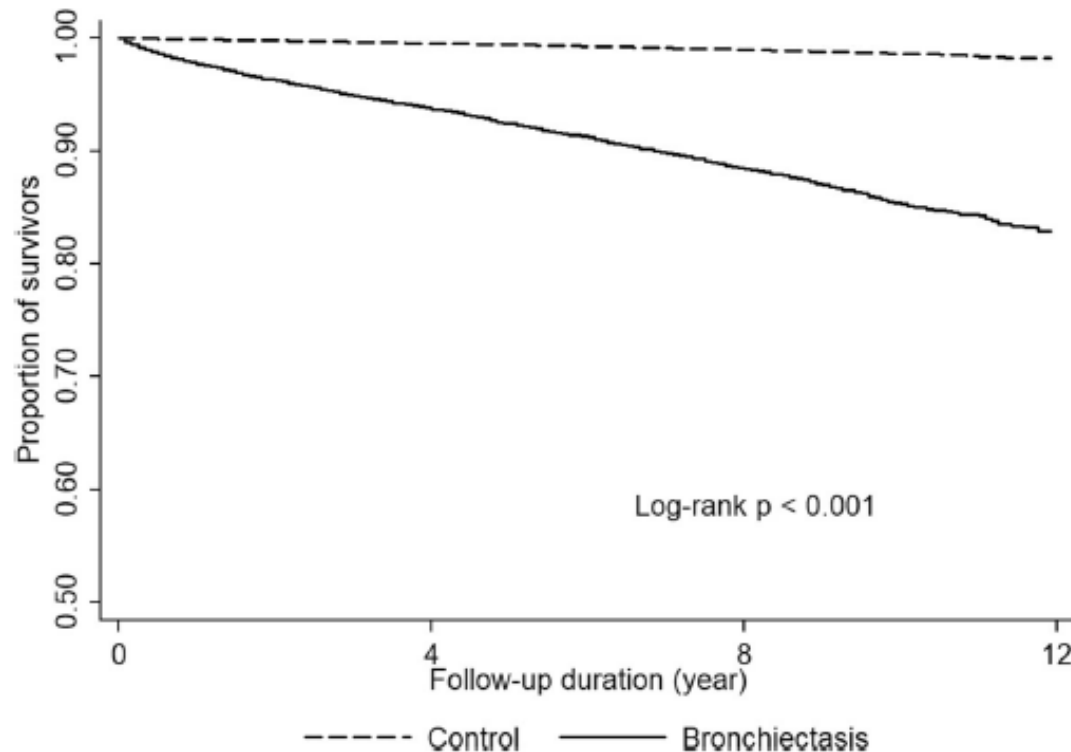
- Korean NHANES data

Variable	Control	COPD	Bronchiectasis
Respiratory symptoms			
Univariable	Ref	2.06 (1.33–3.79)	7.40 (1.79–30.59)
Multivariable*	Ref	1.62 (0.92–2.85)	7.96 (2.10–30.12)
Limitation of physical activity			
Univariable	Ref	5.96 (3.28–10.81)	18.19 (5.23–63.28)
Multivariable*	Ref	1.84 (0.64–5.27)	9.43 (1.06–83.79)

*Adjusted for age, sex, BMI, smoking status, education level, family income, asthma, tuberculosis, and FEV₁

Bronchiectasis: Mortality

- Retrospective cohort
 - ◆ Patients with chest CT between 2005–2016
 - ◆ Bronchiectasis group (n=18,134) VS. Control group (n=90,313)

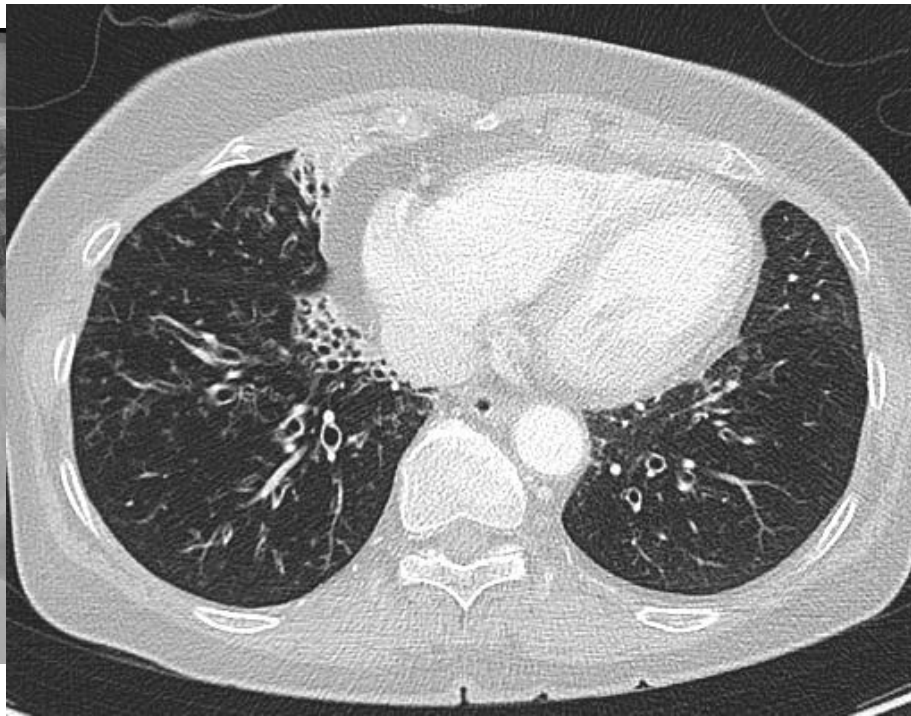


Approach to Diagnosis

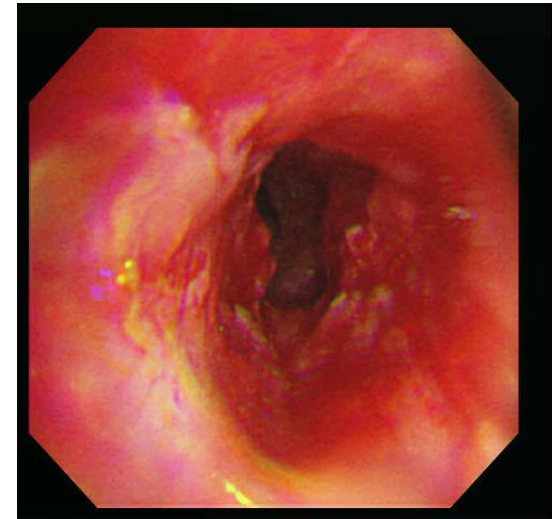
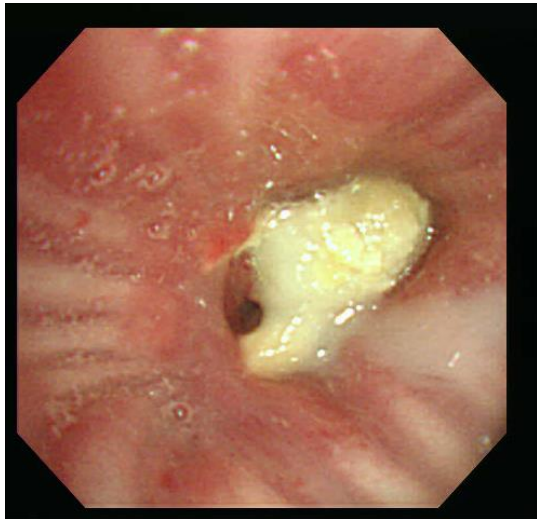
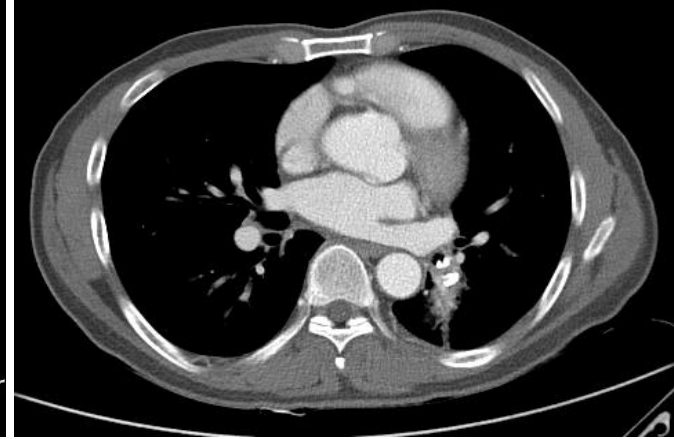
- Clinical history: productive cough, recurrent infections, dyspnea, fatigue, hemoptysis..
- Presence of extrapulmonary symptoms or signs (RA, CTD...)
- HR chest CT: focal vs. multifocal bronchiectasis
- Presence of associated conditions
 - ◆ Asthma
 - ◆ COPD
 - ◆ RA
- **Spirometry**
- **Microbiology**

Typical case of bronchiectasis

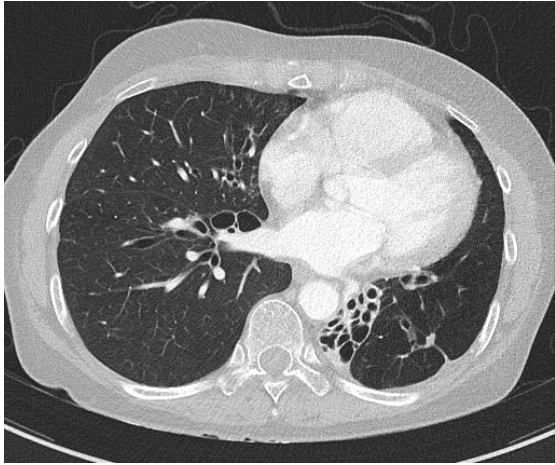
- 60세 여자, non-smoker, BMI 18
- Multiple episodes of cough/productive of green sputum, dyspnea
- Multiple courses of antibiotics (최근 3년간 3회/년 이상 처방)



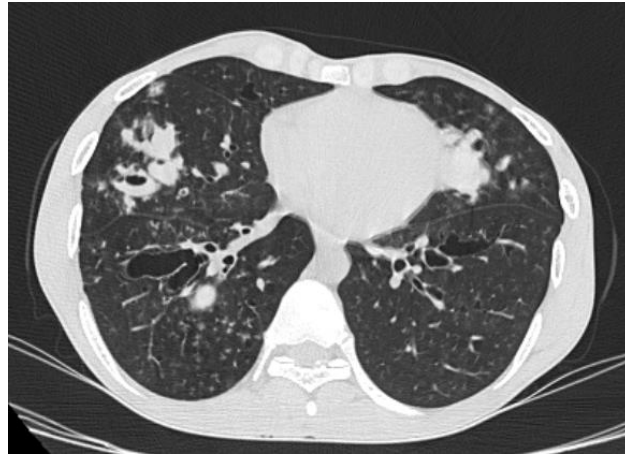
Foreign body in LLL



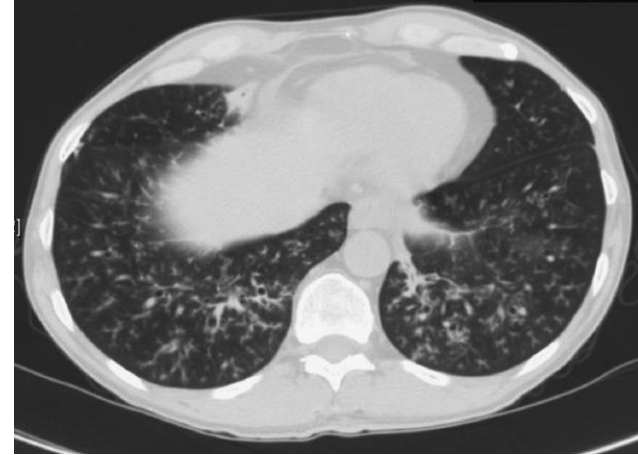
Multifocal bronchiectasis



61/F, no symptoms
h/o measles, h/o TB

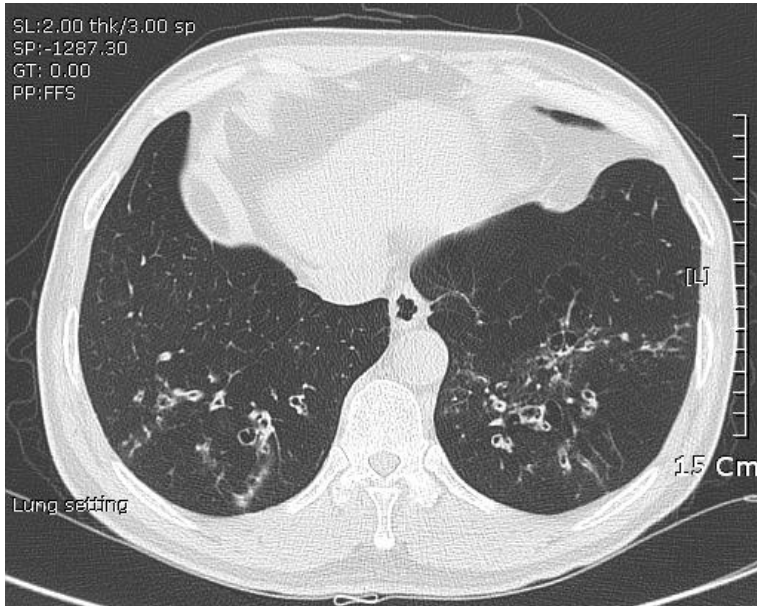


ABPA, allergic
bronchopulmonary
aspergillosis

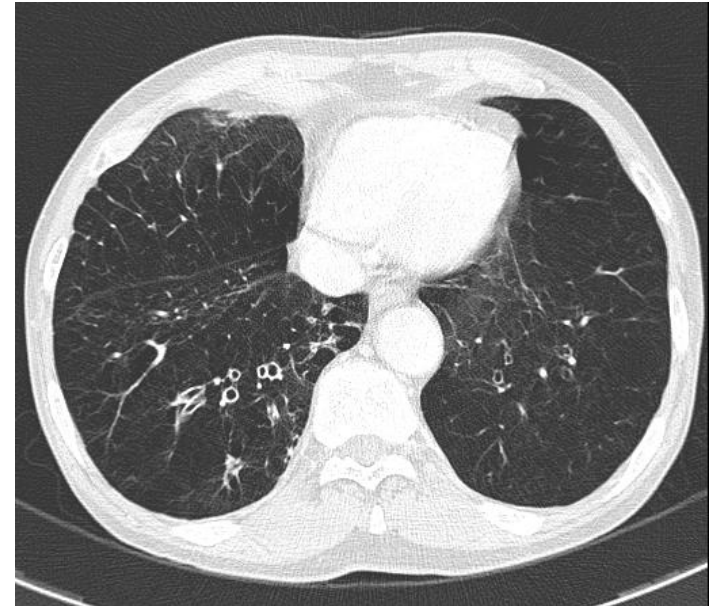


Chronic aspiration

Asthma or COPD unresponsive to usual treatment



- Asthma-Bronchiectasis



- COPD-Bronchiectasis

Standardized diagnostic testing panels

Diagnostic Bundle

	British Thoracic Society guideline (2019)	European Respiratory Society guideline (2017)	American Thoracic Society (2013) ^a
Comprehensive assessment of history and comorbidities Spirometry	○	○	○
Bacterial and mycobacterial culture	○	○	○
IgG, A, and E	○	○	○
Test for ABPA (including IgE)	○	○	
Antibody titers to pneumococcal vaccine	○		○
Auto-antibodies (e.g., ANA, RF, anti-CCP, SSA, SSB Ab, ANCA)	Patients with suspected connective tissue disease		○
CFTR genetic mutation analysis	Patients with suspected cystic fibrosis		○
Alpha-1 antitrypsin level and phenotype	Patients with suspected Alpha-1 anti-trypsinase deficiency		○
Test for primary ciliary dyskinesia	Patients with primary ciliary dyskinesia		Patients with primary ciliary dyskinesia

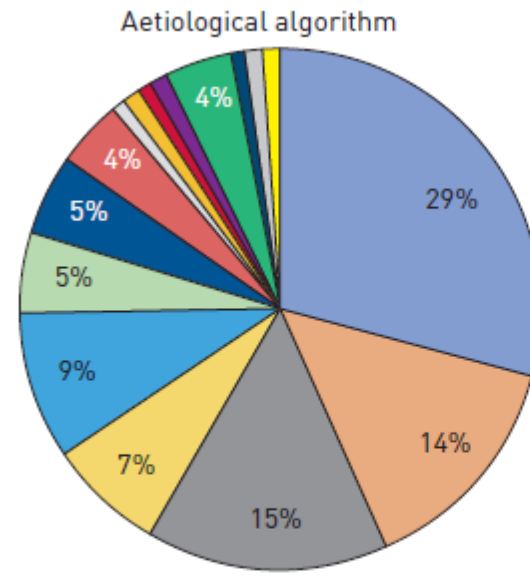
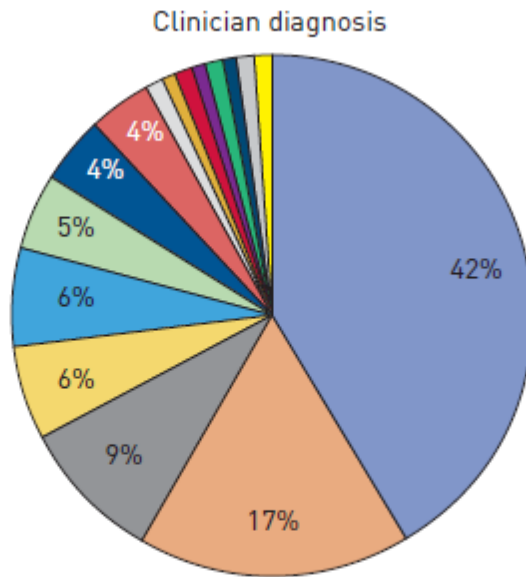
Ig, immunoglobulin; ABPA, allergic bronchopulmonary aspergillosis; CFTR, cystic fibrosis transmembrane conductance regulator; ANA, antinuclear antibody; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; SSA/SSB, Sjögren syndrome associated antigen A/B.

^aConcise review.

Hyun Lee and Yeon-Mok Oh. Korean J Med 2020;95:141-150
Hill AT, et al. Thorax 2019;74(Suppl 1):1-69.
Polverino et al. Eur Respir J 2017;50:1700629
Am J Respir Crit Care Med 2013;188:647-656.

Standardized etiologic algorithm

b)



- Idiopathic ■ Post-infective ■ COPD ■ Asthma ■ CTD ■ ABPA ■ Immunodeficiency ■ post-TB
- IBD ■ PCD ■ NTM ■ Sarcoidosis ■ GORD/aspiration ■ Other ■ Two aetiologies ■ A1ATD

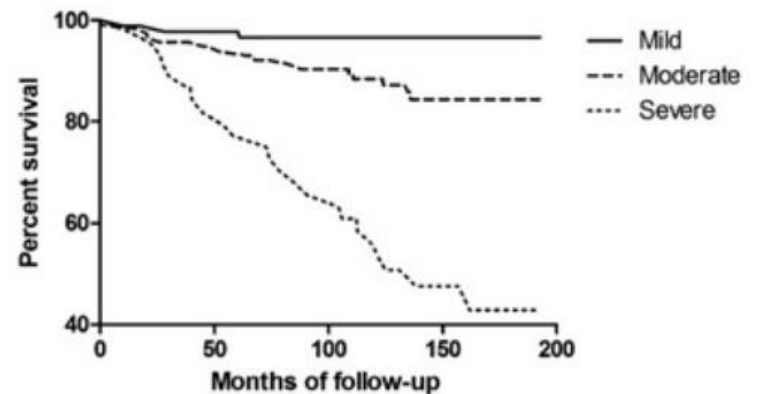
Idiopathic etiology: **42%** → **29%**

Spirometry

- Bronchiectasis and Chronic Airway Disease
 - ◆ COPD and Asthma

- Bronchiectasis Severity Index (BSI)

Age
BMI
FEV₁, % predicted
Hospital admission
Exacerbations
MRC dyspnea scale
Pseudomonas colonization
Colonization with other organisms
≥ 3 lobes involved or cystic Bronchiectasis



FACED/E-FACED score

Table 6. FACED/E-FACED score

Points	FEV ₁ , %predicted	Age (years)	<i>P. aeruginosa</i> colonization	Extension (radiologic severity)	Dyspnea (mMRC dyspnea scale)	At least one severe exacerbation requiring hospitalization in the previous year ^a
0	≥ 50%	< 70	No	1-2 lobes	0-2	No
1			Yes	≥ 3 lobes	≥ 3	
2	< 50	≥ 70				Yes

The FACED index is classified into mild (0-2 points), moderate (3-4 points) and severe (5-7 points). The E-FACED score is classified into mild (0-3 points), moderate (4-6 points) and severe (7-9 points).

FACED, FEV₁, age, colonization, extension, dyspnea; E-FACED, exacerbation-FACED; mMRC, modified medical research council, FEV₁, forced expiratory volume in one second.

^aIncluded in E-FACED score only.

Microbiology

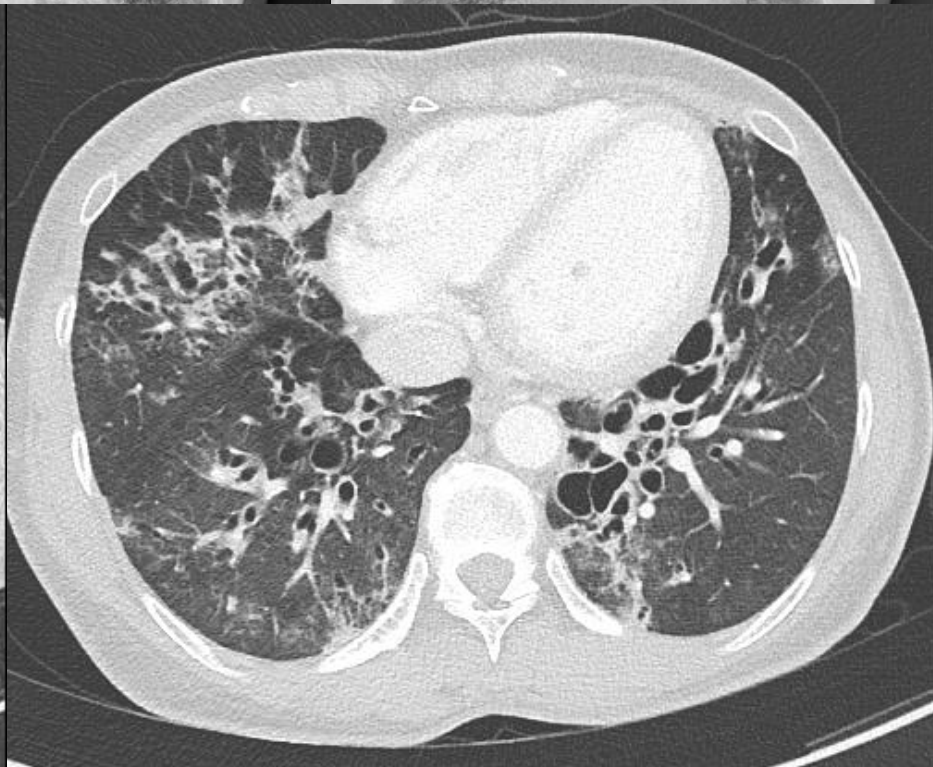
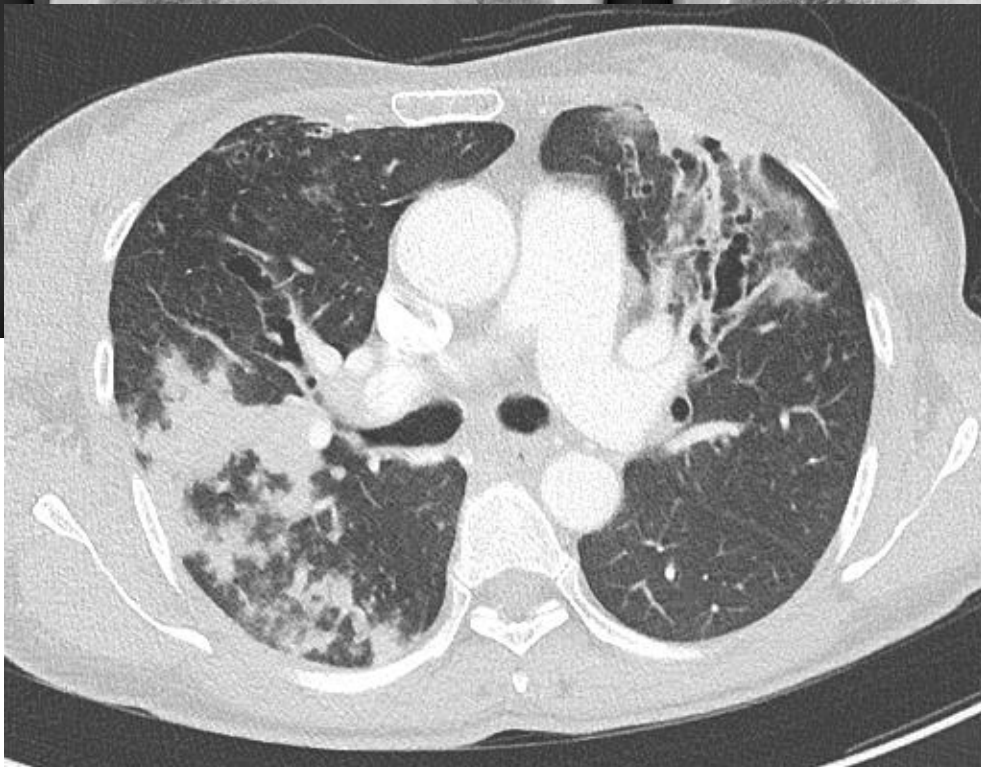
- Help guide the use of antibiotics
 - ◆ Acute exacerbation
 - ◆ Chronic suppressive therapy
- NTM
- *S. aureus* – might indicate CF
- *A. fumigatus* – may prompt investigations of ABPA
- ***P. aeruginosa***
 - ◆ rapid lung function decline
 - ◆ exacerbation ↑
 - ◆ hospitalization & mortality ↑

ABPA (Allergic BronchoPulmonary Aspergillosis)

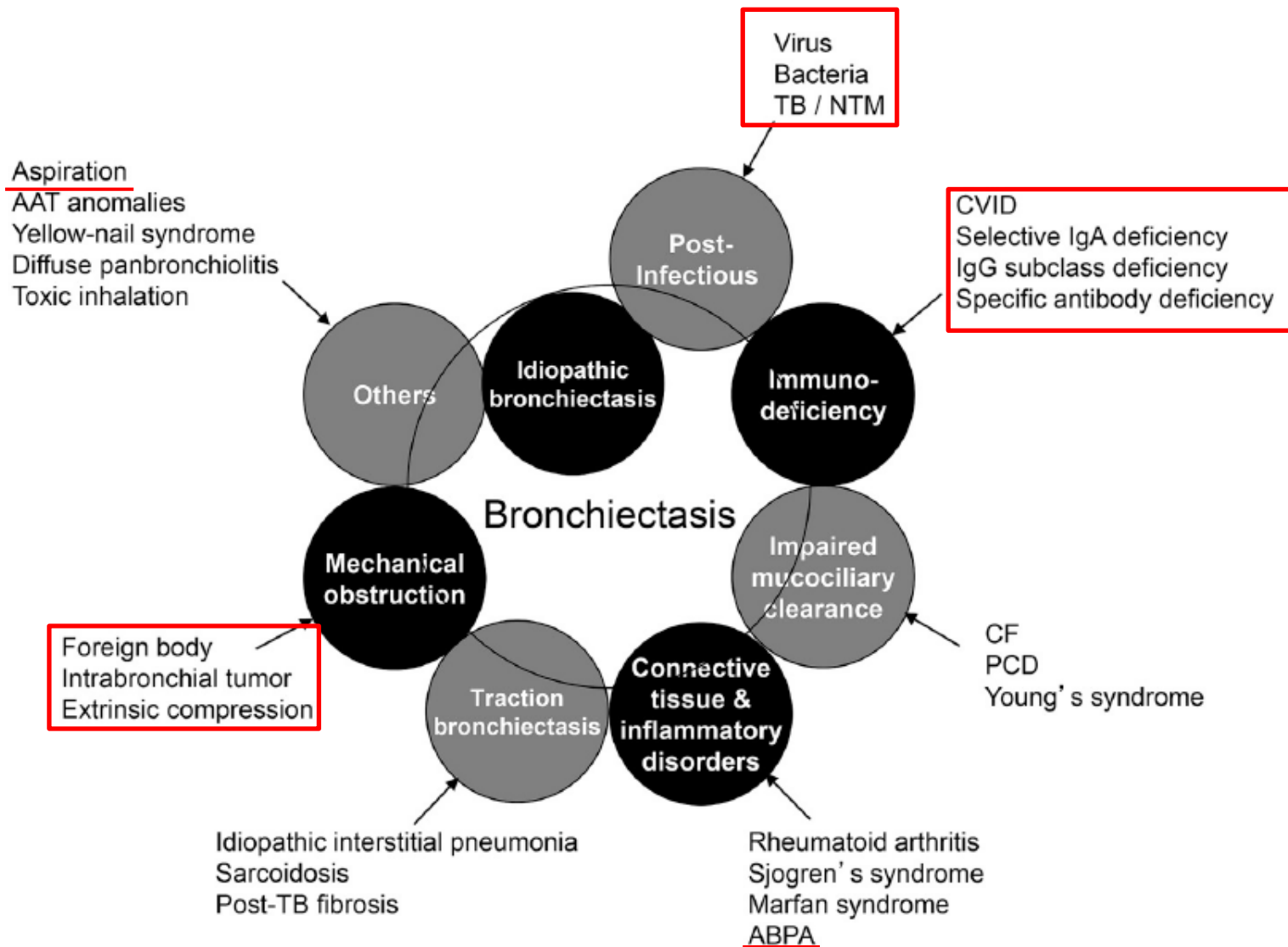
- ABPA prevalence
 - ◆ **1–11%** of bronchiectasis patients in UK
- Expert consensus for steroid naïve patients
 - ◆ Associated with clinical deterioration (**Asthma**)
 - ◆ Total serum **IgE level > 500 IU/mL**
 - ◆ Immediate cutaneous reaction to *Aspergillus* (**Skin prick test**) or
 - ◆ Increased ***Aspergillus* species specific IgE Ab** (> 0.35 kUA/L)
 - ◆ New radiologic infiltrates and/or high attenuation mucus plugging

ABPA testing is included in **minimum bundle** of ERS Guidelines
- Serum IgE level, specific IgE and IgG, (or *Aspergillus* skin test)

ABPA case



Heterogeneity



성인 기관지확장증 약물치료의 최신지견

최 하 영¹ · 이 현² · 나 승 원³ · 오 연 목⁴

¹한림대학교 의과대학 강남성심병원 호흡기내과

²한양대학교 의과대학 내과학교실 호흡기내과

³울산대학교 의과대학 울산대학교병원 호흡기내과

⁴울산대학교 의과대학 서울아산병원 호흡기내과

Update on pharmacotherapy for adult bronchiectasis

Non-pharmacotherapy



Chronic bronchial infection

Long-term inhaled or oral antibiotic therapy
Eradication of new pathogenic microorganisms
Antibiotic treatment of exacerbations

Structural lung disease

Long-term bronchodilator therapy
Surgery
Pulmonary rehabilitation



Inflammation

Long-term anti-inflammatory therapies

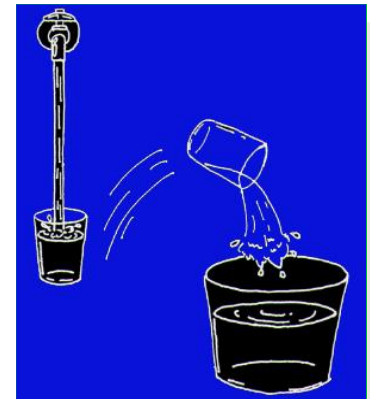
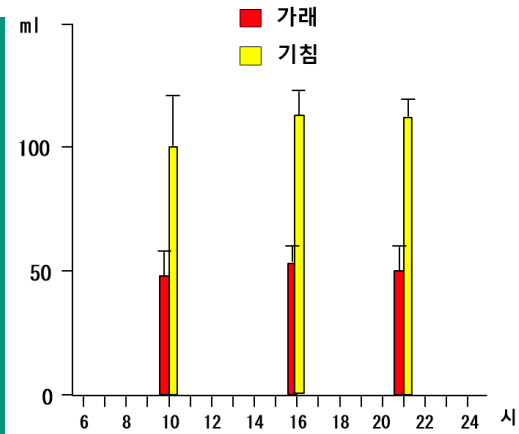
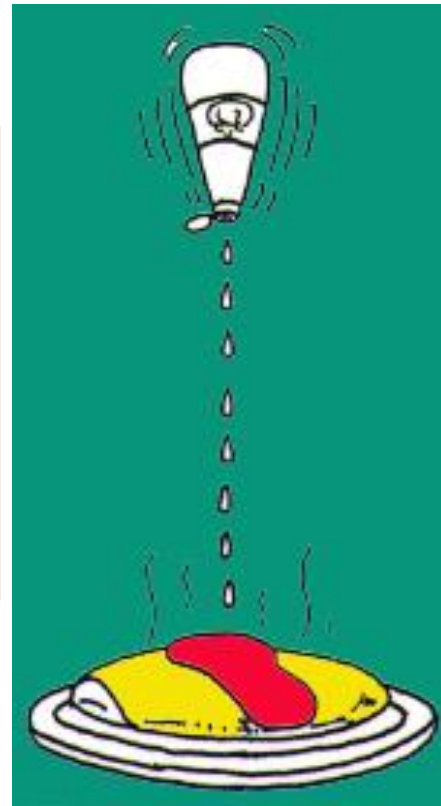
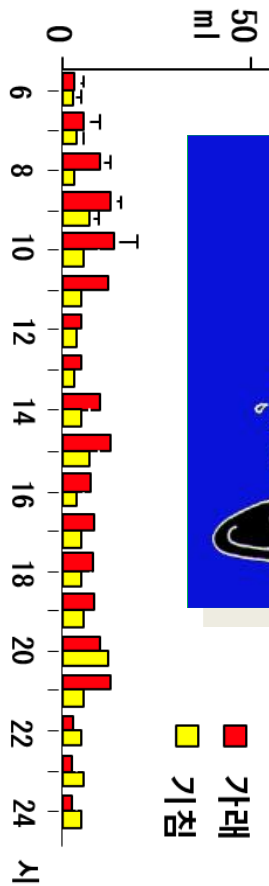
Impaired mucociliary clearance

Long-term mucoactive treatments
Airway clearance



Bronchiectasis: Treatment and Prevention

Theodore L. Badger, M.D.[†]



항염증 치료

- 흡입 스테로이드
 - ◆ 천식이나 만성폐쇄성폐질환을 동반한 기관지확장증 환자 외에는 권고하지 않음.
- 경구 스테로이드, 메틸잔틴계 약물, 스타틴 (statin), PDE-4 (phosphodiesterase-4) 억제제, 류코트리엔 수용체 길항제 (LTRA)
 - ◆ 기관지확장증 환자 치료에 있어 효과가 정립되지 않았다.
- Brensocaticib: neutrophil serine protease inhibitor
 - ◆ Phase 2 RCT (WILLOW study) – 24주간 치료군 42% 악화 감소 효과 증명

기관지확장제

- 호흡곤란을 호소하는 기관지확장증에서 지속성 기관지확장제 투여를 고려해 볼 수 있다고 권고를 하고 있지만, 근거는 매우 미약
- Asthma-bronchiectasis, COPD-bronchiectasis 환자에서는 진료지침 따라서 투여

Oral or inhaled mucolytics

2017 ERS recommendation

ERS GUIDELINES | E. POLVERINO ET AL.

There is insufficient evidence to permit evaluation of the use of oral mucolytics such as carbocysteine for bronchiectasis [89].

2019 BTS guideline

Oral mucolytics can improve sputum expectoration. (1-)

Good practice points

- ✓ Consider a trial of mucoactive treatment in patients with bronchiectasis who have difficulty in sputum expectoration.
- ✓ Perform an airway reactivity challenge test when inhaled mucoactive treatment is first administered.
- ✓ Consider pre-treatment with a bronchodilator prior to inhaled or nebulised mucoactive treatments especially in individuals where bronchoconstriction is likely (patients with asthma or bronchial hyper-reactivity and those with severe airflow obstruction $FEV_1 < 1$ litre).
- ✓ If carbocysteine is prescribed, a 6 month trial should be given and continued if there is ongoing clinical benefit.

Mucoactive substances and Nebulizer

Drug	Device	Indication	Proposed Mechanism of Action	Notes
<i>Expectorants</i>				
Hypertonic saline 7%	Nebulizer	Cystic fibrosis, and bronchiectasis	Increases the amount of sodium and chloride in airway surface liquid, thereby increasing the osmotic gradient and rehydrating the mucus layer [5,7]	Improves lung function and quality of life in bronchiectasis [8]. Should not be given via a vibrating mesh nebulizer. Improves mucus clearance, airflow, and reduces rates of exacerbation among patients with cystic fibrosis [4,9].
<i>Classical mucolytics</i>				
<u>NAC (Mucomyst®)</u>	Nebulizer	<u>ABPA</u>	Severs disulfide bonds that link mucin monomers to polymers, and solubilizes sputum antioxidant and anti-inflammatory	No evidence for use in any lung disease.

J. Fungi 2018, 4, 117; doi:10.3390/jof4040117.

Table 1 Summary of benefit

Strength of findings [†]	Low	Unclear	High	No benefit
Bronchiectasis		Mannitol ^{6,7,11–14}	<u>HS</u> ^{18,19,23,33} NS ^{23,33}	Dornase alfa ^{‡24,35}
COPD	NS ^{20,21,25,26,34} Mesna ^{§9,29,31}	NAC ^{15,27,32}		HS ^{9,34}
Asthma	Dornase alfa ^{¶30}	HS ¹² NAC ^{8,17} Mannitol ¹⁰		

Definition of a BE pulmonary exacerbation

- a deterioration in ≥ 3 of key symptoms for at least **48 h**:

- 1) Cough

- 2) Sputum volume and/or consistency

- 3) Sputum purulence

- 4) Breathlessness and/or exercise tolerance

- 5) Fatigue and/or malaise

- 6) Hemoptysis

AND

a clinician determines that a **change in BE treatment**

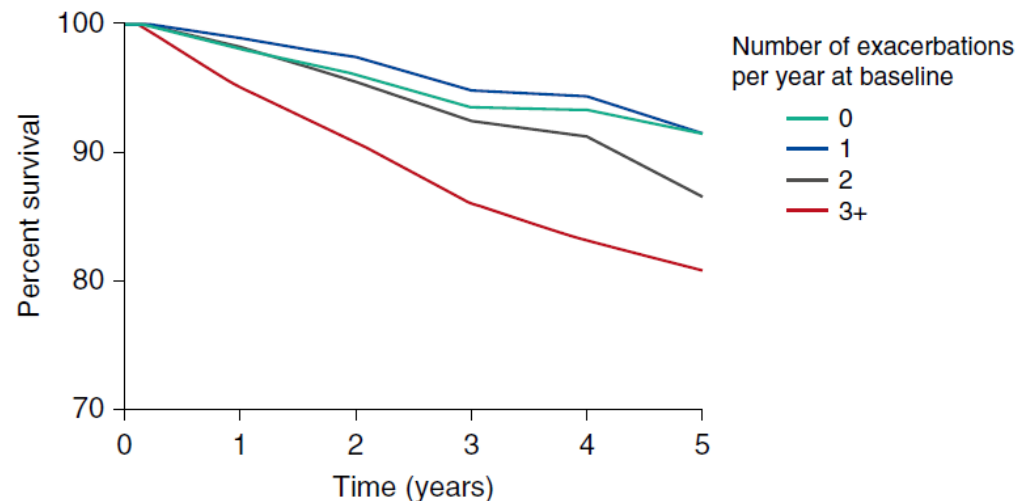
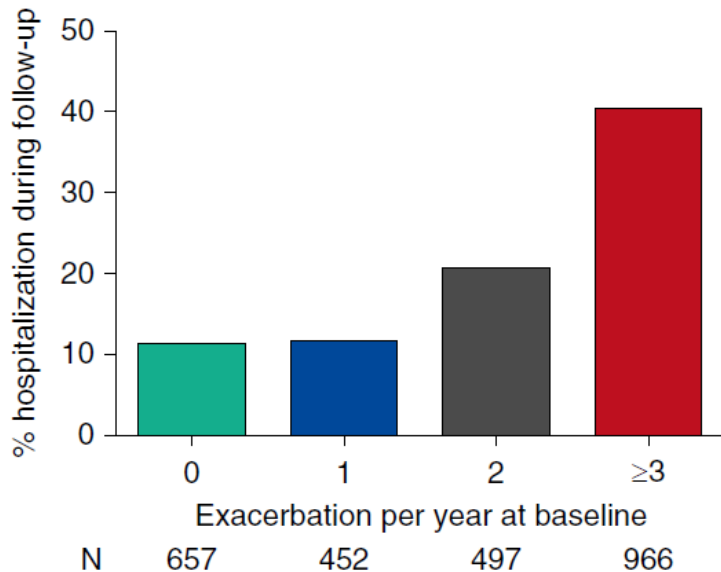
- ◆ a new treatment with antibiotics and/or systemic steroids, or an increase in airways clearance, inhaled therapy or another intervention

“Frequent BE Exacerbator” Phenotype

- History of frequent exacerbations ≥ 3 /year
 - ◆ Was a strong predictor of future exacerbations (IRR 5.97, $p=0.0001$)
 - ◆ Worse QOL, hospital admission \uparrow , mortality \uparrow
- Independent predictors for frequent exacerbators:
 - ◆ *P. aeruginosa* & *H. influenza* infection
 - ◆ $FEV_1 < 50\%$ predicted
 - ◆ Radiological severity
 - ◆ Co-existing COPD

Definition of Frequent BE exacerbator

- 유럽과 이스라엘 10개 기관, 2753명 → 5년간 f/u
- CF, NTM lung disease, traction BE from ILD 제외
- **37%** had ≥ 3 /yr, 19% had 2/yr, about 40% had 0-1/yr exacerbations



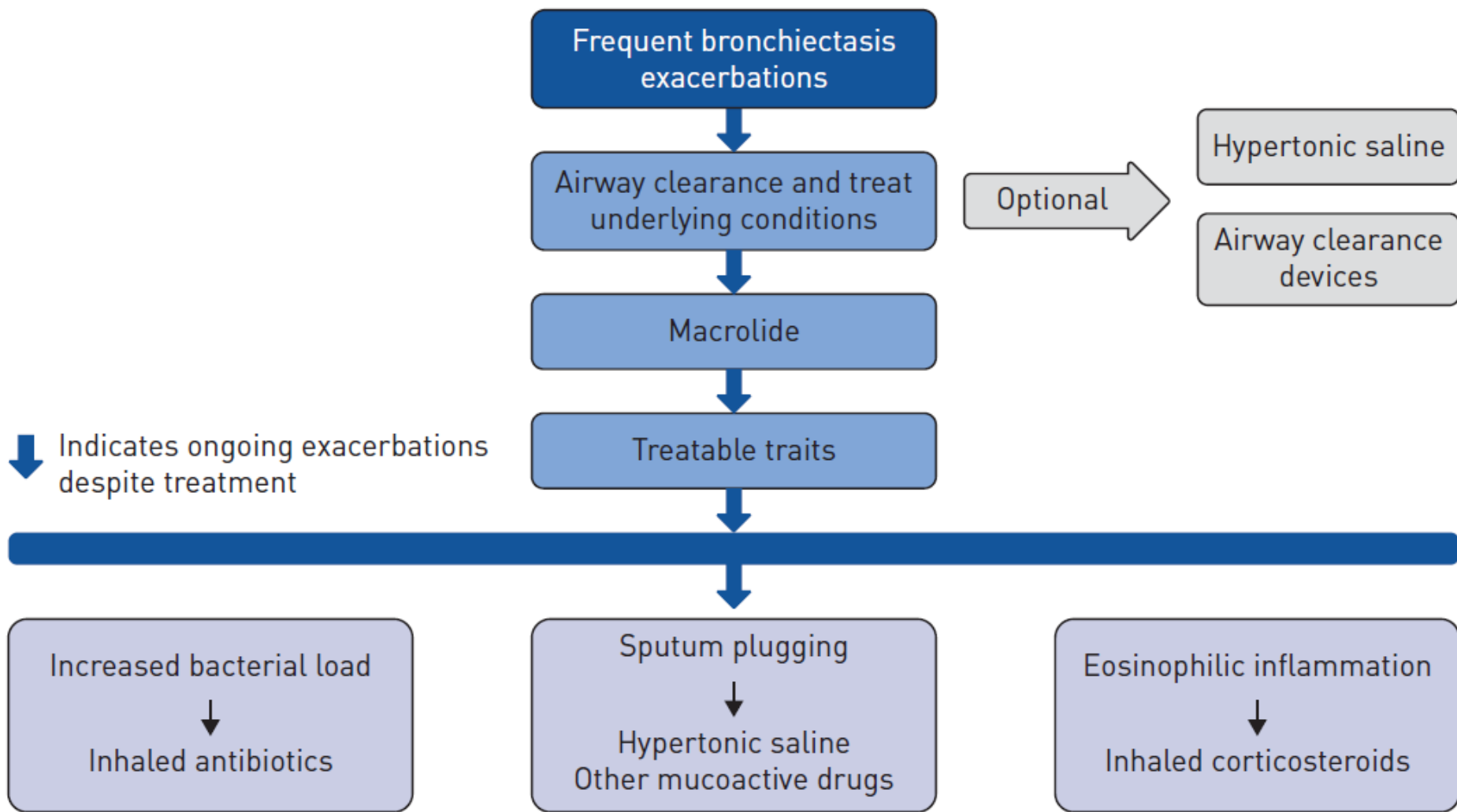
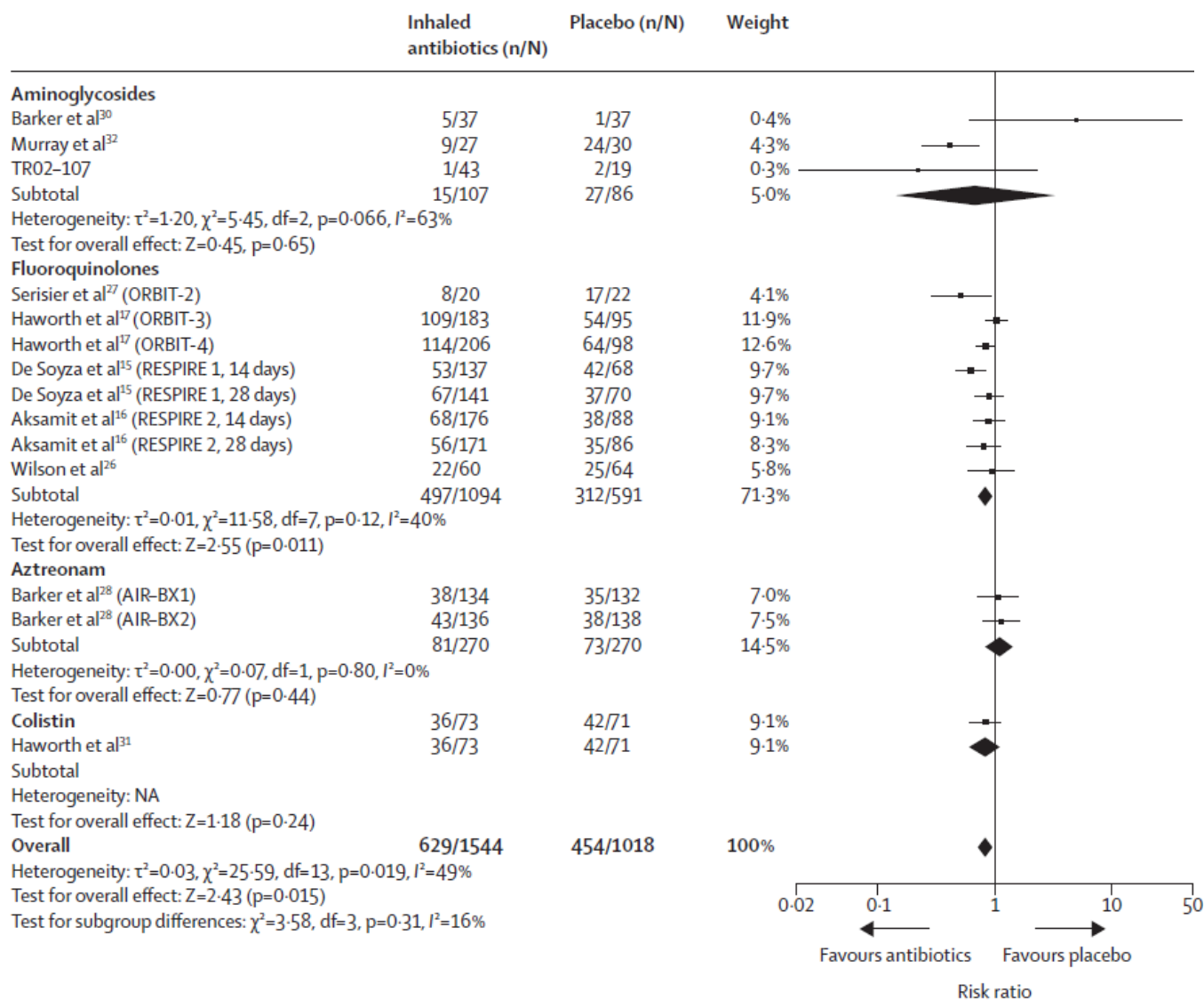


FIGURE 1 A simple schematic for exacerbation prevention in bronchiectasis.

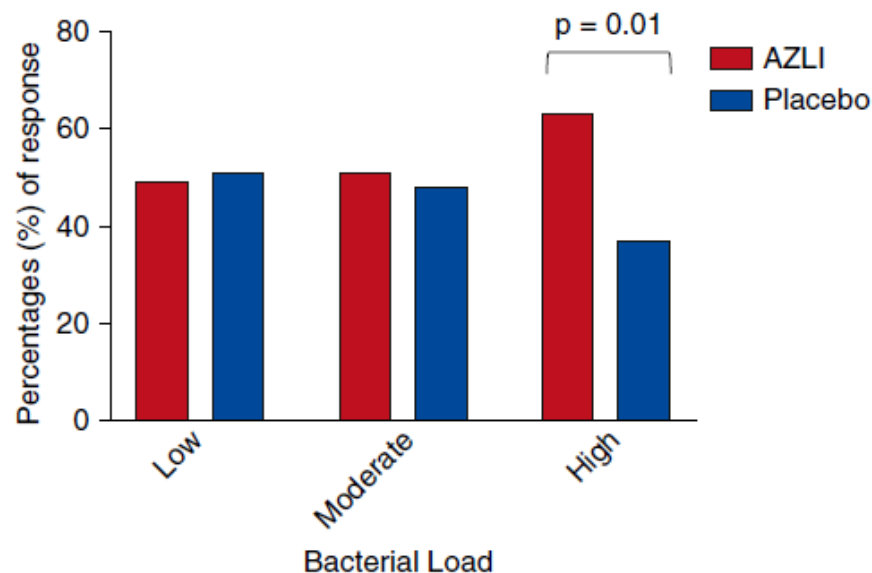
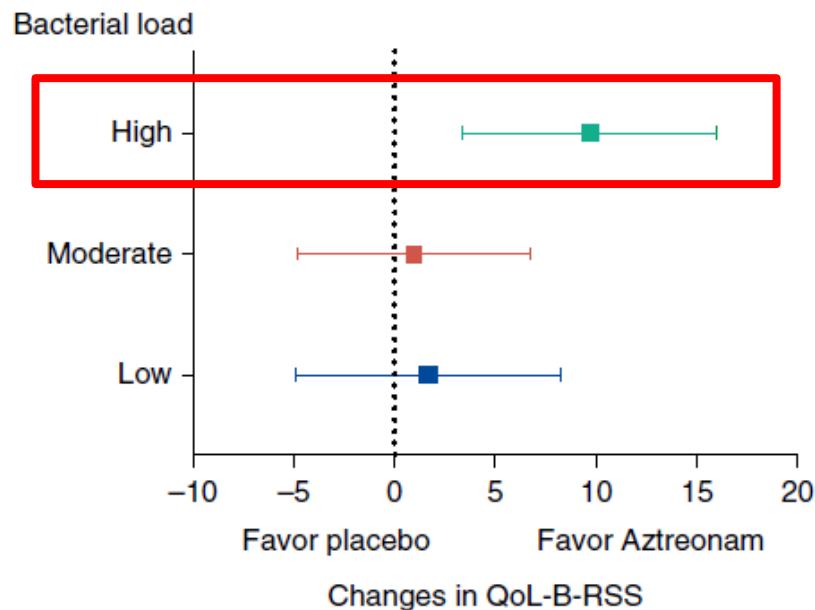
Inhaled antibiotics & exacerbations in BE



- 14 trials (n=2,562)
- 16-19% reduction in exacerbation rate or number
- High heterogeneity

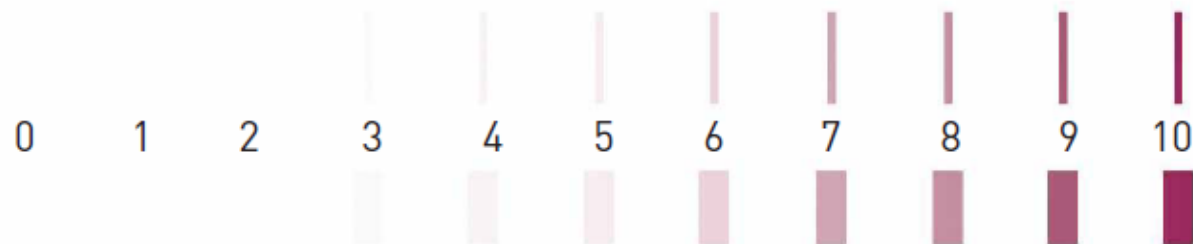
Airway Bacterial Load and Inhaled Antibiotic Response in Bronchiectasis

High bacterial load in sputum ($\geq 10^7$ cfu/g).

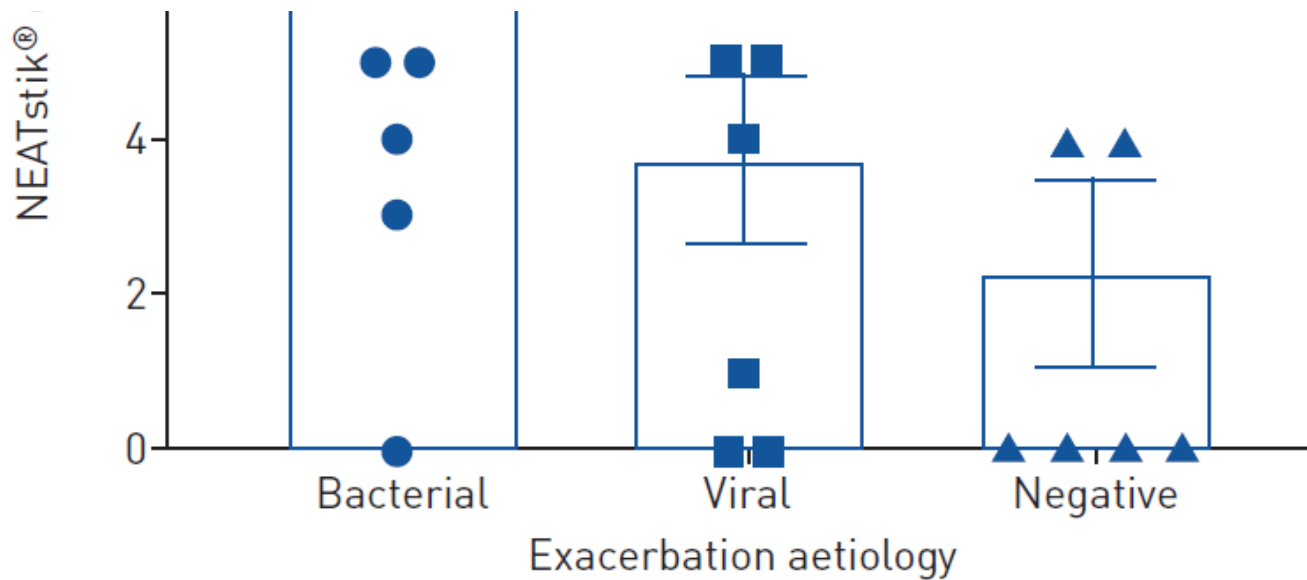
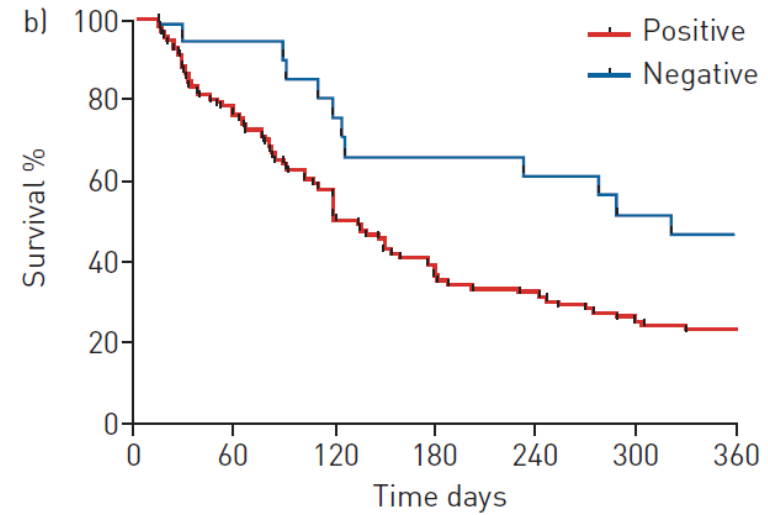
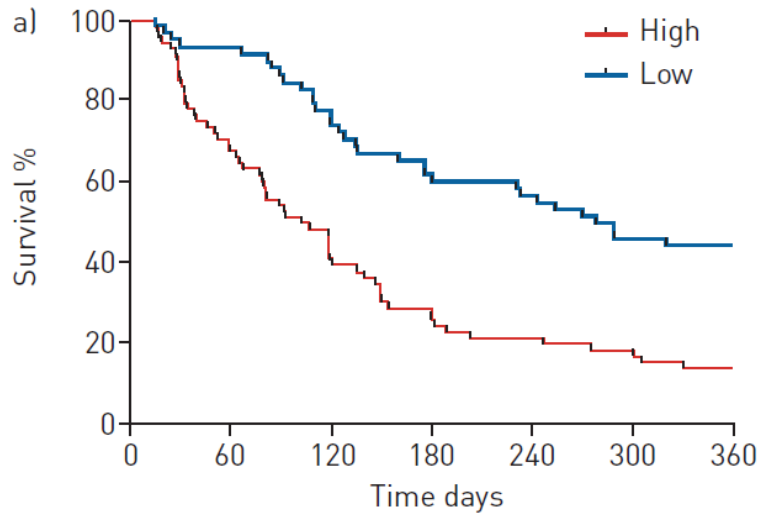


Neutrophil Elastase Airway Test stick (NEATstick)

- Scientists trial 'pregnancy test' for chest infection by University of Dundee



Sputum neutrophil elastase predicts exacerbations



Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis

James D Chalmers*, Wim Boersma*, Mike Loneran, Lata Jayaram, Megan L Crichton, Noel Karalus, Steven L Taylor, Megan L Martin, Lucy D Burr, Conroy Wong, Josje Altenburg

Lancet Respir Med, Published Online, August 9, 2019
[http://dx.doi.org/10.1016/S2213-2600\(19\)30191-2](http://dx.doi.org/10.1016/S2213-2600(19)30191-2)

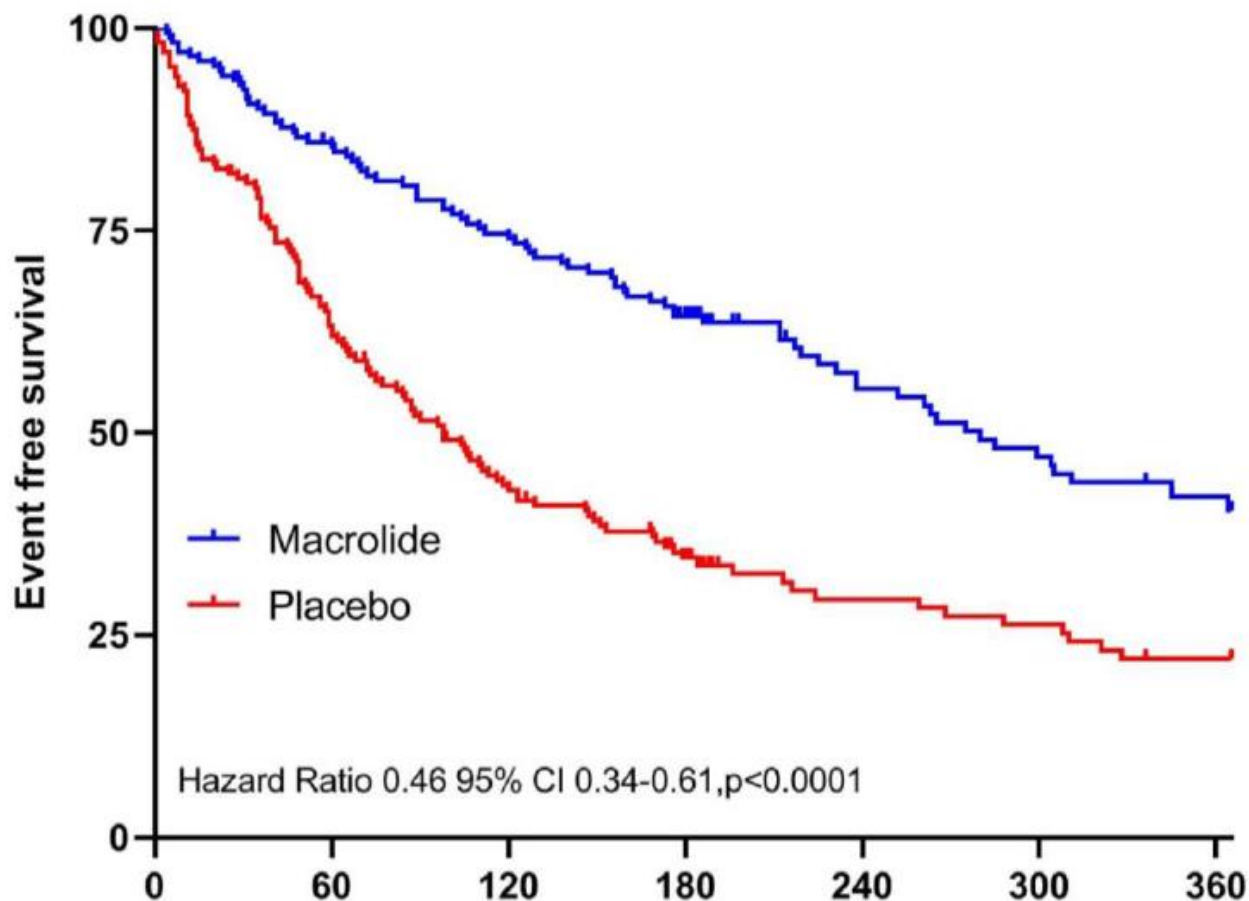
Setting	Key inclusion criteria	Age per group (intervention vs placebo), years	Number of participants	Macrolide treatment	Number of participants per group (intervention vs placebo)	Study duration	
Altenburg et al (2013) ¹⁴	14 hospitals in the Netherlands (2008–2010)	≥3 exacerbations; positive sputum culture in the year before baseline	59.9 (12.3) vs 64.6 (9.1)	83 (30 men, 53 women)	Azithromycin (250 mg daily)	43 vs 40*	12 months with a 3-month run-out period
Serisier et al (2013) ¹⁵	Single centre in Australia (2008–2011)	≥2 exacerbations; daily sputum production	61.1 (10.5) vs 63.5 (9.5)	117 (46 men, 71 women)	Erythromycin ethylsuccinate (400 mg twice daily)	59 vs 58	48 weeks with a 4-week washout period
Wong et al (2012) ¹⁶	Three centres in New Zealand (2008–2009)	≥1 exacerbation in the previous year	60.9 (13.6) vs 59.0 (13.3)	141 (43 men, 98 women)	Azithromycin (500mg three times per week)	71 vs 70	6 months of treatment followed by 6 months of observation without treatment

Data are mean (SD), unless otherwise specified. *Two patients in the azithromycin group and four patients in the placebo group were excluded after randomisation before receiving the first dose of drug; these patients were not included in our individual-patient data analysis.

Table 1: Randomised controlled trials of macrolide use in patients with bronchiectasis

Time to first exacerbation (n=3 studies)

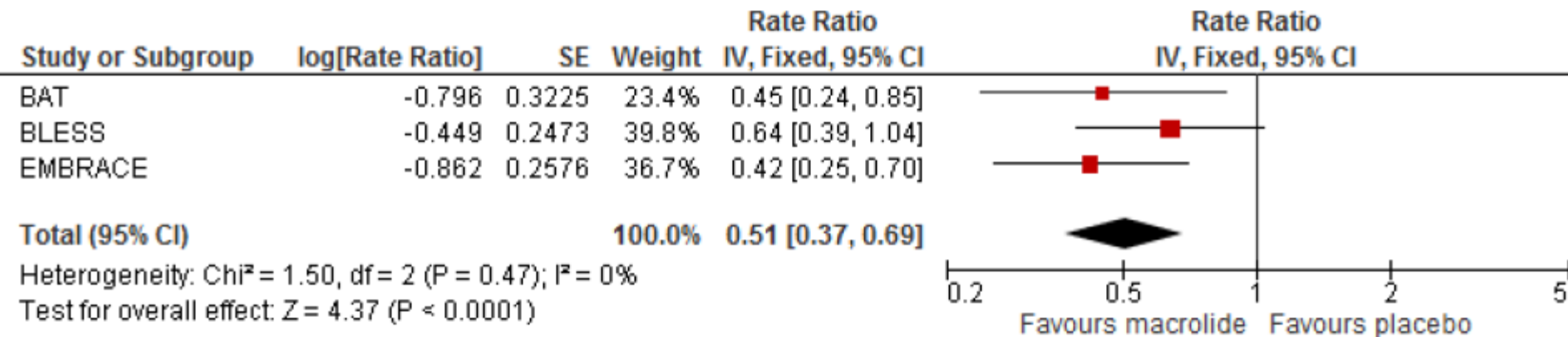
Lancet Respir Med, Published Online, August 9, 2019



Numbers at risk

Macrolide	173	145	125	105	56	46	25
Placebo	168	104	70	50	29	26	21

Meta-analysis of the primary outcome of frequency of exacerbations



Baseline exacerbation rate	Annual Mean exacerbation frequency		Number needed to treat
	Macrolide group	Placebo group	
1-2 per year	0.32	1.00	1.5
3 per year	0.77	1.35	1.7
4 or more per year	1.14	2.11	1.0

Table E3. Absolute risk reductions in the macrolide and placebo groups (N=341 pooled across 3 studies).

	Number of participants (intervention vs placebo)	Incident rate ratio (95% CI)	p value	p _{interaction} value
Baseline concentration of C-reactive protein (mg/L)	0.27
<2	98 (49 vs 49)	0.60 (0.34–1.03)	0.065	..
2–5	95 (51 vs 44)	0.52 (0.30–0.92)	0.023	..
5.1–10	71 (36 vs 35)	0.33 (0.15–0.73)	0.0061	..
>10	60 (30 vs 30)	0.35 (0.17–0.76)	0.0086	..
Baseline FEV ₁ (% predicted)	0.51
≥80	137 (64 vs 73)	0.52 (0.32–0.84)	0.0088	..
50–79	144 (82 vs 62)	0.43 (0.27–0.70)	0.0015	..
<50	60 (27 vs 33)	0.55 (0.27–1.12)	0.10	..
SGRQ total score	0.90
<30	139 (72 vs 67)	0.50 (0.29–0.84)	0.0082	..
30–49	123 (64 vs 59)	0.45 (0.27–0.74)	0.0024	..
≥50	79 (37 vs 42)	0.50 (0.28–0.90)	0.022	..
<i>Pseudomonas aeruginosa</i> infection	0.45
Yes	61 (31 vs 30)	0.36 (0.18–0.72)	0.0044	..
No	280 (142 vs 138)	0.53 (0.38–0.74)	<0.0001	..

Treatable traits of bronchiectasis

1. Infection
2. Airway flow obstruction
3. Eosinophilia
4. ABPA, Connective tissue diseases, IBD, immunodeficiencies, CF
5. Comorbidities
6. Respiratory insufficiency ($\text{PaO}_2 < 55 \text{ mmHg}$, $\text{PaCO}_2 > 45 \text{ mmHg}$)
- 7. Frequent exacerbators**

Summary

- Bronchiectasis is **not uncommon** and is associated with **significant morbidity and mortality**
- Bronchiectasis should be considered when respiratory **infections are severe, persistent, unusual or recurrent**
- **Exacerbation prevention**
 - ◆ Frequent exacerbator $\geq 3/\text{year}$ - **Treatable traits!**
 - ◆ Optimizing airway clearance and increasing adherence is important!
 - Antibiotics is **not always necessary!**
 - ◆ Inhaled antibiotics – inconsistent results, need precision medicine
 - ◆ Long-term Macrolide
 - Caution with NTM resistance, ototoxicity, long QT
 - ◆ 국내 연구 자료 절실