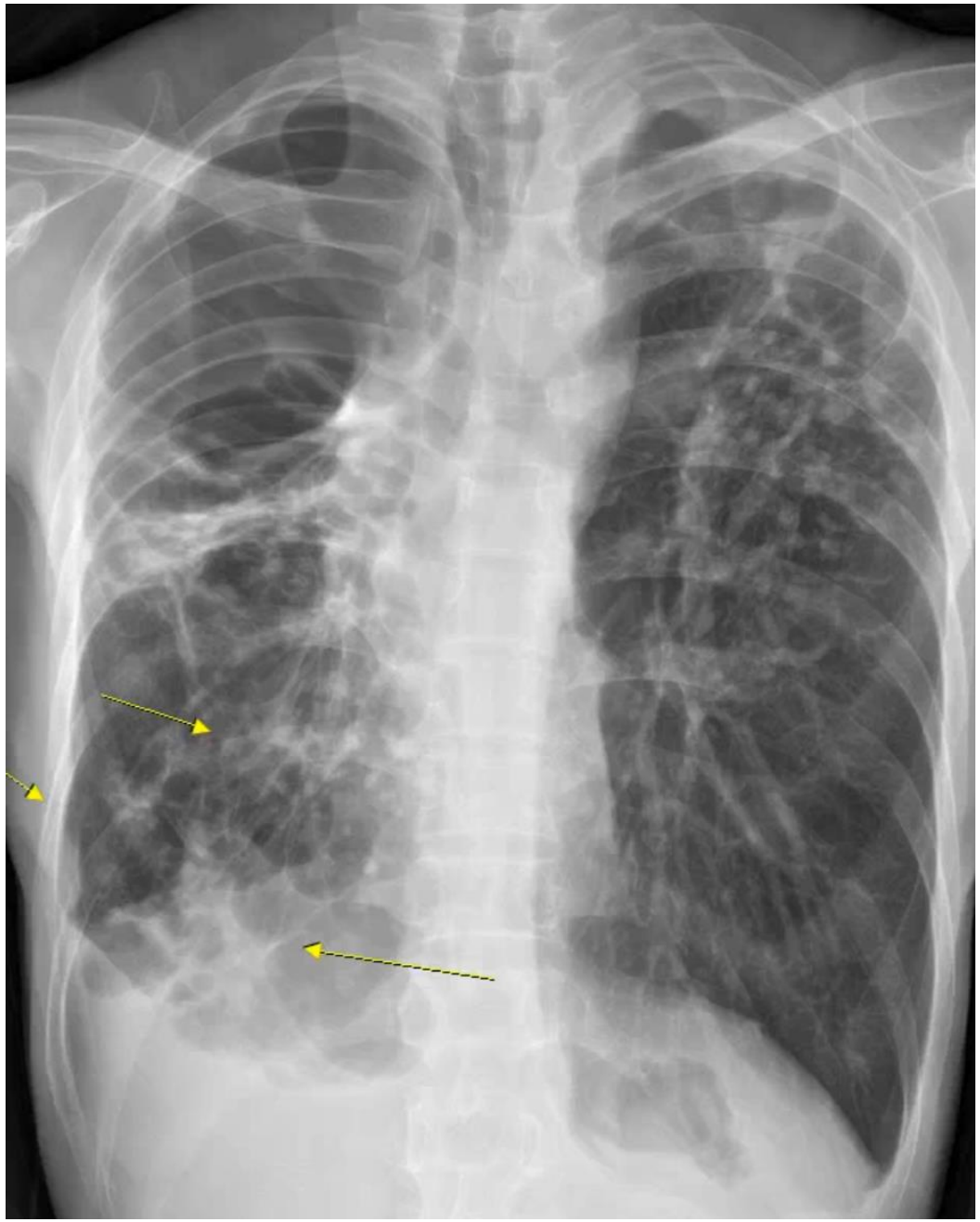
Anti-infectious Strategies for Bacterial and Non-Bacterial infections in Bronchiectasis

한양대학교 의과대학
호흡기알레르기내과
이현

Case

- 48/M
- Ex-smoker (30 PY)
- 2019.03-2020.10 NTM-PD (*M. kansasii)* 치료

- Post-BD FEV1/FVC < 0.45, FEV1 1.10, 28.1%
- 주기적인 객담 Gram S/C, AFB S/C에서 배양된 균 없음



2020.03

2020.10

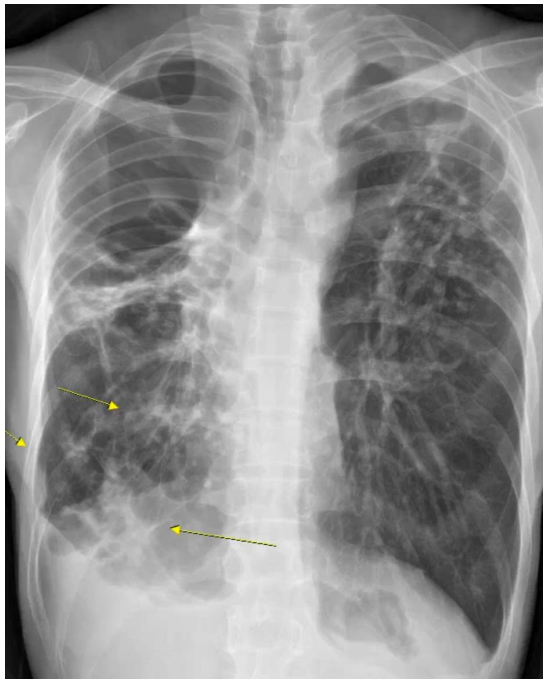
Case

Diagnosis

1) Bronchiectasis/COPD overlap
2) s/p NTM-PD (*M. kansasii*)
3) BPF

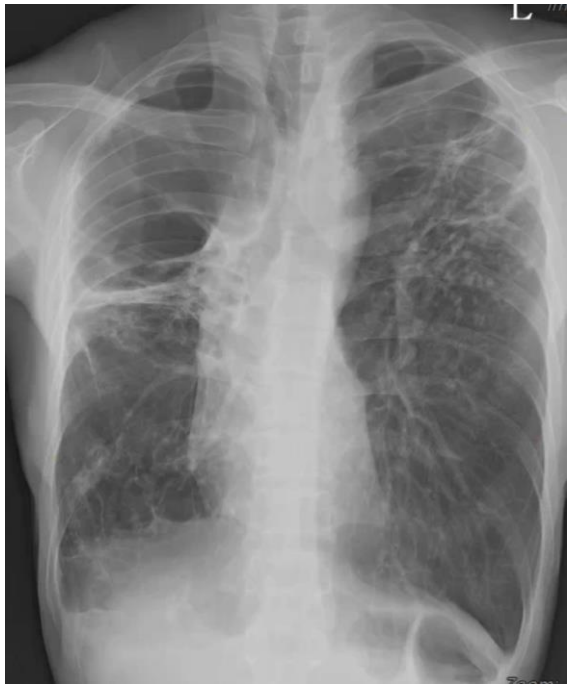
- 치료 약물
  - LABA/LAMA
  - Oral mucoactive drugs

- 약물 부작용
  - Azithromycin
    - 청력 저하, 이명으로 이비인후과 진료 후 단기간 OCS 사용



2021.05

CAT 25



2021.07/10

CAT 30/33

최근 객혈
기침 가래 악화

항생제 처방 (x2)

2022.01-07

CAT 33

<u>호흡곤란 악화</u>
화농성 가래 증가

항생제 처방 (x3)

Your plan?

■ 진료계획
* 치료계획 # 추후 AE시에는 Roflu 고려

Gram S/C, AFB S/C에서 배양된 균주 없음

Your plan?

1) Inhaled antibiotics
2) Long-term oral antibiotics
3) Macrolide
4) Roflumilast
5) Bronchoscopic airway clearance (B-ACT)

Contents

- **Bacterial infection**
  - **Inhaled antibiotics**
  - ***Pseudomonas aeruginosa* eradication**
  - **Antibiotics for the management of exacerbations**
  - **Culture vs. Microorganism interaction**
- **Fungal infection – Pulmonary aspergillosis**
- **COVID-19**

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Bronchiectasis management in adults: state of the art and future directions

Hayoung Choi, Pamela J. McShane, Stefano Aliberti, James D. Chalmers
European Respiratory Journal 2024; **DOI:** 10.1183/13993003.00518-2024

Abstract

Formerly regarded as a rare disease, bronchiectasis is increasingly recognised. A renewed interest in this disease has led to significant progress in bronchiectasis research. Randomised clinical trials have demonstrated the benefits of airway clearance techniques, inhaled antibiotics and long-term macrolide therapy in bronchiectasis patients. However, the heterogeneity of bronchiectasis remains one of the most challenging aspects of management. Phenotypes and endotypes of bronchiectasis have been identified to help find “treatable traits” and partially overcome disease complexity. The

Vol 64 Issue 2 Table of Contents

Table of Contents
Index by author

CHEST

The Efficacy and Safety of Inhaled Antibiotics for the Treatment of Bronchiectasis in Adults

Updated Systematic Review and Meta-Analysis

Ricardo Cordeiro, MD; Hayoung Choi, PhD; Charles S. Haworth, MD; and James D. Chalmers, MBChB, PhD

BACKGROUND: Inhaled antibiotics are recommended conditionally by international bronchiectasis guidelines for the treatment of patients with bronchiectasis, but results of individual studies are inconsistent. A previous meta-analysis demonstrated promising results regarding the efficacy and safety of inhaled antibiotics in bronchiectasis. Subsequent publications have supplemented the existing body of evidence further in this area.

RESEARCH QUESTION: To what extent do inhaled antibiotics demonstrate both efficacy and safety as a treatment option for adults with bronchiectasis?

STUDY DESIGN AND METHODS: Systematic review and meta-analysis of randomized controlled trials of inhaled antibiotics in adult patients with bronchiectasis. We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov for eligible studies. Studies were included if they enrolled adults with bronchiectasis diagnosed by CT imaging and had a treatment duration of at least 4 weeks. The primary end point was exacerbation frequency, with additional key efficacy end points including severe exacerbations, bacterial load, symptoms, quality of life, and FEV_1. Data were pooled through random-effects meta-analysis.

Eradication treatment for *Pseudomonas aeruginosa* infection in adults with bronchiectasis: a systematic review and meta-analysis

Mariana Conceição[1], Michal Shteinberg[2], Pieter Goeminne[3], Josje Altenburg[4] and James D. Chalmers[5]

[1]Pulmonology Department, Centro Hospitalar Tondela-Viseu, Viseu, Portugal. [2]Pulmonology Institute and CF Center, Carmel Medical Center, Haifa, Israel. [3]Department of Respiratory Medicine, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands. [4]Department of Respiratory Disease, AZ Nikolaas, Sint-Niklaas, Belgium. [5]Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK.

Corresponding author: James D. Chalmers (jchalmers@dundee.ac.uk)

Shareable abstract (@ERSpublications)
A meta-analysis of *Pseudomonas aeruginosa* eradication treatment in bronchiectasis reports successful eradication in 40% of cases at 12 months. The data suggest superior results with the inclusion of an inhaled antibiotic. https://bit.ly/3QDmIi8

Cite this article as: Conceição M, Shteinberg M, Goeminne P, *et al*. Eradication treatment for *Pseudomonas aeruginosa* infection in adults with bronchiectasis: a systematic review and meta-analysis. *Eur Respir Rev* 2024; 33: 230178 [DOI: 10.1183/16000617.0178-2023].

Abstract

Introduction: *Pseudomonas aeruginosa* is the most commonly isolated pathogen in bronchiectasis and is associated with worse outcomes. Eradication treatment is recommended by guidelines, but the evidence base is limited. The expected success rate of eradication in clinical practice is not known.

Methods: We conducted a systematic review and meta-analysis according to Meta-Analysis of Observational Studies in Epidemiology guidelines. PubMed, Embase, the Cochrane Database of Systematic Reviews and Clinicaltrials.gov were searched for studies investigating *P. aeruginosa* eradication treatment

Contents

- **Bacterial infection**
  - **Inhaled antibiotics**
    - *Pseudomonas aeruginosa* eradication
    - Antibiotics for the management of exacerbations
    - Culture vs. Microorganism interaction
- **Fungal infection - Aspergillosis**
- **COVID-19**

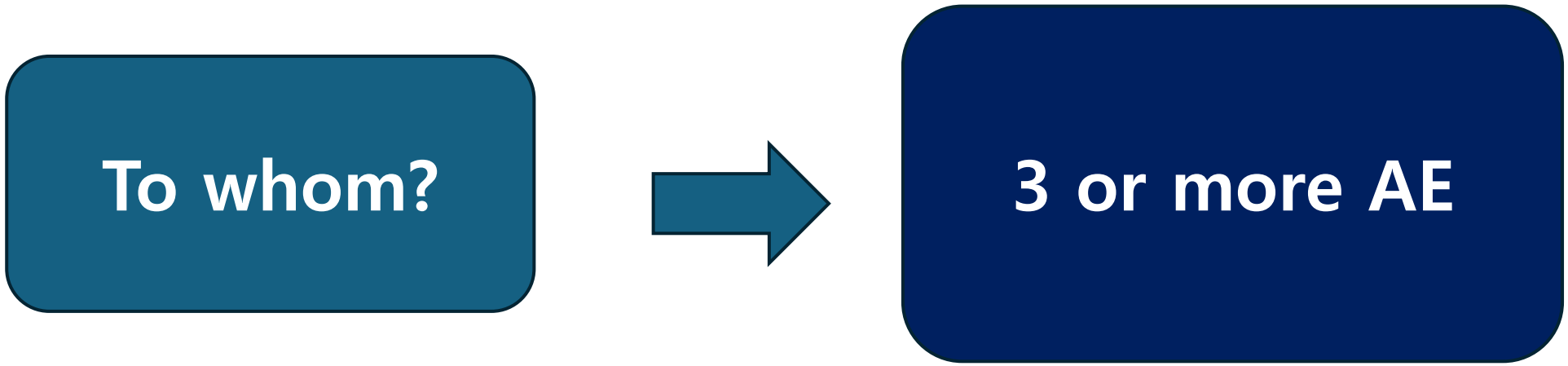
Etiology & treatment

	Korea (n=598)	Australia (n=653)	Europe (n=2596)	India (n=2195)
Etiology				
1st	Idiopathic (41%)	Idiopathic (29%)	Idiopathic (42%)	TB (36%)
2nd	TB (20%)	Post-infective (27%)	Post-infective (17%)	Post-infective (22%)
3rd	Post-infective (20%)	NTM (7%)	COPD (9%)	Idiopathic (21%)
4th	Asthma (5%)	PCD (4%)	Asthma (6%)	ABPA (9%)
5th	NTM (4%)	ABPA (4%)	CTD (6%)	COPD (5%)
Treatment				
Long-term antibiotics	23 (3.9)	205 (31.4)	503 (19.4)	271 (12.3)
Inhaled antibiotics	0	27 (4.1)	166 (6.4)	79 (3.6)

Data are presented as numbers (%).

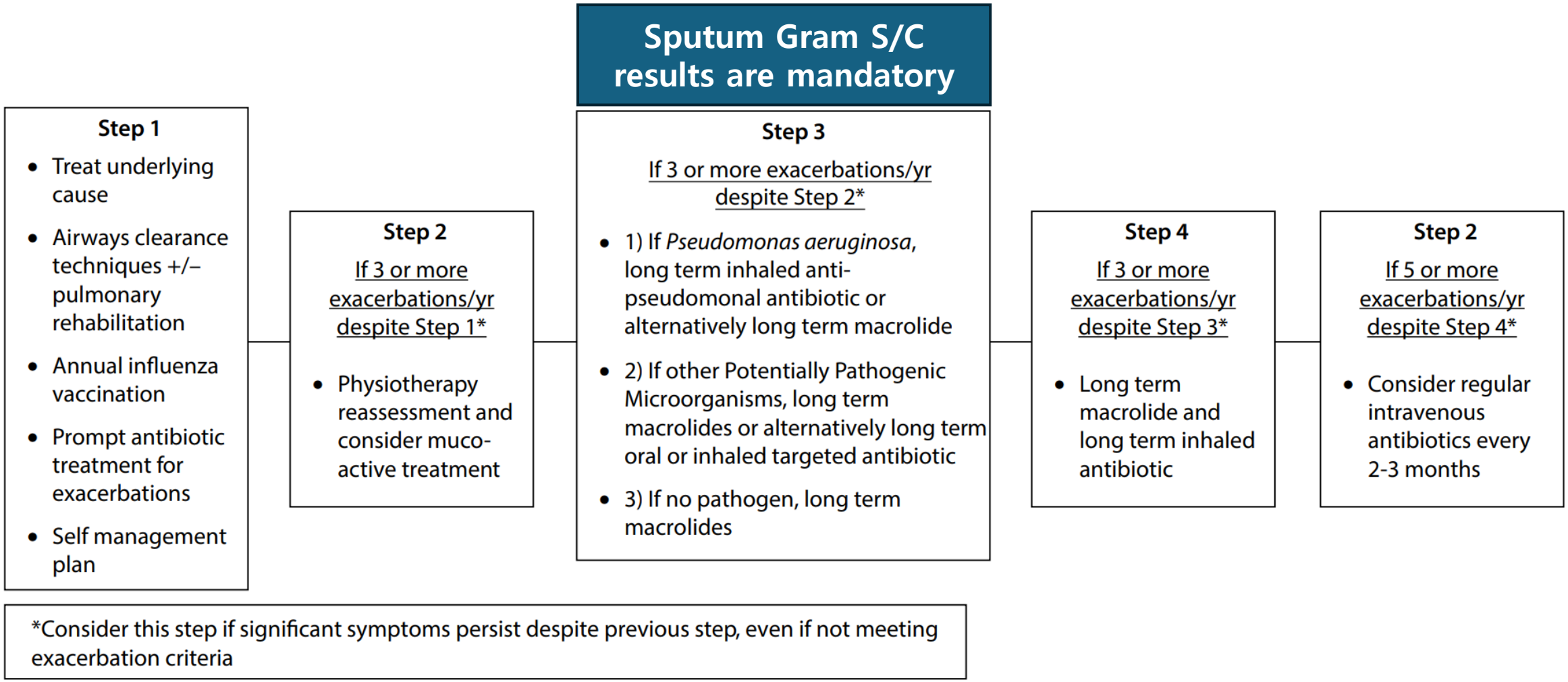
Lee and Choi, Respirology 2021;26:619

Long-term antibiotics



Consider long term antibiotics in patients with bronchiectasis who experience 3 or more exacerbations per year. (A)

BTS guideline 2018



Antibiotics are used to treat exacerbations that present with an acute deterioration (usually over several days) with worsening local symtoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset. The flow diagram refers to three or more annual exacerbations.

Figure 2 Stepwise management.

BTS guideline 2018

P. aeruginosa colonization

- **Inhaled colistin (IC)**

- Alternative
  - inhaled gentamicin (alternative to IC)
  - Azithromycin or erythromycin (alternative to IA)

- Add on
  - Azithromycin or erythromycin + IA

BTS guideline 2018

Non-P. aeruginosa colonization

- **AZIT or EM**

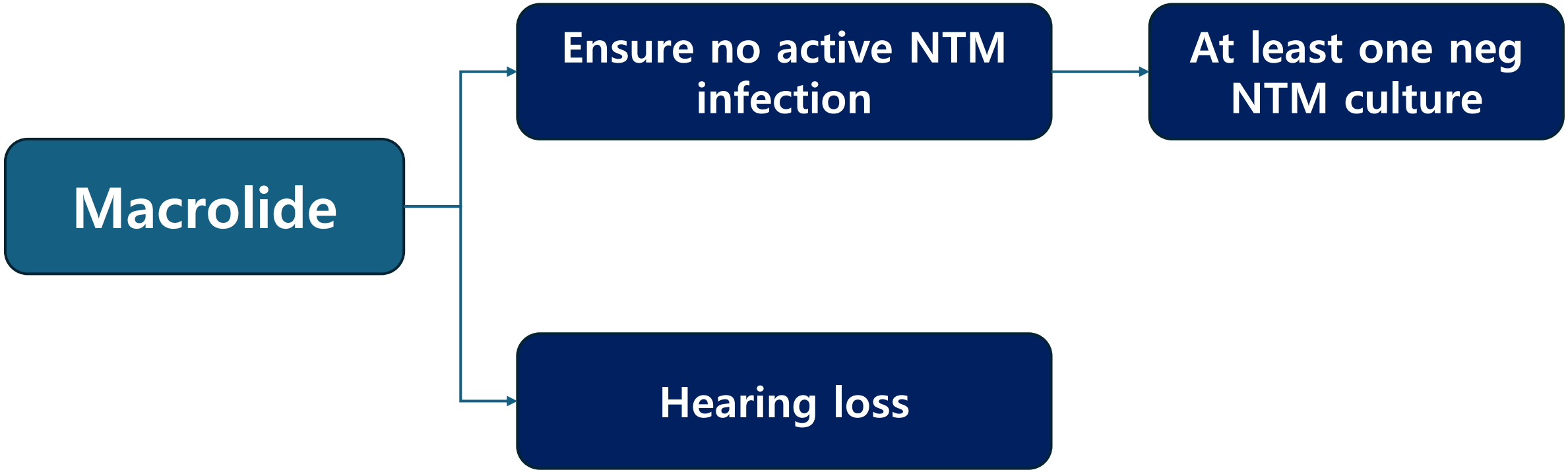
- Alternative
  - inhaled gentamicin (alternative to macrolide)
  - Azithromycin or erythromycin (alternative to IA)
  - Doxycycline (intolerant of macrolide or when ineffective)

BTS guideline 2018

No pathogen

- Long-term macrolide

Good practice points



BTS guideline 2018

Good practice points

BTS guideline 2018

Long-term inhaled Antibiotics vs. macrolide

	Inhaled antibiotics	Macrolide
Studies	RESPIRE 1,2 (≥ 2 AE) ORBIT 2-4 (≥ 2 AE) AIR-Bx 1-2 Nebulized tobramycin, ceftazidime, gentamicin, colistin	BAT (≥ 3AE) – AZIT 250mg QD BLESS (≥ 2 AE) – ETM 400mg BID Daily EMBRACE (≥ 1AE) – AZIT 500mg TIW
Outcomes		
AE	Improved Rate ratio = **0.81(0.67-0.97)** Time to first AE (HR) = **0.83(0.69-0.99)** Severe AE – Rate ratio = **0.43(0.24-0.78)**	Improved Adjusted incidence rate ratio = **0.49(0.36-0.66)** Time to first AE (HR) = **0.46(0.34-0.61)** *P. Aeruginosa* – **IRR, 0.36(0.18-0.72)**
QoL	No effect	Improved QoL measured by the **SGRQ (mean improvement 2.93 points [0.03-5.83])**
FEV_1	No improvement (Toward to deterioration) (−2.00 to 0.26%pred)	No improvement (toward to improvement) (67 mL at 1 year, −22-112)

Laska, Lancet Respir Med. 2019;7(10):855-869.
Chalmers, Lancet Respir Med. 2019;7(10):845-854.

CHEST

The Efficacy and Safety of Inhaled Antibiotics for the Treatment of Bronchiectasis in Adults

Updated Systematic Review and Meta-Analysis

Ricardo Cordeiro, MD; Hayoung Choi, PhD; Charles S. Haworth, MD; and James D. Chalmers, MBChB, PhD

BACKGROUND: Inhaled antibiotics are recommended conditionally by international bronchiectasis guidelines for the treatment of patients with bronchiectasis, but results of individual studies are inconsistent. A previous meta-analysis demonstrated promising results regarding the efficacy and safety of inhaled antibiotics in bronchiectasis. Subsequent publications have supplemented the existing body of evidence further in this area.

RESEARCH QUESTION: To what extent do inhaled antibiotics demonstrate both efficacy and safety as a treatment option for adults with bronchiectasis?

STUDY DESIGN AND METHODS: Systematic review and meta-analysis of randomized controlled trials of inhaled antibiotics in adult patients with bronchiectasis. We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov for eligible studies. Studies were included if they enrolled adults with bronchiectasis diagnosed by CT imaging and had a treatment duration of at least 4 weeks. The primary end point was exacerbation frequency, with additional key efficacy end points including severe exacerbations, bacterial load, symptoms, quality of life, and FEV_1. Data were pooled through random-effects meta-analysis.

Long-term inhaled Antibiotics vs. macrolide

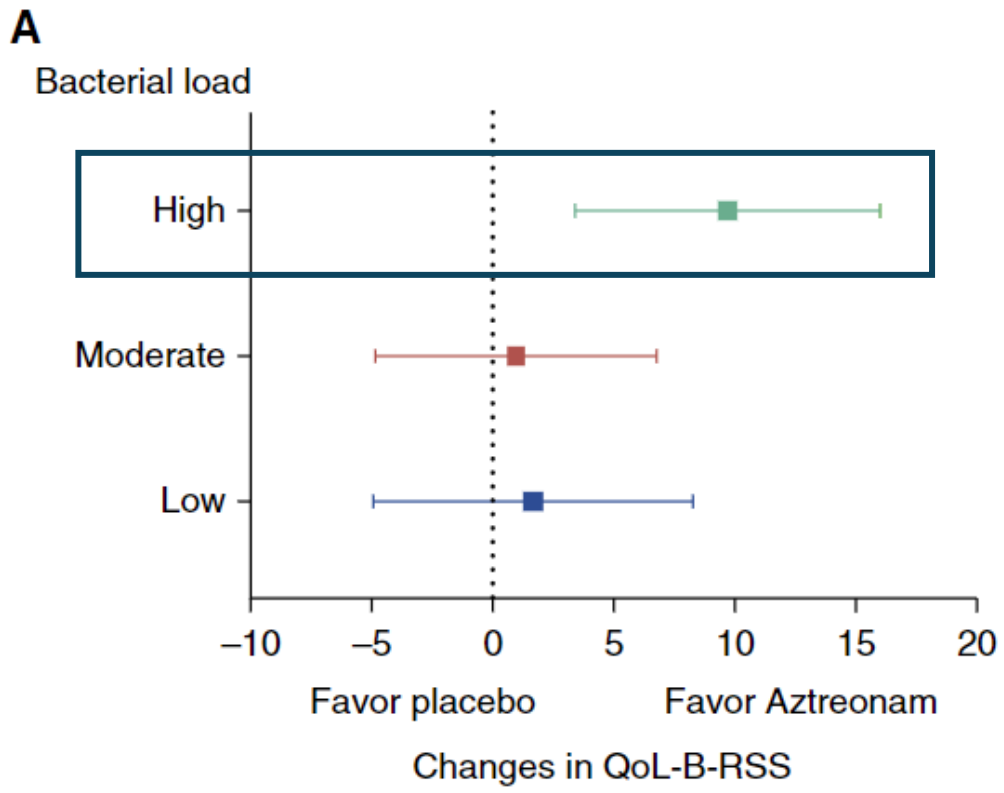
	Inhaled antibiotics	Macrolide
Studies	RESPIRE 1,2 (≥ 2 AE) ORBIT 2-4 (≥ 2 AE) AIR-Bx 1-2 Nebulized tobramycin, ceftazidime, gentamicin, colistin, **etc.**	BAT (≥ 3AE) – AZIT 250mg QD BLESS (≥ 2 AE) – ETM 400mg BID Daily EMBRACE (≥ 1AE) – AZIT 500mg TIW
Outcomes		
AE	Improved Rate ratio = **0.85 (0.75-0.96** Time to first AE (HR) = **0.80 (0.68-0.94** Severe AE – Rate ratio = **0.48 (0.31-0.74)**	Improved Adjusted incidence rate ratio = **0.49(0.36-0.66)** Time to first AE (HR) = **0.46(0.34-0.61)** *P. Aeruginosa* – **IRR, 0.36(0.18-0.72)**
QoL	Improved QoL B(mean 2.51[0.44-4.31], SGQR (mean improvement 3.13[0.32-5.93])	Improved QoL measured by the **SGRQ (mean improvement 2.93 points [0.03-5.83])**
FEV_1	No improvement	No improvement (toward to improvement) (67 mL at 1 year, −22-112)

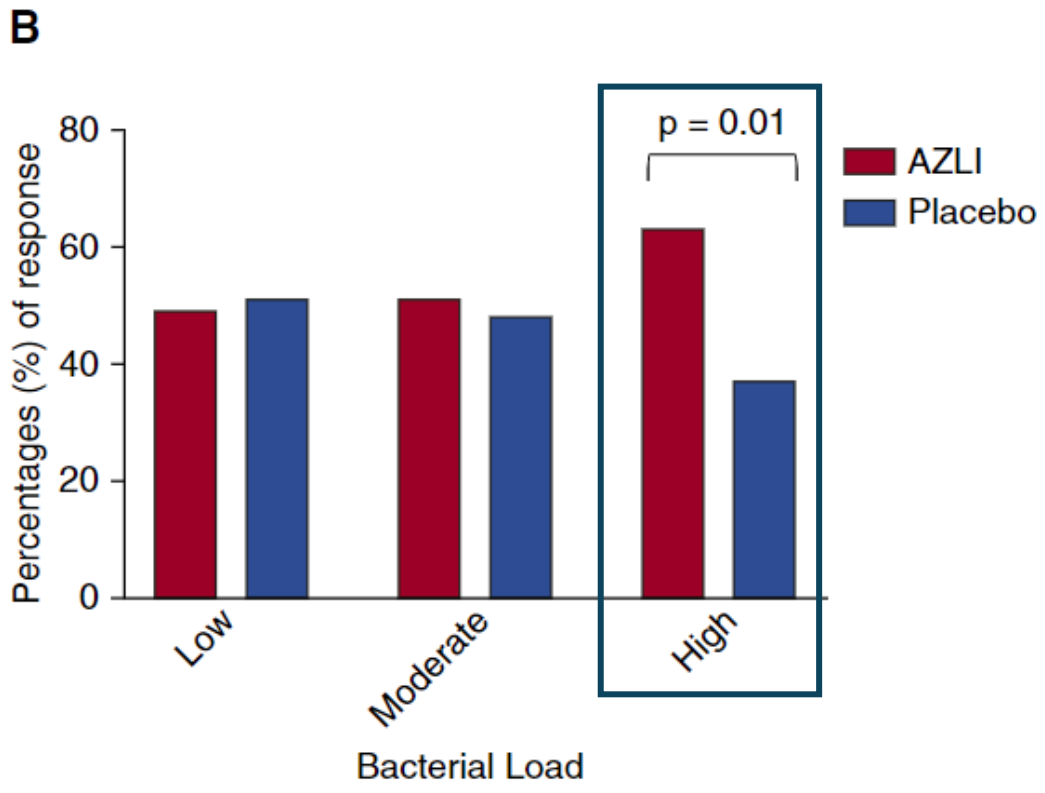
Cordeiro, CHEST 2024; 166(1):61-80
Laska, Lancet Respir Med. 2019;7(10):855-869.
Chalmers, Lancet Respir Med. 2019;7(10):845-854.

TABLE 2] Key Findings of a Meta-Analysis of Inhaled Antibiotics for the Treatment of Adult Patients With Bronchiectasis

Outcomes	Anticipated Absolute Effects (95% CI)[a]		Relative Effect (95% CI)	No. of Participants (Studies)	Certainty of Evidence[b]	Comments
	Risk With Placebo	Risk With Inhaled Antibiotics				
Frequency of exacerbations	93 per 100	73 per 100 (63-84)	RR, 0.78 (0.68-0.90)	2,930 (12 RCTs)	⨁⨁⨁⨁ high[c]	Inhaled antibiotics result in a slight reduction in frequency of exacerbations.
Frequency of severe exacerbations	29 per 100	14 per 100 (9-21)	RR, 0.48 (0.31-0.74)	828 (7 RCTs)	⨁⨁⨁◯ moderate[d]	Inhaled antibiotics likely reduce frequency of severe exacerbations.
Time to first exacerbation	0 per 100	NaN per 100 (— to —)	HR, 0.80 (0.68-0.94)	2,725 (12 RCTs)	⨁⨁◯◯ low[ef]	Inhaled antibiotics may increase time to first exacerbation slightly.
Change from baseline QOL-B RSS score (scale, 0-100)	Mean change from baseline QoL-B RSS score was 4.9 points[g]	MD 2.37 points higher (0.44 higher-4.31 higher)	NA	2,315 (11 RCTs)	⨁⨁⨁⨁ high[ch]	Inhaled antibiotics probably result in a slight increase in change from baseline QOL-B RSS score, without reaching the minimal clinical important difference of 8 points.
Change from baseline SGRQ score (scale, 0-100)	Mean change from baseline SGRQ score was −0.62 points[i]	MD 3.13 points lower (5.93 lower-0.32 lower)	NA	1,338 (10 RCTs)	⨁◯◯◯ very low[jk1,mn]	Inhaled antibiotics may reduce or have little to no effect on change from baseline SGRQ score, but the evidence is uncertain.
Isolates with resistant MIC at the end of treatment	9 per 100	17 per 100 (14-21)	Risk ratio, 1.86 (1.51-2.30)	2,619 (17 RCTs)	⨁⨁⨁◯ moderate[n]	Inhaled antibiotics likely result in an increase in isolates with resistant MIC at the end of treatment.
No. of patients reporting TEAE	80 per 100	80 per 100 (75-84)	OR, 0.99 (0.75-1.30)	3,207 (15 RCTs)	⨁⨁⨁◯ moderate[ao]	Inhaled antibiotics likely result in little to no difference in number of patients reporting TEAEs.

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

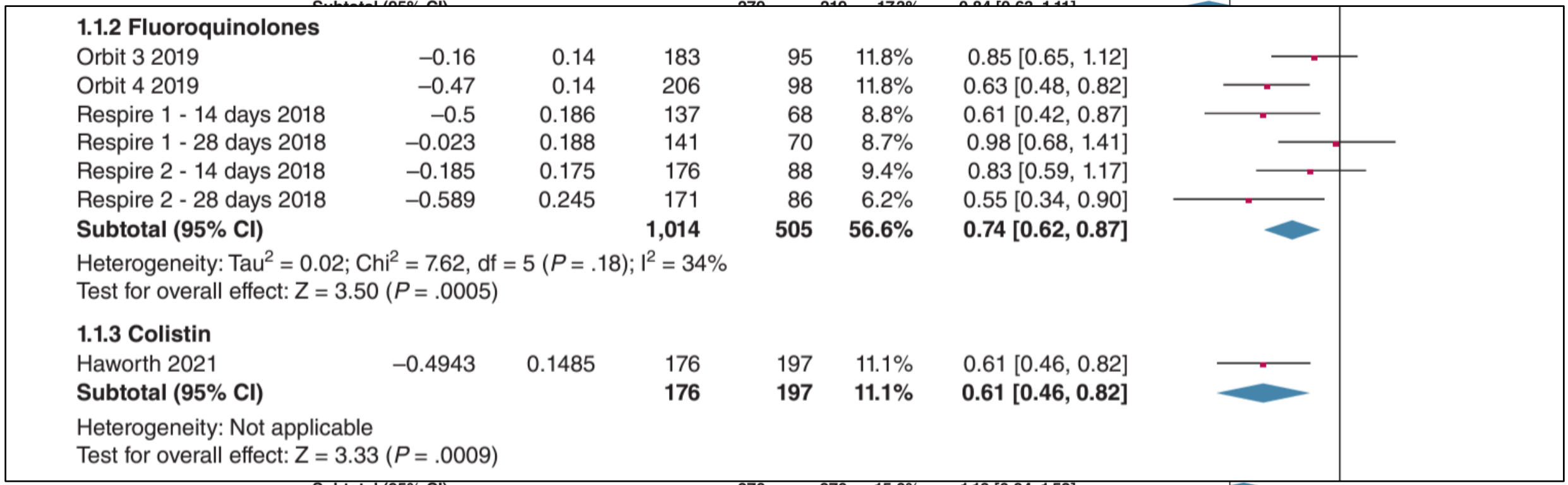




More than MID – 8.0 point

Sibila, AJRCCM 2019;200(1):33-41

A



Study or Subgroup	log[Rate Ratio]	SE	Inhaled Antibiotics Total	Inhaled Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
1.1.1 Aminoglycosides						
Loebinger 2022	–0.3112	0.3651	86	21	3.3%	0.73 [0.36, 1.50]
Terpstra 2022	–0.3011	0.2103	26	26	7.6%	0.74 [0.49, 1.12]
Wei-jie Guan 2022	0.0339	0.2386	167	172	6.4%	1.03 [0.65, 1.65]
1.1.2 Fluoroquinolones						
Orbit 3 2019	–0.16	0.14	183	95	11.8%	0.85 [0.65, 1.12]
Orbit 4 2019	–0.47	0.14	206	98	11.8%	0.63 [0.48, 0.82]
Respire 1 - 14 days 2018	–0.5	0.186	137	68	8.8%	0.61 [0.42, 0.87]
Respire 1 - 28 days 2018	–0.023	0.188	141	70	8.7%	0.98 [0.68, 1.41]
Respire 2 - 14 days 2018	–0.185	0.175	176	88	9.4%	0.83 [0.59, 1.17]
Respire 2 - 28 days 2018	–0.589	0.245	171	86	6.2%	0.55 [0.34, 0.90]
Subtotal (95% CI)			**1,014**	**505**	**56.6%**	**0.74 [0.62, 0.87]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.62$, df = 5 ($P = .18$); $I^2 = 34\%$						
Test for overall effect: Z = 3.50 ($P = .0005$)						
1.1.3 Colistin						
Haworth 2021	–0.4943	0.1485	176	197	11.1%	0.61 [0.46, 0.82]
Subtotal (95% CI)			**176**	**197**	**11.1%**	**0.61 [0.46, 0.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.33 ($P = .0009$)						
Subtotal (95% CI)			**270**	**270**	**15.0%**	**1.13 [0.84, 1.52]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 ($P = .62$); $I^2 = 0\%$						
Test for overall effect: Z = 0.82 ($P = .41$)						
Total (95% CI)			**1,739**	**1,191**	**100.0%**	**0.79 [0.68, 0.91]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 18.82$, df = 11 ($P = .06$); $I^2 = 42\%$						
Test for overall effect: Z = 3.33 ($P = .0009$)						
Test for subgroup differences: $chi^2 = 9.51$, df = 3 ($P = .02$), $I^2 = 68.5\%$						

Rate Ratio IV, Random, 95% CI

0.5 0.7 1 1.5 2

Favors Antibiotic | Favors Placebo

Cordeiro, CHEST 2024; 166(1):61-80

RCT Abstract - The efficacy and safety of colistimethate sodium delivered via the I-neb in bronchiectasis: the PROMIS-I randomized controlled trial

Charles S Haworth, Michal Shteinberg, Kevin L Winthrop, Francesco Blasi, Katerina Dimakou, Lucy Morgan, Felix C Ringshausen, Oriol S Vidal, Rachel Thompson, Kelly Sharp, Ischa Vissers, Dearbhla Hull, James D Chalmers

European Respiratory Journal 2021 58: RCT4267; **DOI:** 10.1183/13993003.congress-2021.RCT4267

Medscape

https://www.medscape.com › ... › WBC 2023

Pandemic Blamed for Failed Trial of Inhaled Antibiotic

Jul 31, 2023 — The key entry criterion of **PROMIS** I and **PROMIS** II, each with nearly 90 participating **study** sites, was a history of **bronchiectasis** and ≥ two P.

exacerbation in the CMS I-neb group (HR 0.59, 95% CI 0.43-0.81, p=0.00074). Severe exacerbations were also reduced (RR 0.41 95% CI 0.23-0.74, p=0.003). The percentage of patients with adverse events was similar between groups. Bronchospasm and antibiotic resistance were infrequently observed (2.8% and 1% respectively).

CMS I-neb significantly reduced the annual rate of exacerbations and severe exacerbations in patients with bronchiectasis and *P. aeruginosa*. Treatment was safe and well tolerated.

Summary

- **Proper candidates for inhaled antibiotics**
  - **Frequent exacerbators with positive bacterial culture**

- **Efficacy of inhaled antibiotics**
  - **15-20% reduction of AE**
  - **May improve QoL**
  - **Measuring bacterial load might be helpful**

Contents

- **Bacterial infection**
  - Inhaled antibiotics
  - ***Pseudomonas aeruginosa*** **eradication**
  - Antibiotics for the management of exacerbations
  - Culture vs. Microorganism interaction
- **Fungal infection - Aspergillosis**
- **COVID-19**

Question

- 추적관찰 중에 객담에서 녹농균이 "**처음**" 배양되었습니다. 녹농균 제거를 시도하겠습니까?

Question 3: Is eradication treatment beneficial for treating bronchiectasis patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?

Recommendations

We suggest that adults with bronchiectasis with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment (*conditional recommendation, very low quality of evidence*).

We suggest not offering eradication antibiotic treatment to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa* (*conditional recommendation, very low quality of evidence*)

This guideline does not address attempted eradication of chronic *P. aeruginosa* infection, where the infection has been present for many years, as this is thought unlikely to be successful.

Eur Respir J 2017; 50: 1700629

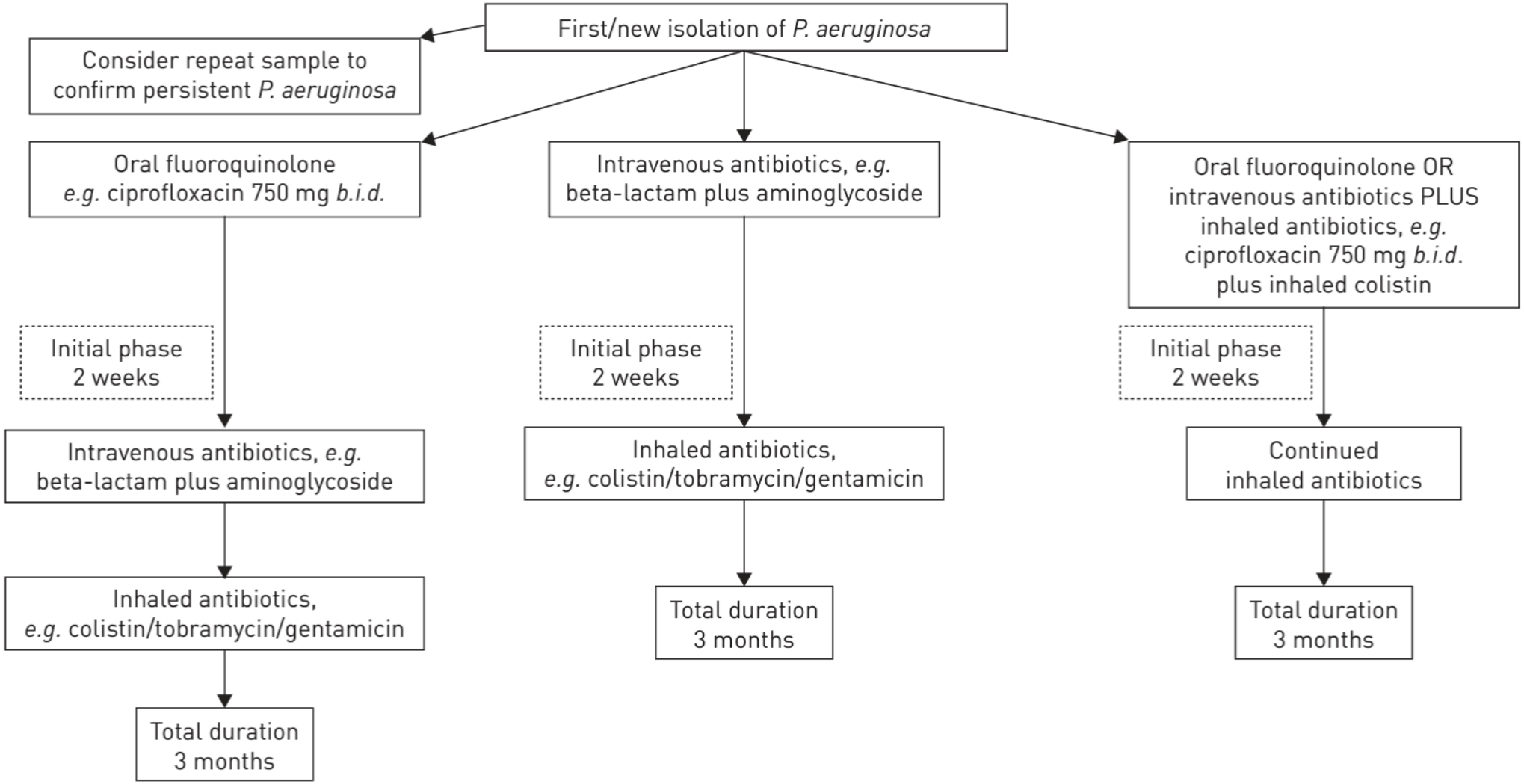


FIGURE 3 Three possible and alternative eradication treatment pathways based on what is commonly used in clinical practice. After each step it is recommended to repeat sputum sampling for *Pseudomonas aeruginosa* and to progress to the next step if the culture remains positive.

P. Aeruginosa eradication

Study	Eradication n	Subjects n	Weight %	Eradication rate %
Blanco-Aparicio	27	67	23.7	40 (28–53)
Orriols (1)[#]	6	11	2.3	55 (23–83)
Orriols (2)[#]	5	17	9.2	29 (10–56)
Pieters	25	60	20.1	42 (29–55)
Suarez Cuartin	20	38	8.3	53 (36–69)
Vallières	23	64	27.1	36 (24–49)
White	13	30	9.4	43 (26–63)
Pooled	119	287	100	40 (34–45)

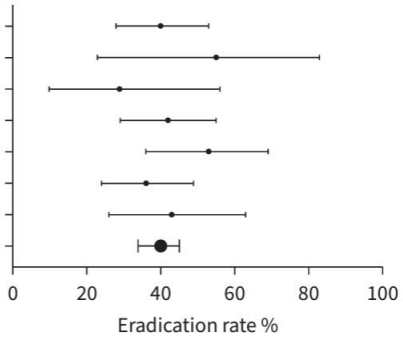
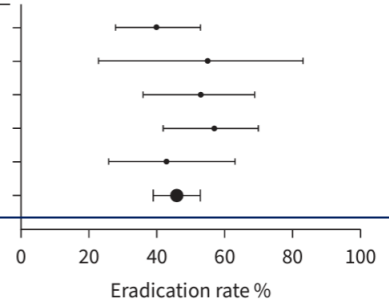


FIGURE 2 Forest plot of *Pseudomonas aeruginosa* eradication rate in sputum at 12 months [16–21]. [#]: two arms of the Orriols *et al.* [21] study, which were treated as separate cohorts for the purposes of analysis.

40%

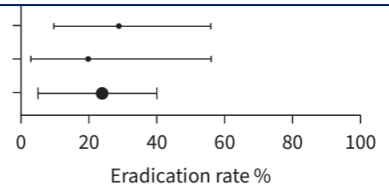
Study	Eradication n	Subjects n	Weight %	Eradication rate %
Blanco-Aparicio	27	67	33.3	40 (28–53)
Orriols	6	11	5.9	55 (23–83)
Suarez-Cuartin	20	38	19.1	53 (36–69)
Vallières	30	53	26.5	57 (42–70)
White	13	30	15.2	43 (26–63)
Pooled[#]	96	199	100	48 (41–55)



Systemic + Inhaled antibiotics

20%

Orriols	5	17	62.1	29 (10–56)
Vallières	2	10	37.9	20 (3–56)
Pooled[¶]	7	27	100	27 (13–45)

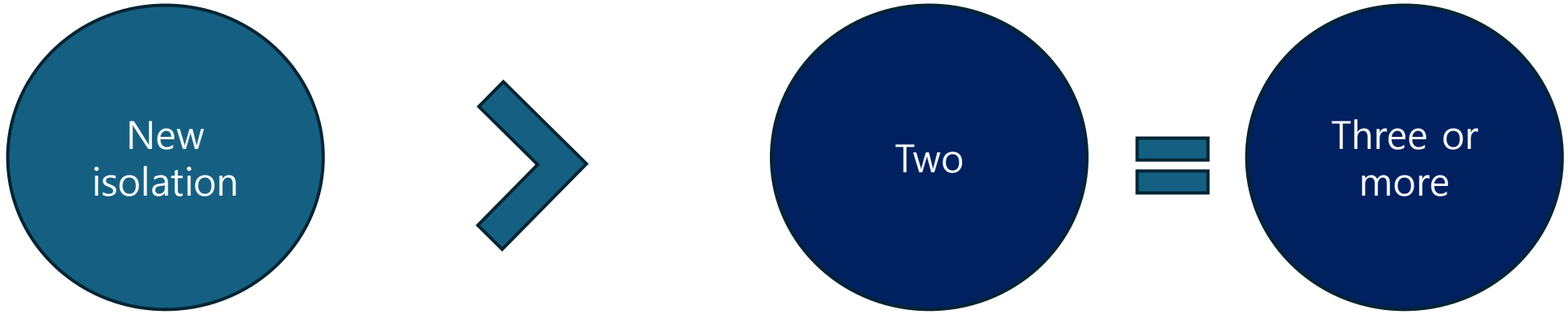


Systemic antibiotics

Cordeiro, CHEST 2024; 166(1):61-80

P. aeruginosa eradication

- Eradication rate



73% at 6 months
60% at 1 year
42% during median follow-up period of 36 months

Eur Respir J 2019; 53: 1802081

53% at 6 months
47% at 1 year

50% at 6 months
38% at 1 year

Chron Respir Dis. 2019;16:1479973119872513.

Efficacy of *P. aeruginosa* eradication

- **AE** (two studies)
  - mean difference −0.91 exacerbations over 12 months (95% CI −1.64 to −0.17
  - Not affecting hospitalization

- **QoL**
  - No data - pre- and post-eradication
  - No difference in SGRQ changes between interventional and placebo arms (1 study)

Efficacy of eradication of first isolation of *P. aeruginosa*

TABLE 1 Clinical outcome of *Pseudomonas aeruginosa* eradication

	Pre-eradication	Post-eradication	p-value[#]
FEV_1 % predicted median (range)	68 (54–82)	74 (59–89)	0.549
Exacerbation frequency			**0.011**
No exacerbations	6 (10%)	16 (27%)	
One exacerbation	19 (32%)	17 (28%)	
Two or more exacerbations	35 (58%)	27 (45%)	
Hospital admissions			1.000
No exacerbations	40 (67%)	40 (67%)	
One or more exacerbation(s)	20 (33%)	20 (33%)	

FEV_1: forced expiratory volume in 1 s. [#]: 12 months pre-eradication *versus* 12 months post-eradication, analysed with paired t-test for continuous variables and Chi-squared test for categorical variables. Bold indicates statistically significant p-values.

Pieters, Eur Respir J 2019; 53: 1802081

Summary

- Eradication of *P. aeruginosa*
  - Eradication rate at 1 year - 40%
    - Systemic + Inhaled antibiotics **>** systemic antibiotics
    - Eradication of first isolation **>** multiple isolation
  - Lower rate of AE
  - May not change QoL and pulmonary function

Contents

- **Bacterial infection**
  - Inhaled antibiotics
  - Pseudomonas aeruginosa eradication
  - **Antibiotics for the management of exacerbations**
  - Culture vs. Microorganism interaction
- Fungal infection - Aspergillosis
- COVID-19

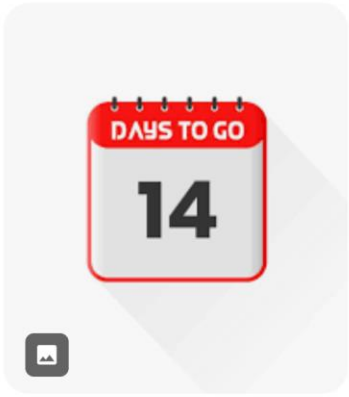
Antibiotics for the treatment of AE

Shutterstock
584 Countdown 14 D…

Freepik
14 days to go sign la…

Vecteezy
14 Days To Go Vector Art, Icon…

Shutterstock
Days Go Last Cou…



Vecteezy
14 Days To Go Vecto…

iStock
14 Days To Go Neon…

Question 2: Are courses of 14–21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult bronchiectasis patients with an acute exacerbation?

Recommendation

We suggest acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics (*conditional recommendation, very low quality of evidence*).

Eur Respir J 2017; 50: 1700629

Does antibiotic therapy improve outcomes in patients with an exacerbation of bronchiectasis?

Good practice points

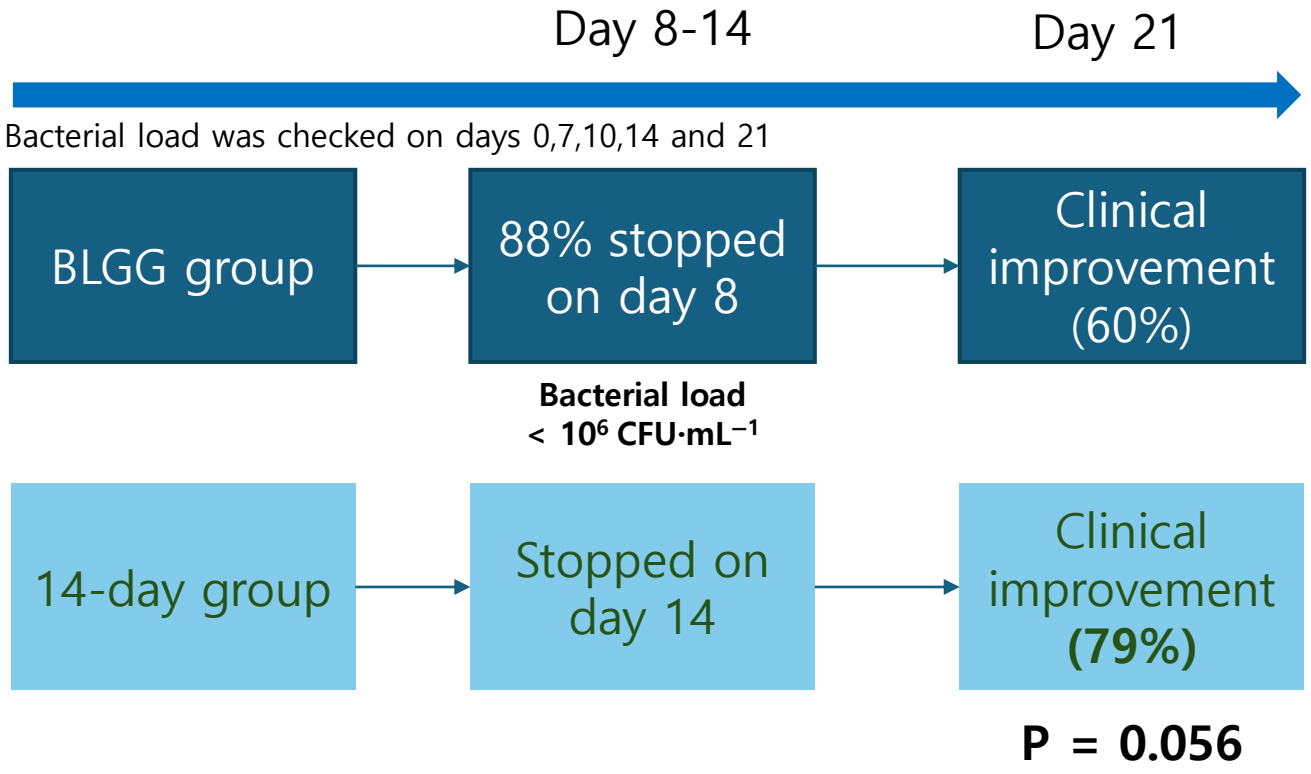
- ✓ A patient self management plan should be considered, an example is provided here https://www.brit-thoracic.org.uk/standards-of-care/quality-standards/bts-bronchiectasis-quality-standards/)
- ✓ There should be prompt treatment of exacerbations and suitable patients should have antibiotics to keep at home.
- ✓ Previous sputum bacteriology results can be useful in deciding which antibiotic to use. Table 6 highlights the first-line and alternative treatments for the common bacterial pathogens implicated in exacerbations of bronchiectasis.
- ✓ Where possible, sputum (spontaneous or induced) should be obtained for culture and sensitivity testing prior to commencing antibiotics.
- ✓ Empirical antibiotics can then be started while awaiting sputum microbiology.
- ✓ Once a pathogen is isolated, antibiotics can be modified if there is no clinical improvement, with treatment guided by antibiotic sensitivity results.
- ✓ In general, antibiotic courses for 14 days are standard and should always be used in patients infected with *P. aeruginosa*. Shorter courses may suffice in patients with mild bronchiectasis.

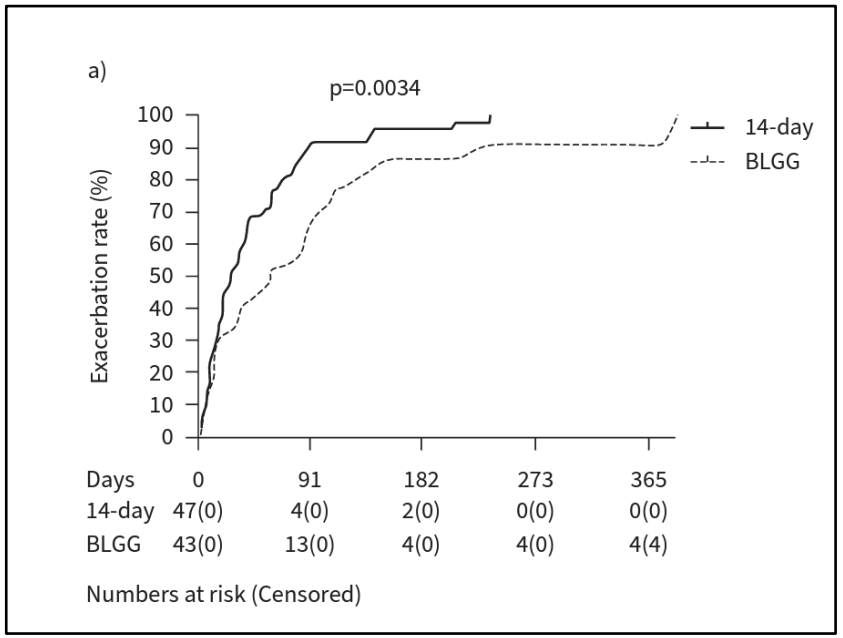
BTS guideline 2018

IV antibiotic therapy (N=90)
bacterial load-based Tx vs. 14 days' Tx

1) aged ⩾18 years
2) bronchiectasis confirmed on chest CT

Primary outcome: Time to next AE requiring antibiotics
Rate of participants in the BLGG in whom antibiotics could be stopped early (day 8, 11)





HR=1.80, 95%CI=1.16–2.80

Bedi P, Eur Respir J. 2021;58(6):2004388.

Contents

- **Bacterial infection**
  - Inhaled antibiotics
  - *Pseudomonas aeruginosa* eradication
  - Antibiotics for the management of exacerbations
  - **Culture vs. Microorganism interaction**
- Fungal infection - Aspergillosis
- COVID-19

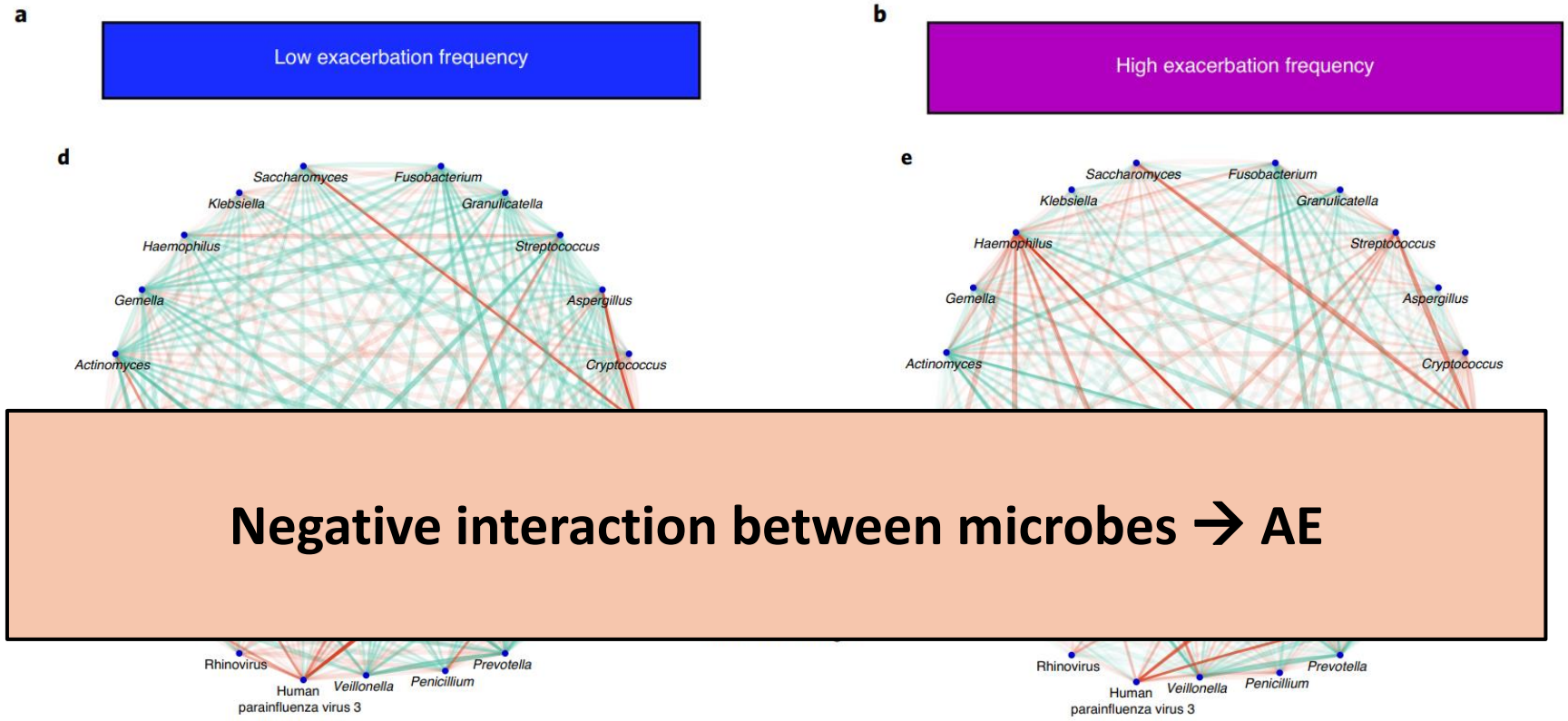
Sensitivity test?

Table 6 Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents- adults

Organism	Recommended first line treatment	Length of treatment	Recommended second line treatment	Length of treatment
Streptococcus pneumoniae	Amoxicillin 500 mg Three times a day	14 days	Doxycycline 100 mg BD	14 days
Haemophilus influenzae- beta lactamase negative	Amoxicillin 500 mg Three times a day Or Amoxicillin 1G Three times a day Or Amoxicillin 3G BD	14 days	Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Haemophilus influenzae- beta lactamase positive	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Doxycycline 100 mg bd Or Ciprofloxacin 500 mg or 750 mg BD Or Ceftriaxone 2G OD (IV)	14 days
Moraxella catarrhalis	Amoxicillin with clavulanic acid 625 one tablet Three times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Ciprofloxacin 500 mg or 750 mg BD	14 days
Staphylococcus aureus (MSSA)	Flucloxacillin 500 mg Four times a day	14 days	Clarithromycin 500 mg BD Or Doxycycline 100 mg BD Or Amoxicillin with clavulanic acid 625 one tablet Three	14 days

BTS guideline 2018

내성균주가 배양되었는데도 항생제를 쓰면 좋아져요.



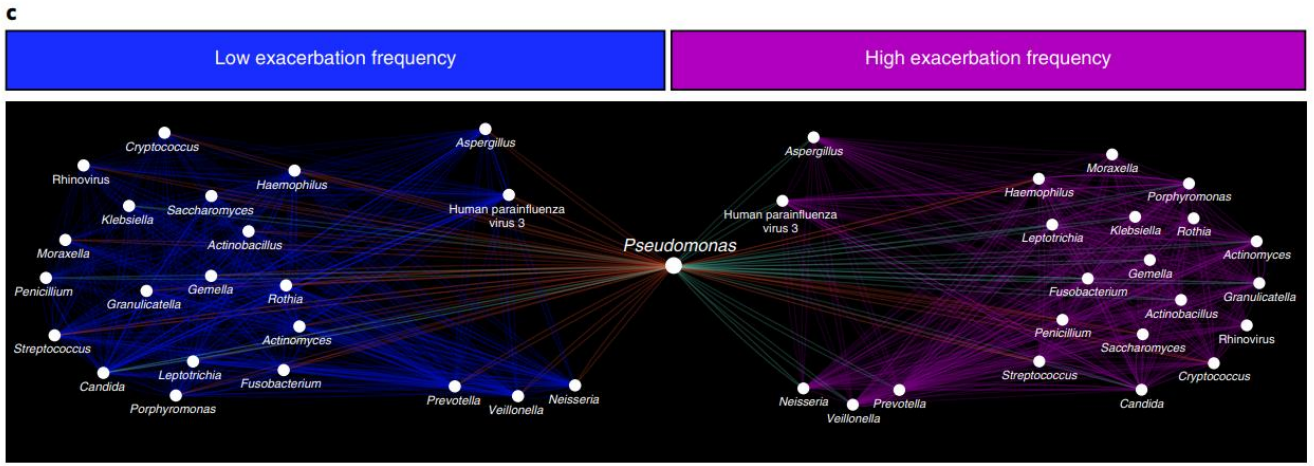
Negative interaction between microbes → AE

c

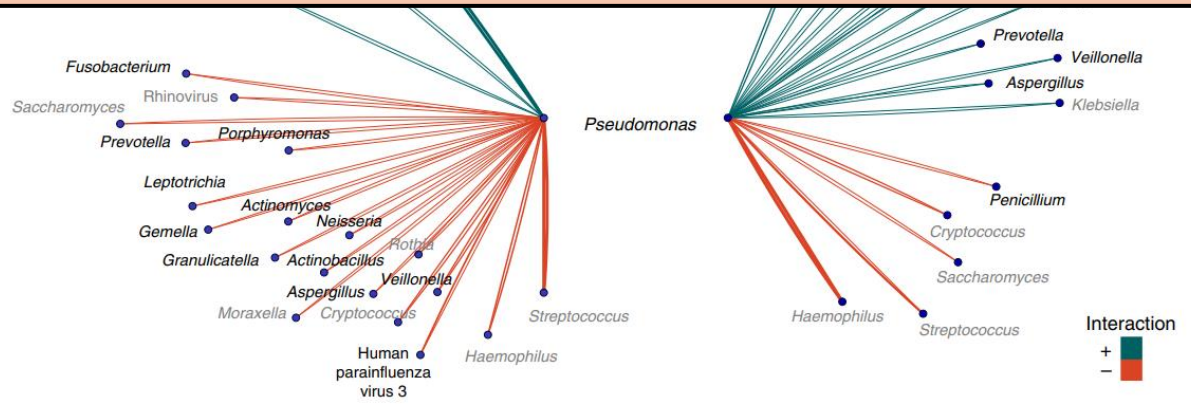
	Low exacerbation frequency	High exacerbation frequency	Percentage change
Total no. of microbes in network (no. of nodes)	455	243	–46.6
Total no. of interactions between microbes (no. of edges)	56,221	22,837	–59.4
Total no. of negative interactions as a proportion of total interactions (no. of negative edges)	14,646/56,221 (26%)	7,306/22,837 (32%)	(+6)

Aogáin, Nature Med 2021;27:689-699

녹농균을 죽이지 못하는 항생제를 써도 좋아져요.

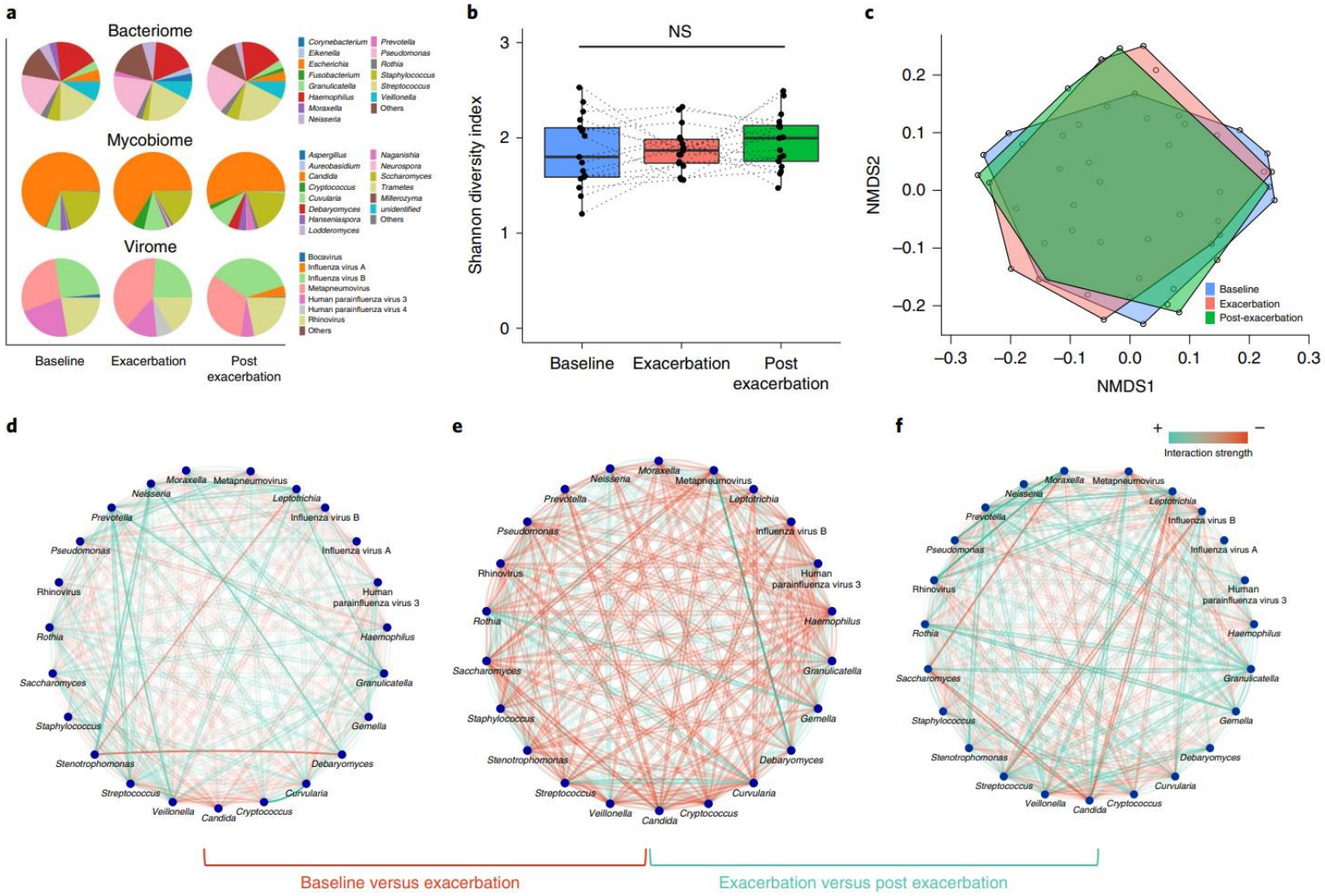


Negative interaction between microbes → High AE
Negative interaction against Pseudomonas → High AE



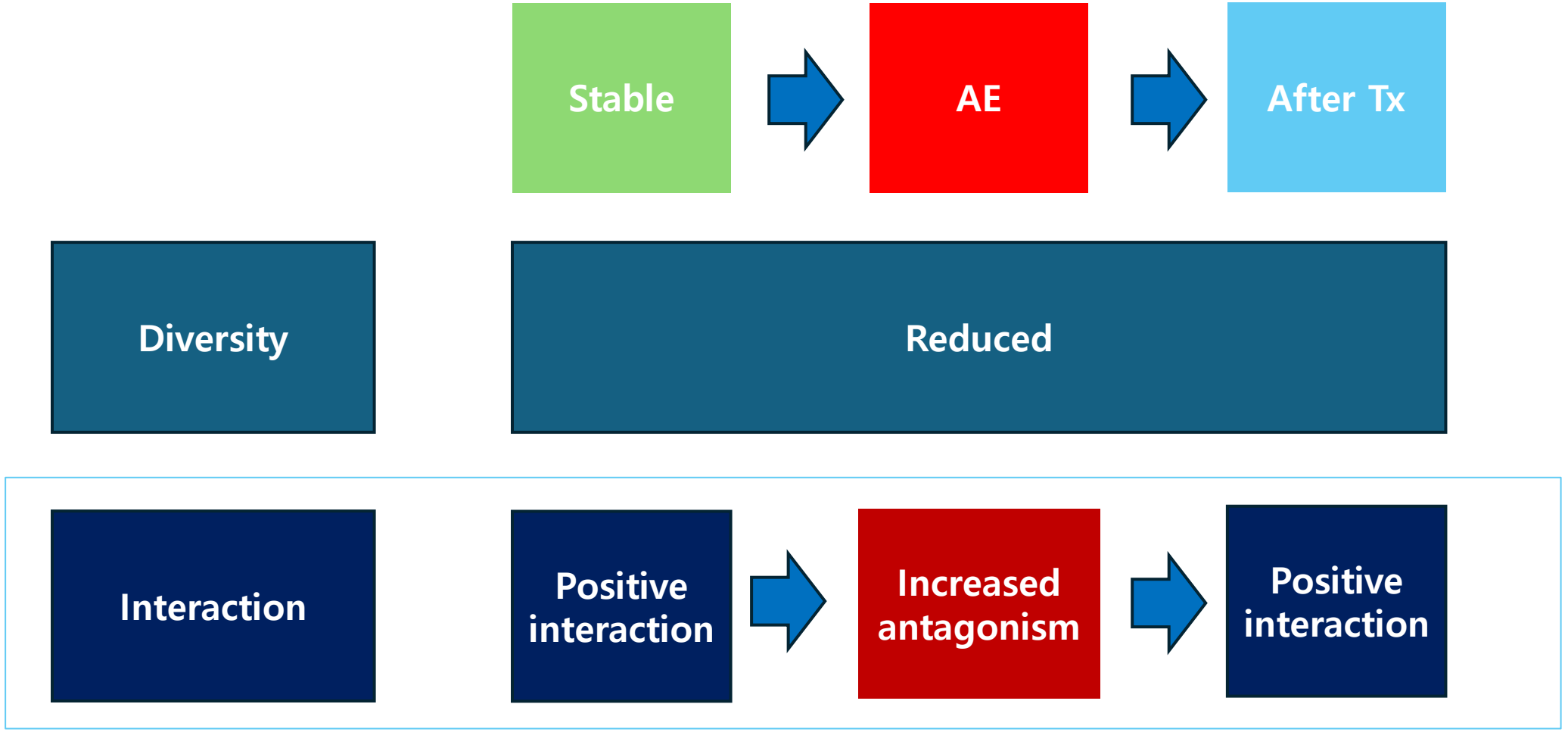
Aogáin, Nature Med 2021;27:689-699

Interaction > diversity



Aogáin, Nature Med 2021;27:689-699

Antibiotics



Summary

- Bacterial-load guided antibiotics might reduce unnecessary antibiotics

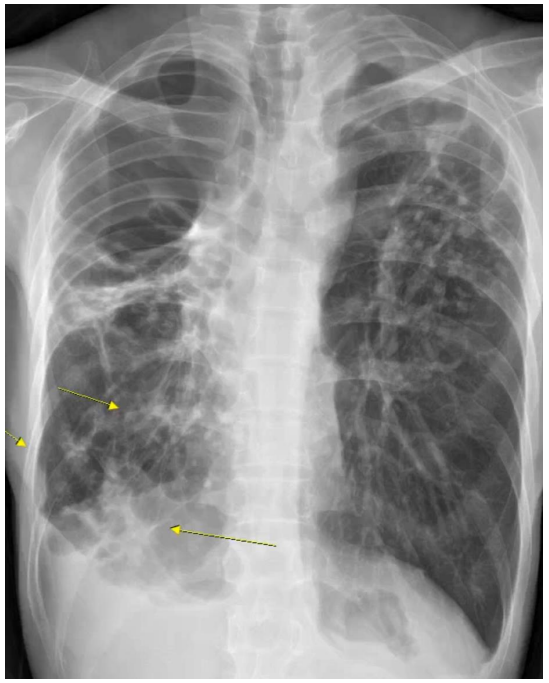
- Microbial interaction might be more important than bacterial abundance.

Contents

- Bacterial infection
  - Inhaled antibiotics
  - *Pseudomonas aeruginosa* eradication
  - Antibiotics for the management of exacerbations
  - Culture vs. Microorganism interaction

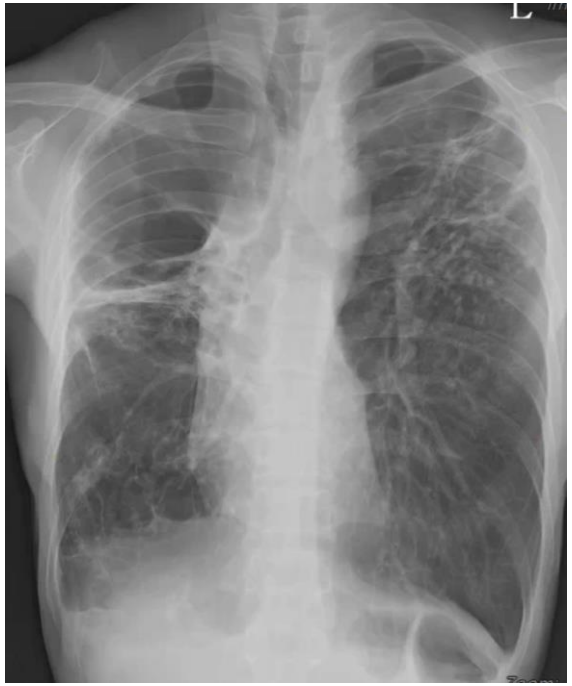
- **Fungal infection – Pulmonary Aspergillosis**

- COVID-19



2021.05

CAT 25



2021.07-10

CAT 30/33

최근 객혈
기침 가래 악화

항생제 처방 (x2)

2022.01-07

CAT 33

호흡곤란 악화
화농성 가래 증가

항생제 처방 (x3)

2021.10

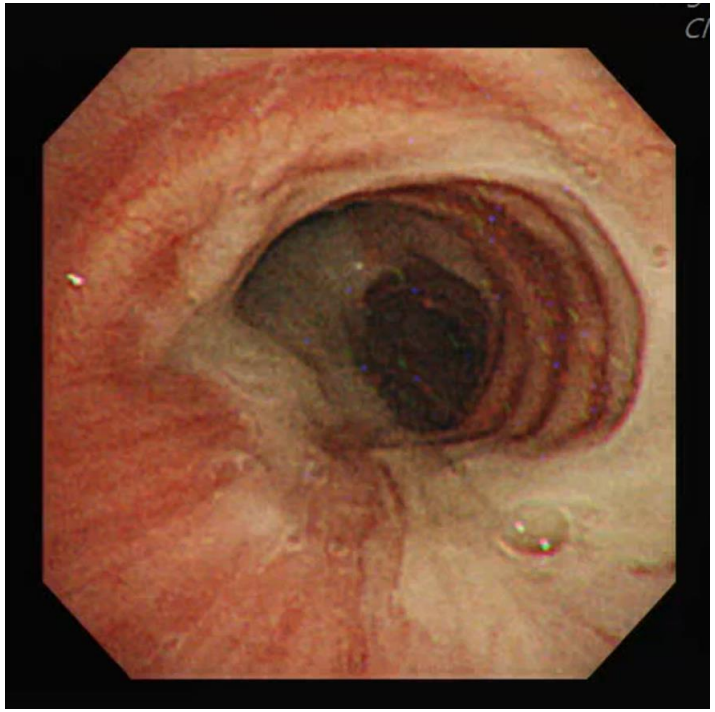
CAT 35

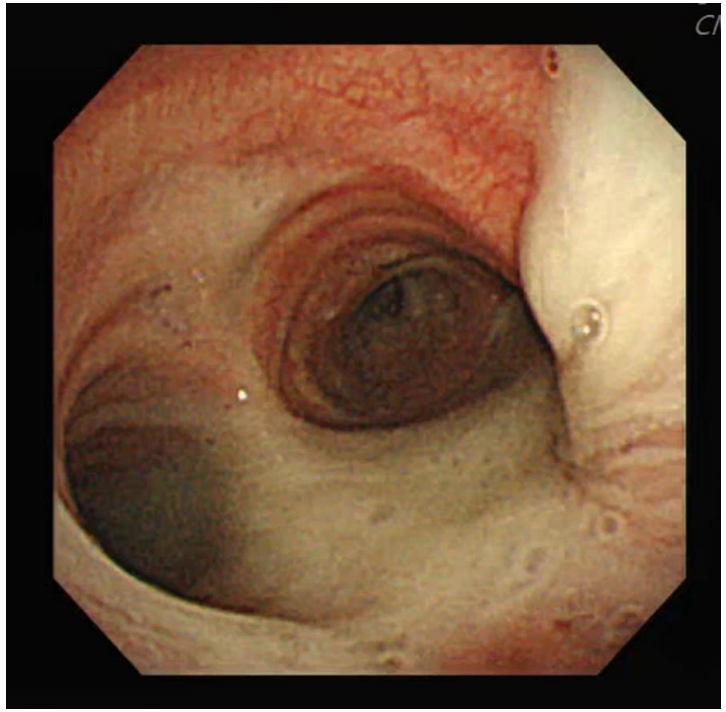
호흡곤란 악화
객혈
기침, 가래 악화

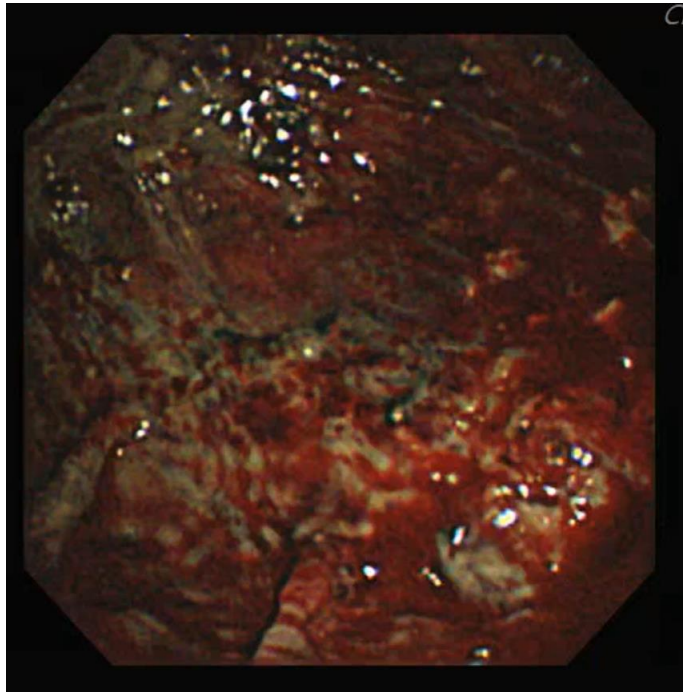
Your plan?

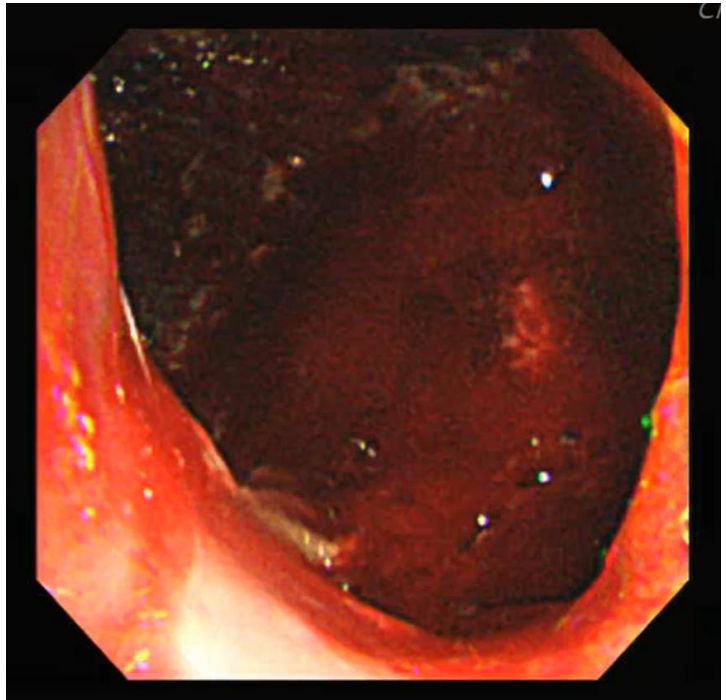
1) Inhaled antibiotics
2) Long-term oral antibiotics
3) Macrolide
4) Roflumilast
5) **Bronchoscopic airway clearance (B-ACT)**

Fungus C, Aspergillus Ag/Ab









==========

【검사명】 폐/경기관지_LT- 생검 (Lung/Transbronchial_LT- Biop [P13065] 【구분】 입원
【처방일】 2022-11-22 【접수일】 2022-11-22 13:03 【검사일】 2022-11-22 13:03 【보고일】 2022-11-24 14:07
※ 이 결과지는 전자서명법에 의하여 전자서명된 문서입니다.

==========

**** 【최종보고】 ****

【검체】 Lung 【병리번호】 S2214273

▣ 결론 및 진단

Lung, upper lobe, right, transbronchial biopsy:
1. Fungal organisms, morphologically Aspergillus spp.
2. Extensive inflammatory cells and histiocytic infiltration

<Special staining results>
PAS: positive
GMS: positive

==========

【환자번호】 02760907 【환자명】 최석로 (M/49)
【검사명】 Fungus culture [L4210] 【구분】 입원 【진료과】 호흡기알레르기내과 【의뢰의사】 이현
【처방일】 2022-11-22 【접수일】 2022-11-22 11:43 【검사일】 2022-11-22 13:39 【보고일】 2022-12-02 09:56

==========

**** 【최종보고】 ****
【판독의3】 이양순
【검체】 Bronchial asp.
▣ 결론 및 진단

==========

Isolate : #01
Organism : Candida albicans, 2 CFU

==========

Isolate : #02
Organism : Aspergillus flavus, Few

==========

검사코드	검사명 (*:중간보고)	결과	단위	Min	Max	검체
L7161	Aspergillus Ab IgG	Positive ...	U/mL			Blood
L7162	Aspergillus Ag	Positive 4...				Blood

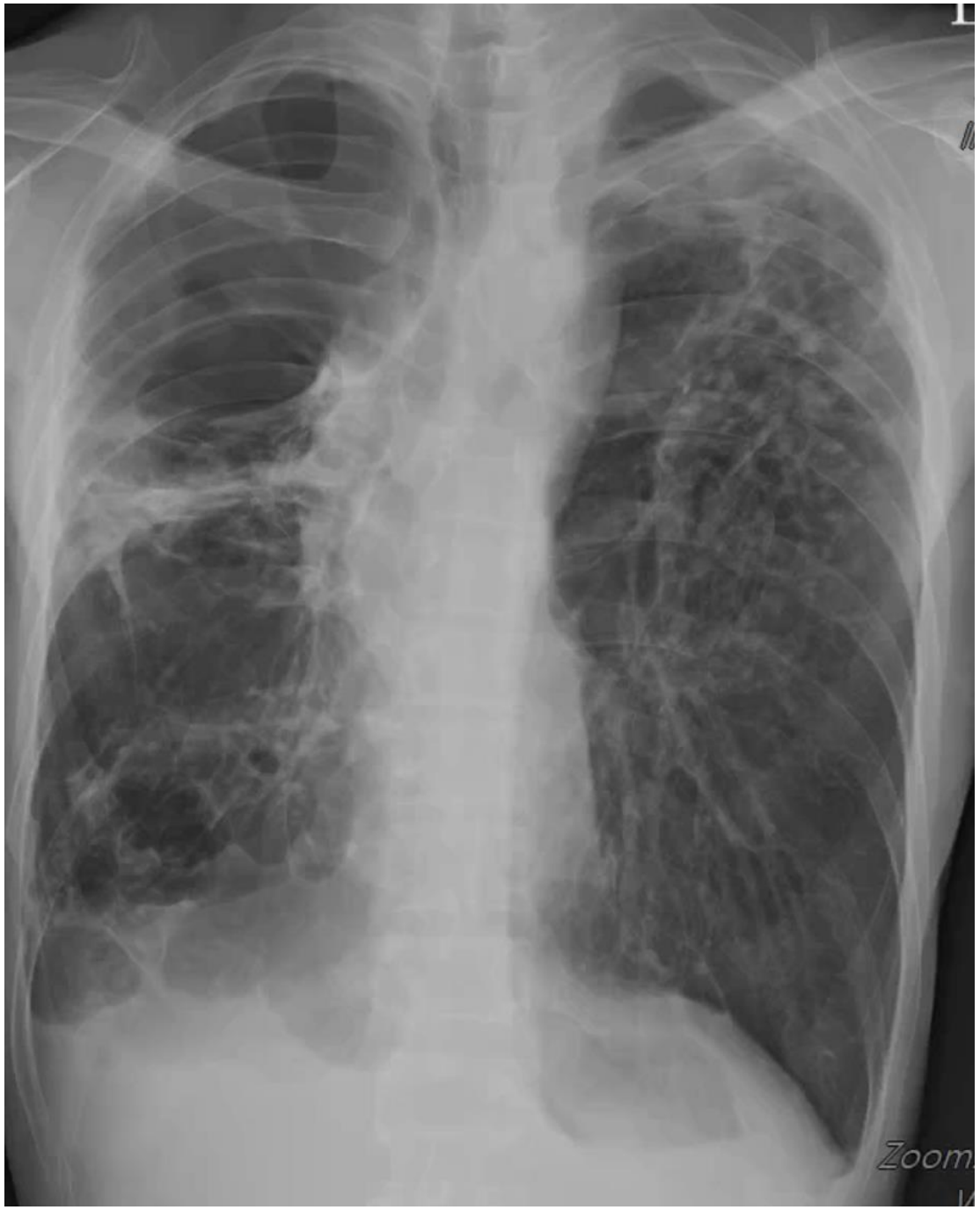
- 2022.11. Voriconazole과 Azithromycin 투여

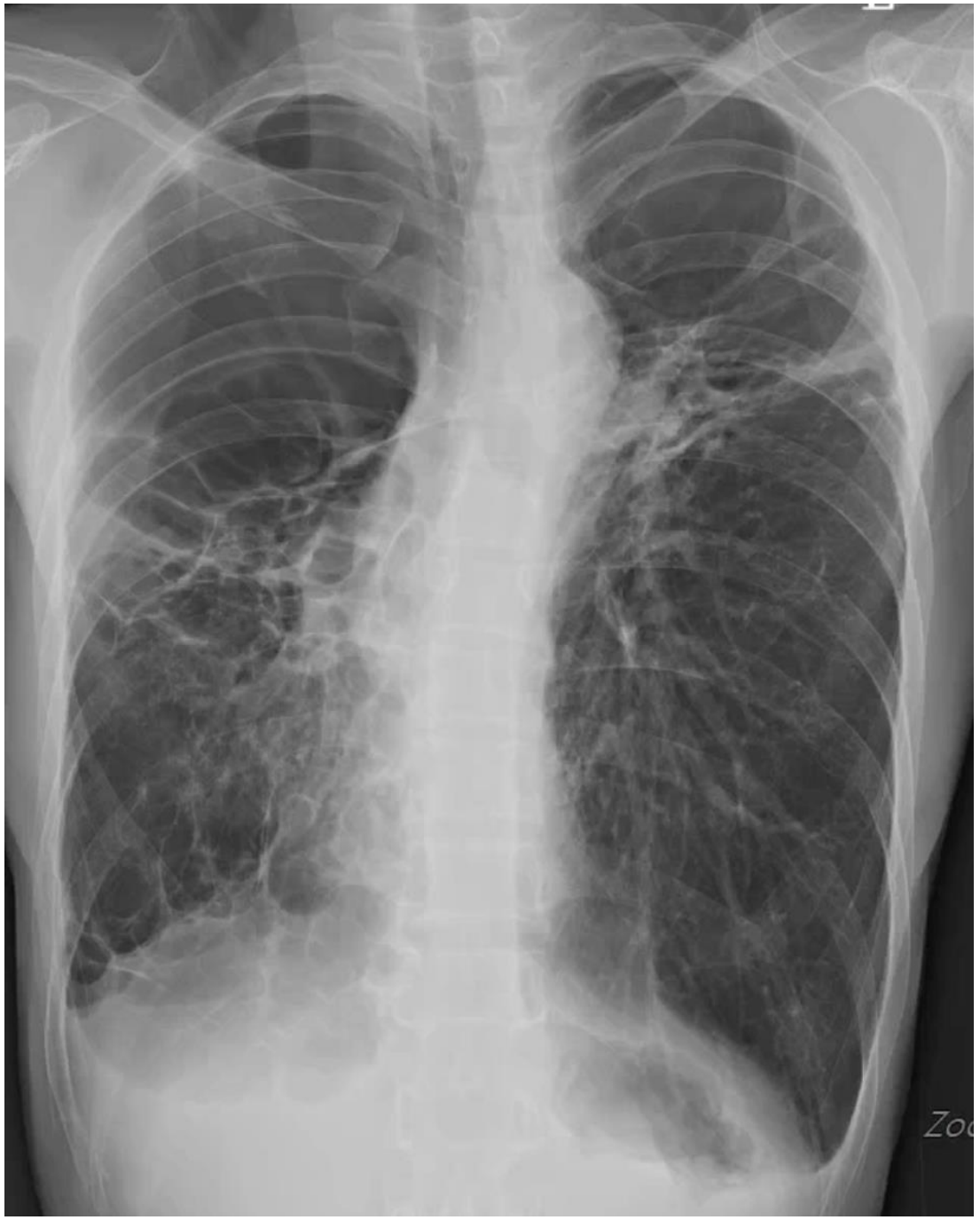
- 2022.12 Azithromycin 중단

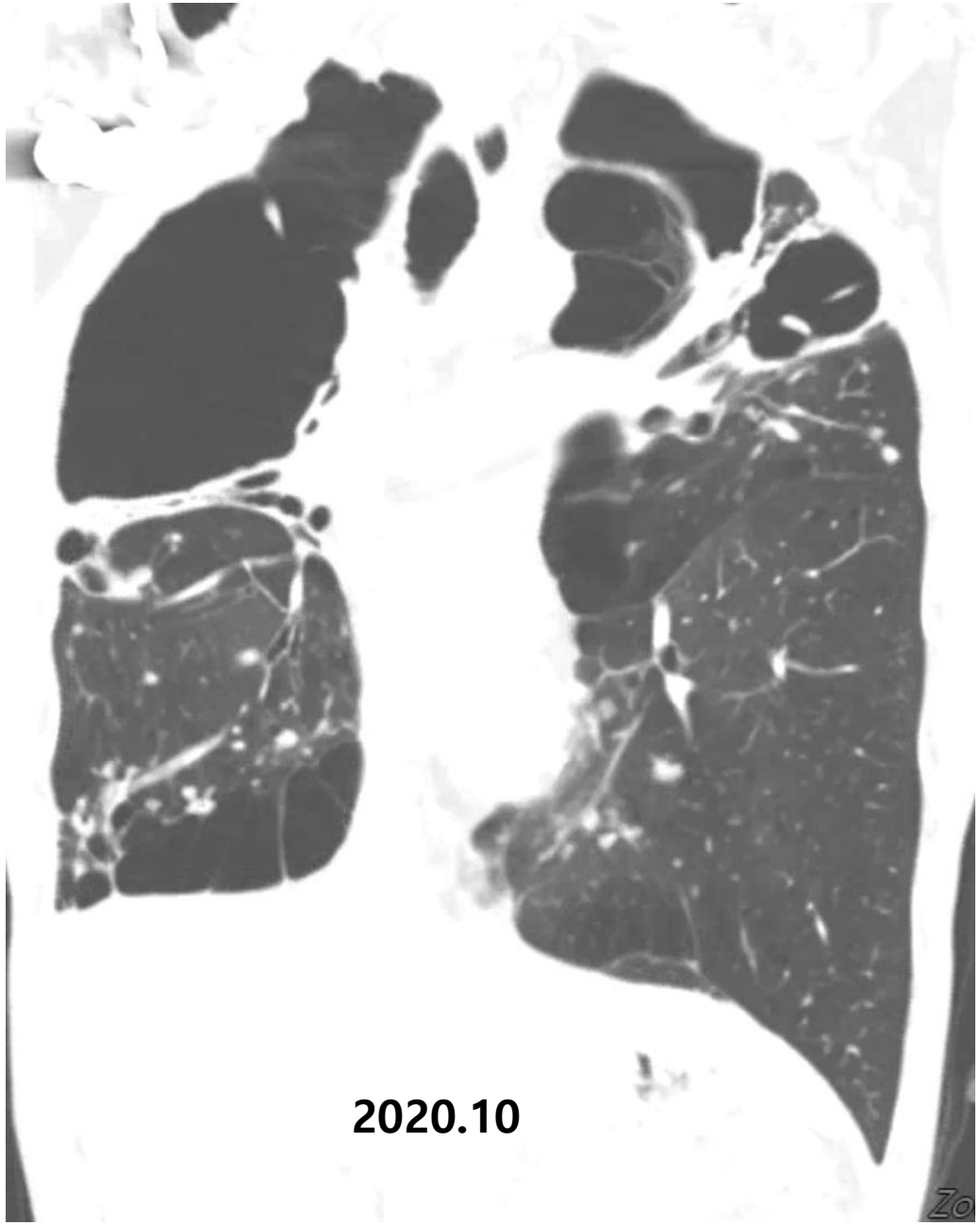
이후 AE?

- 2023년 – 1회 항생제 투여
- 2024년 – 항생제 투여 무

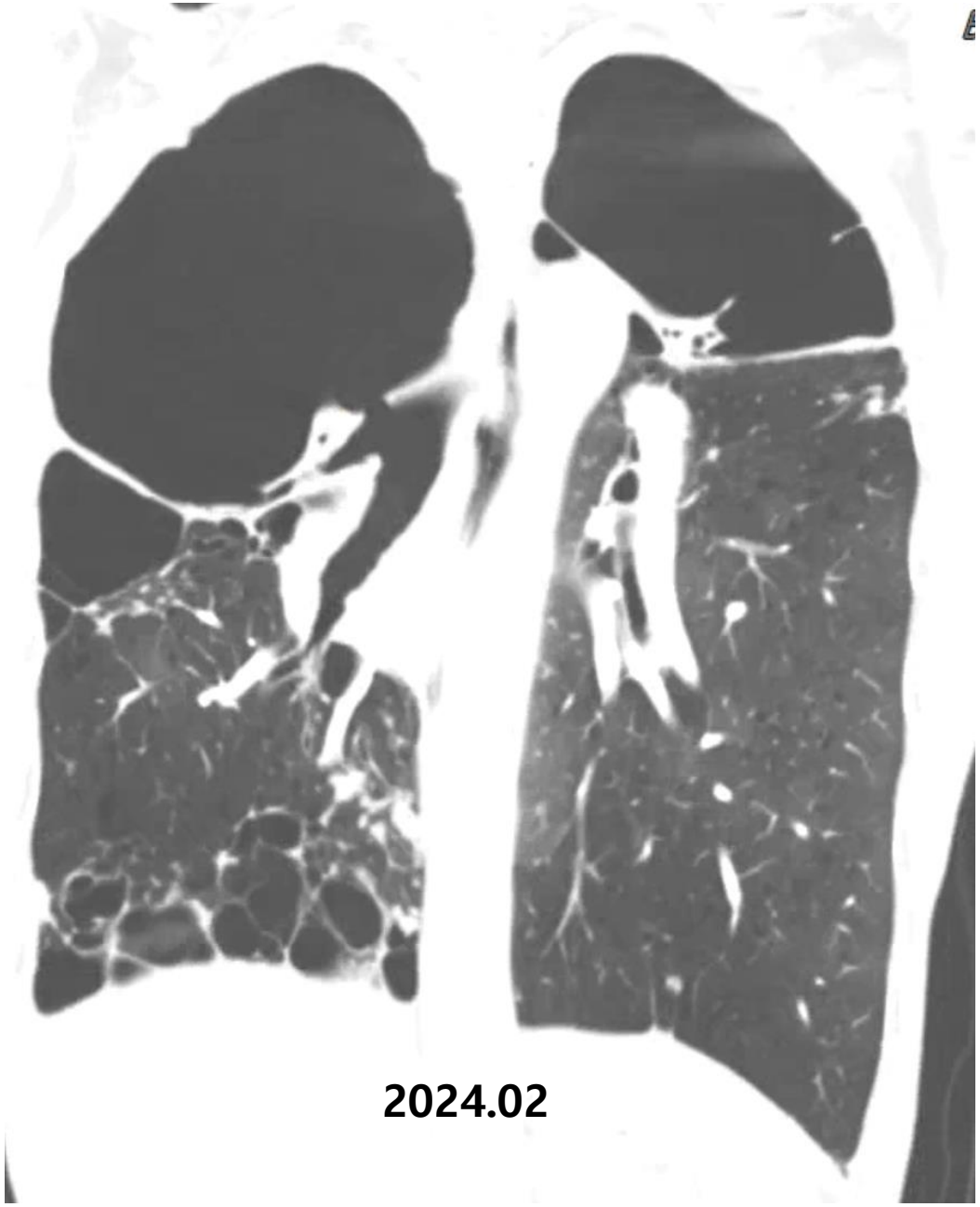
- 하지만…







2020.10



2024.02

BE and risk of pulmonary aspergillosis

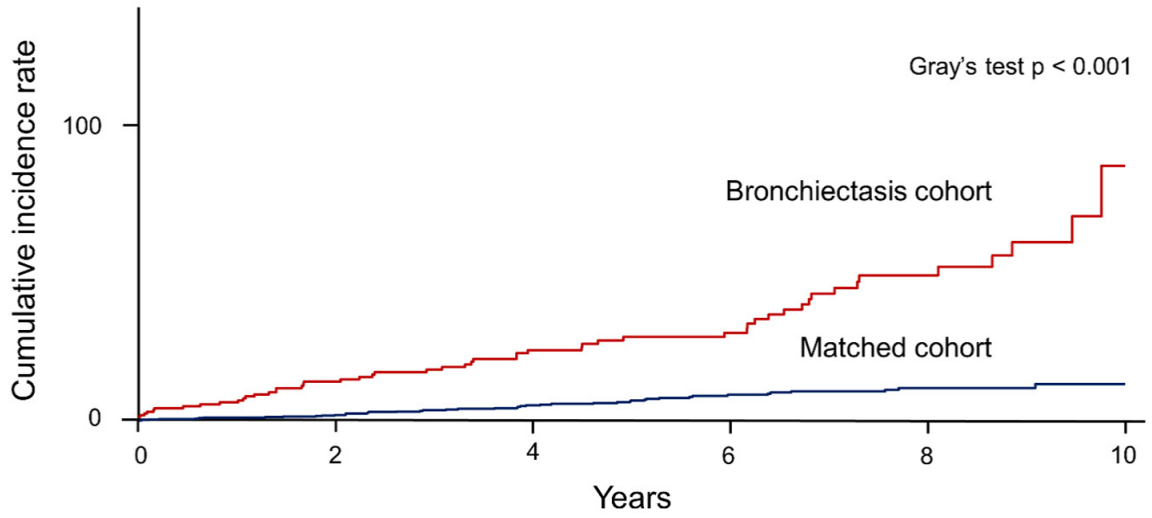


Figure 2. Cumulative incidence of aspergillosis (/100,000 person-years) in the bronchiectasis and matched cohorts.

	Total (N = 84,675)			
	Case	**IR**	**sdHR**	**95% CI**
Overall				
Matched	45	10.9	Ref	
Bronchiectasis	51	50.2	4.53	3.25–6.32

Yang, Kim, Ryu, J Pers Med. 2021;11(5):422.

Table 3. Risk factors for aspergillosis in patients with bronchiectasis.

	Numbers at Risk (N = 16,906)	Aspergillosis (n = 51)	Univariable Analysis		Multivariable Analysis	
			HR	95% CI	Adjusted HR	95% CI
Age						
≤39	2340 (13.8)	2/2340 (0.1)	Ref	Ref	Ref	Ref
40–49	2706 (16.0)	11/2706 (0.4)	4.91	1.09–22.16	4.43	0.98–20.01
50–59	3800 (22.5)	14/3800 (0.4)	5.30	1.20–23.34	4.01	0.90–17.81
60–69	4112 (24.3)	13/4112 (0.3)	4.57	1.03–20.27	2.77	0.61–12.52
≥70	3948 (23.4)	11/3948 (0.3)	5.32	1.17–24.06	3.16	0.68–14.66
Sex						
Female	7986 (47.2)	27/7986 (0.3)	Ref	Ref		
Male	8920 (52.8)	24/8920 (0.3)	1.35	0.78–2.34		
Type of insurance						
Self-employed health insurance	6426 (38.0)	19/6426 (0.3)	Ref	Ref		
Employee health insurance	9993 (59.1)	31/9993 (0.3)	1.16	0.66–2.06		
Medical aid	487 (2.9)	1/487 (0.2)	1.73	0.23–13.02		
Comorbidities						
COPD	4679 (27.7)	27/4679 (0.6)	3.09	1.78–5.35	1.95	1.07–3.57
Asthma	5819 (34.4)	28/5819 (0.5)	2.27	1.31–3.93	1.27	0.68–2.37
Previous pulmonary tuberculosis	2035 (12.0)	19/2305 (0.8)	4.83	2.74–8.53	3.67	2.03–6.64
NTM pulmonary disease	19 (0.1)	1/19 (5.3)	28.73	3.96–208.41	11.25	1.49–85.18
Diabetes mellitus	3442 (20.4)	11/3442 (0.3)	1.32	0.68–2.58		
Rheumatologic disease	1022 (6.1)	3/1022 (0.3)	0.93	0.29–2.99		
Lung cancer	639 (3.8)	3/639 (0.5)	1.65	0.52–5.31		
Medication						
Use of ICS						
No use	13,149 (77.8)	27/13,149 (0.2)	Ref	Ref	Ref	Ref
<1 year	2540 (15.0)	14/2540 (0.6)	2.50	1.31–4.77	1.83	0.92–3.63
≥1 year	1217 (7.2)	10/1217 (0.8)	3.39	1.64–7.01	1.69	0.74–3.89
Systemic corticosteroids *						
No use	3602 (21.3)	5/3602 (0.1)	Ref	Ref	Ref	Ref
<10 mg/day	12,764 (75.5)	41/12,764 (0.3)	1.43	0.56–3.65	1.29	0.50–3.31
≥10 mg/day or more	540 (3.2)	5/540 (0.9)	3.60	1.04–12.50	2.15	0.59–7.86

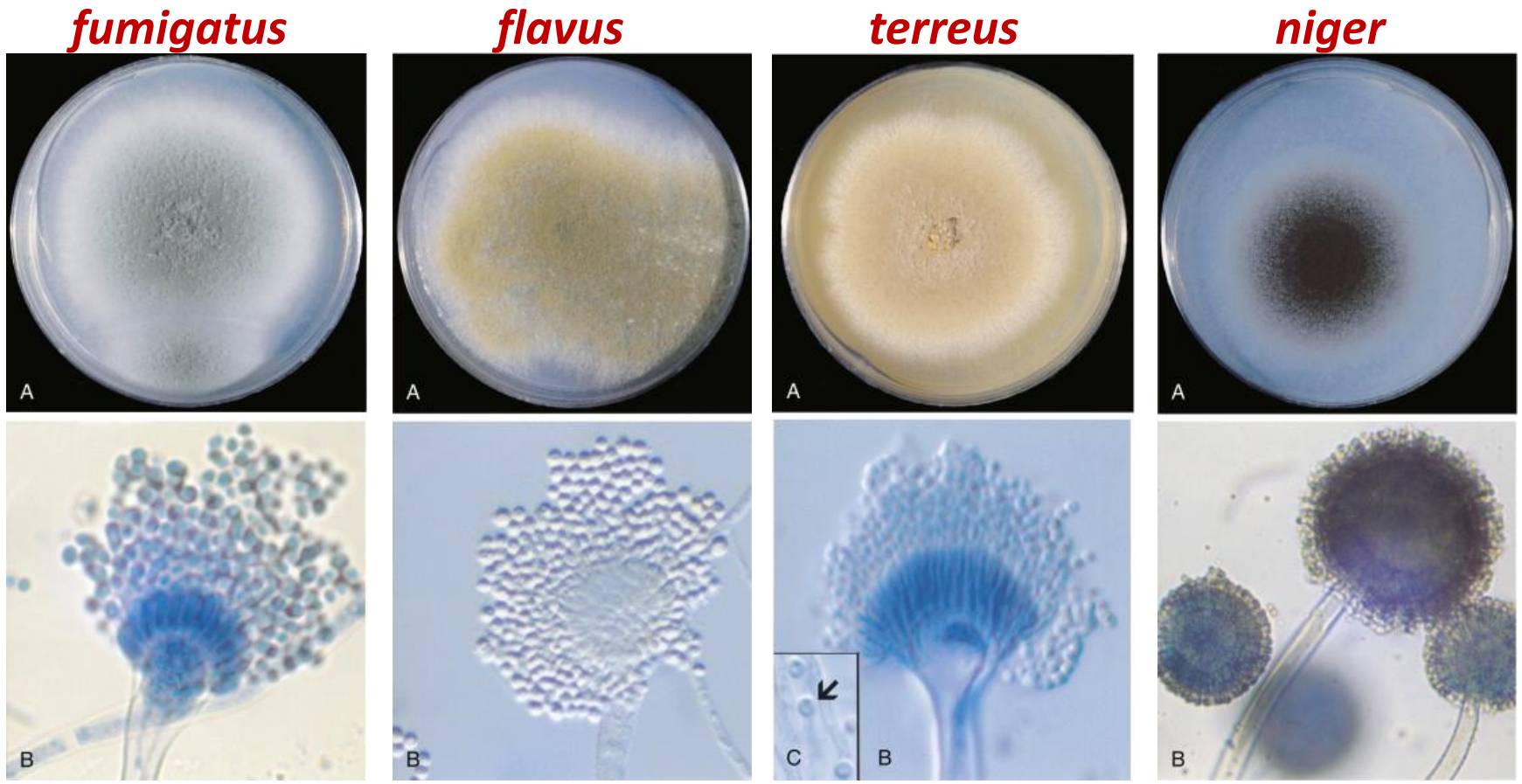
Data are presented as number (percentage), ratio (percentage), or hazard ratios (95% CIs). * Systemic corticosteroids are presented as a prednisolone-equivalent dose. Abbreviations: COPD, chronic obstructive pulmonary disease; NTM, non-tuberculous mycobacteria; ICS, inhaled corticosteroids; HR, hazard ratio; CI, confidence interval; Ref, reference.

Genus *Aspergillus*

- Aspergillum

Mandell, Principles and Practice of Infectious Diseases 7th 2009

Aspergillus species



Mandell, Principles and Practice of Infectious Diseases 7th 2009

Pulmonary Aspergillosis

- Invasive pulmonary aspergillosis (IPA)

- Chronic forms
  - Chronic necrotizing pulmonary aspergillosis, CNPA)
    = (Subacute invasive pulmonary aspergillosis, SAIA)
  - Simple aspergilloma
  - Chronic cavitary pulmonary aspergillosis (CCPA)
  - Chronic fibrosing pulmonary aspergillosis (CFPA)
  - Aspergillus nodule

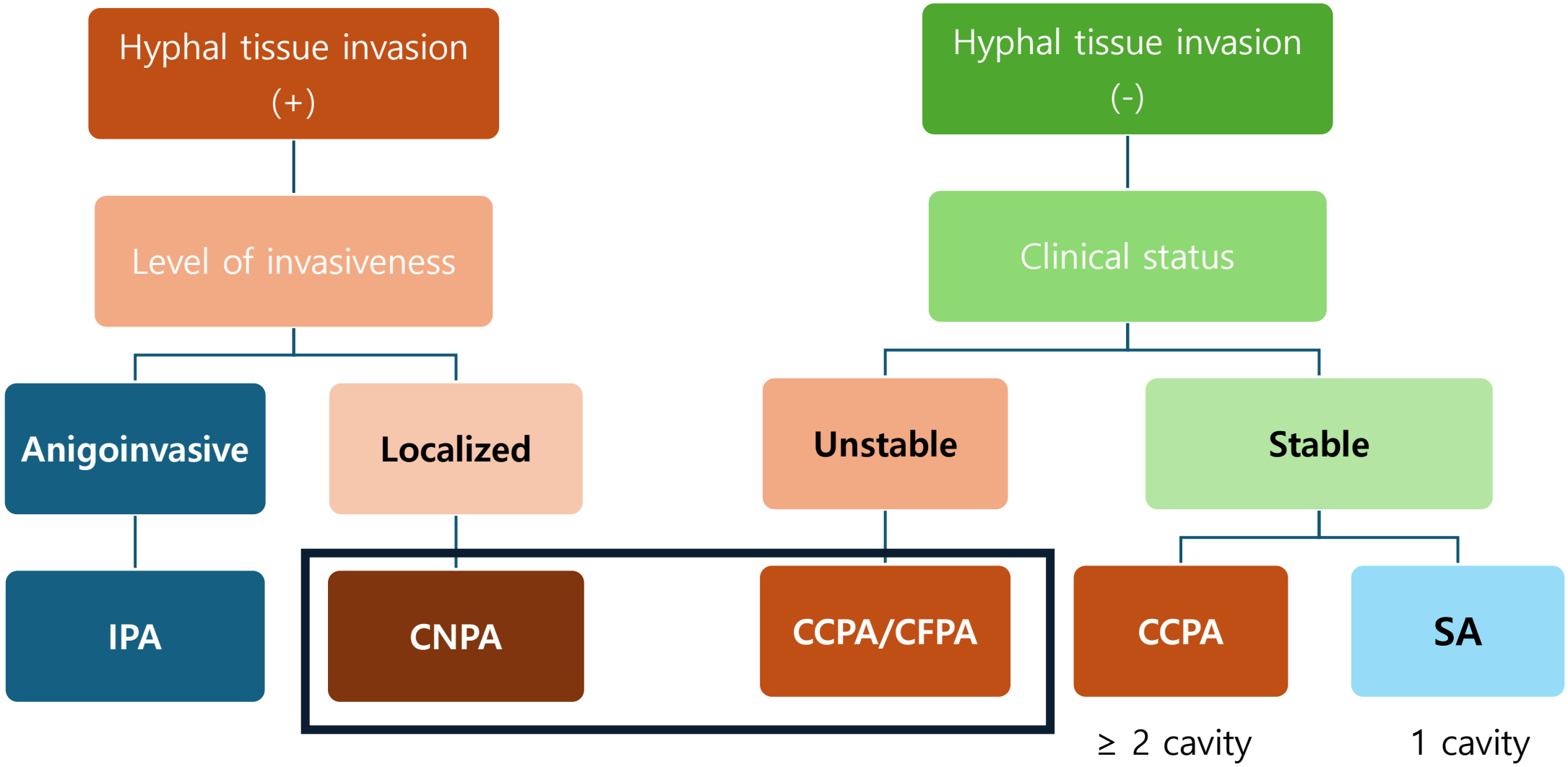
- Allergic forms
  - Allergic bronchopulmonary aspergillosis (ABPA)

Pulmonary Aspergillosis

Terms	Immune state	Clinical course	Radiology	Pathology
Invasive PA	Markedly ↓↓	< 1 month	Consolidation ± "halo'' sign	Hyphae in tissue ± angioinvasive
CNPA or SAIA	Mildly ↓	1-3 months	Cavitation, Nodules, abscess formation	Hyphae (+tissue invasion)
CCPA	Non-compromised	At least 3 months	Cavities ≥ 1 ± fungal ball	Hyphae (- tissue invasion)
CFPA	Non-compromised	At least 3 months	Fibrotic destruction ≥ 2	Fibrotic destruction
Simple aspergilloma	Non-compromised	At least 3 months	Single cavity + fungal ball	Hyphae in cavity

Smith et al. Eur Respir J 2011;37:865-72

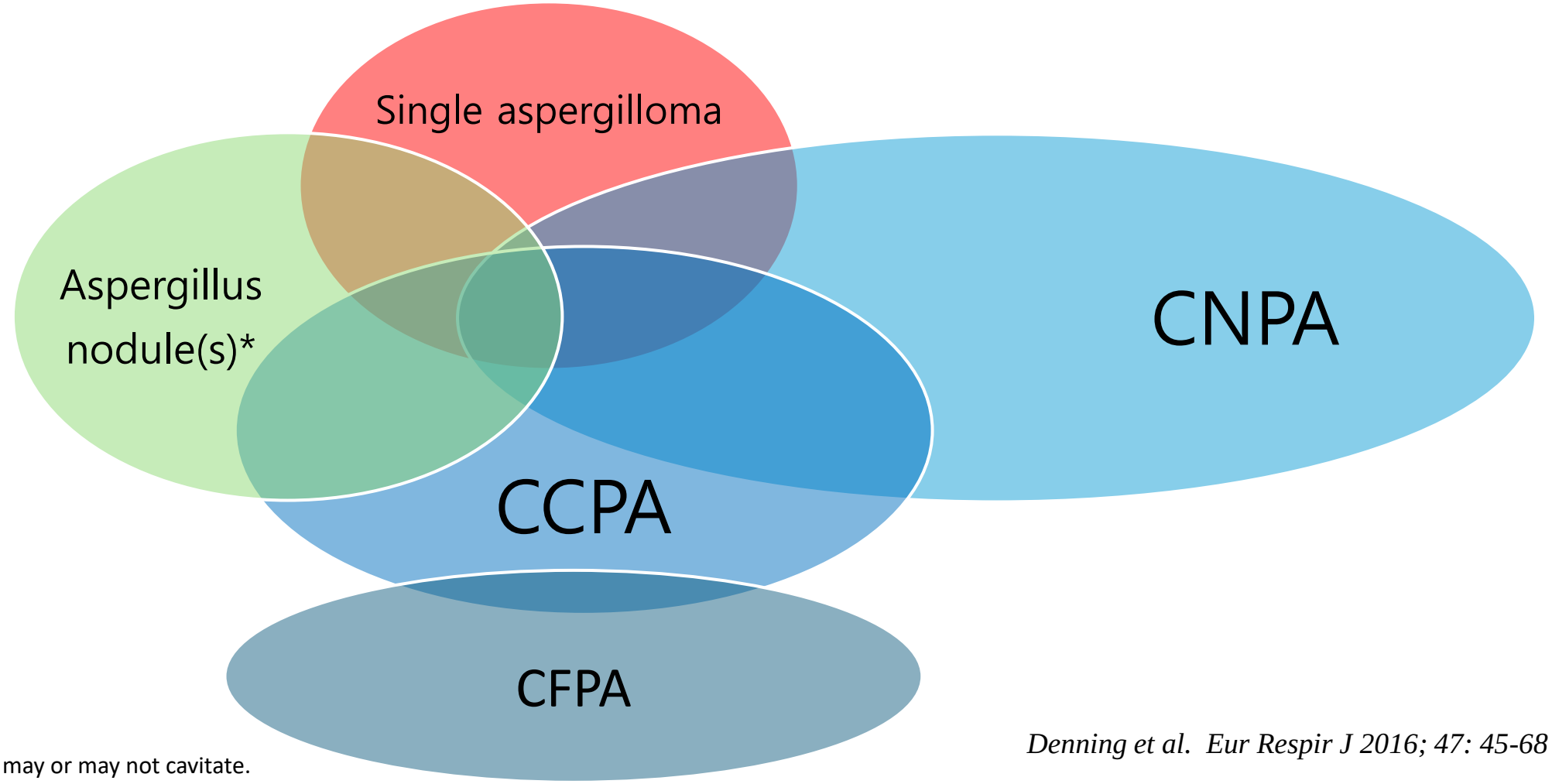
Pathologic diagnosis



Chronic Pulmonary Aspergillosis (CPA)

	Radiologic findings			Symptoms	Serological or microbiological evidence
	Cavity	Aspergilloma	Progression over at least 3months		
Simple aspergilloma	1	1	No	minor or none	Yes
CCPA	≥ 1	≥ 1 (irregular material)	Yes	Significant	Yes
CFPA	Severe fibrotic destruction of ≥ 2 lobes		Yes	Significant With major loss of lung function	Yes
Aspergillus nodule	One or more nodules which may or may not cavitate		-	-	Only histologically diagnosed
SAIA	Cavitation, progressive consolidation with "abscess formation"		Over 1-3 months	Significant	Yes (*Aspergillus* Ag+)

Pulmonary Aspergillosis



Denning et al. Eur Respir J 2016; 47: 45-68

*One or more nodules which may or may not cavitate.
Only histologically diagnosed.

Contents

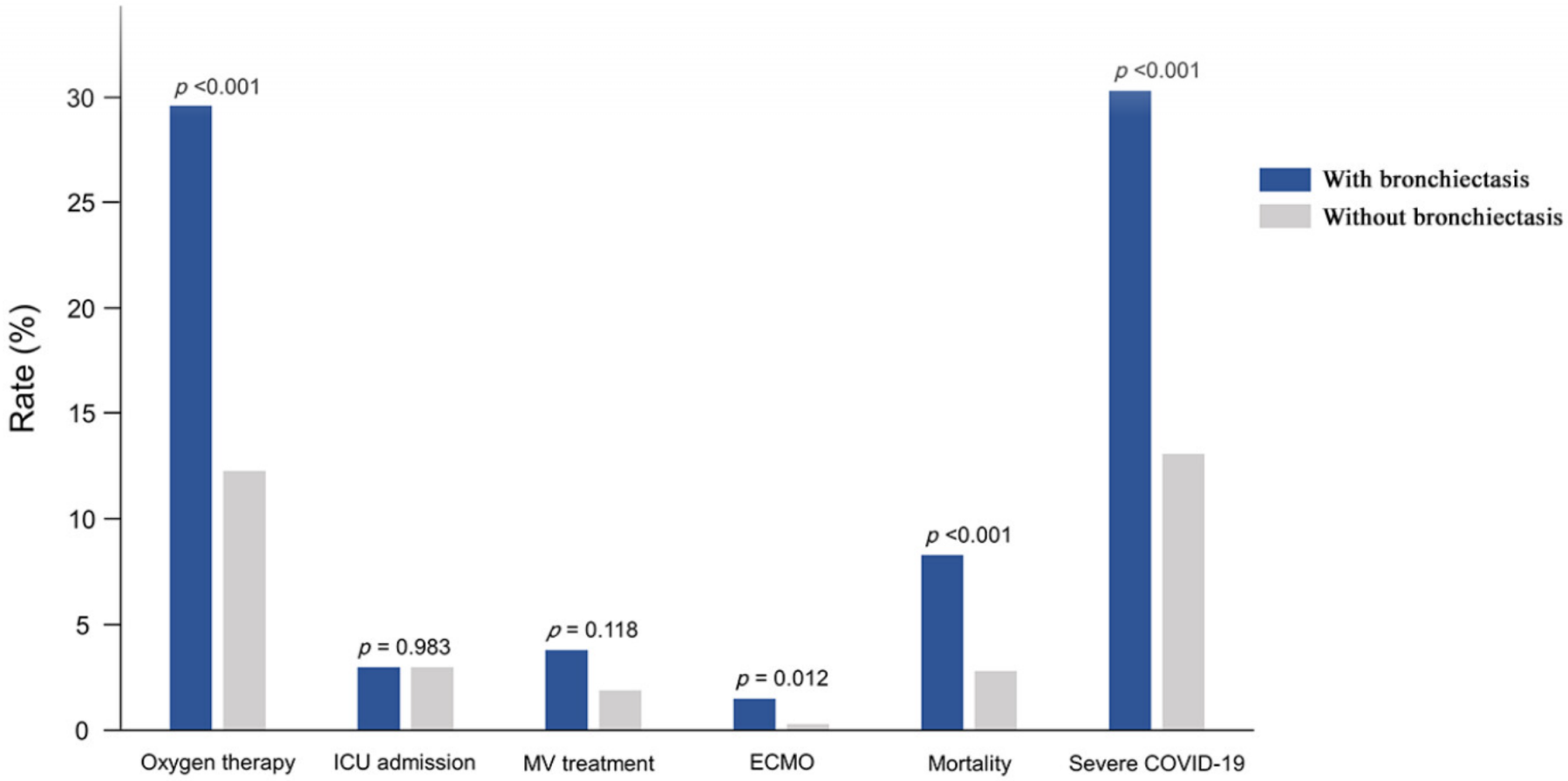
- Bacterial infection
  - Inhaled antibiotics
  - *Pseudomonas aeruginosa* eradication
  - Antibiotics for the management of exacerbations
  - Culture vs. Microorganism interaction
- Fungal infection – Pulmonary aspergillosis
- **COVID-19**

Susceptibility to COVID-19

- Susceptibility to COVID-19
  - **1.22**-fold increased OR (95% confidence interval = 1.01–1.45)

Ther Adv Respir Dis. 2021;15:1753466621995043

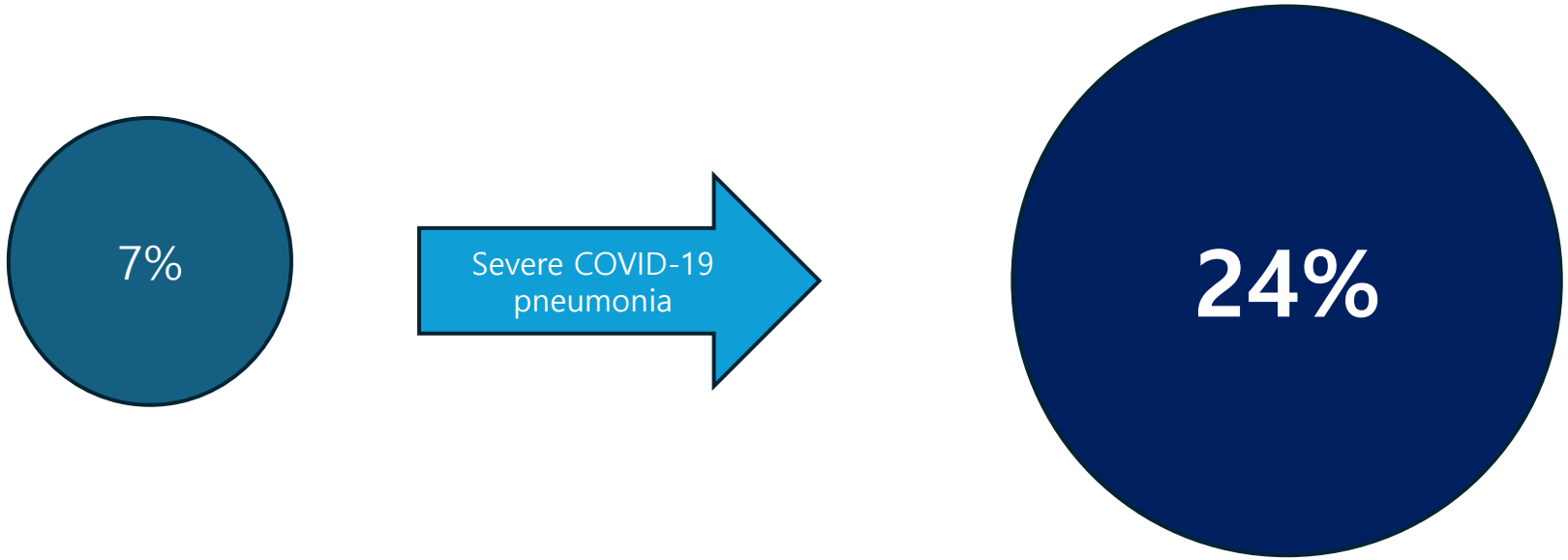
Short-term outcome



Choi, Lee, Ther Adv Respir Dis. 2021;15:1753466621995043

COVID-19 → Bronchiectasis development?

- CT analysis (n=114)
  - About 25% had BE after severe COVID-19 pneumonia
  - Bilateral lower lobe predominance



Han, Fan, Radiology 2021;299:E177-E186

Table E2 Comparison of CT Findings and Scores between Two Serial Examinations in Recovered Patients Who Had Severe COVID-19

Characteristic	Initial CT Scans (*n* = 114)	Follow-up CT Scans (*n* = 114)	*P* Value
Lung involvement			<.001
Normal	0 (0)	25 (22)	
Unilateral	1 (0.88)	5 (4.4)	
Bilateral	73 (64)	44 (39)	
Predominant CT pattern			<.001
Normal	0 (0)	25 (22)	
Ground-glass opacities	44 (39)	24 (21)	
Consolidation	17 (15)	3 (2.6)	
Reticulation	13 (11)	22 (19)	
Presence of nodule or mass	2 (1.8)	19 (17)	<.001
Pleural effusion	7 (6.1)	0 (0)	.01
Emphysema	2 (1.8)	2 (1.8)	.99
Thickening of the adjacent pleura	27 (24)	37 (32)	.10
Interlobar pleural traction	9 (7.9)	19 (17)	.04
Honeycombing	2 (1.8)	3 (2.6)	>.99
Pulmonary atelectasis	4 (3.5)	13 (11)	.02
Bronchiectasis	8 (7.0)	27 (24)	<.001
CT score*			
Total lesions	15 (9)	3 (8)	<.001
Ground-glass opacities	10 (10)	2 (8)	<.001
Consolidation	5 (8)	0 (0)	<.001
Reticulation	5 (7)	2 (5)	.19
Fibrotic-like changes	0 (0)	0 (4)	<.001

Han, Fan, Radiology 2021;299:E177-E186

Reversible?

- Of 41 COVID-19 survivors after ARDS
  - 68% (n=28) had traction bronchiectasis
    - Disappeared in 75% (n=21) / Attenuated in 25% (n=7)

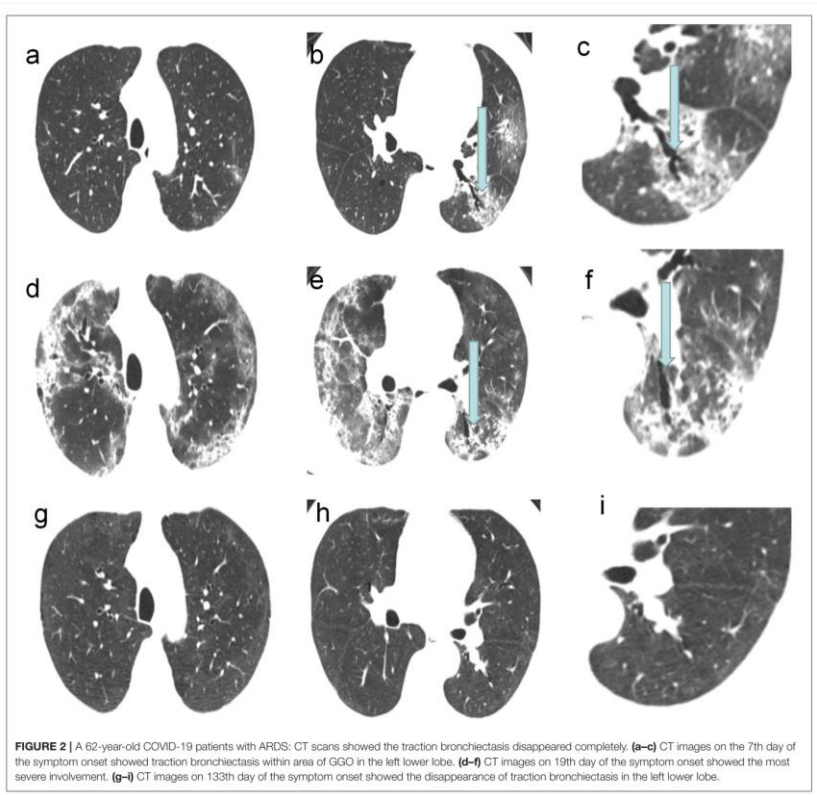


FIGURE 2 | A 62-year-old COVID-19 patients with ARDS: CT scans showed the traction bronchiectasis disappeared completely. **(a–c)** CT images on the 7th day of the symptom onset showed traction bronchiectasis within area of GGO in the left lower lobe. **(d–f)** CT images on 19th day of the symptom onset showed the most severe involvement. **(g–i)** CT images on 133th day of the symptom onset showed the disappearance of traction bronchiectasis in the left lower lobe.

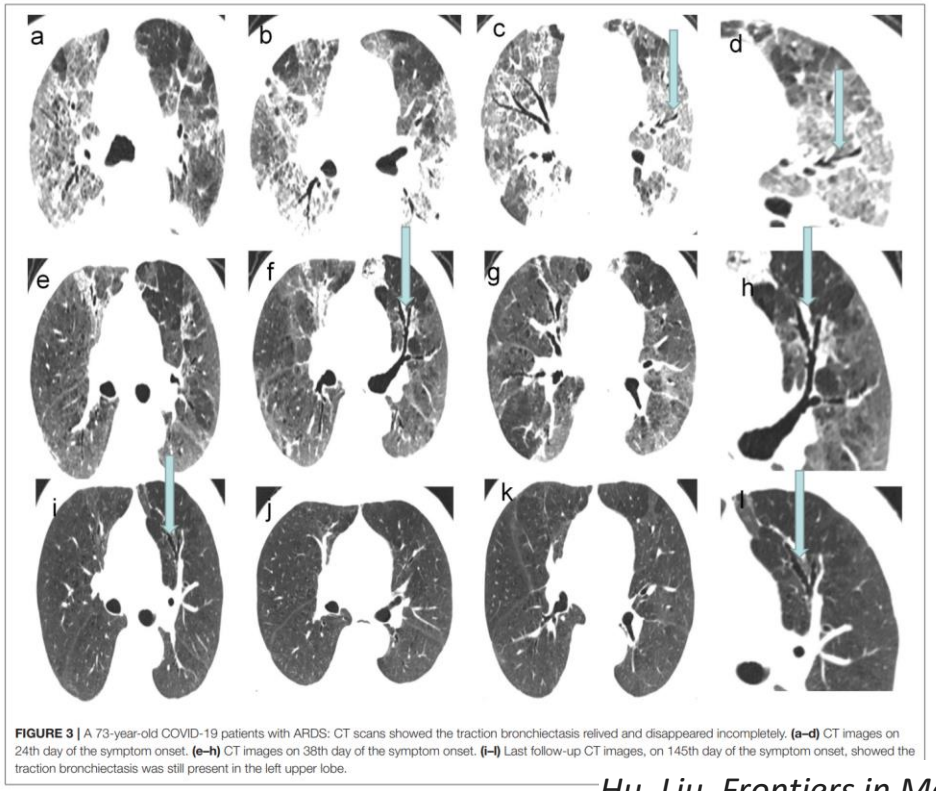
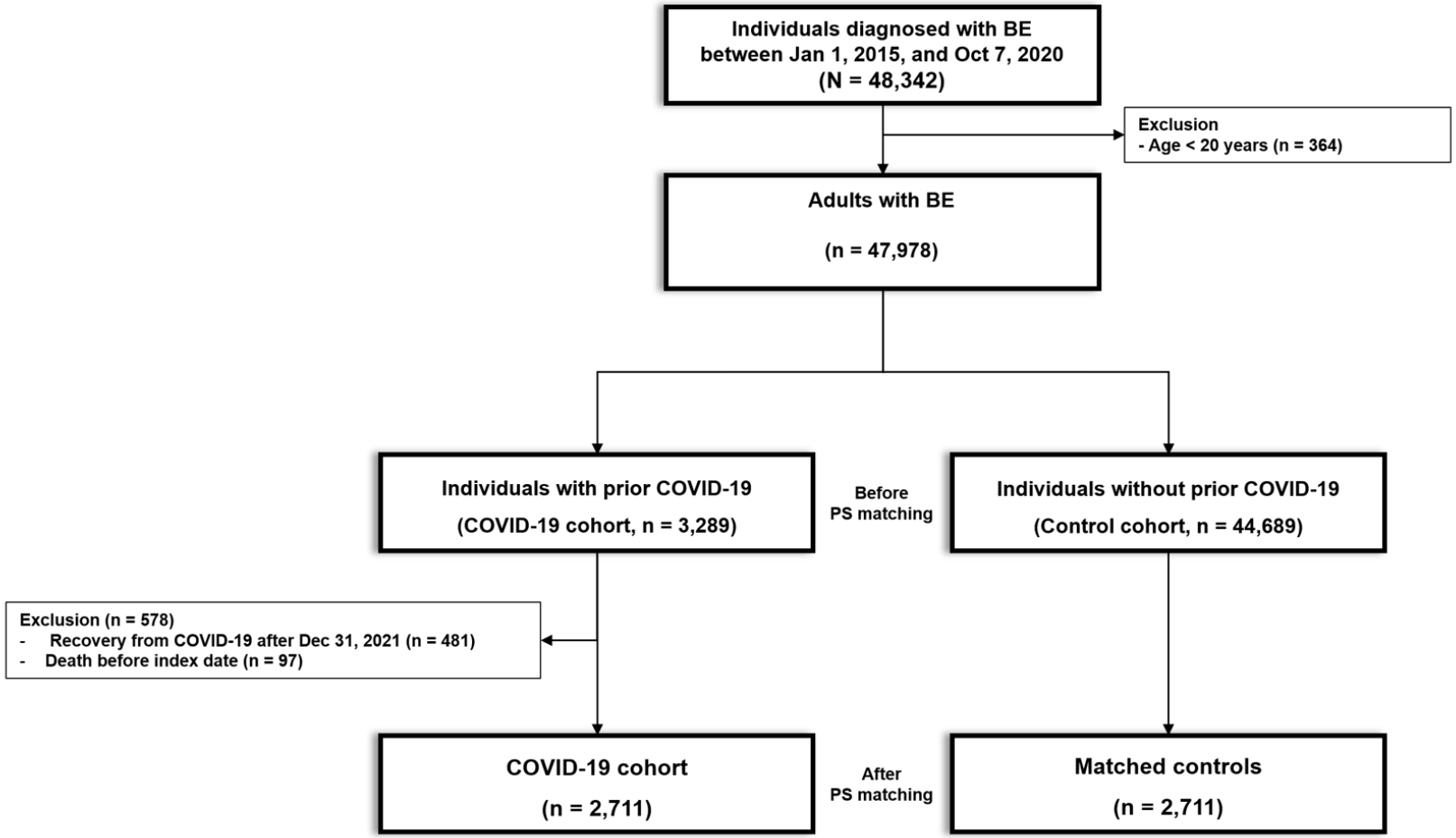


FIGURE 3 | A 73-year-old COVID-19 patients with ARDS: CT scans showed the traction bronchiectasis relived and disappeared incompletely. **(a–d)** CT images on 24th day of the symptom onset. **(e–h)** CT images on 38th day of the symptom onset. **(i–l)** Last follow-up CT images, on 145th day of the symptom onset, showed the traction bronchiectasis was still present in the left upper lobe.

Hu, Liu, Frontiers in Medicine 2021;8:739857

Long-term effect of COVID-19 in BE



Unpublished data (submitted)

Severe AE

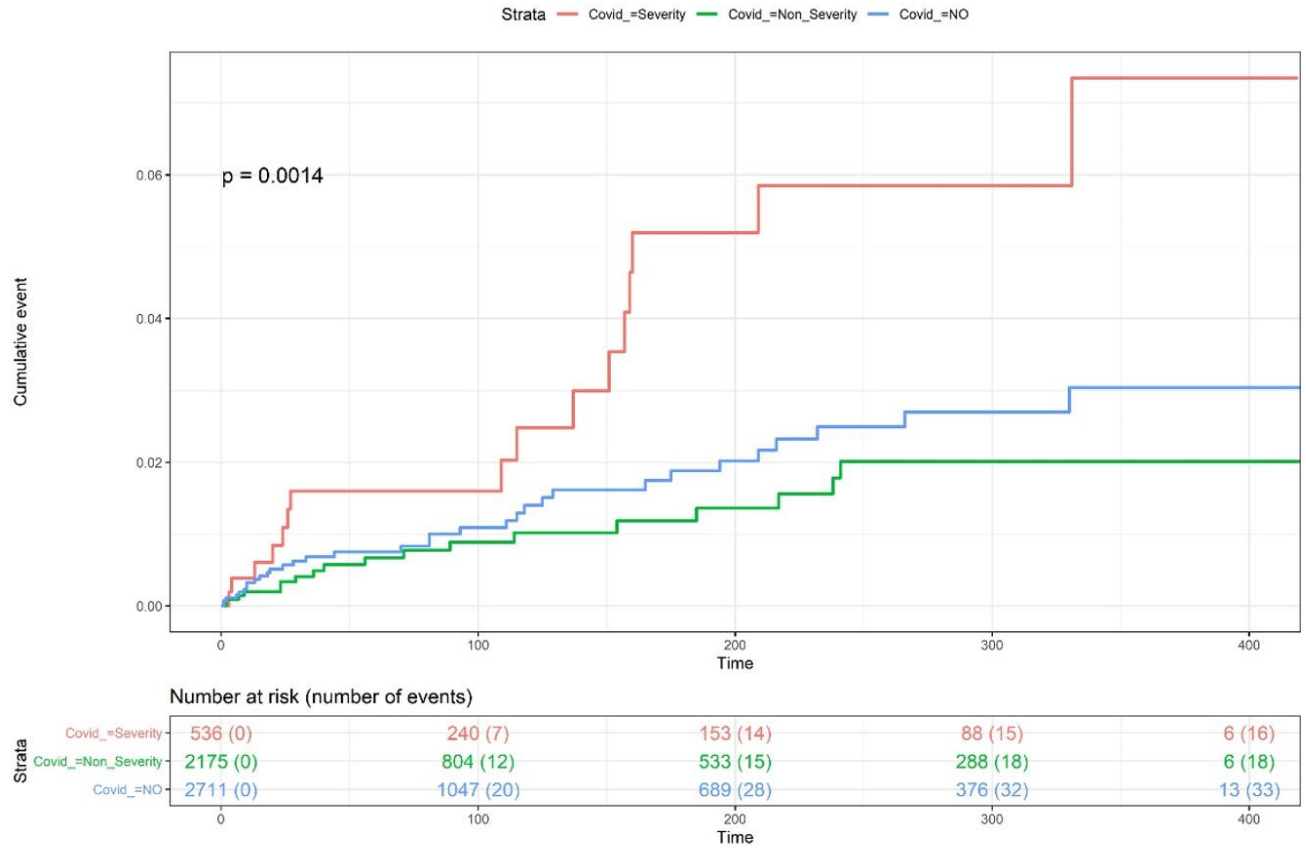


Table 2. Impact of previous COVID-19 infection and its severity on risk of severe exacerbation in patients with bronchiectasis

	No. of participants	No. of incident cases	Incidence (/10,000 PY)	Hazard ratio (95% CI)
Hospitalization				
Control cohort	2,711	33	389.1	1 (Reference)
COVID-19 cohort	2,711	34	402.3	1.03 (0.64–1.67)
Hospitalization				
Control cohort	2,711	33	389.1	1 (Reference)
COVID-19 cohort				
Non-severe COVID-19	2,175	18	273.3	0.70 (0.39–1.24)
Severe COVID-19	536	16	856.9	2.24 (1.23–4.08)

Incidence rate of severe exacerbation was calculated by dividing the numbers of incident cases by the total follow-up durations and the hazards of exacerbation and death in COVID-19 cohort was estimated with use of Cox proportional-hazards regression analyses.

Abbreviations: COVID-19, coronavirus disease 2019; PY, person-year; CI, confidence interval.

Unpublished data (submitted)

Long-term mortality

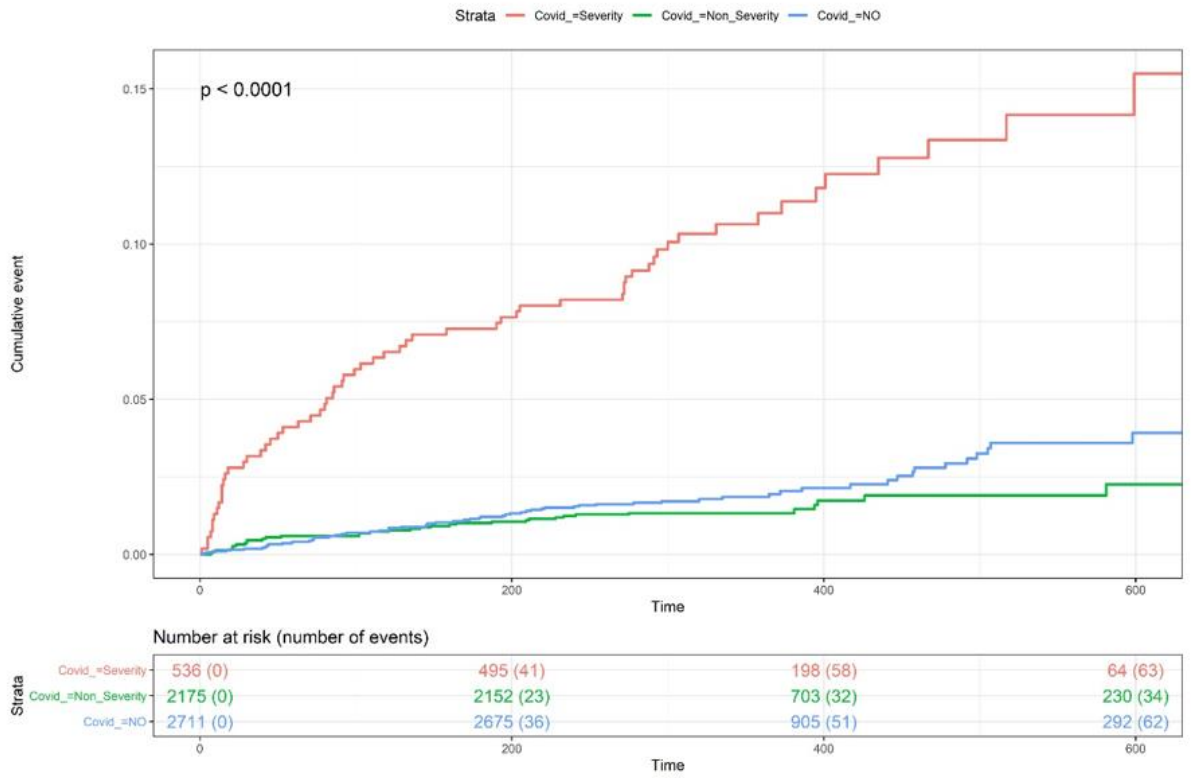


Table 3. Impact of previous COVID-19 infection and its severity on risk of mortality in patients with bronchiectasis

	No. of participants	No. of incident cases	Incidence (/10,000 PY)	Hazard ratio (95% CI)
Deaths				
Control cohort	2,711	62	723.2	1 (Reference)
COVID-19 cohort	2,711	97	1133.8	1.57 (1.14–2.16)
Deaths				
Control cohort	2,711	62	723.2	1 (Reference)
COVID-19 cohort				
Non-severe COVID-19	2,175	34	511.6	0.71 (0.47–1.07)
Severe COVID-19	536	63	3298.9	4.61 (3.25–6.55)

Incidence rate of death was calculated by dividing the numbers of incident cases by the total follow-up durations and the hazards of exacerbation and death in COVID-19 cohort was estimated with use of Cox proportional-hazards regression analyses.

Abbreviations: COVID-19, coronavirus disease 2019; PY, person-year; CI, confidence interval.

Unpublished data (submitted)

Summary

- **Proper candidates for inhaled antibiotics**
  - **Frequent exacerbators with positive bacterial culture**

- **Efficacy of inhaled antibiotics**
  - **15-20% reduction of AE**
  - **May improve QoL**
  - **Measuring bacterial load might be helpful**

Summary

- Eradication of *P. aeruginosa*
  - Eradication rate at 1 year - 40%
    - Systemic + Inhaled antibiotics **>** systemic antibiotics
    - Eradication of first isolation **>** multiple isolation
  - Lower rate of AE
  - May not change QoL and pulmonary function

Summary

- Pulmonary aspergillosis – underrecognized comorbidity of BE
- Bronchiectasis
  - is associated with increased susceptibility and severity to COVID-19
- About ¼ can develop BE after severe COVID-19 pneumonia
- COVID-19 related BE can be reversible
- COVID-19 has negative impact on long-term outcomes in patients with bronchiectasis