Bronchiectasis exacerbation

한림의대 호흡기내과
최하영

Agenda

- Bronchiectasis exacerbation 101
- Endotypes of bronchiectasis exacerbation
- Exacerbation prevention and inhaled antibiotics

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Case study (M/65)

1989 20세 도말음성 폐결핵 치료

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2006 건강검진 기관지확장증 진단

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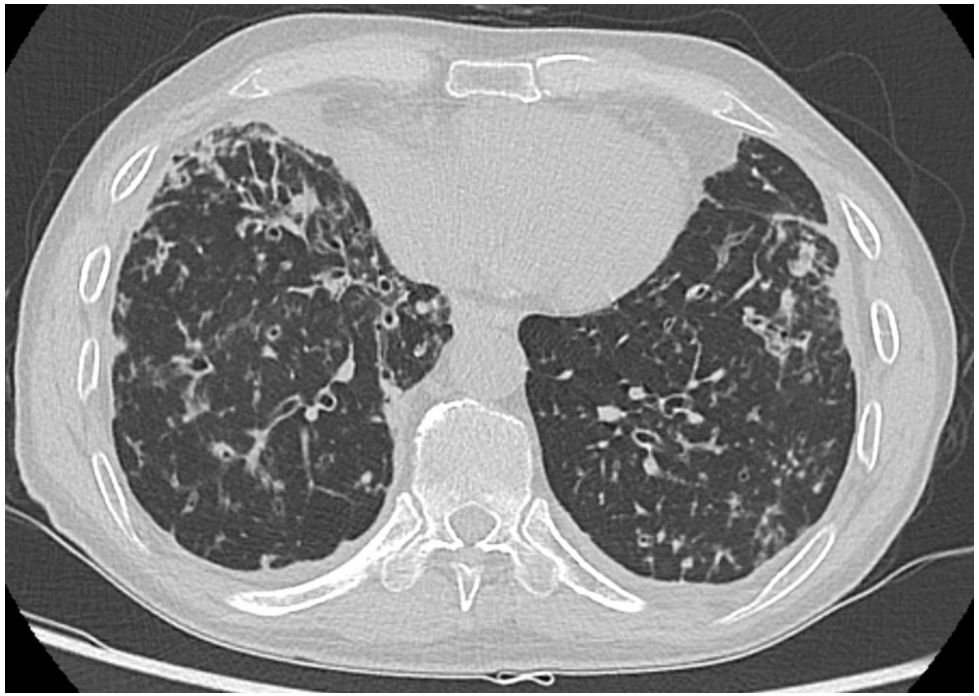
…

2024-10 본원 호흡기내과 초진

- 잦은 악화, 녹농균 배양
- PFT: FEV1/FVC 50%, FEV1 29%, FVC 45%
- ACT 교육, Long-term macrolide 시작

2025-04 증상 악화

- 객담 양, 화농성 증가, 호흡곤란, 피로감,…



Definition of bronchiectasis exacerbation

- 정의
  1. **48시간** 동안 아래 증상 중 **세 가지 이상의 증상이 악화**
     - 기침
     - 객담의 양, 농도
     - 객담의 화농성
     - 객혈
     - 호흡곤란
     - 운동능력 저하
     - 피로, 불쾌감

  2. 담당 의사가 **치료 변경이 필요하다고 판단(대부분 항생제)**

Hill AT et al. *Eur Respir J* 2017;49:1700051
Choi H et al. *J Korean Med Assoc* 2020;63:486
Choi H and Chalmers JD *Ann Transl Med* 2023;11:25

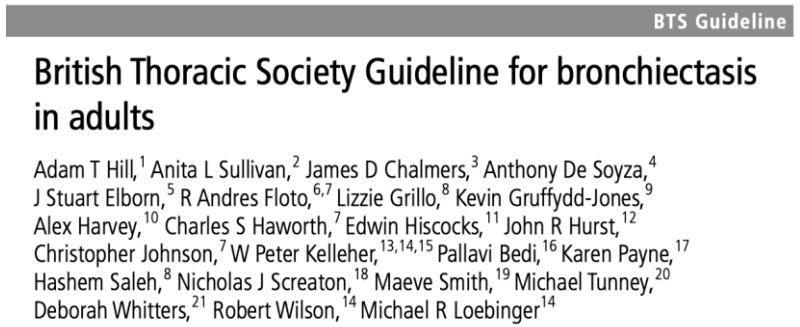
Treatment of bronchiectasis exacerbation

- **항생제**
  - Cephalosporin or Fluoroquinolone
  - 객담 세균배양 및 항생제 감수성 정보에 따라 조정
  - 치료기간: 2주(국제진료지침 권고 – 근거는 부족)
    - ***Pseudomonas aeruginosa*는 2주간 치료**
    - *P. aeruginosa* 가 배양되지 않고 중증도가 낮은 경우 1주 치료도 가능


TASK FORCE REPORT
ERS GUIDELINES

European Respiratory Society guidelines for the management of adult bronchiectasis

Eva Polverino[1], Pieter C. Goeminne[2,3], Melissa J. McDonnell[4,5,6], Stefano Aliberti[7], Sara E. Marshall[8], Michael R. Loebinger[9], Marlene Murris[10], Rafael Cantón[11], Antoni Torres[12], Katerina Dimakou[13], Anthony De Soyza[14,15], Adam T. Hill[16], Charles S. Haworth[17], Montserrat Vendrell[18], Felix C. Ringshausen[19], Dragan Subotic[20], Robert Wilson[9], Jordi Vilaró[21], Bjorn Stallberg[22], Tobias Welte[19], Gernot Rohde[23], Francesco Blasi[7], Stuart Elborn[9,24], Marta Almagro[25], Alan Timothy[25], Thomas Ruddy[25], Thomy Tonia[26], David Rigau[27] and James D. Chalmers[28]


BTS Guideline

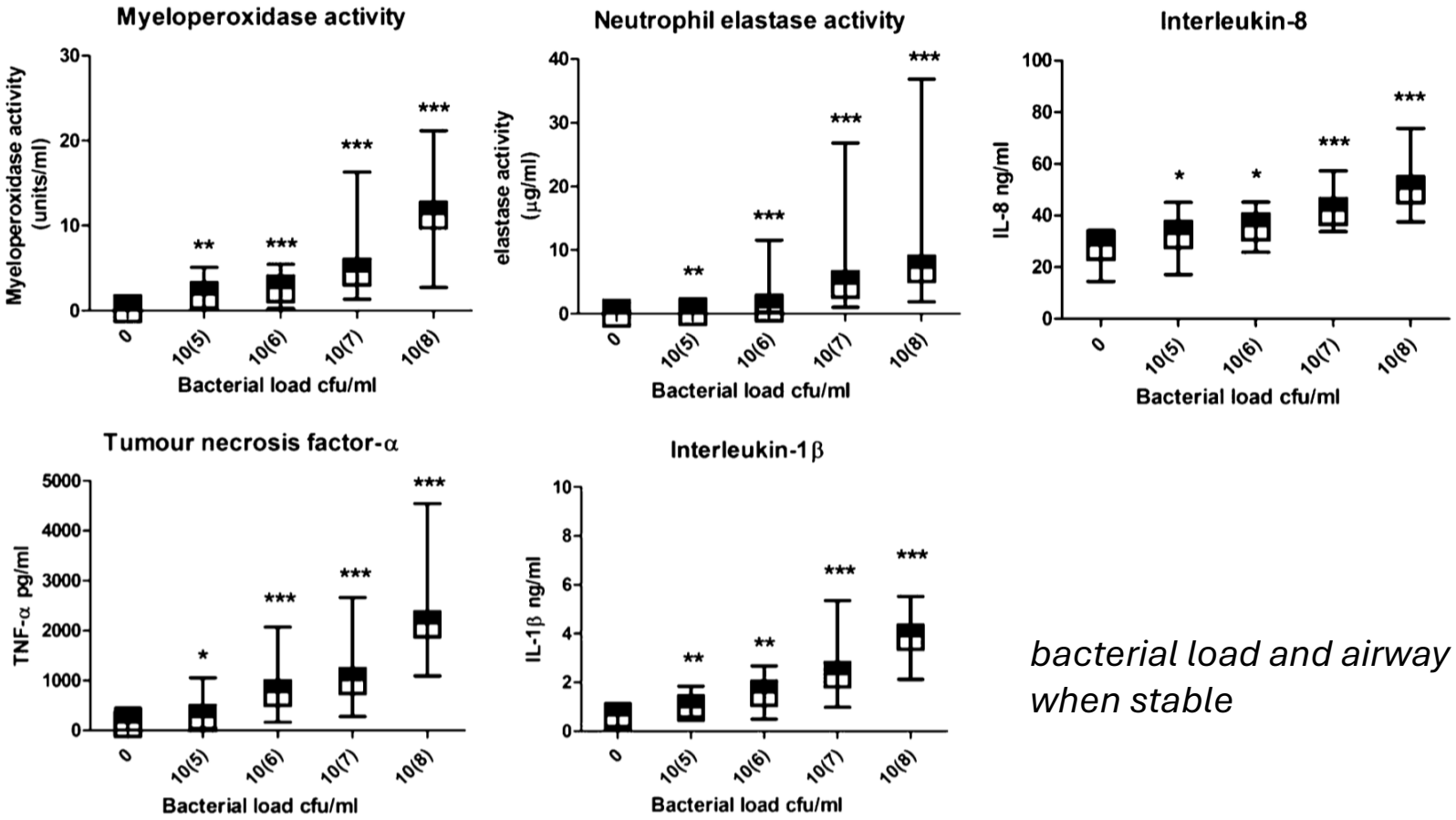
British Thoracic Society Guideline for bronchiectasis in adults

Adam T Hill,[1] Anita L Sullivan,[2] James D Chalmers,[3] Anthony De Soyza,[4] J Stuart Elborn,[5] R Andres Floto,[6,7] Lizzie Grillo,[8] Kevin Gruffydd-Jones,[9] Alex Harvey,[10] Charles S Haworth,[7] Edwin Hiscocks,[11] John R Hurst,[12] Christopher Johnson,[7] W Peter Kelleher,[13,14,15] Pallavi Bedi,[16] Karen Payne,[17] Hashem Saleh,[8] Nicholas J Screaton,[18] Maeve Smith,[19] Michael Tunney,[20] Deborah Whitters,[21] Robert Wilson,[14] Michael R Loebinger[14]

Choi H et al. *Eur Respir J* 2024;63:2400518
Choi H and Chalmers JD *Ann Transl Med* 2023;11:25

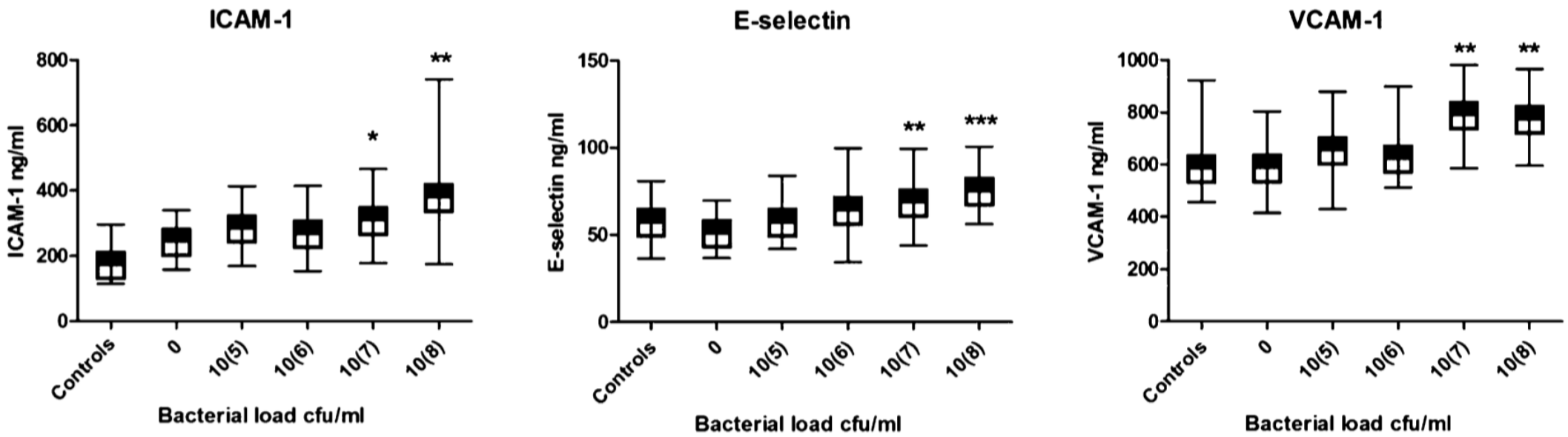
Short- and Long-Term Antibiotic Treatment Reduces Airway and Systemic Inflammation in Non–Cystic Fibrosis Bronchiectasis

James D. Chalmers[1], Maeve P. Smith[2], Brian J. McHugh[1], Cathy Doherty[3], John R. Govan[3], and Adam T. Hill[1,2]



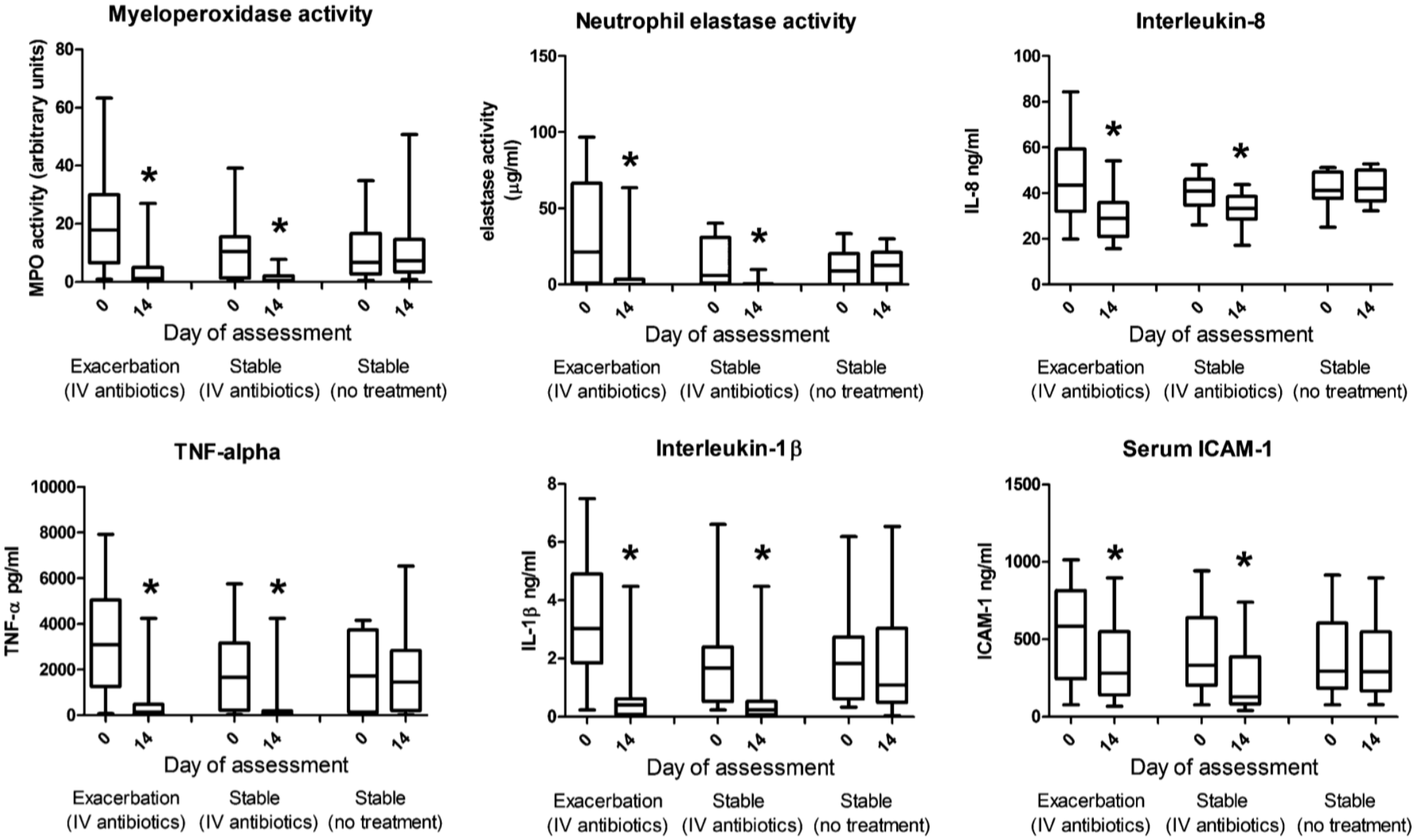
bacterial load and airway inflammation in sputum when stable

Chalmers JD et al. *Am J Respir Crit Care Med* 2012;186:657



bacterial load and systemic inflammation in sputum when stable

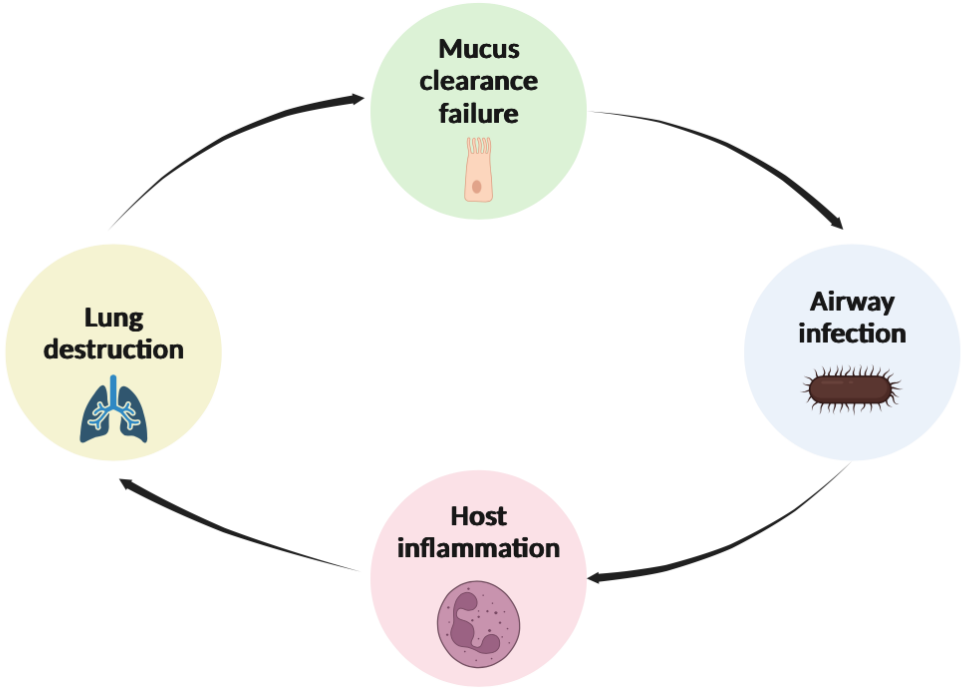
Chalmers JD et al. *Am J Respir Crit Care Med* 2012;186:657



Chalmers JD et al. *Am J Respir Crit Care Med* 2012;186:657

Rationale for using antibiotics

1. Antibiotic treatment reduces bacterial load
2. Reduced bacterial load is followed by reduced airway and systemic inflammation, plus symptoms



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Organism #1 : Pseudomonas aeruginosa		
Piperacillin-tazobactam	S	<=4/4
Ceftazidime-avibactam	S	1/4
Ceftolozane-tazobactam	S	<=1/4
Ceftazidime	S	2
Cefepime	S	2
Aztreonam	S	4
Imipenem	S	2
Meropenem	S	1
Amikacin	S	<=4
Gentamicin	R	<=2
Tobramycin	S	<=2
Colistin	S	<=1
Ciprofloxacin	S	<=0.125
Levofloxacin	S	<=0.5
Carbapenemase	-	Neg

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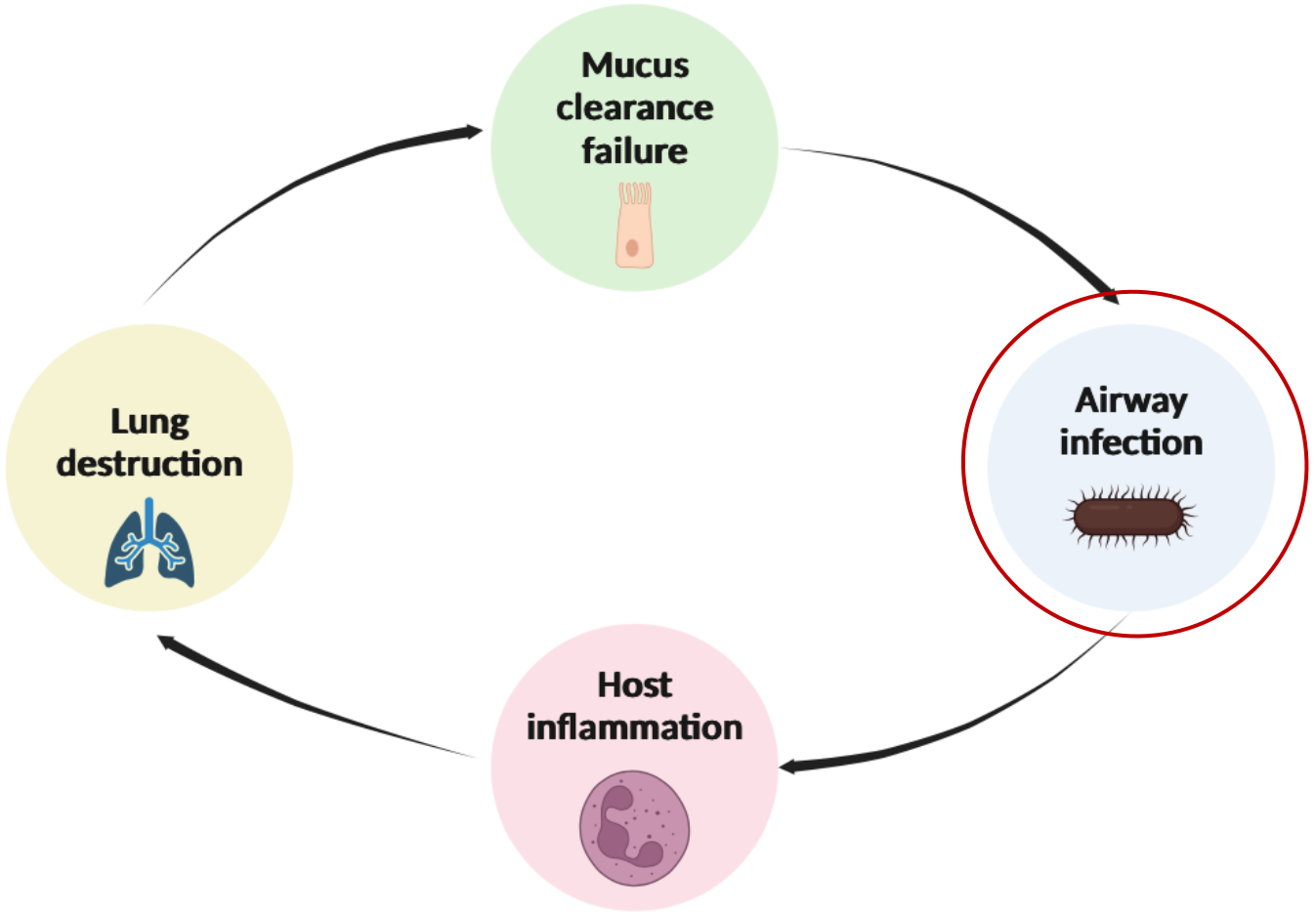
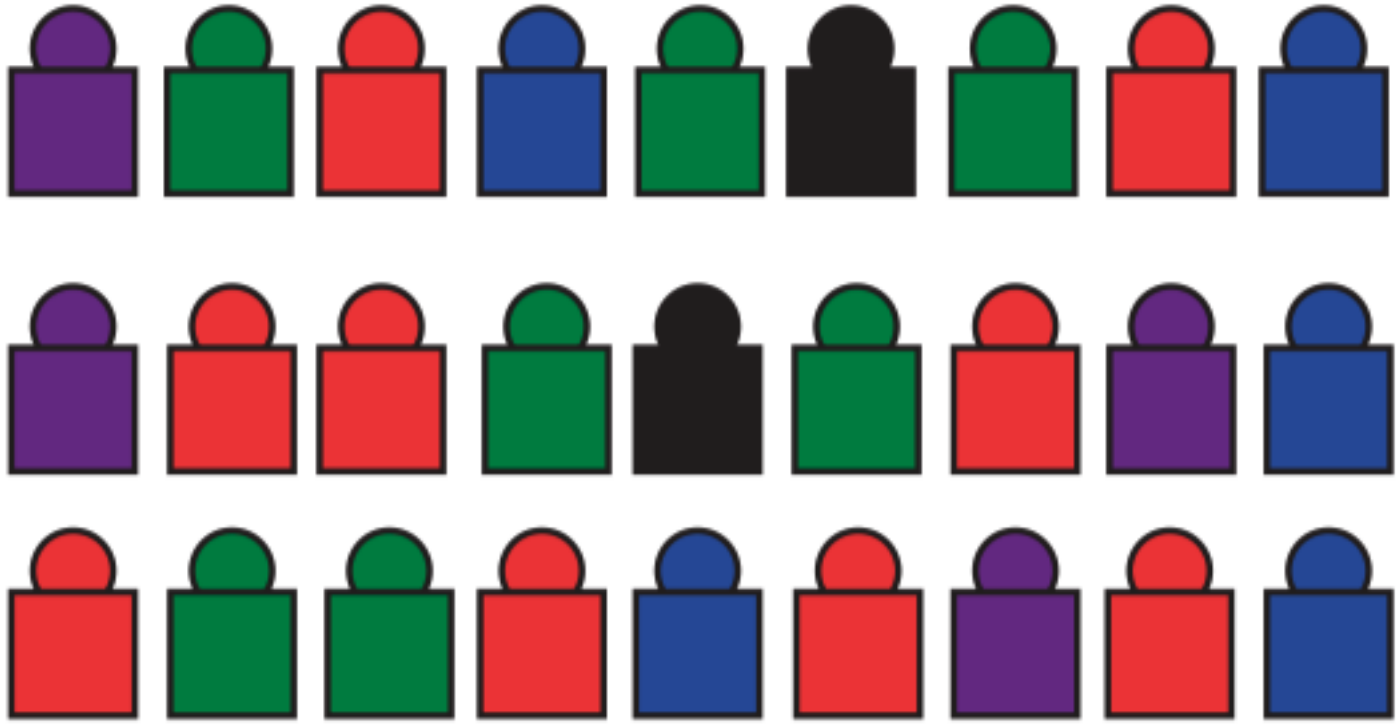
Textbook teaching of exacerbation



Bacterial infection!

Bronchiectasis – heterogeneous disease

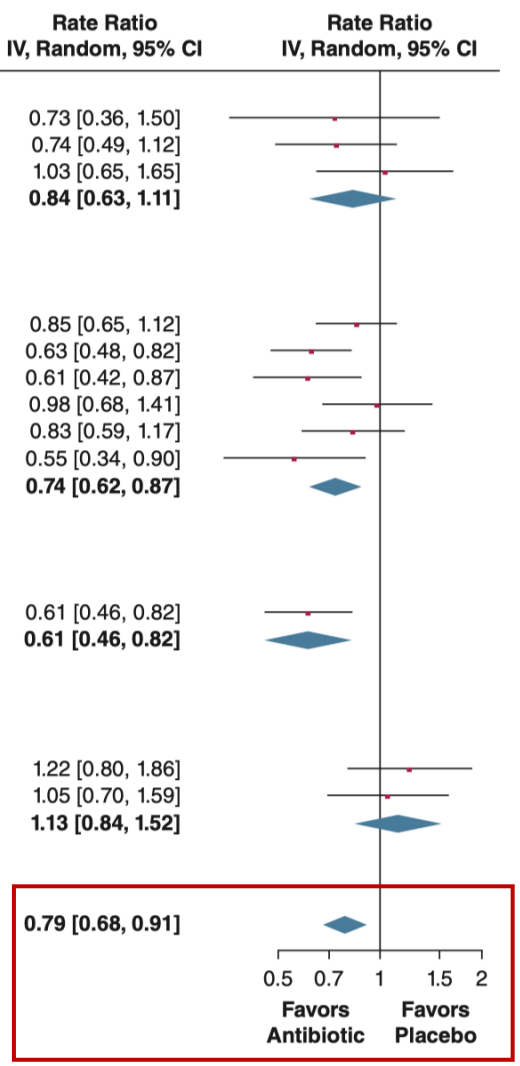


Chalmers JD. *ERS Monograph Bronchiectasis* 2018

Q1. Effect of inhaled antibiotics?

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]
Subtotal (95% CI)			**279**	**219**	**17.3%**	**0.84 [0.63, 1.11]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.26$, df = 2 ($P = .53$); $I^2 = 0\%$						
Test for overall effect: Z = 1.24 ($P = .22$)						
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 ($P = .0009$)						
1.1.4 Aztreonam						
Air-BX1 2014	0.2	0.215	134	132	7.4%	1.22 [0.80, 1.86]
Air-BX2 2014	0.05	0.21	136	138	7.6%	1.05 [0.70, 1.59]
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 ($P = .02$), $I^2 = 68.5\%$						



reducing exacerbation by “20%”

Cordeiro R et al. *Chest* 2024;166:61

Q2. Role of viral infection in exacerbation?

The Impact of the COVID-19 Pandemic on Exacerbations and Symptoms in Bronchiectasis: A Prospective Study

To the Editor:

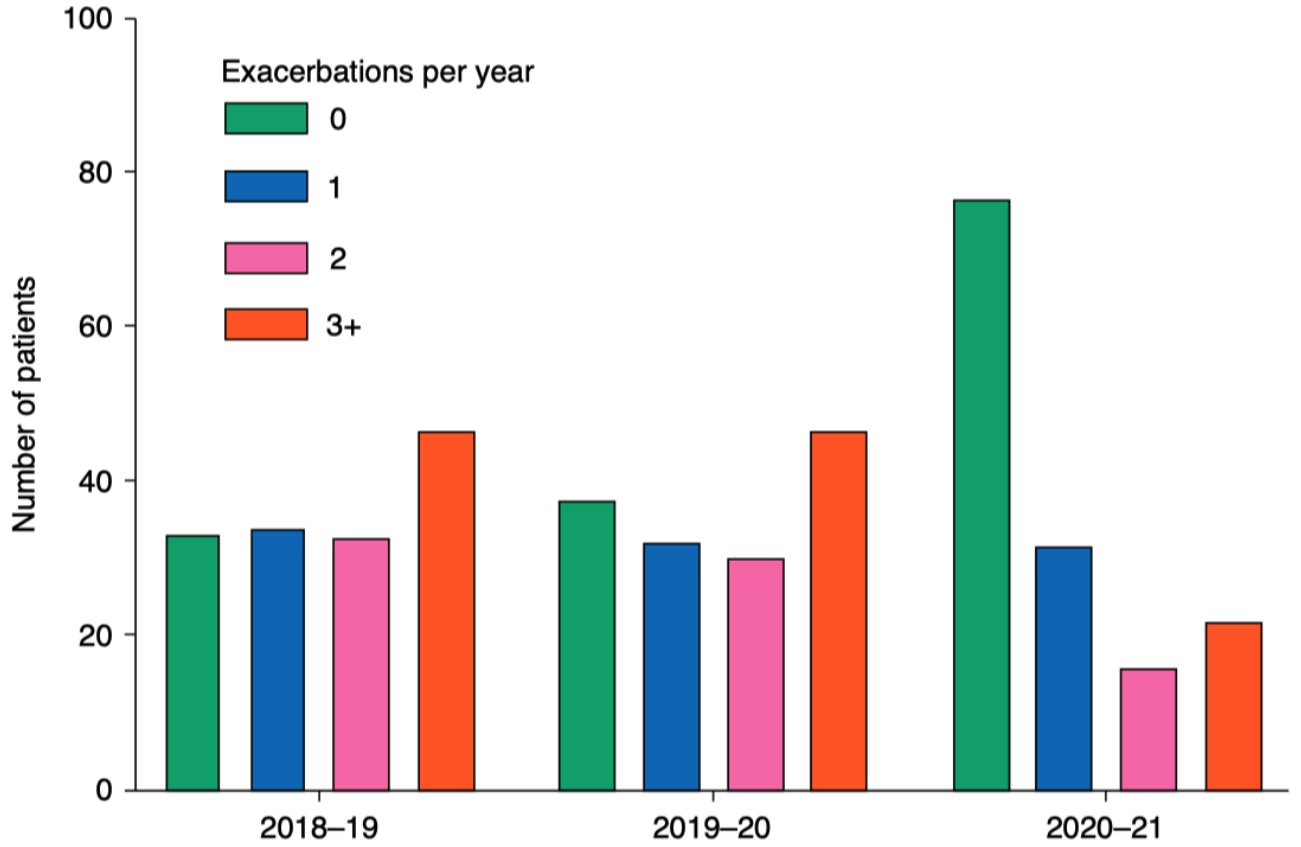


Figure 1. Absolute number of patients experiencing 0, 1, 2, and 3+ exacerbations per year during the 3 years of observation ($n = 147$ total patients for each year).

Crichton ML et al. *Am J Respir Crit Care Med* 2021

Endotypes of Exacerbation in Bronchiectasis
An Observational Cohort Study

Yonghua Gao[1], Hollian Richardson[2], Alison J. Dicker[2], Alun Barton[2], Elena Kuzmanova[2], Michal Shteinberg[3], Lidia Perea[4], Pieter C. Goeminne[5], Erin Cant[2], Chandani Hennayake[2], Jennifer Pollock[2], Hani Abo Leyah[6], Hayoung Choi[7], Eva Polverino[8], Francesco Blasi[9], Tobias Welte[10†], Stefano Aliberti[11], Merete Long[2], Amelia Shoemark[2], Oriol Sibila[4], Jeffrey T. J. Huang[2], and James D. Chalmers[2]

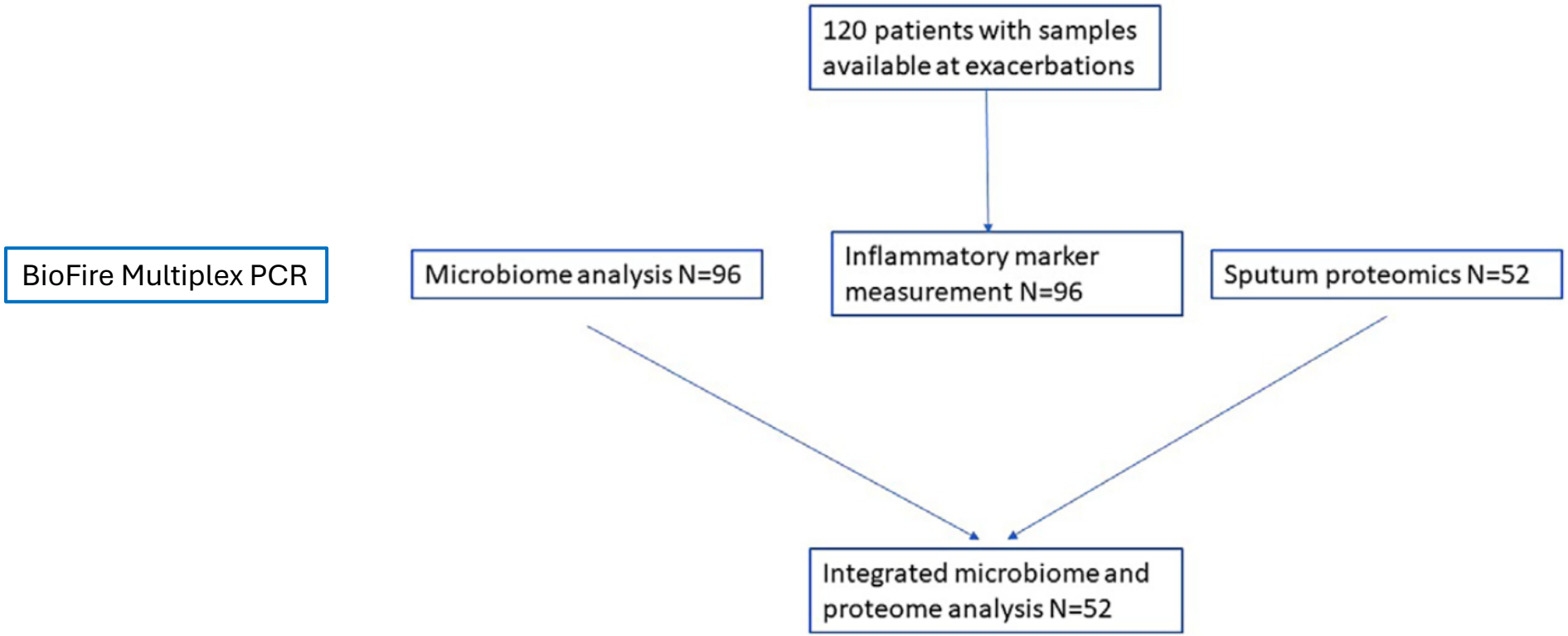


Figure 1. Flow chart showing the number of samples included in each stage of the analysis.

Gao YH et al. *Am J Respir Crit Care Med* 2024;210:77

Table 2. Frequency of Bacteria and Viruses Identified at Exacerbation ($N = 120$ Patients with Bronchiectasis) Using the Biofire Pneumonia PCR Panel

Bacteria	At Least One Bacterium >10^7	At Any Load
⩾1 Bacterium	81 (67.5)	103 (85.8)
2 Bacteria detected	29 (24.2)	33 (27.5)
3 Bacteria detected	12 (10)	17 (14.2)
⩾4 Bacteria detected	6 (5)	8 (6.7)
Haemophilus influenzae	32 (26.7)	61 (50.8)
Pseudomonas aeruginosa	29 (24.2)	41 (34.2)
Staphylococcus aureus	9 (7.5)	24 (20)
Moraxella catarrhalis	10 (8.3)	18 (15)
Streptococcus pneumoniae	7 (5.8)	14 (11.7)
Other gram-negatives (*Escherichia coli*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, *Acinetobacter*, *Serratia marcescens*, *Proteus mirabilis*)	11 (9.2)	31 (25.8)
Viruses	**With Bacterial Coinfection**	**Overall**
⩾1 Virus detected	46 (38.3)	55 (45.8)
2 Viruses detected	12 (10)	16 (13.3)
Rhinovirus	27 (22.5)	37 (30.8)
Parainfluenza virus	6 (5)	10 (8.3)
Respiratory syncytial virus	8 (6.7)	8 (6.7)
Coronavirus	7 (5.8)	8 (6.7)
Influenza A	2 (1.7)	5 (4.2)
Adenovirus	2 (1.7)	2 (1.7)
Influenza B	1 (0.8)	1 (0.8)

Data are given as *n* (%).

Gao YH et al. *Am J Respir Crit Care Med* 2024;210:77

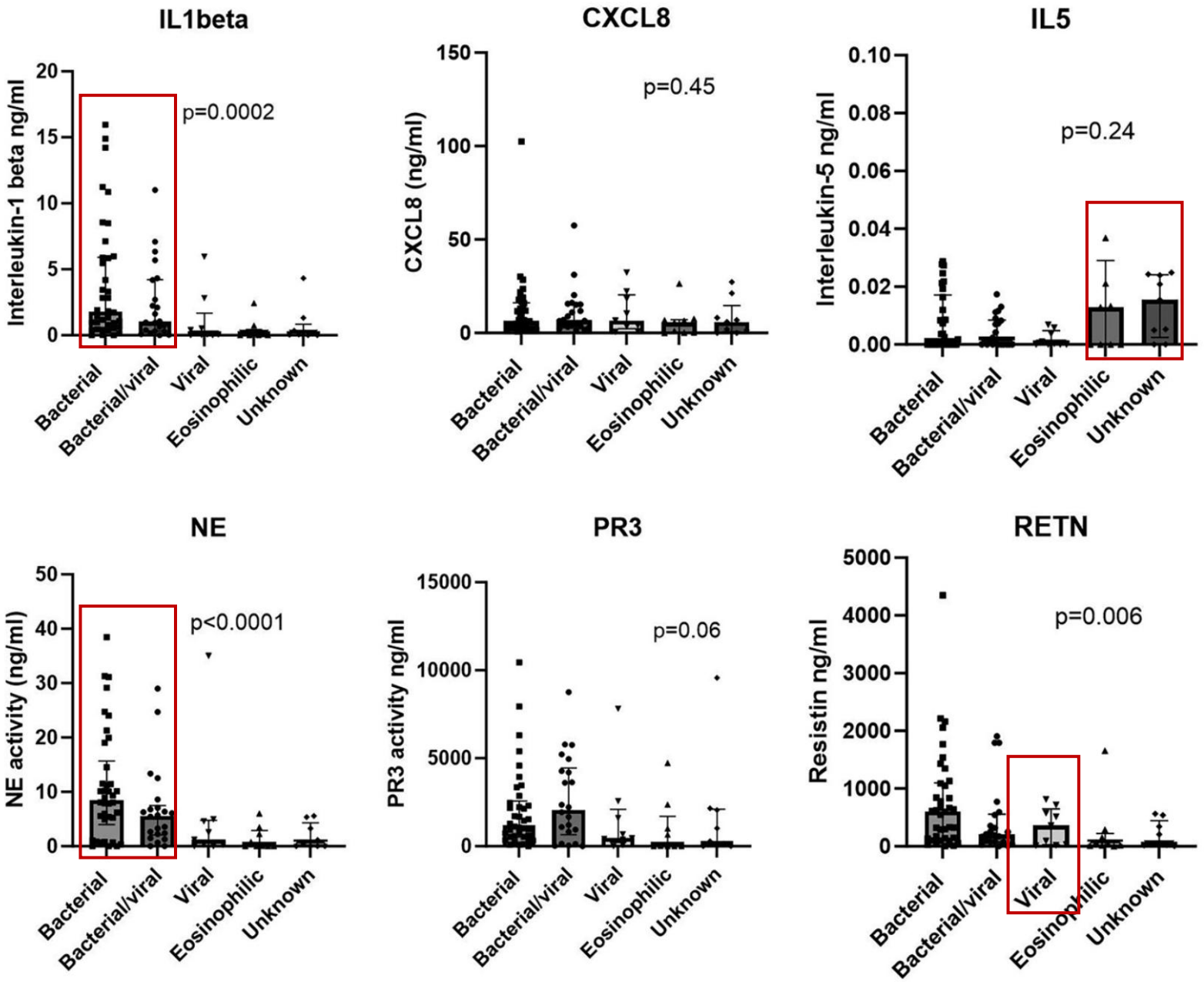


Figure 2. Inflammatory mediators according to inflammatory subtypes of exacerbation. Data are shown as median with interquartile range.

Gao YH et al. *Am J Respir Crit Care Med* 2024;210:77

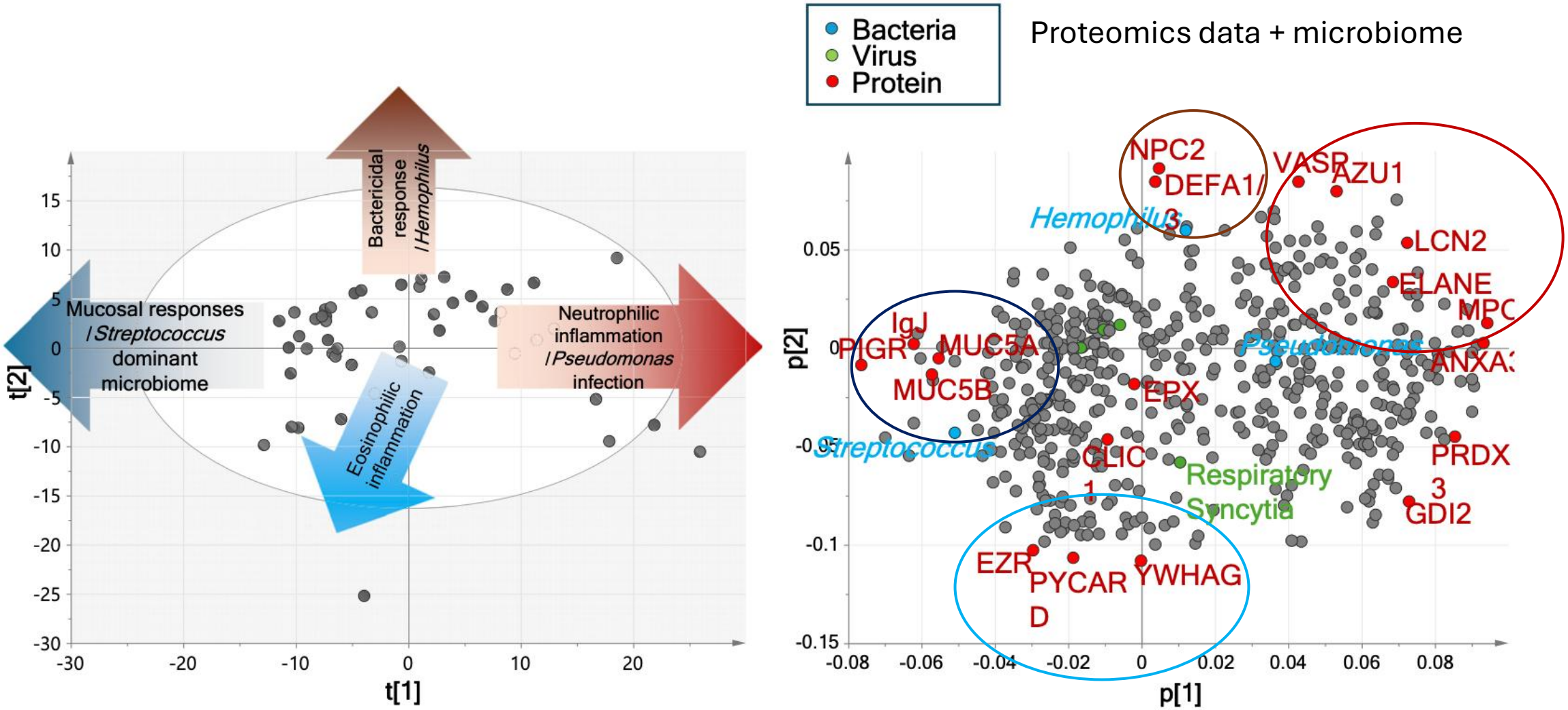
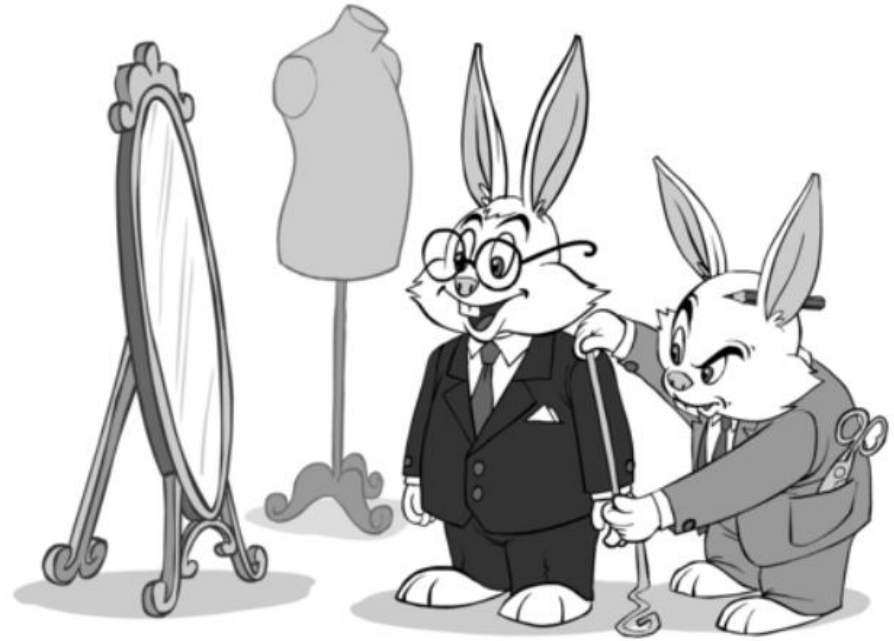


Figure 5. (*A*) Clusters of exacerbation based on 52 exacerbation samples. Principal component analysis. (*B*) Loadings plot illustrating the protein and microbiome parameters associated with distinct microbiome clusters.

Gao YH et al. *Am J Respir Crit Care Med* 2024;210:77

ONE SİZE
FİTS ALL

All exacerbations are the same.



MADE TO
MEASURE

Bronchiectasis exacerbation endotype 1?

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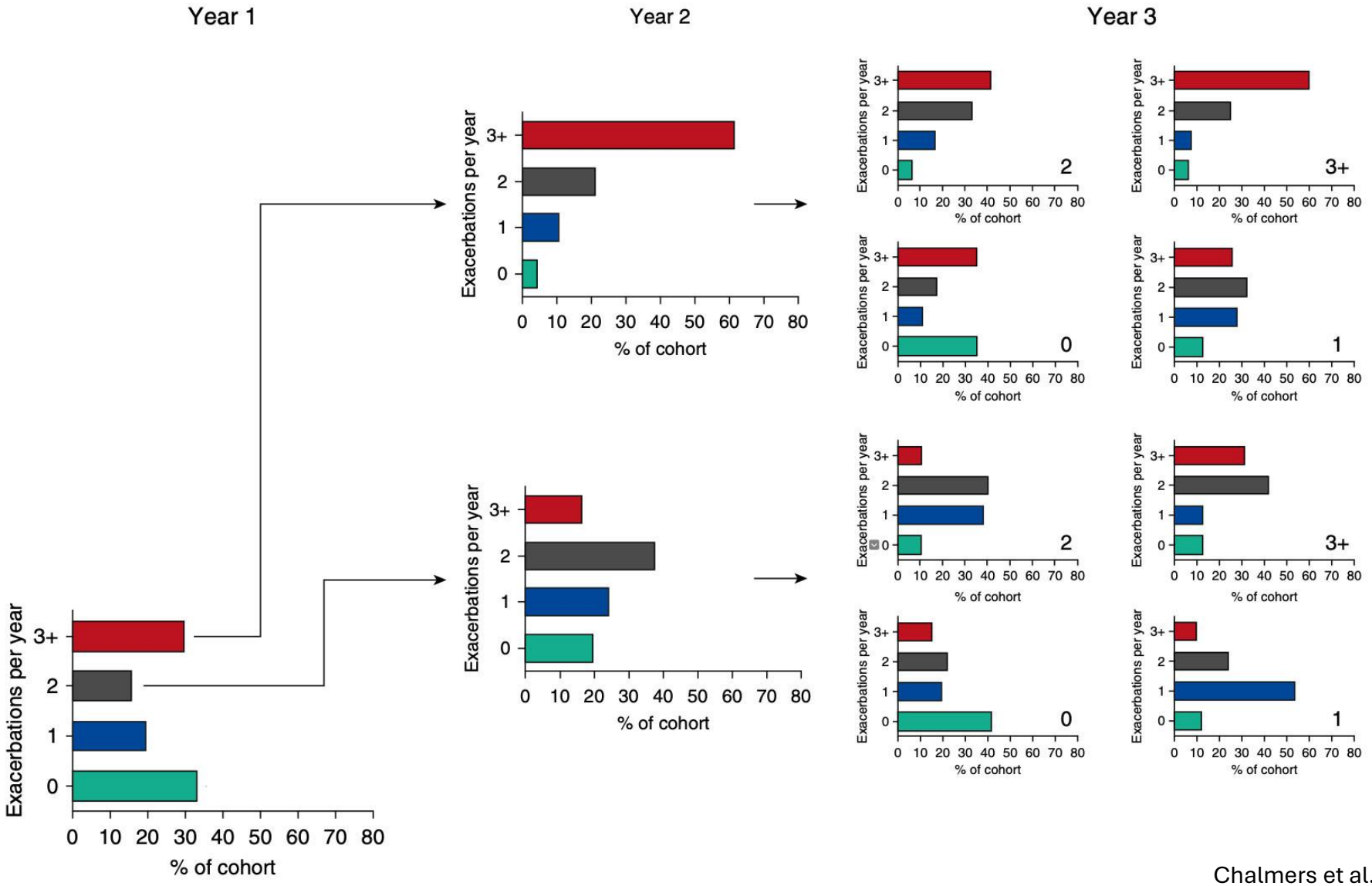
Why should we prevent bronchiectasis exacerbation?



유럽 기관지확장증 환자 608명
→ 5년간 추적

Chalmers et al. *Am J Respir Crit Care Med* 2018;197:1410

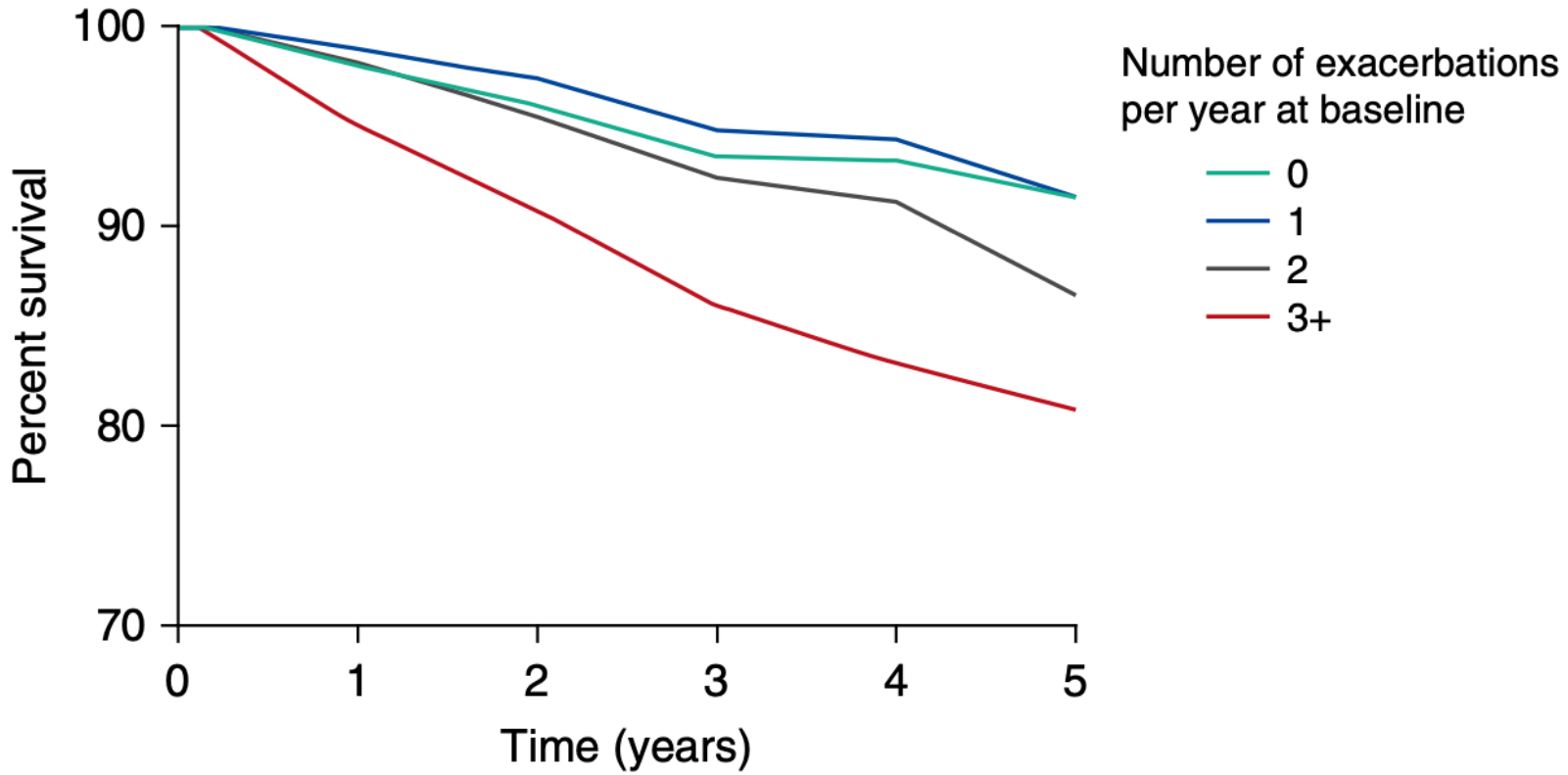
Table 2. Adjusted and Unadjusted Incident Rate Ratios for Exacerbation Frequency during Follow-up

	Unadjusted			Adjusted		
	IRR	95% CI	*P* Value	IRR	95% CI	*P* Value
0 Exacerbations	1.0 (reference)			1.0 (reference)		
1 Exacerbation	1.73	1.47–2.02	<0.0001	1.81	1.54–2.12	<0.0001
2 Exacerbations	3.14	2.70–3.66	<0.0001	3.07	2.62–3.60	<0.0001
3 Exacerbations	5.97	5.27–6.78	<0.0001	5.18	4.51–5.95	<0.0001
Age (per 10 yr)	1.00	0.96–1.03	0.8	0.96	0.95–1.03	0.6
Sex (M)	1.11	1.00–1.23	0.04	0.95	0.86–1.06	0.4
MRC dyspnea score	1.24	1.19–1.29	<0.0001	1.02	0.97–1.07	0.4
FEV_1% predicted (per 10%)	0.88	0.87–0.90	<0.0001	0.96	0.94–0.98	0.001
Reiff score	1.04	1.03–1.06	<0.0001	1.02	1.00–1.03	0.05
Smoking history	1.22	1.10–1.35	<0.0001	0.95	0.85–1.06	0.3
Haemophilus influenzae	1.07	0.96–1.20	0.2	1.13	1.01–1.28	0.04
Moraxella catarrhalis	0.94	0.78–1.14	0.5	0.94	0.77–1.15	0.5
Staphylococcus aureus	1.19	0.97–1.45	0.1	1.08	0.88–1.32	0.5
Enterobacteriaceae	1.30	1.08–1.57	0.006	0.99	0.82–1.20	0.9
Pseudomonas aeruginosa	1.94	1.69–2.23	<0.0001	1.20	1.04–1.40	0.01
Asthma	1.22	1.03–1.44	0.02	1.16	0.98–1.38	0.09
COPD	1.89	1.66–2.16	<0.0001	1.43	1.22–1.67	<0.0001
Idiopathic	0.72	0.65–0.79	<0.0001	0.92	0.83–1.02	0.1

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; IRR = incident rate ratio; MRC = Medical Research Council.

Baseline exacerbation	Adjusted IRR (95% CI) for future exacerbation
1 per year	**1.8** (1.54–2.12)
2 per year	**3.1** (2.62–3.60)
3+ per year	**5.2** (4.51–5.95)

Chalmers JD et al. *Am J Respir Crit Care Med* 2018;197:1410



Numbers at risk

0	657	654	600	554	522	153
1	452	444	402	381	351	134
2	497	490	437	407	376	196
3 or more	966	958	836	771	694	365

Chalmers JD et al. *Am J Respir Crit Care Med* 2018;197:1410

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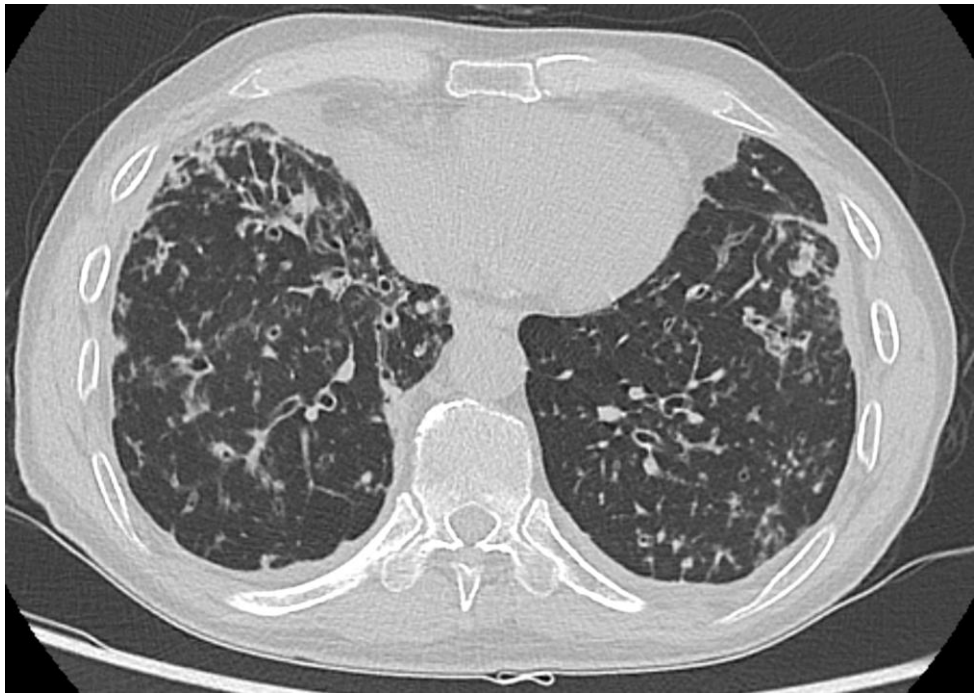
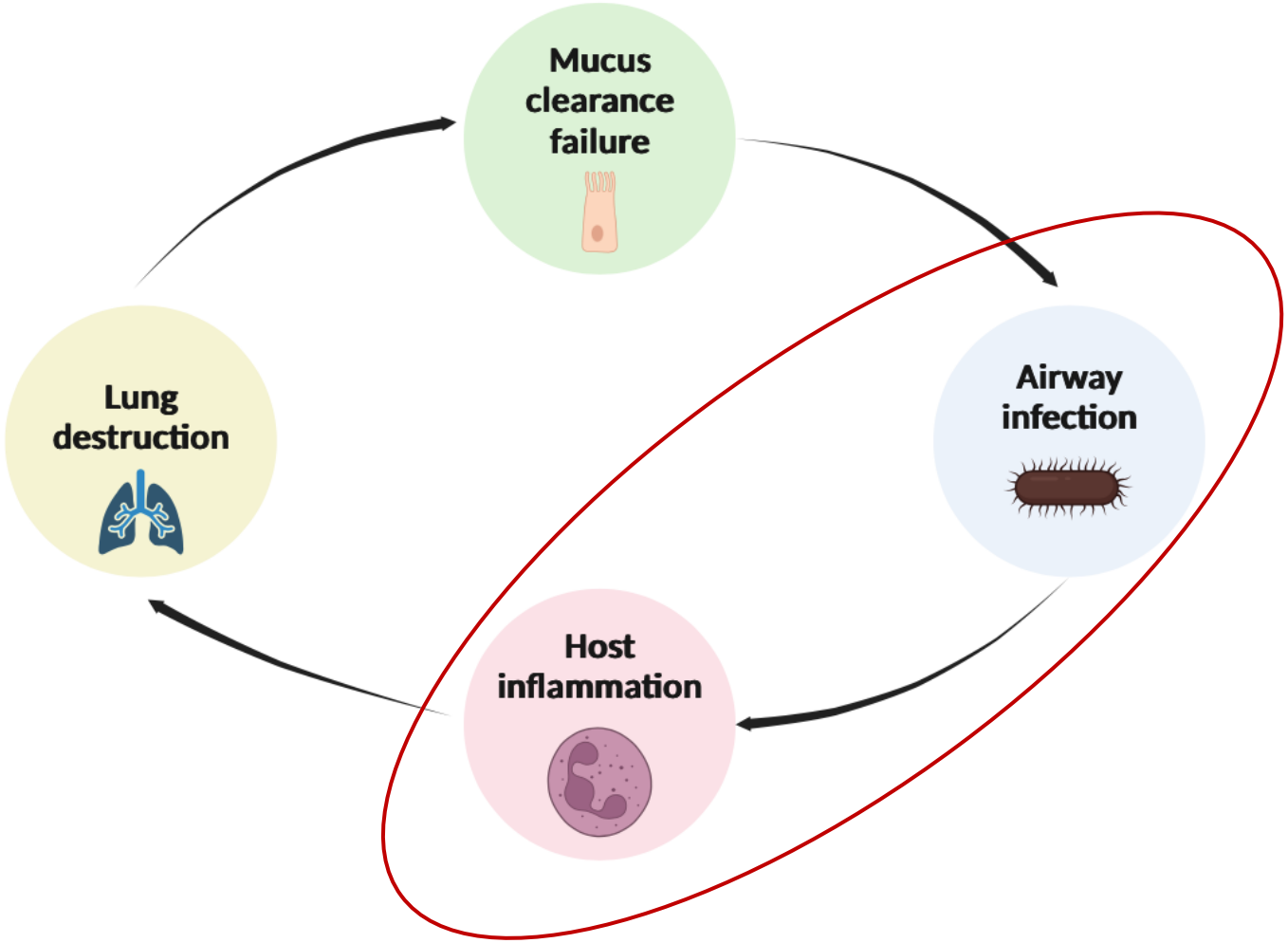
Future 기관지확장증 악화 반복?



Exacerbation and disease activity

bronchiectasis with high disease activity



Im Y et al. *Tuberc Respir Dis* 2025;88:109
Flume et al. *Lancet* 2018;392:880

Rationale for inhaled antibiotics in bronchiectasis?

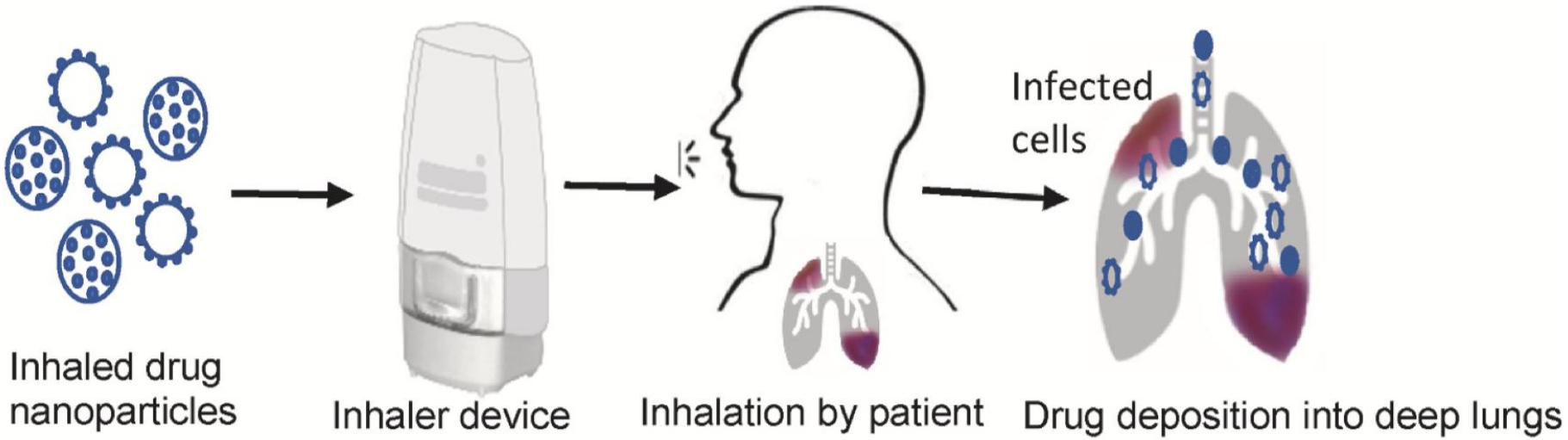


Fig. 1. Schematic diagram of drug deposition into deep lungs by inhalation.

Choi H et al. *Eur Respir J* 2024;63:2400518
Islam N and Reid D *Respir Med* 2024;227:107661

Summary of RCTs of inhaled antibiotics for bronchiectasis

Agent and study	Primary outcome	
Ciprofloxacin DPI	Bacterial load	**Success**
Ciprolofixacin DPI – RESPIRE 1	Exacerbation	**Failure**
Ciprolofixacin DPI – RESPIRE 2	Exacerbation	**Failure**
Liposomal ciprofloxacin – ORBIT 1	Exacerbation	**Failure**
Aztreonam – AIR-BX1 and AIR-BX2	Quality of life	**Failure**
Tobramycin	Bacterial load	**Success**
Tobramycin – TORNASOL	Bacterial load and QoL	**Success**
Tobramycin – BATTLE	Exacerbation	**Failure**
Tobramycin inhalation powder - iBEST	Bacterial load	**Success**
Gentamicin	Bacterial load	**Success**
Colistin – PROMIS 1	Time to first exacerbation	**Failure**
…	…	

Choi H et al. *Eur Respir J* 2024;63:2400518

Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with *Pseudomonas aeruginosa* (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials

Charles S Haworth, Diana Bilton, James D Chalmers, Angela M Davis, Juergen Froehlich, Igor Gonda, Bruce Thompson, Adam Wanner, Anne E O'Donnell

Key inclusion criteria

1. At least **two exacerbations** in the past 12 months
2. Chronic ***P. aeruginosa*** infection

Haworth CS et al. *Lancet Respir Med* 2019; 7:213

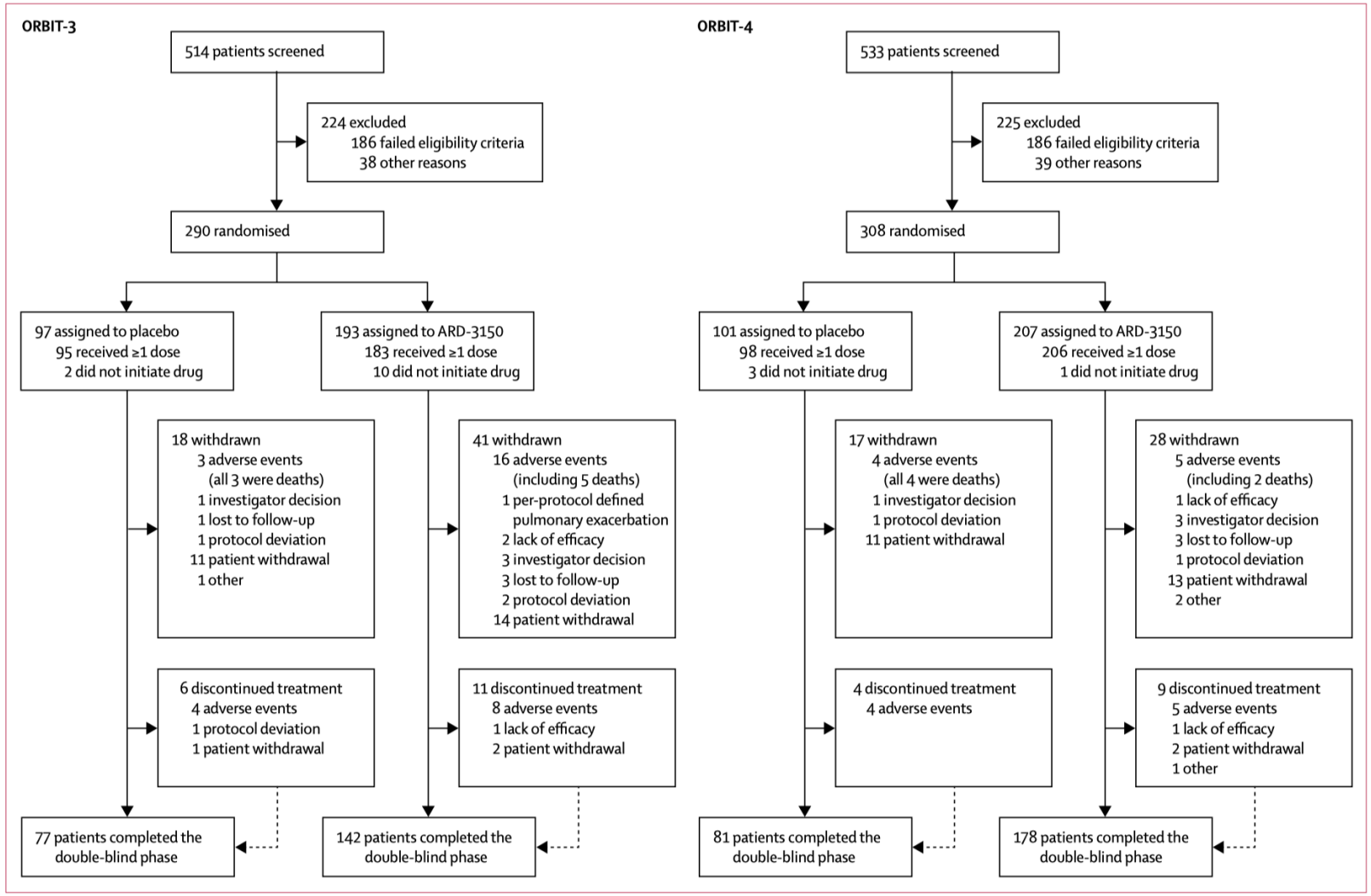


Figure 1: **Trial profiles**

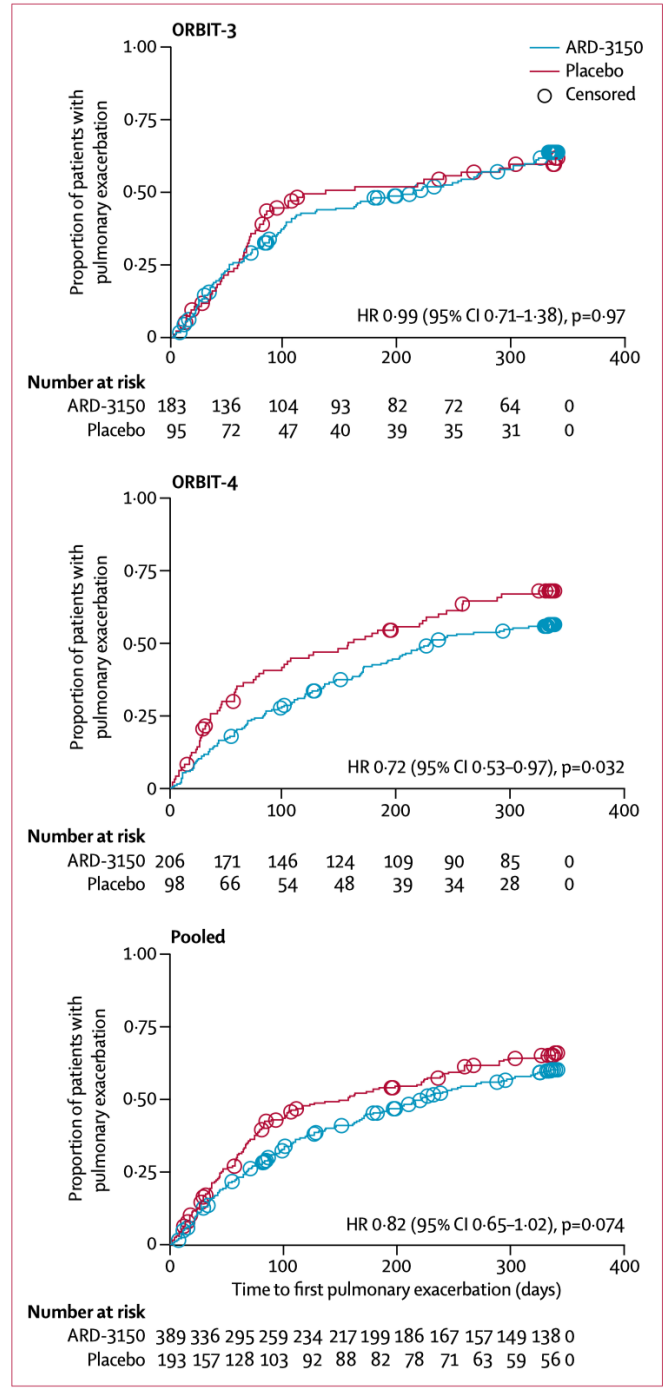


Figure 2: **Time to first pulmonary exacerbation**

Haworth CS et al. *Lancet Respir Med* 2019; 7:213

ORIGINAL ARTICLE

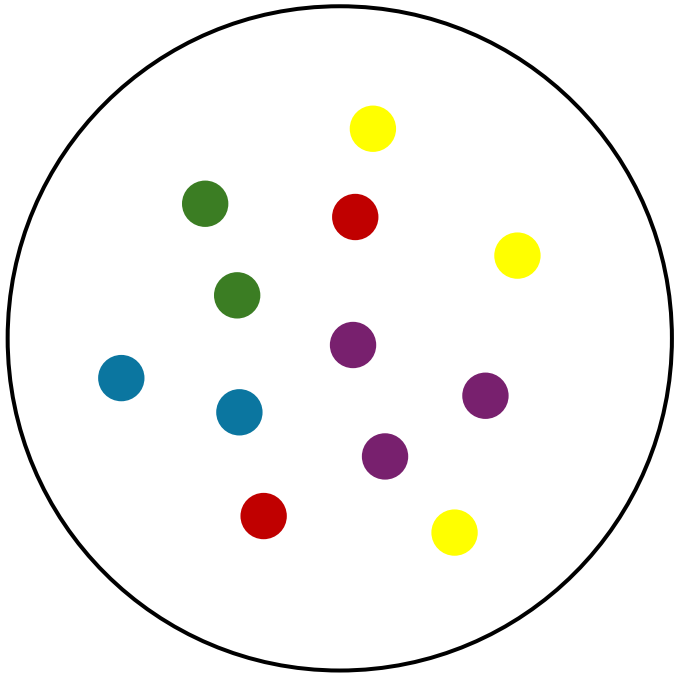
Endotypes of *Pseudomonas aeruginosa* Infection in Bronchiectasis Are Associated with Inhaled Antibiotic Response

Results from Two Randomized, Double-Blind, Placebo-controlled Phase III Trials (ORBIT 3 and ORBIT 4)

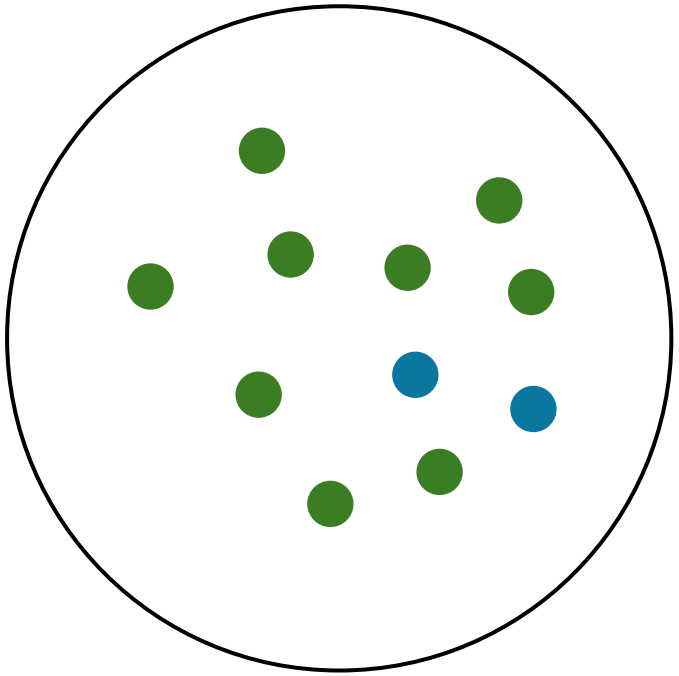
Rebecca C. Hull[1], Jamie Stobo[1], Hani Abo-Leyah[1], Hollian Richardson[1], Daniela Alferes de Lima Headley[1], Merete B. Long[1], Chandani Hennayake[1], Amy Gilmour[1], Emma D. Johnson[1], Michael Tunney[4], Alison J. Dicker[2], Eleanor Kewin[2], Jeffrey T. J. Huang[3], Charles S. Haworth[5], and James D. Chalmers[1]

- Endotypes of *P. aeruginosa* infection in bronchiectasis
  - Sputum samples – ORBIT-3 and ORBIT-4
  - **Microbiome** – 16s rRNA sequencing
  - Inflammation – proteomics

Hull RC et al. *Am J Respir Crit Care Med* 2025; 8:1397

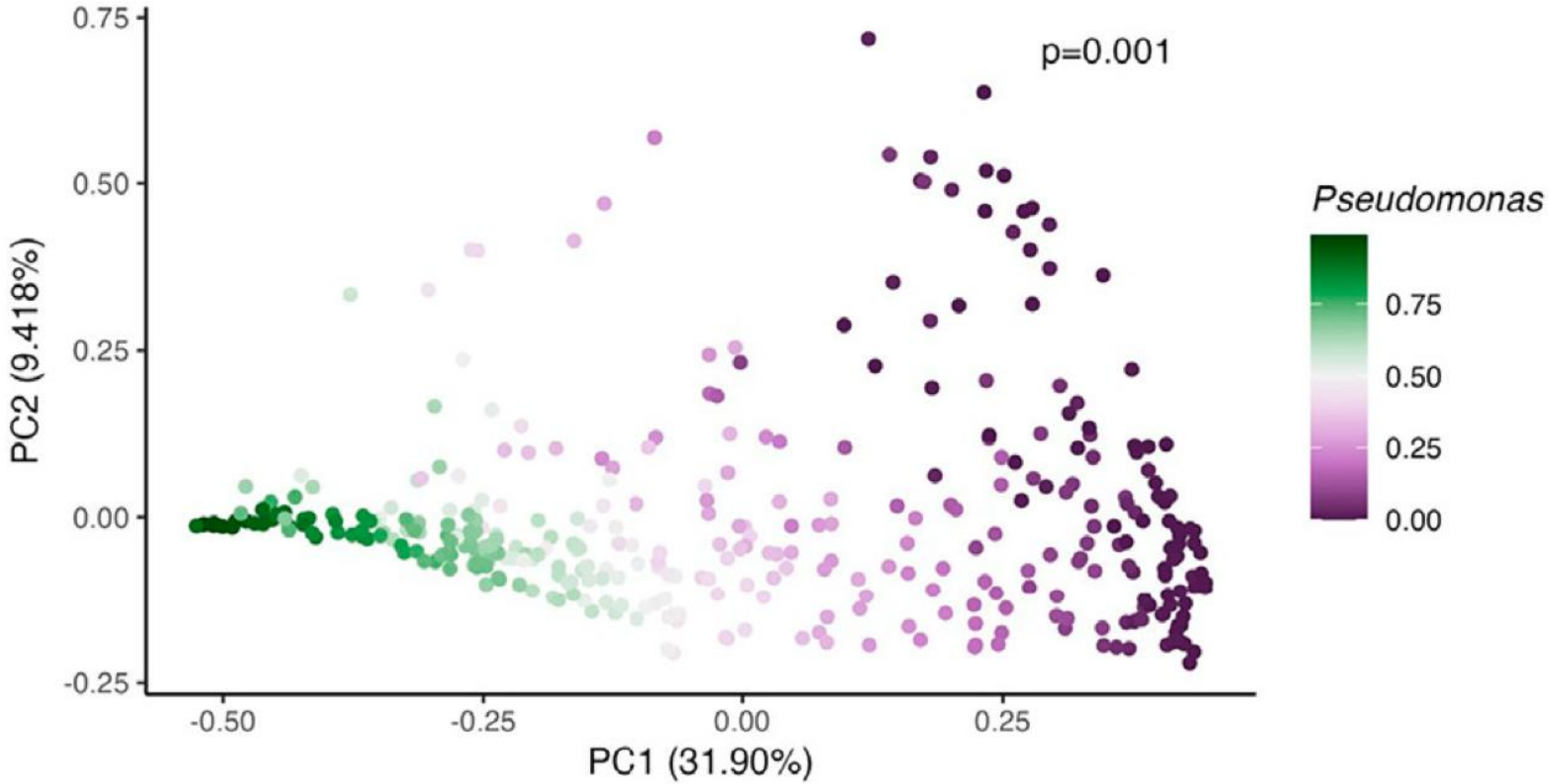


High diversity
= Stability and resistance against pathogens



Low diversity (dysbiosis)
= Diseased state

Richardson HR et al. *Eur Respir Rev* 2019; 28:190048



Microbiome diversity

Hull RC et al. *Am J Respir Crit Care Med* 2025; 8:1397

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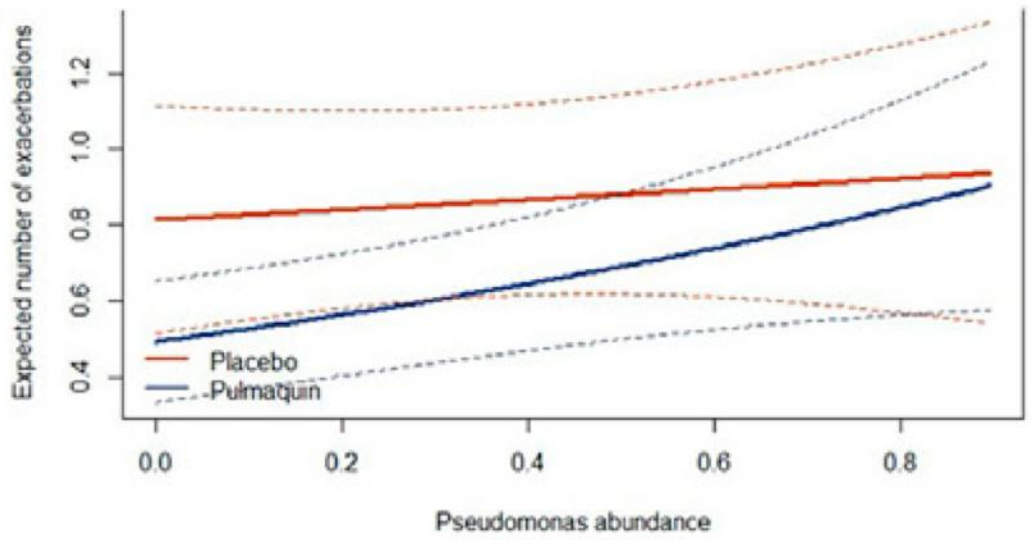
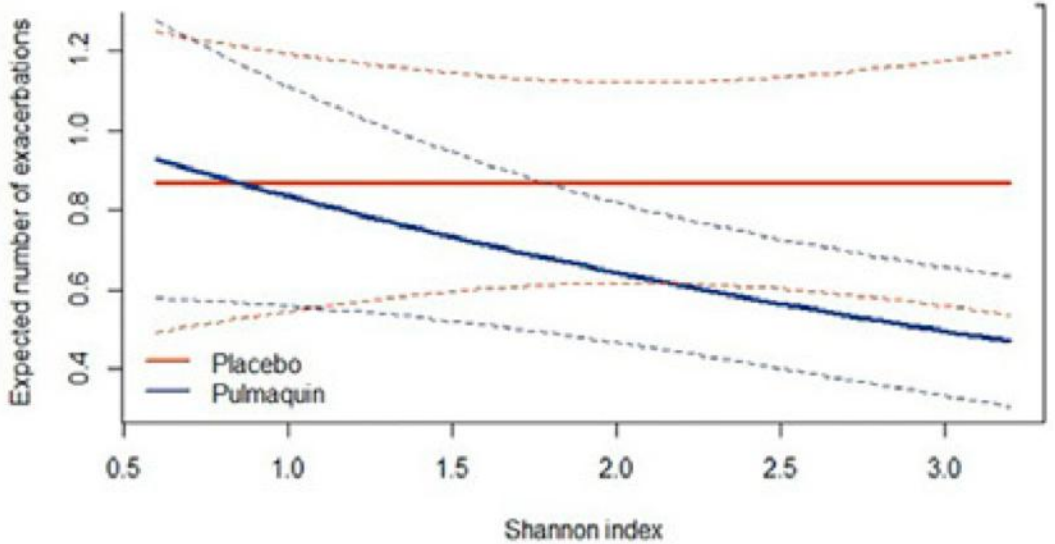


Pseudomonas abundance,
in the microbiome, increases

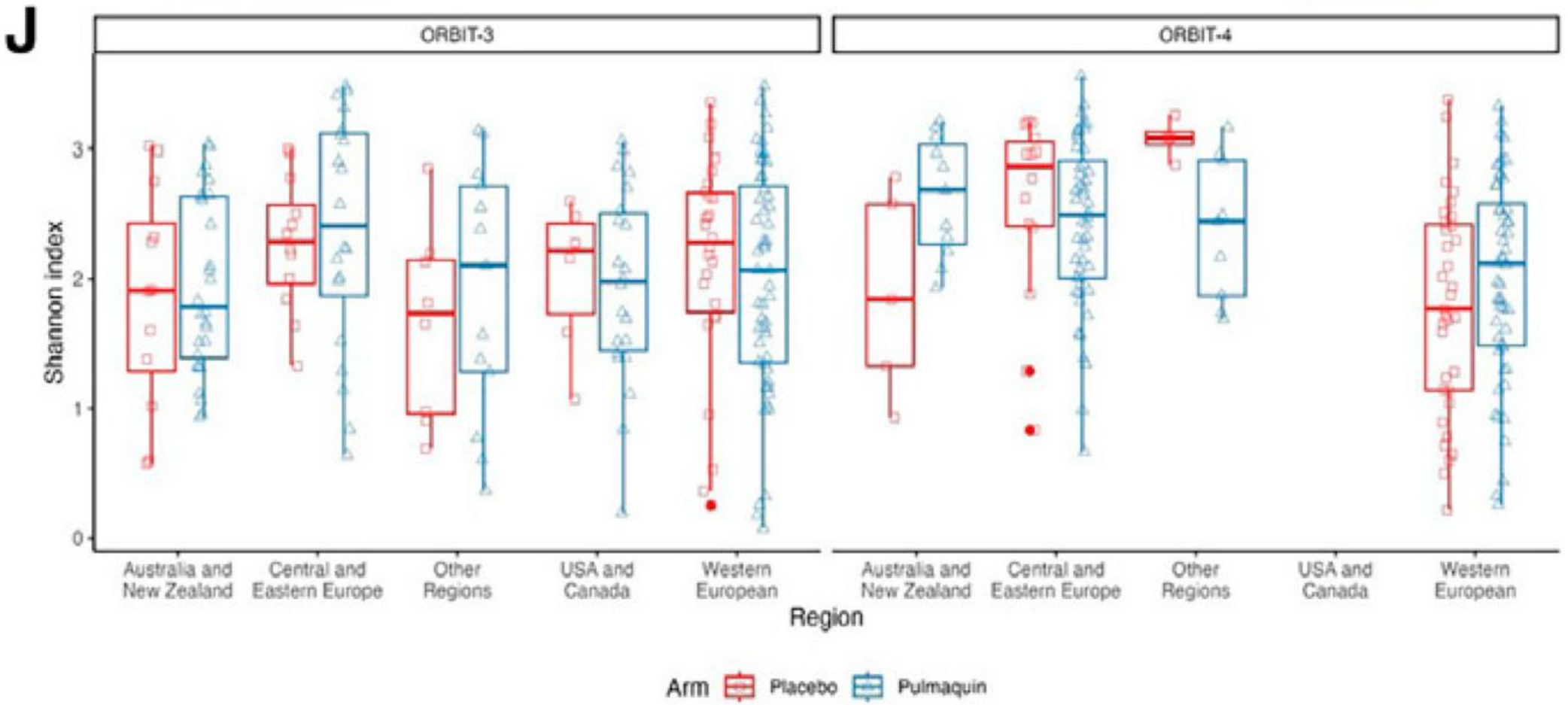
I



Microbiome diversity increases

Hull RC et al. *Am J Respir Crit Care Med* 2025; 8:1397

Failure **Success**



Hull RC et al. *Am J Respir Crit Care Med* 2025; 8:1397

Treatment estimates of two RCTs

	Failure	Success
	ORBIT-3	**ORBIT-4**
Published data		
Rate ratio (95% CI)	0.85 (0.65–1.12)	0.63 (0.48–0.82)
Adjusted 1. Microbiome profile 2. Geographic region		
Rate ratio (95% CI)	**0.81** (0.54–1.22)	**0.82** (0.56–1.22)

Hull RC et al. *Am J Respir Crit Care Med* 2025; 8:1397

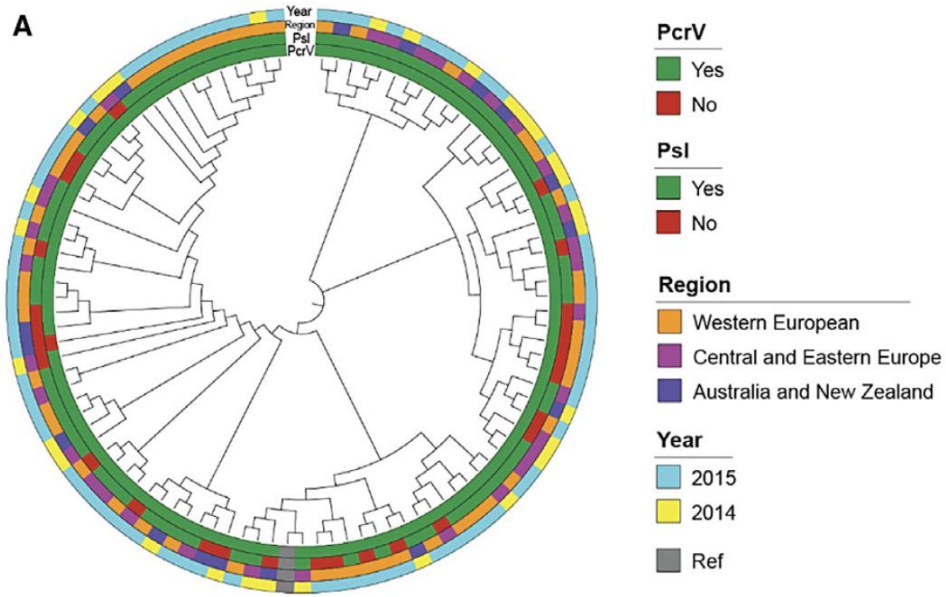
ORIGINAL ARTICLE

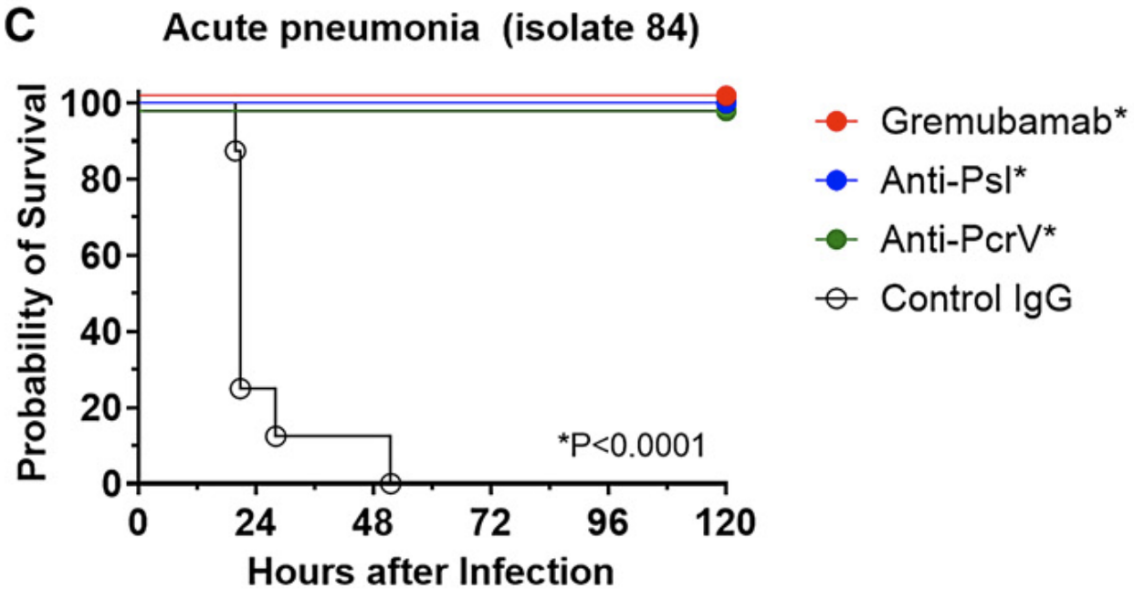
A Bispecific Monoclonal Antibody Targeting Psl and PcrV Enhances Neutrophil-Mediated Killing of *Pseudomonas aeruginosa* in Patients with Bronchiectasis

Merete B. Long[1], Amy Gilmour[1], Margaret Kehl[2], David E. Tabor[2], Ashley E. Keller[2], Paul Warrener[2], Vancheswaran Gopalakrishnan[2], Sanna Rosengren[3], Megan L. Crichton[1], Eve McIntosh[1], Yan Hui Giam[1], Holly R. Keir[1], Wayne Brailsford[4], Rod Hughes[5], Maria G. Belvisi[4], Bret R. Sellman[2], Antonio DiGiandomenico[2], and James D. Chalmers[1]

Gremubamab (monoclonal Ab binding Psl and PcrV)

- **Psl**: anchors biofilm and shields bacteria from immune defences
- **PcrV**: acute virulence via toxin injection





Development stage?

- GREAT-2 (Phase 2a) completed
- CLEAR (Phase 2b) and ICON (Phase 3) planning

Long MB et al. *Am J Respir Crit Care Med* 2024;210:35

Summary

- Bronchiectasis exacerbation – identification and antibiotics
- Exacerbations may not be the same
- Exacerbation prevention is important – the effect of controlling infection is limited?

감사합니다

Thank you~!