The impact of NTM and Pseudomonas on Non-Cystic Fibrosis Bronchiectasis

2019-6-23

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Outline

- Introduction
- The assessment of Non-Cystic Fibrosis Bronchiectasis (Non-CF BE)
- The impact of NTM and Pseudomonas on Non-CF BE
- Summary

Review Article

Medical Progress

BRONCHIECTASIS

ALAN F. BARKER, M.D.

This affection of the bronchia is always produced by chronic catarrh, or by some other disease attended by long, violent, and often repeated fits of coughing.

R.T.H. Laënnec[1]

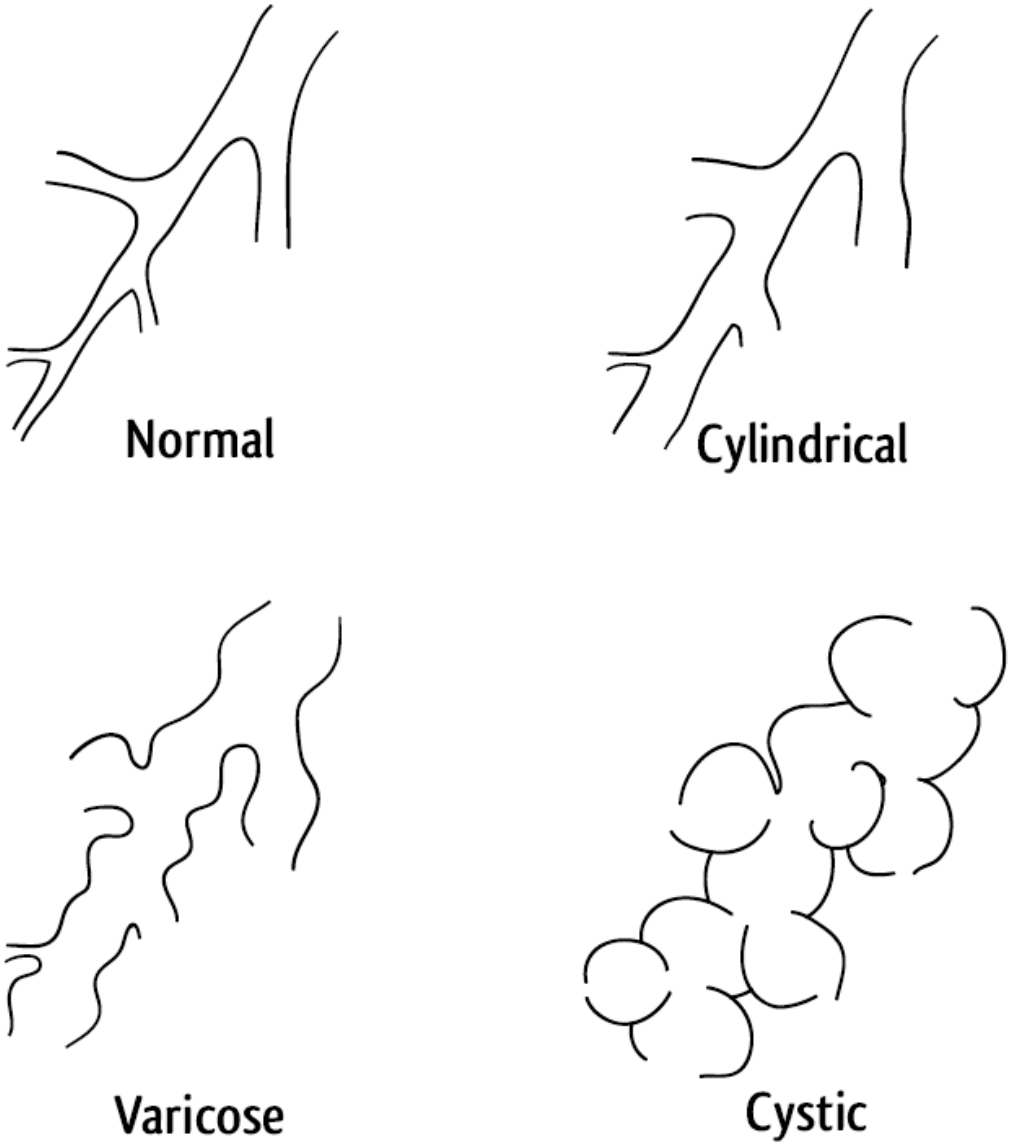
BRONCHIECTASIS is an uncommon disease with the potential to cause devastating illness, including repeated respiratory infections requiring antibiotics, disabling productive cough, shortness of breath, and occasional hemoptysis. Landmarks in the history of bronchiectasis include the vivid descriptions of patients with suppurative phlegm that appeared in the writings of René Théophile Hyacinthe Laënnec in the early 19th century; the 1922 introduc-

dilated airways alone and is sometimes seen as a residual effect of pneumonia; varicose bronchiectasis (so named because its appearance is similar to that of varicose veins) is characterized by focal constrictive areas along the dilated airways that result from defects in the bronchial wall; and saccular or cystic bronchiectasis is characterized by progressive dilatation of the airways, which end in large cysts, saccules, or grape-like clusters (this finding is always indicative of the most severe form of bronchiectasis).[2]

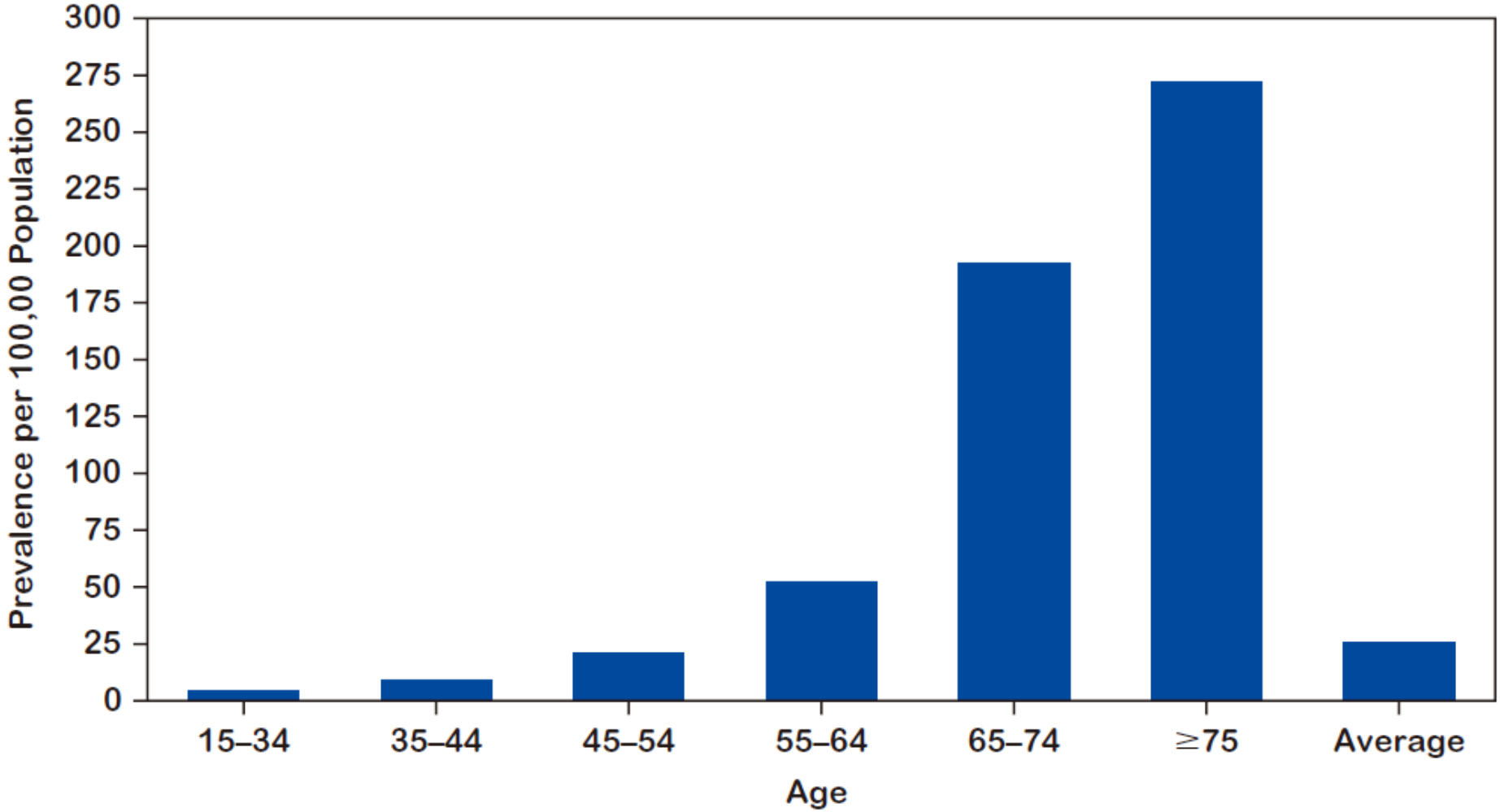
The prevalence of bronchiectasis in the United States and worldwide is unknown. There are reports of high prevalence in relatively isolated populations with poor access to health care and high rates of respiratory tract infections during childhood, such as Alaskan Natives in the Yukon–Kuskokwim Delta.[3]

PATHOPHYSIOLOGY

Bronchiectasis is primarily a disease of the bronchi and bronchioles involving a vicious circle of transmural infection and inflammation with mediator release.[4] Illness is related to retained inflammatory secretions and microbes that cause obstruction and damage


Normal
Cylindrical
Varicose
Cystic

Prevalence of Bronchiectasis



Bronchiectasis increases with age. It is likely to be much more common than reported here because it is not usually detected, reported, or treated (2).

Pathophysiology of Bronchiectasis

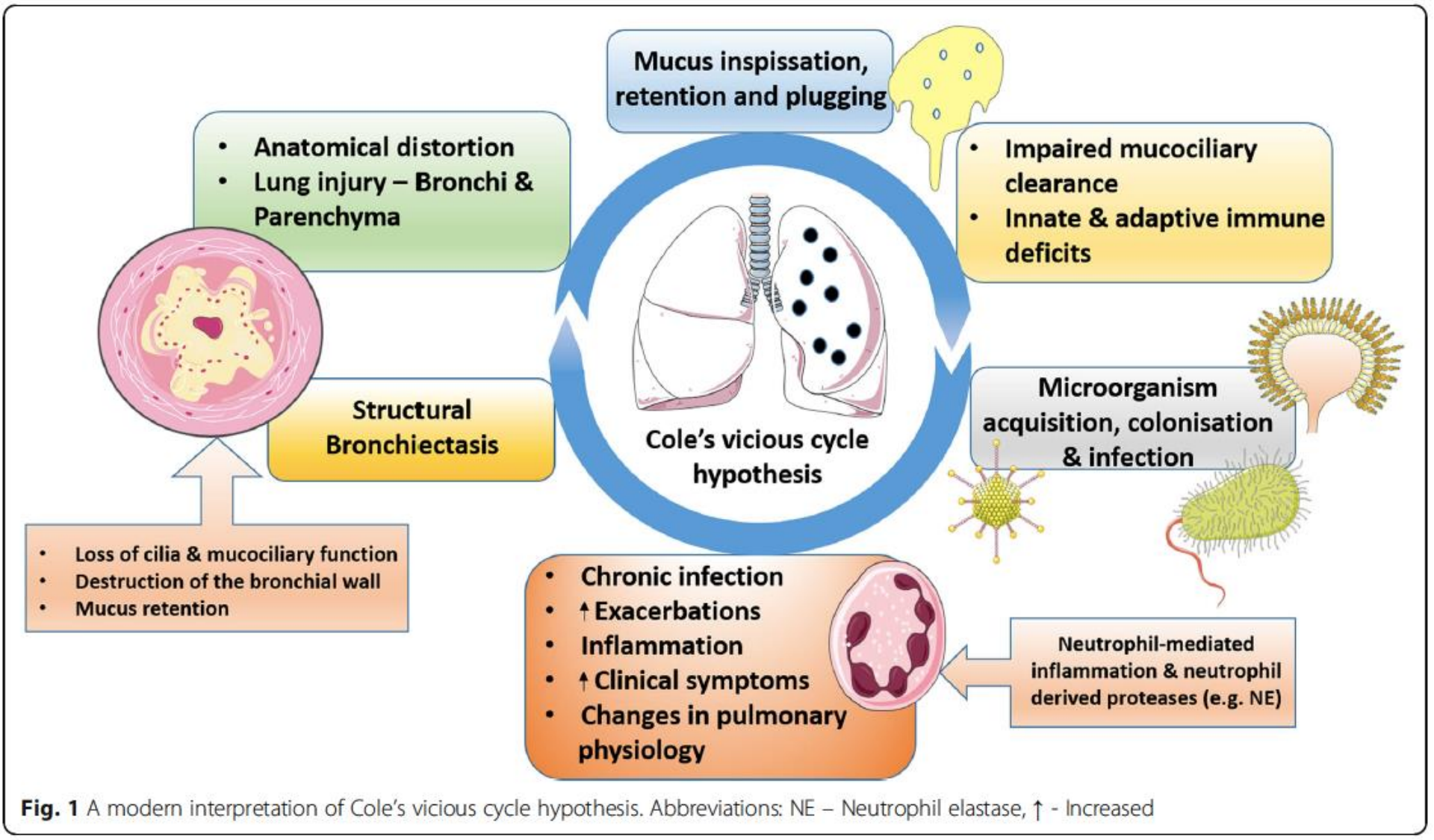
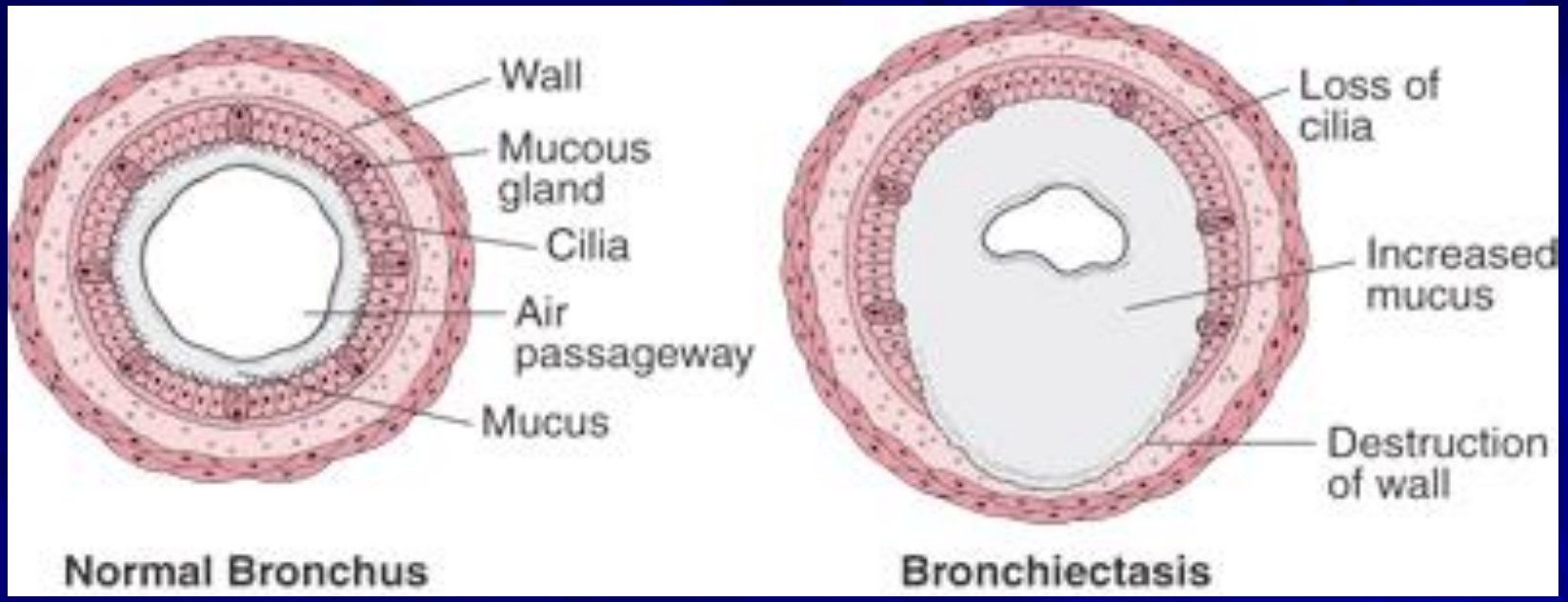


Fig. 1 A modern interpretation of Cole's vicious cycle hypothesis. Abbreviations: NE – Neutrophil elastase, ↑ - Increased

Chandrasekaran et al. BMC Pulmonary Medicine (2018) 18:83

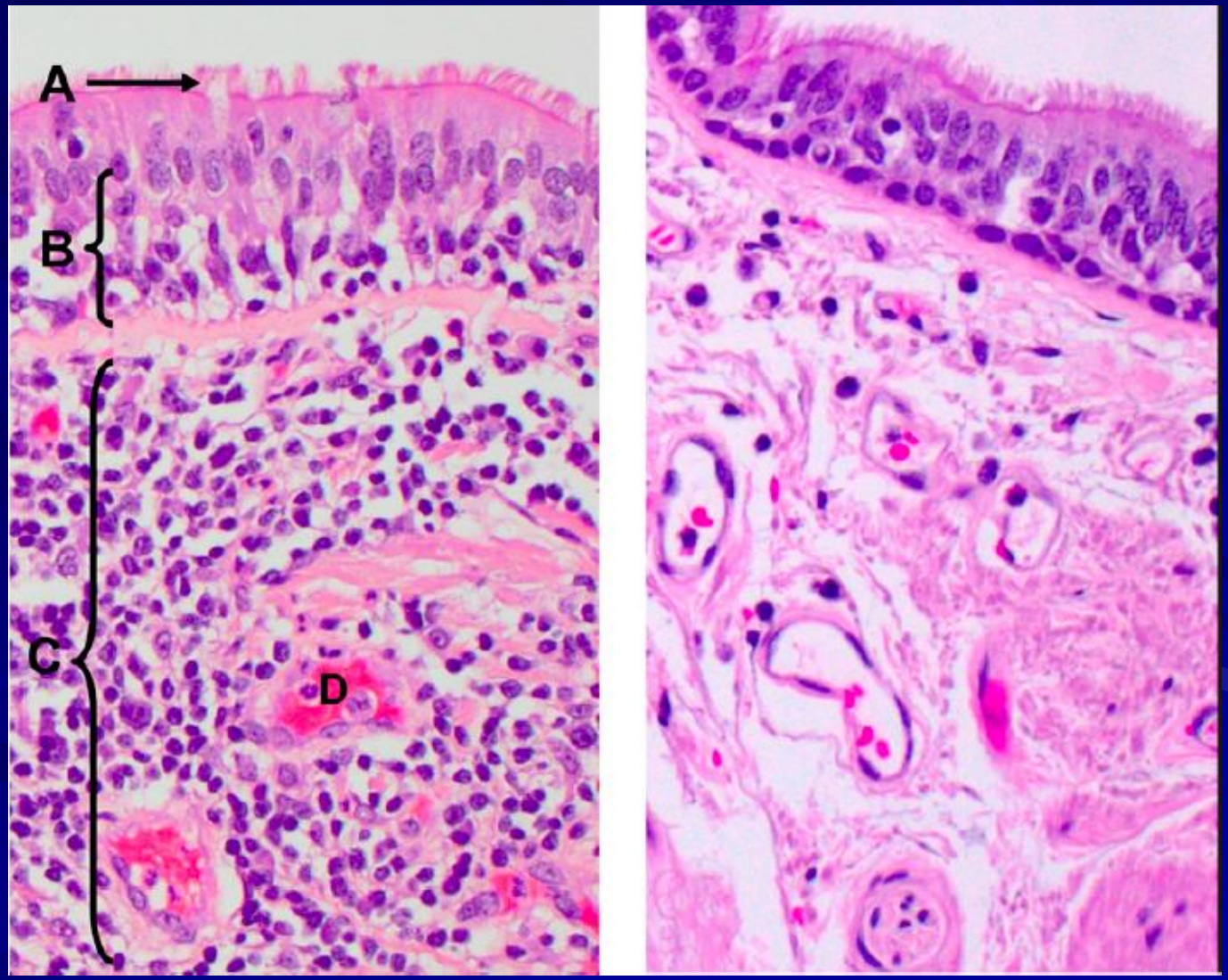


1. Patent airways
2. Effective mucus clearance
3. Normal mucociliary function

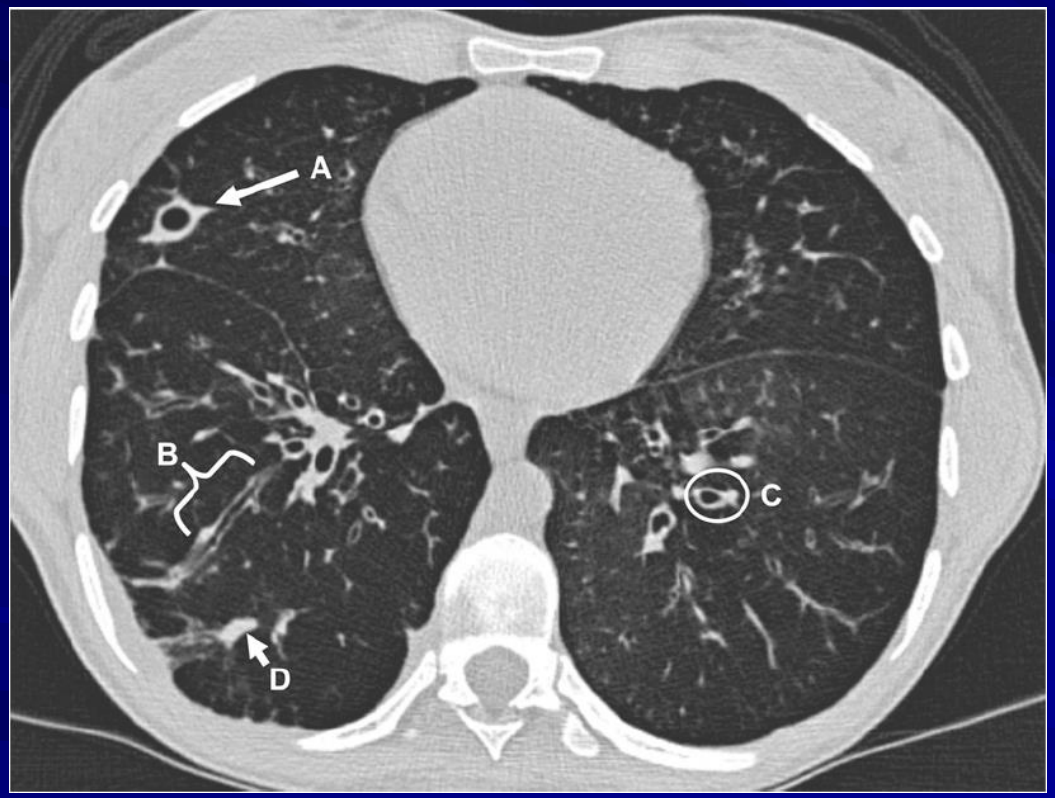
1. Obstructed airways
2. In-Effective mucus clearance
3. Abnormal mucociliary function

Repeated inflammation or Infection

HE stain of the bronchial wall



Diagnosis : HRCT



Radiographic signs of BE.

A . Bronchus terminating in a cyst;

B . lack of bronchial tapering as it travels to the periphery of the lung;

C . signet ring sign (bronchus is larger than the accompanying vessel);

D . mucus plug (mucus completely filling the airway lumen).

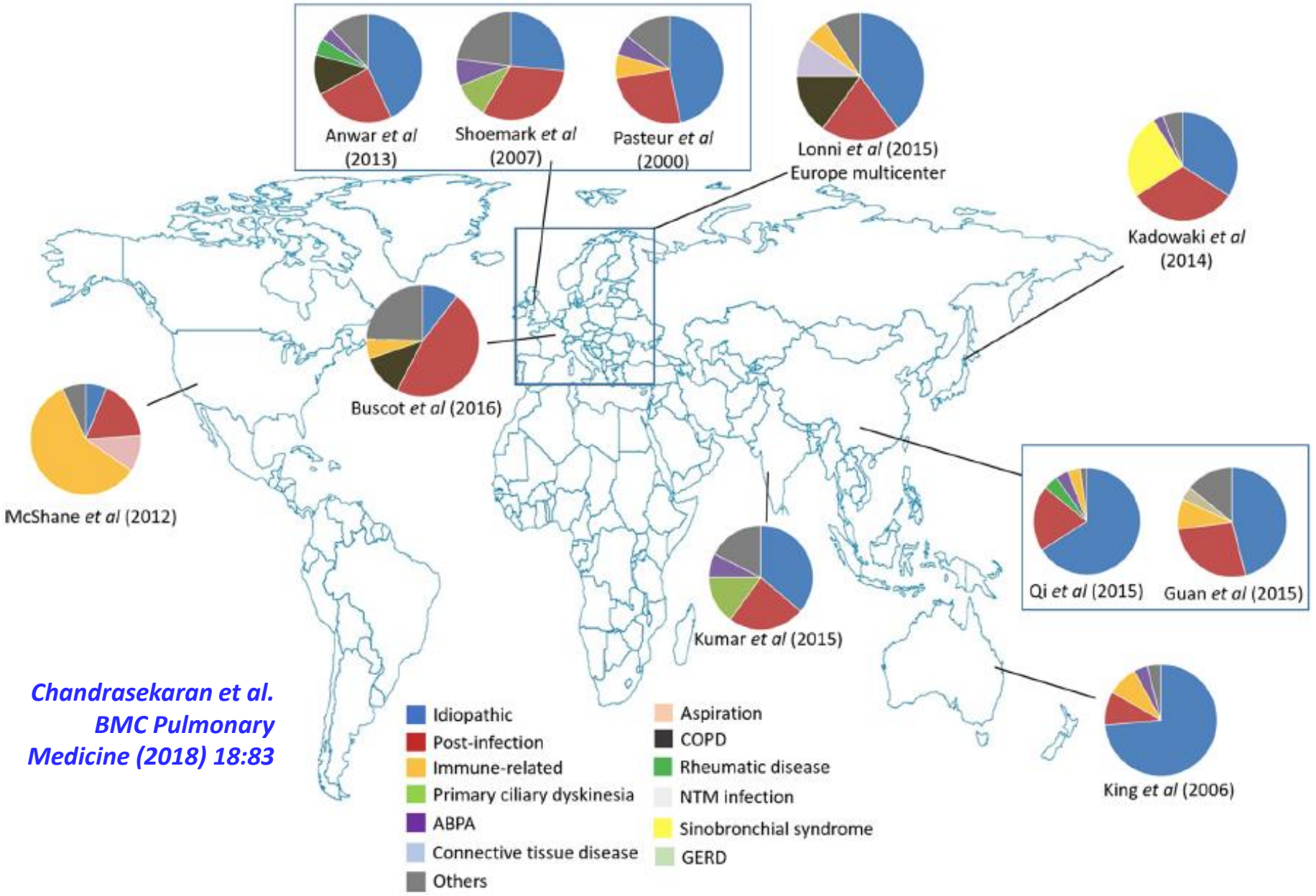


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Fig. 2 Predominant aetiologies across different geographic regions and ethnic populations. The individual pie charts indicate the top aetiologies (top 4 or 5) in each cohort. Abbreviations: ABPA – Allergic Broncho-Pulmonary Aspergillosis, COPD – Chronic Obstructive Pulmonary Disorder, NTM – Non-Tuberculosis Mycobacteria, GERD – Gastro-Esophageal Reflux Disease

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Mortality in Bronchiectasis : does knowing etiology matter ?

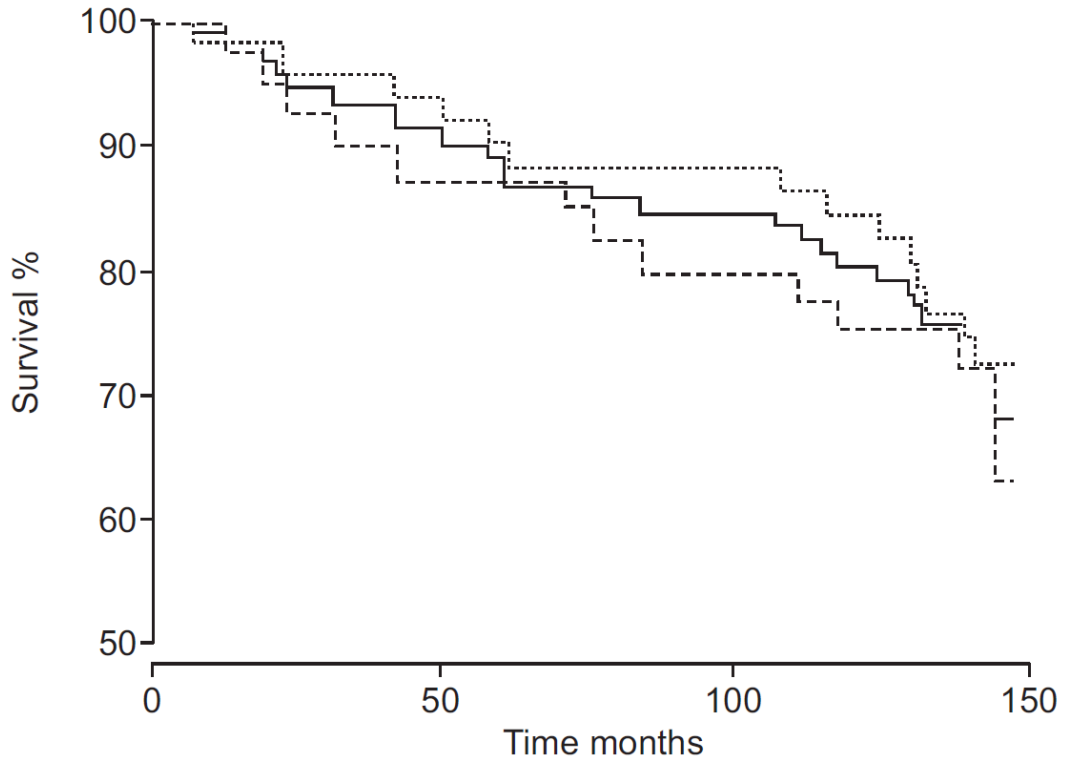


FIGURE 2. Kaplan–Meier plot illustrating the survival of all the bronchiectasis patients (——), in addition to the idiopathic (·····) and known (– – – –) aetiology subgroups. There are no statistically significant differences between the plots (log rank test; p=0.85).

M.R. Loebinger
Eur Respir J 2009;
34: 843–849

ORIGINAL ARTICLE

The Bronchiectasis Severity Index

An International Derivation and Validation Study

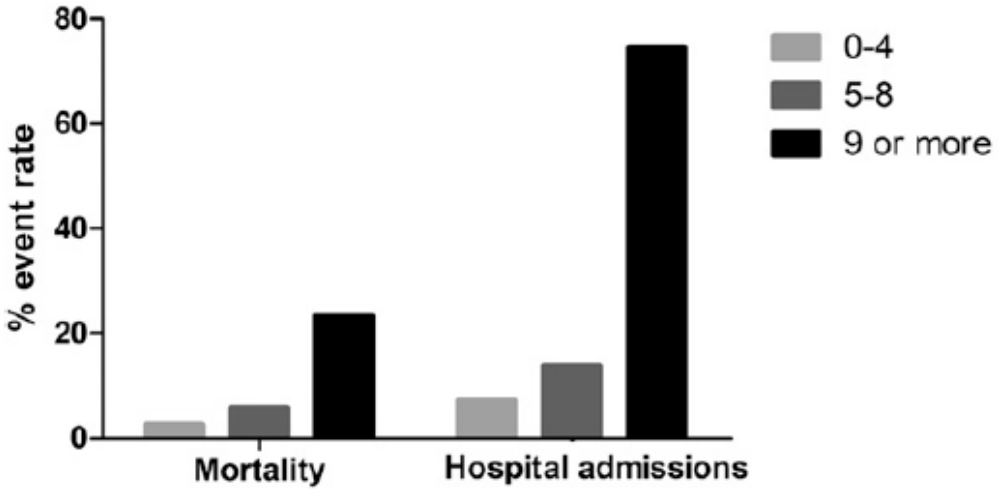
James D. Chalmers[1], Pieter Goeminne[2], Stefano Aliberti[3], Melissa J. McDonnell[4,5], Sara Lonni[3], John Davidson[4], Lucy Poppelwell[1], Waleed Salih[1], Alberto Pesci[3], Lieven J. Dupont[2], Thomas C. Fardon[1], Anthony De Soyza[4,5], and Adam T. Hill[6]

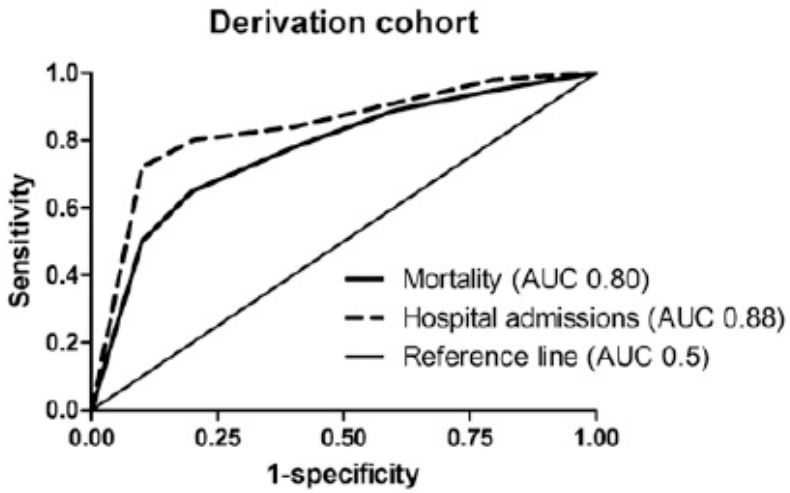
[1]Tayside Respiratory Research Group, University of Dundee, Dundee, United Kingdom; [2]Respiratory Medicine, University Hospital Gasthuisberg, Leuven, Belgium; [3]Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Monza, Italy; [4]Adult Bronchiectasis Service and Sir William Leech Centre for Lung Research, Freeman Hospital, Newcastle upon Tyne Hospitals, Heaton, Newcastle, United Kingdom; [5]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; and [6]Department of Respiratory Medicine Royal Infirmary of Edinburgh and the University of Edinburgh, Edinburgh, United Kingdom

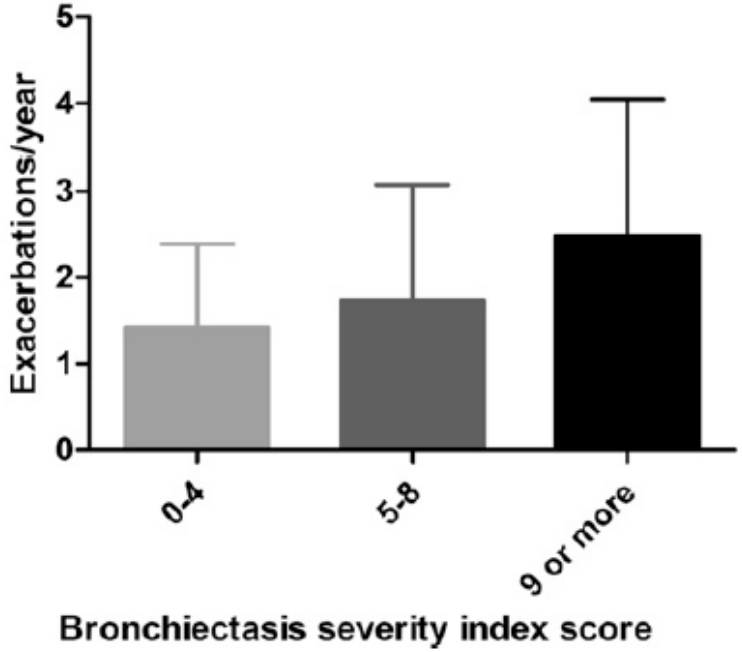
Am J Respir Crit Care Med Vol 189, Iss 5, pp 576–585, Mar 1, 2014

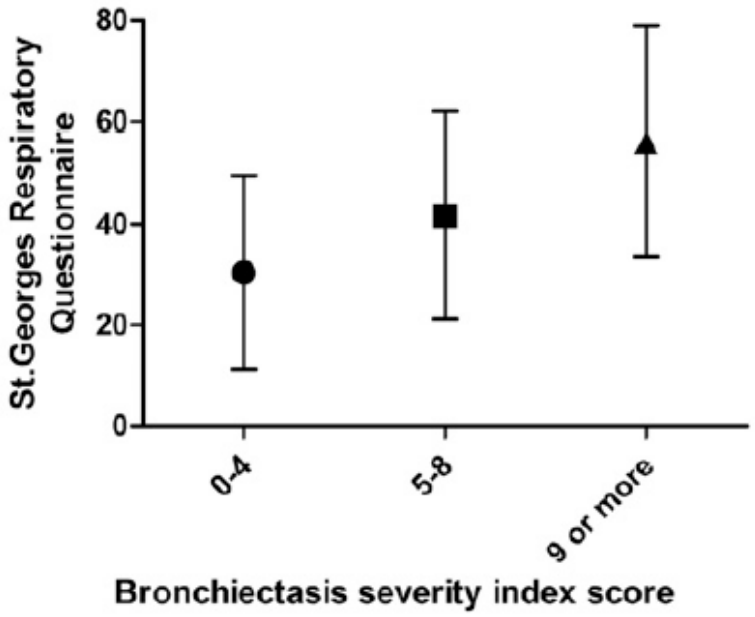
Table 3: Results of the Cox Proportional Hazard Regression Analysis for Mortality and Hospitalization

Severity Marker	HR (95% CI) for Hospital Admissions during Follow-up	HR (95% CI) for Mortality	Score Points
Age, yr			
<50	1.0 (reference)	1.0 (reference)	0
50–69	1.38 (0.73–2.56)	2.21 (0.28–17.5)	2
70–79	1.50 (0.79–2.82)	8.57 (1.15–63.63)	4
80+	1.76 (0.89–3.50)	23.16 (3.09–173.7)	6
BMI			
<18.5	1.23 (0.73–2.08)	2.25 (1.09–4.67)	2
18.5–25	1.0 (reference)	1.0 (reference)	0
26–29	0.90 (0.62–1.30)	0.91 (0.46–1.81)	0
30 or more	1.14 (0.76–1.70)	1.38 (0.68–2.81)	0
FEV_1 % predicted			
≥80	1.0 (reference)	1.0 (reference)	0
50–80	1.17 (0.74–1.85)	1.34 (0.67–2.67)	1
30–49	1.40 (0.68–2.85)	1.58 (0.72–3.46)	2
<30	1.52 (1.03–2.25)	4.47 (1.60–12.53)	3
Hospital admission before study			
No	1.0 (reference)	1.0 (reference)	0
Yes	13.5 (9.40–19.46)	2.43 (1.30–4.53)	5
Exacerbations before the study			
0	1.0 (reference)	1.0 (reference)	0
1–2	1.67 (0.78–3.58)	1.78 (0.80–3.98)	0
3 or more	2.25 (0.89–5.70)	2.03 (1.02–4.03)	2
MRC dyspnea score			
1–3	1.0 (reference)	1.0 (reference)	0
4	2.42 (1.66–3.52)	1.05 (0.50–2.20)	2
5	2.69 (1.59–4.53)	1.15 (0.50–2.63)	3
Pseudomonas colonization			
No	1.0 (reference)	1.0 (reference)	0
Yes	2.16 (1.36–3.43)	1.58 (0.75–3.34)	3
Colonization with other organisms			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.66 (1.12–2.44)	1.10 (0.54–2.24)	1
Radiological severity: ≥3 lobes involved or cystic bronchiectasis			
No	1.0 (reference)	1.0 (reference)	0
Yes	1.48 (1.02–2.15)	1.05 (0.57–1.94)	1


80
60
40
20
0
% event rate
0-4
5-8
9 or more
Mortality
Hospital admissions


Derivation cohort
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
Mortality (AUC 0.80)
Hospital admissions (AUC 0.88)
Reference line (AUC 0.5)
0.00
0.25
0.50
0.75
1.00
1-specificity


5
4
3
2
1
0
Exacerbations/year
0-4
5-8
9 or more
Bronchiectasis severity index score


80
60
40
20
0
St.Georges Respiratory Questionnaire
0-4
5-8
9 or more
Bronchiectasis severity index score

Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score

Miguel Á. Martínez-García[1,2], Javier de Gracia[2,3,4], Monserrat Vendrell Relat[2,5], Rosa-Maria Girón[6], Luis Máiz Carro[7], David de la Rosa Carrillo[8] and Casilda Olveira[9]

Affiliations: [1]Pneumology Service, Hospital Universitario y Politécnico La Fe, Valencia, [2]CIBER de Enfermedades Respiratorias, Banyoles, [3]Pneumology Service, Hospital Vall D'Hebrón, Barcelona, [4]Universidad Autónoma de Barcelona, Barcelona, [5]Pneumology Service, Institut d'Investigació Biomèdica Girona, Hospital Dr Trueta, Girona, [6]Pneumology Service, Hospital La Princesa, Madrid, [7]Pneumology Service, Hospital Ramón y Cajal, Madrid, [8]Pneumology Unit, Hospital Plató, Barcelona, and [9]Pneumology Service, Hospital Universitario Regional de Málaga, Insituto de Biomedicina de Málaga, Univesidad de Málaga, Málaga, Spain.

Correspondence: M.Á. Martínez-García, Servicio de Neumología, Hospital Universitario y Politécnico La Fe, Valencia, Carrera Malilla s/n, 46006, Valencia, Spain. E-mail: mianmartinezgarcia@gmail.com

Eur Respir J 2014; 43: 1357–1367

FACED score

F: forced expiratory volume in 1 s % predicted (cut-off 50%, maximum value 2 points);

A: age (cut-off 70 years, maximum value 2 points);

C: chronic colonisation by Pseudomonas aeruginosa (maximum value 1 point);

E: radiological extension (lobes affected, cut-off two lobes, maximum value 1 point);

D: dyspnea (cut-off grade II on the mMRC scale, maximum value 1 point)

TABLE 5 Predictive capacity for mortality of the different dichotomised variables included in the final score

	OR (95% CI)	p-value	β-coefficient	
			Initial	Rounded
Age >70 years *versus* ⩽70 years	4.98 (2.67–9.28)	0.0001	1.61	2
Dyspnoea mMRC score III–IV *versus* I–II	2.75 (1.46–5.18)	0.002	1.01	1
Post-bronchodilator FEV1 <50% *versus* ⩾50% predicted	5.19 (2.76–9.75)	0.0001	1.65	2
Extension >2 lobes *versus* 1–2 lobes	1.87 (1.01–3.46)	0.04	0.62	1
Chronic colonisation by *Pseudomonas aeruginosa* yes *versus* no	2.37 (1.28–4.58)	0.006	0.86	1

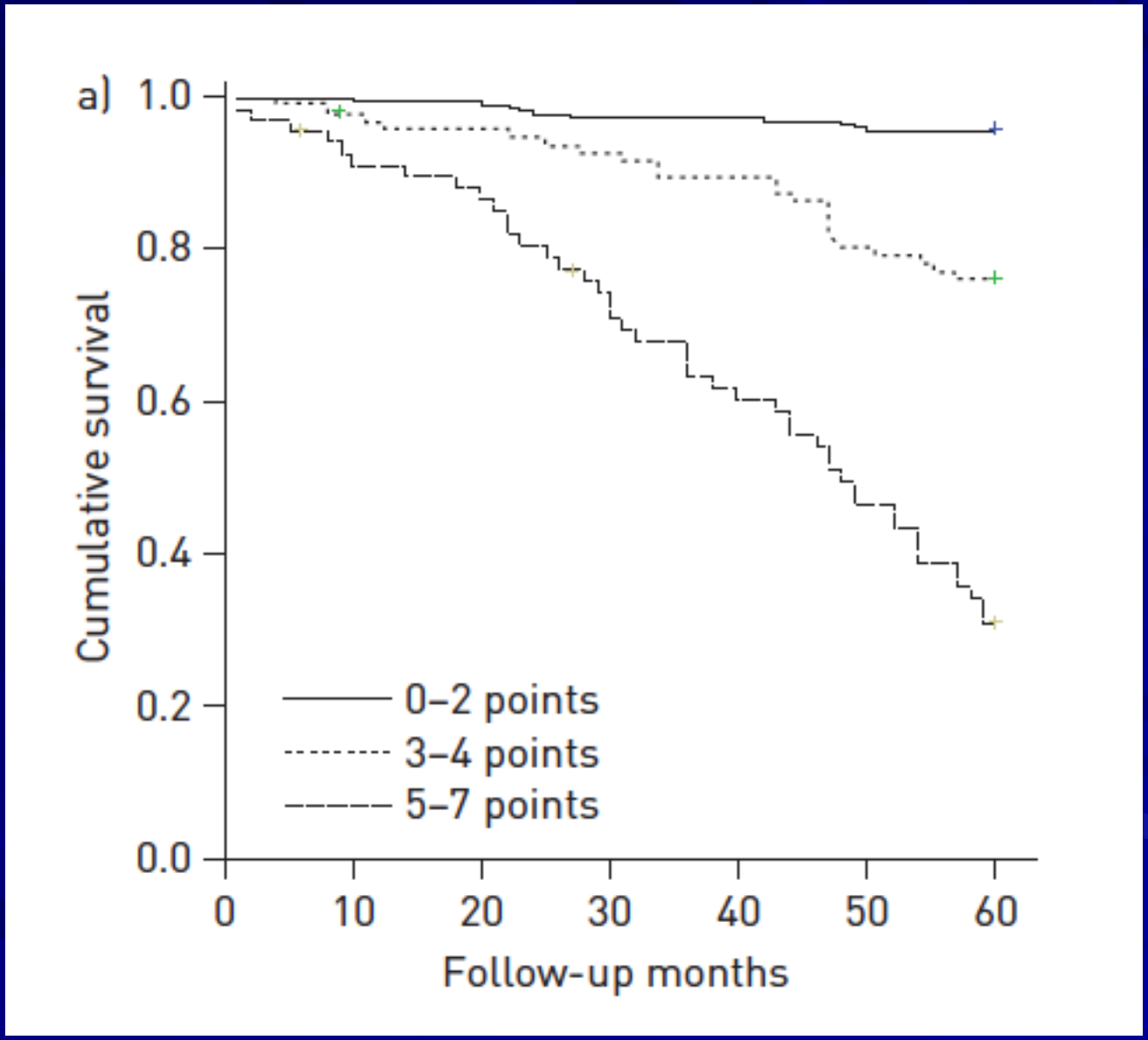
mMRC: modified Medical Research Council; FEV1: forced expiratory volume in 1 s.

TABLE 6 Final score, cut-off points of the dichotomised variables and scoring of each variable

	Points
Chronic colonisation by *Pseudomonas aeruginosa*	
No	0
Yes	1
Dyspnoea mMRC score	
0–II	0
III–IV	1
FEV1 % predicted	
⩾50%	0
<50%	2
Age	
<70 years	0
⩾70 years	2
Number of lobes	
1–2	0
>2	1

Maximum score 7 points. mMRC: modified Medical Research Council; FEV1: forced expiratory volume in 1 s.

Eur Respir J 2014; 43: 1357–1367



Eur Respir J 2014; 43: 1357–1367

Summary

BSI
Bronchiectasis Severity Index

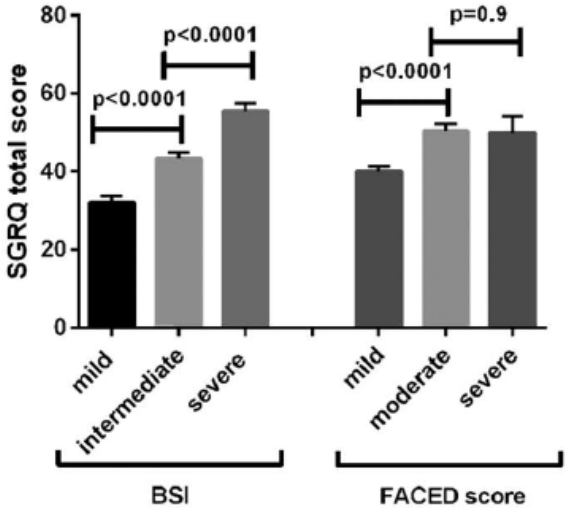
- Age
- BMI
- FEV1
- Admissions
- Exacerbations
- MRC
- Colonization
- Radiologic severity

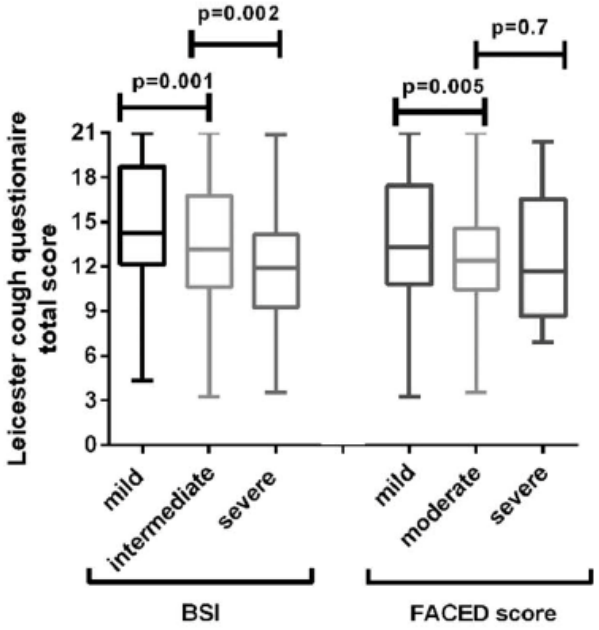
FACED

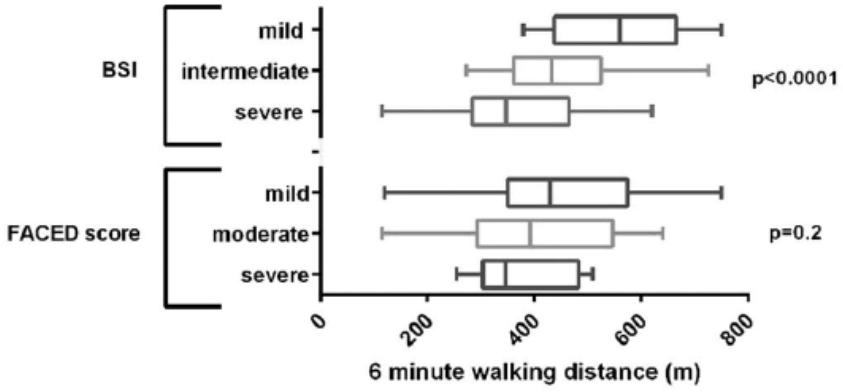
- FEV1
- Age
- Chronic Colonization
- Extension
- Dyspnea

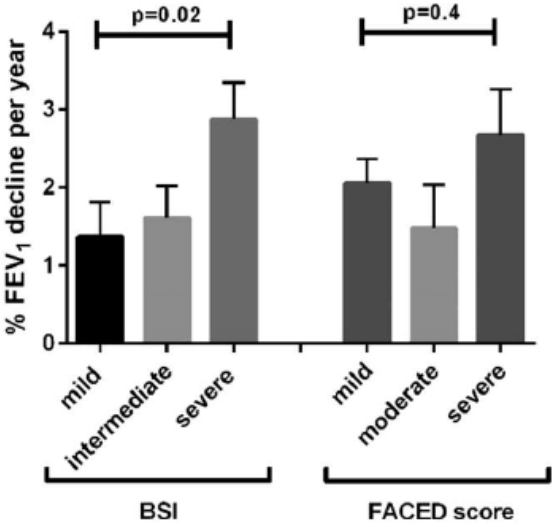
Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts.

McDonnell MJ, et al. Thorax 2016;71:1110–1118



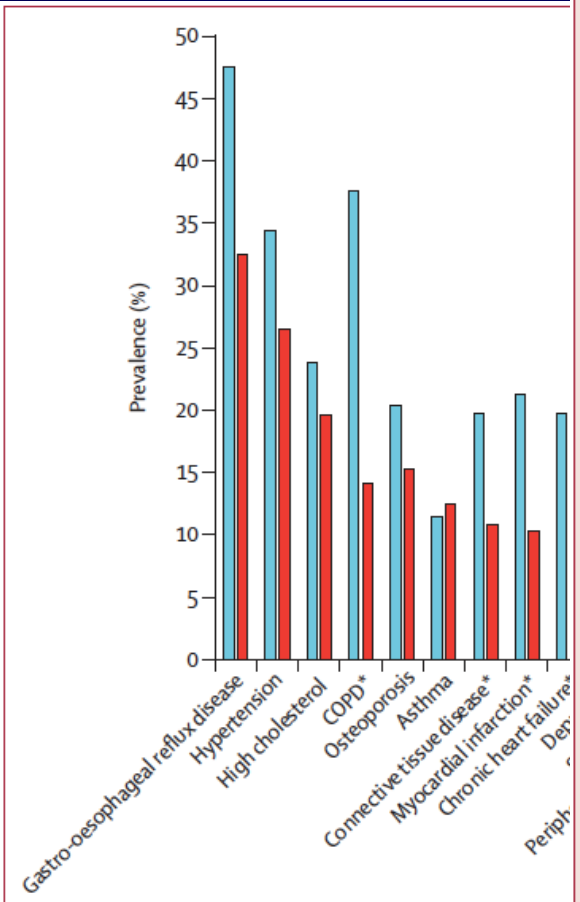






Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study

Melissa J McDonnell et al. Lancet Respir Med 2016; 4: 969–79



	Derivation cohort (n=986)
Age, years	67 (57–74)
Women	589 (60%)
Body-mass index (kg/m²)	24·6 (21·2–27·8)
Smokers or ex-smokers	379 (38%)
Clinical status	
Medical Research Council dyspnoea score	2 (1–3)
Exacerbations in the previous year	2 (1–3)
At least one hospitalisation in the previous year	224 (23%)
Lung function	
% predicted FEV_1	75% (54–95)
% predicted FEV_1/FVC	70% (59–79)
Reiff radiological score	4 (2–6)
Microbiological status	
Pseudomonas aeruginosa colonisation	122 (12%)
Other colonisation	229 (23%)
BSI score	6 (4–10)
0–4 (mild)	312 (32%)
5–8 (moderate)	351 (36%)
≥9 (severe)	323 (33%)
Number of comorbidities	4 (2–6)
Range	0–20

Data are n (%) or median IQR, unless otherwise specified. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. BSI=Bronchiectasis Severity Index.

Table 1: **Derivation cohort patient characteristics**

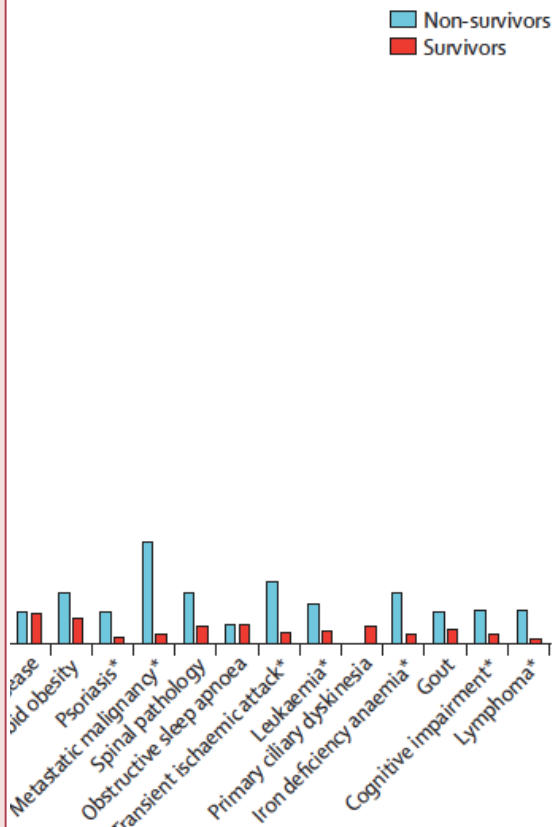
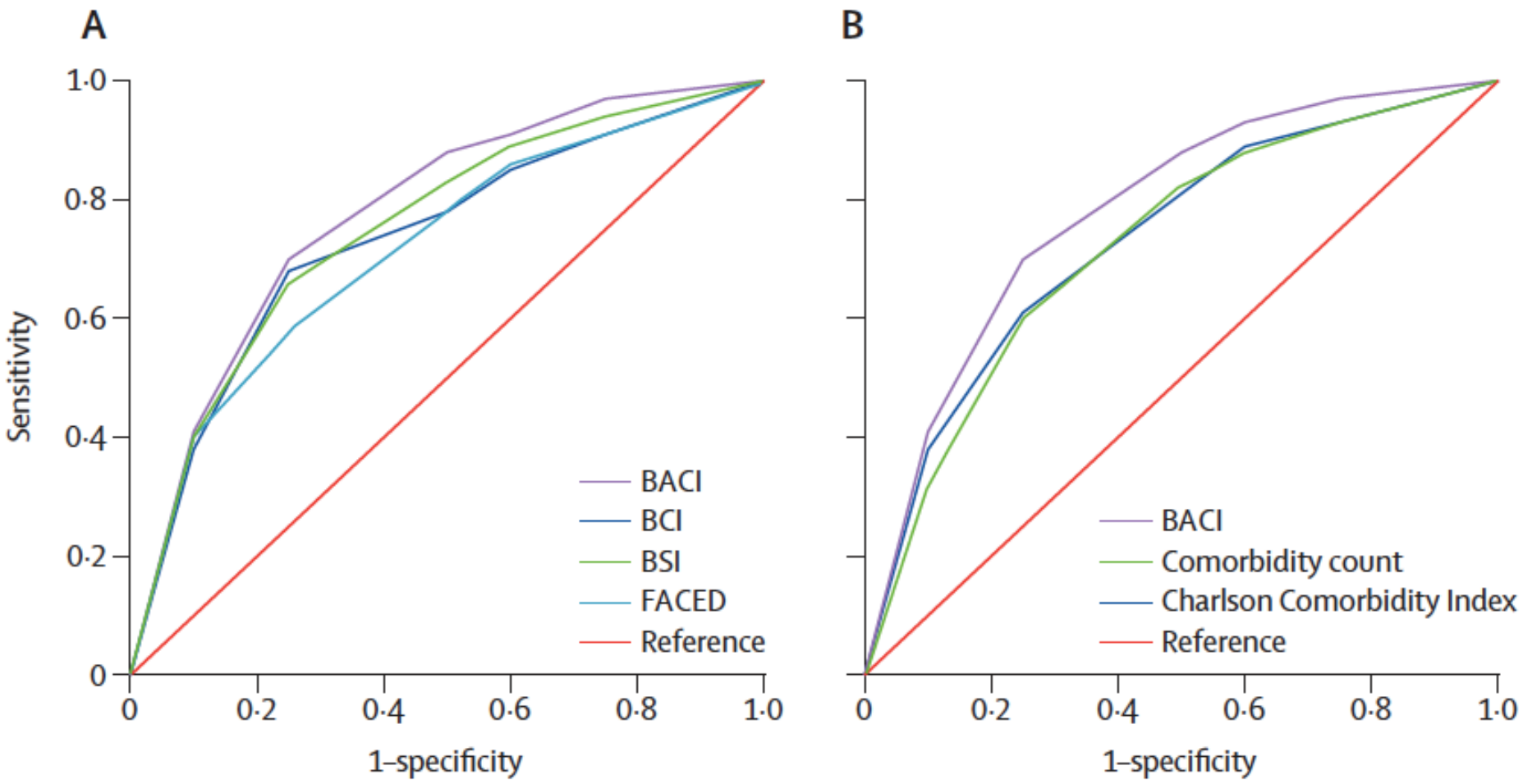


Figure 1: **Comorbidities in order of overall prevalence amo**
*Comorbidity with a significantly higher prevalence in non-

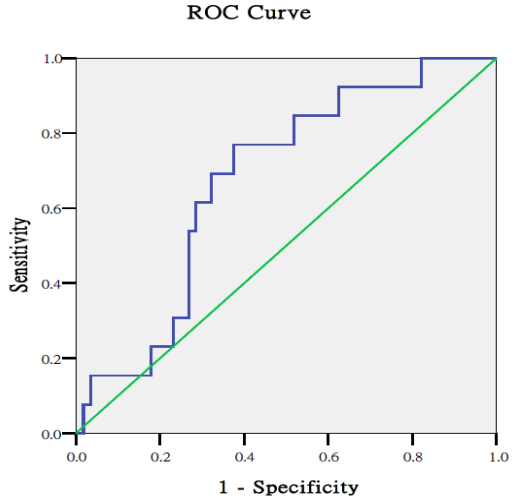
Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study

Melissa J McDonnell et al. Lancet Respir Med 2016; 4: 969–79

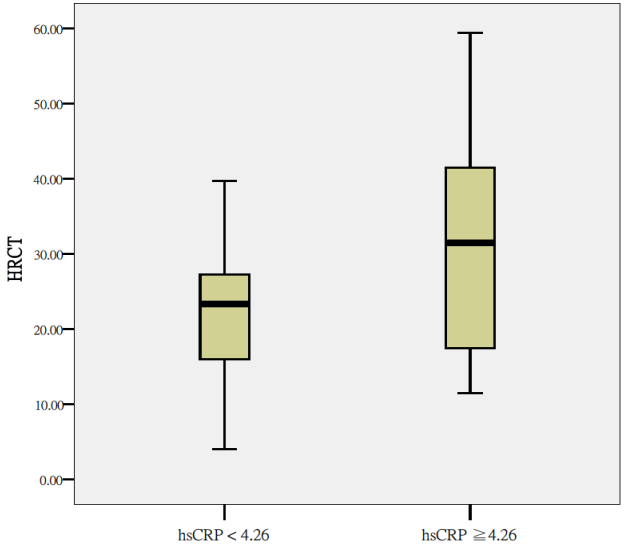


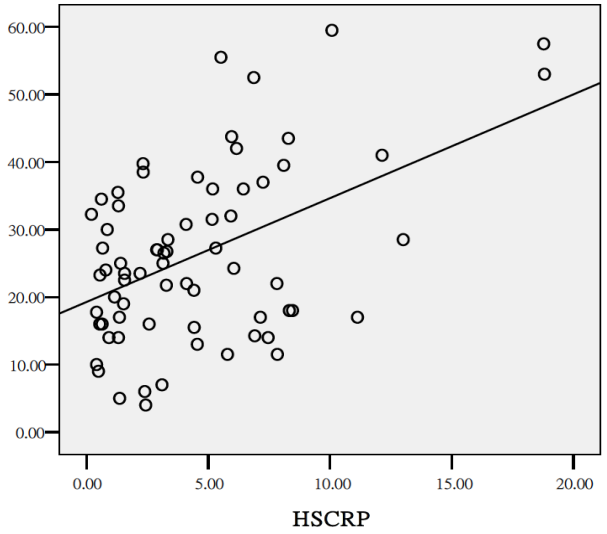
The Role of the High-Sensitivity C-Reactive Protein in Patients with Stable Bronchiectasis

ROC curve of hs-CRP for prediction patients with repeated hospitalization(**≥2 exacerbation related hospitalization events**)



hs-CRP cutoff	Sensitivity (%)	Specificity (%)
3.72	76.9	58.9
4.10	76.9	60.7
4.26	76.9	62.5
4.42	69.2	62.5
4.49	69.2	64.3
4.56	69.2	66.1





Pulmonary Medicine 2013

More score…

Original Article

Distance-saturation product of the 6-minute walk test predicts mortality of patients with non-cystic fibrosis bronchiectasis

Meng-Heng Hsieh[1], Yueh-Fu Fang[1], Fu-Tsai Chung[1], Chung-Shu Lee[1], Yu-Chen Chang[2], Yuan-Zhang Liu[3], Cheng-Hsien Wu[3], Horng-Chyuan Lin[1]

[1]Department of Thoracic Medicine, [2]Department of Nuclear Medicine, [3]Department of Radiology, Chang Gung Medical Foundation, Chang Gung University, College of Medicine, Taoyuan, Taiwan

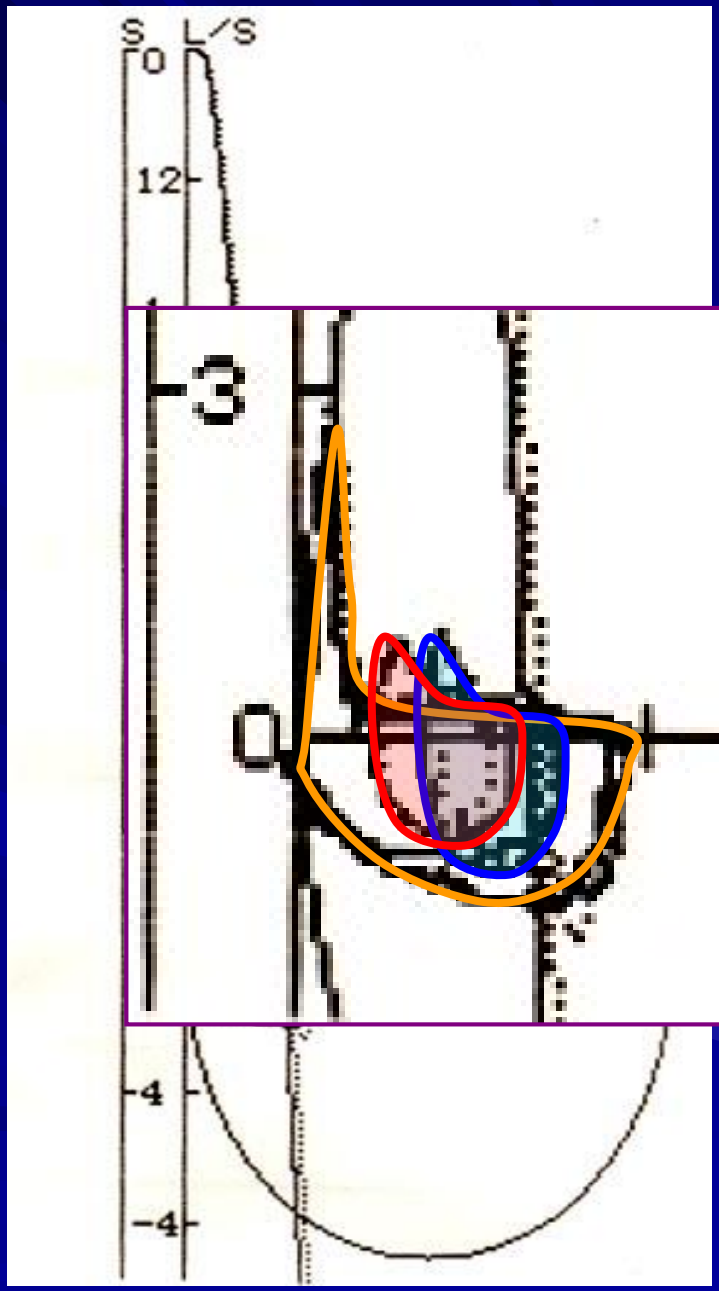
Contributions: (I) Conception and design: MH Hsieh, YF Fang, HC Lin; (II) Administrative support: MH Hsieh, YF Fang, HC Lin; (III) Provision of study materials or patients: MH Hsieh, FT Chung, CS Lee, YC Chang, YZ Liu, HC Lin; (IV) Collection and assembly of data: MH Hsieh, FT Chung, CS Lee, YC Chang, YZ Liu, CH Wu, HC Lin; (V) Data analysis and interpretation: MH Hsieh, YF Fang, YC Chang, CH Wu, HC Lin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Horng-Chyuan Lin. Department of Thoracic Medicine, Chang Gung Medical foundation, Chang Gung University, Taoyuan, Taiwan. Email: lin53424@ms13.hinet.net.

J Thorac Dis 2017; 9(9): 3168-3176

Six-min walking test

	Pre-Exercise			Post-Exercise	
FUNCTION	PRED	MEAS	%PR	MEAS	%CH
FVC	3.26	0.95	29	0.90	-3
FEV.5		0.21		0.23	10
FEV1	2.39	0.30	13	0.33	10
FEV3		0.59		0.63	7
FEV1%T					
FEV1%G	69.8	31.6	45	36.7	16
FEV3%T					
FEV3%G		62.1		70.0	13
MEFR		0.04		0.04	0
MMEF	3.35	0.13	4	0.15	15
EX TIME		6.95		5.48	-20
V EXT		0.02		0.03	50
FIVC		1.05		0.90	-11
FIV.5		0.46		0.51	9
FIV1		0.83		0.82	0
FIV1/FVC		87.4		91.1	4
FIV1/FIVC		79.0		91.1	15
FEV.5/FIV.5		0.46		0.45	0
O2 sat (%)	**93%**			**85%**	
Heart rate (/min)	**120**			**112**	
6 MWD (m)	**120**				



DSP: Distance-Saturation Product

- The product of the final distance walked in meters and the lowest room air oxygen saturation during the 6-min walk test.
- For example, a patient walking a total of 300m who's lowest oxygen saturation fell to 90% would have a **DSP** of 270 m% (e.g., 300×0.90).

Respiratory Medicine (2006) 100, 1734–1741

ELSEVIER

respiratoryMEDICINE

The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis ☆

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DSP predicts mortality in IPF

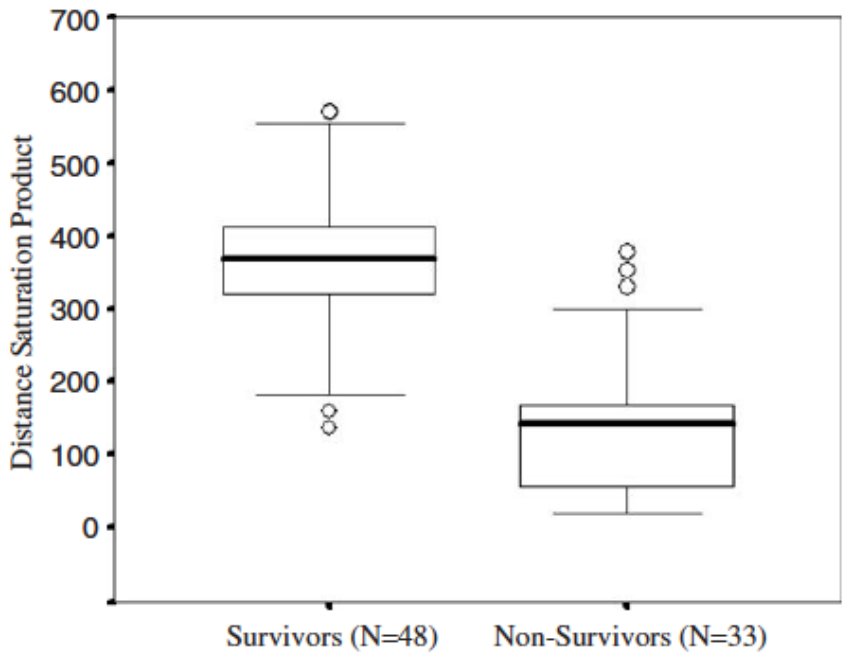


Figure 1 Distance saturation product.

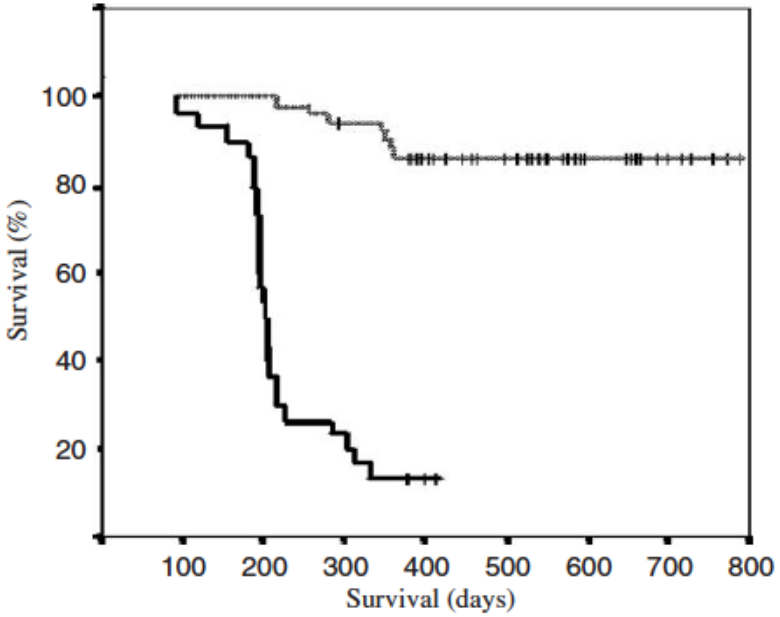
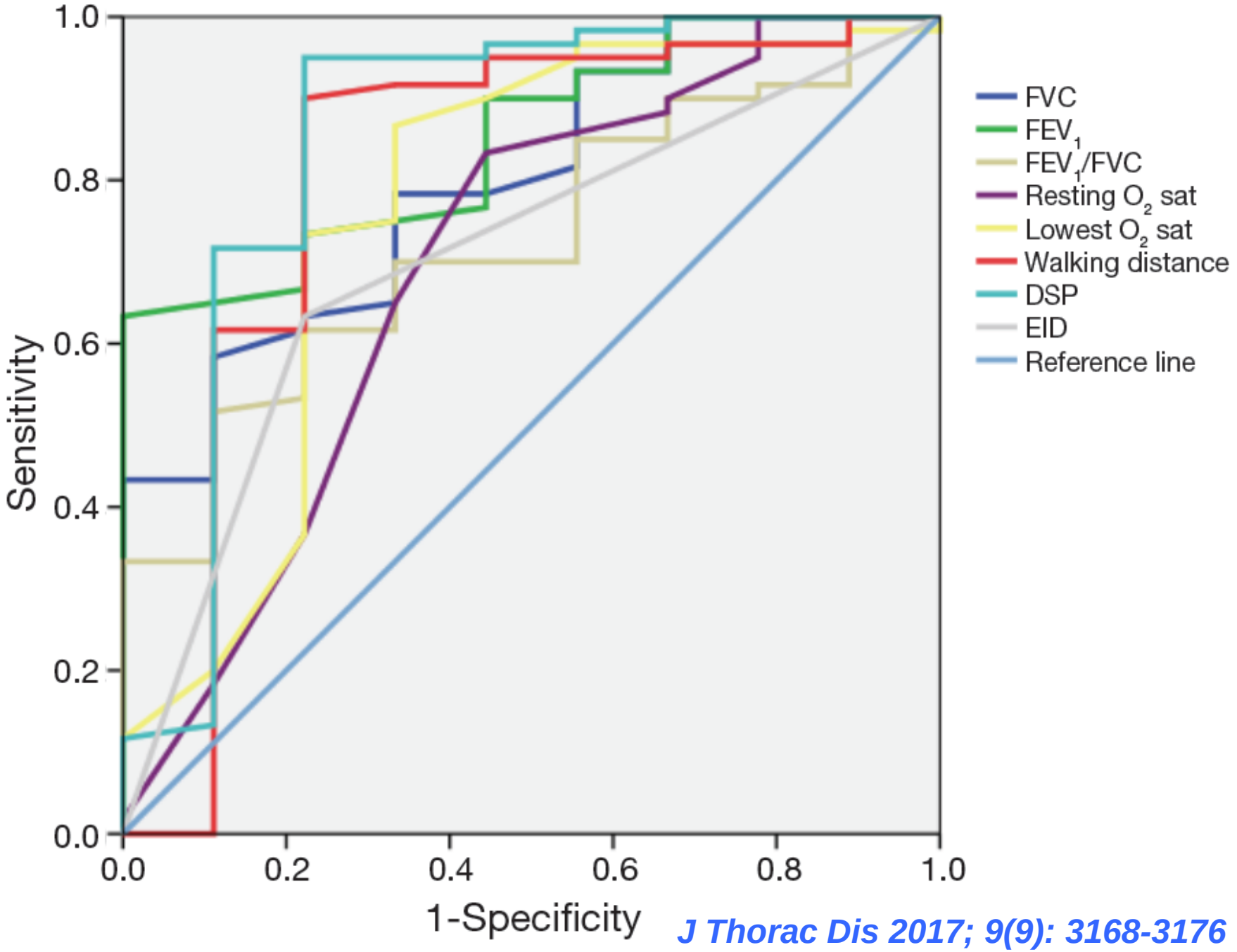


Figure 3 DSP⩽200 m% as a predictor of 12-month survival.

Resp Med 2006; 100; 1734-1741



J Thorac Dis 2017; 9(9): 3168-3176

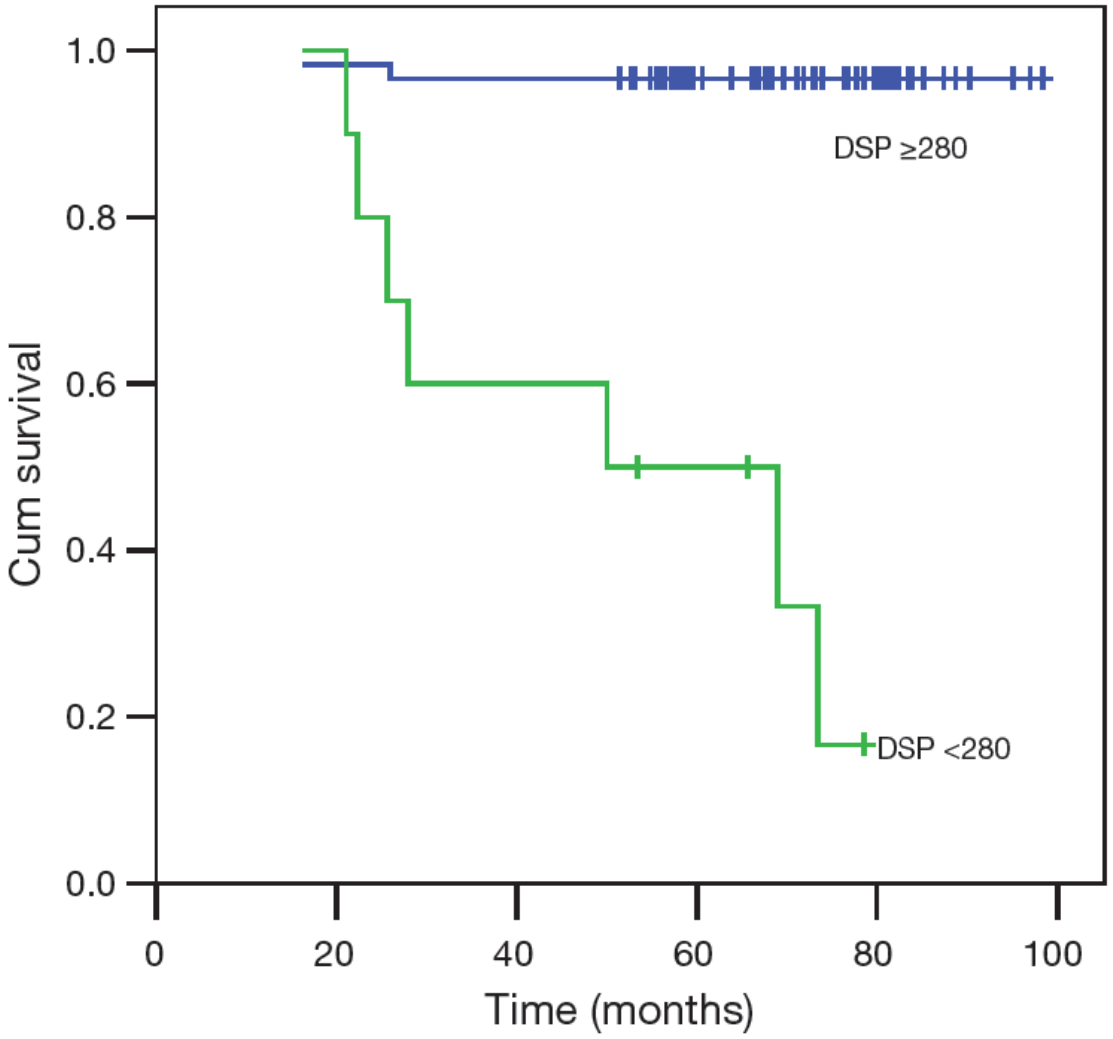
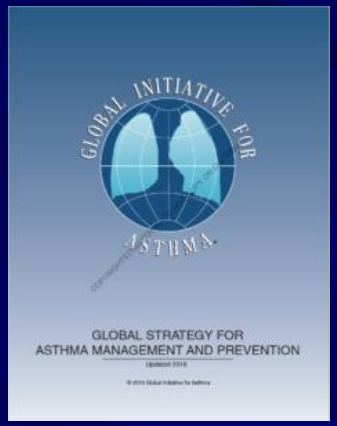
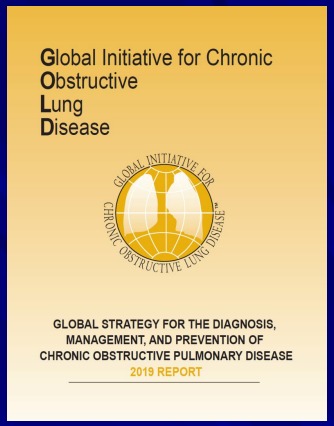


Figure 4 Kaplan-Meier survival curve for patients with non-CF bronchiectasis grouped by distance-saturation product (DSP, cut-off value: 280 m%) during the 6MWT (blue line: higher group; P<0.001). Non-CF, non-cystic fibrosis; 6MWT, 6-minute walk test.



COPD



Acute exacerbation ?

Bronchiectasis

Mortality ?

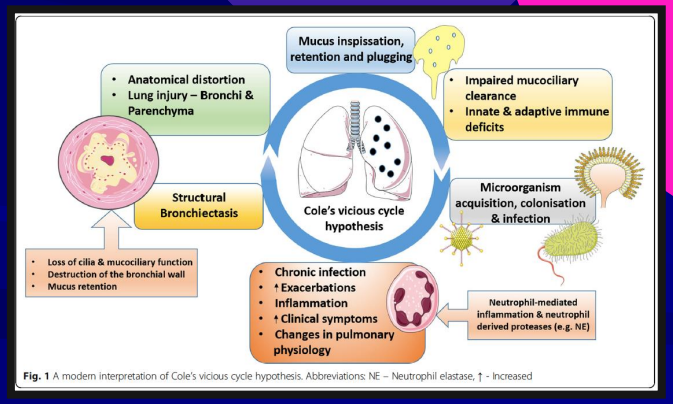
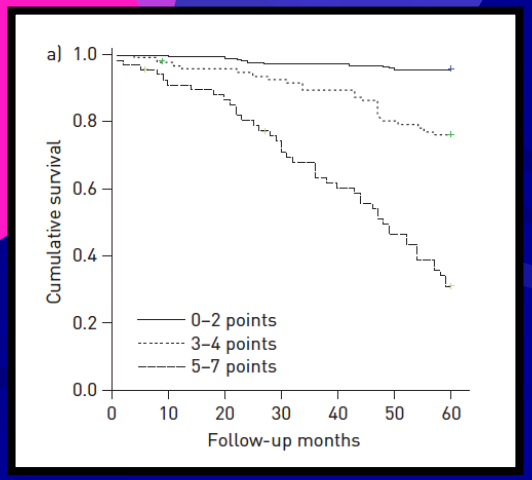
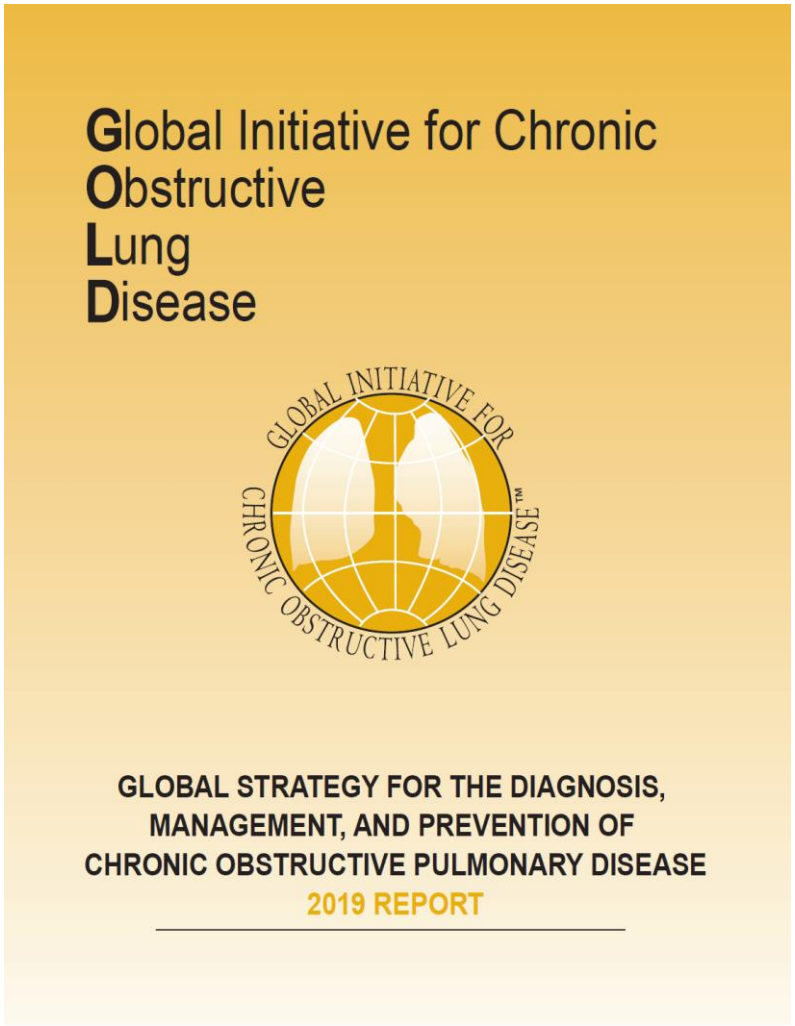


Fig. 1 A modern interpretation of Cole's vicious cycle hypothesis. Abbreviations: NE – Neutrophil elastase, ↑ - Increased



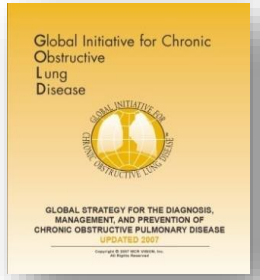
Asthma

GOLD 2019 Report: Chapters



1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations
6. COPD and Comorbidities

Exacerbations



COPD Comorbidities

- **Cardiovascular disease**
  - Major comorbidity, Most frequent, Most important
- **Bronchiectasis**
  - Longer exacerbation and increased mortality
- **Metabolic syndrome and Diabetes**
- **Osteoporosis**
- **Anxiety and Depression**
  - Major comorbidities
    Under-diagnosed
    Poor health status and Prognosis
- **Lung cancer**
  - Frequently in COPD
    Most frequent cause of death in mild COPD
- **Infections**

GOLD 2014 - Should be actively looked for and treated appropriately if present

Bacterial microbiome of lungs in COPD and BE

Bronchiectasis, Exacerbation Indices, and Inflammation in COPD

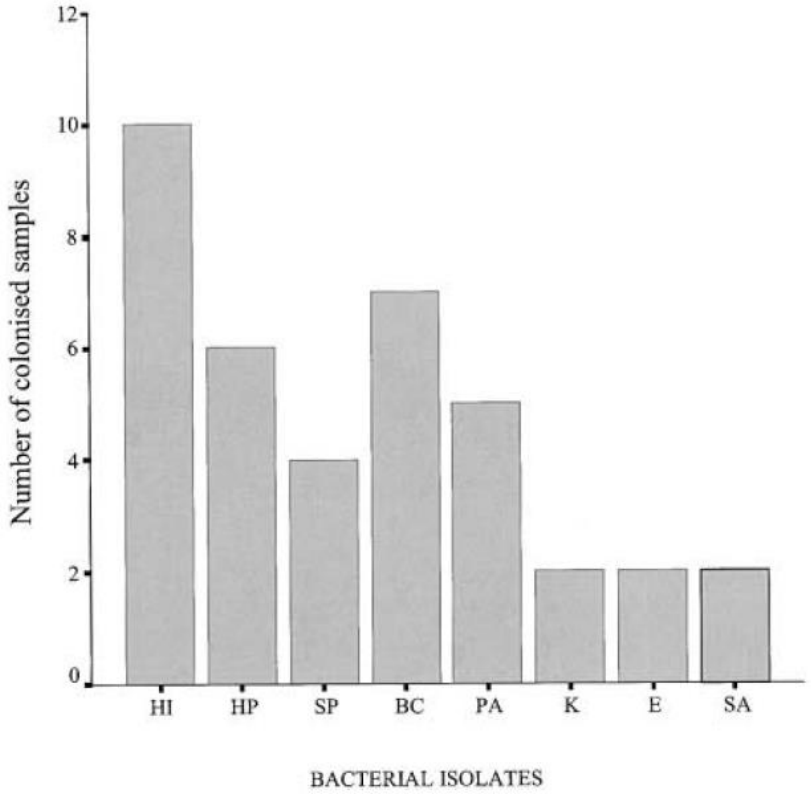


Figure 2. Potential pathogens isolated in 52 sputum samples. BC = *Branhamella catarrhalis*; E = *Enterobacter* species; HI = *Haemophilus influenzae*; HP = *Haemophilus parainfluenzae*; K = *Klebsiella* species; PA = *Pseudomonas aeruginosa*; SA = *Staphylococcus aureus*; SP = *Streptococcus pneumoniae*.

52 sputum samples were obtained from patients in the stable state, of which 43 (82.7%) were spontaneous and 9 (17.3%) were induced samples.

AJRCCM 170. pp 400–407, 2004

Factors Associated With Bronchiectasis in Patients With COPD

Table 3—*Analytic, Microbiologic, and Functional Characteristics of Subjects With COPD, With and Without Bronchiectasis*

Parameter	Whole Group	COPD With Bronchiectasis	COPD Without Bronchiectasis	*P* Value
Subjects, No. (%)	92	53 (57.6)	39 (42.4)	…
Fibrinogen, mg/dL	397 (86.3)	417.2 (93.6)	367.9 (66.6)	.008
Albumin, mg/dL	4.21 (0.35)	4.14 (0.39)	4.31 (0.26)	.025
CRP, IU/mL	7.94 (12.2)	9.9 (15.5)	5.2 (4.09)	ns
α_1-Antitrypsin, ng/dL	162.1 (30.5)	166.3 (29.2)	156.1 (31.8)	ns
Po_2/Pco_2, mm Hg	63.4/42.9	61.9/43.4	65.4/42.3	ns
FEV_1/FVC, % predicted	47.6 (11.8)	45.1 (11,9)	51.2 (10.1)	.02
Post-BD FEV_1, mL	1,210 (433)	1,107 (397)	1,350 (446)	.007
% Predicted	49.9 (15.6)	46.4 (16,3)	54.8 (13.3)	.01
Post-BD FVC, mL	2,607 (753)	2,478 (659)	2,783 (841)	ns
% Predicted	80 (18.6)	77.3 (18.2)	83.7 (18.7)	ns
$FEV_1 \leq 50\%$, No. (%)	51 (55.4)	37 (69.8)	14 (35.9)	.001
Patients with at least one PPM isolate, No. (%)[a]	39 (42.4)	25 (47.2)	14 (35.9)	.01
Patients with chronic colonization by PPM, No. (%)	20 (21.7)	18 (33.9)	2 (5.1)	.001
Pseudomonas aeruginosa isolates, No. (%)	7 (7.6)	6 (11.3)	1 (2.6)	ns
Haemophilus influenzae isolates, No. (%)	28 (30.4)	20 (37.7)	8 (20.5)	ns

CHEST 2011; 140(5):1130–1137

Factors Associated With Bronchiectasis in Patients With COPD

Table 4—*PPMs Found During the Study*

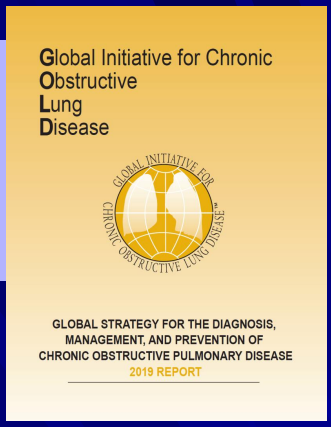
PPM	COPD With Bronchiectasis		COPD Without Bronchiectasis	
	Isolation[a] (n = 25)	Chronic Colonization (n = 18)	Isolation[a] (n = 14)	Chronic Colonization (n = 2)
Haemophilus influenzae	12	8	6	2
Streptococcus pneumoniae	6	3	4	0
Moraxella catarrhalis	4	2	3	0
Pseudomonas aeruginosa	2	4	1	0
Haemophilus parainfluenzae	0	1	0	0
Klebsiella pneumoniae	1	0	0	0

Data from the 44 patients with single isolates of a PPM (left-hand column) or chronic colonization by PPMs (right-hand column). See Table 3 legend for expansion of abbreviation.

[a]Eighteen patients with a single PPM isolate, plus six patients with two separate PPM isolates, plus nine patients with chronic PPM colonization and positive cultures for a separate PPM during the study. Isolates that form part of a chronic colonization were not included (a chronic colonization was defined as at least three isolates in three different months).

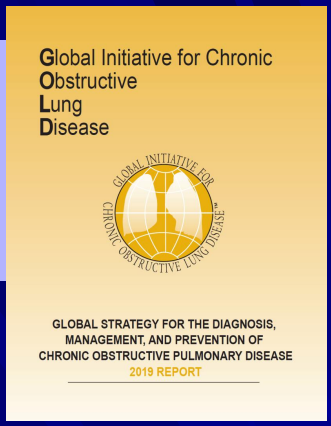
CHEST 2011; 140(5):1130–1137

GOLD report 2019



- With increasing use of CT in the assessment of patients with COPD, the presence of previous unrecognized BE is being identified.
- Whether this diagnosis on radiological criteria has the same impact as a clinical diagnosis of BE **remains unknown** at present, although it is associated with **longer exacerbations and increasing mortality**.

GOLD report 2019



- BE should be treated according to usual guidelines.
- Regarding COPD treatment, some patients may need more aggressive and **prolonged antibiotic** therapy. Inhaled corticosteroids may **not be indicated** in patients with bacterial colonization or recurrent lower respiratory tract infections.

Outline

- Introduction
- The assessment of Non-Cystic Fibrosis Bronchiectasis (Non-CF BE)
- The impact of NTM and Pseudomonas on Non-CF BE
- Summary

The impact of Pseudomonas on Non-CF Bronchiectasis

The effect of Pseudomonas aeruginosa on pulmonary function in patients with bronchiectasis

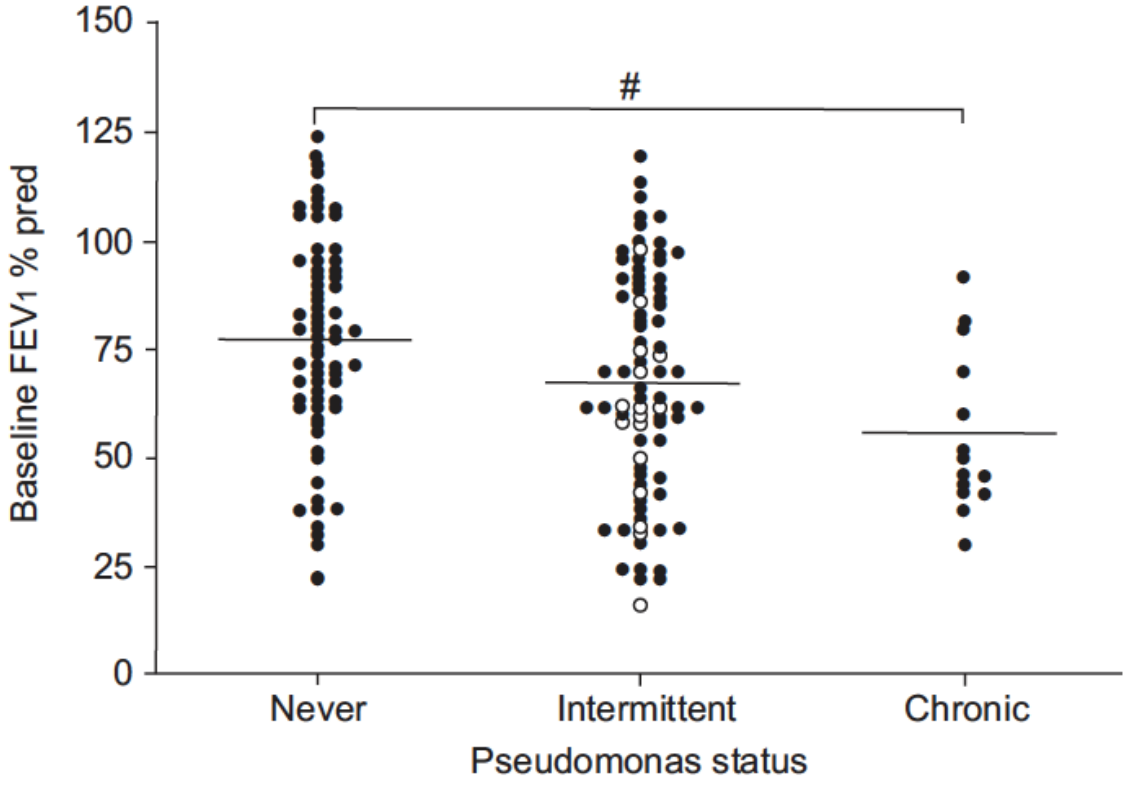


FIGURE 1. Comparison of baseline forced expiratory volume in one second (FEV_1) with pseudomonas status. ○: developed chronic *Pseudomonas aeruginosa* infection. % pred: % predicted. #: $p<0.005$.

G. Daves. Et al. Eur Respir J 2006; 28: 974–979

ORIGINAL RESEARCH

A Comprehensive Analysis of the Impact of *Pseudomonas aeruginosa* Colonization on Prognosis in Adult Bronchiectasis

Simon Finch[1], Melissa J. McDonnell[2], Hani Abo-Leyah[1], Stefano Aliberti[3], and James D. Chalmers[1]

[1]Tayside Respiratory Research Group, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom; [2]Department of Respiratory Medicine, Galway University Hospitals, Galway, Ireland; and [3]Department of Health Science, University of Milan-Bicocca, Pneumology Clinic, San Gerardo Hospital, Monza, Italy

Annals ATS Volume 12 Number 11| November 2015

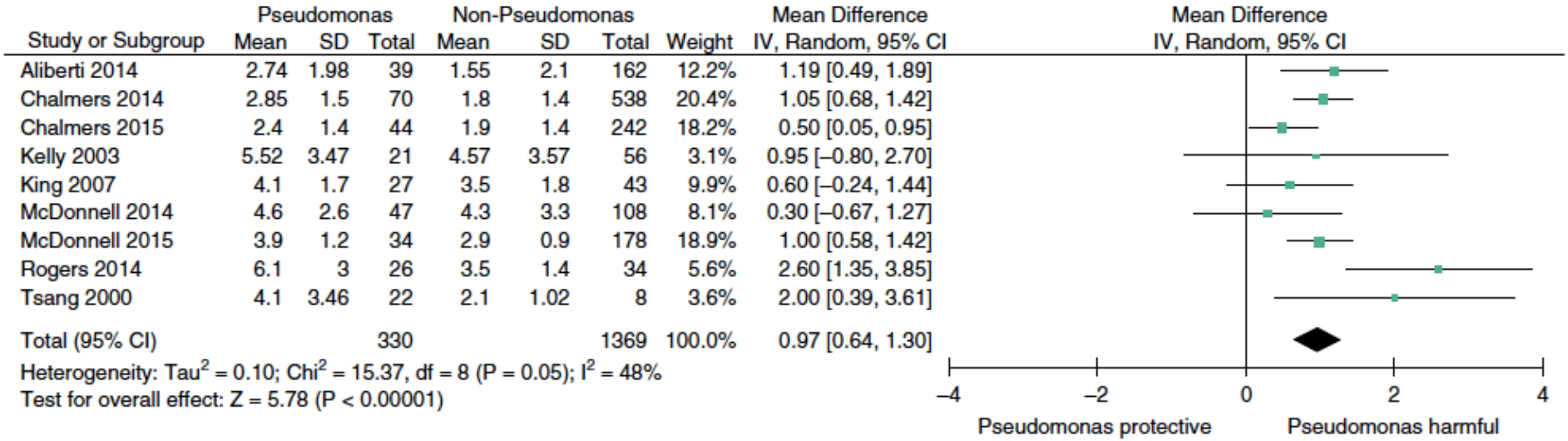
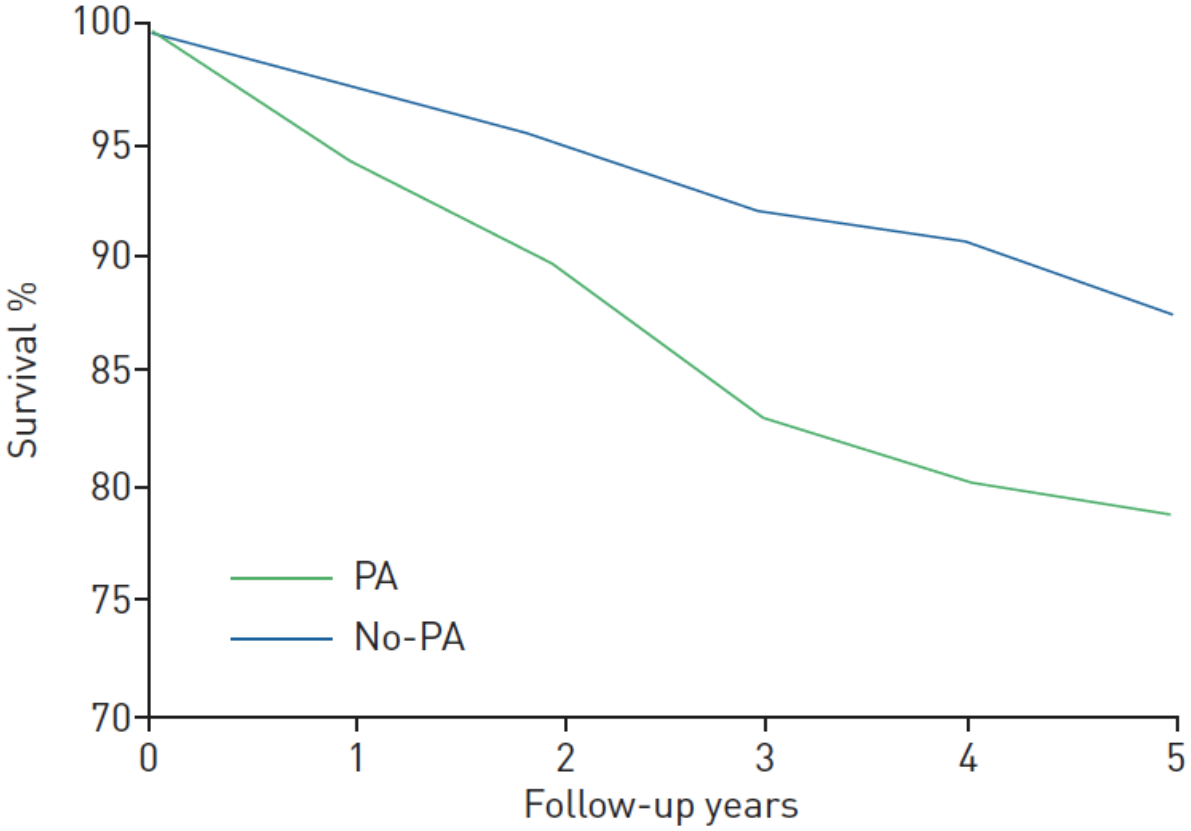


Figure 4. Exacerbation frequency compared between patients with *Pseudomonas aeruginosa* colonization and patients without *P. aeruginosa* colonization. CI = confidence interval; IV = inverse variance.

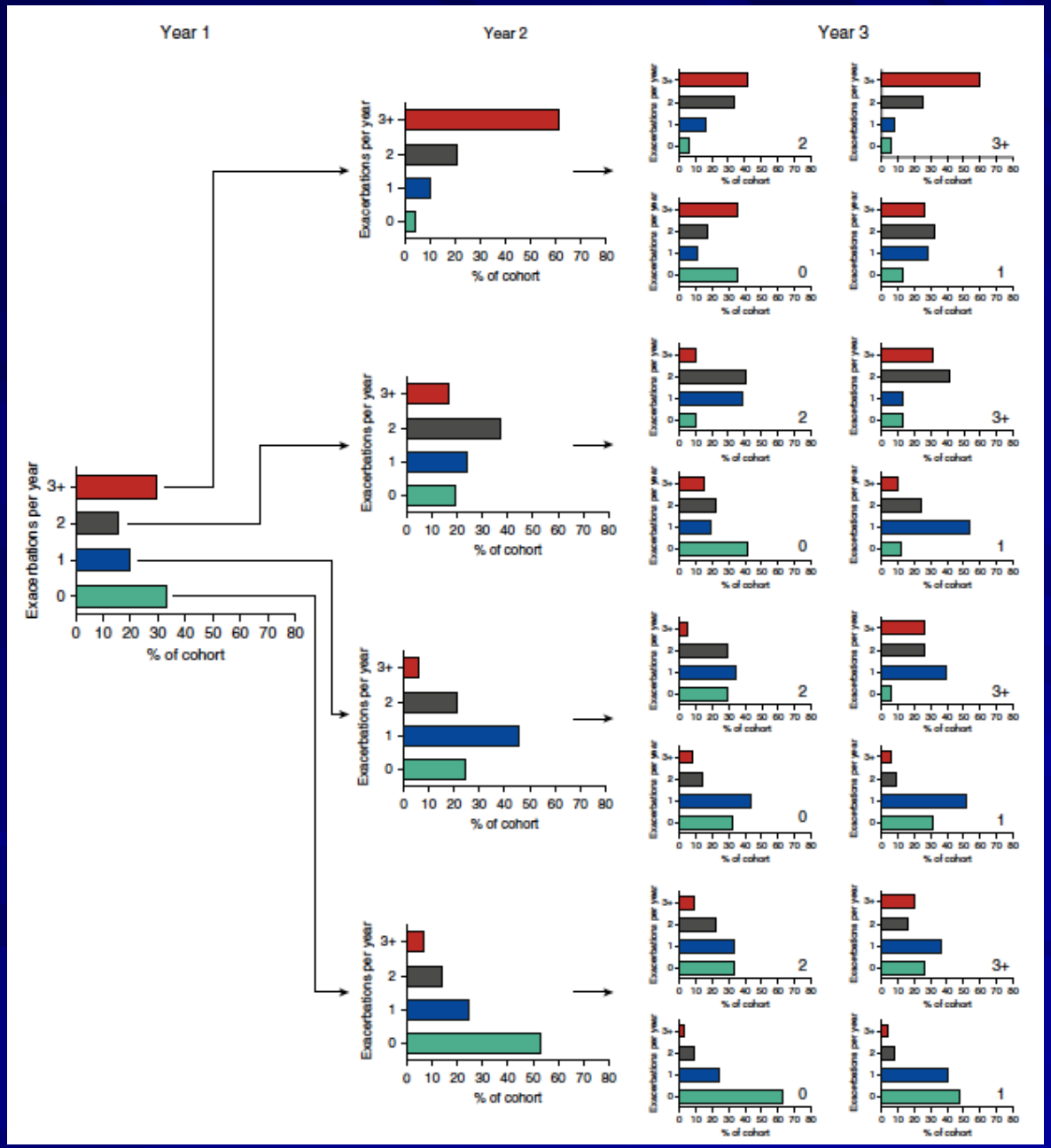
The independent contribution of Pseudomonas aeruginosa infection to long-term clinical outcomes in bronchiectasis



Kaplan–Meier log-rank test survival curve and univariate analysis for mortality: chronic Pseudomonas aeruginosa (PA) infection versus all other patients

Eur Respir J 2018; 51: 1701953

Characterization of the “Frequent Exacerbator Phenotype” in BE



James D. Chalmers1

AJRCCM Vol 197, Iss 11, pp 1410–1420, Jun 1, 2018

Characterization of the "Frequent Exacerbator Phenotype" in BE

James D. Chalmers

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.

AJRCCM Vol 197, Iss 11, pp 1410–1420, Jun 1, 2018

The prevalence of NTM on Non-CF Bronchiectasis

Máiz et al. BM
DOI 10.1186/s

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L. Máiz[1*], R.

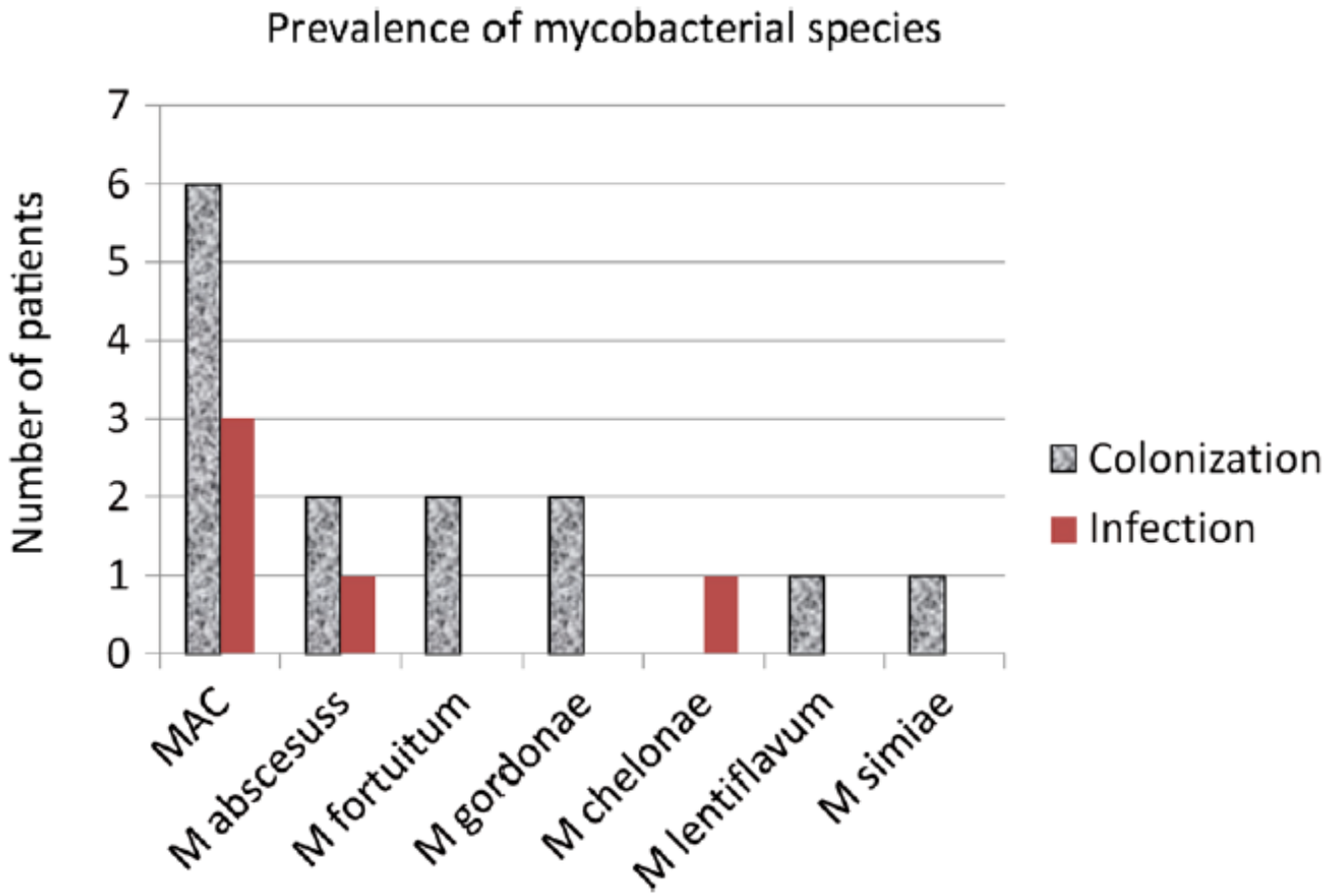


Fig. 1 Number of patients with positive non-tuberculous mycobacterial cultures (NTM), grouped by mycobacterial species. Patients who met American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) microbiologic criteria for NTM disease are represented in the shaded bars and those who did not meet ATS/IDSA criteria are represented in solid bars. The patient with *Mycobacterium simiae* also had *M. avium* complex (MAC)

Variable	NTM positive ($n = 18$)	NTM negative ($n = 200$)	p-value
Age, yr[a]	64 (13.3)	54.9 (15.9)	0.02
Age ≥ 50 years	15 (83.3 %)	126 (63 %)	0.06
Gender (% females)[b]	78 %	60 %	0.2
BMI, kg/m^2[a]	23.5 (4.8)	24.9 (4.6)	0.24
BMI ≤ 23 kg/m^2[b]	11 (61.1 %)	65 (32.5 %)	0.034
Idiopathic	5 (27.8 %)	60 (30 %)	0.79
Post-infection	6 (33.3 %)	72 (36 %)	
Systemic diseases	4 (22.2 %)	24 (12 %)	
Immunodeficiency	1 (5.6 %)	4 (2 %)	
COPD	2 (11.1 %)	28 (14 %)	
Ciliary dyskinesia	0	7 (3.3 %)	
Other	0	5 (2.5 %)	
Smoking history (pack-years)[c]	22.2 (33)	11.6 (25.6)	0.2
Dyspnea (mMRC)	1.29 (1.3)	1.33 (1.13)	0.8
Macroscopic appearance of sputum (muco-purulent or purulent)[a]	7 (39 %)	125 (62.5 %)	0.045
Cystic bronchiectasis[b]	4 (22 %)	52 (26 %)	0.7
Number of affected lobes[a]	2.9 (1.3)	2.6 (1.2)	0.2
FVC, % predicted[a]	82.5 (23)	73.5 (24)	0.09
FVC ≥ 75 % predicted[b]	14 (77.8 %)	94 (47 %)	0.011
FEV_1, % predicted[a]	72.3 (26)	63 (25)	0.15
Chronic *P. aeruginosa* infection[b]	5 (28 %)	88 (44 %)	0.1
Chronic *H. influenzae* infection[b]	2 (11 %)	46 (23 %)	0.1
Chronic bacterial infection, other PPMs[b]	2 (12 %)	90 (45 %)	0.05

Adult Patients With Bronchiectasis

A First Look at the US Bronchiectasis Research Registry

TABLE 2] Symptoms in Patients With Bronchiectasis by NTM Status[a]

Symptom	Data Available (No.)	Overall (N = 1,826)	NTM (n = 1,158)	No NTM (n = 668)	*P* Value[b]
Fatigue, No. (%)	1,770				
Yes		886 (50)	591 (53)	295 (46)	< .01
Daily bouts of coughing, No. (%)	1,804				
Yes, any		1,314 (73)	825 (72)	489 (74)	.32
Daily productive cough, No. (%)	1,788				
Yes, productive cough		951 (53)	568 (50)	383 (59)	< .01
Hemoptysis, No. (%)	175				
Yes		409 (23)	283 (25)	126 (19)	< .01
Dyspnea, No. (%)	1,442				
No, not at rest or when active		663 (46)	420 (46)	243 (46)	.98
Yes, only when active		779 (54)	493 (54)	286 (54)	

Timothy R. Aksamit, MD et al. CHEST 2017; 151(5):982-992

Adult Patients With Bronchiectasis

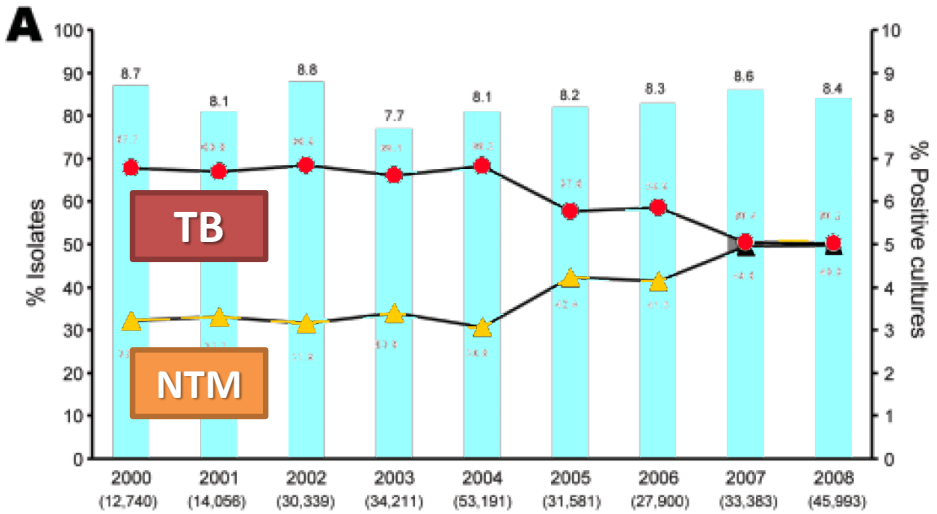
A First Look at the US Bronchiectasis Research Registry

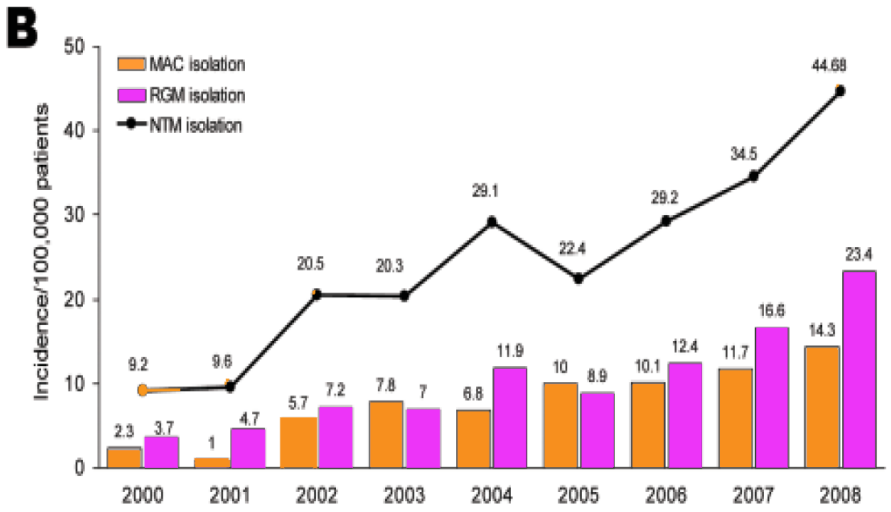
TABLE 3] Spirometric Test Results for Patients With Bronchiectasis

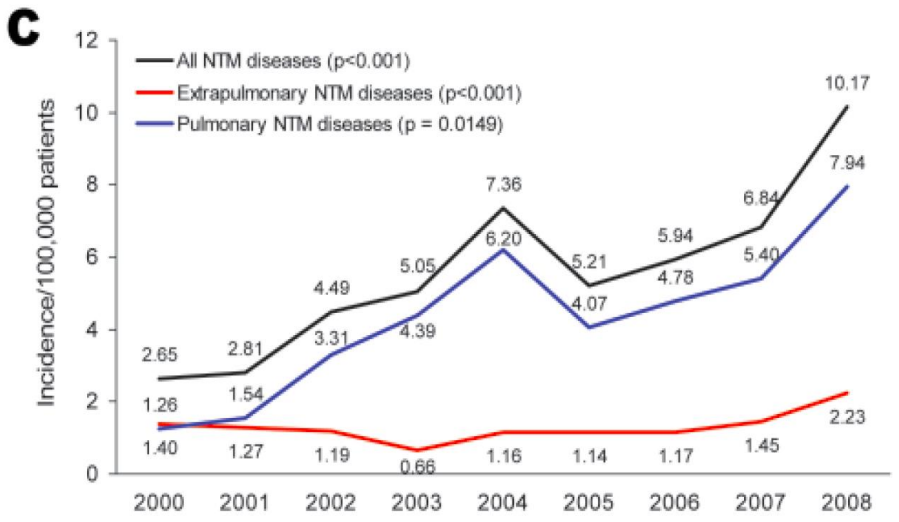
Results	Data Available (No.)	Overall (N = 1,826)	NTM (n = 1,158)	No NTM (n = 668)	*P* Value[a]
Prebronchodilator findings, No. (%)[b]	1,552				
$FEV_1/FVC \geq 0.70$, $FVC \geq 0.80$, and $FEV_1 \geq 0.80$ (normal)		399 (26)	252 (26)	147 (26)	
$FEV_1/FVC \geq 0.70$, $FVC \geq 0.80$, and $FEV_1 < 0.80$ (nearly normal)		363 (23)	229 (23)	134 (24)	
Any obstruction		790 (51)	502 (51)	208 (51)	.86
Mild or moderate obstruction		555 (36)	366 (37)	189 (33)	.11
Severe or very severe obstruction		235 (15)	136 (14)	99 (17)	.06
Restriction		317 (20)	200 (20)	117 (21)	.92
Postbronchodilator findings, No. (%)[c]	963				
FVC or FEV_1 improved $\geq 12\%$		47 (5)	33 (5)	14 (4)	

Timothy R. Aksamit, MD et al. CHEST 2017; 151(5):982-992

Increasing Incidence of Nontuberculous Mycobacteria, Taiwan, 2000–2008







Emerging Infectious Diseases Vol. 16, No. 2, 2010: 294-296

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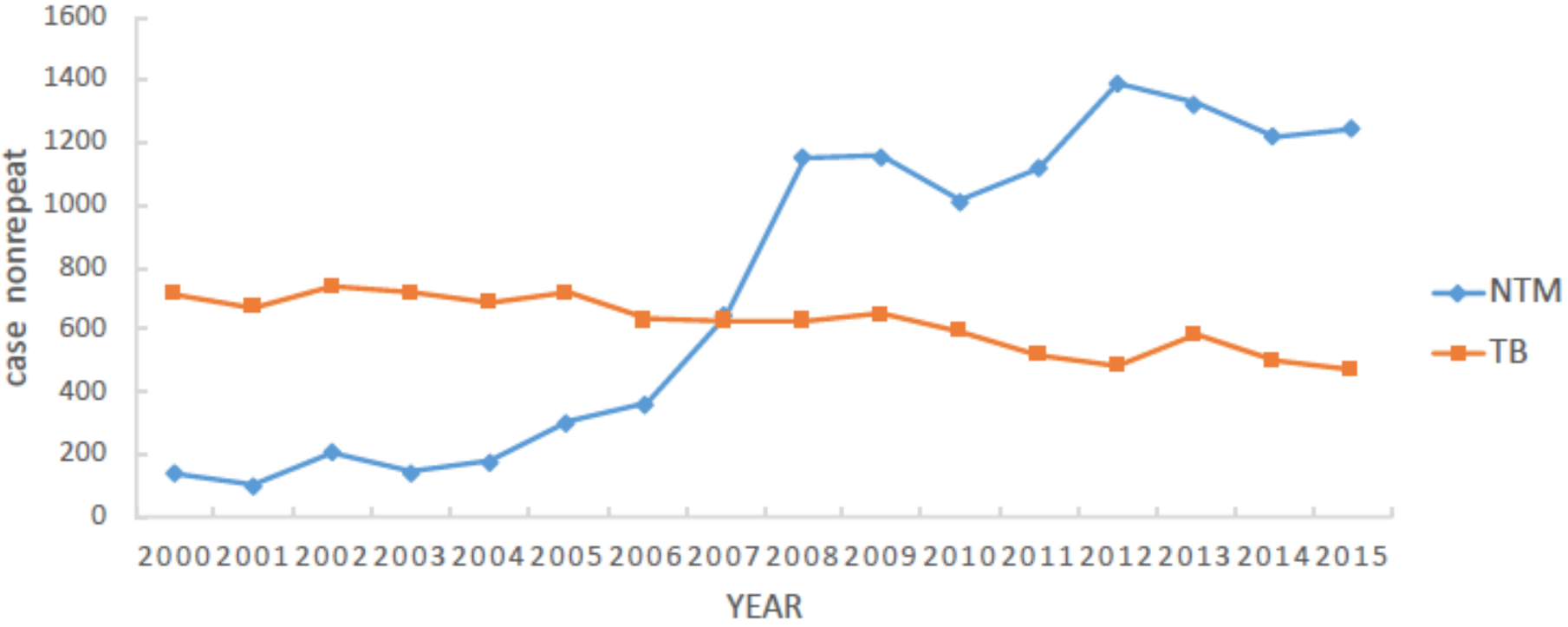


NTM Species

- *M. avium* Complex (MAC)
- *M. kansasii*
- *M. abscessus*
- *M. chelonae*
- *M. fortuitum*
- *M. genavense*
- *M. gordonae*
- *M. haemophilum*
- *M. immunogenum*
- *M. malmoense*
- *M. marinum*
- *M. mucogenicum*
- *M. nonchromogenicum*
- *M. scrofulaceum*
- *M. simiae*

579 isolates from 279 patients

275 isolates from 174 patients

258 isolates from 186 patients

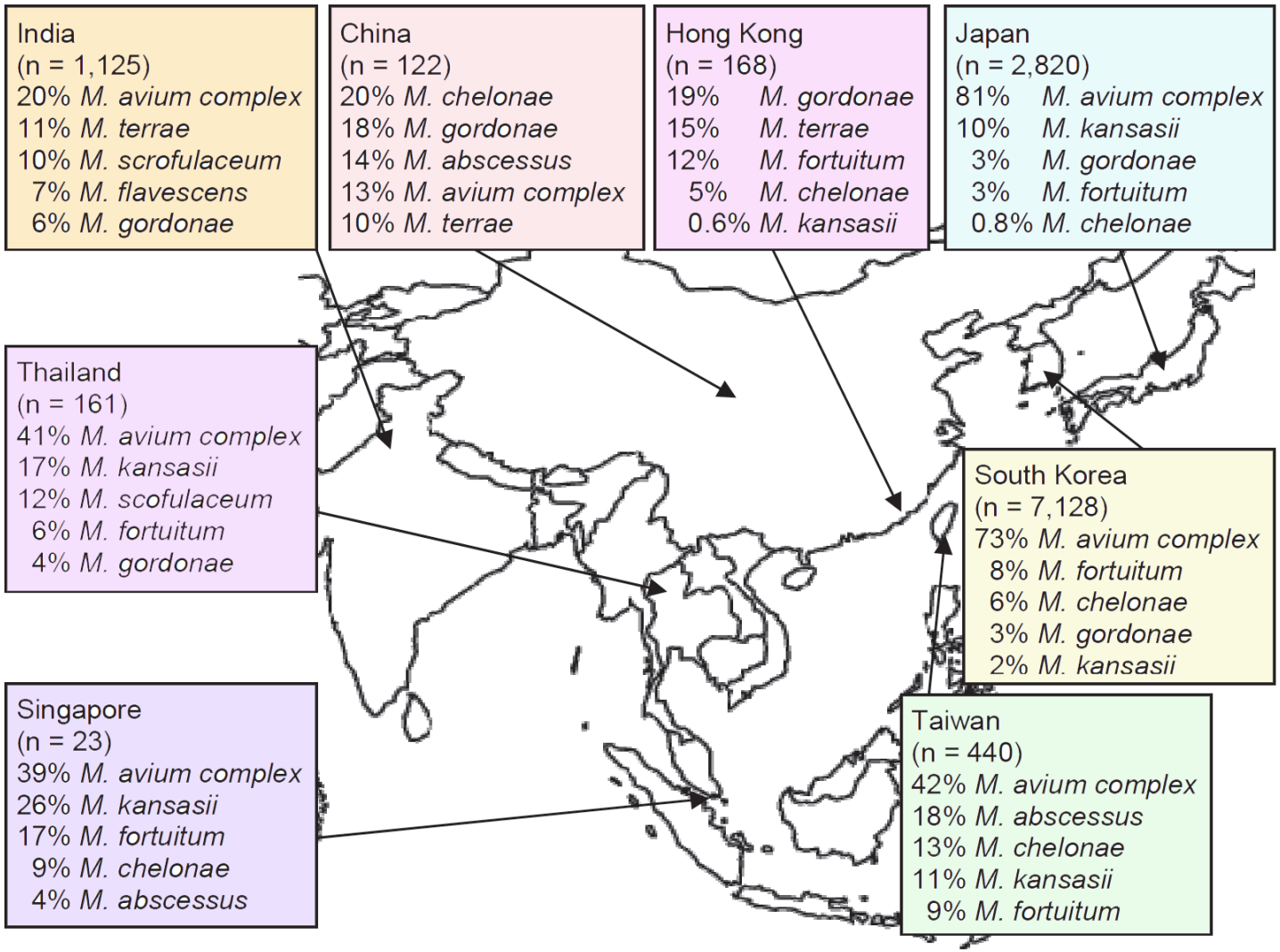
Slow-growing NTM	Rapidly growing NTM
M. avium complex	*M. fortuitum*[a]
M. kansasii	*M. abscessus*
M. malmoense	*M. chelonae*[a]
M. xenopi	*M. celatum*[a]
M. szulgai[a]	
M. scofulaceum[a]	
M. simiae[a]	

[a] Uncommon

An Official ATS/IDSA Statement

NTUH 2009

Nontuberculous Mycobacteria in Respiratory Tract Infections, Eastern Asia



Five most prevalent NTM species in **respiratory specimens,** regardless of clinical relevance, Asia, 1971–2007.

Emerging Infectious Diseases Vol. 17, No. 3, 2011: 343-349

Infection and Drug Resistance

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ORIGINAL RESEARCH

Impact of concomitant nontuberculous mycobacteria and *Pseudomonas aeruginosa* isolates in non-cystic fibrosis bronchiectasis

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Purpose: *Pseudomonas aeruginosa* is associated with pulmonary function decline and high disease severity in non-cystic fibrosis (CF) bronchiectasis. The prevalence of nontuberculous mycobacteria (NTM) in non-CF bronchiectasis patients has increased recently. This study investigated the impact of NTM with or without *P. aeruginosa* isolates in non-CF bronchiectasis patients.
Patients and methods: Our retrospective study included 96 non-CF bronchiectasis patients from January 2005 to December 2014. We recorded the presentation, exacerbations, emergency department (ED) visits, hospitalization, serial pulmonary function, radiologic studies, and sputum culture results. All patients were followed up for at least 2 years.
Results: The 96 patients were divided into four groups: patients with concomitant negative NTM and *P. aeruginosa* isolates (n=41; group 1), patients with positive NTM isolates (n=20; group 2), patients with positive *P. aeruginosa* isolates (n=20; group 3), and patients with concomitant positive NTM and *P. aeruginosa* isolates (n=15; group 4). Compared with group 1

Background

Pseudomonas aeruginosa

- **Greater** pulmonary function decline
- **More** frequent exacerbations
- **More** hospital admissions
- **Increased** mortality

NTM

- Prevalence ranges wildly (2%~37%)
- **Increasing** in recent years

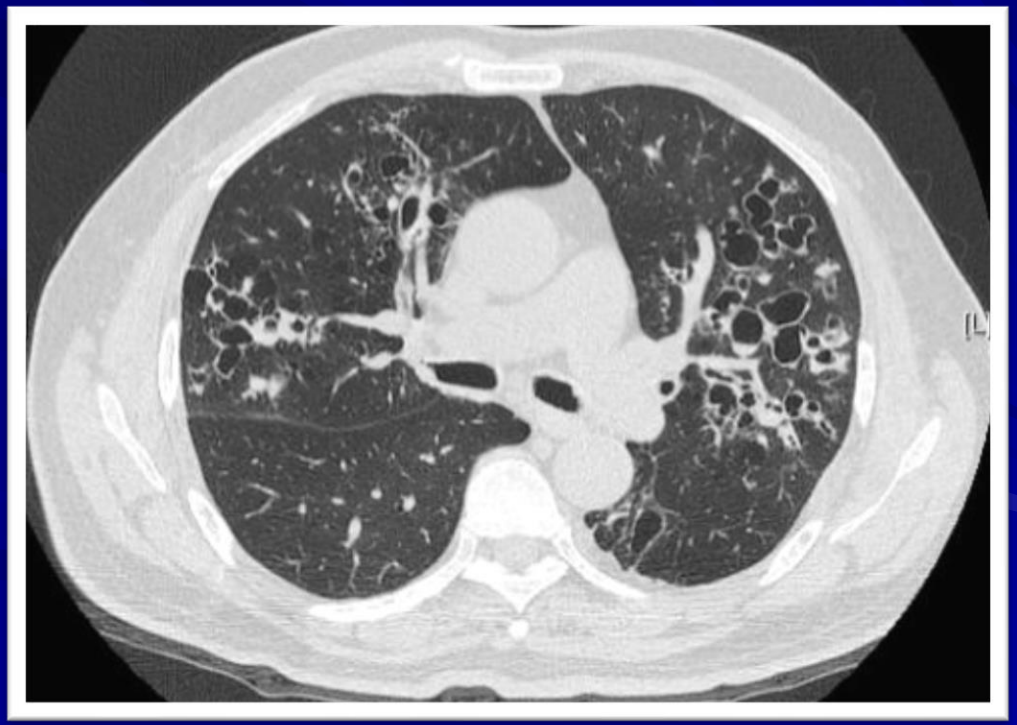
Material and Methods

Jan 2005 ~ Dec 2014

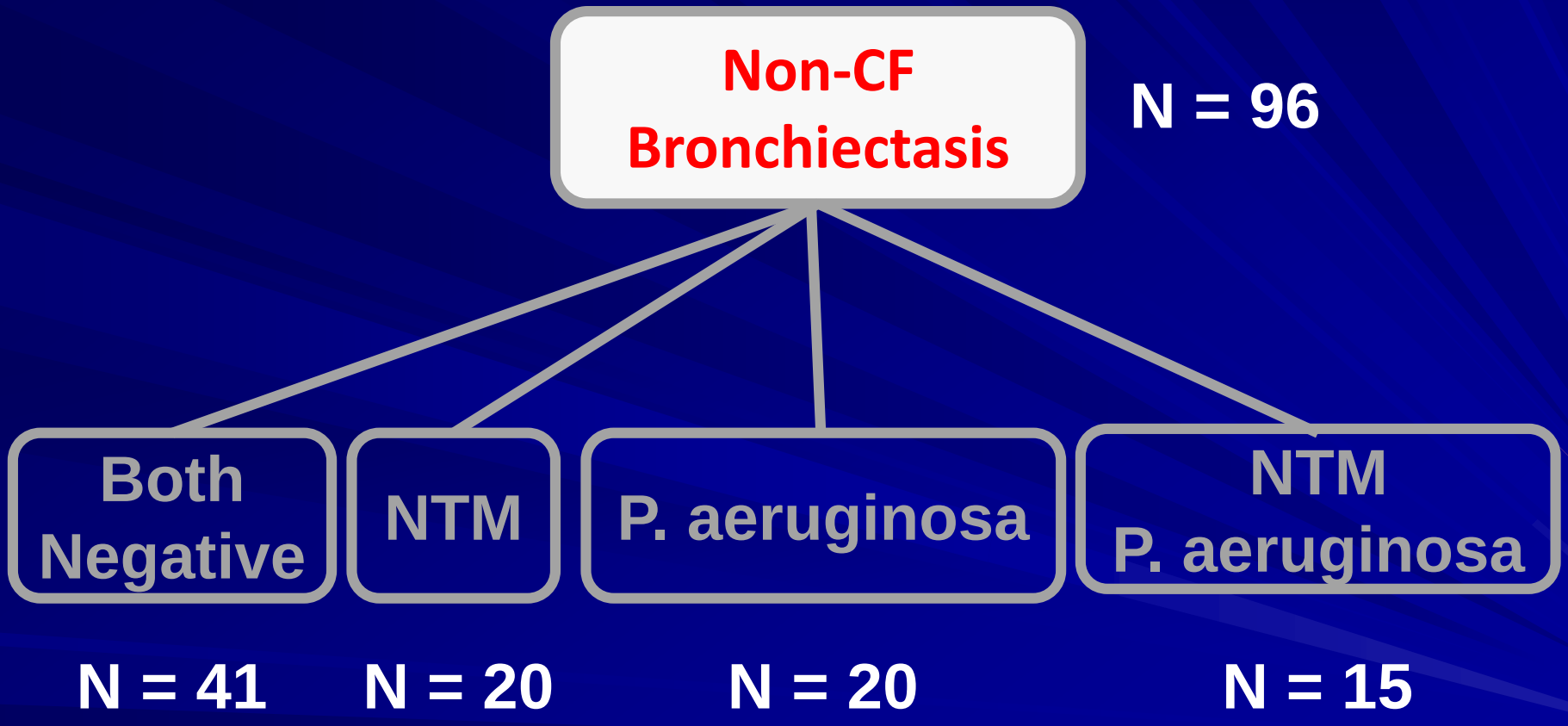
Linkou Medical Center of Chang Gung Memorial Hospital

Retrospective

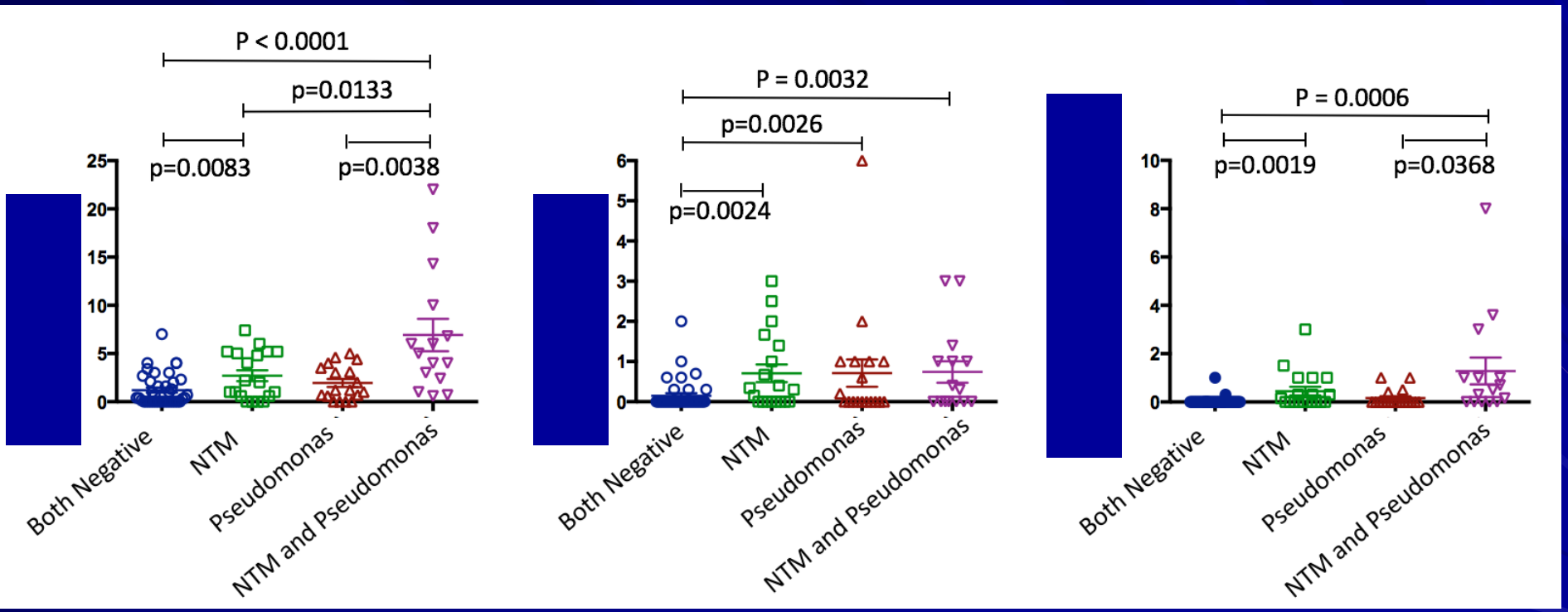
Non-CF Bronchiectasis



Results

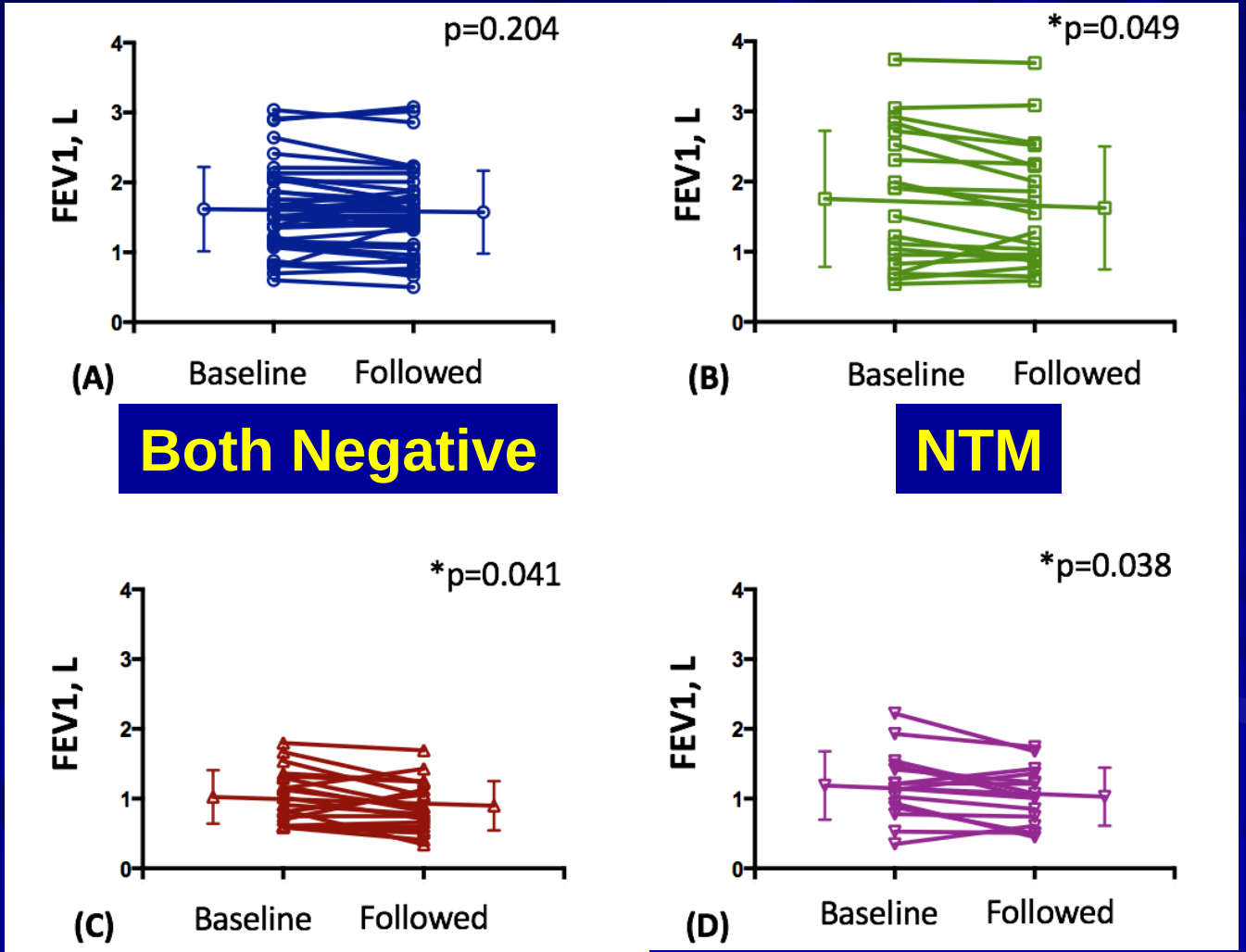

Non-CF Bronchiectasis
N = 96
Both Negative
NTM
P. aeruginosa
NTM P. aeruginosa
N = 41
N = 20
N = 20
N = 15

Results



Exacerbation **ED visit** **Hospitalization**

Results


p=0.204
FEV1, L
4
3
2
1
0
(A)
Baseline
Followed
Both Negative
*p=0.049
FEV1, L
4
3
2
1
0
(B)
Baseline
Followed
NTM
*p=0.041
FEV1, L
4
3
2
1
0
(C)
Baseline
Followed
P. aeruginosa
*p=0.038
FEV1, L
4
3
2
1
0
(D)
Baseline
Followed
NTM and P. aeruginosa

Results

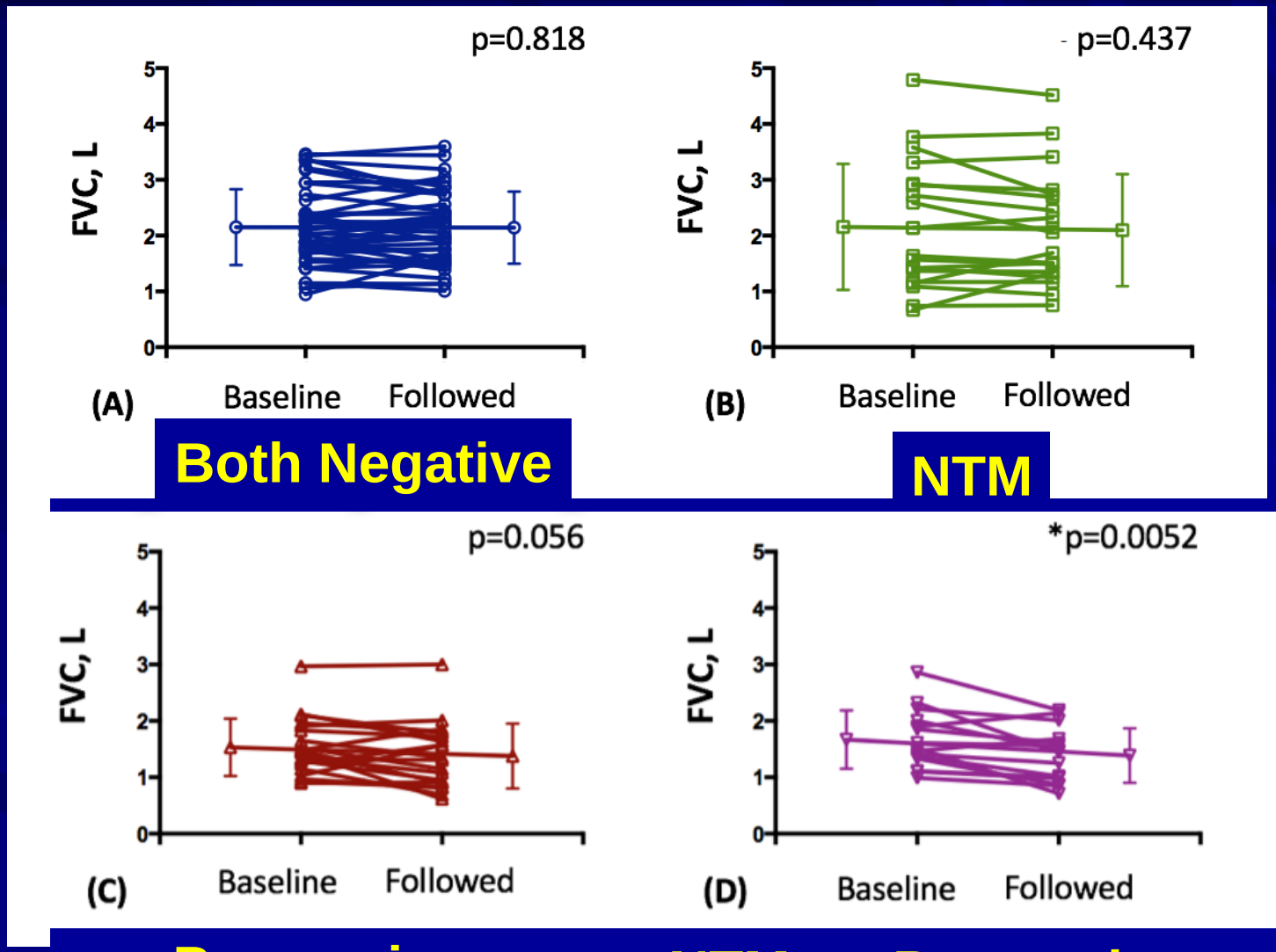

p=0.818
FVC, L
5
4
3
2
1
0
(A)
Baseline
Followed
Both Negative
p=0.437
FVC, L
5
4
3
2
1
0
(B)
Baseline
Followed
NTM
p=0.056
FVC, L
5
4
3
2
1
0
(C)
Baseline
Followed
P. aeruginosa
*p=0.0052
FVC, L
5
4
3
2
1
0
(D)
Baseline
Followed
NTM and P. aeruginosa

Table 3 NTM species isolated from sputum samples in non-CF bronchiectasis patients

NTM species	Group 2 n=20 n (%)	Group 4 n=15 n (%)
Mycobacterium avium–Mycobacterium intracellulare complex	10 (50)	8 (53.3)
Mycobacterium fortuitum	2 (10)	6 (40)
Mycobacterium chelonae	4 (20)	4 (26.7)
Mycobacterium abscessus	2 (10)	3 (20)
Mycobacterium gordonae	2 (10)	2 (13.3)
Mycobacterium kansasii	1 (5)	0 (0)
Mycobacterium mageritense	1 (5)	0 (0)
Mycobacterium scrofulaceum	0 (0)	1 (6.7)
Mycobacterium peregrinum	0 (0)	1 (6.7)
Unidentified	4 (20)	2 (13.3)

Abbreviations: CF, cystic fibrosis; NTM, nontuberculous mycobacteria.

Conclusion

NTM isolation in non-CF bronchiectasis

greater **FEV1** decline

more **Exacerbations**

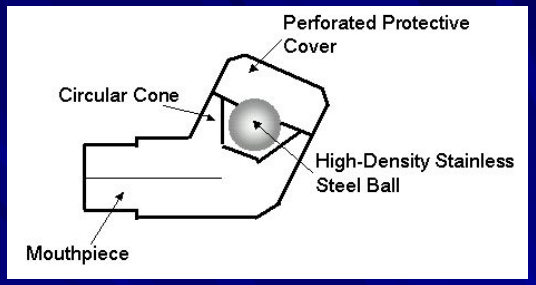
NTM and **P. aeruginosa** isolations

greatest **Pulmonary Function Decline**

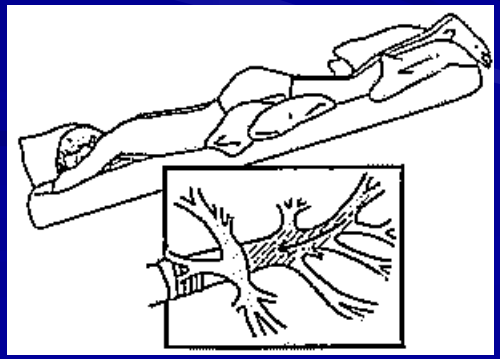
most frequent **Exacerbations**

TREATMENT

Treatments

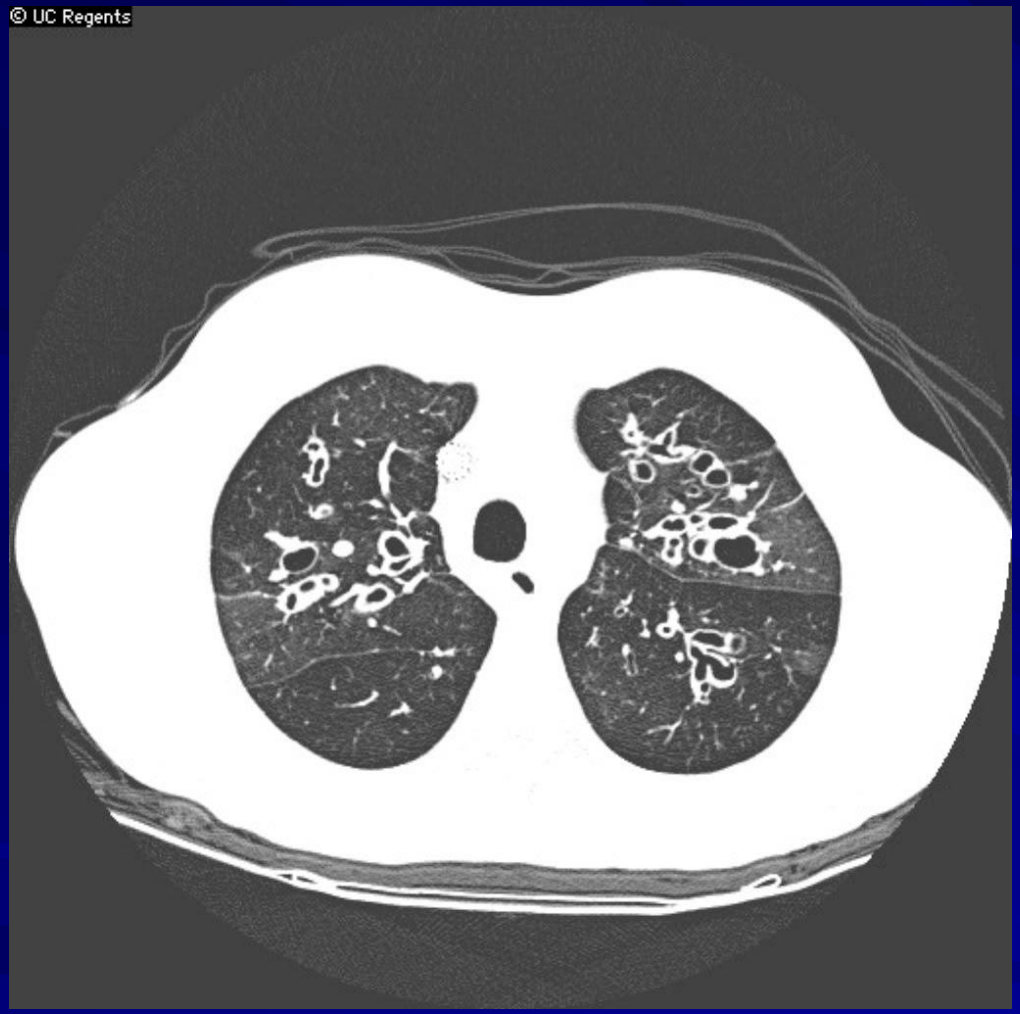


- **Airway Hygiene**
  - Mechanical "valve" devices (Flutter, Pep, Acapella, etc)
  - Postural drainage and chest physiotherapy
- **Mucus-Mobilizing Methods**
  - Inhaled beta-agonists and/or anticholinergic bronchodilators
  - Hypertonic saline or mannitol inhalation
- **Anti-inflammatory Airway Management**
  - Inhaled steroids (ICS)
  - Macrolide antibiotics (MLAs)

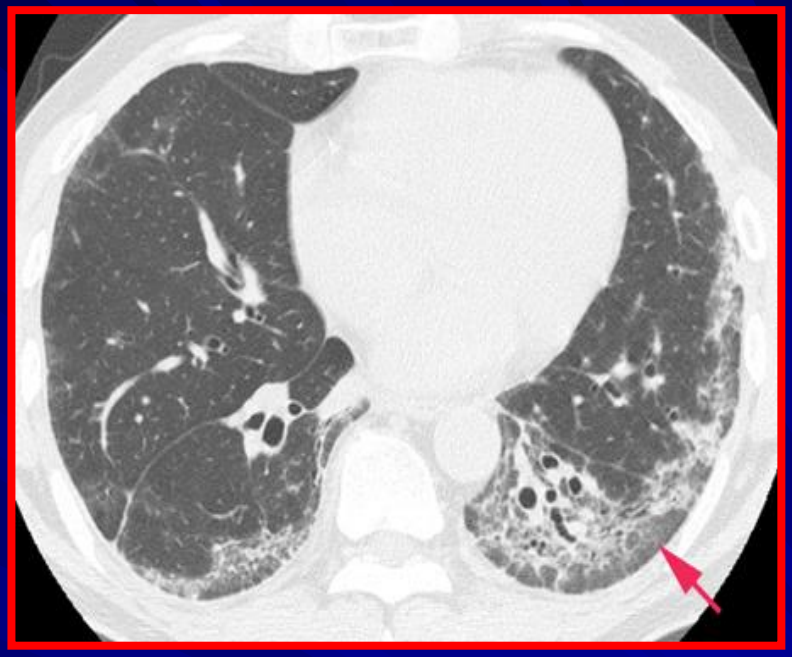


Treatments

- **Anti-aspiration Measures**
  - Anti-GERD management
  - Improved deglutition
  - Reducing gastric acid
- **Antimicrobial Therapy**
  - Episodic, targeted antibiotics
  - Rotating antibiotic therapy
  - Initial empirical followed by targeted antibiotics
- **Surgery**
  - Intractable massive bleeding
  - Uncontrollable infection
  - Aspergillus colonization or Aspergilloma

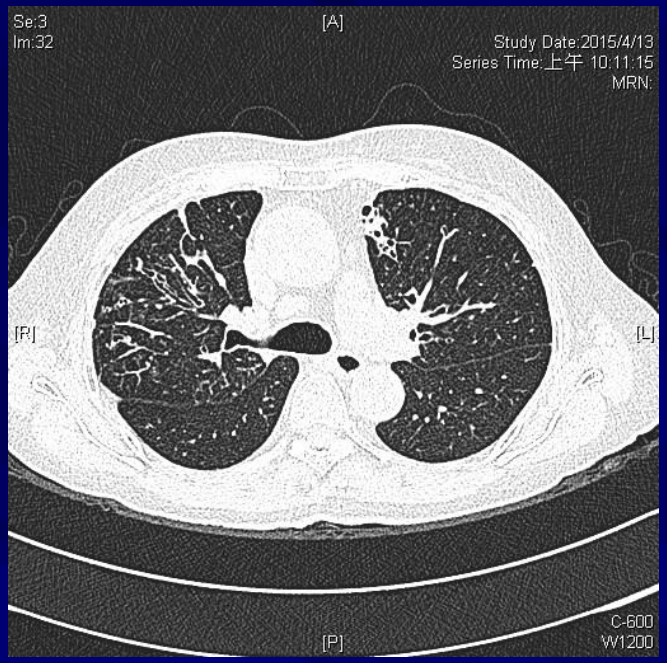


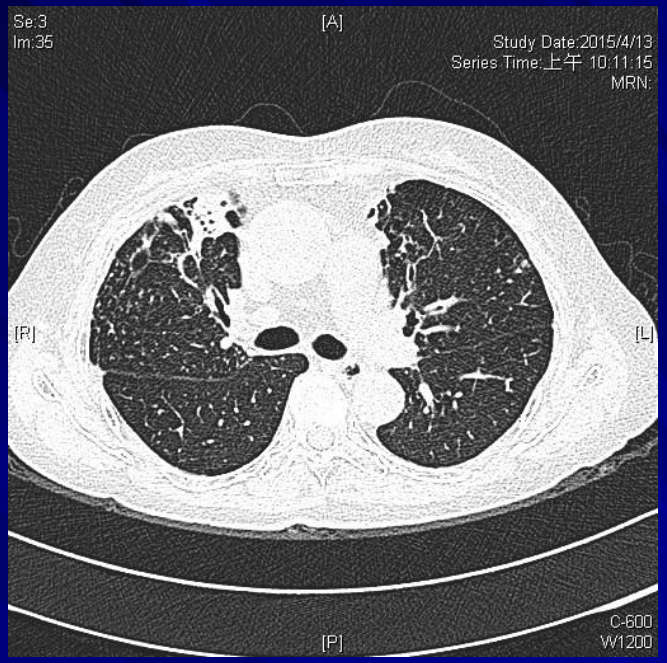
Mucus Retention



Saccular bronchiectasis

Traction bronchiectasis





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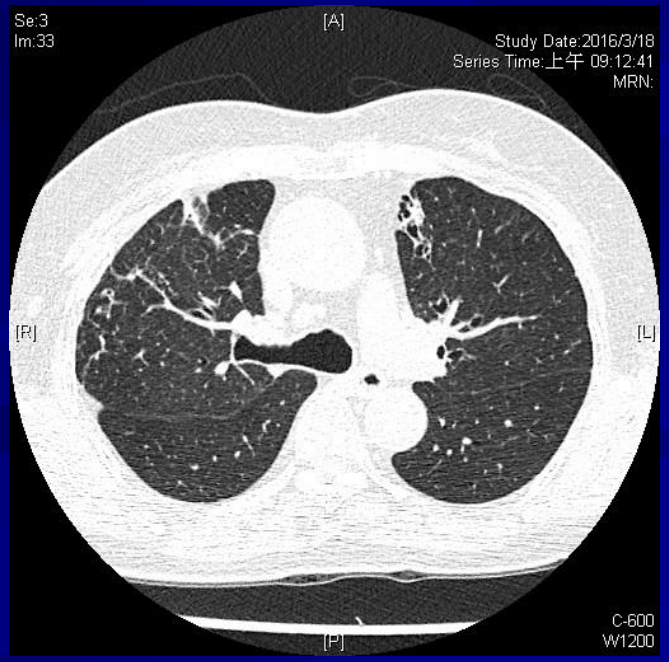

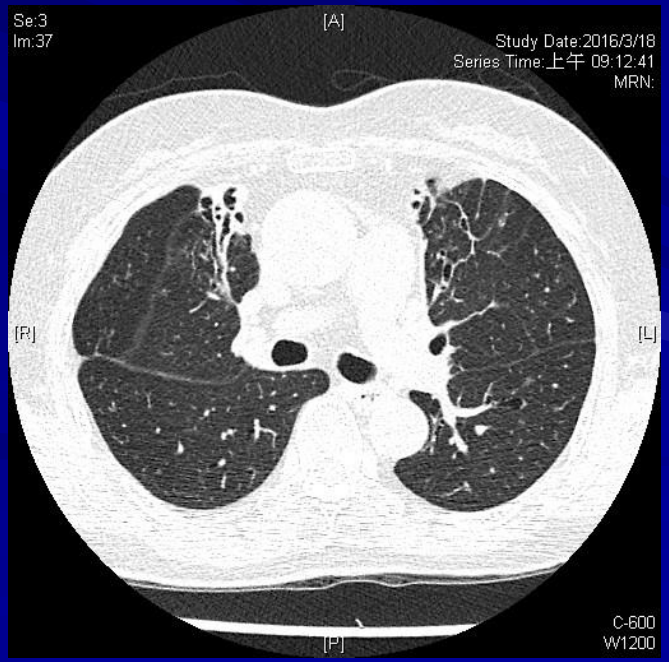

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Summary

- The prevalence of non CF bronchiectasis is increasing
- Two prognostic indices that aid clinical decisions are the bronchiectasis severity index (BSI) and the FACED score
- Patients with concomitant positive NTM and P. aeruginosa isolates have the greatest pulmonary function decline and the most frequent AE

Thanks for Your Attention!!

長庚紀念醫院
Chang Gung Memorial Hospital

TSPCCM