Cutting edge of non-CF Bronchiectasis

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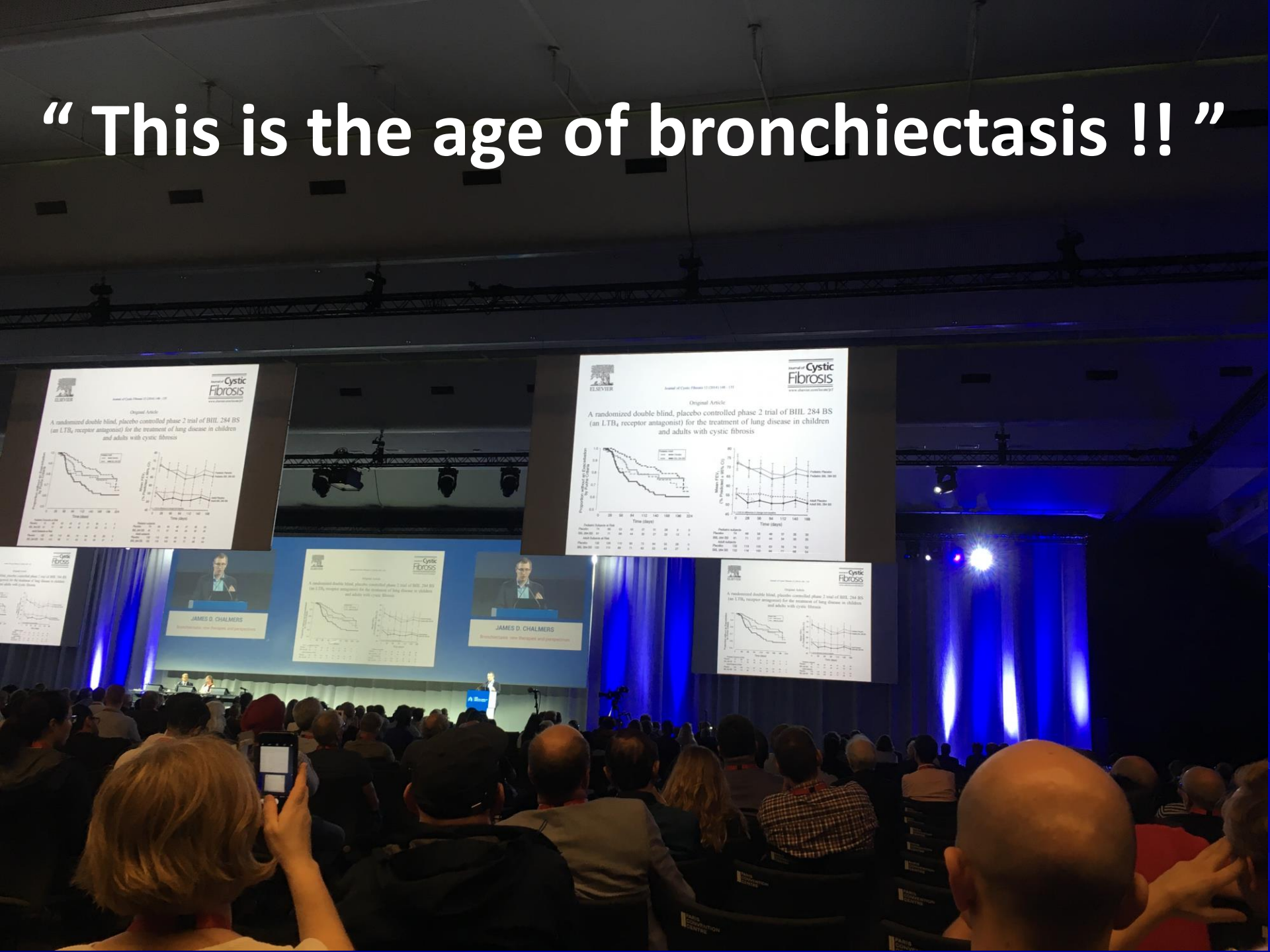
Outline

- Introduction
- The assessment of Non-Cystic Fibrosis Bronchiectasis (Non-CF BE)
- Management approach
- Summary


“ This is the age of bronchiectasis !! ”
Journal of Cystic Fibrosis
Original Article
A randomized double blind, placebo controlled phase 2 trial of BIIL 284 BS (an LTB4 receptor antagonist) for the treatment of lung disease in children and adults with cystic fibrosis
JAMES D. CHALMERS
Bronchiectasis: new therapies and perspectives

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]

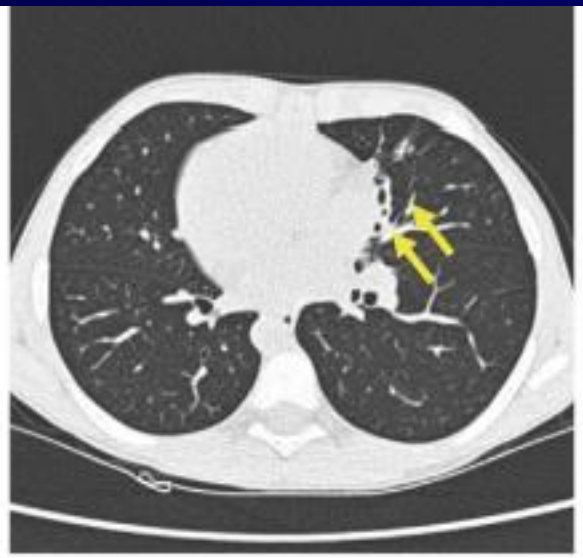
BRONCHIECTASIS is an uncommon disease with the potential to cause devastating illness, including repeated respiratory infections requiring antibiotics, disabling productive cough, shortness of breath, and occasional hemoptysis. Landmarks in the history of bronchiectasis include the vivid descriptions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

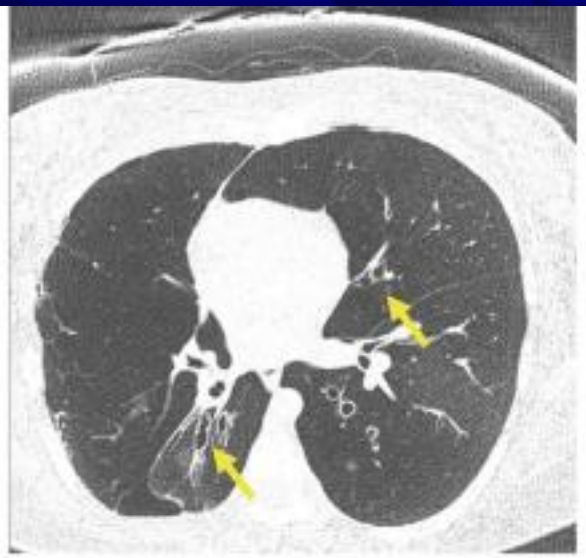
dilated airways alone and is sometimes seen as a residual effect of pneumonia; varicose bronchiectasis (so named because its appearance is similar to that of varicose veins) is characterized by focal constrictive areas along the dilated airways that result from defects in the bronchial wall; and saccular 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]

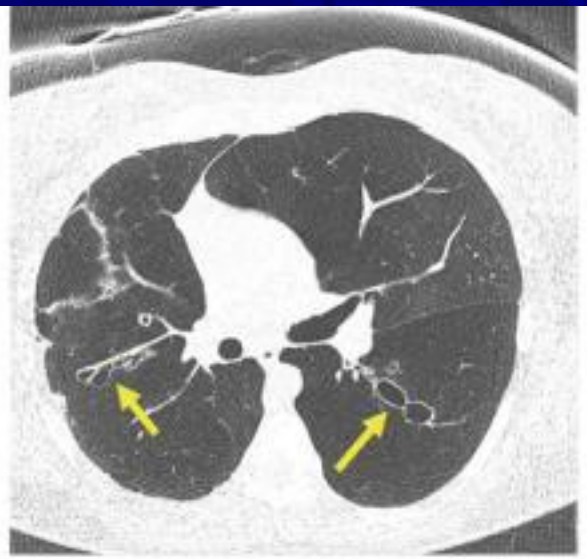
The prevalence of bronchiectasis in the United States and worldwide is unknown. There are reports of high prevalence in relatively isolated populations with poor access to health care and high rates of respiratory tract infections during childhood, such as Alaskan Natives in the Yukon–Kuskokwim Delta.[3]

PATHOPHYSIOLOGY

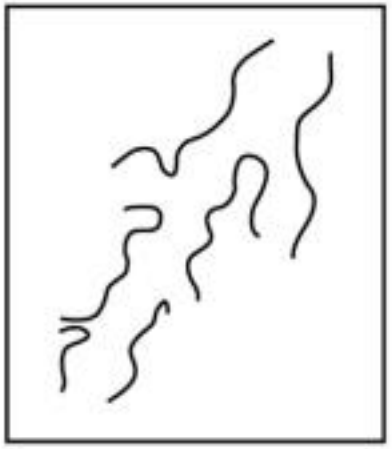
Bronchiectasis is primarily a disease of the bronchi and bronchioles involving a vicious circle of transmural infection and inflammation with mediator release.[4] Illness is related to retained inflammatory secretions and microbes that cause obstruction and damage



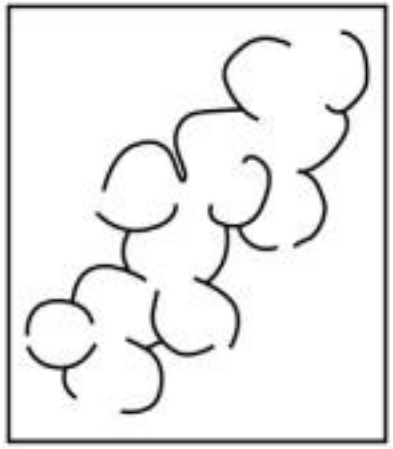




Cyclindrical

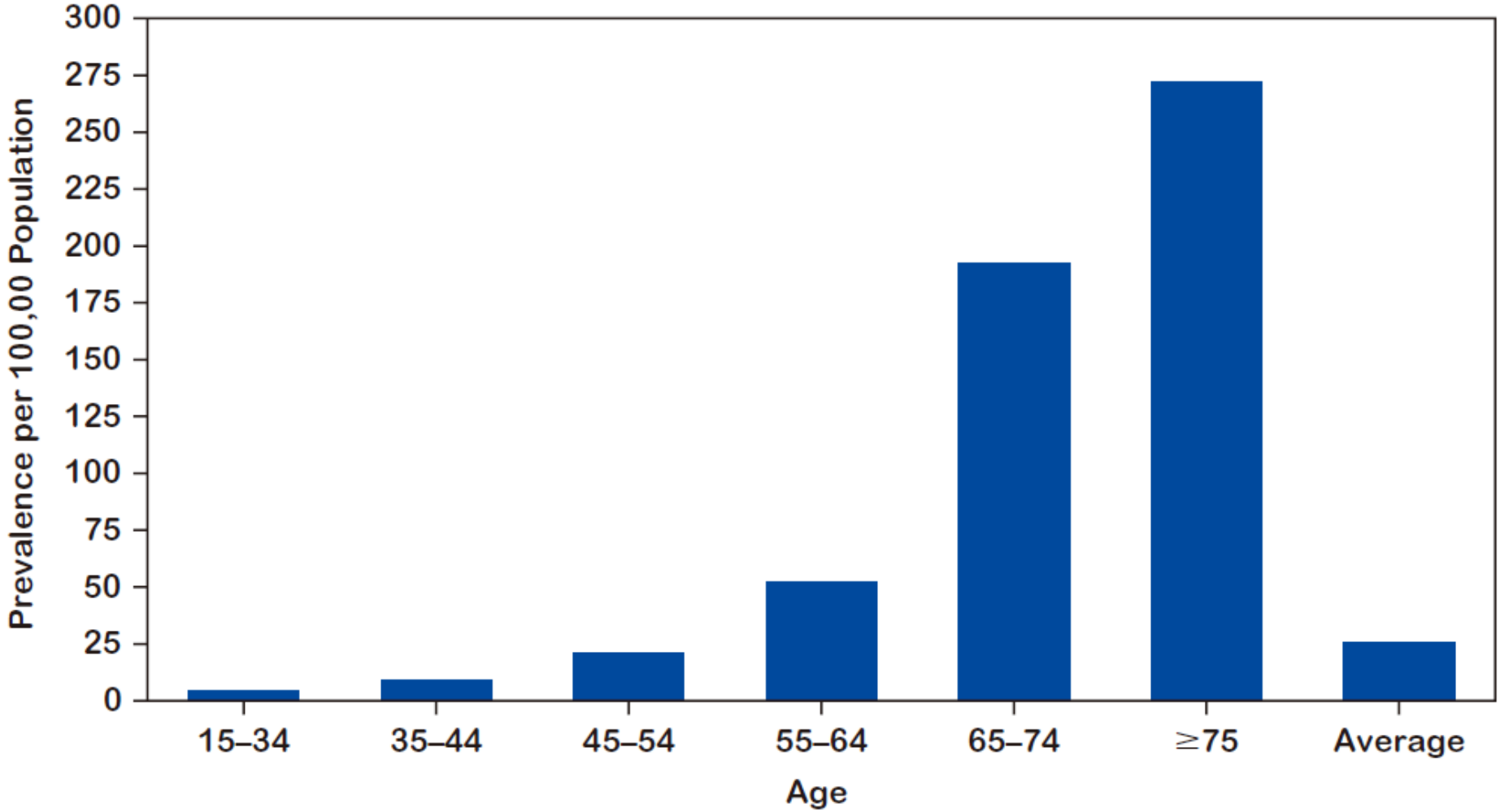


Varicose



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).

Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study

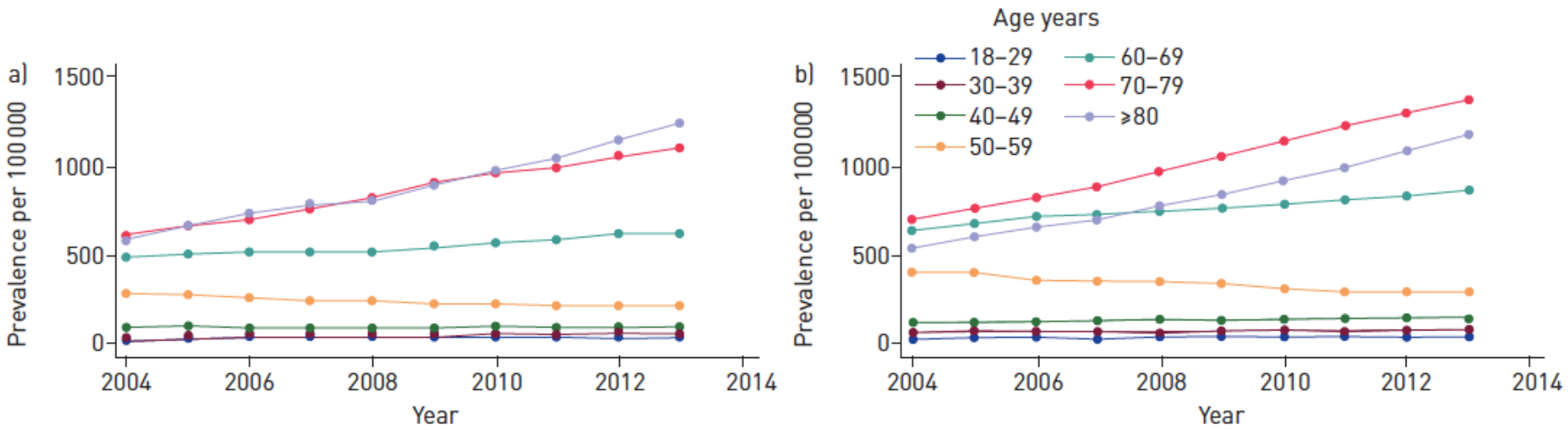


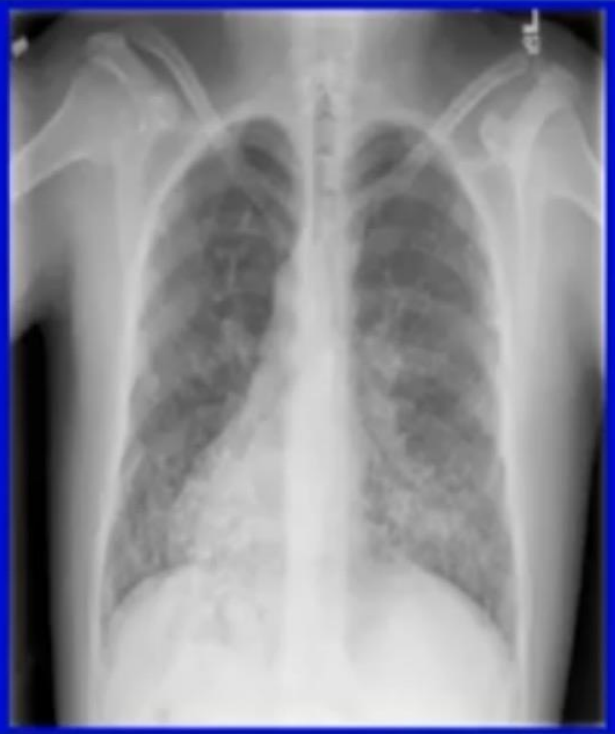
FIGURE 2 Prevalence of bronchiectasis in the UK from 2004 to 2013 stratified by age in a) men and b) women.

Eur Respir J 2016; 47: 186–193

Pathogenesis of Non-CF BE

--any different?

Pathogenesis of Bronchiectasis



Genetic defect

Ciliary Dysmotility

Slow Transport

Thick Airway Secretions

ACT

Vicious cycle

Inflammation

Infection

Aerosol steroids
Macrolides

(Aerosol) antibiotics

Mucous plugging, Tissue Damage, Hemorrhage

Cole,PJ.Eur J Resp Dis suppl 1986;147:6

Fiel,SB: borrowed and adapted

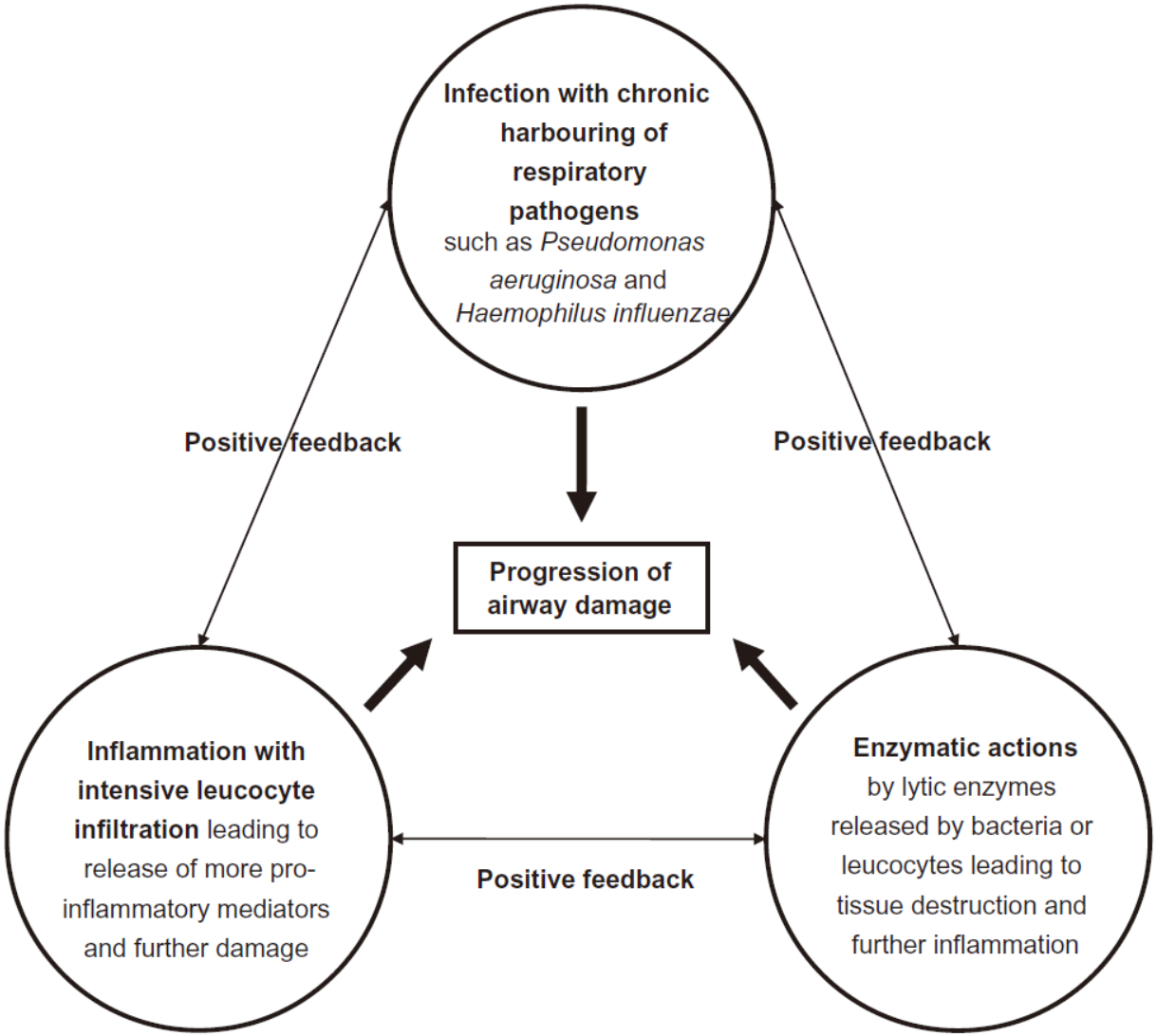


Figure 3 The pathogenesis of bronchiectasis showing the interactive pathogenic elements, namely infection, inflammation and enzymatic actions. These interact to perpetuate the continued airway destruction in bronchiectasis.[1]

K. W. TSANG Respirology (2009) ***14, 637–650***

Pathophysiology of Bronchiectasis

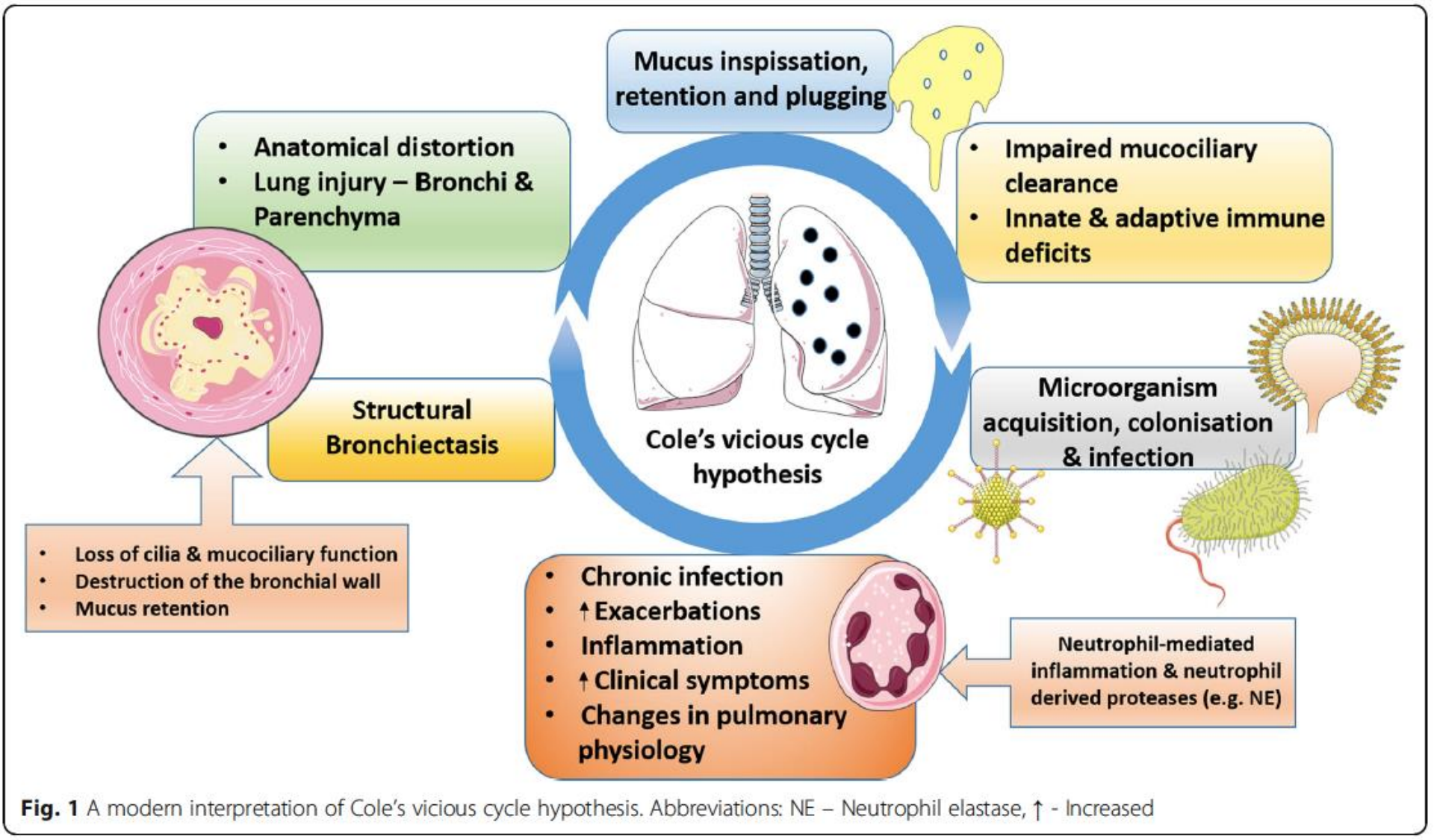
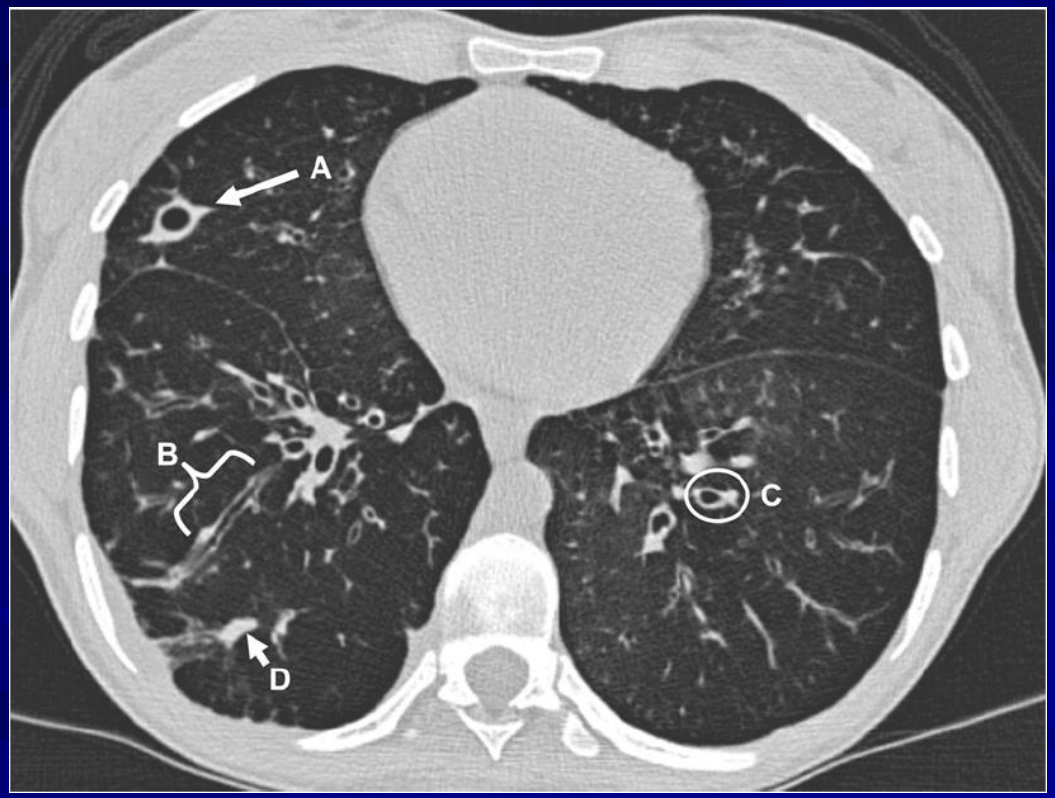


Fig. 1 A modern interpretation of Cole's vicious cycle hypothesis. Abbreviations: NE – Neutrophil elastase, ↑ - Increased

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

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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ETIOLOGY

- Idiopathic
- Congenital and structural abnormalities of the tracheobronchial tree (bronchial wall defects or abnormalities such as tracheomegaly and polychrondritis)
- Bronchial obstruction
  - Intrinsic (post-TB stenosis, foreign body, benign tumour, etc.)
  - Extrinsic (tumour or lymph node compression)
- Gastroesophageal reflux
- Granulomatous diseases (sarcoidosis, TB, etc.)
- Traction (pulmonary fibrosis of any cause including fibrosing alveolitis and severe acute respiratory syndrome)
- Immunodeficiency
  - Primary (pangammaglobulinaemia or selective immunoglobulin deficiency, including IgG subclass deficiency)
  - Secondary (acquired immune-deficiency syndrome or malignancy)
- Diffuse panbronchiolitis
- Primary ciliary dyskinesia (including Kartagener's syndrome)
- Post-infection (TB, pertussis, measles, etc,)
- Post-necrotising pneumonia (Klebsiella pneumoniae, Staphylococcus aureus, etc.)
- Atypical mycobacterial infection
- Allergic bronchopulmonary aspergillosis
- Post-transplantation (heart-lung, lung and bone marrow)
- Miscellaneous (yellow nail syndrome and alpha-1-antitrypsin
- deficiency, etc.)

Risk factors for morbidity and death in non-CF BE: a retrospective crosssectional analysis of CT diagnosed BE

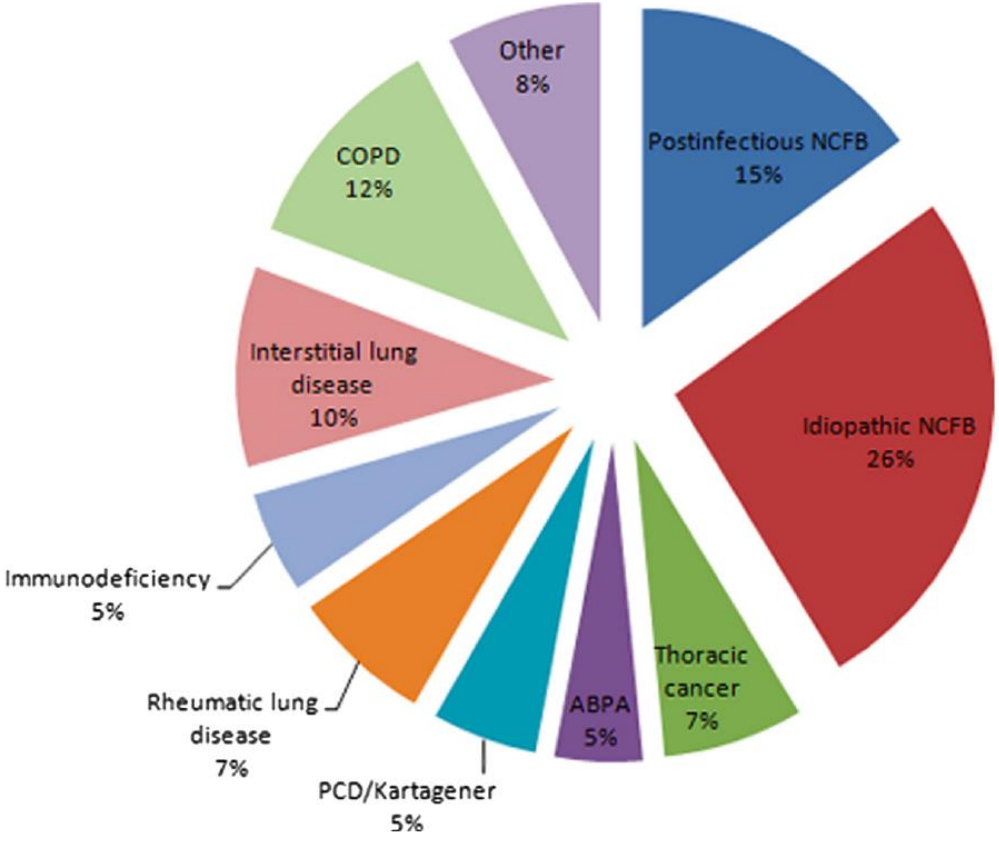
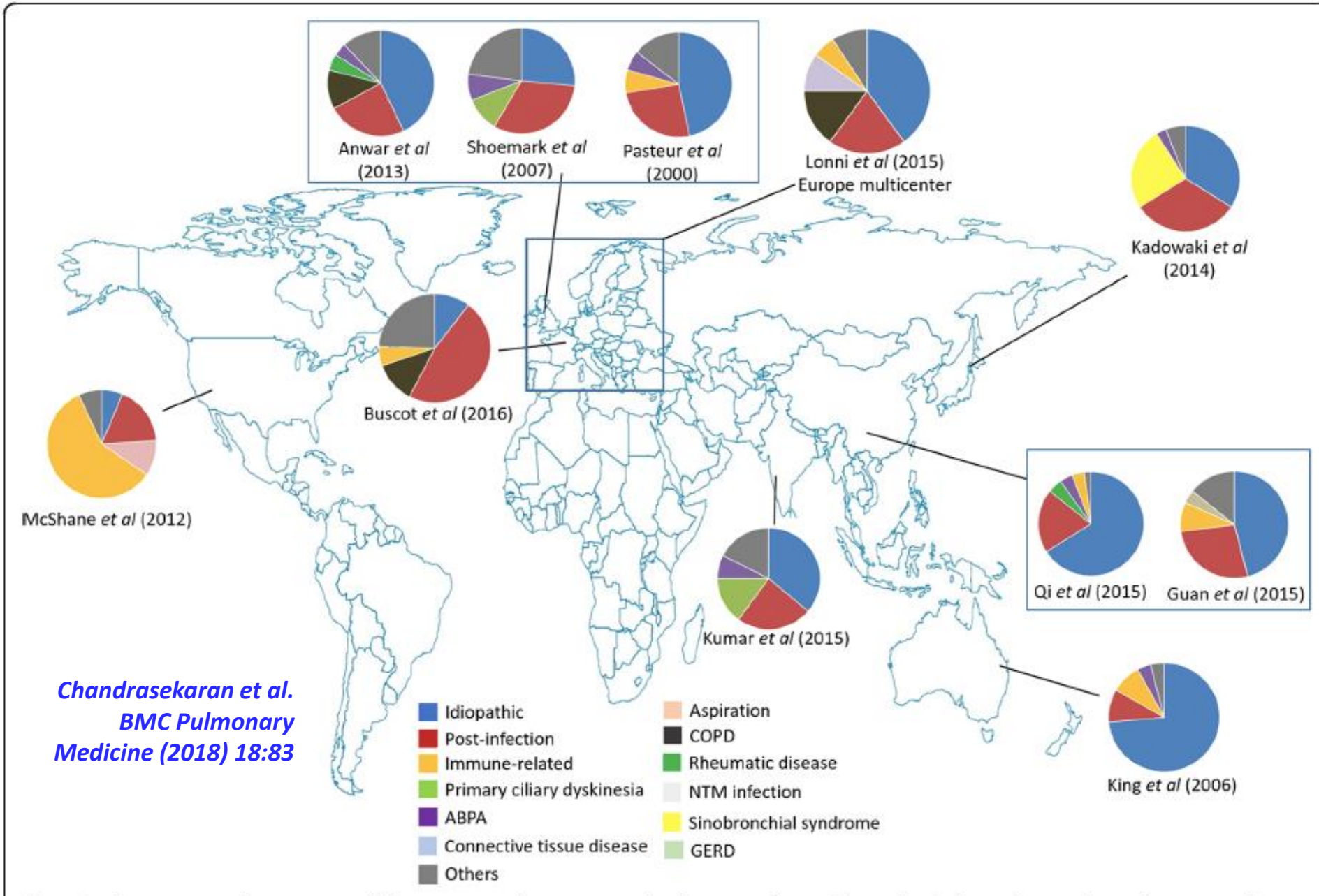


Figure 2 Underlying etiology of the studied population. ABPA = Allergic Bronchopulmonary Aspergillosis; COPD = Chronic Obstructive Lung Disease; PCD = Primary Ciliary Dyskinesia, NCFB = Non Cystic Fibrosis bronchiectasis

Goeminne et al. Respiratory Research 2012, 13:21



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

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

Eur Respir J 2009; 34: 843–849
DOI: 10.1183/09031936.00003709

Mortality in bronchiectasis: a long-term study assessing the factors influencing survival

M.R. Loebinger*, A.U. Wells#, D.M. Hansell¶, N. Chinyanganya*, A. Devaraj¶, M. Meister¶ and R. Wilson*

Why in the majority of patients such progression is slow, whereas in others it occurs much more quickly is poorly understood

Mortality in Bronchiectasis : does knowing etiology matter ?

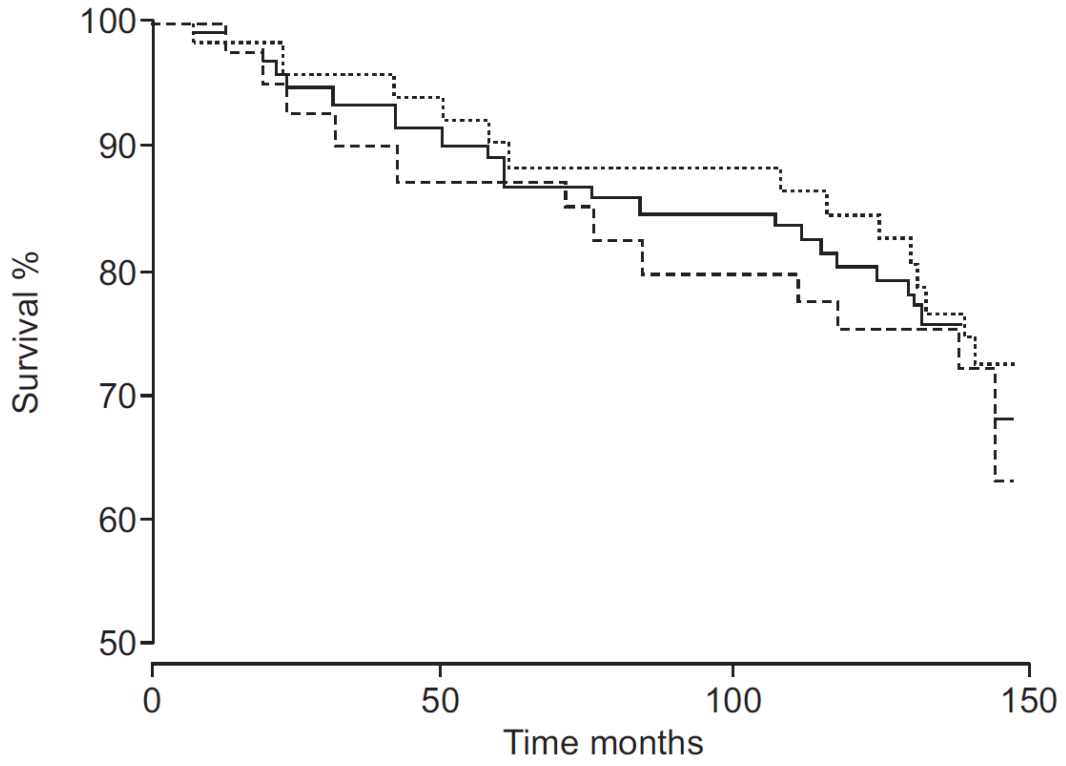


FIGURE 2. Kaplan–Meier plot illustrating the survival of all the bronchiectasis patients (——), in addition to the idiopathic (·····) and known (– – – –) aetiology subgroups. There are no statistically significant differences between the plots (log rank test; p=0.85).

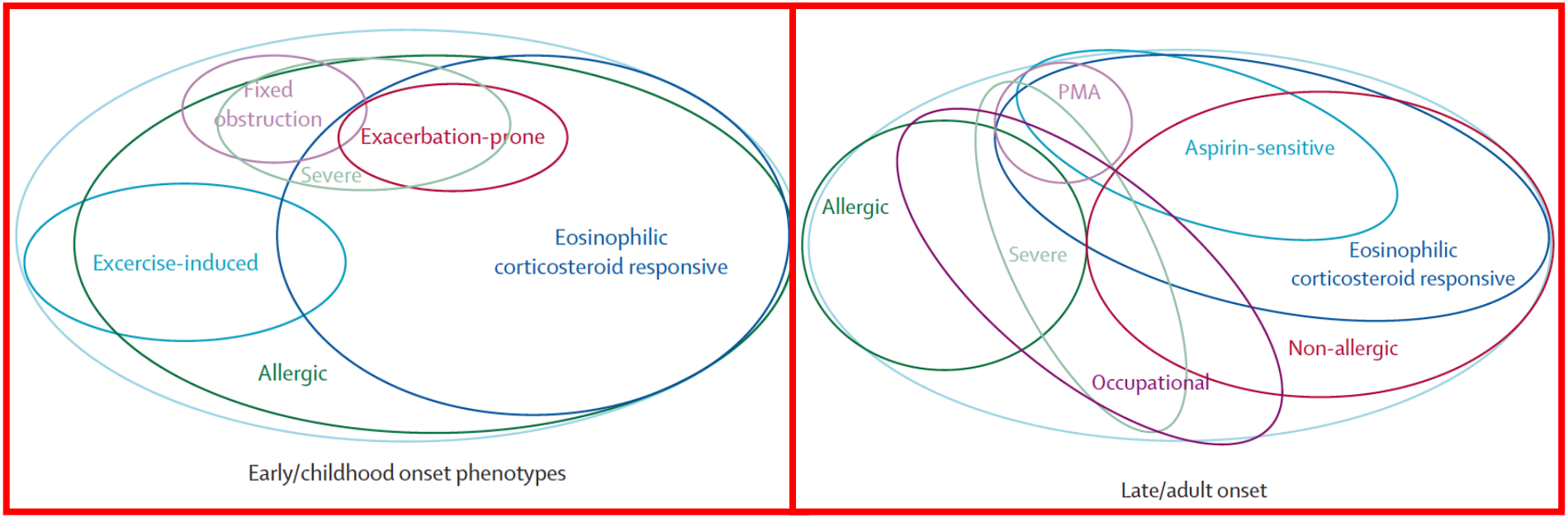
M.R. Loebinger
Eur Respir J 2009;
34: 843–849

Clinical phenotypes

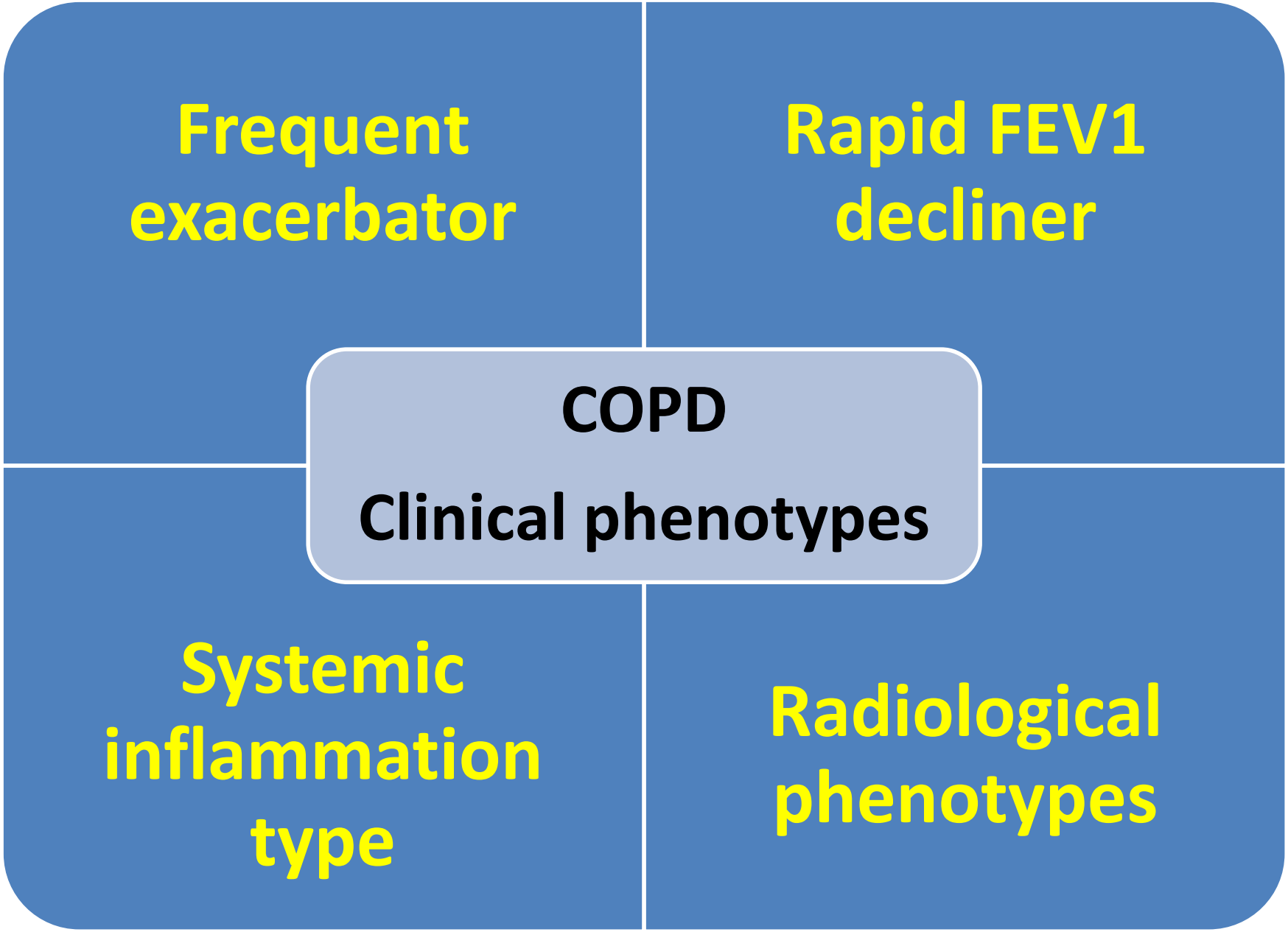
--does it really matter?

Asthma phenotypes

defining of the persistent adult phenotypes

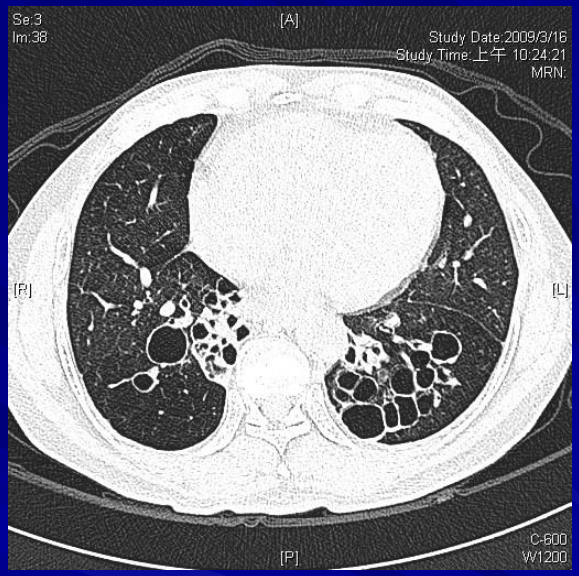


Sally E Wenzel Lancet 2006; 368: 804–13


Frequent exacerbator
Rapid FEV1 decliner
COPD
Clinical phenotypes
Systemic inflammation type
Radiological phenotypes

Four patient stereotypes in BE

- Rapidly progressive
- Slowly progressive
- Indolent disease
- Haemoptysis predominant



K. W. Tsang *INT J TUBERC LUNG DIS 2004: 8(6):691–702*

Clinical phenotypes in adult patients with bronchiectasis

- “Pseudomonas” (16%)
- “Other chronic infection”(24%)
- “Daily sputum”(33%)
- “Dry bronchiectasis”(27%)

5 European databases of prospectively enrolled adult outpatients with bronchiectasis.

Stefano Aliberti , James D. Chalmers ERJ 2016

EMBARC
The European Bronchiectasis Registry

Multiple Clinical Phenotypes

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

Idiopathic
- Lower lobe disease
- Good prognosis
- 60 year old females

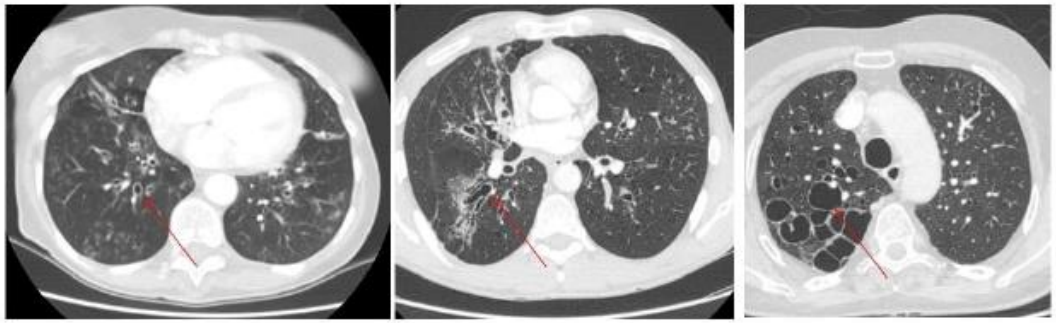
Cystic fibrosis
- Upper lobe disease
- Colonisation with S.aureus/P. aeruginosa
- Early onset

Non tuberculous Mycobacteria
- Middle age females
- Middle lobe disease
- Possible genetic/morphological associations

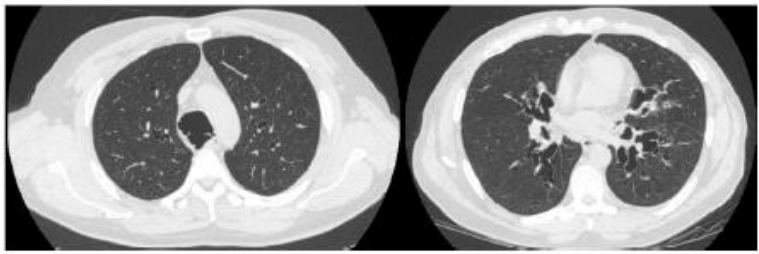
ABPA
- Central disease
- History of asthma
- *Staphylococcus aureus* colonisation

Inflammatory bowel disease
- Aggressive/frequent exacerbations
- May develop or worsen post-surgery
- Steroid responsive

COPD
- Bilateral lower lobe cylindrical bronchiectasis
- Chronic bronchitis
- Severe disease and poor prognosis



Cyclindrical | Varicose | Cystic



Lonni et al, Ann Am Thorac Soc 2015; 12(12):1764-70.

Severity assessment of Non-CF BE --focus on mortality

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

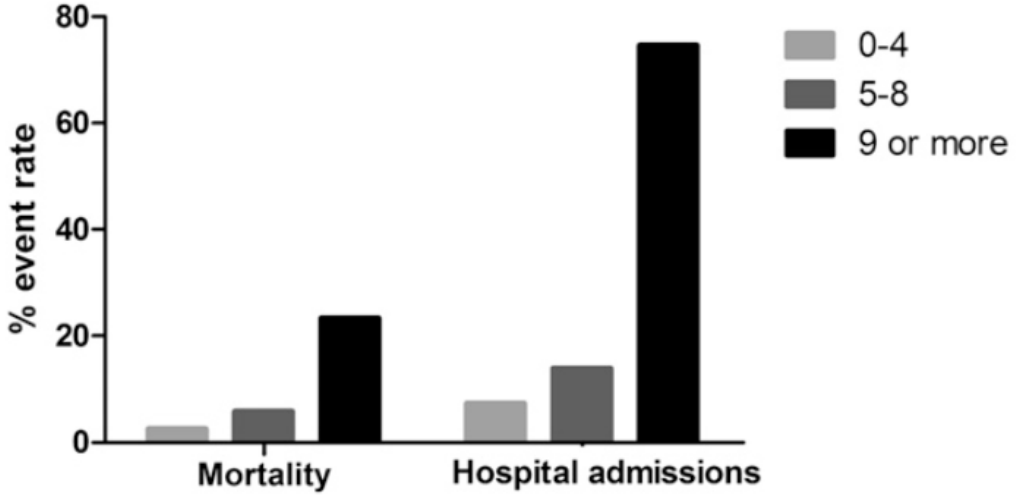
Am J Respir Crit Care Med Vol 189, Iss 5, pp 576–585, Mar 1, 2014

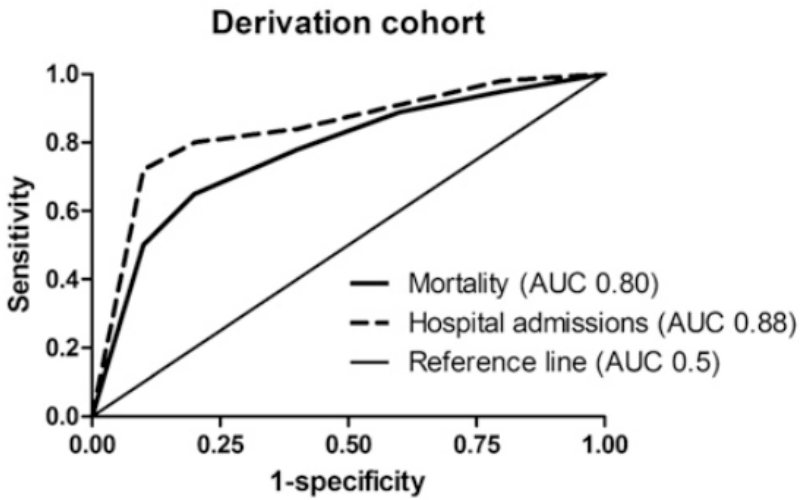
Severity criteria	0 points	1 point	2 points	3 points	4 points	5 points	6 points
Age	<50		50-69	-	70-79	-	80+
BMI kg/m2	≥18.5		<18.5	-	-	-	-
FEV1 % predicted	>80%	50-80%	30-49%	<30%	-	-	-
Hospital admissions in the past 2 years	No					Yes	
Exacerbation frequency in last 12 months	0-2		3 or more				
MRC dyspnoea score	1-3		4	5			
Colonisation status	Not colonised	Chronic colonisation		*P. aeruginosa* colonisation			
Radiological severity	<3 lobes involved	3 or more lobes or cystic changes					

BSI

0~4 **Mild**
5~8 **Moderate**
9+ **Severe**

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 5 | March 1 2014





Prospective Cohort
UK 608 patients
2008-2012
4 years follow-up

Mortality AUC **0.80**
Hospitalization AUC **0.88**

American Journal of Respiratory and Critical Care Medicine Volume 189 Number 5 | March 1 2014

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

F – FEV1 (> 50% = 0 points, ⩽ 50% = 2 points)

A – Age (⩽ 70 years = 0 points, > 70 years = 2 points)

C – Chronic colonisation (no Pseudomonas = 0 points, presence of Pseudomonas = 1 point)

E – Extension (1 lobe = 1 point, ⩾ 2 = 2 points)

D – Dyspnoea (no dyspnoea = 0 points, ⩾ 2 on Medical Research Council scale = 1 point)

FACED

0~2	Mild
3~4	Moderate
5~7	Severe

Eur Respir J 2014; 43: 1357–1367 | DOI: 10.1183/09031936.00026313

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 FEV_1 <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

Observational

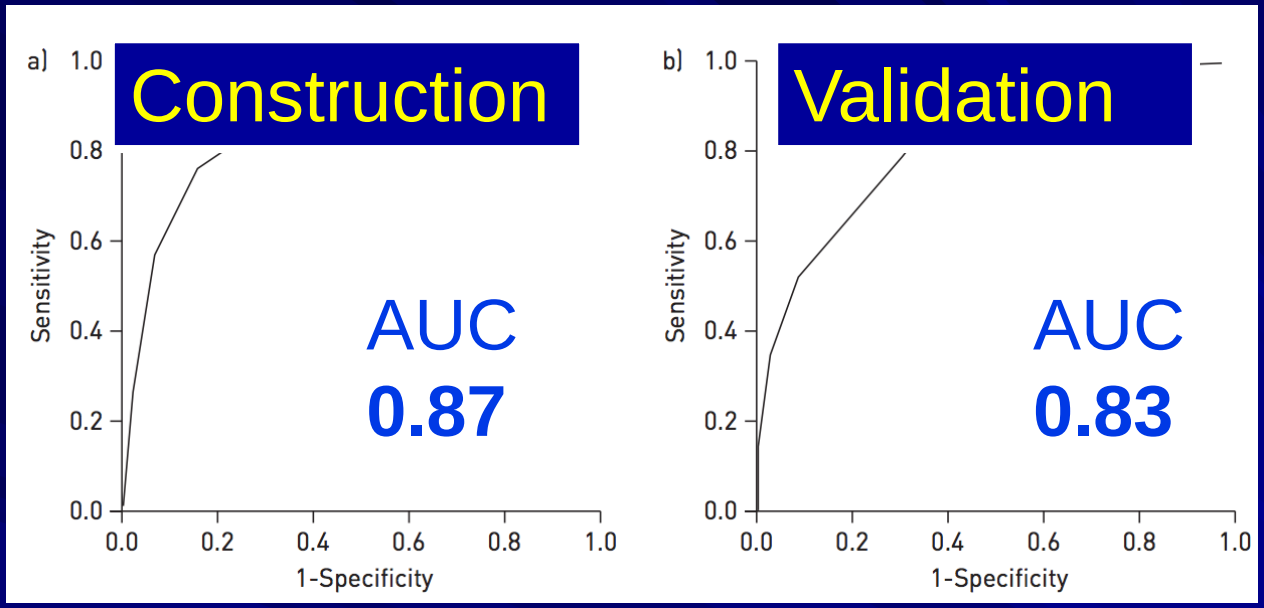
Spain

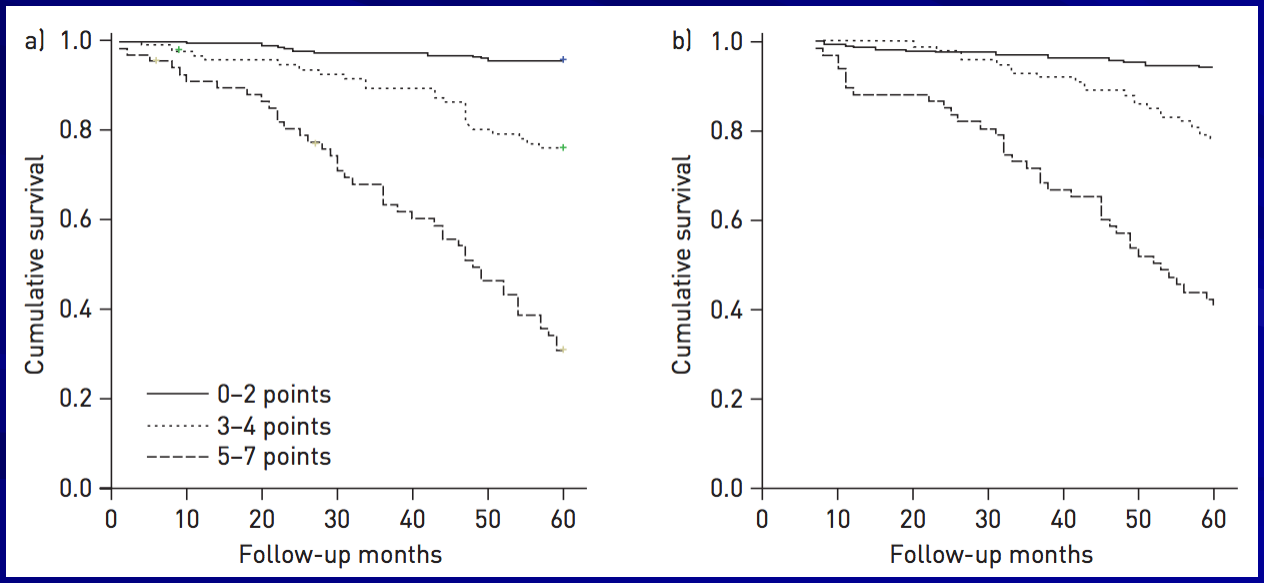
819 patients (397 construction + 422 validation)

5 years follow-up

154 death (18.8%)

Eur Respir J 2014; 43: 1357–1367 | DOI: 10.1183/09031936.00026313





mild

moderate

severe

Summary

BSI
Bronchiectasis Severity Index

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

FACED

- FEV1
- Age
- Chronic Colonization
- Extension
- Dyspnea

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

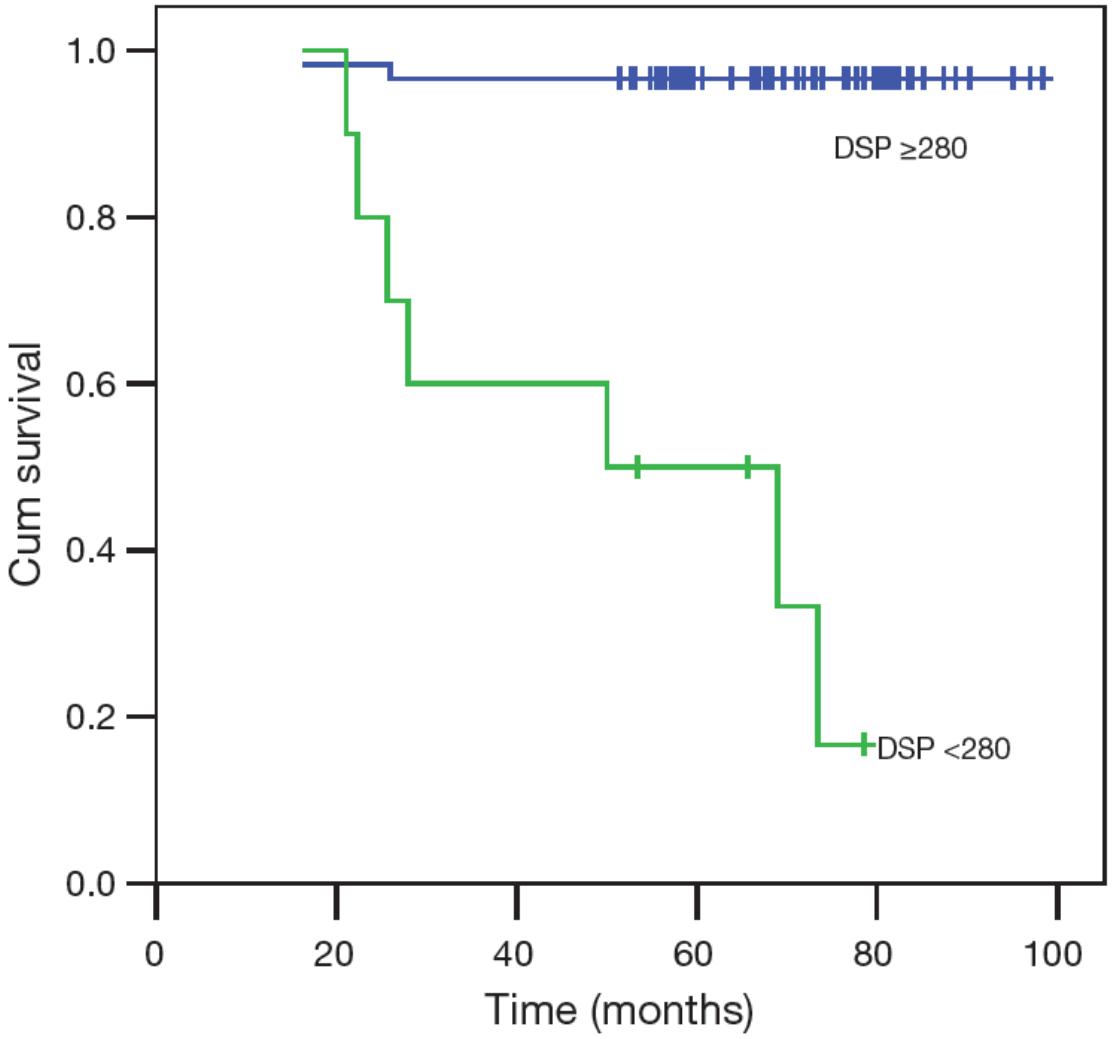
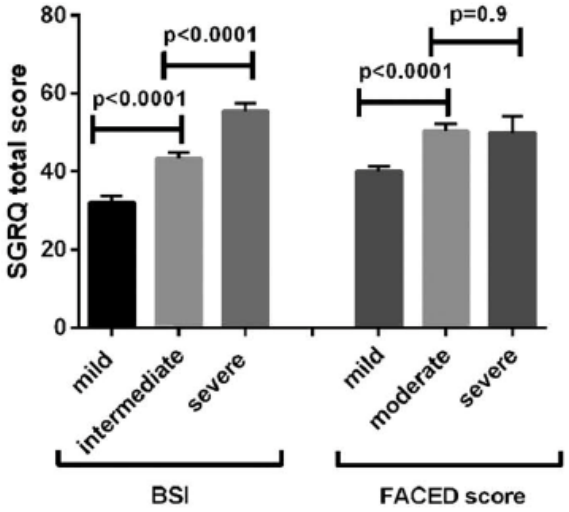
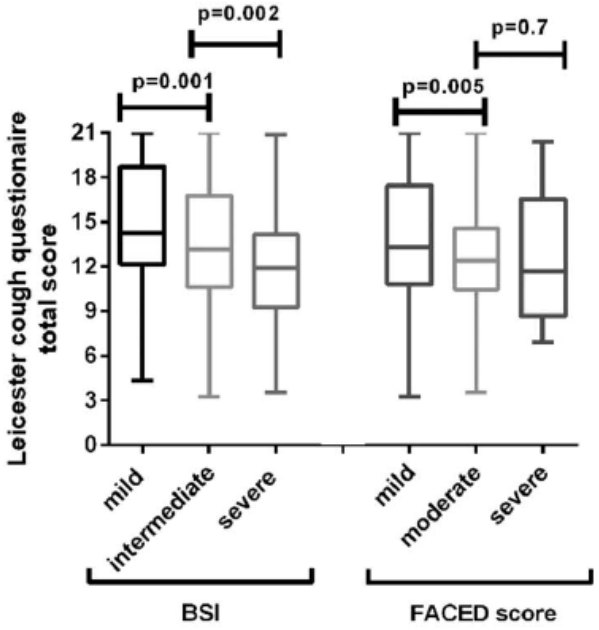


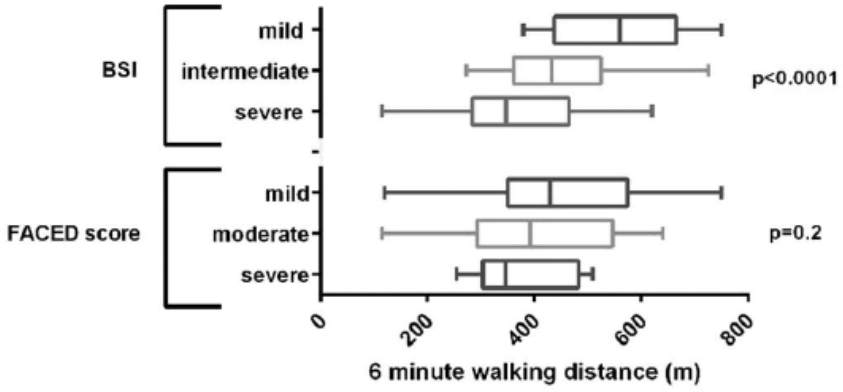
Figure 4 Kaplan-Meier survival curve for patients with non-CF bronchiectasis grouped by distance-saturation product (DSP, cut-off value: 280 m%) during the 6MWT (blue line: higher group; P<0.001). Non-CF, non-cystic fibrosis; 6MWT, 6-minute walk test.

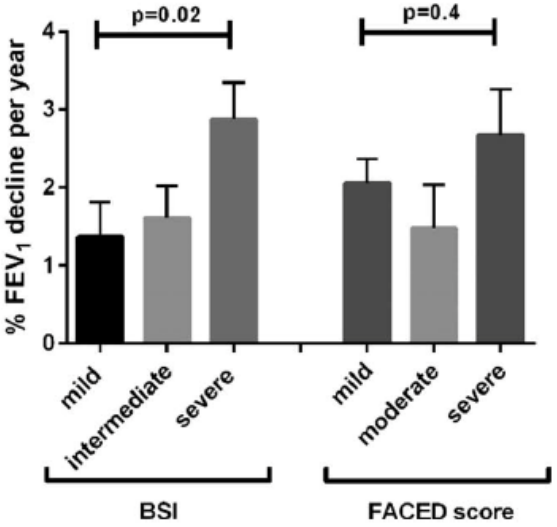
Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts.

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



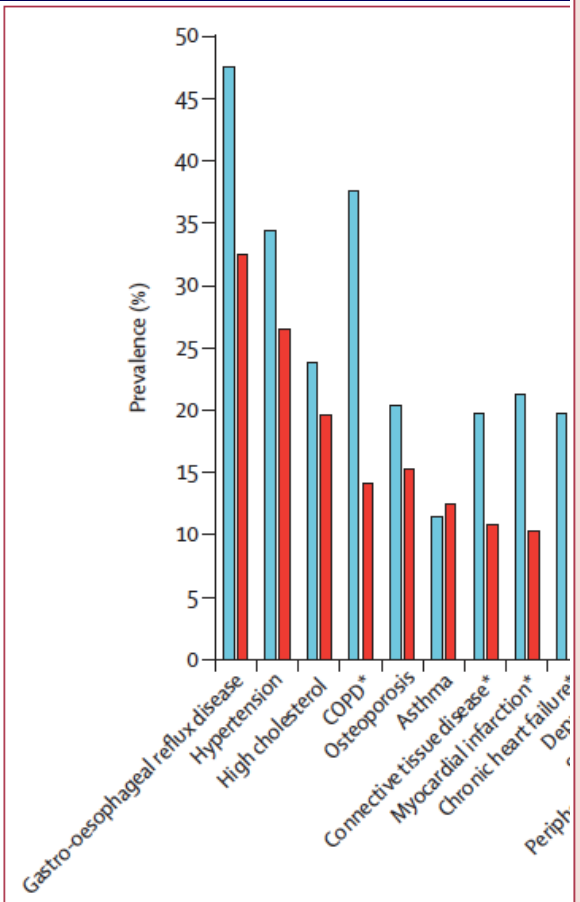






Comorbidities and the risk of mortality in patients with bronchiectasis: an international multicentre cohort study

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**

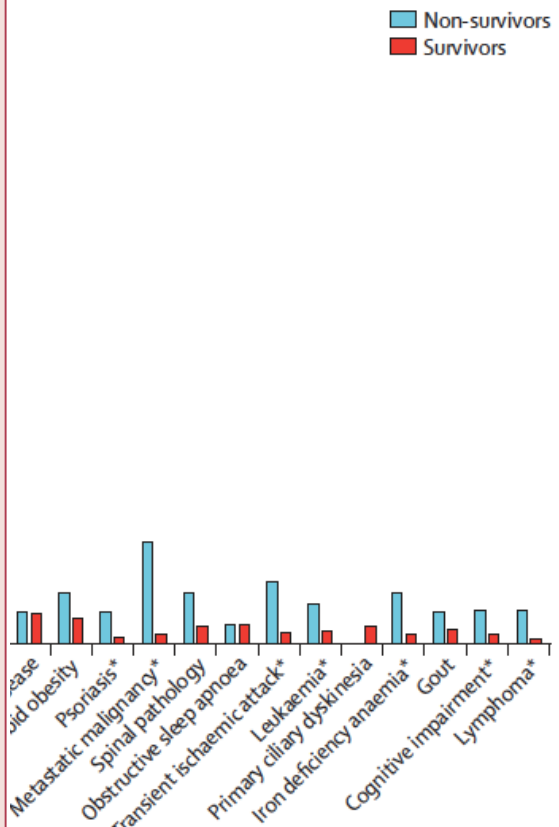
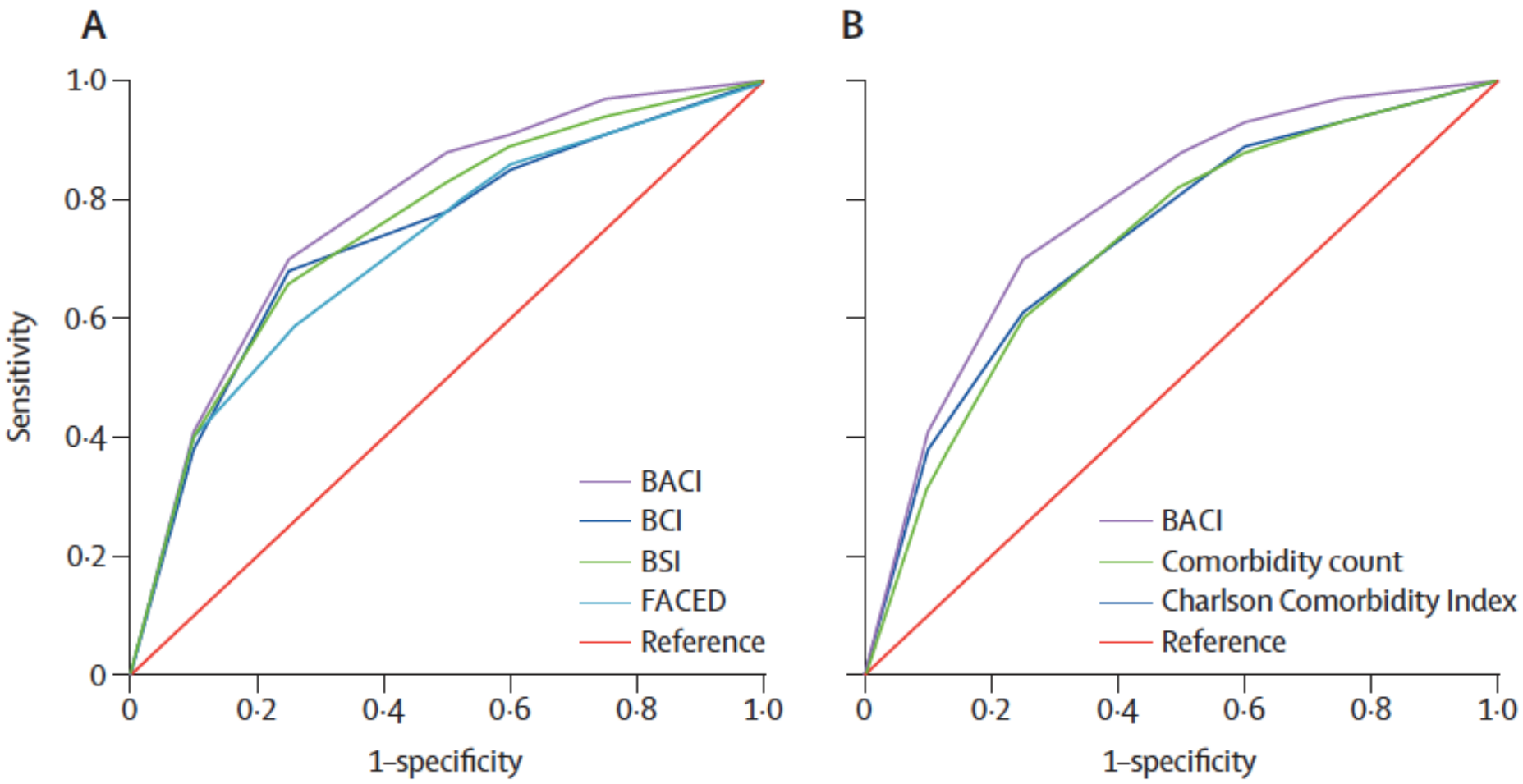


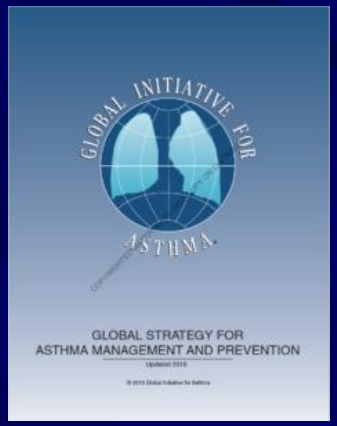
Figure 1: **Comorbidities in order of overall prevalence amo**
*Comorbidity with a significantly higher prevalence in non-

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

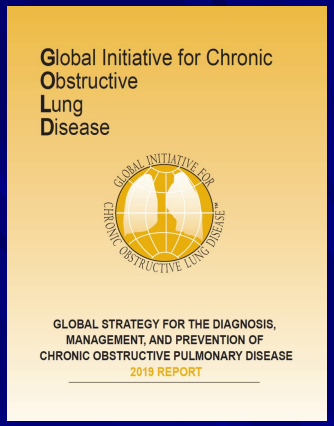
Melissa J McDonnell et al. Lancet Respir Med 2016; 4: 969–79



The impact of Non-CF BE on COPD & Asthma



COPD



Acute exacerbation ?

Bronchiectasis

Mortality ?

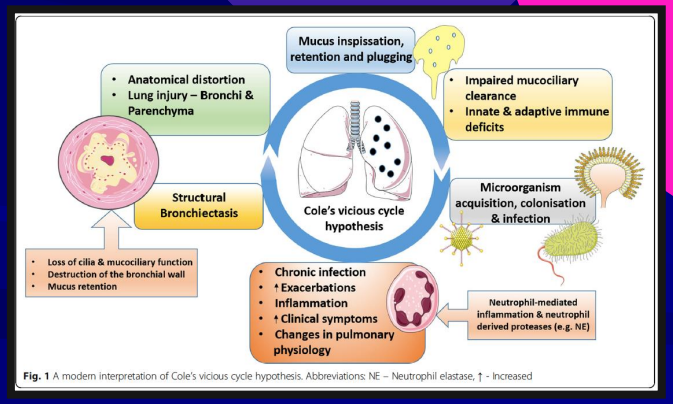
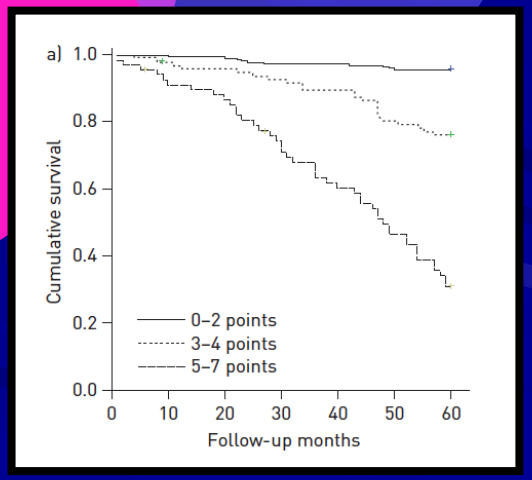
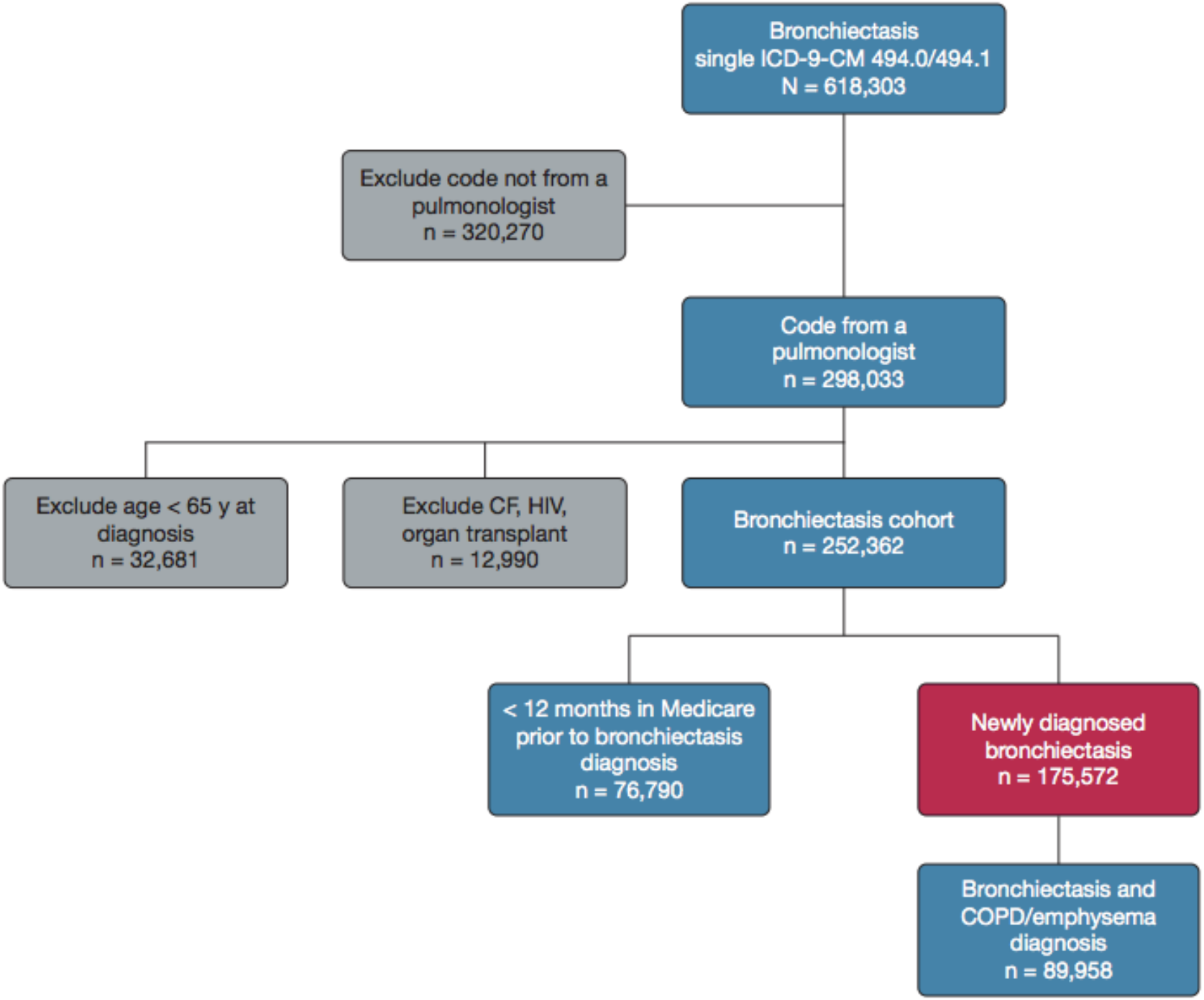


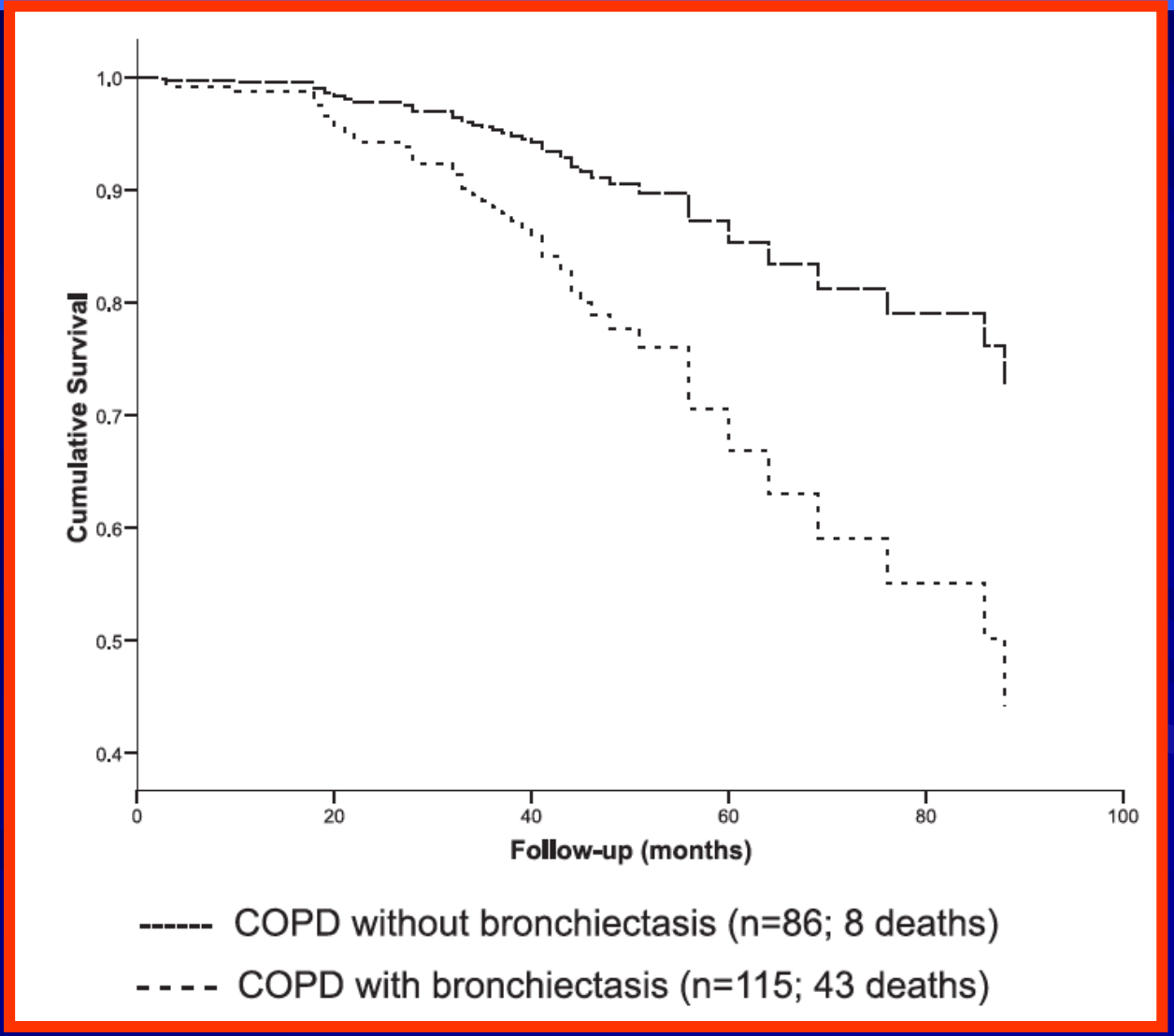
Fig. 1 A modern interpretation of Cole's vicious cycle hypothesis. Abbreviations: NE – Neutrophil elastase, ↑ - Increased



Asthma

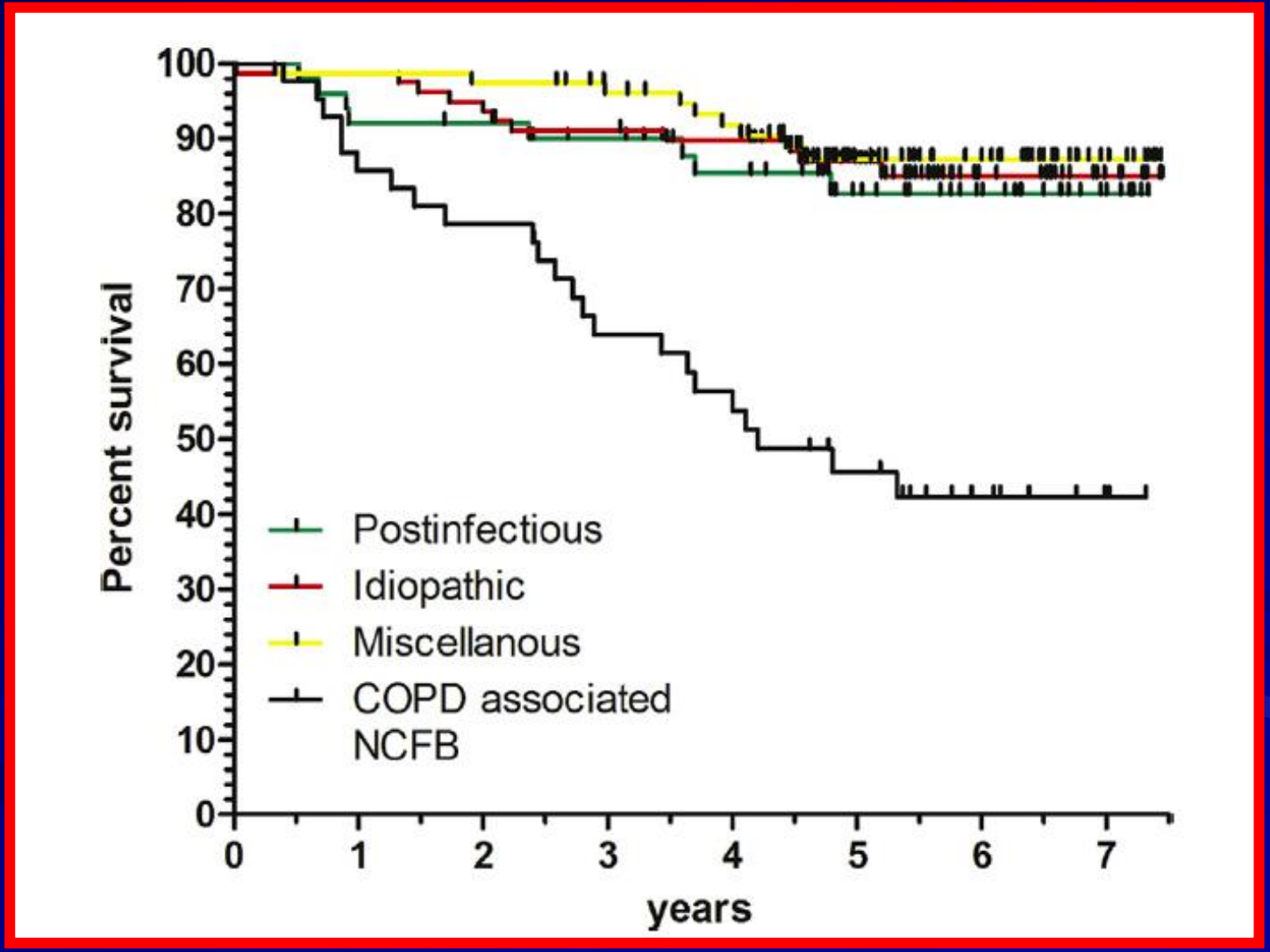

Bronchiectasis
single ICD-9-CM 494.0/494.1
N = 618,303
Exclude code not from a pulmonologist
n = 320,270
Code from a pulmonologist
n = 298,033
Exclude age < 65 y at diagnosis
n = 32,681
Exclude CF, HIV, organ transplant
n = 12,990
Bronchiectasis cohort
n = 252,362
< 12 months in Medicare prior to bronchiectasis diagnosis
n = 76,790
Newly diagnosed bronchiectasis
n = 175,572
Bronchiectasis and COPD/emphysema diagnosis
n = 89,958

Prognostic Value of Bronchiectasis in Patients with Moderate-to-Severe COPD



AJRCCM Vol 187, Iss. 8, pp 823–831, Apr 15, 2013

Mortality in non-CF bronchiectasis: A prospective cohort analysis

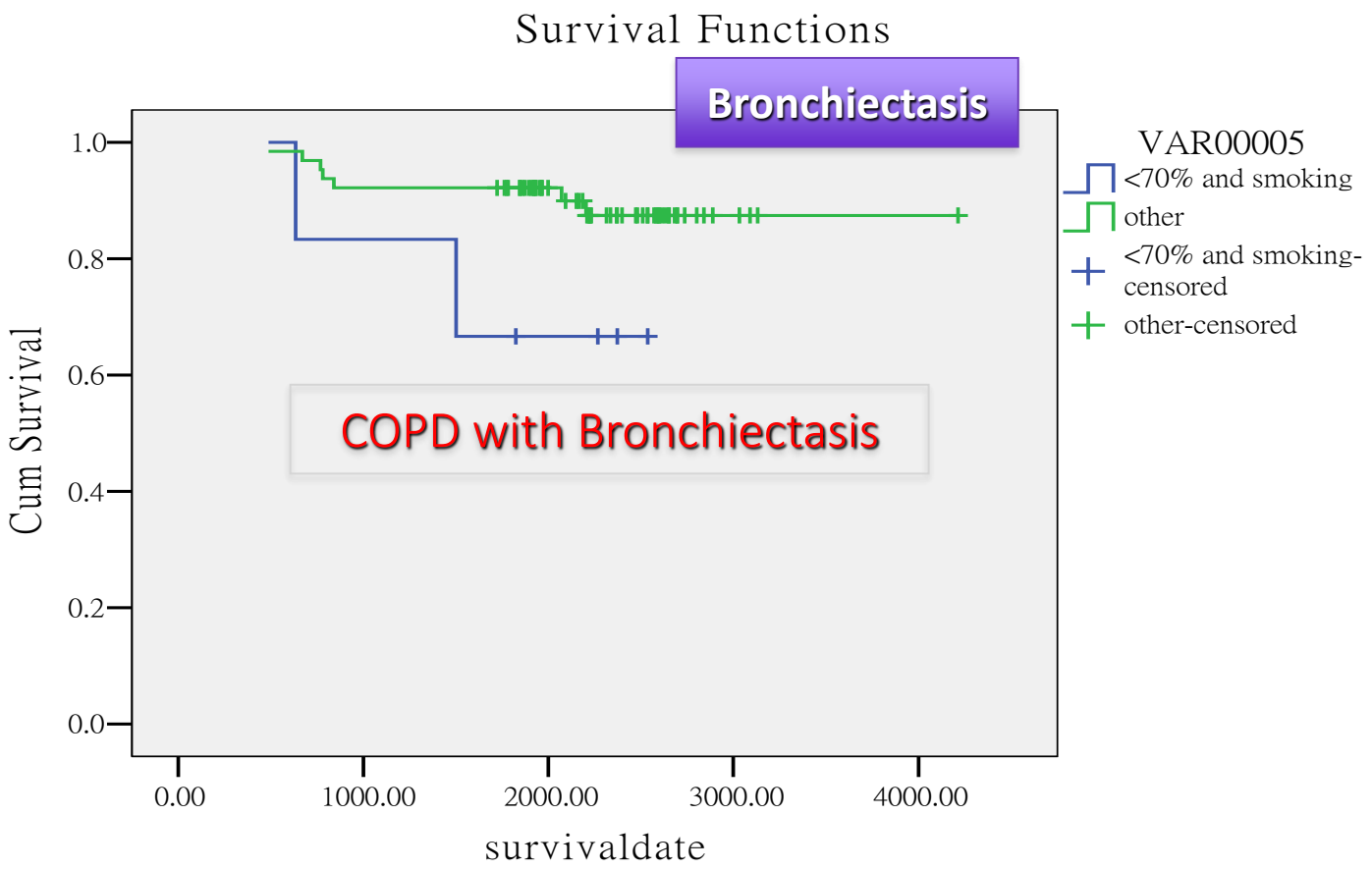


Resp Med 2014 V 108, pp 287e 296

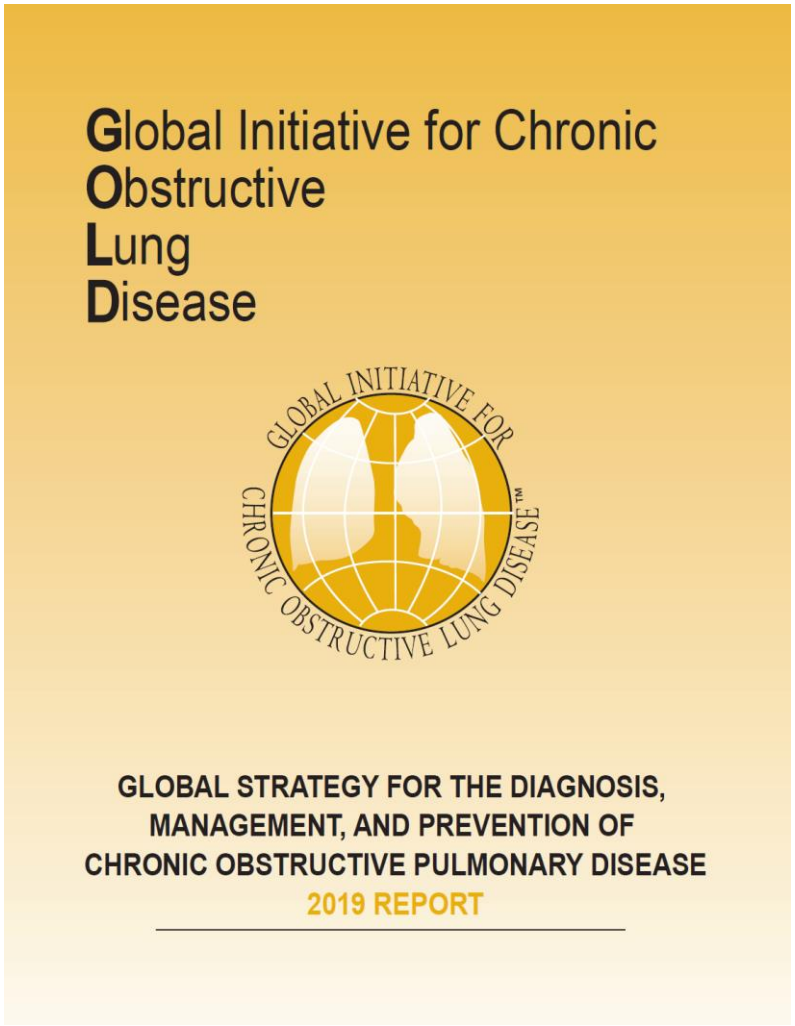
Clinical Study

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

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

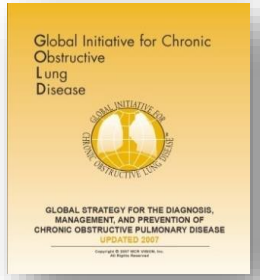


GOLD 2019 Report: Chapters



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

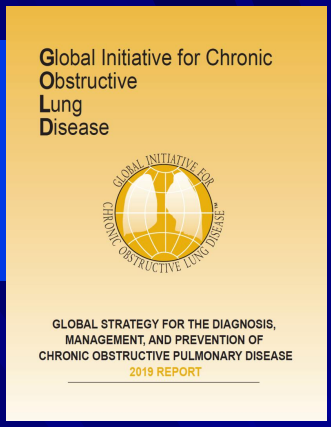


COPD Comorbidities

- **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**

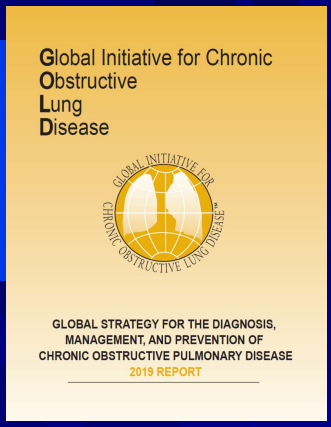
GOLD 2014 - Should be actively looked for and treated appropriately if present

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.

The impact of Non-CF BE on Asthma

Overlap of asthma and bronchiectasis

- Both 2 diseases are of heterogeneity in clinical presentation and outcome
- How could Asthma lead to BE?
  - Recurrent infection → bronchiectasis
  - MMPs imbalance → tissue destruction?
- Bronchiectasis + asthma: 3-8%
- Severe asthma + bronchiectasis: 25-80%

Polverino et al, "The overlap between BE and C.A.D." ERJ 2018; 52: 1800328

Bronchiectasis in asthma

- Consequence of long-lasting, severe, uncontrolled asthma
  - Non-allergic asthma
  - Immunodeficiency from chronic steroid therapy
  - Poor response to high-dose ICS and recurrent infectious symptoms; neutrophilia in sputum
- ABPA: should be identified due to fair response to systemic steroid therapy and anti-fungal treatment

Asthma in bronchiectasis

- Potential influence of asthma on the management and prognosis of bronchiectasis is **unclear**
- Hard to identify asthma in bronchiectasis
  - Asthma-like symptoms could be reported in stable diseases
  - Best biomarker to differentiate under discussion

Asthma in bronchiectasis

TABLE 1 Baseline and clinical characteristics of subjects with bronchiectasis, with and without asthma

Parameter	Bronchiectasis	Bronchiectasis with asthma	p-value
Age years	55.7±13.38	52.0±11.54	**0.002**
Sex male:female n	86:163	78:136	0.668
BMI kg·m^{-2}	20.9±3.64	22.8±3.31	**<0.001**
Smoking	15.3	19.2	0.266
Duration of symptoms years	15.1±14.50	11.7±14.58	**0.001**
Previous pertussis	5.2	2.3	0.109
Previous tuberculosis	12.0	8.9	0.269
Previous anaphylactic rhinitis	9.2	18.9	**0.03**
Moist rales	57.0	35.5	**<0.001**
Dry rales	16.1	45.8	**<0.001**
***Pseudomonas aeruginosa* isolation**	29.3	19.7	**0.022**
FEV$_1$ L	1.86±0.75	1.67±0.74	0.212
FEV$_1$ % pred	61.4±23.17	63.3±24.02	0.418
FVC L	2.20±0.85	2.52±0.80	**<0.001**
FVC % pred	69.3±20.12	78.0±18.52	**<0.001**
FEV$_1$/FVC	71.2±14.21	65.7±14.54	**<0.001**
Type			
Cylindrical	42.4	63.7	
Cystic	25.1	11.0	
Mixed	32.5	25.3	**<0.001**
Location			
Unilateral	20.2	15.1	
Bilateral	79.8	84.9	0.219
Extent			
Affected lobes n	3.5±1.48	3.4±1.46	0.9
Affected segments n	7.5±3.89	8.0±3.86	0.217

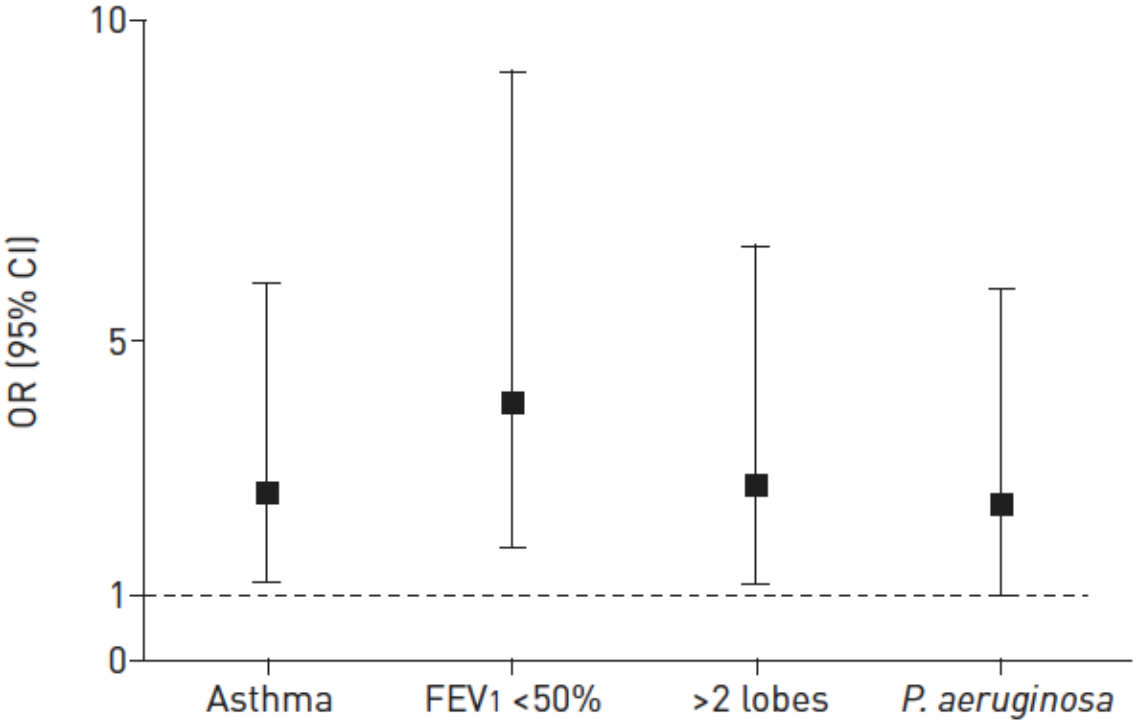
B. Mao et al, "Asthma and bronchiectasis AE" Eur Respir J 2016; 47: 1597–1600

Asthma in bronchiectasis

TABLE 2 Serological indicators of subjects with bronchiectasis, with and without asthma

	Bronchiectasis	Bronchiectasis with asthma	p-value
Haemoglobin $g \cdot L^{-1}$	126.1±14.77	131.8±15.93	**<0.001**
WBC $\times 10^9$ cells$\cdot L^{-1}$	6.5±2.73	7.5±3.20	**<0.001**
Neutrophils %	59.6±11.90	64.7±14.02	**<0.001**
Eosinophils %	3.4±3.81	3.3±4.87	0.951
ESR $mm \cdot h^{-1}$	39.3±29.91	27.1±23.25	**<0.001**
CRP $IU \cdot mL^{-1}$	18.6±33.52	10.1±25.00	**<0.001**
Albumin $mg \cdot dL^{-1}$	37.8±5.03	40.5±3.89	**<0.001**
CD4/CD8	1.9±1.47	1.9±1.41	0.466
IgG $g \cdot L^{-1}$	15.5±7.30	11.8±3.74	**<0.001**
IgA $g \cdot L^{-1}$	3.3±1.75	2.5±1.10	**<0.001**
IgM $g \cdot L^{-1}$	1.2±0.60	1.2±0.65	0.099
C3	1.1±0.26	1.1±0.23	0.42
C4	0.3±0.12	0.3±0.09	0.33
Total IgE			
<100	64.9	40.9	
100–200	11.2	14.5	
>200	23.9	44.6	**<0.001**
P_{O_2} mmHg	83.8±18.75	78.0±16.04	**0.001**
P_{CO_2} mmHg	41.7±7.37	42.2±6.91	0.085
S_{pO_2} %	95.3±4.13	94.5±5.99	0.093

Asthma in bronchiectasis



	OR (95% CI)	p-value
Asthma	2.60 (1.15–5.88)	0.021
FEV1 <50%	4.03 (1.75–9.26)	0.001
Extent >2 lobes	2.73 (1.16–6.45)	0.022
P. aeruginosa isolation	2.41 (1.00–5.79)	0.05

B. Mao et al, "Asthma and bronchiectasis AE" Eur Respir J 2016; 47: 1597–1600

ORIGINAL ARTICLE

Distinct "Immunoallertypes" of Disease and High Frequencies of Sensitization in Non–Cystic Fibrosis Bronchiectasis

Micheál Mac Aogáin[1*], Pei Yee Tiew[1,2*], Albert Yick Hou Lim[3], Teck Boon Low[4], Gan Liang Tan[2], Tidi Hassan[5], Thun How Ong[2], Sze Lei Pang[6,7], Zi Yang Lee[6], Xiao Wei Gwee[6], Christopher Martinus[6], Yang Yie Sio[6], Sri Anusha Matta[6], Tan Ching Ong[6], Yuen Seng Tiong[6], Kang Ning Wong[6], Sriram Narayanan[8], Veonice Bijin Au[8], Damien Marlier[8], Holly R. Keir[9], Augustine Tee[4], John Arputhan Abisheganaden[3], Mariko Siyue Koh[2], De Yun Wang[10], John E. Connolly[8], Fook Tim Chew[6], James D. Chalmers[9], and Sanjay H. Chotirmall[1]

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; [2]Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore; [3]Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore; [4]Department of Respiratory and Critical Care Medicine, Changi General Hospital, Singapore; [5]Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; [6]Department of Biological Sciences, National University of Singapore, Singapore; [7]Institute of Systems Biology, Universiti Kebangsaan Malaysia, Bangi, Selangor, Malaysia; [8]Institute of Molecular and Cell Biology, A*STAR, Singapore; [9]University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland; and [10]Department of Otolaryngology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

ORCID IDs: 0000-0002-1726-7700 (M.M.A.); 0000-0003-0417-7607 (S.H.C.).

Abstract

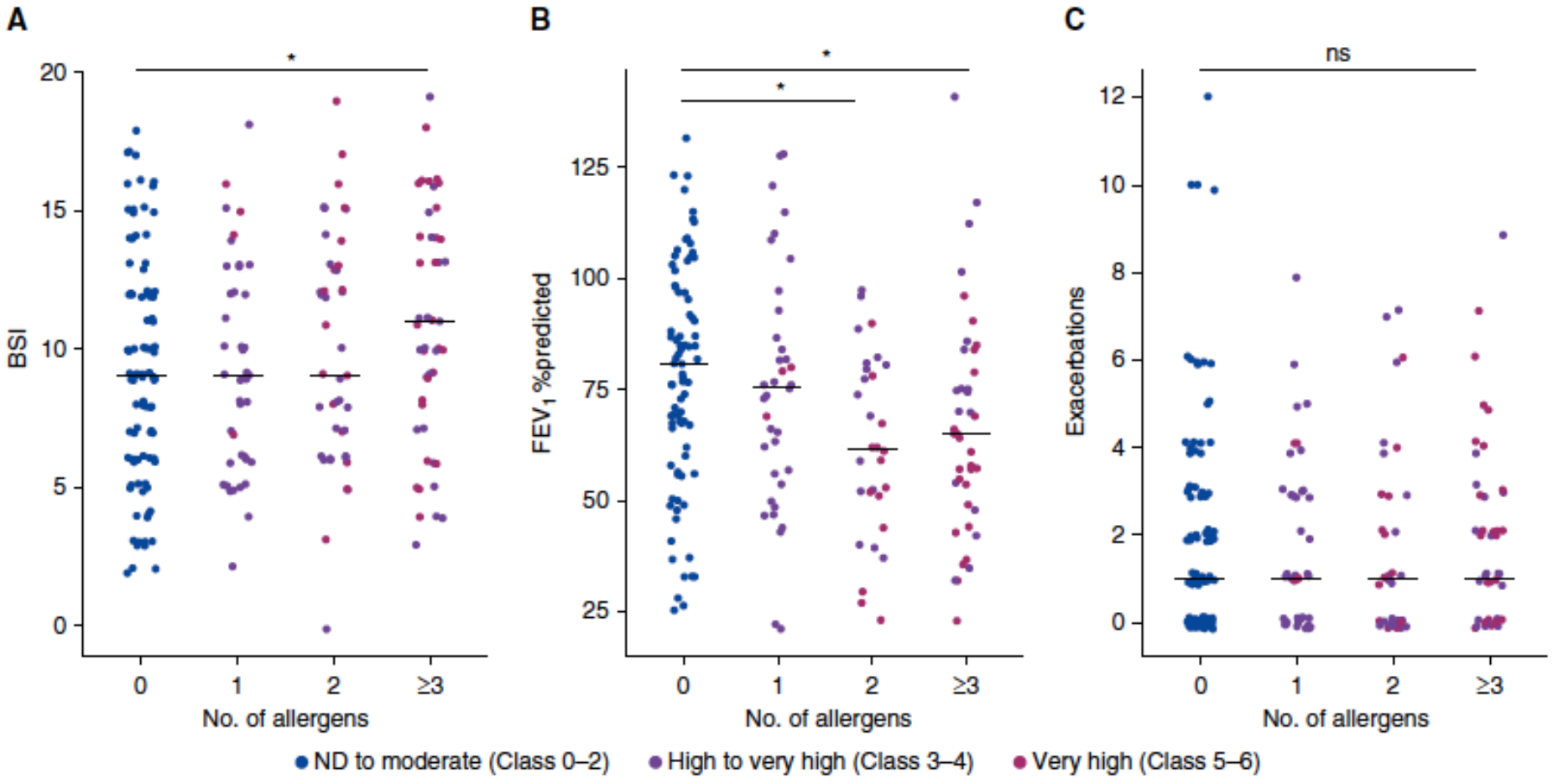
Rationale: Allergic sensitization is associated with poor clinical outcomes in asthma, chronic obstructive pulmonary disease, and cystic fibrosis; however, its presence, frequency, and clinical significance in non–cystic fibrosis bronchiectasis remain unclear.

Objectives: To determine the frequency and geographic variability that exists in a sensitization pattern to common and specific allergens, including house dust mite and fungi, and to correlate such patterns to airway immune-inflammatory status and clinical outcomes in bronchiectasis.

Measurements and Main Results: A high frequency of sensitization to multiple allergens was detected in bronchiectasis, exceeding that in a comparator cohort with allergic rhinitis ($n = 149$). Sensitization was associated with poor clinical outcomes, including decreased pulmonary function and more severe disease. "Sensitized bronchiectasis" was classified into two immunoallertypes: one fungal driven and proinflammatory, the other house dust mite driven and chemokine dominant, with the former demonstrating poorer clinical outcome.

AJRCCM Vol 199 Num 7 April 1 2019

Immunoallergic type of BE



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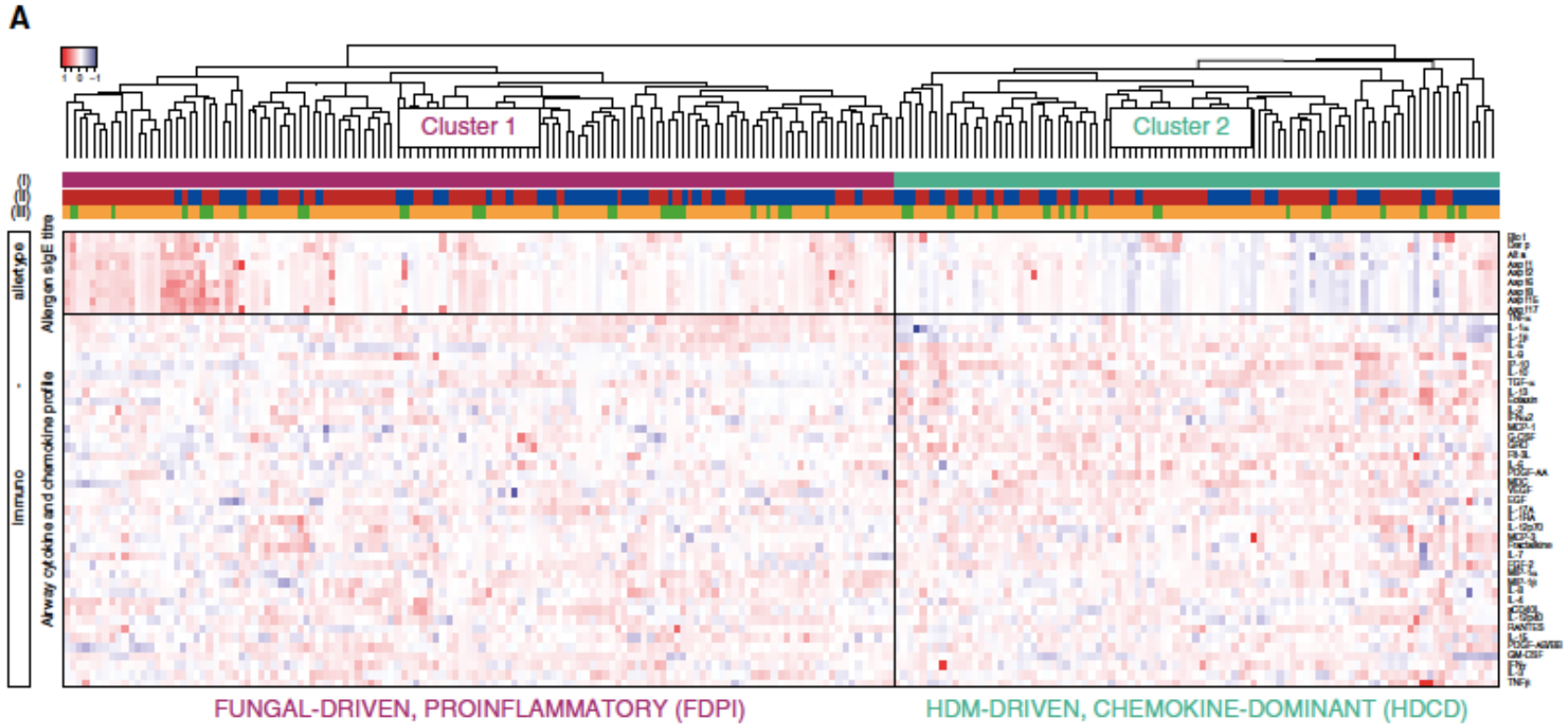
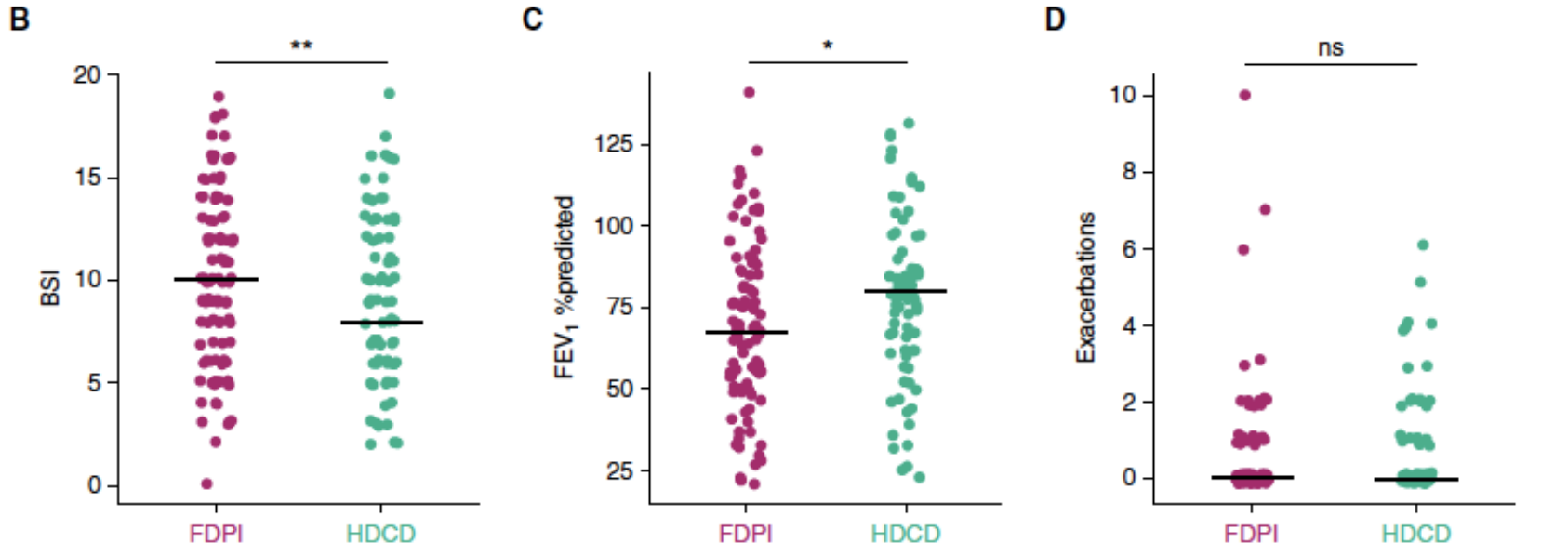

A
Cluster 1
Cluster 2
IgE
allergen sIgE titre
Allergen sIgE profile
immuno
Airway cytokine and chemokine profile
FUNGAL-DRIVEN, PROINFLAMMATORY (FDPI)
HDM-DRIVEN, CHEMOKINE-DOMINANT (HDCD)


B
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BSI
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75
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Exacerbations
10
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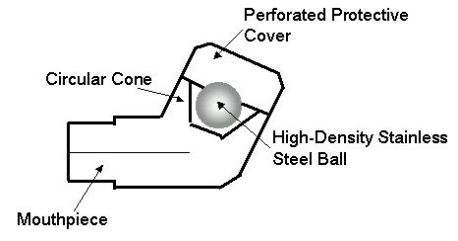
6
4
2
0
FDPI
HDCD

Outline

- Introduction
- The assessment of Non-Cystic Fibrosis Bronchiectasis (Non-CF BE)
- Management approach
- Summary

Summary of recommendations from the ERS guidelines for management of adult bronchiectasis

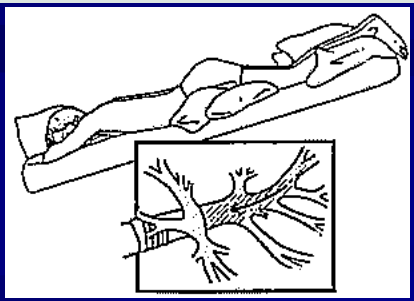


	Strength of recommendation	Quality of evidence
Do a minimum bundle of tests, including differential blood count, serum immunoglobulins, and testing for ABPA in newly diagnosed patients	Conditional	Very low
Treat acute exacerbations of bronchiectasis with 14 days of antibiotics	Conditional	Very low
Patients with a new isolation of *Pseudomonas aeruginosa* should be offered eradication antibiotic treatment	Conditional	Very low
Do not offer eradication antibiotic treatment to patients after new isolation of pathogens other than *P aeruginosa*	Conditional	Very low
Do not offer inhaled corticosteroids for the treatment of bronchiectasis	Conditional	Low
Do not offer statins for the treatment of bronchiectasis	Strong	Low
Offer long-term antibiotic treatment for patients with three or more exacerbations per year*	Conditional	Moderate

James D Chalmers, Lancet Respir Med 2018; 6: 715–26

Summary of recommendations from the ERS guidelines for management of adult bronchiectasis

Offer mucoactive treatment for patients with difficulty expectorating sputum and poor quality of life when standard airway clearance techniques have failed to control symptoms	Conditional	Low
Do not offer recombinant DNase for the treatment of bronchiectasis	Strong	Moderate
Do not routinely offer long-acting bronchodilators for patients with bronchiectasis	Conditional	Very low
Offer long-acting bronchodilators for patients with clinically significant breathlessness on an individual basis	Conditional	Very low
Do not offer surgical treatments, except to patients with localised disease and high exacerbation frequency despite optimum medical care	Conditional	Very low
Patients with chronic productive cough or difficulty expectorating should be taught airway clearance techniques	Conditional	Low
Patients with impaired exercise capacity should participate in pulmonary rehabilitation and take regular exercise	Strong	High



James D Chalmers, Lancet Respir Med 2018; 6: 715–26

Treatable traits in bronchiectasis

Treatable (therapeutic) traits

Chronic airway infection
- Antibiotic therapy
  - Inhaled
  - Targeted
  - Macrolides

Pathogen acquisition
- *Pseudomonas aeruginosa* eradication therapy

Immunodeficiency
- Immunoglobin replacement
- Prophylactic antibiotics

NTM
- Antibiotic therapy

ABPA
- Corticosteroids
- +/– antifungals

Airflow obstruction and functional impairment
- Pulmonary rehabilitation
- Bronchodilators

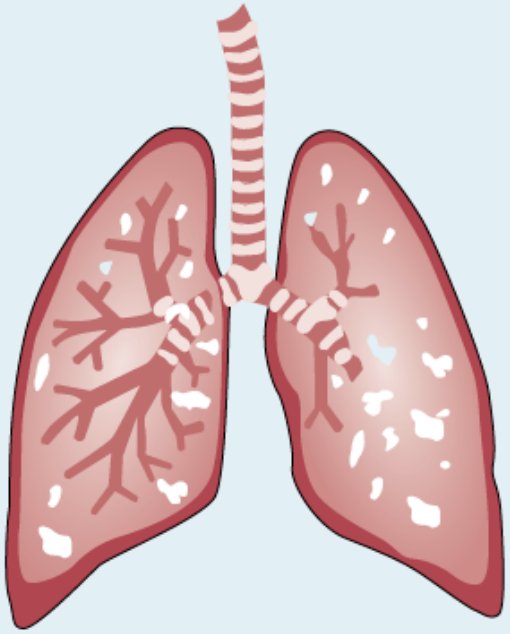
Sputum production
- Airway clearance
- Mucoactive drugs

Asthma and eosinophilia
- Inhaled corticosteroids

Low BMI
- Nutrition

GORD
- PPI
- +/– prokinetics

Other comorbidities
- Treat appropriately



Other factors
- Ethnic differences
- Environmental exposures
- Climatic variation
- Lifestyle
- Psychosocial

Targetable (endophenotypic) traits

Microbial (bacterial) dysbiosis
- Probiotics

Mycobiome (fungal) dysbiosis
- Antifungals

Neutrophil dysfunction
- Neutrophli elastase inhibitors

Protease-mediated lung damage
- Protease inhibitors

Ciliary dysfunction (primary or secondary)
- Airway clearance
- CFTR potentiator therapy

Systemic inflammation and vascular dysfunction
- Anti-inflammatory therapy

CFTR dysfunction
- CFTR potentiators
- CFTR correctors

Innate immune deficiency
- TLR-based therapeutics
- Antibiotic prophylaxis

James D Chalmers, Lancet Respir Med 2018; 6: 715–26

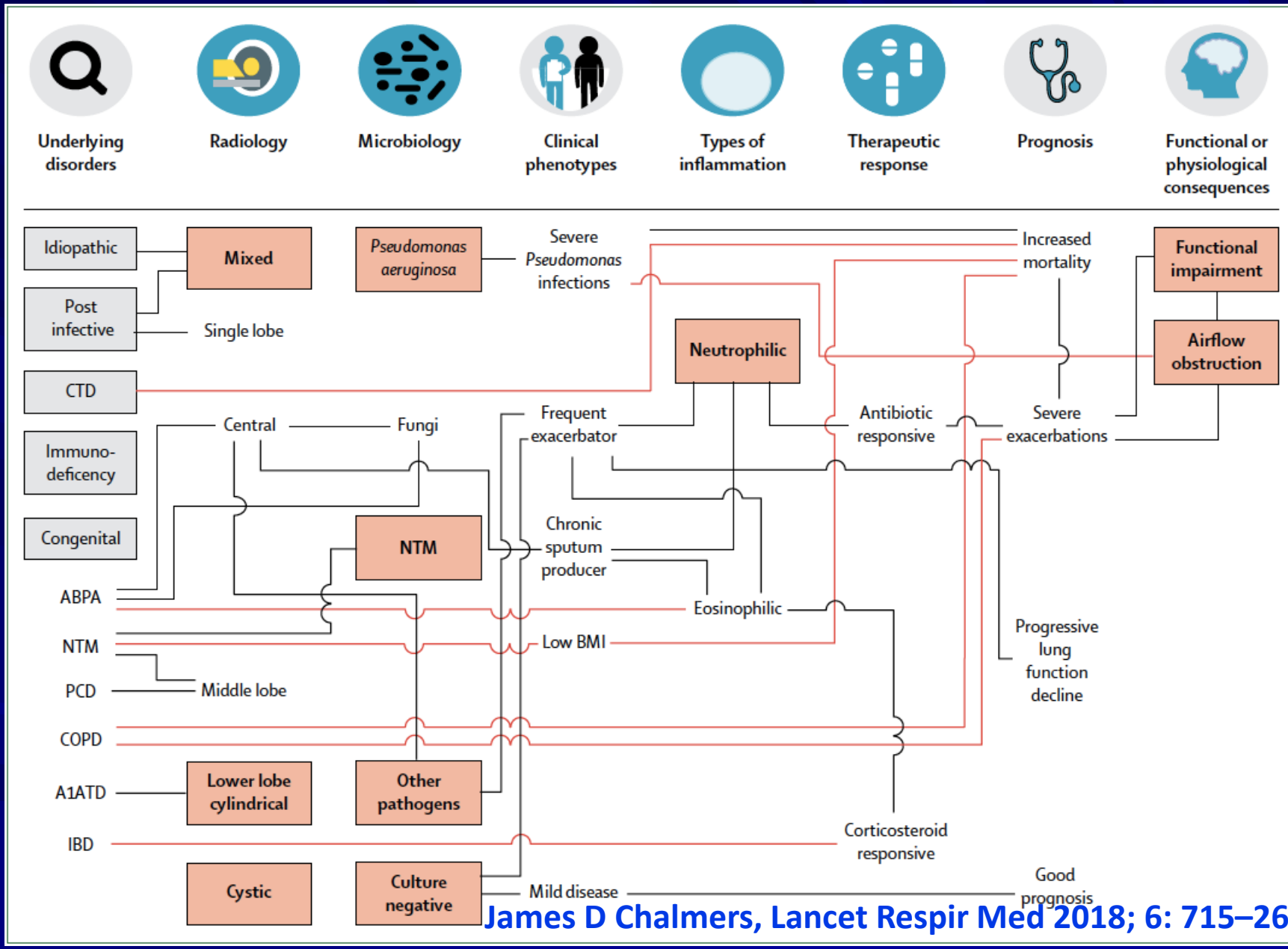
Outline

- Introduction
- The assessment of Non-Cystic Fibrosis Bronchiectasis (Non-CF BE)
- Management approach
- Summary

Summary

- Bronchiectasis is a heterogeneous disease of persist lung inflammation, interplay between immnogenetic susceptibility, immune dysregulation, bacterial infection and lung damage
- Two prognostic indices that aid clinical decisions are the bronchiectasis severity index (BSI) and the FACED score

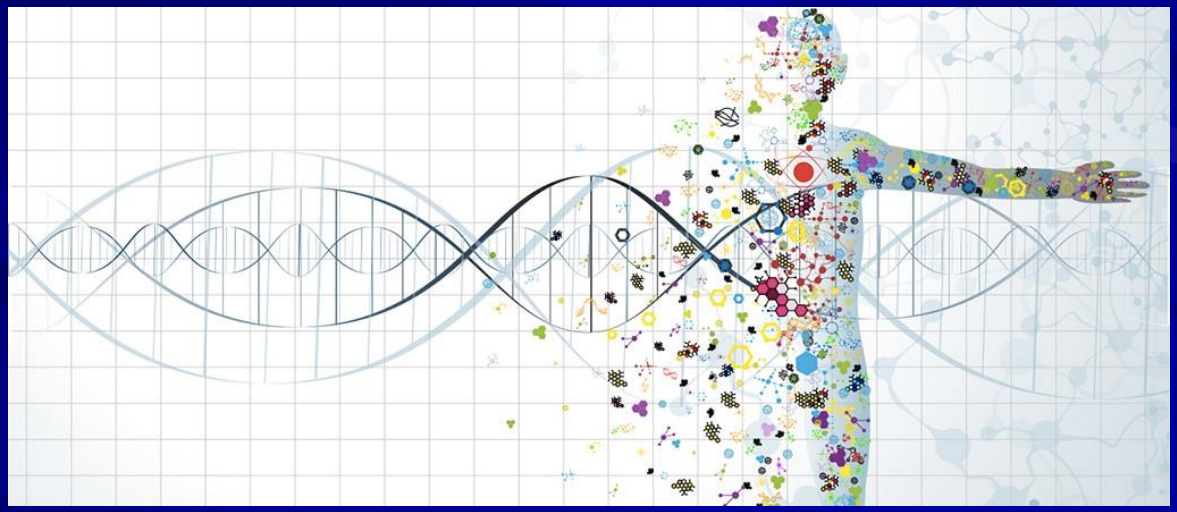
Current classification of bronchiectasis



James D Chalmers, Lancet Respir Med 2018; 6: 715–26

Summary: Precision medicine

- Establishing the primary diagnosis is important, as it has implications for optimal management.




Thanks your
attention !