Bronchiectasis: How Bad Is It?

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Disclosures

- ✓ **Research grant support:**
  - **Bronchiectasis Research Registry/COPD Foundation**
- ✓ **Advisory Board:**
  - **Bayer**
  - **Grifols**
  - **Aradigm**

When Should You Suspect Bronchiectasis?

- ✓ **Persistent productive cough**
  - **Daily, large volume sputum production**
  - **Symptoms for many years**
  - **Sputum colonization with *Pseudomonas aeruginosa***
- ✓ **Recurrent respiratory tract infections**
- ✓ **Non-smokers thought to have COPD with recurrent exacerbations**
- ✓ **Unexplained hemoptysis**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65:i1-58.

Approach to Diagnosis

- ✓ **Age of the patient**
- ✓ **Presence of extrapulmonary symptoms**
- ✓ **Presence of diagnoses known to predispose to bronchiectasis**
- ✓ **Radiological characteristics**
- ✓ **Microbiology**

Radiological Distribution

Focal Disease

- ✓ **Postinfectious**
  - Bacterial
  - Viral
  - Mycobacterial (TB, NTM)
- ✓ **Airway obstruction**
  - Foreign body
  - Bronchial stricture (i.e., RML syndrome)
  - Endobronchial mass

Diffuse Disease

- ✓ **Postinfectious**
  - Measles, pertussis
  - Mycobacterial (TB, NTM)
- ✓ **Congenital syndromes**
  - Cystic fibrosis
  - Primary ciliary dyskinesia
- ✓ **Immunodeficiency states**
  - Immunoglobulin deficiency/CVID
  - HIV/AIDS
- ✓ **Immune-mediated diseases**
  - ABPA
  - Rheumatoid arthritis
  - Sjogren's syndrome
  - Inflammatory bowel disease
- ✓ **GERD/Aspiration**

•**Barker AF.** ***N Engl J Med*** **2002; 346.**
•**Mysliwiec V, Pina JS.** ***Postgrad Med*** **1999; 106.**
•**Pasteur MC, et al.** ***Am J Respir Crit Care Med*** **2000; 162.**

Work-up: ERS Guidelines

✓ **Minimum tests**

- **CBC with differential count**
- **Serum immunoglobulins (A, G, M)**
- **ABPA testing: serum IgE level, specific IgE and IgG, *Aspergillus* skin test**
- **Routine sputum culture**

Other testing as dictated by clinical data

ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.
Conditional recommendation

- ✓ **CF testing (*both* sweat chloride tests and CFTR genetic mutation analysis):**
  - **All children and all adults up to the age of 40**

- ✓ **Consider CF testing in others with:**
  - **Upper lobe bronchiectasis**
  - **Persistent isolation of *S. aureus* in sputum**
  - **Features of malabsorption**
  - **Male primary infertility**
  - **Recurrent pancreatitis**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65: i1-i58.
ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.

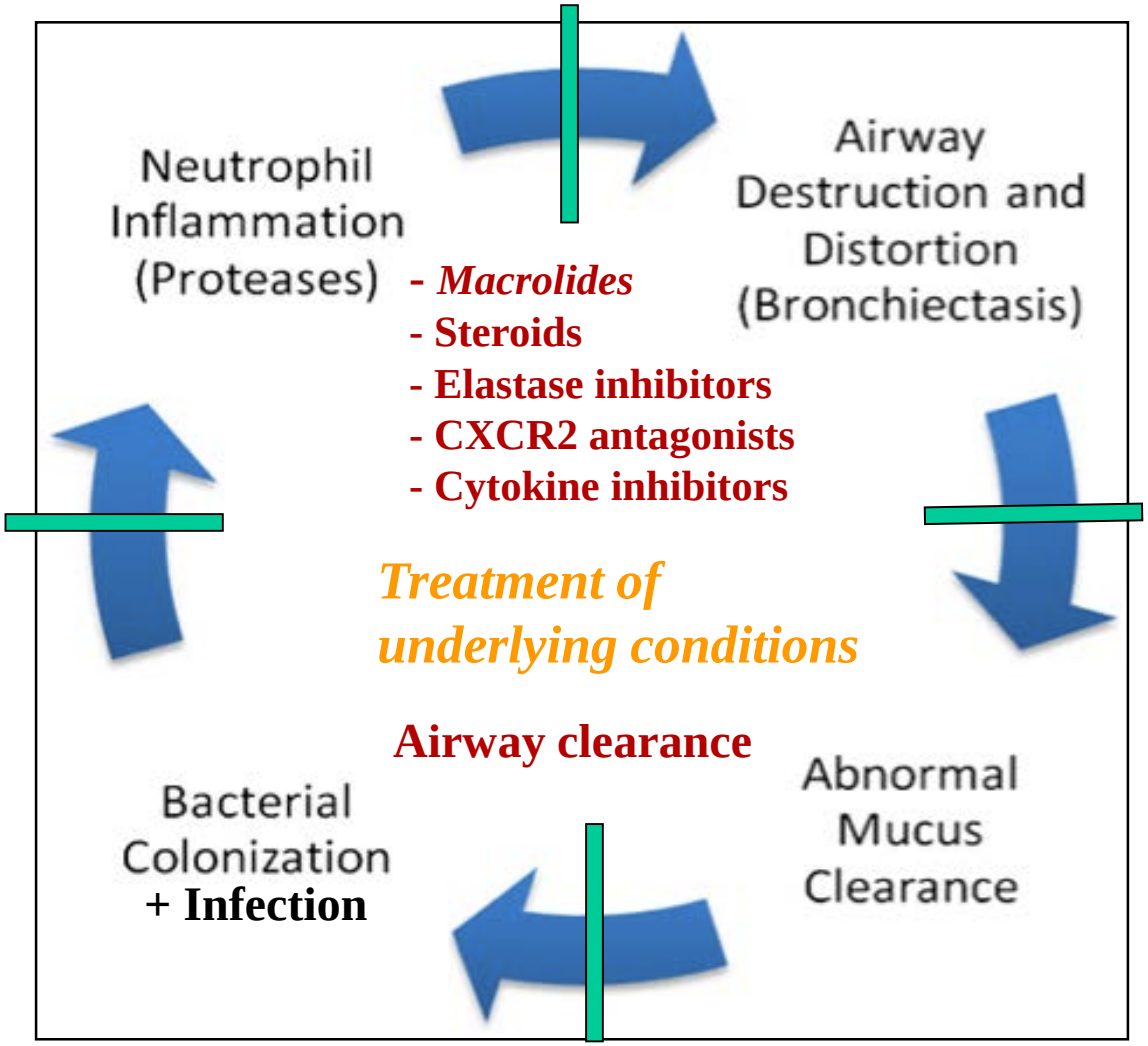
- ✓**PCD testing:**
  - **Neonatal respiratory distress**
  - **Chronic rhinosinusitis or otitis media**
  - **Infertility or dextrocardia**

- ✓**Work-up for gastric aspiration should be considered in selected patients**

- ✓**Bronchoscopy: not routinely warranted**

BTS Guideline. Pasteur et al. *Thorax* 2010; 65: i1-i58.
ERS Guideline. Polverino et al. *Eur Resp J* 2017; 50.

Bronchiectasis: Treatment



Antibiotics
- **Systemic**
- **Inhaled**

Surgery

Am J Resp Crit Care Med **2013; 188.**

Assessing Severity and Prognosis

- ✓ **Clinical course and natural history of bronchiectasis are variable**
- ✓ **Some patients have minimal symptoms and infrequent exacerbations, while others are greatly impacted**

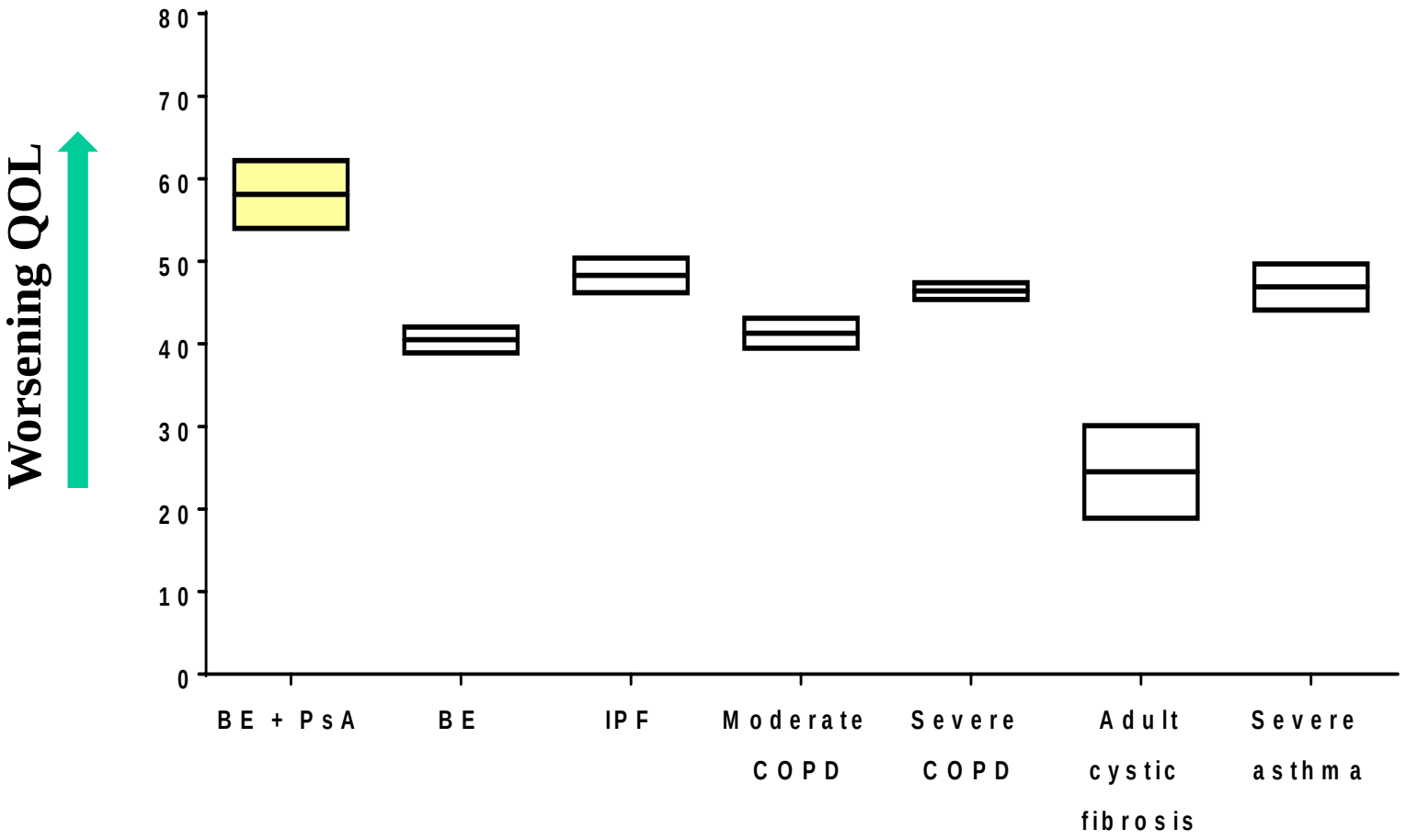
Assessing Severity and Prognosis

- ✓ **Our ability to accurately assess severity and prognosis was an unmet need….**

  …. but we've made significant progress

Bronchiectasis: Impact on Quality of Life

SGRQ total score



1. Kreuter, et al. *Respir Res.* 2017. 2. Kerwin, et al. *Intl J COPD*. 2017. 3. Magnussen, et al. *NEJM*. (Oct) 2014. 4. Padilla, et al. *Arch Bronconeumol.* 2007. 5. Ortega, et al. *NEJM.* (Sept) 2014.

Factors influencing QOL

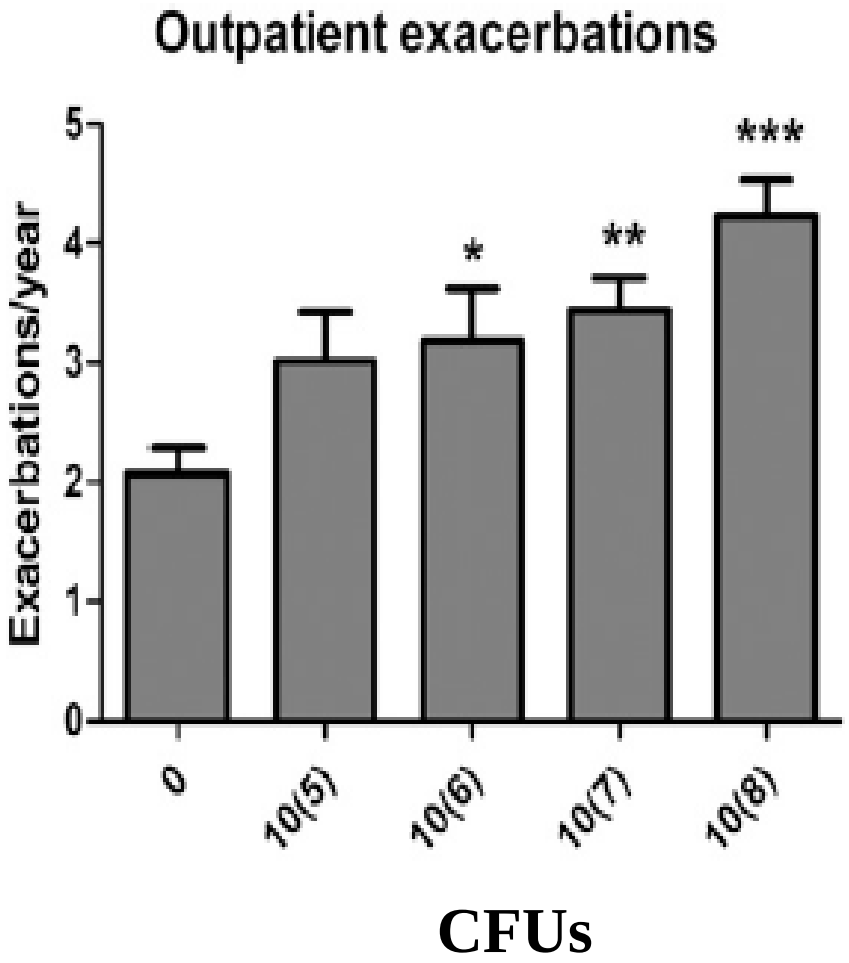
- ✓ **Dyspnea**
- ✓ **FEV_1**
- ✓ **Sputum volume**
- ✓ ***Pseudomonas aeruginosa* infection**

•**Wilson et al. *Eur Respir J* 1997;10.**

•**Martinez-Garcia et al. *Chest* 2005; 128.**

Impact of Bacterial Load

- ✓ **High bacterial load (CFUs) linked to:**
  - **Risk of future exacerbations**
  - **Future hospitalizations for exacerbations**
  - **Markers of lung inflammation**

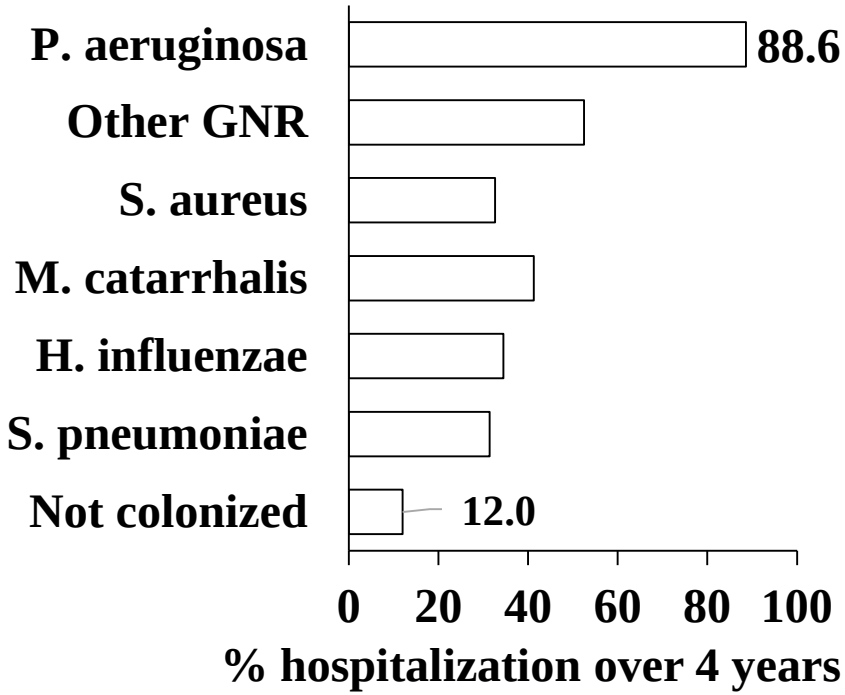


Antibiotics reduce bacterial load and markers of inflammation

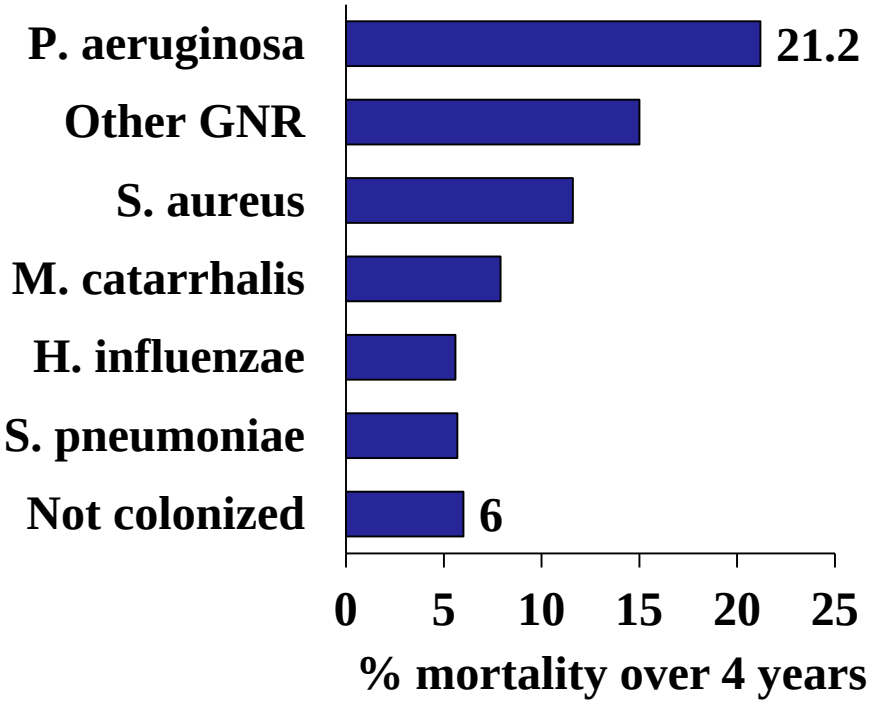
Chalmers, et al. *Am J Respir Crit Care Med* 2012; 186.

Impact of *Pseudomonas* Infection

7× Higher Risk of Hospitalization



3× Higher Mortality



- Chalmers, et al. *AJRCCM.* 2014; 189.
- Finch, et al. *Annals ATS*. 2015; 12.

Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research

Eur Resp J 2017; 49.

Adam T. Hill[1,26], Charles S. Haworth[2,26], Stefano Aliberti[3], Alan Barker[4], Francesco Blasi[3], Wim Boersma[5], James D. Chalmers[6], Anthony De Soyza[7], Katerina Dimakou[8], J. Stuart Elborn[9], Charles Feldman[10], Patrick Flume[11], Pieter C. Goeminne[12,13], Michael R. Loebinger[14], Rosario Menendez[15], Lucy Morgan[16], Marlene Murris[17], Eva Polverino[18], Alexandra Quittner[19], Felix C. Ringshausen[20], Gregory Tino[21], Antoni Torres[18], Montserrat Vendrell[22], Tobias Welte[20], Rob Wilson[14], Conroy Wong[23], Anne O'Donnell[24,27] and Timothy Aksamit[25,27] for the EMBARC/BRR definitions working group

Definition of a bronchiectasis pulmonary exacerbation for clinical trials

A person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 h:

1) Cough
2) Sputum volume and/or consistency
3) Sputum purulence
4) Breathlessness and/or exercise tolerance
5) Fatigue and/or malaise
6) Haemoptysis

AND a clinician determines that a change in bronchiectasis treatment is required#

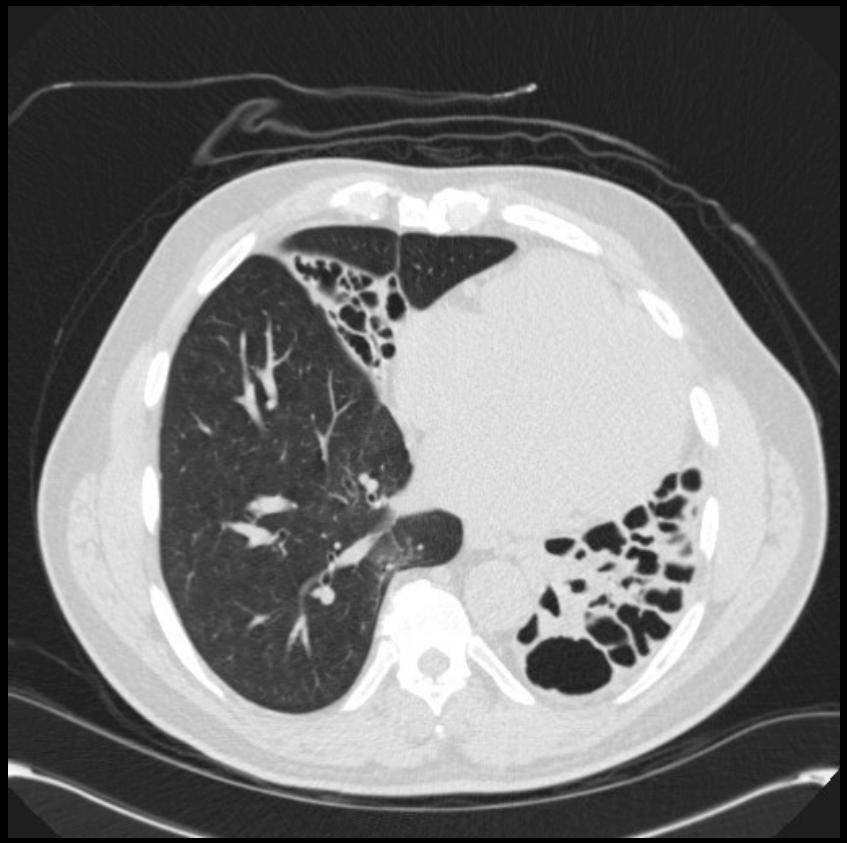
Mortality in Bronchiectasis

- ✓ **91 patients in the UK followed over 13 years starting in 1994; 56% had idiopathic BE**
- ✓ **Mean age: 52 years**
- ✓ **29.7% died**
  - **Expected death rate 14.7% for males, and 8.9% for females**
- ✓ **Respiratory causes accounted for 70.4% of deaths**
- ✓ **Predictors: older age, *P. aeruginosa infection*, lower FEV_1, SGRQ**

Loebinger et al. *Eur Respir J* 2009; 34.

77 y.o. African-American man:

- ✓ **Diagnosed with bronchiectasis at age 12 after a pneumonia at 18 months of age**
- ✓ **Tuberculosis excluded**



Clinical Course

- ✓ **Left pneumonectomy recommended, but declined by his parents**
- ✓ **Did well as teenager and adult**
- ✓ **Managed for many years with rotating antibiotics + chest physiotherapy**

PFT

	2014	2004
FEV_1:	1.65L (72% pred)	2.17L
FVC:	2.10 L (68% pred)	2.70L
FEV_1 / *FVC ratio:*	78%	80%

Clinical Course

- ✓ **Has quinolone-resistant chronic *Pseudomonas aeruginosa* infection**
- ✓ **3-4 exacerbations per year requiring IV antibiotics**
- ✓ **Daily sputum production - 40ml/day**
- ✓ **Perceives QOL as declining**

How would you assess the severity of this patient's bronchiectasis?

Bronchiectasis Severity Index (BSI)

- ✓ **Clinical prediction tool for disease severity**
- ✓ **Derived from a prospective cohort study in the UK - 608 patients**
- ✓ **Validated in several independent cohorts**
- ✓ **Patients with active NTM excluded**
- ✓ **9 parameters**

Chalmers et al. *AJRCCM* 2013; 189.

BSI Parameters

- ✓ **Age**
- ✓ **BMI**
- ✓ **FEV_1**
- ✓ **Hospital admission**
- ✓ **Exacerbations**
- ✓ **MRC dyspnea score**
- ✓ ***Pseudomonas* colonization**
- ✓ **Colonization with other organisms**
- ✓ **Radiological severity**

Chalmers et al. *AJRCCM* 2013; 189.

Bronchiectasis Severity Index

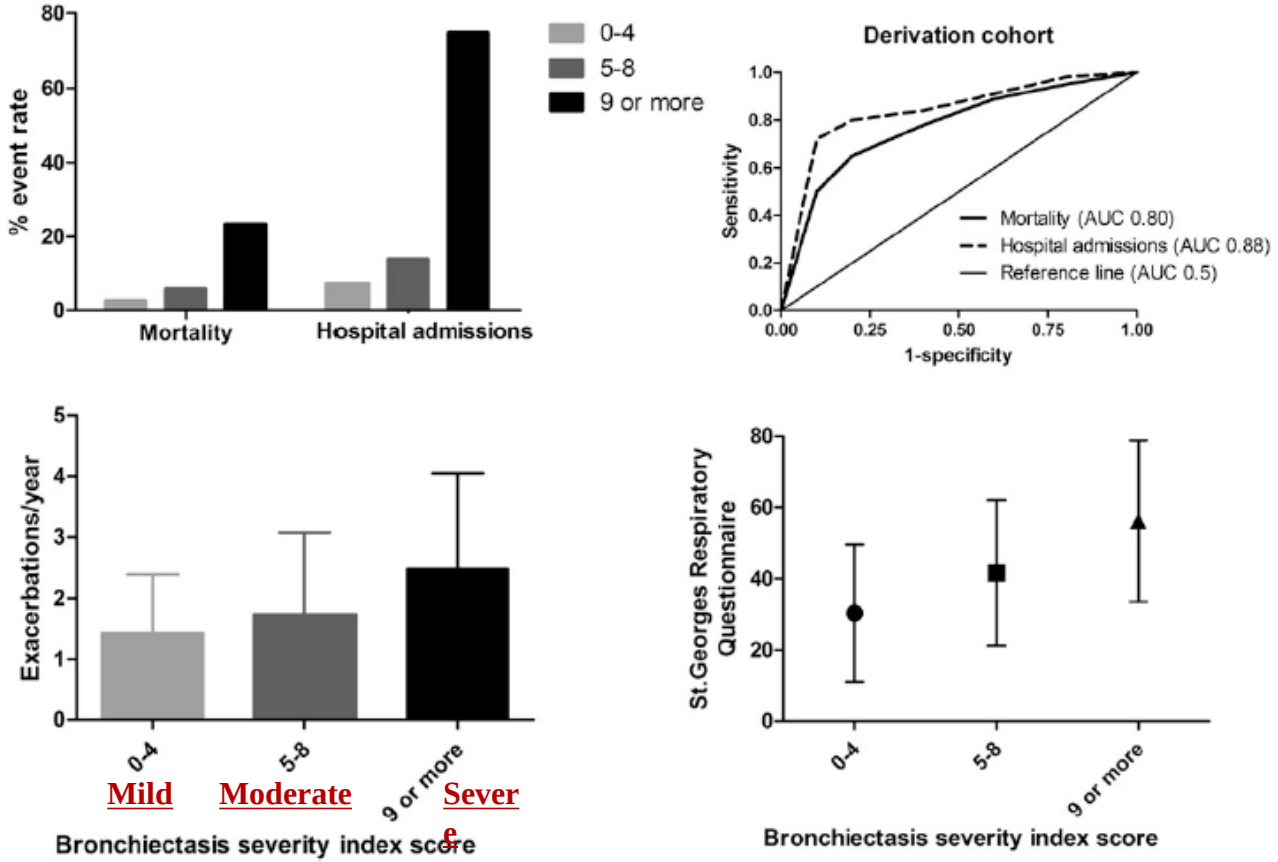


Figure 1. The performance of the Bronchiectasis Severity Index in predicting mortality, hospital admissions, exacerbations, and quality of life. All between-group comparisons were statistically significant ($P < 0.0001$). The exacerbation and quality-of-life data are presented as mean with SD. AUC = area under the receiver operator characteristic curve.

Chalmers et al. *AJRCCM* 2013; 189.

Bronchiectasis Severity Index

- ✓ **Independent predictors of hospitalization**
  - **Prior admissions**
  - **MRC dyspnea score > 4**
  - **FEV_1 < 30%**
  - ***Pseudomonas* colonization**
  - **3 or more lobes involved on HRCT**

Chalmers et al. *AJRCCM* 2013; 189.

Bronchiectasis Severity Index

- ✓ **Independent predictors of mortality**
  - **Older age**
  - **Low FEV_1**
  - **Lower BMI**
  - **Prior hospitalization**
  - **3 or more exacerbations in previous year**

Chalmers et al. *AJRCCM* 2013*; 189*.

FACED Score

- ✓ **Classifies severity according to prognosis**
- ✓ **Derived from an observational study from 7 centers in Spain - 819 patients**
- ✓ **5 variables, 7 point score**
  - **Mild: 0-2 points**
  - **Moderate: 3-4 points**
  - **Severe: 5-7 points**

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.

Martinez-Garcia et al. *ERJ* 2014; 43

FACED Score

✓**Validated to predict 5-year all-cause mortality**

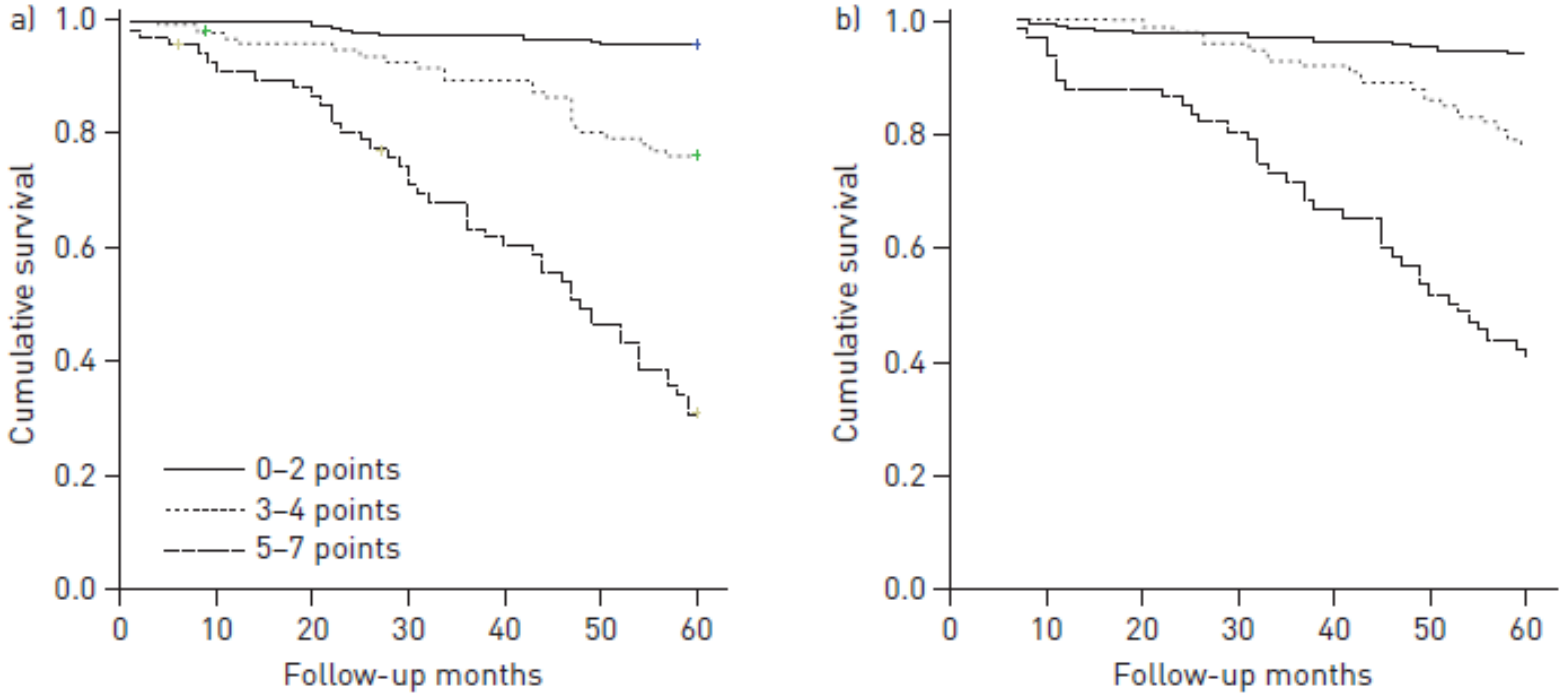


FIGURE 3 Kaplan–Meier curves for all-cause mortality corresponding to the three bronchiectasis scoring groups (mild 0–2 points, moderate 3–4 points and severe 5–7 points) in a) the construction cohort and b) the validation cohort. Log-

Martinez-Garcia et al. *ERJ* 2014; 43.

E-FACED Score

- **Expanded the capacity of the original tool to predict exacerbations**

Table 3 The E-FACED score

Variable	Values	Points
At least one severe exacerbation in previous year	No	0
	Yes	2
FEV_1 (% predicted)	At least 50%	0
	<50%	2
Age	<70 years	0
	At least 70 years	2
Chronic colonization by *Pseudomonas aeruginosa*	Yes	1
	No	0
Extension (n° of pulmonary lobes affected)	1–2 lobes	0
	>2 lobes	1
Dyspnea (mMRC)	0–II	0
	III–IV	1
	Range	0–9 points

Abbreviations: FEV_1, forced expiratory volume in 1 s; mMRC, Modified Medical Research Council.

Table 4 Comparison between the prognostic capacity of E-FACED and FACED for the number and severity of exacerbations in the validation cohort (n=651)

	FACED	E-FACED	*P*-value
At least one exacerbation per year (n=228; 35%)	0.70 (0.67–0.75)	0.76 (0.72–0.80)	<0.05
At least two exacerbation per year (n=117; 17.9%)	0.72 (0.68–0.78)	0.82 (0.78–0.87)	<0.05
At least one hospitalization per year (n=56; 8.6%)	0.82 (0.78–0.87)	0.89 (0.85–0.92)	<0.05
At least two exacerbations per year or one hospitalization per year (n=150; 23%)	0.78 (0.74–0.82)	0.87 (0.83–0.90)	<0.05

Note: Data are presented as AUC-ROC (95% confidence interval).

Martinez-Garcia et al. *Int J COPD* 2017; 12.

Bronchiectasis Mortality: BSI vs FACED

- ✓ **Evaluated in a 91 patient cohort followed since 1994 in the UK; median follow-up 18.8 years**
- ✓ **Both scores were similarly predictive of 5-year and 15-year mortality; FACED did slightly better for the latter**

TABLE 5 Comparison of receiver operating characteristics (ROCs) for mortality at different time points between bronchiectasis severity index (BSI) and FACED scores

Mortality	BSI	FACED	p-value
5-year	0.79 (0.64–0.94)	0.80 (0.65–0.95)	0.876
10-year	0.71 (0.55–0.86)	0.84 (0.72–0.95)	0.082
15-year	0.69 (0.55–0.82)	0.82 (0.72–0.93)	0.049

Data are presented as area under the curve (95% CI), unless otherwise stated. p-values calculated using DeLong's test for two correlated ROC curves.

Huw et al. *ERJ* 2016; 47.

Bronchiectasis: Clinical Phenotypes

- ✓ **Four clusters identified in European cohort; 3-year follow-up**

Cluster	% of patients	Median SGRQ	Hospitalizations during 1-yr follow-up	Mortality during 1-year follow-up
Chronic *Pseudomonas*	15.8%	58	42%	5.1%
Other chronic infection	24.1%	43	16%	1.5%
Daily sputum	33.0%	39	16%	3.6%
Dry bronchiectasis	27.1%	29	14%	4.9%

(N=1145)

Aliberti S, et al. *Eur Respir J* 2016; 47.

“Frequent Exacerbator” Phenotype

- ✓ **2572 patients from 10 sites in Europe and Israel**
- ✓ **Prior and frequent exacerbations were strongest predictor of future exacerbations**
- ✓ **Other independent predictors:**
  - ***H. flu* and *P. aeruginosa* infection**
  - **Low FEV_1**
  - **Radiological severity**
  - **Co-existing COPD**

Chalmers et al. *AJRCCM 2018; Epub.*

“Frequent Exacerbator” Phenotype

- ✓ **Frequent exacerbators also had worse QOL, high disease severity and increased mortality**
- ✓ **About 40% of patients had 0-1 exacerbations, 37% had 3 or more**

Chalmers et al. ***AJRCCM 2018; Epub.***

Bronchiectasis: Comorbidities

Condition	Men			Women		
	Individuals With Bronchiectasis (n = 8,325)	Individuals Without Bronchiectasis (n = 842,757)	RP	Individuals With Bronchiectasis (n = 13,971)	Individuals Without Bronchiectasis (n = 1,156,878)	RP
PNTM	217 (2.61)	480 (0.06)	43.5	752 (5.38)	638 (0.06)	89.67
Acute bronchitis	5,046 (60.61)	207,621 (24.64)	2.46	9,110 (65.21)	329,981 (28.52)	2.29
Rheumatoid arthritis	636 (7.64)	29,260 (3.47)	2.20	1,749 (12.52)	75,494 (6.53)	1.92
Postinflammatory pulmonary fibrosis[a]	2,975 (35.74)	49,447 (5.87)	6.09	4,778 (34.20)	62,892 (5.44)	6.29
Lung malignancies	1,080 (12.97)	38,564 (4.58)	2.83	1,112 (7.96)	36,196 (3.13)	2.54
Inflammatory bowel disease	186 (2.23)	7,976 (0.95)	2.35	327 (2.34)	13,410 (1.16)	2.02
Other genetic disorders[b]	177 (2.13)	1,211 (0.14)	15.21	252 (1.80)	1,764 (0.15)	12.0

Data are presented as No. (%), unless otherwise indicated. PNTM = pulmonary nontuberculous mycobacterial disease; RP = relative prevalence.
[a]Postinflammatory pulmonary fibrosis: *International Classification of Diseases, Ninth Revision, Clinical Modification* code 515.
[b]Congenital cartilage deficiency, situs inversus, common variable immunodeficiency, IgG deficiency, allergic bronchopulmonary aspergillosis, α_1-antitrypsin deficiency.

Seitz AE, et al. *CHEST* 2012; 142.

Bronchiectasis Aetiology Comorbidity Index (BACI)

- ✓ **Cohort analysis of 986 outpatients**
- ✓ **Assesses impact of comorbidities on mortality**
  - **Median of 4 comorbidities**
  - **13 comorbidities independently predicted mortality -> BACI**

	Hazard ratio (95% CI)	p value	Points
Metastatic malignancy	6·69 (3·53–12·68)	<0·0001	12
Haematological malignancy	2·85 (1·17–6·97)	0·02	6
COPD	2·22 (1·53–3·23)	<0·0001	5
Cognitive impairment	2·21 (0·82–6·01)	0·12	5
Inflammatory bowel disease	2·01 (0·75–5·40)	0·17	4
Liver disease	1·94 (0·80–4·72)	0·14	4
Connective tissue disease	1·78 (1·19–2·68)	0·005	3
Iron deficiency anaemia	1·78 (0·80–2·68)	0·16	3
Diabetes	1·76 (1·10–2·80)	0·02	3
Asthma	1·65 (1·00–2·73)	0·050	3
Pulmonary hypertension	1·58 (0·88–2·84)	0·12	3
Peripheral vascular disease	1·50 (1·00–2·25)	0·052	2
Ischaemic heart disease	1·31 (0·91–1·89)	0·14	2

These variables were then formed into prediction tools using the rounded averaged β coefficient to award points for each variable. The sum of the points intends to capture the effect of an individual disease or a combination of diseases on each patient.

Table 2: Derivation of the Bronchiectasis Aetiology Comorbidity Index (BACI) and points allocation

McDonnell et al. *Lancet* 2016; 4.

Bronchiectasis Aetiology Comorbidity Index (BACI)

- ✓ **Predicts 5-year mortality rate, hospitalizations, QOL across all BSI risk strata**
- ✓ **Validated in 2 independent cohorts: UK and Serbia**

McDonnell et al. *Lancet* 2016; 4.

How would you assess the severity of this patient's bronchiectasis?

BSI score - 13

FACED score - 5

Both scores - c/w severe bronchiectasis

Summary

- ✓ **Natural history and prognosis of bronchiectasis may be difficult to predict**
- ✓ **A number of validated tools have been developed - BSI, FACED**
- ✓ **Specific factors associated with worse outcomes**
  - **Older age, worse lung function, chronic *P. aeruginosa* infection, frequency of exacerbations and comorbidities**