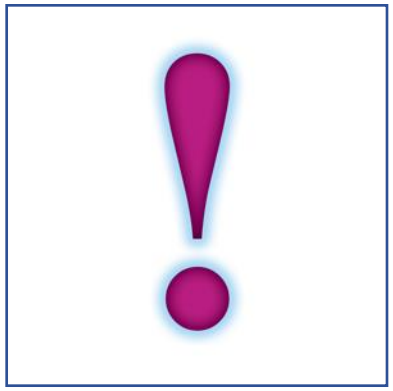
Pneumo Update Europe 2017

9-10 June, Vienna

Hot Topic: Bronchiectasis



James Chalmers, UK

Epidemiology and Diagnosis

State of the Art

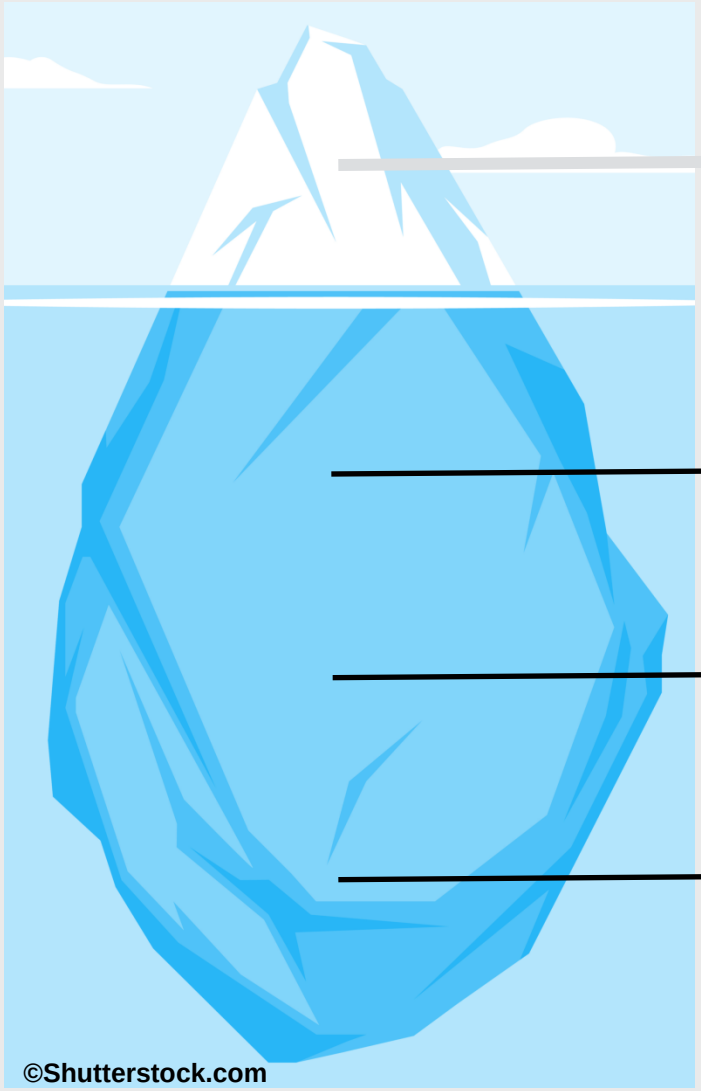
Bronchiectasis has been regarded as an orphan disease

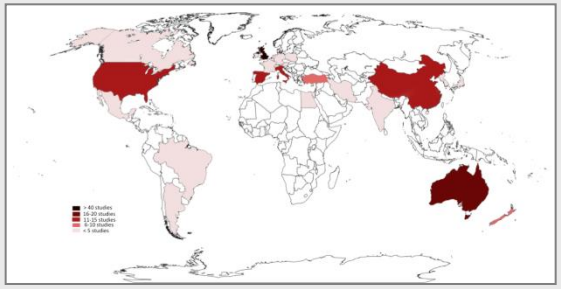
The definition of an orphan disease in the EU is 1 in 2000 (50 in 100,000)

Awareness of bronchiectasis is increased with broader use of CT

Bronchiectasis is now frequently reported in association with airways disease (Asthma/COPD)

State of the Art





Prevalence data
67/100.000 Germany
52/100.000 USA

Mild-to-moderate patients with bronchiectasis (Secondary Care and Primary Care)

Patients with Signs / Symptoms without a radiological diagnosis of bronchiectasis (COPD)

Asymptomatic patients with a radiological diagnosis

ORIGINAL ARTICLE
BRONCHIECTASIS

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

Jennifer K. Quint[1,2], Elizabeth R.C. Millett[2], Miland Joshi[1], Vidya Navaratnam[3], Sara L. Thomas[2], John R. Hurst[4], Liam Smeeth[2] and Jeremy S. Brown[4]

CPRD

More dimensions to data

14 million patients
660 primary care practices

N= 18,793
Diagnosis of bronchiectasis 2004-2013

Comparison to matched cohort of healthy individuals

Annual prevalence per 100,000 population

Mortality rate post diagnosis

Quint et al. Eur Respir J 2016; 47(1):186-93

Prevalence data

UK Clinical Practice Research datalink (CPRD) 2004-2013

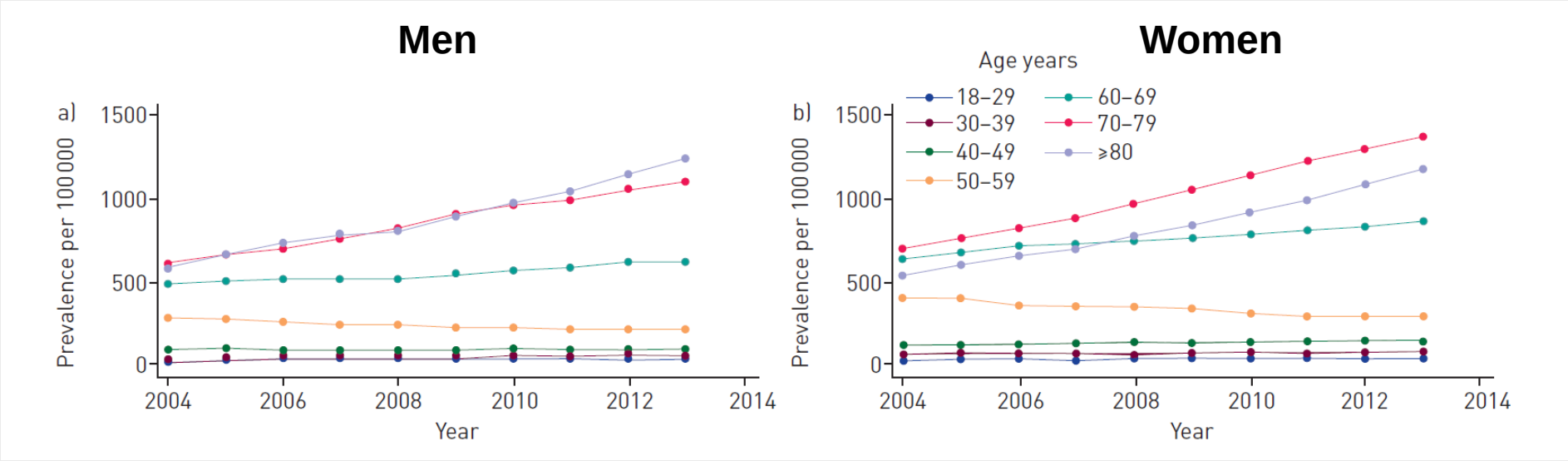
Headline prevalence

566/100,000 in women in 2013

485 per 100,000 in men

CPRD

More dimensions to data

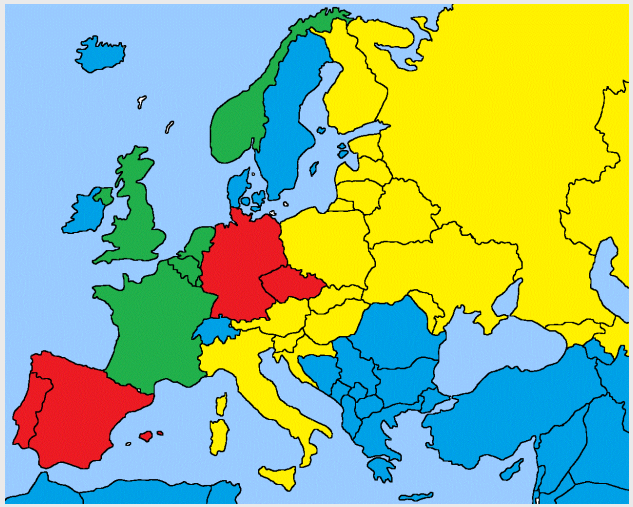


Quint et al. Eur Respir J 2016; 47(1):186-93

Comparing the prevalence of BE to COPD in Europe

Rate of bronchiectasis prevalence increasing in several European countries

COPD
7.6%



Bronchiectasis
0.07%-0.56%

Prevalence in > 65 years:
14.2%

Incidence >65 years
0.2%-0.87%

14-108 cases of COPD for each case of bronchiectasis

References

1.Quint JK, et al Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004-2013: a population based cohort study. *Eur Respir J* 2015; Nov 5. pii: ERJ-01033-2015. doi: 10.1183/13993003.01033-2015. [Epub ahead of print]

2.Ringshausen FC et al. Bronchiectasis in Germany: a population-based estimation of disease prevalence. *Eur Respir J* 2015; 46(6):1805-7.

3.Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.

Patient characteristics- routine data

TABLE 4 Coexisting diagnoses associated with bronchiectasis[#]

Study population	18793
Asthma	7988 (42.5)
Chronic obstructive pulmonary disease	6774 (36.1)
HIV	1300 (6.9)
Rheumatoid arthritis	1163 (6.2)
Other connective tissue diseases	969 (5.2)
Inflammatory bowel disease	527 (2.8)
Bone marrow transplant	20 (0.11)
Hypogammaglobulinaemia	172 (0.9)
Allergic bronchopulmonary aspergillosis	339 (1.8)
None of these comorbidities	6422 (34.2)

Data are presented as n or n (%). [#]: some patients had multiple comorbidities.

Quint et al. Eur Respir J 2016; 47(1):186-93

Mortality rates

TABLE 5 Crude mortality rates by age group in 2010

Age years	Men		Women	
	General population	Bronchiectasis cohort	General population	Bronchiectasis cohort
18–49	1.3 (1.3–1.4)	13.1 (3.4–22.8)	0.8 (0.7–0.8)	6.4 (0.8–12.0)
50–59	5.1 (5.0–5.2)	10.0 (2.6–17.3)	3.4 (3.4–3.5)	7.8 (2.4–13.2)
60–69	12.5 (12.3–12.6)	29.5 (20.6–38.4)	7.9 (7.8–8.0)	16.0 (10.6–21.5)
70–79	33.77 (33.4–33.9)	58.6 (46.4–70.7)	22.8 (22.6–23.0)	43.9 (34.9–52.8)
≥80	111.8 (111.1–112.5)	144.6 (115.4–173.9)	98.9 (98.4–99.4)	160.1 (136.1–184.1)

Data are presented as mortality rate (95% CI), per 1000 population. Rates have been calculated using a mid-year population estimate for 2010.

Limitations

- **No clinical or CT confirmation of bronchiectasis**
- **How accurate is read coding for BE?**

- **No validation of co-morbidity data**
- **Do they really have asthma and COPD or misdiagnosis?**

- **No clinical data e.g microbiology/radiology**

Quint et al. Eur Respir J 2016; 47(1):186-93

ORIGINAL ARTICLE

Bronchiectasis and the risk of cardiovascular disease: a population-based study

Vidya Navaratnam,[1,2,3] Elizabeth R C Millett,[2] John R Hurst,[4] Sara L Thomas,[2] Liam Smeeth,[2] Richard B Hubbard,[1] Jeremy Brown,[4] Jennifer K Quint[2,5]

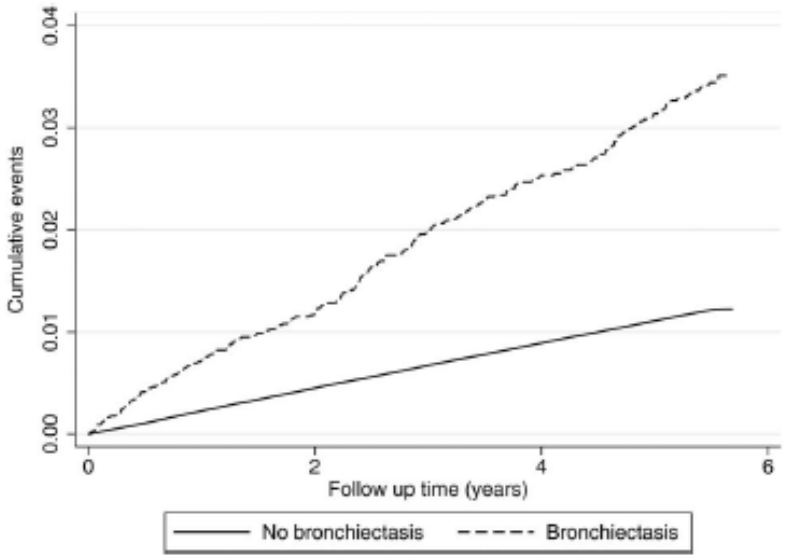


Figure 1 Nelson-Aalen cumulative incidence of coronary heart disease in people with bronchiectasis and those without bronchiectasis is shown.

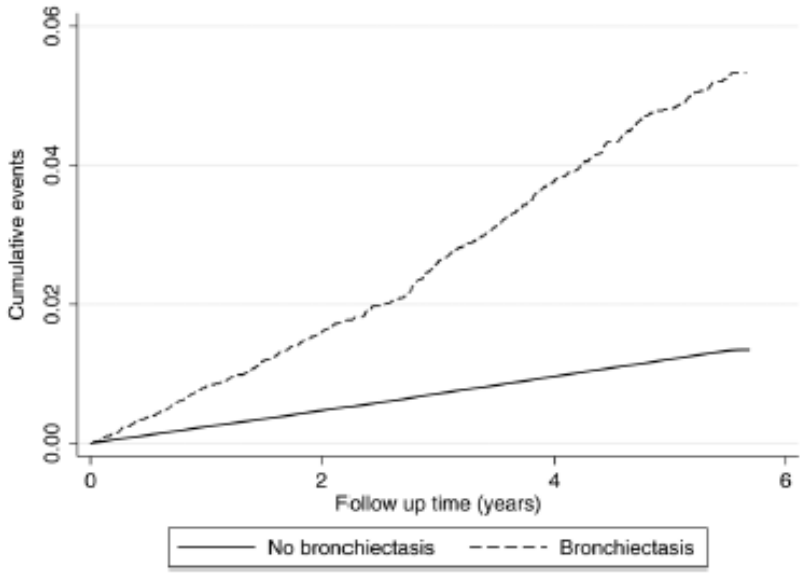
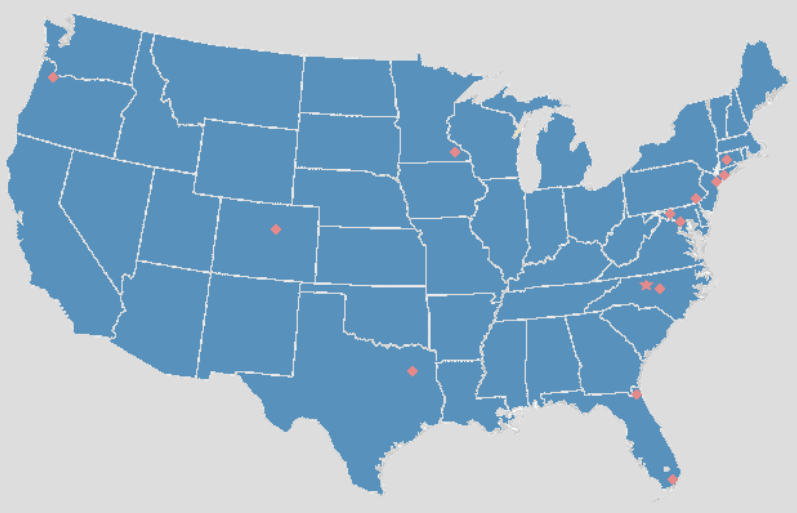


Figure 2 Nelson-Aalen cumulative incidence of stroke in people with bronchiectasis and those without bronchiectasis is shown.

Navaratnam et al, *Thorax* 2017;72:161-166

What about bronchiectasis in the United States?

Bronchiectasis and NTM
Research Registry



Adult Patients With Bronchiectasis
A First Look at the US Bronchiectasis Research Registry

Timothy R. Aksamit, MD; Anne E. O'Donnell, MD; Alan Barker, MD; Kenneth N. Olivier, MD; Kevin L. Winthrop, MD; M. Leigh Anne Daniels, MD, MPH; Margaret Johnson, MD; Edward Eden, MD; David Griffith, MD; Michael Knowles, MD; Mark Metersky, MD; Matthias Salathe, MD; Byron Thomashow, MD; Gregory Tino, MD; Gerard Turino, MD; Betsy Carretta, MPH; and Charles L. Daley, MD; for the Bronchiectasis Research Registry Consortium

United States Bronchiectasis Registry

13 centres
Adult patients only
Inclusion criteria
- **Physician established diagnosis of bronchiectasis**

Exclusion criteria
- **Cystic fibrosis**

Sponsored by the COPD foundation

Aksamit et al. Chest 2017;151(5):982-992.

Characteristics of bronchiectasis in the US bronchiectasis registry

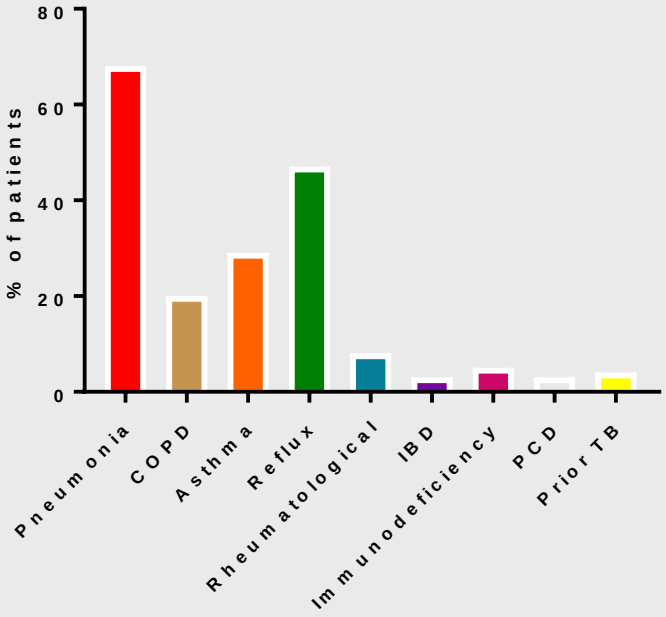
N=1826 patients from 2008 to 2014.

79% female

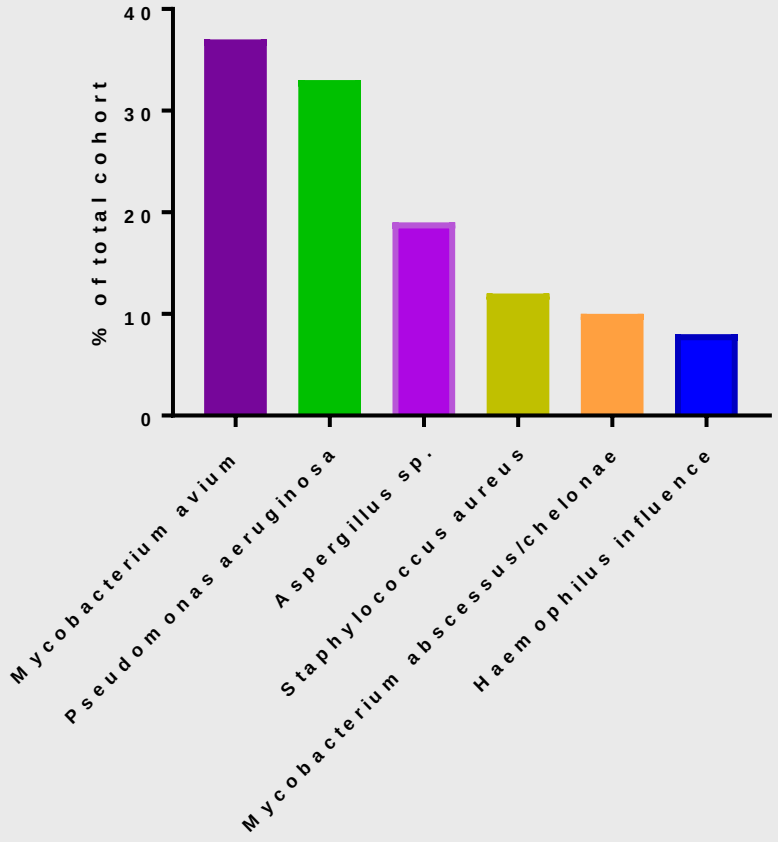
60% never smokers

Mean age 64 years

Underlying causes and co-morbidities

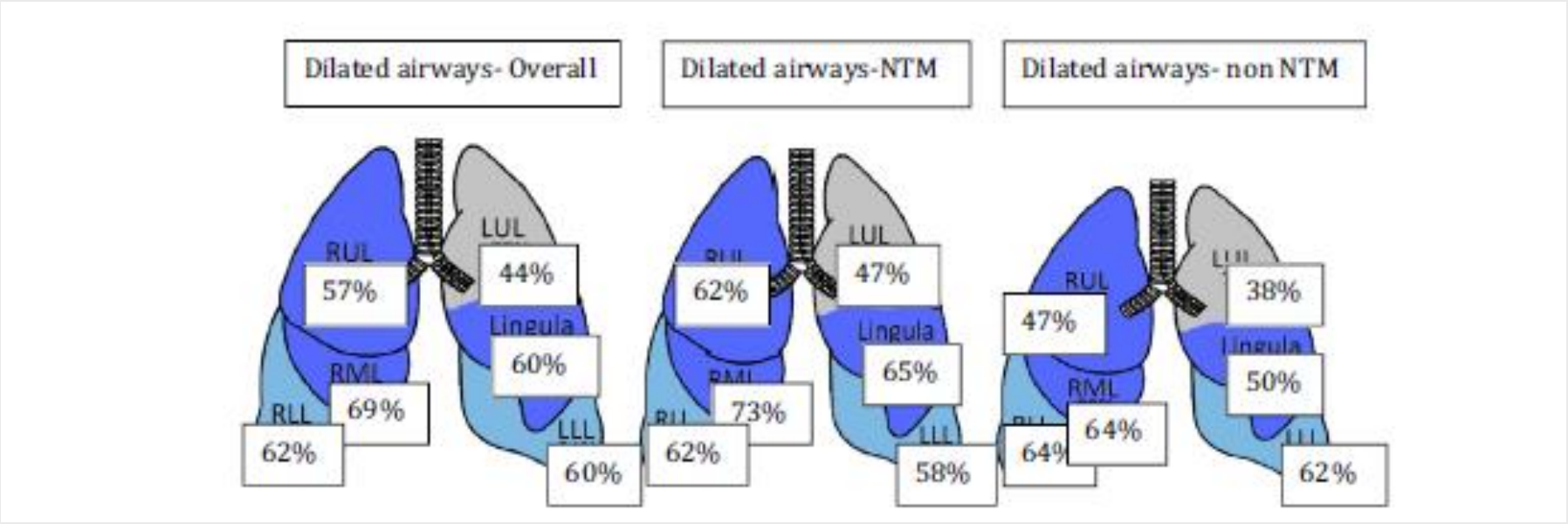


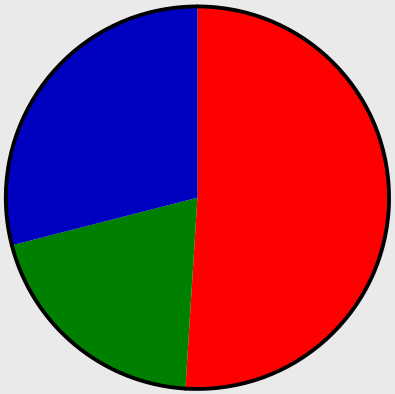
Microbiology



Aksamit et al. Chest 2017;151(5):982-992.

Patterns of disease





Obstruction
Restriction
"normal"

Mean 3 exacerbations in the previous 2 years (i.e 1.5 per year)

36% did not have any exacerbations over 2 years

Aksamit et al. Chest 2017;151(5):982-992.

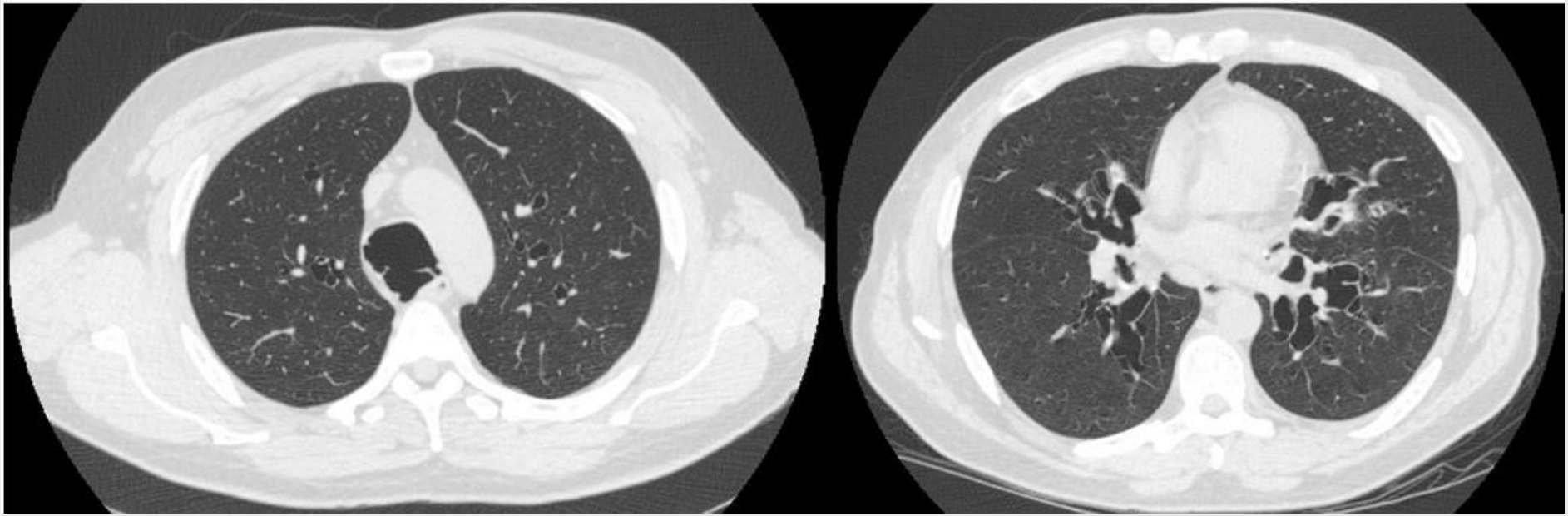
Radiological heterogeneity

Lower lobes
- Idiopathic
- COPD associated
- Post-infectious
- Aspiration
- PCD

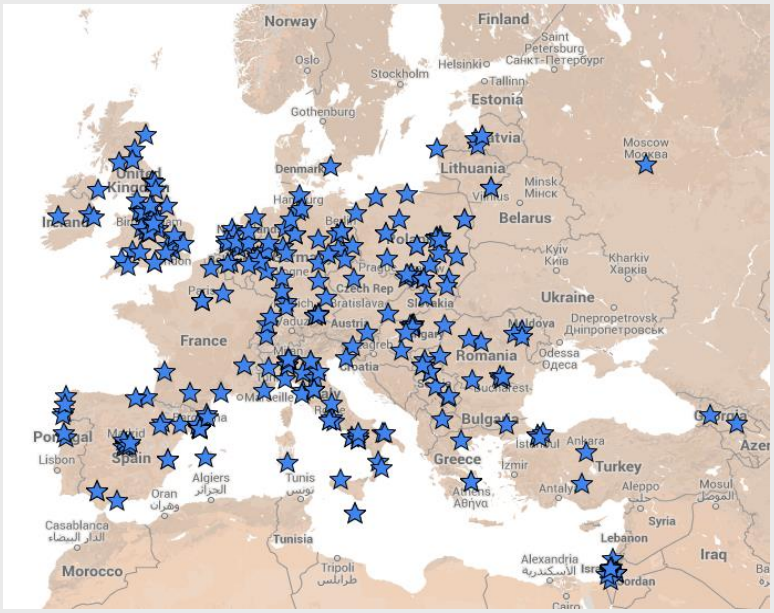
Middles lobes
- NTM infection

Central
- ABPA
- Tracheobronchomegaly

Upper lobes
- Cystic fibrosis



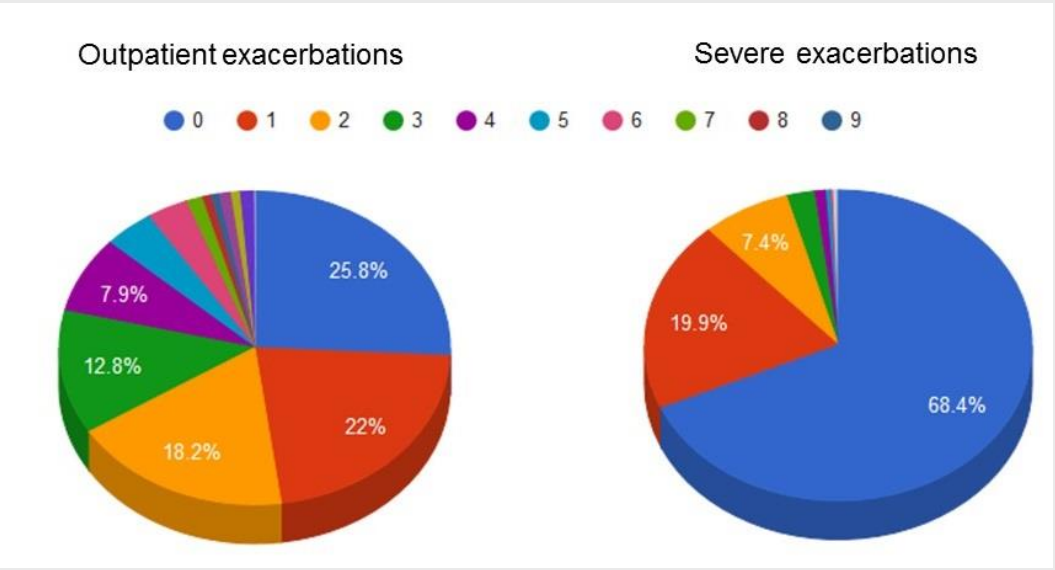
How does this compare to the rest of the world?

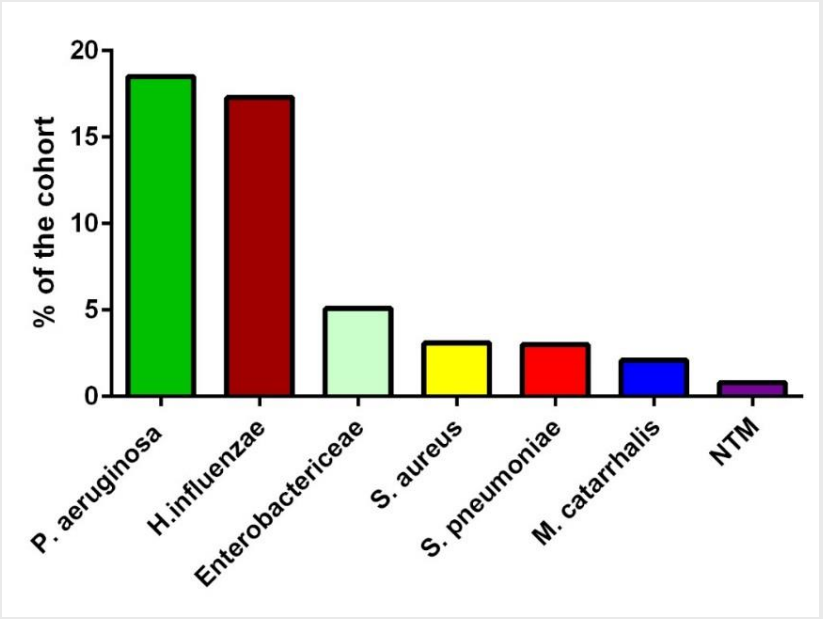


Patients enrolled: 7841 from 25 countries

Demographics
58% female
Median age= 68 years (IQR 58-75)

Never smoked =55.9%
Ex smoker= 38.3%



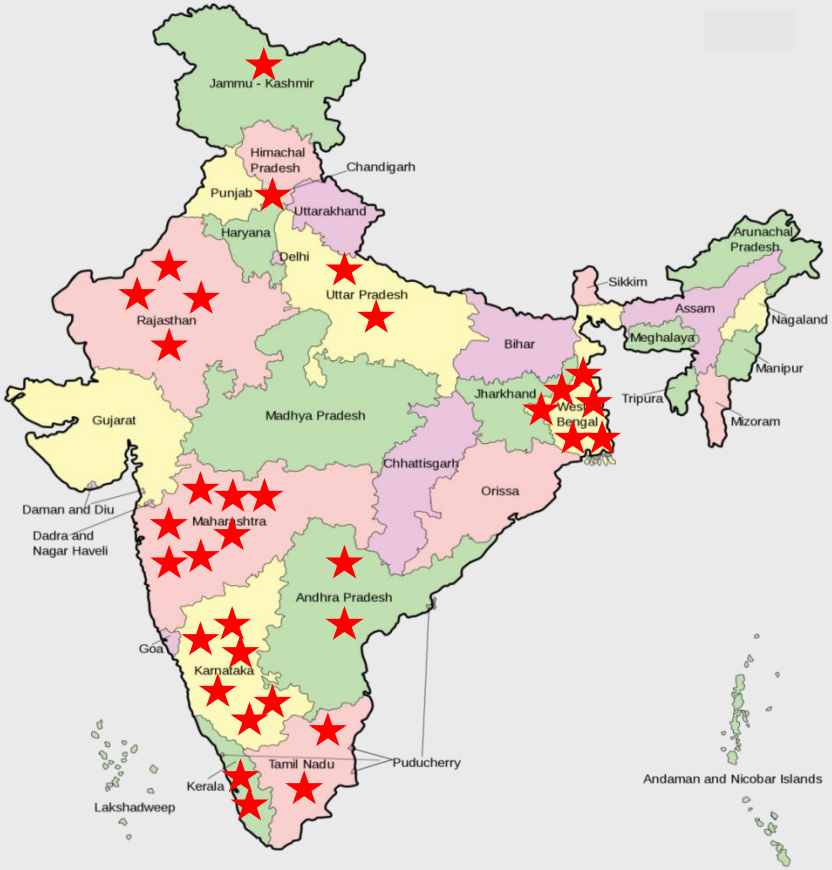


Chalmers et al. *ERJ Open Res.* 2016; 2: 81

CHINA

Guangzhou
Mean age 44 years
63% female
Aetiology- post-infectious- 26%, immunodeficiency 12%, idiopathic 45%

EMBARC INDIA



N=680
Mean age 51 years
60% male
73.5% never smoked
Aetiology- Post-TB 29.8%, idiopathic 26.3%, post infection 21.2%, ABPA 12%.

Take Home Message

Bronchiectasis is *very* common – not a rare disease

Patients are highly heterogeneous- most are elderly and female but different phenotypes exist

Radiological appearance and location, as well as ethnicity can give a clue to underlying cause

Bronchiectasis is now frequently reported in patients with COPD or asthma

COPD and Bronchiectasis Overlap

State of the Art

- COPD/BE overlap is common, and associated with severity of disease

Single centre studies

- **50-60% of patients with moderate to severe COPD**
- **More bacterial colonisation**
- **More *P. aeruginosa***
- **Independent predictor of death**

N=3636
Bronchiectasis
20.8%- associated with more exacerbations, worse FEV_1

N=2164
Bronchiectasis
5% GOLD III, 7% GOLD IV

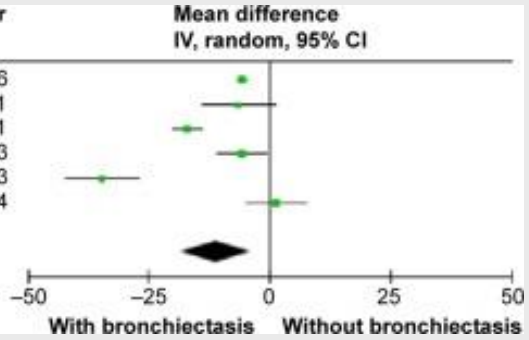
Stewart et al Am J Respir Crit Care Med 2012;185:A3656
Agusti et al- Respir Res. 2010;11:122. doi: 10.1186/1465-9921-11-22.
Martinez-Garcia et al Am J Respir Crit Care Med. 2013;187(8):823-31
Gatheral COPD. 2014;11(6):605-14

Meta-analysis

FEV1% predicted

Study or subgroup	With bronchiectasis Mean	SD	Total	Without bronchiectasis Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Fujimoto et al[11]	42	2.2	44	47.5	2.5	39	18.4%	−5.50 (−6.52, −4.48)	2006
Martínez-García et al[7]	77.3	18.2	53	83.7	18.7	39	15.3%	−6.40 (−14.05, 1.25)	2011
Bafadhel et al[1]	45	4.3	33	62	5	13	17.9%	−17.00 (−20.09, −13.91)	2011
Martínez-García et al[13]	68.6	17.8	115	74.3	18.5	86	16.9%	−5.70 (−10.79, −0.61)	2013
Tulek et al[12]	39.6	12.3	27	74.2	15.7	26	15.3%	−34.60 (−42.21, −26.99)	2013
Gatheral et al[4]	52.4	24.4	135	51	19	63	16.2%	1.40 (−4.84, 7.64)	2014
Total (95% CI)			**407**			**266**	**100%**	**−11.06 (−18.27, −3.85)**	

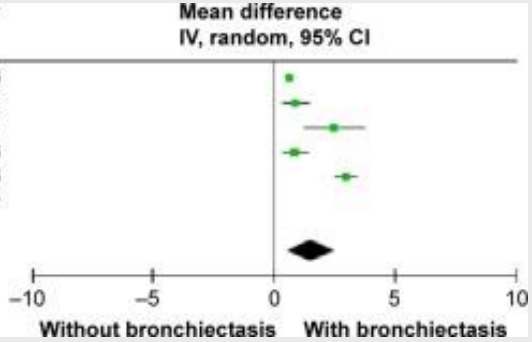
Heterogeneity: τ^2=73.23; χ^2=106.20, *df*=5 (*P*<0.00001); I^2=95%
Test for overall effect: *Z*=3.01 (*P*=0.003)



Exacerbations

Study or subgroup	With bronchiectasis Mean	SD	Total	Without bronchiectasis Mean	SD	Total	Weight	Mean difference IV, random, 95% CI	Year
Fujimoto et al[11]	1.36	0.35	44	0.7	0.22	39	21.8%	0.66 (0.54, 0.78)	2006
Bafadhel et al[1]	4.6	0.6	33	3.7	0.9	13	20.5%	0.90 (0.37, 1.43)	2011
Martínez-García et al[7]	4.87	3.82	53	2.36	2.28	39	16.1%	2.51 (1.26, 3.76)	2011
Martínez-García et al[13]	1.88	2.13	115	1	1.48	86	20.7%	0.88 (0.38, 1.38)	2013
Tulek et al[12]	3.3	1.03	27	0.3	0.5	26	20.9%	3.00 (2.57, 3.43)	2013
Gatheral et al[4]	0	0	0	0	0	0		Not estimable	2014
Total (95% CI)			**272**			**203**	**100%**	**1.54 (0.56, 2.53)**	

Heterogeneity: τ^2=1.15; χ^2=110.26, *df*=4 (*P*<0.00001); I^2=96%
Test for overall effect: *Z*=3.07 (*P*=0.002)



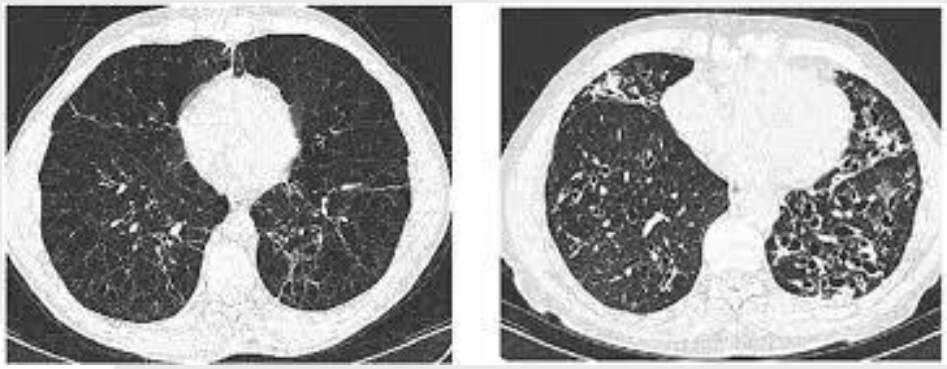
"The meta-analysis identified clear evidence of publication bias, with large effect sizes in small studies not replicated in larger studies"

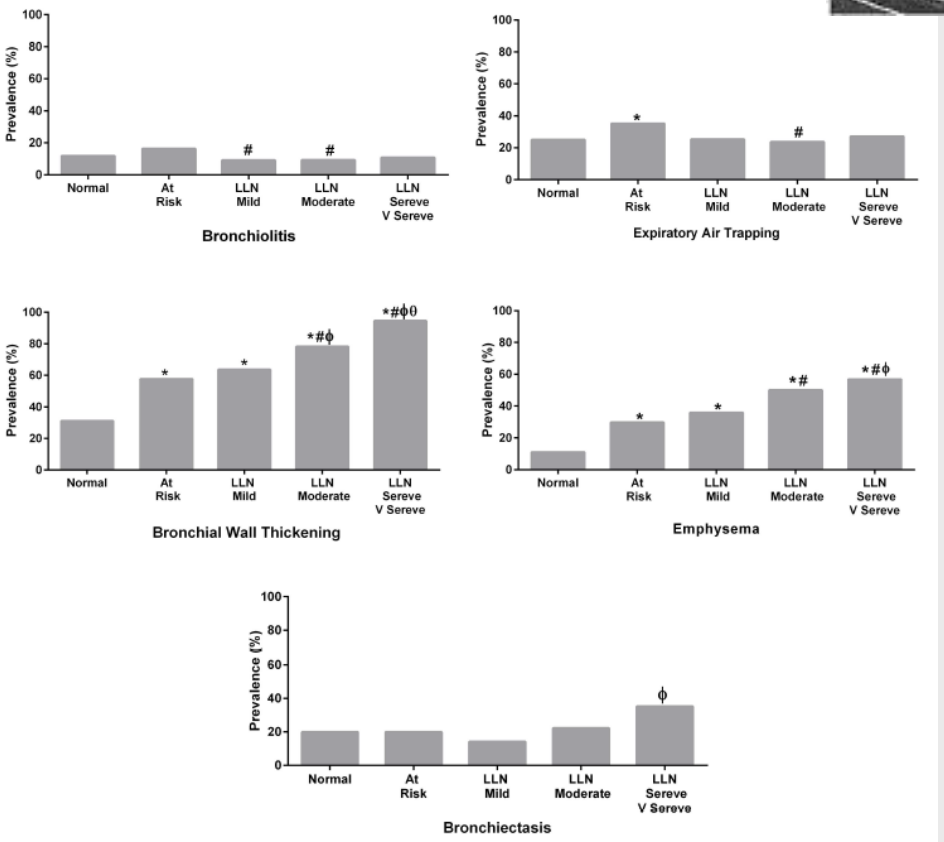
Ni et al, Int J Chron Obstruct Pulmon Dis 2015;10:1465-1475.

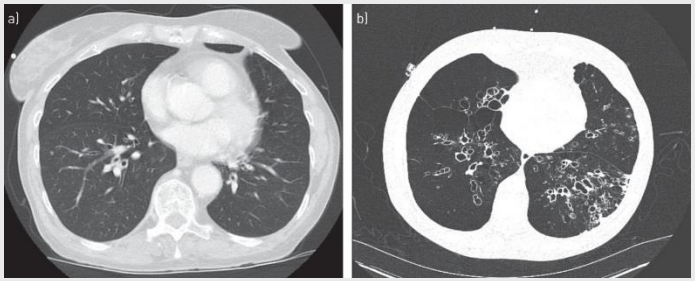
RESEARCH ARTICLE

Findings on Thoracic Computed Tomography Scans and Respiratory Outcomes in Persons with and without Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study

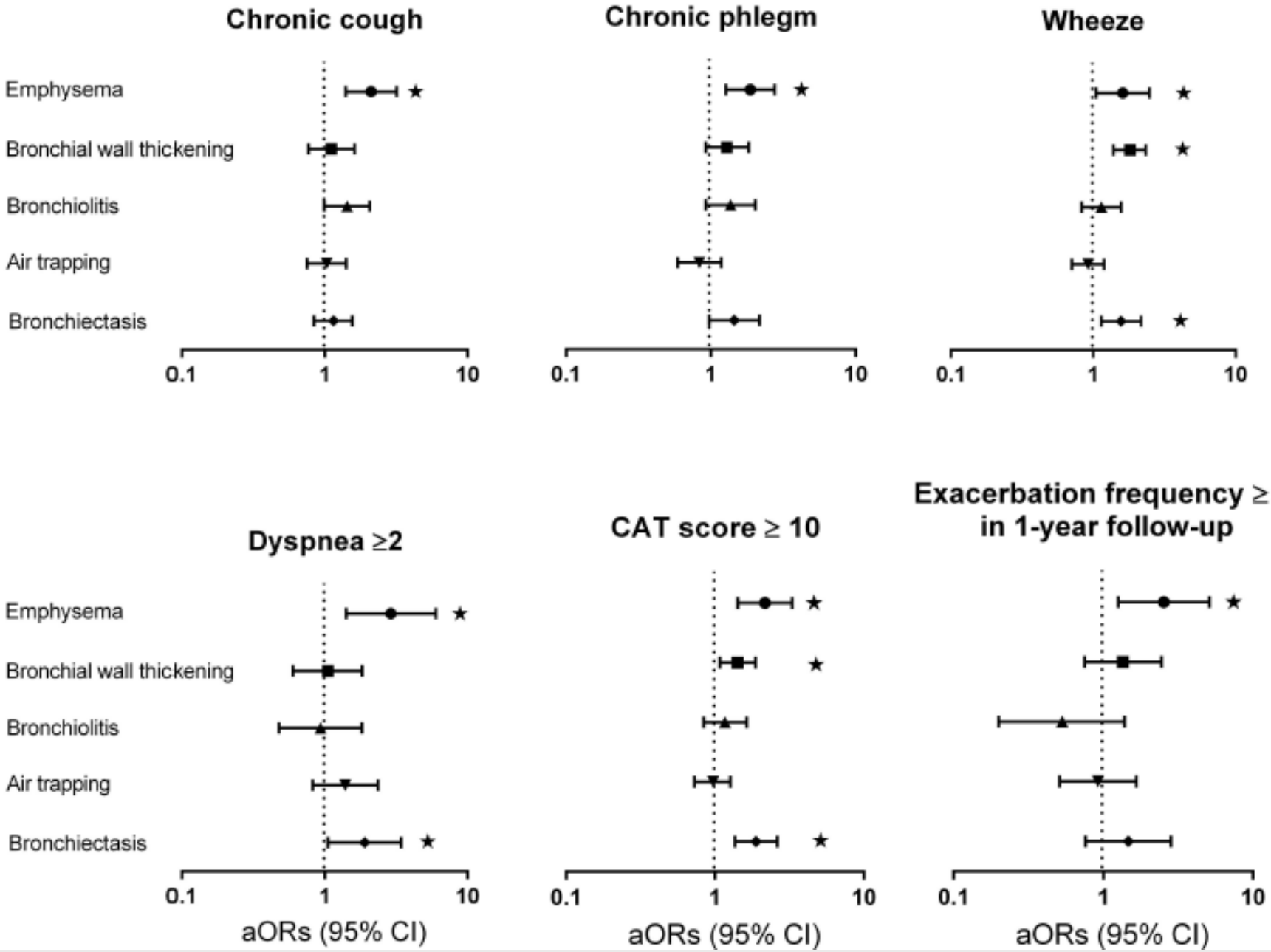
Wan C. Tan[1]*, Cameron J. Hague[2], Jonathon Leipsic[2], Jean Bourbeau[3], Liyun Zheng[1], Pei Z. Li[3], Don D. Sin[1], Harvey O. Coxson[1], Miranda Kirby[1], James C. Hogg[1], Rekha Raju[2], Jeremy Road[4], Denis E. O'Donnell[5], Francois Maltais[6], Paul Hernandez[7], Robert Cowie[8], Kenneth R. Chapman[9], Darcy D. Marciniuk[10], J. Mark FitzGerald[4], Shawn D. Aaron[11], Canadian Respiratory Research Network and the CanCOLD Collaborative Research group[¶]





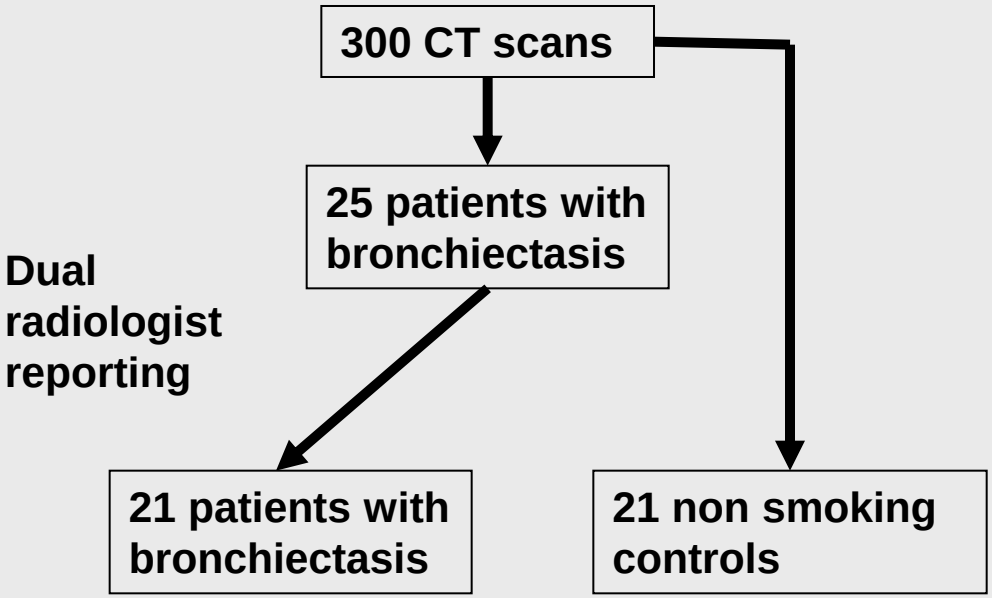


Tan et al., PLoS One. 2016 Nov 18;11(11):e0166745

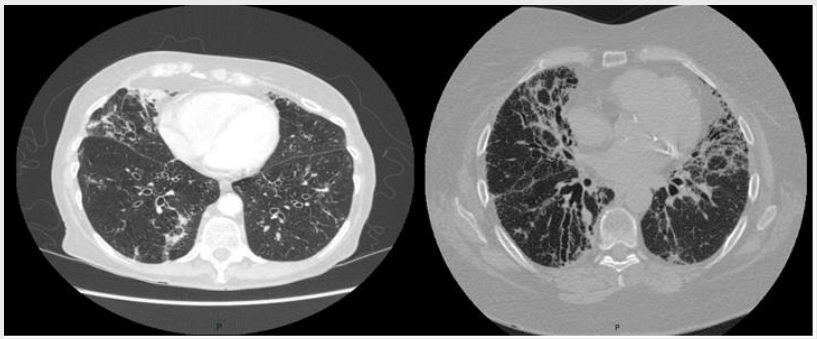


Tan et al., PLoS One. 2016 Nov 18;11(11):e0166745

Quantitative CT measures of bronchiectasis in smokers.



Bronchiectasis was associated with increased bronchial arterial ratio, wall thickness and wall area



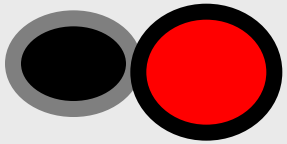
Diaz et al, Chest 2016 pii: S0012-3692(16)62460-1

Challenging paradigms: Is BE due to vascular disease in COPD?

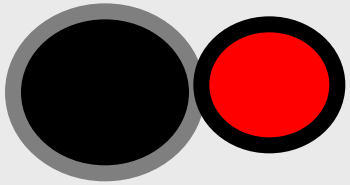
COPDgene cohort
21 patients with bronchiectasis and COPD compared to 21 non-smoking healthy controls

No difference in bronchial diameter between cases and controls. Bronchiectasis "caused" by reduced vessel diameter

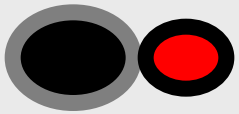
Airway Vessel



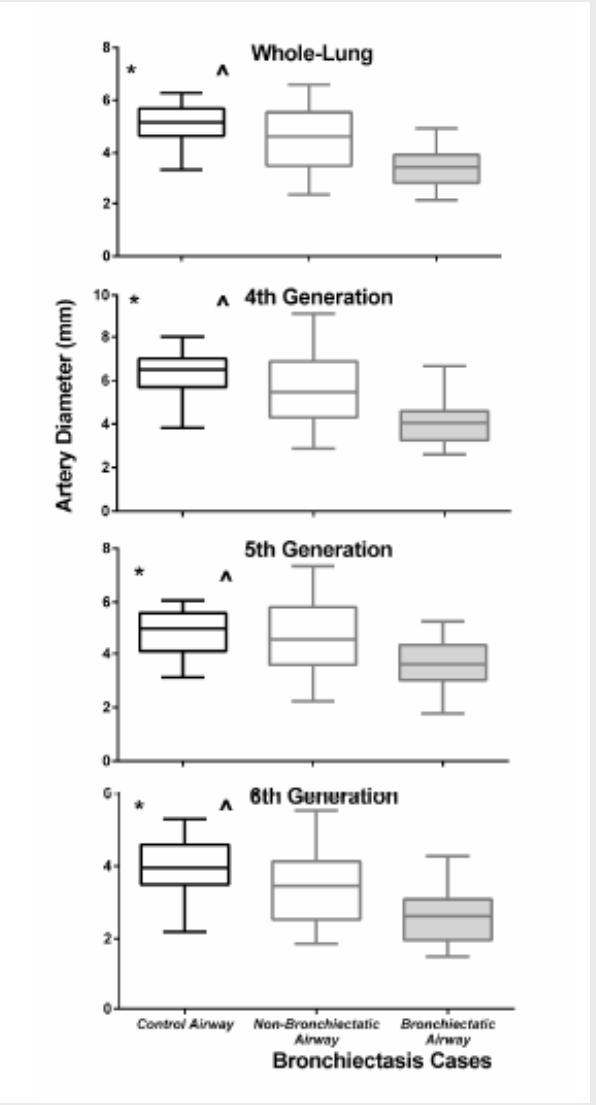
Normal



Bronchiectasis



Bronchiectasis in COPD?



Diaz et al, Chest 2016 pii: S0012-3692(16)62460-1

History- Deteriorating COPD

Thank you for referring this **71 year old lady** to our respiratory clinic. I reviewed her today . She has had **COPD for around 20 years**. She smoked between the age of 16 and 55 between 20-30 cigarettes a day. She also has a past medical history of ischaemic heart disease and hypertension. Her current medication includes Diltiazem, Citalopram, Bendroflumethiazide, **Salbutamol, Seretide 250 evohaler, Ipratropium MDI 40mcg tds**. She has around **3 exacerbations** of her COPD in the last **year**.

She gets her annual flu jab and she has had the pneumovax.

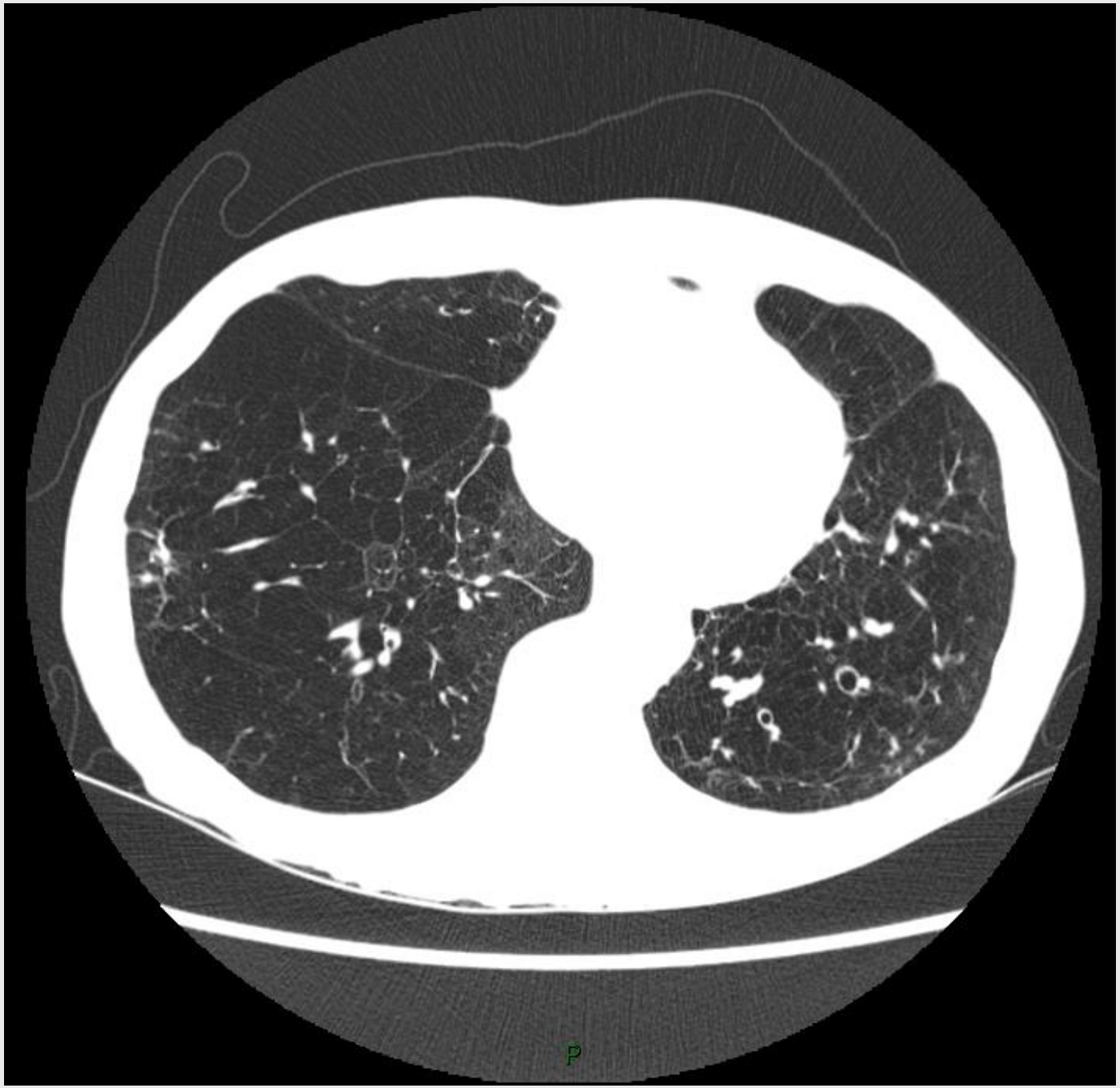
Spirometry today shows an FVC of 1.97 liters (88% predicted) and **FEV1 0.69 liters** (42% predicted).

She complains of feeling incredibly short of breath on minimal exertion and has difficulty getting out of the house.

She asked specifically about home oxygen and her oxygen saturations in clinic were actually good at 94%

She has deteriorated markedly in the past 2 years. She is now quite underweight with a **BMI of 17** and says she is often too tired to eat. She has developed a worsening cough, which is non-productive and which does not respond to her inhalers. She has vague chest pains. She denies night sweats and has had no haemoptysis.

CT scan in 2011 (4 years ago) showed no bronchiectasis



NTM infection: common in COPD

Andrejak et al, Thorax 2013- COPD increased the risk of NTM infection by 16 fold. Inhaled corticosteroid therapy increased the risk by a factor of 29

Treatment with ICS doses >800bdp per day were associated with a 47x increased risk

Char et al, BMC Pulmonary Medicine 2014; 14:124

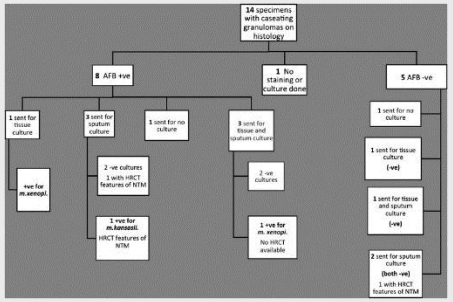
N=142 patients undergoing
LVRS - 10% had NTM infection

ORIGINAL ARTICLE

Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis

Claire Andréjak,[1,2,3,4] Rikke Nielsen,[1] Vibeke Ø Thomsen,[5] Pierre Duhaut,[3,6] Henrik Toft Sørensen,[1] Reimar Wernich Thomsen[1]

Hoefsloot et al, J Infect 2013
N= 73 COPD exacerbations
22% had +ve NTM cultures, 5.4% had >1 +ve NTM culture.



Andréjak et al, Thorax 2013; 68(3):256-62

Conclusion: The patient with COPD and bronchiectasis

Infection (*H.influenzaeIP. aeruginosa)*

Vascular disease

Patient

NTM infection

“Incidentaloma”

Take Home Message

Bronchiectasis as a radiological diagnosis is reported in 10-60% of COPD patients

Bronchiectasis as a clinical diagnosis requires the presence of cough, sputum, recurrent infections and/or bacterial infection

NTM infection should be suspected in patients with COPD and cavities or nodular bronchiectasis on CT

Bronchiectasis can be a “normal” finding on CT or false bronchiectasis can appear due to vascular disease so it is crucial to take a good history and not treat the radiological appearance

Causes and Co-morbidities of Bronchiectasis

State of the Art

A large number of different diseases (infectious, autoimmune, allergic and genetic) can cause bronchiectasis

Some diseases need a specific treatment and should not be missed (ABPA, NTM, Immunodeficiency)

Some diseases may be associated with a worse outcome requiring closer follow-up

Co-morbidities are also common since the BE patient group is predominantly elderly

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

Melissa J McDonnell, Stefano Aliberti, Pieter C Goeminne, Marcos I Restrepo, Simon Finch, Alberto Pesci, Lieven J Dupont, Thomas C Fardon, Robert Wilson, Michael R Loebinger, Dusan Skrbic, Dusanka Obradovic, Anthony De Soyza, Chris Ward, John G Laffey, Robert M Rutherford, James D Chalmers

Definitions

- **Exacerbation: Antibiotic treatment for increased respiratory symptoms (BTS definition)**
- **Quality of life: St. George's Respiratory Questionnaire**
- **Severity of disease: Bronchiectasis severity index (BSI)**
- **Mortality score: FACED**

Methods

Facilitating Research Into Existing National Datasets (FRIENDS) Registry- https://www.bronchiectasis.eu/friends

10 centres across Europe and Israel
Inclusion criteria

- **Adult outpatients**
- **HRCT confirmed bronchiectasis**
- **Clinical diagnosis of bronchiectasis**

Exclusion criteria

- **Cystic fibrosis**
- **Traction bronchiectasis due to ILD**

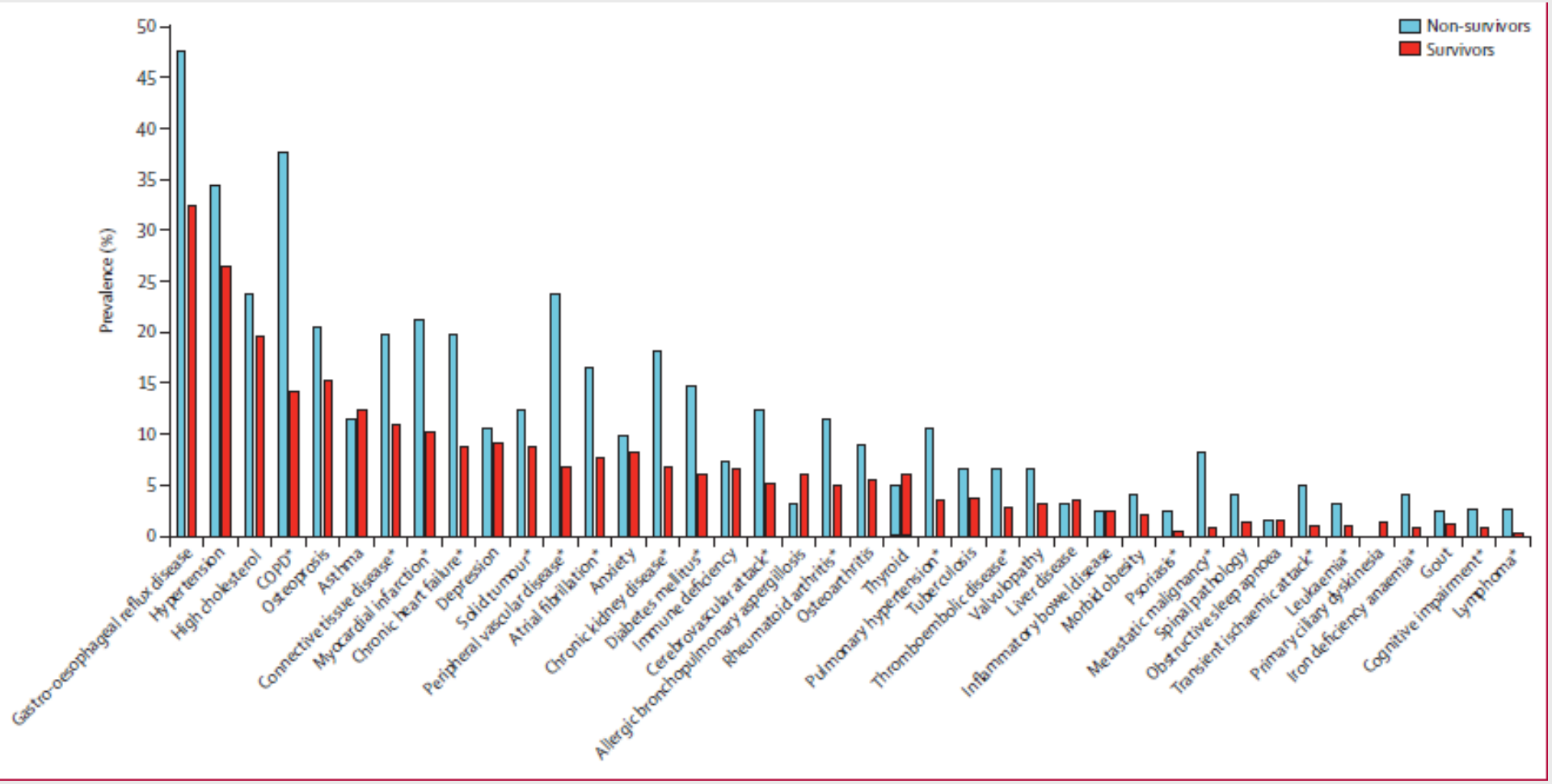
Up to 5 years follow-up

Abbreviations:
BTS= British Thoracic Society
HRCT= high resolution CT
ILD= interstitial lung disease

McDonnell, et al. *Lancet Respir Med*. 2016;4(12):969-979

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

Melissa J McDonnell, Stefano Aliberti, Pieter C Goeminne, Marcos I Restrepo, Simon Finch, Alberto Pesci, Lieven J Dupont, Thomas C Fardon, Robert Wilson, Michael R Loebinger, Dusan Skrbic, Dusanka Obradovic, Anthony De Soyza, Chris Ward, John G Laffey, Robert M Rutherford, James D Chalmers



McDonnell, et al. *Lancet Respir Med*. 2016;4(12):969-979

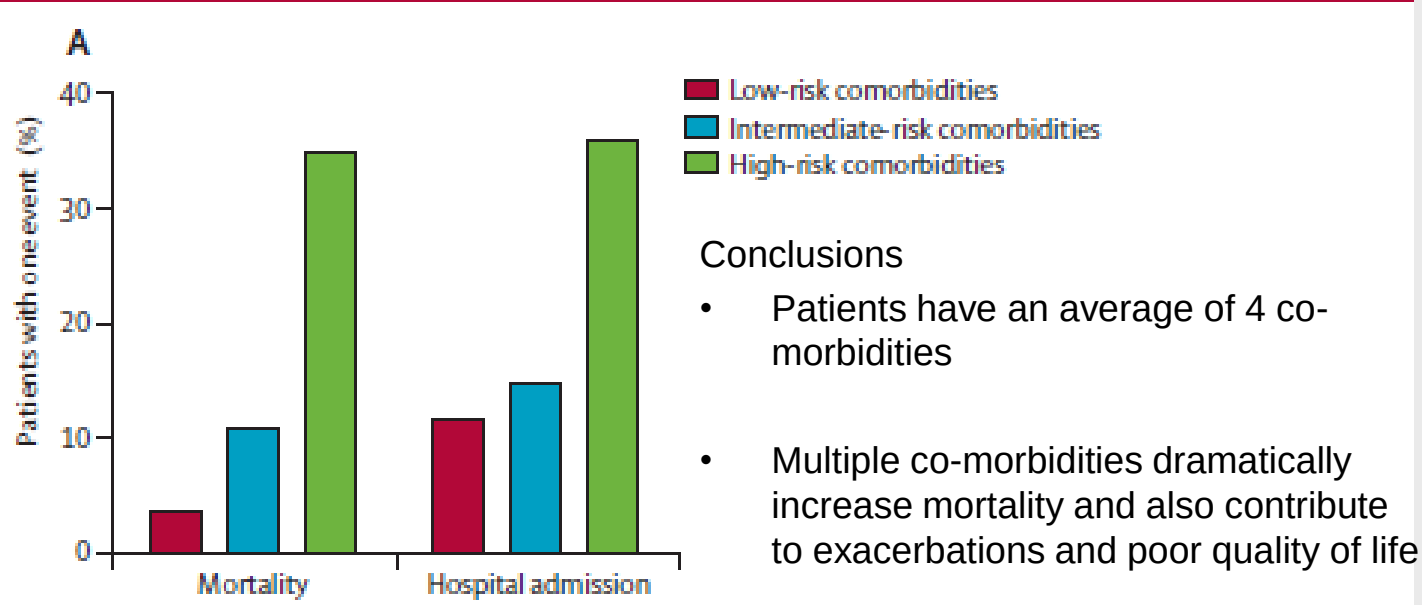
Risk factors for mortality

	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.

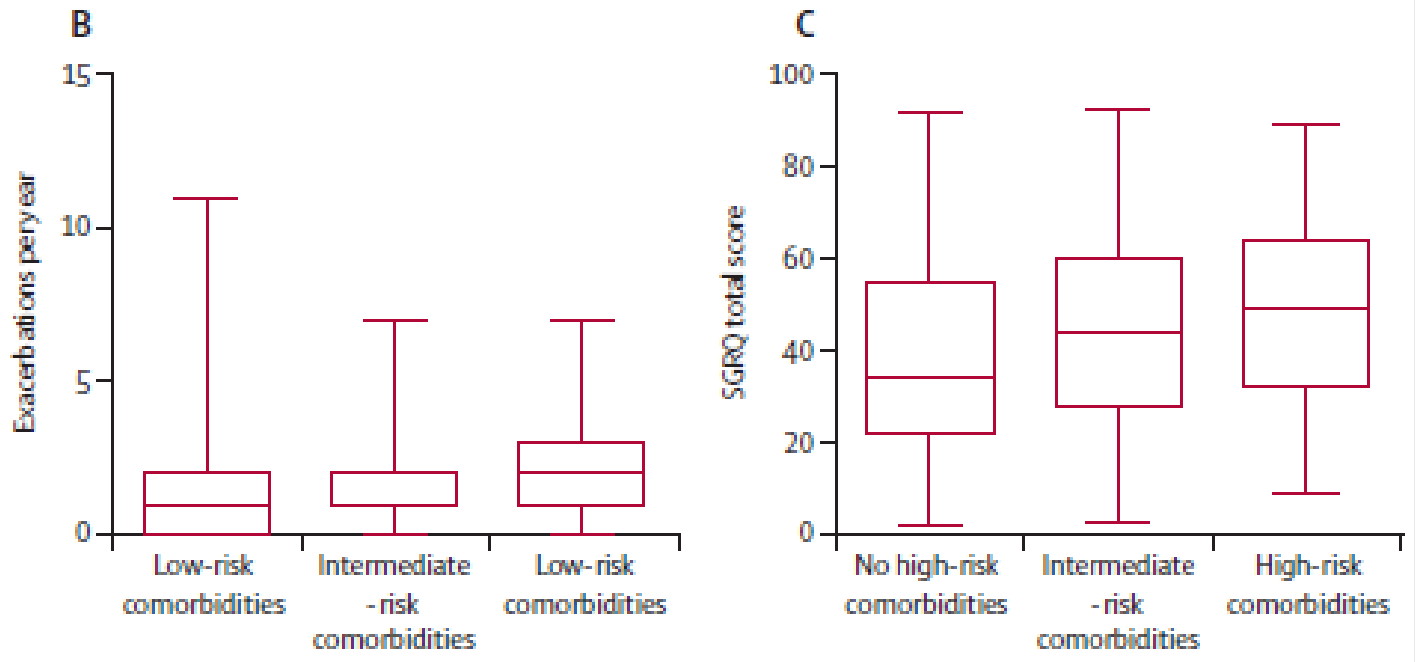
Table 2: Derivation of the Bronchiectasis Aetiology Comorbidity Index (BACI) and points allocation

McDonnell, et al. *Lancet Respir Med*. 2016;4(12):969-979



Conclusions

- Patients have an average of 4 co-morbidities
- Multiple co-morbidities dramatically increase mortality and also contribute to exacerbations and poor quality of life



McDonnell, et al. *Lancet Respir Med*. 2016;4(12):969-979

Recommended investigations

All patients

- **History and physical exam**
- **HRCT**
- **Immunoglobulins**
- **Functional antibodies**
- **Testing for ABPA***
- **Sputum culture and AAFB**
- **Autoantibodies**
- **Serum electrophoresis**

*will include total IgE, specific IgE to *Aspergillus* and Aspergillus skin test and/or IgG

**will include sweat test and/or CFTR genetics

Selected patients

- **Testing for cystic fibrosis****
- **Nasal NO (screening for PCD)**
- **Alpha-1 antitrypsin**
- **Testing for GORD**
- **Bronchoscopy**
- **Advanced immunological testing**

Disorders requiring specific treatment:

- **ABPA**
- **Immunodeficiency**
- **NTM**
- **Haematological malignancy**
- **GORD**
- **CF**
- **PCD**

Take Home Message

Test all patients for treatable causes of bronchiectasis

COPD, rheumatoid arthritis, inflammatory bowel disease, and patients with immunodeficiency have worse outcomes and should be carefully followed-up

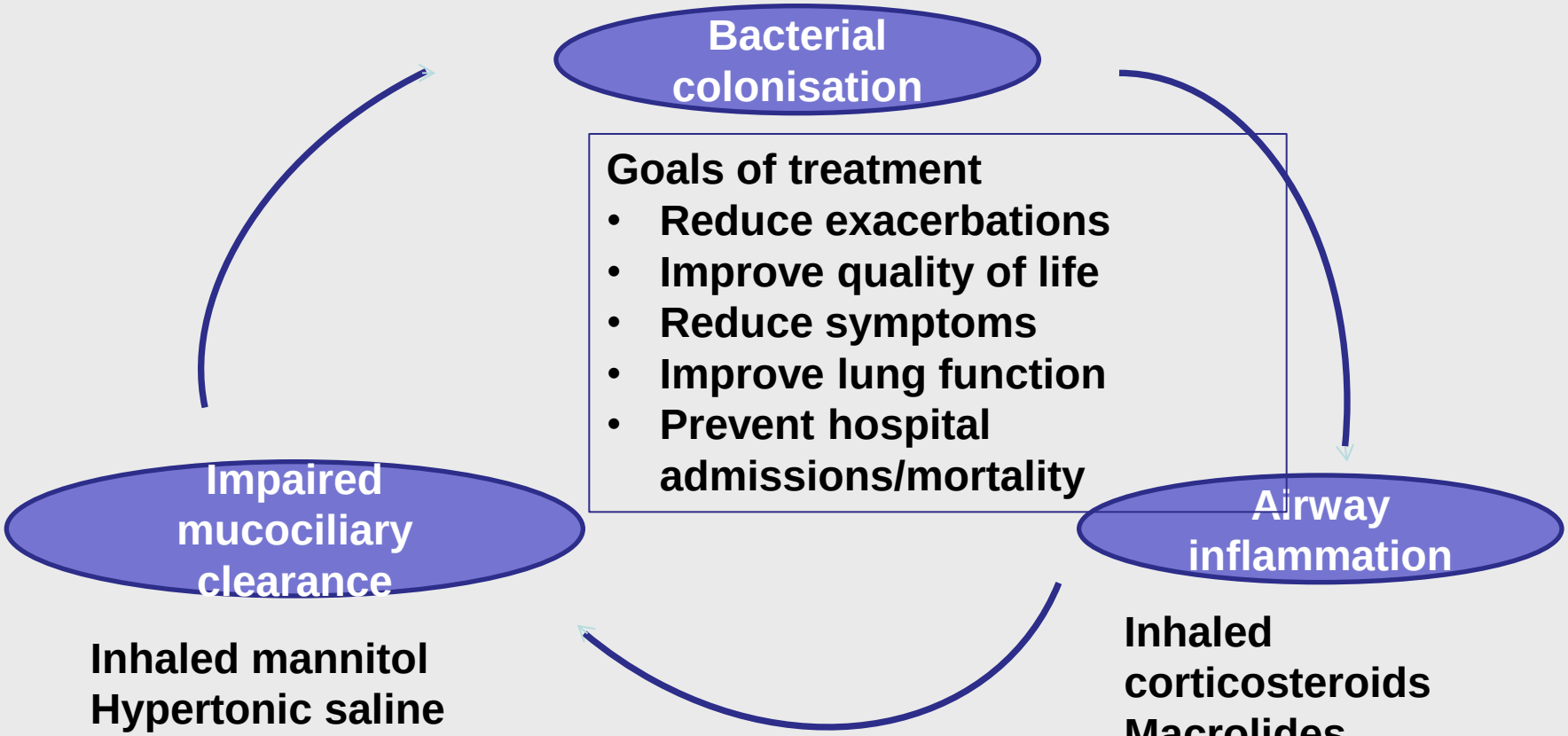
Treat associated co-morbidities (Gastrooesophageal reflux, Ischaemic heart disease)

Treatment- including new Trials

State of the Art

Tobramycin
Aztreonam
Colistin
Ciprofloxacin

Tetracyclines
Other oral antibiotics
Gentamicin
Macrolides



Inhaled mannitol
Hypertonic saline
N-acetylcysteine
Physiotherapy and devices

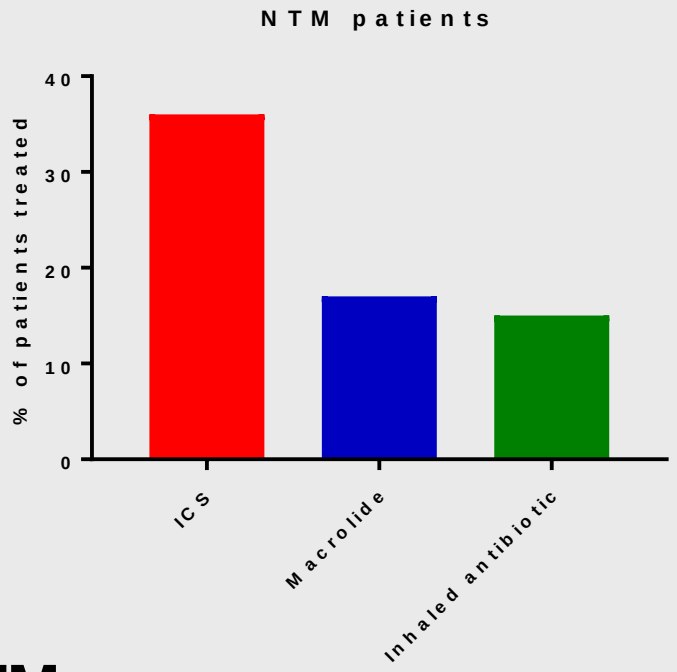
Inhaled corticosteroids
Macrolides

1247 bronchiectasis patients with NTM

43% suppressive antibiotics

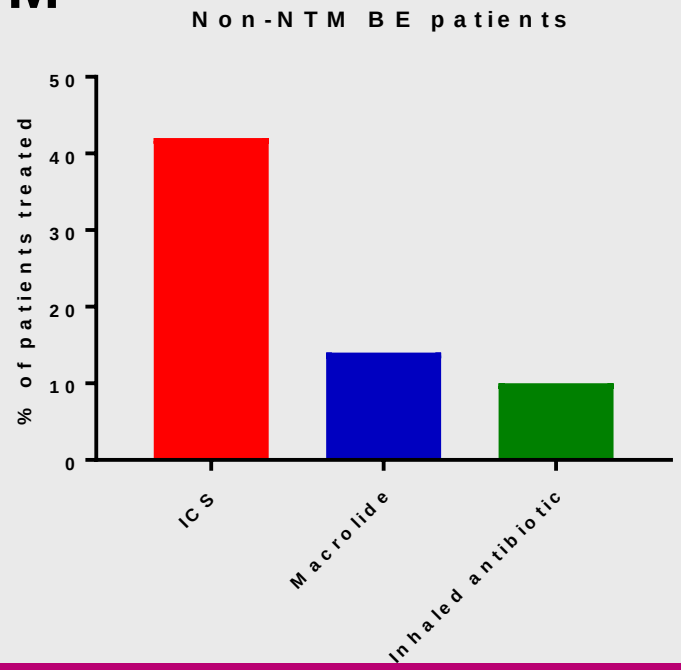
10% oral steroids

59% performing chest clearance techniques

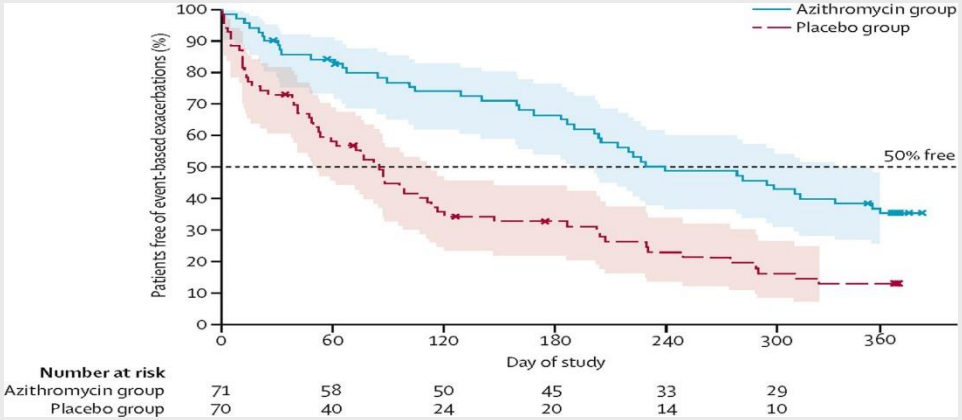


776 bronchiectasis patients without NTM

ICS	Asthma (aOR 3.1 95% CI 1.2-4.3) and *P. aeruginosa* aOR 1.8 95% CI 1.2-2.6)
Macrolide	*P. aeruginosa* aOR 2.2 95% CI 1.4-3.4) and Age under 65 years 1.66 95% CI 1.1-2.5)
Inhaled antibiotic	*P. aeruginosa* aOR 5.9 95% CI 3.4-10.5) and Prior hospitalisation 2.6 95% CI 1,1-5.9)

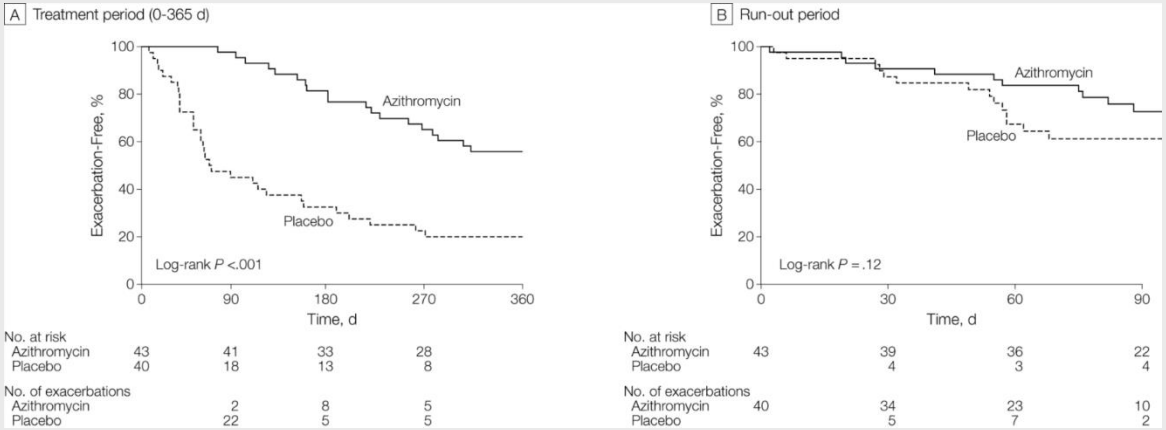


Henkle et al, *Chest*. 2017 May 4. pii: S0012-3692(17)30810-3

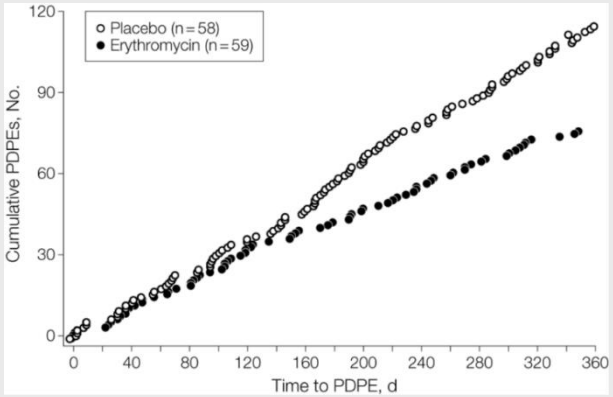


Altenburg et al, JAMA 2013; 309: 1251–1259.
Serisier et al, JAMA 2013; 309: 1260–1267.
Wong et al, Lancet 2012; 380: 660–667.

Dose= 500mg three time per week



Dose= 250mg daily
Note- high rate of GI side effects observed in this study



Erythromycin

Inhaled antibiotics

Most common in Europe

- Colistimethate sodium
- Gentamicin
- Tobramycin

None licensed for bronchiectasis

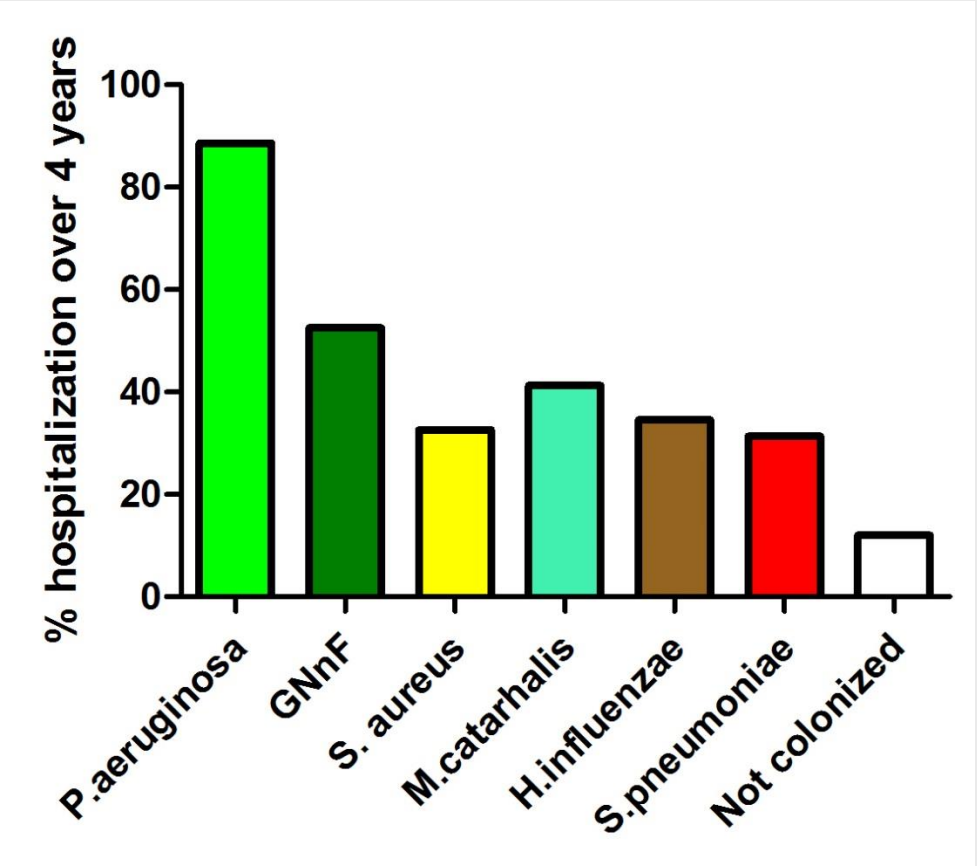
Tobramycin, tobramycin dry powder, aztreonam, colistimethate sodium and the dry powder “Colobreathe” licensed in CF

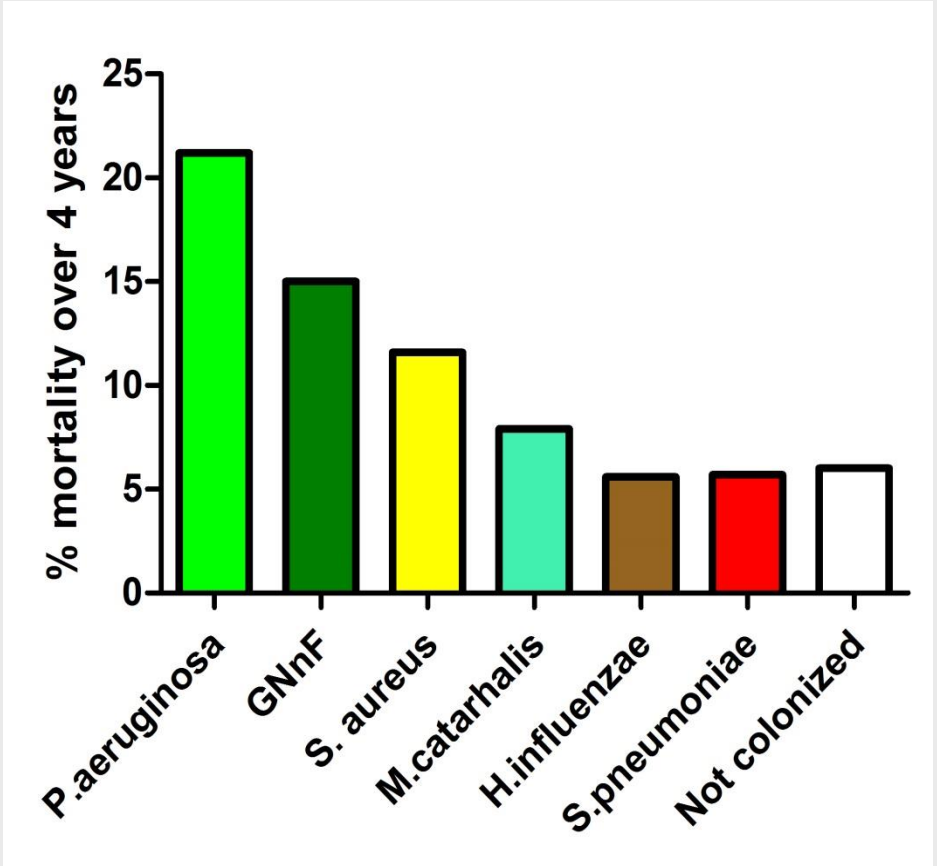
Most used for Pseudomonas aeruginosa

Limited evidence in bronchiectasis

Prognostic impact of airway infection

n=608 patients over 4 years in a single centre Scottish study





Chalmers et al, *Am J Respir Crit Care* Med. 2014;189(5):576-85

ORBIT studies- Inhaled liposomal ciprofloxacin

Patients ≥18 years with a confirmed diagnosis of NCFBE by CT and at least 2 PEs treated with antibiotics in the preceding 12 months

Key Inclusion Criteria

- **CT-confirmed diagnosis of bronchiectasis**
- **Documented history of at least 2 PEs treated with antibiotics within the previous 12 months**
- **Documented history of chronic lung infection with PA and presence of at least 1 nonresistant PA isolate at the screening visit**
- **FEV_1 ≥25% predicted at the screening visit**
- **Stable respiratory disease at randomization**

Key Exclusion Criteria

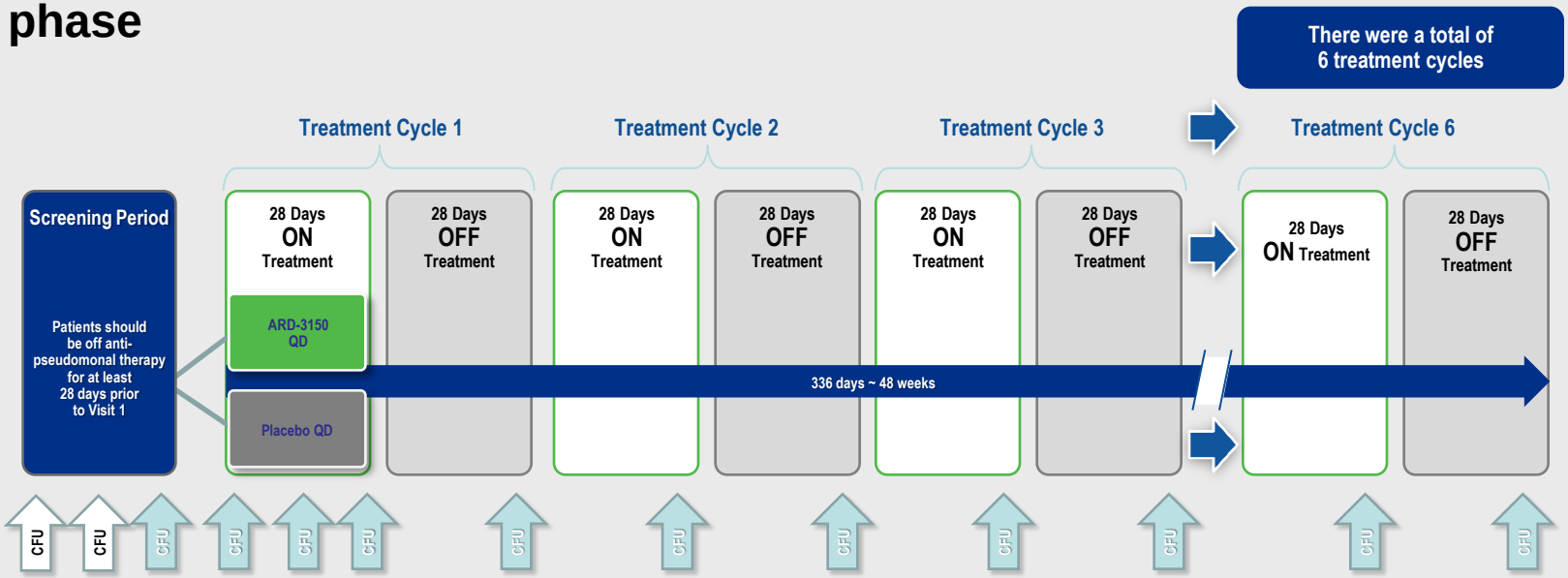
- **Clinical diagnosis of cystic fibrosis**
- **Primary diagnosis of COPD and smoking history of >10 cigarette pack-years**
- **NTM infection requiring treatment**
- **Active tuberculosis**
- **PE during screening requiring treatment with inhaled, oral, or intravenous antibiotics**
- **Intravenous, oral, or inhaled antipseudomonal antibiotics (except chronic macrolides) within 28 days of randomization**

CT, computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; NTM, non-tuberculosis mycobacterial

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Study Design – ORBIT-3 and ORBIT-4

Nebulized ARD-3150 or placebo were administered once daily for 6 cycles of 28 days on treatment, separated by 28 days off treatment, during the 48-week double-blind phase



CFU, colony forming units of *P. aeruginosa*, determined from sputum analysis
QD, once daily

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Baseline Demographics

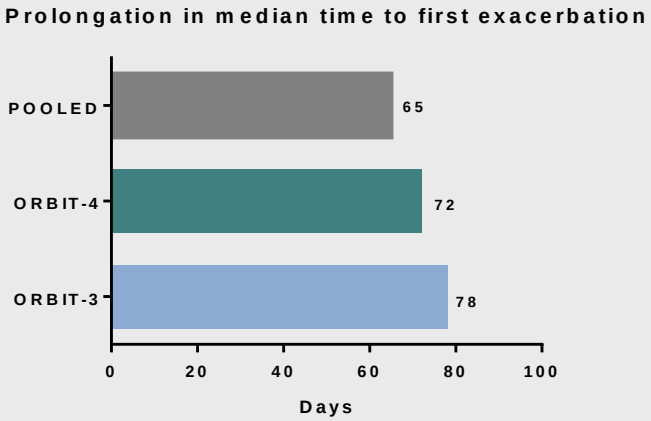
	ORBIT-3		ORBIT-4	
	ARD-3150 (n=183)	Placebo (n=95)	ARD-3150 (n=206)	Placebo (n=98)
Age (years), mean ± SD	64 ± 14	67 ± 11	63 ± 13	64 ± 13
Race, n (%)				
White	161 (88)	89 (94)	168 (82)	82 (84)
Asian	15 (8)	4 (4)	11 (5)	4 (4)
Black or African American	3 (2)	1 (1)	2 (1)	1 (1)
Other / Not Reported	4 (2)	1 (1)	25 (12)	11 (11)
Ethnicity, n (%)				
Hispanic or Latino	6 (3)	3 (3)	25 (12)	9 (9)
Nonsmoker, n (%)	180 (98)	94 (99)	204 (99)	98 (100)
Baseline FEV_1 % predicted*, mean ± SD	57 ± 22	57 ± 20	63 ± 22	60 ± 21
Number of PEs, n (%)				
2–3	141 (77)	69 (73)	167 (81)	76 (78)
4–7	39 (21)	25 (26)	38 (18)	18 (18)
>7	3 (2)	0	2 (1)	3 (3)

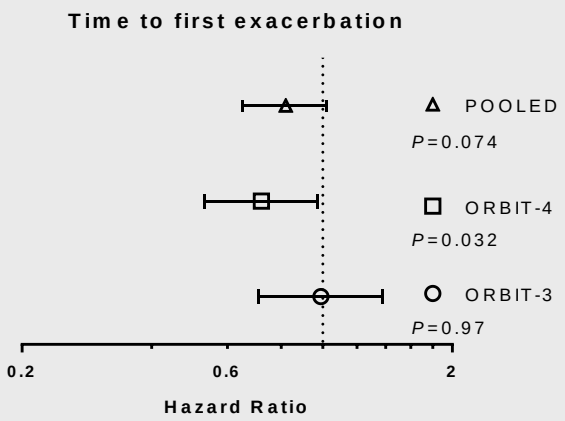
*n for FEV_1 for ORBIT-3: ARD-3150 = 183, placebo = 95; for ORBIT-4: ARD-3150 = 205, placebo = 98
SD, standard deviation; FA population

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Time to First PE - all severities

ARD-3150 significantly increased median time to first PE (all severities) in ORBIT-4





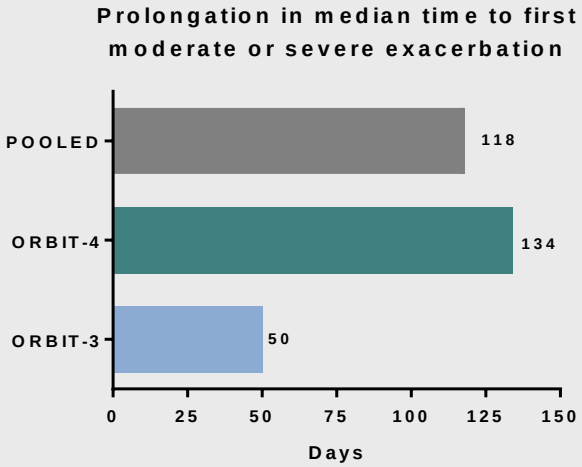
Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit
0.82	0.65	1.02
0.72	0.53	0.97
0.99	0.71	1.38

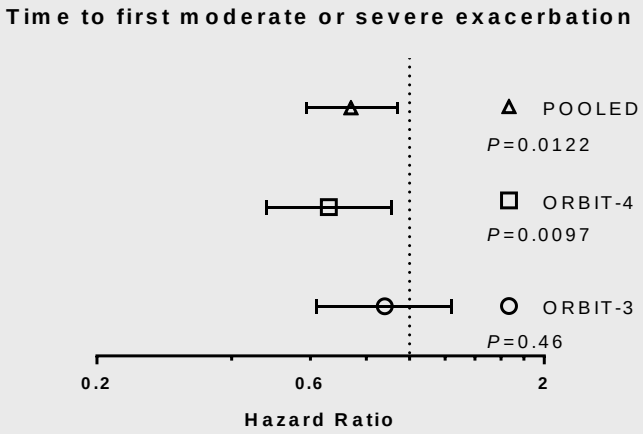
Stratified unweighted log-rank test
Stratification factors: sex and previous number of exacerbations in the past 12 months prior to randomization

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Time to First Moderate or Severe PE

ARD-3150 significantly increased median time to first PE that required treatment with antibiotics in ORBIT-4 and the pooled data analysis





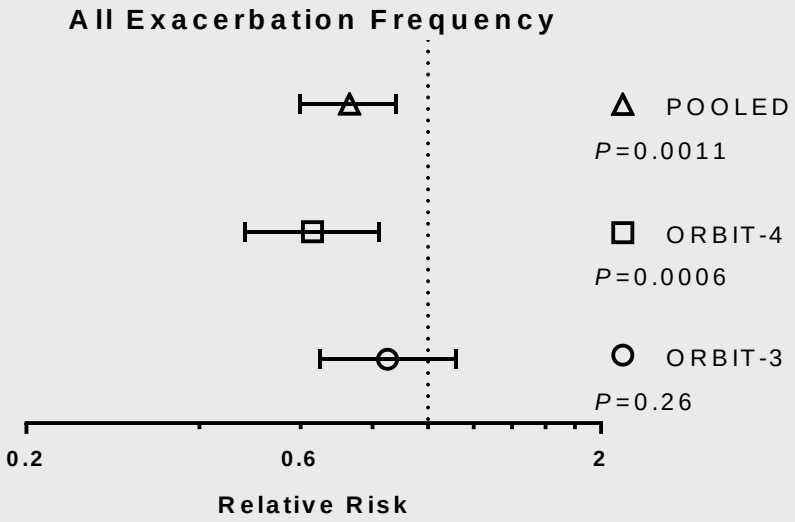
Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit
0.74	0.59	0.94
0.66	0.48	0.91
0.88	0.62	1.24

Stratified unweighted log-rank test
Stratification factors: sex and previous number of exacerbations in the past 12 months prior to randomization

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Frequency of all PEs

ARD-3150 was associated with a significant reduction in the point estimate of the annual frequency of PEs in ORBIT-4 and the pooled analysis



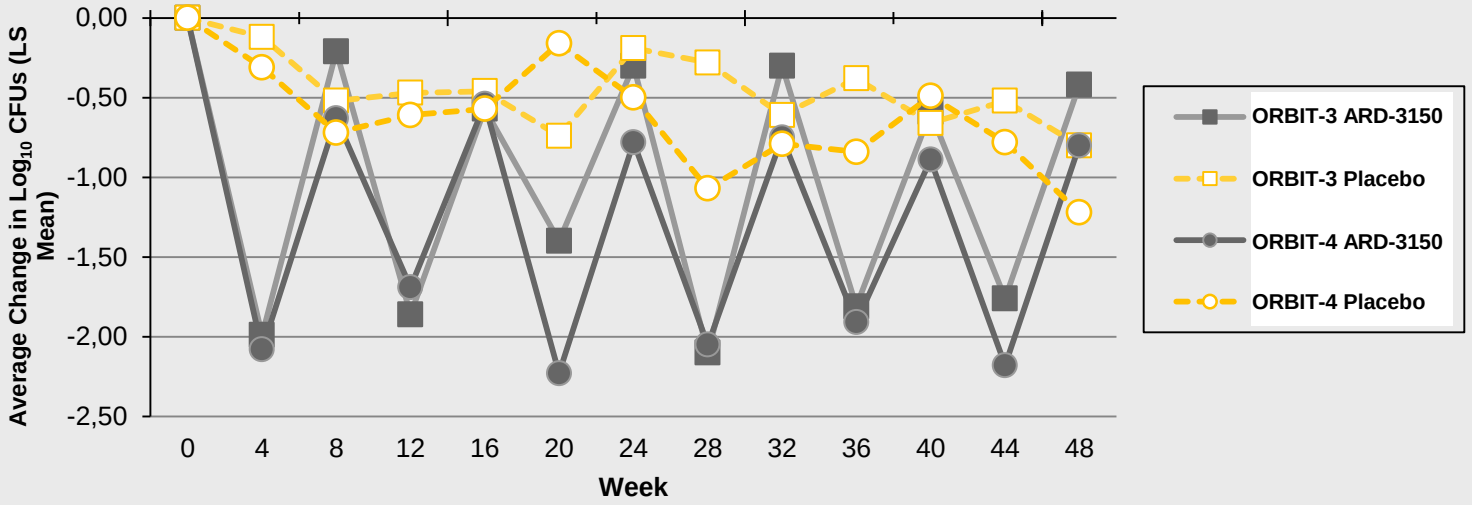
	Relative Risk	Lower Confidence Limit	Upper Confidence Limit
POOLED	0.73	0.60	0.88
ORBIT-4	0.63	0.48	0.82
ORBIT-3	0.85	0.65	1.12

Stratified negative binomial regression; stratified by sex and prior PEs

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Change in Sputum Density of *P. aeruginosa*

ARD-3150 significantly reduced sputum density of *P. aeruginosa* while on treatment over the 48-week period



With the exception of 1 visit in ORBIT-3, statistically significant reductions were observed at the end of every on-treatment period throughout the course of both studies

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Adverse Events

N (%)	ORBIT-3		ORBIT-4	
	ARD-3150 (N=183)	Placebo (N=95)	ARD-3150 (N=206)	Placebo (N=98)
TEAE / Related to study drug	164 (90%) / 78 (43%)	87 (92%) / 32 (34%)	178 (86%) / 58 (28%)	95 (97%) / 34 (35%)
SAE / Related to study drug	56(31%) / 6(3%)	24(25%) / 1(1%)	35(17%) / 1(0.5%)	28(28%) / 1(1%)
Discontinued due to TEAE	16 (9%)	3 (3%)	5 (2%)	4 (4%)
TEAEs leading to Death*	5 (3%)	3 (3%)	1 (0.5%)	2 (2%)
AEs related to study drug reported in ≥5% of patients				
Cough	24 (13%)	16 (17%)	18 (9%)	10 (10%)
Dyspnea	14 (8%)	7 (7%)	11 (5%)	6 (6%)
Wheezing	10 (6%)	7 (7%)	10 (5%)	3 (3%)
Other AE of interest				
Bronchospasm/ bronchial hyper-reactivity	4 (2%)	1 (1%)	1 (0.5%)	1 (1%)

- **There were no significant differences in changes in FEV_1 % predicted, FVC, or DLCO at week 48 between the ARD-3150 and placebo groups in ORBIT-3 and ORBIT-4**

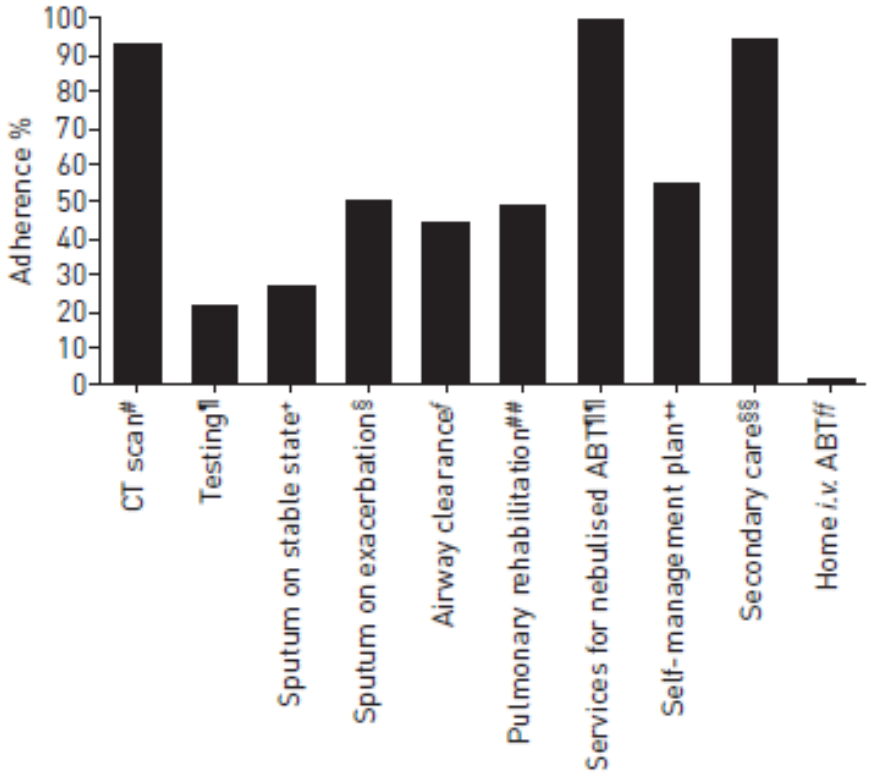
* No deaths were considered related to study drug

AE, adverse event; DLCO, diffusing capacity of the lungs for carbon monoxide; TEAE, treatment-emergent adverse event; SAE, serious adverse event

Haworth et al, Am J Respir Crit Care Med 2017;195:A7604

Quality standards for the management of bronchiectasis in Italy: a national audit

32 Italian Hospitals 2014-2015
N=1361



1. Diagnosis confirmed by CT chest (using 1mm slices).

2. taught appropriate airway clearance techniques by a specialist respiratory physiotherapist and advised of the frequency and duration with which these should be carried out

3. Sputum bacteriology culture when clinically stable recorded at least once each year.

4. Sputum is sent for bacterial culture at the start of an exacerbation before starting antibiotics. Empirical antibiotic therapy to start as soon as feasible and not await the sputum culture results.

5. People with bronchiectasis to attend pulmonary rehabilitation if they have breathlessness affecting their activities of daily living

6. An objective evaluation of the efficacy of IV antibiotic treatment and the result recorded

7. provision of nebulised prophylactic antibiotics for suitable patients supervised by a respiratory specialist

8. investigated for allergic bronchopulmonary aspergillosis (ABPA), common variable immunodeficiency (CVID) and cystic fibrosis (latter if indicated) as these are specific treatable causes.

Aliberti et al, Eur Respir J. 2016 Jul;48(1):244-8

Take-Home Message

Macrolides and inhaled antibiotics reduce exacerbations in patients with bronchiectasis chronically infected with pathogens.

Inhaled antibiotics are primarily used, and have primary efficacy against *Pseudomonas aeruginosa*

All patients should be taught chest clearance techniques

Compliance with guidelines and use of simple measures is poor.

ERS Guidelines will be published in 2017!!!!

List of References

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18. Chalmers et al, *Am J Respir Crit Care* Med. 2014;189(5):576-85
19. Haworth et al, Am J Respir Crit Care Med 2017;195:A7604
20. Aliberti et al, Eur Respir J. 2016 Jul;48(1):244-8