CURRENT UNDERSTANDING REGARDING ETIOPATHOGENESIS OF BRONCHIECTASIS

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19.06.2020

BACKGROUND

- Bronchiectasis is a progressive respiratory disease characterized by permanent dilation of bronchi and associated with clinical syndrome of cough, sputum production and recurrent respiratory infections
- Bronchiectasis is independent risk factor for cardiovascular disease (30-90% increased risk) in adults

EPIDEMIOLOGY

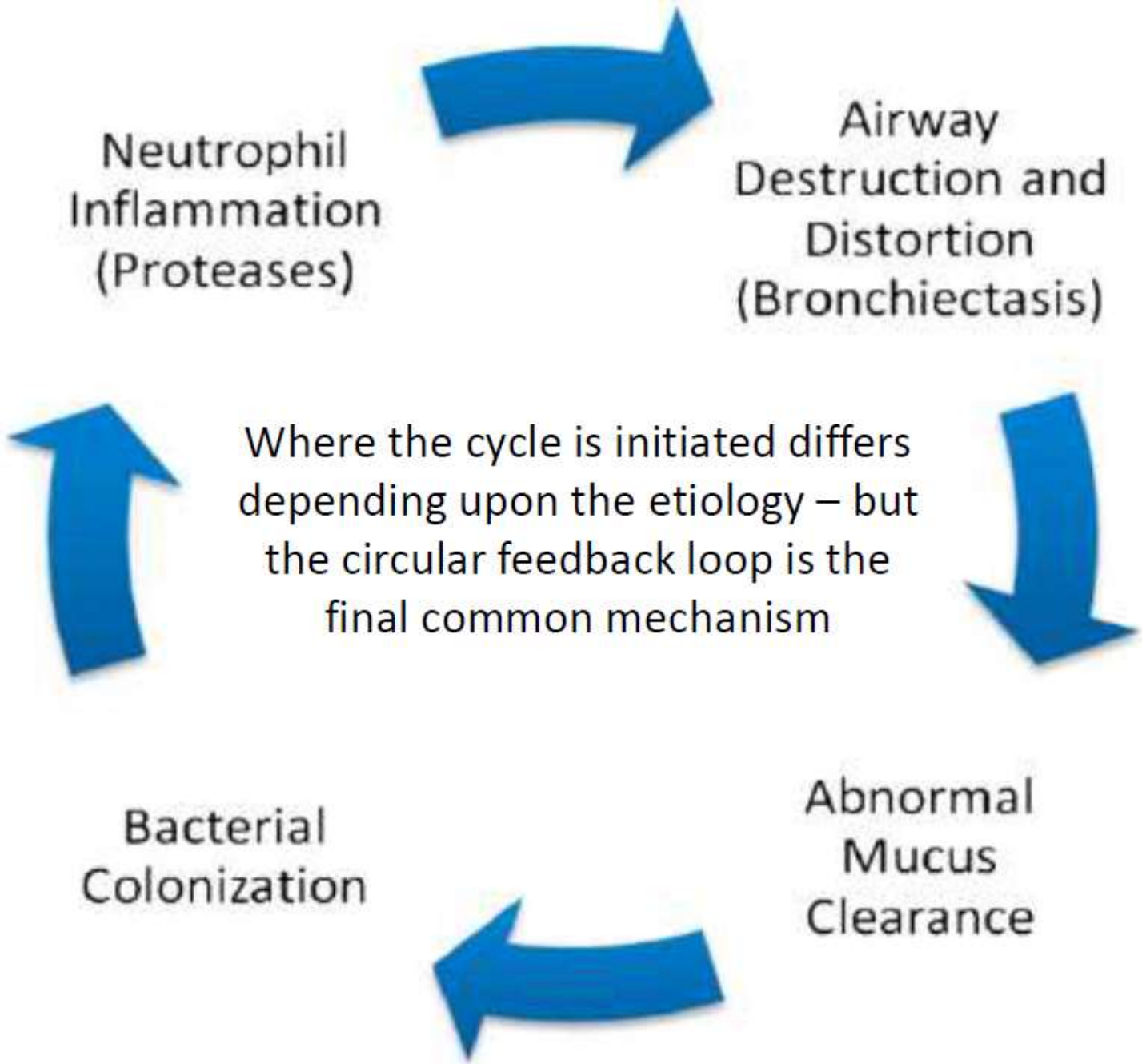
- Incidence of bronchiectasis increases with age, mean age across Europe is 65 yrs. (range 59.4-68.3) and in India 56 yrs
- Across all age groups, incidence of bronchiectasis increased in UK from 2004 to 2013 (from 21 to 35 per 100,000 person years in women and from 18 to 27 per 100,000 person years in men)

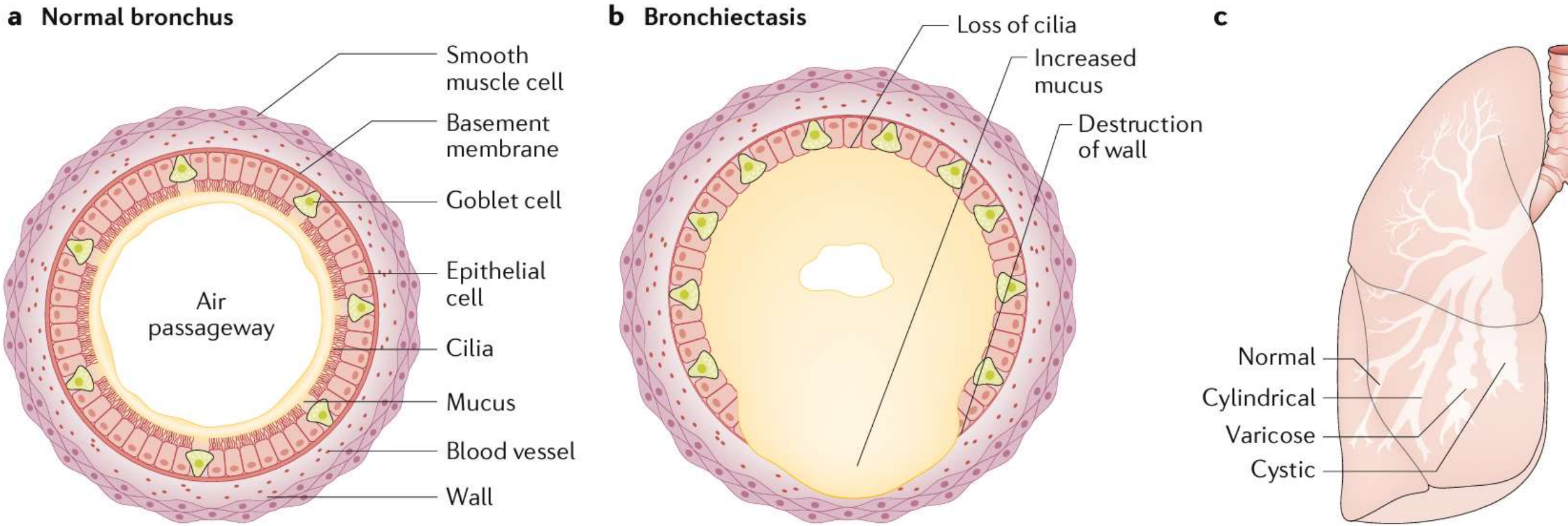
Quint et al. Eur. Respir. J. 2016
Blackall et al. S. R. Respirology 2018
EMBARC Study lancetgh Sept 2019

TWO EDGED SWORD

- Widely known model of development – Cole's "vicious cycle hypothesis"
- Environmental insult on background of genetic susceptibility impairs mucociliary clearance resulting in persistence of microbes in sinobronchial tree and microbial colonization
- Microbial infection caused chronic inflammation resulting in tissue damage and impaired mucociliary motility
- More infection with cycle of progressive inflammation causing lung damage

Cole et al. Eur J respire Dis Suppl. 1986


Neutrophil Inflammation (Proteases)
Airway Destruction and Distortion (Bronchiectasis)
Abnormal Mucus Clearance
Bacterial Colonization
Where the cycle is initiated differs depending upon the etiology – but the circular feedback loop is the final common mechanism

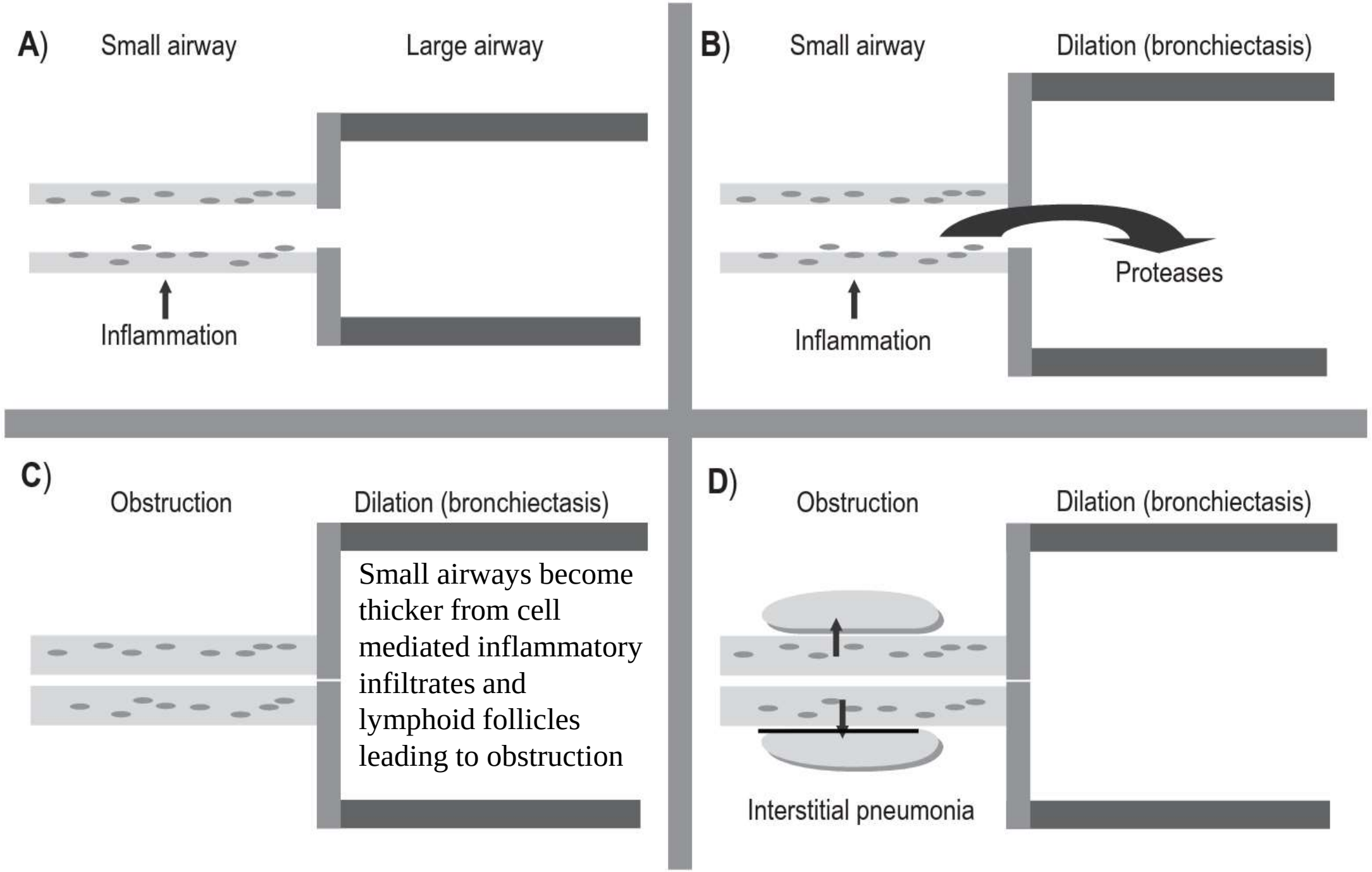

a Normal bronchus
Smooth muscle cell
Basement membrane
Goblet cell
Epithelial cell
Air passageway
Cilia
Mucus
Blood vessel
Wall
b Bronchiectasis
Loss of cilia
Increased mucus
Destruction of wall
c
Normal
Cylindrical
Varicose
Cystic

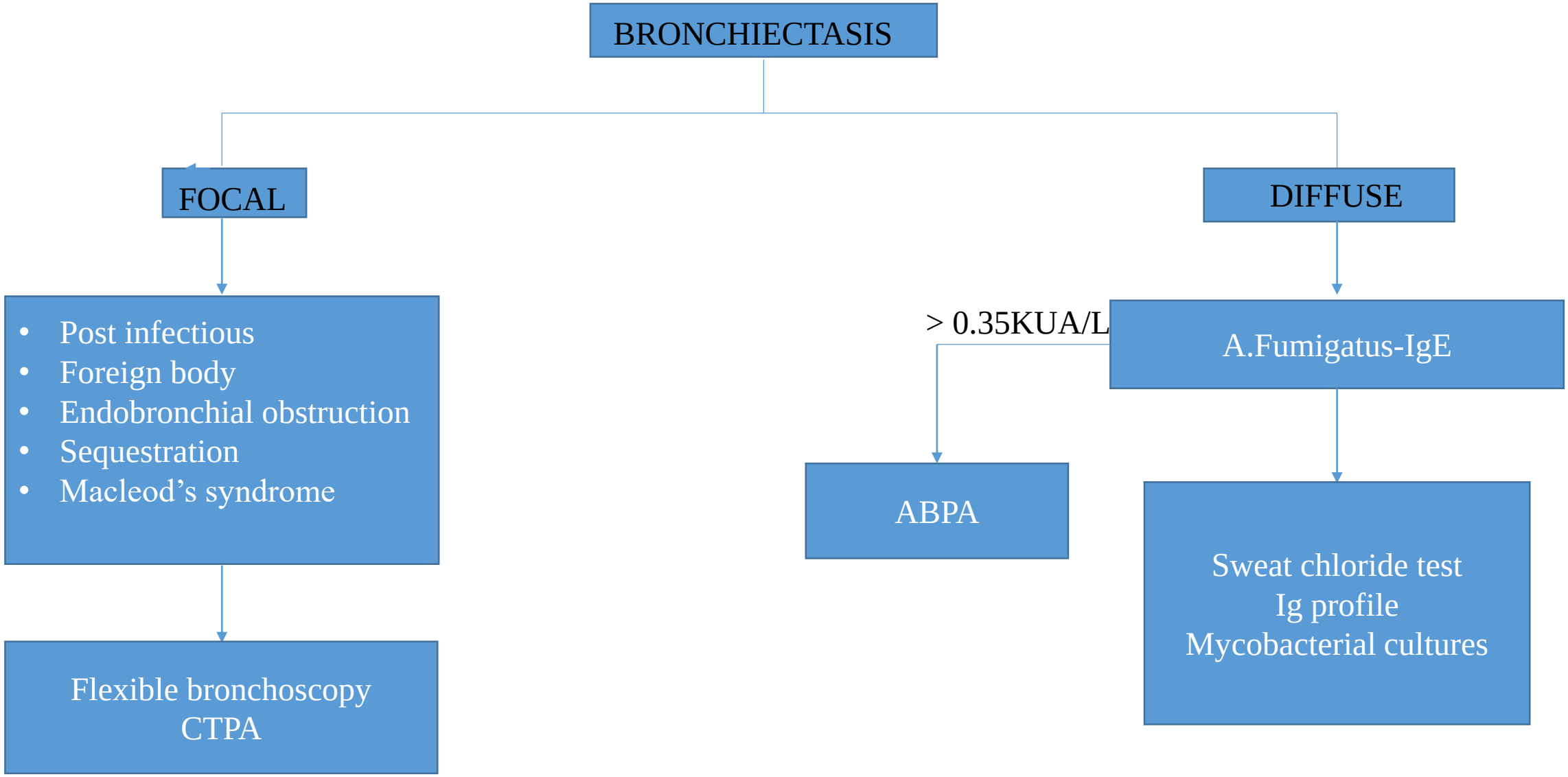
Pathological features

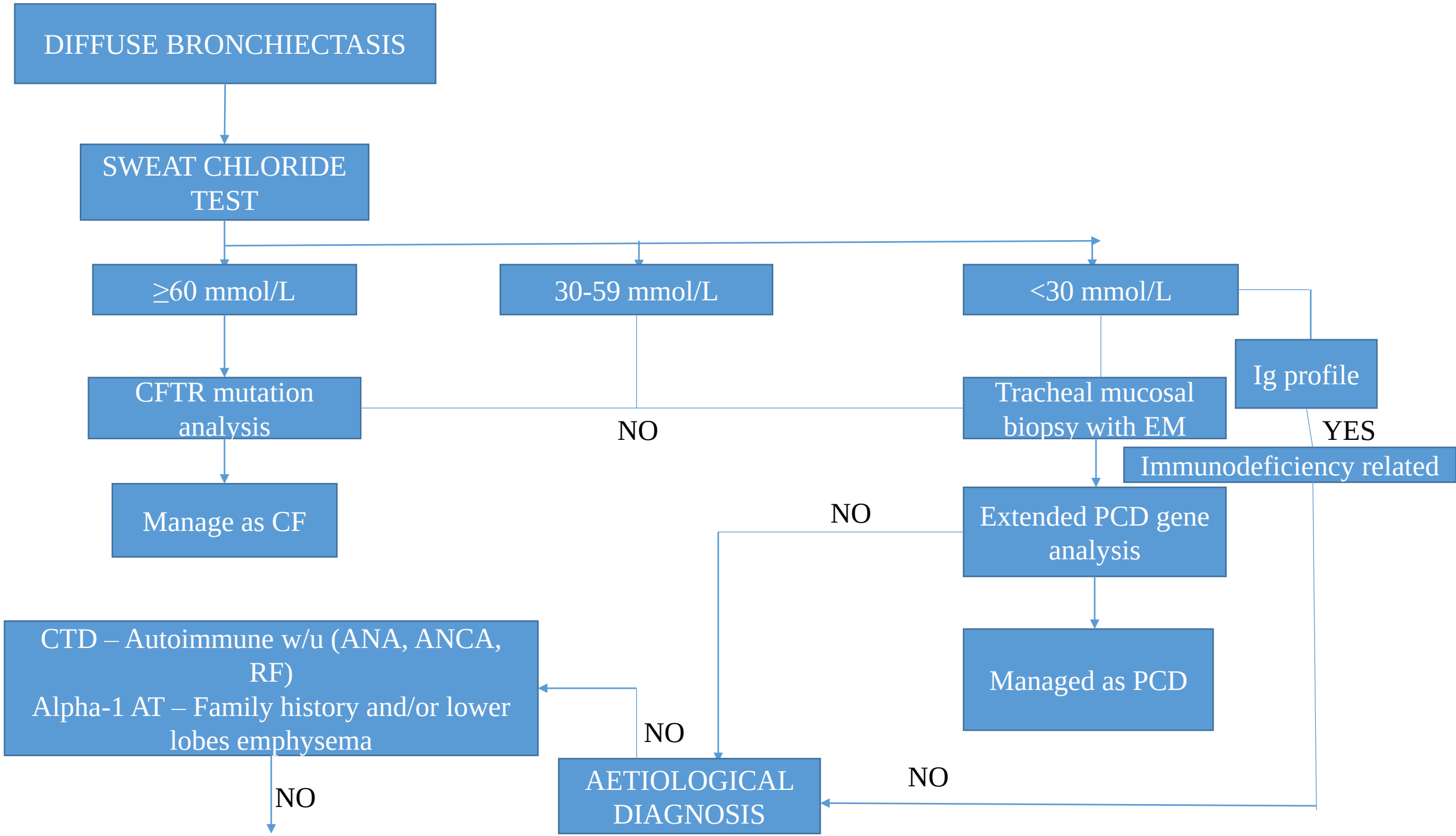
- Performed by Whitwell on 200 lung operative specimens
- Marked inflammation of bronchial wall principally in smaller airways
- Bronchial dilation characterized by deficiency/loss of elastin and more advance disease by destruction of muscle and cartilage
- Classified bronchiectasis into three different types:

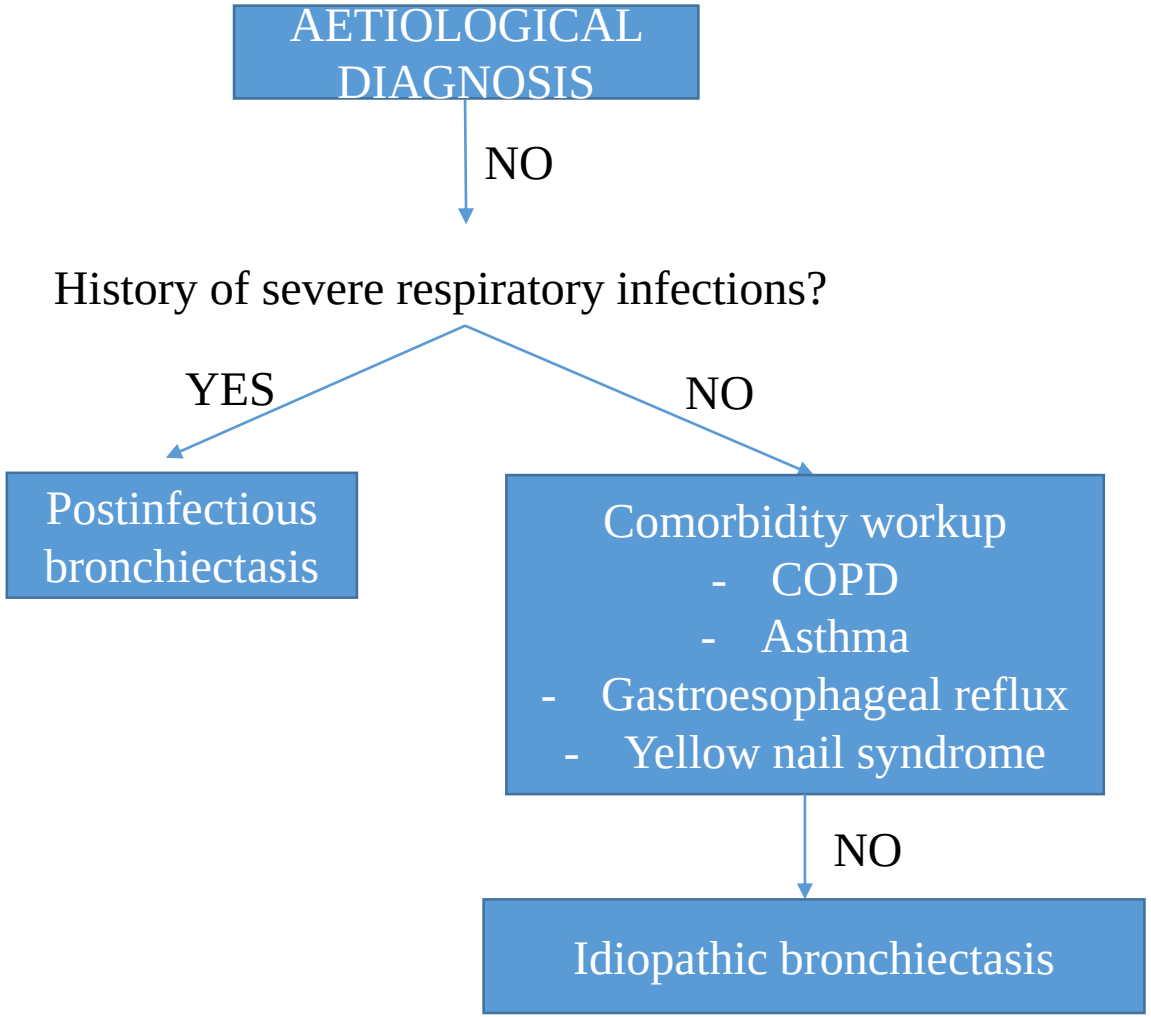
  Follicular, saccular and atelectatic
- Follicular is the dominant form and corresponds to tubular bronchiectasis

Whitwell F. Thorax 1952;7:213-219


A)
Small airway
Large airway
Inflammation
B)
Small airway
Dilation (bronchiectasis)
Proteases
Inflammation
C)
Obstruction
Dilation (bronchiectasis)
Small airways become thicker from cell mediated inflammatory infiltrates and lymphoid follicles leading to obstruction
D)
Obstruction
Dilation (bronchiectasis)
Interstitial pneumonia


BRONCHIECTASIS
FOCAL
DIFFUSE
• Post infectious
• Foreign body
• Endobronchial obstruction
• Sequestration
• Macleod's syndrome
Flexible bronchoscopy
CTPA
> 0.35KUA/L
A.Fumigatus-IgE
ABPA
Sweat chloride test
Ig profile
Mycobacterial cultures


DIFFUSE BRONCHIECTASIS
SWEAT CHLORIDE TEST
≥60 mmol/L
30-59 mmol/L
<30 mmol/L
CFTR mutation analysis
Tracheal mucosal biopsy with EM
Ig profile
NO
YES
Immunodeficiency related
Manage as CF
NO
Extended PCD gene analysis
Managed as PCD
CTD – Autoimmune w/u (ANA, ANCA, RF)
Alpha-1 AT – Family history and/or lower lobes emphysema
NO
NO
NO
AETIOLOGICAL DIAGNOSIS



AETIOLOGIES

Postinfectious
- Necrotising pneumonia
- Tuberculosis and NTM
- Viruses (adenovirus, measles and other childhood infections)

Immunodeficiencies
- Antibody deficiency, combined immunodeficiency, neutrophil dysfunction, Wiskott-Aldrich syndrome
- Secondary – HIV infection, haematological malignancies, chemotherapy, transplant

Inflammatory bowel disease
- Ulcerative colitis
- Crohn's disease

Inflammatory pneumonitis
- Aspiration and GERD
- Toxic inhalation (drugs, gases)

Congenital defects of airway
- Tracheobronchomegaly (Mounier-Kuhn syndrome)
- Cartilage defects (Williams-Campbell Syndrome)
- Pulmonary sequestration
- Tracheobronchomalacia

	Age of onset	Radiology	Microbiology	Symptoms or features	Physiology or lung function
Idiopathic	Women post menopausal (any age)	Any	P.aeruginosa, Haemophilus influenza or none	Any	Any
Post infective bronchiectasis	Any	Any pattern, unilobular	Any pathogens	Should have onset of symptoms soon after severe infection	Any
Connective tissue disease	Any	Any	Any	Poor prognosis or rapidly progressive, features of systematic disease	Airflow obstruction
Immune deficiency	Primary immune deficiency often at young age, secondary immune deficiency at any age	Lower lobe	Any	Frequent exacerbations, pneumonia, non respiratory infections	Airflow obstruction
ABPA	Any	Central bronchiectasis, infiltrates	Typically staphylococcus aureus	Thick sputum, wheeze, recurrent exacerbations, background of asthma	Airflow obstruction

	Age of onset	Radiology	Microbiology	Symptoms or features	Physiology or lung function
Non tuberculous mycobacteria	Women post menopausal (any age)	Middle lobe and lingual bronchiectasis, tree in bud, nodular changes	Can have P.aeruginosa	Dry bronchiectasis, chronic cough, malaise, weight loss, systemic features, low BMI, scoliosis, pectus excavatum	Any
Primary ciliary dyskinesia	Usually presents in childhood	Middle or lower lobes	H.influenza, any	Chronic rhinosinusitis, recurrent otitis media	Any
COPD	Smokers or ex-smokers older than 40 yrs	Lower lobe cylindrical bronchiectasis	Any	Recurrent exacerbations or sputum production	More common with severe airflow obstruction
Inflammatory bowel disease	Any	Any lobes affected, bronchiolitis, could include other features of IBD associated lung disease	Often no pathogens isolated	Gross bronchorrea responsive to corticosteroids	Airflow obstruction
Cystic fibrosis	Young age at onset but can present in adulthood	Upper lobes	P. aeruginosa Staphylococcus aureus	Rhinosinusitis, infertility, pancreatitis, malabsorption, gastrointestinal symptoms	Airflow obstruction

	Pasteur et al. (n=150)	King et al. (n=103)	Shoemark et al. (n=165)	Anwar et al. (n=189)	Lonni et al. (n=1258)
Mean age (SD)	52,7 (15,2)	56 (14)	49 (16)	66,1 (11,5)	67 (58-75)*
Gender (% M/F)	38/62	37/63	35/65	49/51	40/60
Idiopathic (%)	53	74	26	43	40
Postinfectious (%)	29	10	32	24	20
Immunodeficiencies (%)	8	9	7	2	6
ABPA (%)	7	4	8	4	5
Connective tissue diseases (%)	3	2	2	5	10
COPD (%)	-	-	-	12	15
Asthma (%)	-	-	-	3	3
Inflammatory intestinal disease (%)	1	-	3	2	2
Cystic Fibrosis (%)	3	0	1	<1	0
Ciliary dysfunction (%)	2	1	10	1	2
AAT Deficiency (%)	0	0	0	1	<1
Aspiration / GER (%)	4	0	1	1	<1
Panbronchiolitis (%)	<1	0	2	0	0
Young's Syndrome (%)	3	1	3	<1	0
Yellow nail Syndrome (%)	-	-	2	-	<1
Congenital defect of the airway (%)	<1	0	-	-	<1
Pink's disease (%)	<1	-	-	<1	<1
Other (%)	-	-	Mycobacteria Infection: 2	-	Bronchial obstruction: <1

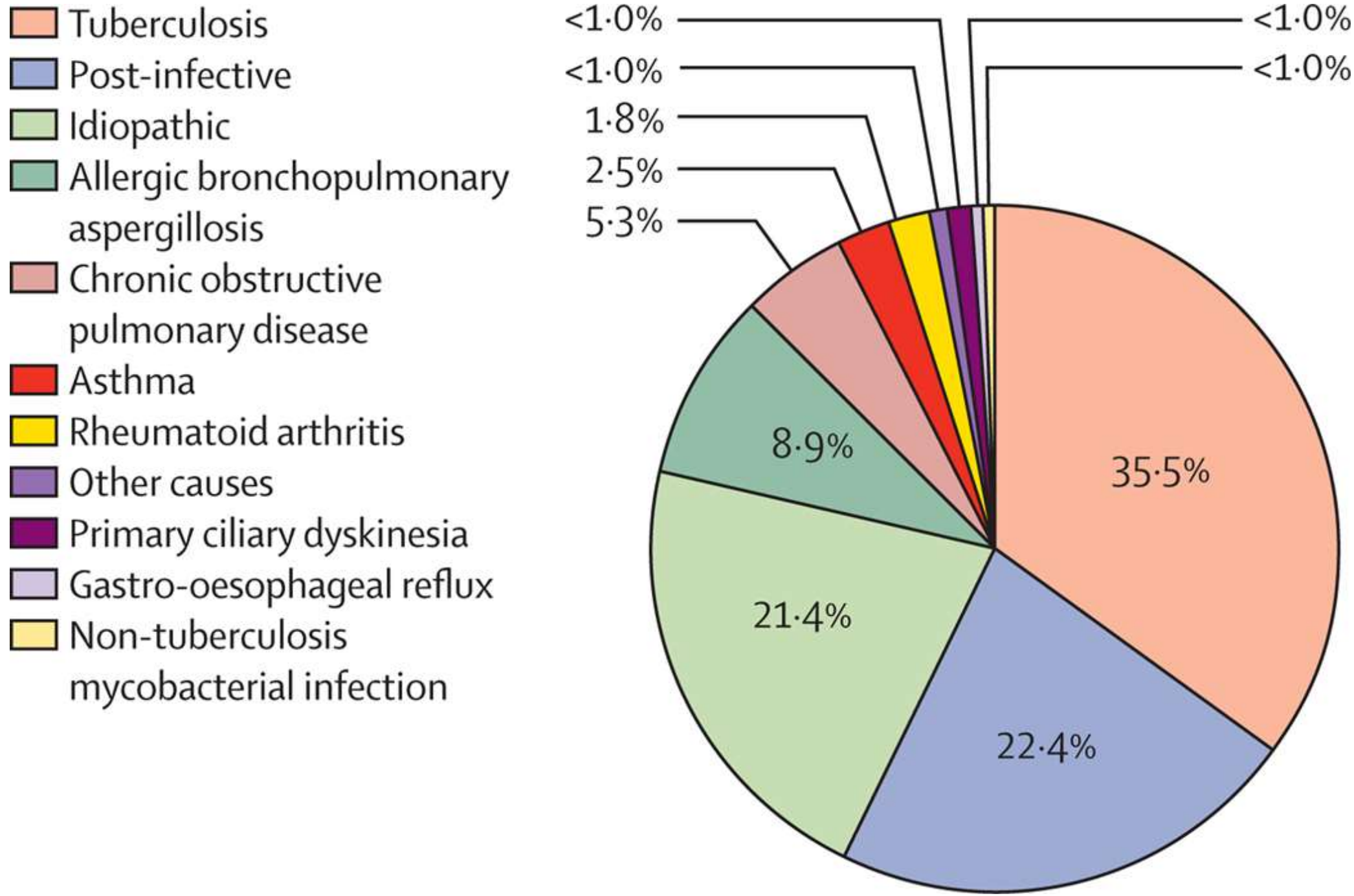
Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry

Raja Dhar, Sheetu Singh, Deepak Talwar, Murali Mohan, Surya Kant Tripathi, Rajesh Swarnakar, Sonali Trivedi, Srinivas Rajagopala,

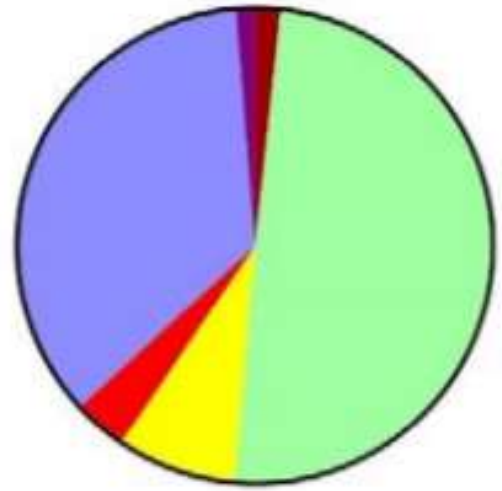
- Observational, prospective study
- Multicentric, 31 centres in India
- Inclusion criteria – Age ≥ 18 years with bronchiectasis on CT chest and clinical symptoms of bronchiectasis
- Exclusion criteria – Bronchiectasis due to cystic fibrosis and traction bronchiectasis associated with ILD
- Cohort – 2195 patients
- Study period – June 2015 to Sept 2017

	India (n=2195)	Europe* (n=2596)	p value
Demographics			
Age (years)	56 (41–66)	67 (57–74)	<0·0001
Men	1249 (56·9%)	1010 (38·9%)	<0·0001
Body-mass index	21·5 (18·5–24·5)	24·8 (21·8–28·1)	<0·0001
Current or former smokers	619 (28·2%)	990 (38·1%)	<0·0001
Comorbidity			
Ischaemic heart disease	355 (16·2%)	453 (17·5%)	0·2
Stroke	9 (0·4%)	152 (5·9%)	<0·0001
Diabetes	315 (14·4%)	260 (10·0%)	<0·0001
Liver disease	18 (0·8%)	41 (1·6%)	0·0002
Chronic renal failure	26 (1·2%)	154 (5·9%)	<0·0001
Chronic obstructive pulmonary disease	512 (23·3%)	431 (16·6%)	<0·0001
Asthma	485 (22·1%)	226 (8·7%)	<0·0001
Osteoporosis	130 (5·9%)	192 (7·4%)	0·04
Gastro-oesophageal reflux disease	346 (15·8%)	394 (15·2%)	0·6
Solid tumour	17 (0·8%)	164 (6·3%)	<0·0001

Disease severity			
BSI score	7 (3–10)	6 (4–10)	<0·0001
BSI score risk class			
Mild	728 (33·2%)	753 (29·0%)	0·0004
Moderate	674 (30·7%)	926 (35·7%)	
Severe	793 (36·1%)	917 (35·3%)	
Radiological status			
Reiff score	6 (3–9)	4 (2–6)	<0·0001
Clinical status			
Modified Medical Research Council Dyspnoea score	2 (1–3)	2 (1–3)	0·3
Exacerbations in the previous year	1 (0–2)	2 (0–3)	<0·0001
≥1 hospital admission in the previous year	851 (38·8%)	672 (25·9%)	<0·0001
Functional status			
FEV_1 (% predicted)	61·4 (41·9–80·5)	73·8 (54·0–92·1%)	<0·0001
Microbiology			
Pseudomonas aeruginosa	301 (13·7%)	389 (15·0%)	0·2
Haemophilus influenzae	11 (0·5%)	569 (21·9%)	<0·0001
Staphylococcus aureus	50 (2·3%)	156 (6·0%)	<0·0001
Moraxella catarrhalis	22 (1·0%)	154 (5·9%)	<0·0001
Enterobacteriaceae	215 (9·8%)	158 (6·1%)	<0·0001
Treatment			
Long-term oral antibiotic treatment	271 (12·3%)	503 (19·4%)	<0·0001
Inhaled antibiotic treatment	79 (3·6%)	166 (6·4%)	<0·0001

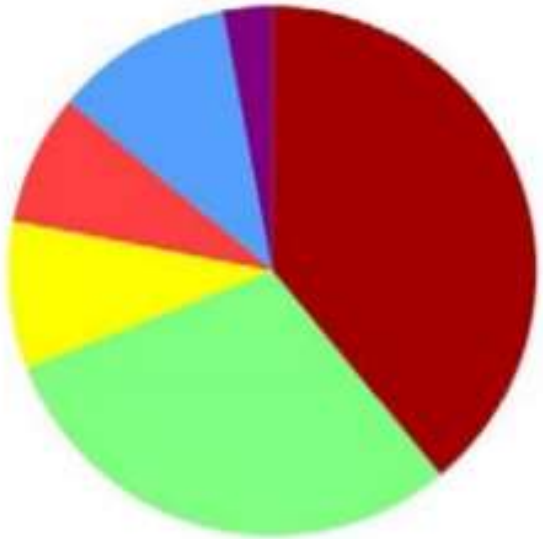

Tuberculosis
Post-infective
Idiopathic
Allergic bronchopulmonary aspergillosis
Chronic obstructive pulmonary disease
Asthma
Rheumatoid arthritis
Other causes
Primary ciliary dyskinesia
Gastro-oesophageal reflux
Non-tuberculosis mycobacterial infection
<1·0%
<1·0%
1·8%
2·5%
5·3%
<1·0%
<1·0%
35·5%
22·4%
21·4%
8·9%

A



Indian Bronchiectasis Registry

B



European Bronchiectasis Registry

- Haemophilus influenzae
- Pseudomonas aeruginosa
- Staphylococcus aureus
- Moraxella catarrhalis
- Enterobacteriaceae
- NTM

C

US Bronchiectasis Registry

RESULTS

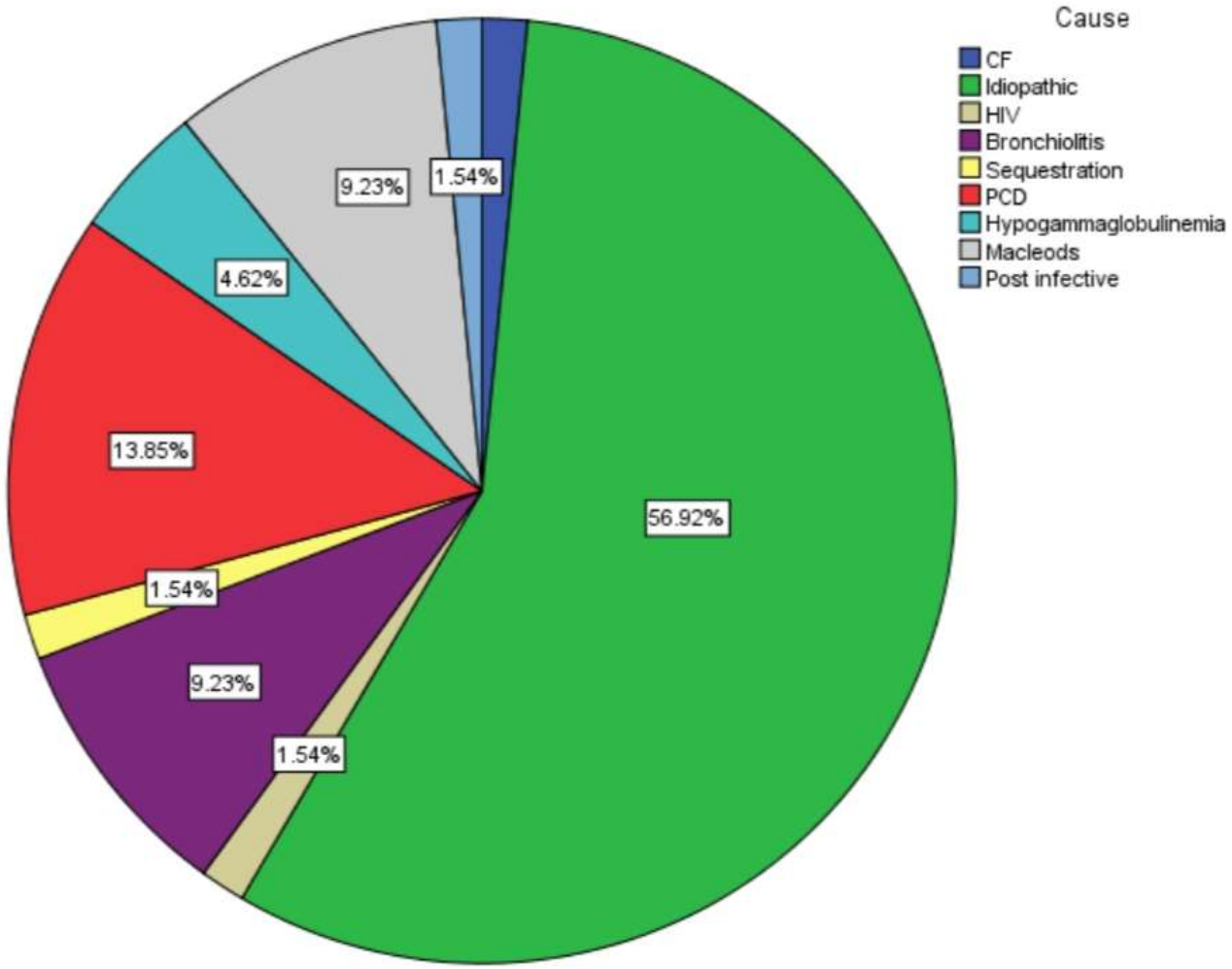
- Bronchiectasis in India is more severe, occurs at early age and is associated with more in hospital management of exacerbations
- Post tuberculosis sequelae is one of the most important cause and contributes to 58% when combined with other severe infections
- Different microbiologic profile with predominantly *P.aeruginosa*, enterobacteriaceae (Klebsiella and E.coli)

RESULTS

- Exacerbations were strongly associated with men, *P.aeruginosa* infection, history of pulmonary tuberculosis, mMRD, daily sputum production and radiological severity
- Low adherence to guidelines recommended care – only 388 patients tested for ABPA and 82 patients for immunoglobulins
- Eradication for *P.aeruginosa* attempted in 67% of the patients
- Only 34% of patients received prophylactic therapy for frequent exacerbation

PGI experience

- Over last 1 year
- All ABPA excluded
- All false bronchiectasis excluded
- 80 screened
- 65 with basic work up



Courtesy Dr Inderpaul Singh Sehgal

PEDIATRIC BRONCIECTASIS

- In children bronchiectasis is misdiagnosed as asthma (49%) and delay in receiving correct diagnosis was up to 14.8 years from symptom onset
- Primary prevention of bronchiectasis is possible with timely detection
- Risk of future bronchiectasis is reduced by early treatment
- Mild bronchiectasis is potentially reversible

Estham et al. Thorax 59, 324-327 (2004)

	Total number	% of total
No association	308	34%
Infectious	174	19%
Primary immunodeficiency	158	17%
Aspiration/foreign body	91	10%
Primary ciliary dyskinesia	66	7%
Congenital malformation	34	4%
Secondary immunodeficiency	29	3%
Asthma	16	2%
Bronchiolitis obliterans	12	1%
Skeletal diseases	11	1%
Others	7	1%

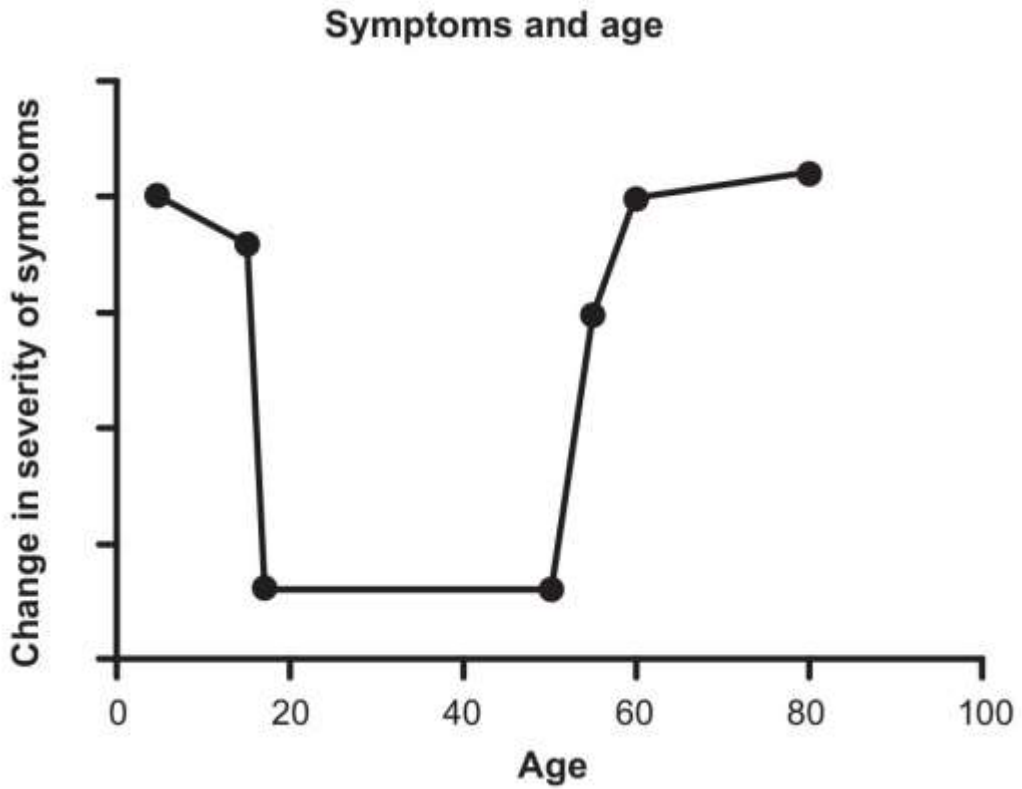
Systematic review involving 12 studies involving 989 children found 63% had underlying cause

IN EVERY CHILD ATTEMPT SHOULD BE MADE AT IDENTIFYING THE ETIOLOGY AS IT WILL ALTER MANAGEMENT

Brower KS et al. BMC Pediatr 2014

BRONCHIECTASIS AND AGE

- Immune system is less effective in young children and elderly adults with increased incidence of infection in these two groups



Study done by many authors showed improvement in symptoms in late adolescence regardless of treatment

Likely common feature of childhood-onset bronchiectasis is improvement with adulthood and then clinical deterioration again beyond age of 50 years

King et al. International Journal of COPD 2009:4 411-419

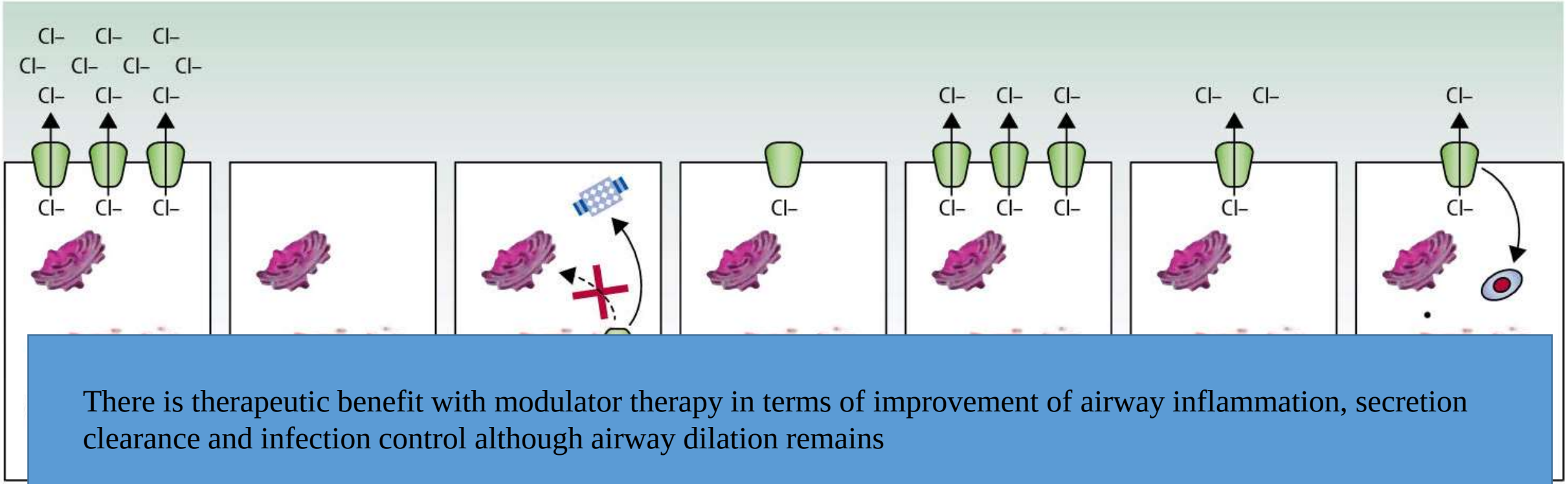
CYSTIC FIBROSIS

- Disorder of mucociliary clearance caused by altered epithelial ion transport
- Autosomal recessive
- Multisystem disorder caused by mutations in gene that encodes CF transmemebrane conductor regulator (CFTR) protein, chloride channel expressed in epithelial cells

CYSTIC FIBROSIS

- An upper lobe predominant distribution of cylindrical, cystic and varicose bronchiectasis associated with airway thickening, mucus plugging and parenchymal opacities should raise suspicion of CF
- Around 7% of patients with CF are diagnosed as adults

Hubert D et al. J Cyst Fibros 2004



There is therapeutic benefit with modulator therapy in terms of improvement of airway inflammation, secretion clearance and infection control although airway dilation remains

Defect types	No protein	No traffic	No function	Less function	Less protein	Less stable
Mutation examples	Gly 542 x Arg 553 x Trp 1282 x	Gly 85 Glu Δ Ile 507 Δ Phe 508 Asn 1303 lys	Val 520 Phe Ser 549 Arg Gly 551 Asp	Arg 117 His Arg 334 Trp Ser 1235 Arg	Ala 455 Glu 1680–886 A→G 2657+5 G→A	Δ Phe 508 Gln 1412 x
Required approaches	Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation or correct misplicing	Promote protein stability
Approved drugs	..	Lumacaftor, Tezacaftor	Ivacaftor	Ivacaftor	..	..

- CLINICAL IMPLICATIONS :

- To screen for CF in all patients presenting with bronchiectasis before age of 50yrs

- All patients with bronchiectasis symptoms onset during childhood irrespective of age of presentation

- Presence of upper lobe disease, *Staphylococcus aureus* or *P.aeruginosa in sputum* or extrapulmonary features such as malabsorption, pancreatitis or infertility irrespective of the age of the patient

CFTR RELATED DISORDER

- Defined as disease limited to only one organ system associated with some evidence of CFTR dysfunction that does not meet full genetic or functional criteria
- Clinical manifestations – isolated obstructive azoospermia, chronic sinusitis or chronic pancreatitis
- Should undergo complete gene sequencing including evaluation for gene duplications and deletions

CFTR- RELATED METABOLIC SYNDROME

- An asymptomatic infant with positive newborn screening results and

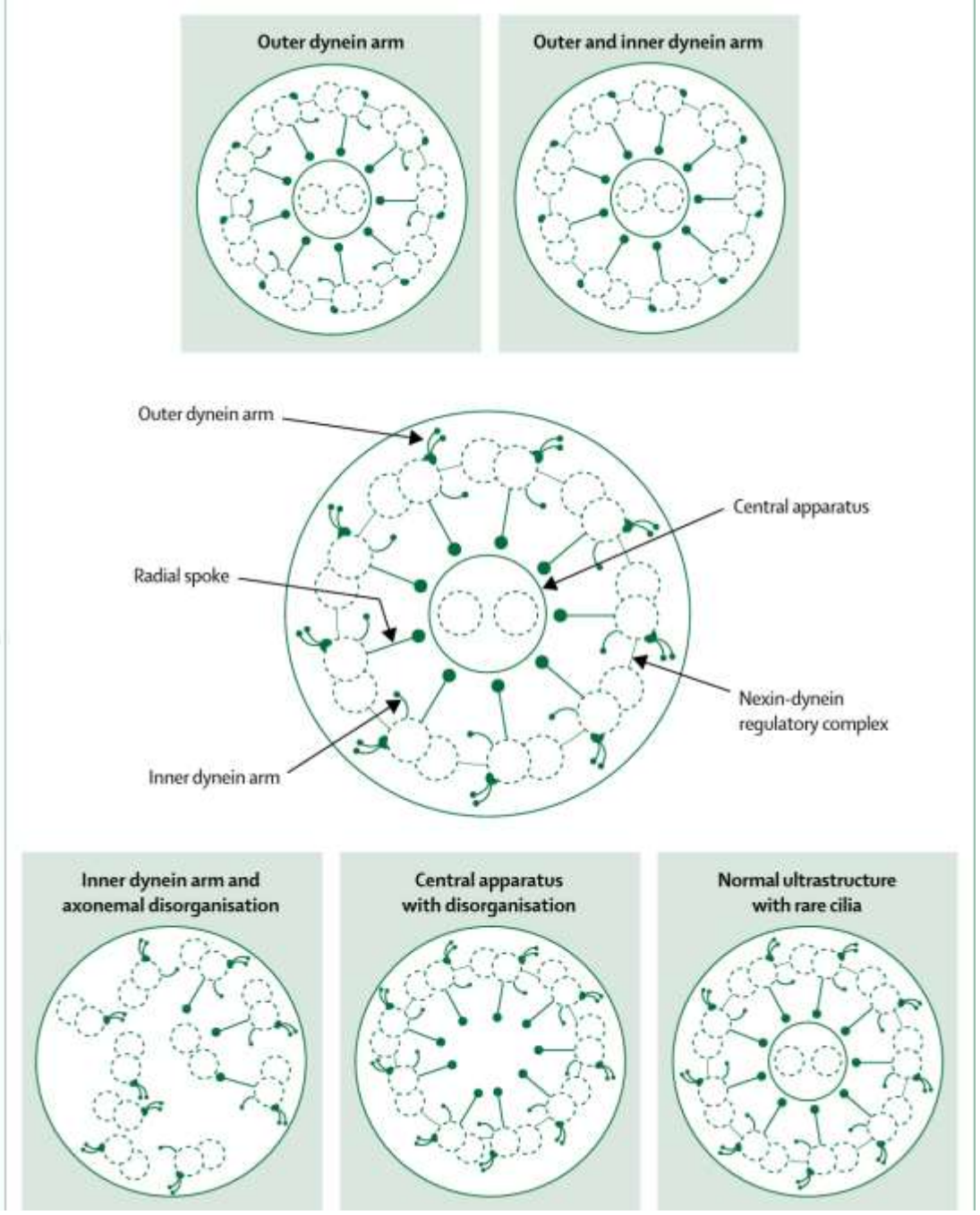
- Intermediate sweat chloride results (30 to 59 mmol/L) on two separate occasions and fewer than 2 CF-causing variants

OR

- Normal sweat chloride results (≤ 29 mmol/L) on 2 separate occasions and two CFTR variants, at least one of which is not clearly categorized as CF causing

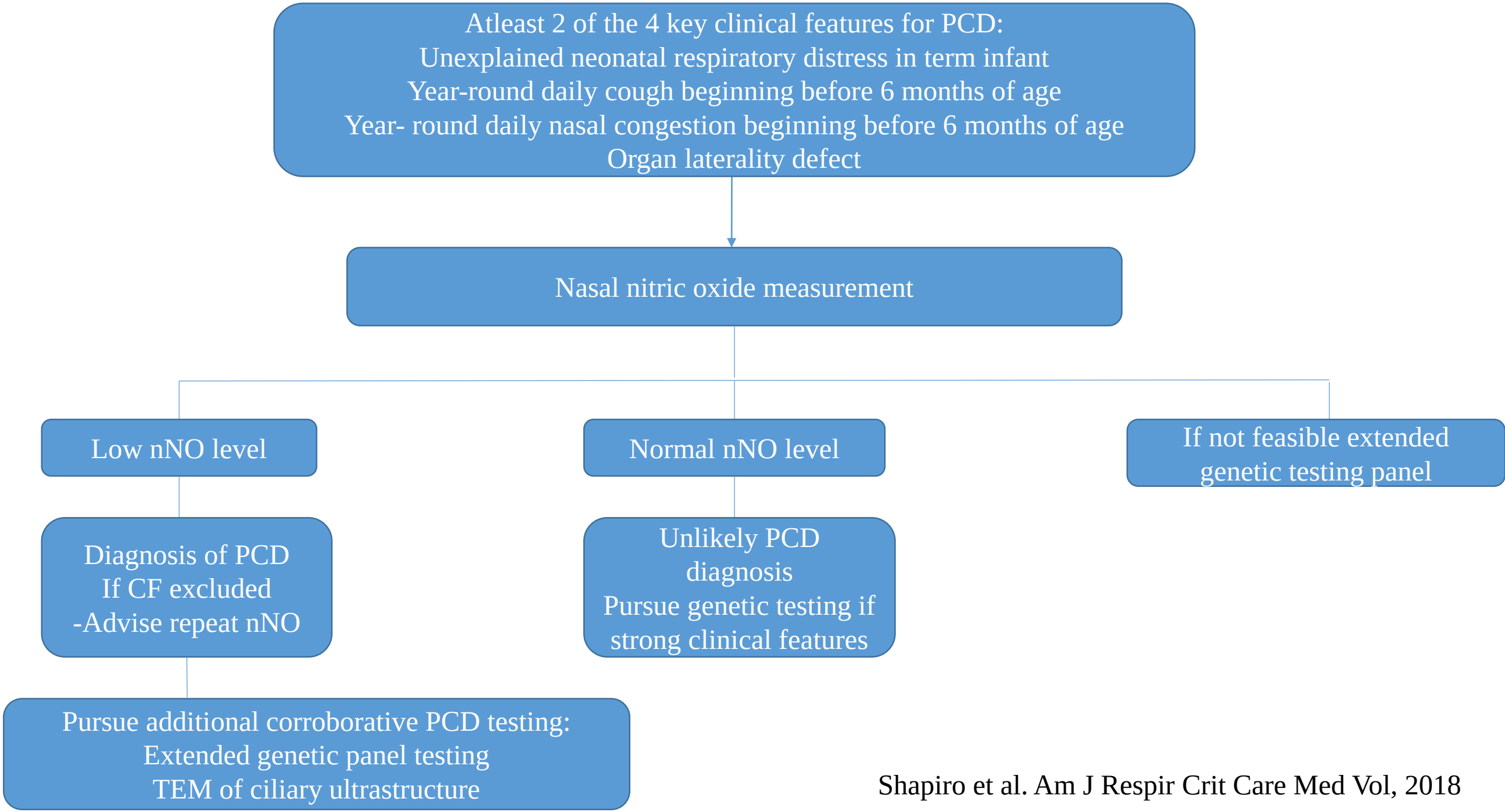
PRIMARY CILIARY DYSKINESIA

- Disorder of mucociliary clearance characterized by disordered function of motile cilia
- Genetically heterogeneous and predominantly autosomal recessive disorder caused by biallelic pathogenic mutation in one of many identified PCD causative genes (39 to date)

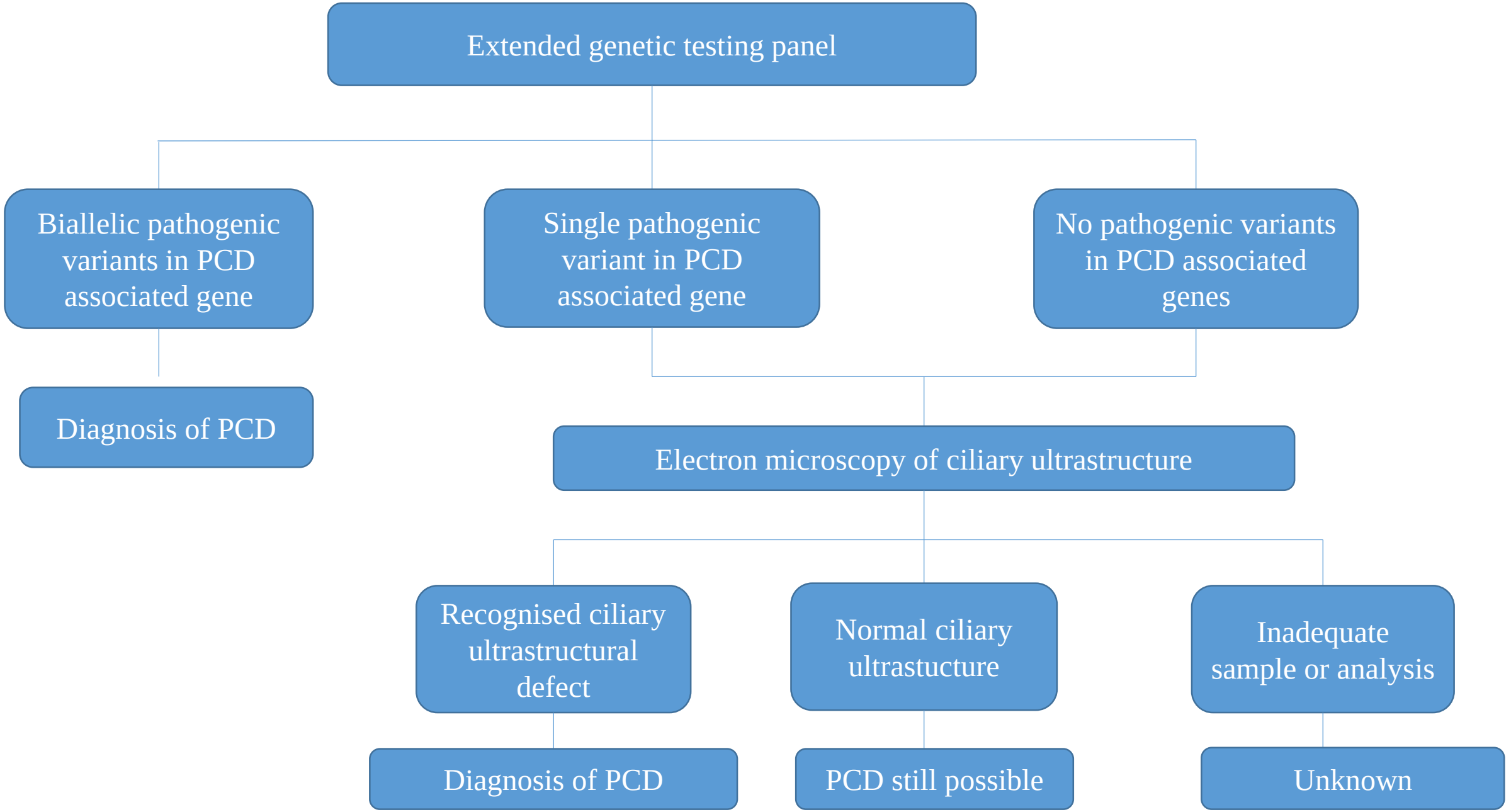


Defects in cilia gene classified on basis of ultrastructural effects seen on cross sectional examination of cilia with EM

- Genes associated with outer dynein arm include DNAH5, DNAI1, DNAI2, TXNDC3, DNAL1, ARMC4, CCDC114 and CCDC151
- Genes associated with inner and outer arm include LLRC6, DNAAF1, DNAAF2, DNAAF3, CCDC103, ZMYD10, HEARTR2, DYX1C1, SPAG1 and C21orf59
- Genes associated with inner dynein arm and axonemal disorganization include CCDC39 and CCDC40
- Genes associated normal ultrastructure are DNAH11, CCDC164, CCDC65 and RSPH1



Shapiro et al. Am J Respir Crit Care Med Vol, 2018



Shapiro et al. Am J Respir Crit Care Med Vol, 2018

BRONCHIECTASIS WITH OTHER FEATURES

SINUSITIS

- CF
- PCD
- Young’s Syndrome
- Diffuse panbronchiolitis
- ABPA
- CVID
- Hyper IgE syndrome

INFERTILITY OR REDUCED FERTILITY

- CF
- PCD
- Young’s Syndrome

BRONCHIECTASIS AND CTD

- CTD associated with bronchiectasis are
- Rheumatoid Arthritis
- Sjogren’s Syndrome
- Systemic sclerosis
- SLE
- Ankylosing spondylitis
- Relapsing polycondritis
- Marfan syndrome
- Ehlers Danlos Syndrome

BRONCHIECTASIS AND CTD

- Prevalence of bronchiectasis in patients with systemic sclerosis, SLE and RA is found to be 59%, 21% and 30% respectively
- Patients with RA especially and bronchiectasis present with higher activity and severity of disease and higher levels of anti-citrullinated peptide antibodies when compared with RA only
- Bronchiectasis associated with CTD and in particular RA is associated with poorer prognosis and requires intensive monitoring

Andonopoulos et al. Rheumatol. 19. 2001
Fenlon et al. AJR. Am. J. Roentgenol. 1996

BRONCHIECTASIS AND IBD

- Bronchiectasis is common pulmonary manifestation of IBD (1-3%)

  more commonly with ulcerative colitis

- Most common presentation is appearance of coughing with chronic

  bronchorrhea

- Treatment with inhaled and oral glucocorticoids is effective

McShane et al. CHEST J. 2012

BRONCHIECTASIS AND NTM

- Prevalence of NTM with bronchiectasis is 9.3%
- Ubiquitous organism in environment and can be inhaled or ingested from water, soil and dust
- Most common species is MAC (includes *M.intercellulare*, *M.avium* and *M.chimaera*)

Chu et al. Arch Med Sci 2014

BRONCHIECTASIS AND NTM

- Diagnosis based on respiratory symptoms, radiological features consistent with NTM, exclusion of other diagnosis and microbiological criteria (positive culture from one bronchial lavage, Atleast 2 NTM-positive sputum cultures or lung biopsy with mycobacterial histologic features plus NTM positive culture)

BRONCHIECTASIS AND NTM

- Two major radiological patterns:

- Nodular/bronciectatic – multiple small centrilobular nodules and cylindrical bronchiectasis especially localized to middle lobe and lingula

Frequently associated with MAC infection and with Lady Windermere Syndrome

- Fibrocavitary- Increased opacity areas and cavitations, usually in upper lobes with or without calcifications

BRONCHIECTASIS AND NTM

- Right middle lobe bronchus is long, bends sharply at its bifurcation and of relatively small caliber
- Collar of lymph nodes surround proximal bronchus and any condition that leads to prolong enlargement of these nodes lead to obstruction and secondary bronchiectasis

BRONCHIECTASIS AND COPD

- Data from meta-analysis including 6 observational studies showed mean prevalence of bronchiectasis – 54.3%
- Population study of 18793 patients with bronchiectasis (2004-2013) shown 36% of patients had COPD
- In ECLIPSE study (N = 2161) bronchiectasis reported in only 2% of males with GOLD II COPD (<1% of females), increasing to 9% of females and 7% of males in very severe COPD (GOLD IV)

Brien et al. Eur. Respir. J. 47 (2016)
Agusti et al. Respir. Res. 11 (2010)
Ni et al Int. J. Chron. Obstruct Pulmon. Dis 10 (2015)

International Journal of COPD

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REVIEW

Clinical characteristics of patients with chronic obstructive pulmonary disease with comorbid bronchiectasis: a systemic review and meta-analysis

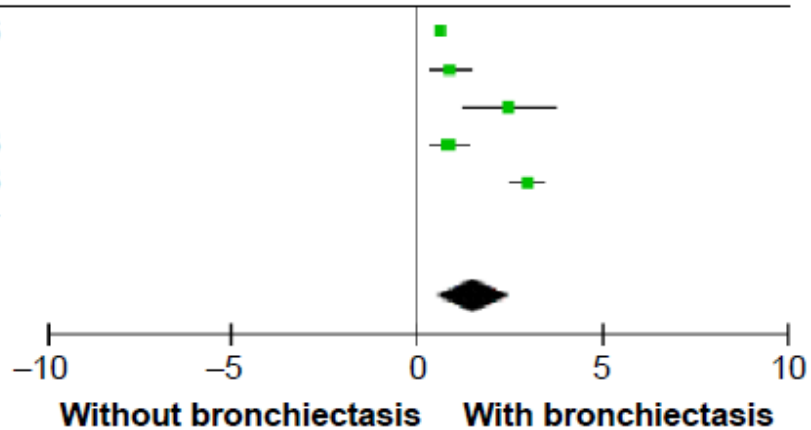
Yingmeng Ni et al.

- Six observational studies
- Cohort – 881 patients
- Bronchiectasis confirmed either by CT or HRCT
- Clinicopathological or demographic profile compared between COPD patients with or without bronchiectasis

AUTHORS	RECRUITMENT PERIOD	SEVERITY OF COPD/ PATIENTS	OUTCOMES
Fijimoto et al 2006	Sept 2002 – Sept 2004	Moderate, severe 172	COPD with bronchiectasis showed large sputum production, higher rate of exacerbation or hospitalization and greater reversibility to beta2 agonist
Martinez-Garcia et al 2011	Jan 2004-Dec 2006	Moderate, severe 92	Increased prevalence of bronchiectasis with moderate to severe COPD and associated with isolation of PPM from sputum and hospitalization from exacerbation
Bafadhel et al 2011	NA	NA	CT based differentiation of emphsematous and bronchiectatic phenotype of COPD. No difference was found between exacerbations or bacterial load
Martinez-Garcia et al 2013	Jan 2004-Feb 2007	Moderate, severe 99	Bronchiectasis was associated with independent increased risk of all cause mortality
Tulek et al 2013	Jan 2010-May 2012	Mild, moderate, severe, very severe /80	HRCT used for differentiation . There was lower FEV1, FEV1/FVC in emphysema and bronchiectasis with more exacerbations and hospitalisations
Gatheral et al 2014	Jan 1998 – Sept 2008	NA 406	COPD related bronchiectasis is associated with increased respiratory infection and hospitalisations

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)**	

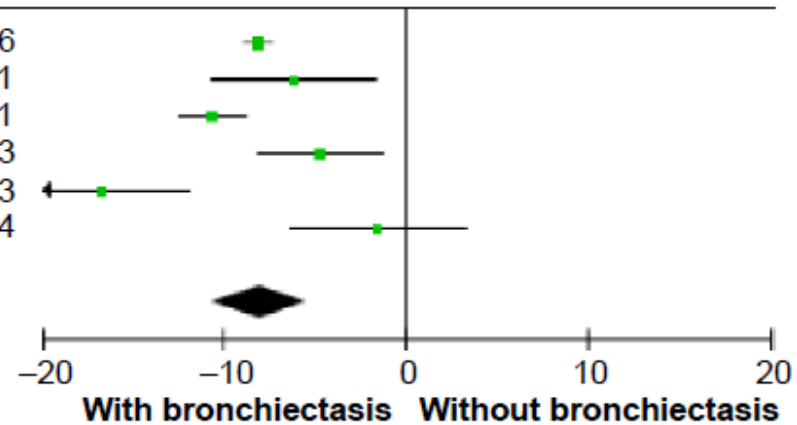
Heterogeneity: τ^2=1.15; χ^2=110.26, *df*=4 (*P*<0.00001); I^2=96%
Test for overall effect: *Z*=3.07 (*P*=0.002)



Forest plot of mean difference in exacerbations in COPD patients with or without bronchiectasis

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]	43.5	1.6	44	51.6	1.8	39	22.9%	–8.10 (–8.84, –7.36)	2006
Martínez-García et al[7]	45.1	11.9	53	51.2	10.1	39	13.7%	–6.10 (–10.61, –1.59)	2011
Bafadhel et al[1]	48.4	2.3	33	59	3	13	21.0%	–10.60 (–12.41, –8.79)	2011
Martínez-García et al[13]	50.5	12.9	115	55.2	11.8	86	16.6%	–4.70 (–8.13, –1.27)	2013
Tulek et al[12]	48.1	10.9	26	64.8	6.2	26	13.0%	–16.70 (–21.52, –11.88)	2013
Gatheral et al[4]	53.5	16.7	135	55	16	63	12.9%	–1.50 (–6.35, 3.35)	2014
Total (95% CI)			**406**			**266**	**100%**	**–8.05 (–10.65, –5.45)**	

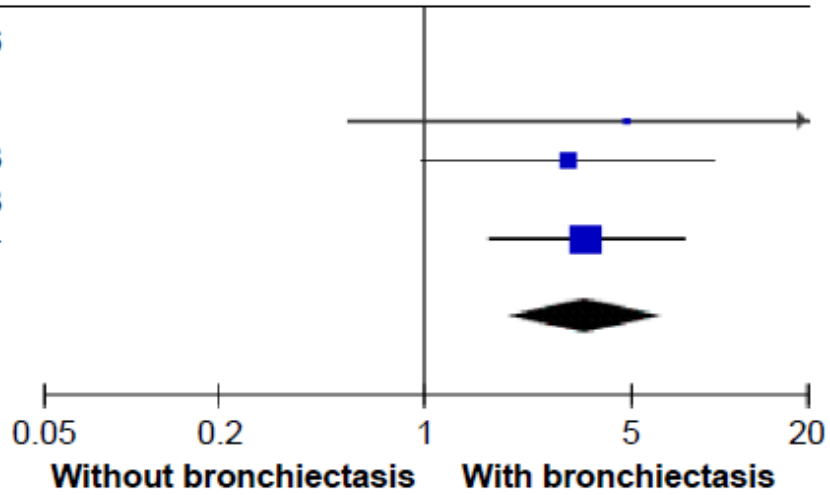
Heterogeneity: τ^2=7.57; χ^2=30.84, *df*=5 (*P*<0.0001); I^2=84%
Test for overall effect: *Z*=6.06 (*P*<0.00001)



Forest plot of mean difference of postbronchodilator FEV1/FVC in COPD with or without bronchiectasis

Study or subgroup	With bronchiectasis Events	Total	Without bronchiectasis Events	Total	Weight	Odds ratio M–H, fixed, 95% CI	Year
Fujimoto et al[11]	0	0	0	0		Not estimable	2006
Bafadhel et al[1]	0	0	0	0		Not estimable	2011
Martínez-García et al[7]	6	53	1	39	7.4%	4.85 (0.56, 42.05)	2011
Martínez-García et al[13]	15	115	4	86	28.7%	3.08 (0.98, 9.62)	2013
Tulek et al[12]	0	0	0	0		Not estimable	2013
Gatheral et al[4]	53	278	8	128	63.9%	3.53 (1.63, 7.67)	2014
Total (95% CI)		**446**		**253**	**100%**	**3.50 (1.89, 6.47)**	
Total events	74		13				

Heterogeneity: χ^2=0.14, *df*=2 (*P*=0.93); I^2=0%
Test for overall effect: *Z*=4.00 (*P*<0.0001)



Forest plot of odd ratios of *P.aeruginosa* isolation in COPD patients with or without bronchiectasis

CONCLUSION

- Coexistence of bronchiectasis and COPD more common in elderly male with long smoking history
- There is an association of *P.aeruginosa isolation* with bronchiectasis in COPD
- P. aeruginosa is associated with severe disease, higher 3 year mortality, more hospital admissions, higher BODE index and more systemic steroid treatment

CONCLUSION

- There was association between lower albumin level and higher CRP level in COPD and comorbid bronchiectasis indicating higher level of acute phase protein
- Presence of bronchiectasis in patients with COPD correlated with chronic bronchitis phenotype (thicker bronchial wall, greater daily sputum production and high number of exacerbations) than those with emphysematous phenotype

BRONCHIECTASIS AND ASTHMA

	POPULATION	CENTRES	OUTCOME
Anwar et al. 2013	Observational study 189 patients with bronchiectasis	2 centres	Prevalence of bronchiectasis associated with asthma about 3%
Lonni et al.	Prospective study 1258 patients with bronchiectasis	Multicentric	Asthma as etiology of bronchiectasis in 3.3% of patients
Menzies et al.	Observational study with 133 patients of asthma	Multicentric	*A.Fumigatus* sensitization was associated with 2.01 increased hazard ratio of bronchiectasis and more obstructive spirometry
Quint et al.	Observational study N - 11862	Multicentric	Asthma was associated with large number of bronchiectasis approx. 42.5%

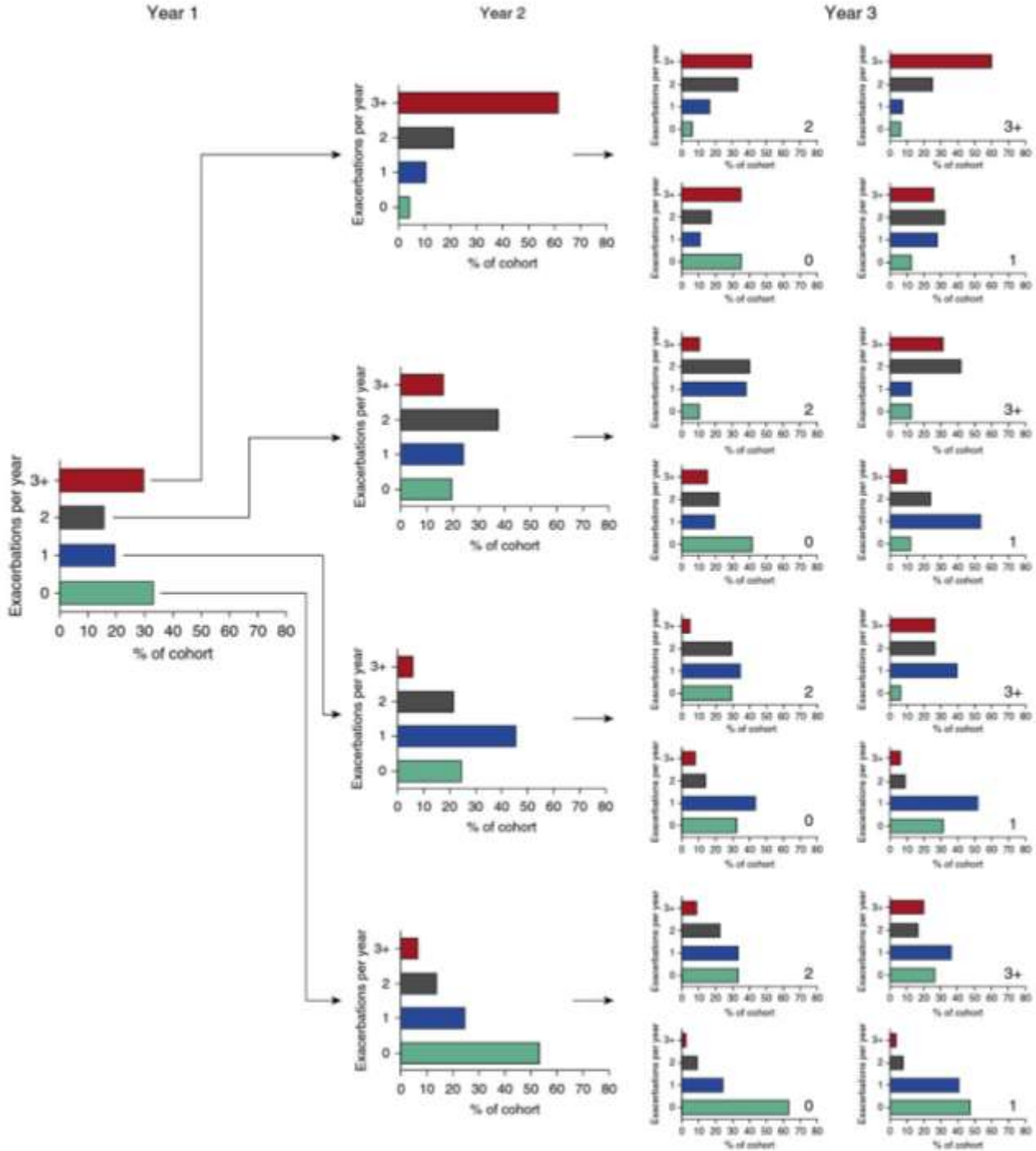
CLINICAL PHENOTYPES

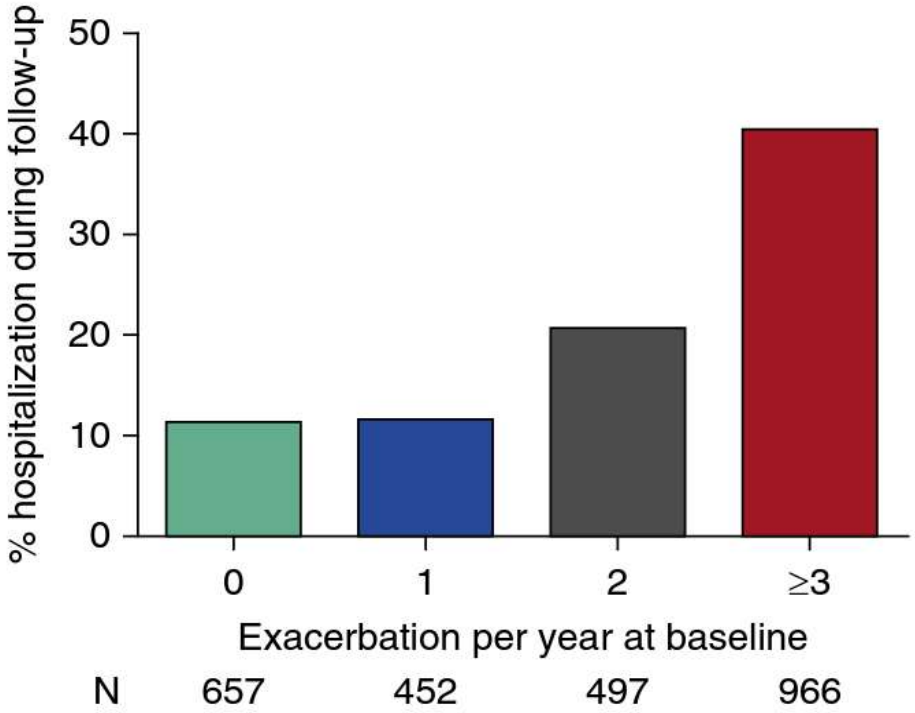
ORIGINAL ARTICLE

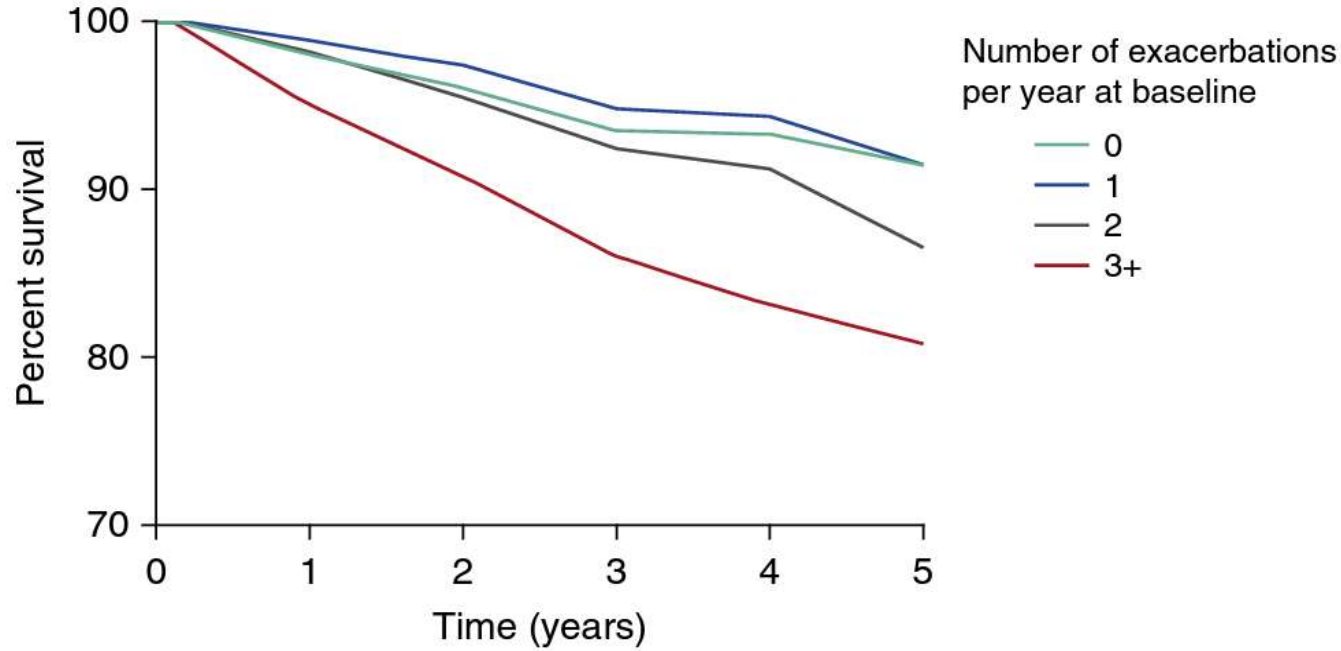
Characterization of the "Frequent Exacerbator Phenotype" in Bronchiectasis

James D. Chalmers[1], Stefano Aliberti[2,3], Anna Filonenko[4], Michal Shteinberg[5], Pieter C. Goeminne[6,7], Adam T. Hill[8,9], Thomas C. Fardon[1], Dusanka Obradovic[10], Christoph Gerlinger[4,11] Giovanni Sotgiu[12], Elisabeth Operschall[4], Robert M. Rutherford[13], Katerina Dimakou[14], Eva Polverino[15], Anthony De Soyza[16,17], and Melissa J. McDonnell[13,17]

- Prospective study of 2596 patients
- Multicentric study 10 centres across Europe
- Between 2007 to 2013


Year 1
Year 2
Year 3
Exacerbations per year
3+
2
1
0
% of cohort
0 10 20 30 40 50 60 70 80





Numbers at risk

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

CONCLUSION

- Exacerbation frequency showed relative stability over time, particularly in those with three or more exacerbations
- Associated increased risk of death and independent increase in SGRQ and hospitalizations
- BSI – Bronchiectasis Severity Index – includes exacerbation in contrast to FACED score (FEV1/age/colonization/extension and dyspnea) making it less reliable tool for prediction of severity of disease

CONCLUSION

- CLINICAL UTILITY – Attempts towards reducing exacerbations i.e. macrolides, inhaled antibiotics, mucoactive therapies and pulmonary rehabilitation

ORIGINAL RESEARCH

The Multiple Faces of Non–Cystic Fibrosis Bronchiectasis

A Cluster Analysis Approach

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

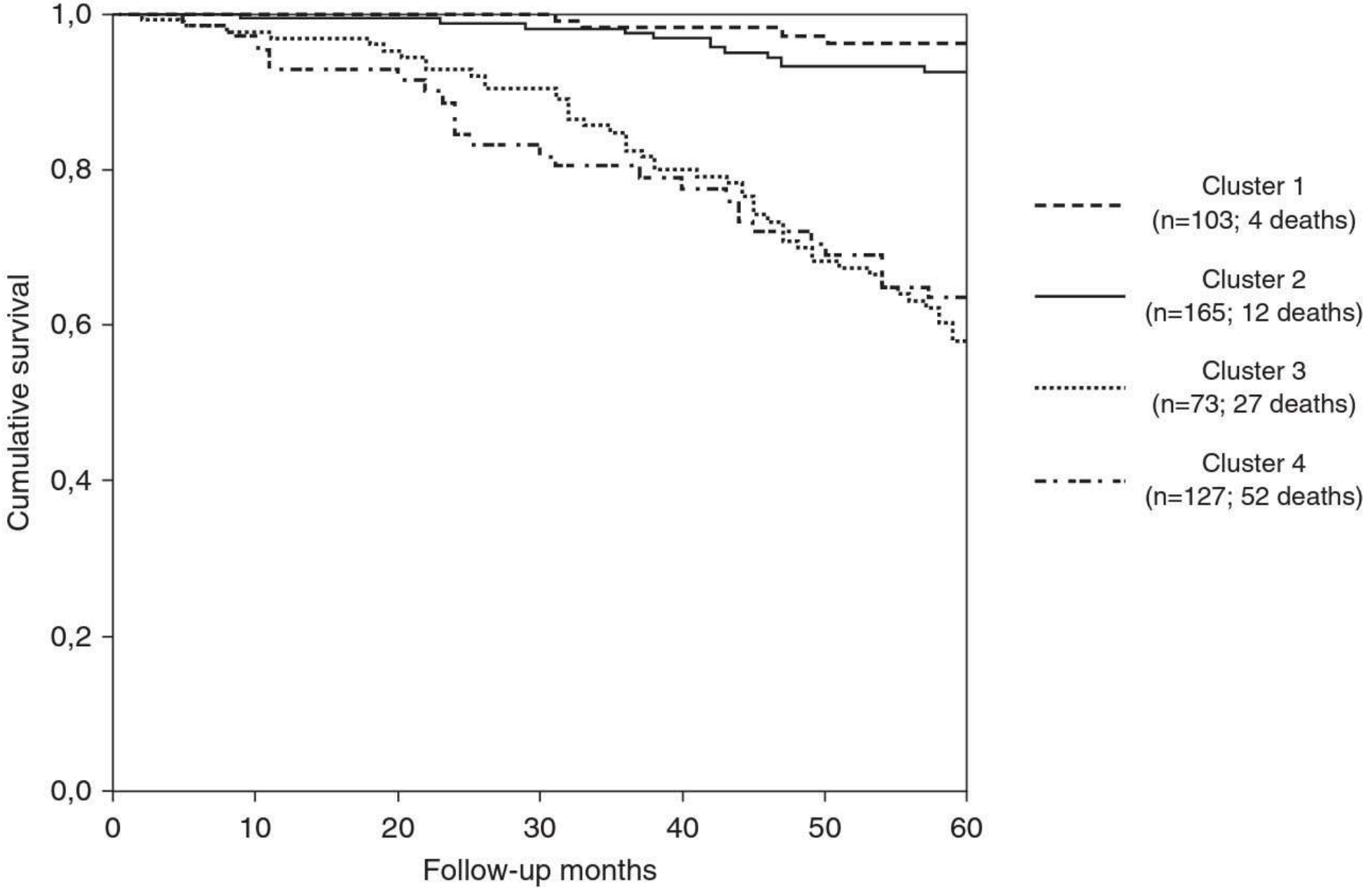
- Observational, multicenter study of six centres
- Cohort of 468 patients
- Hierarchial cluster analysis done
- Clusters are

1. Phenotype 1 – Young women, not overweight, mild disease, genetic and/or immune deficiency etiologies or idiopathic bronchiectasis (Young/mild)

2. Phenotype 2 – Elderly overweight with mild disease and idiopathic or postinfectious etiologie (elderly/mild)

3. Phenotype 3 – Elderly men with severe disease, high prevalence of chronic bronchial infection, severe flow obstruction, multiple exacerbations, postinfectious bronchiectasis and associated COPD (elderly/severe/exacerbator)

4. Phenotype 4 – Elderly patient with severe disease but low number of exacerbations (elderly/severe/non exacerbator)


1,0
0,8
0,6
0,4
0,2
0,0
Cumulative survival
0
10
20
30
40
50
60
Follow-up months
Cluster 1
(n=103; 4 deaths)
Cluster 2
(n=165; 12 deaths)
Cluster 3
(n=73; 27 deaths)
Cluster 4
(n=127; 52 deaths)

	Phenotype 1: Young with Mild Disease	Phenotype 2: Elderly with Mild Disease	Phenotype 3: Elderly with Frequent Exacerbations	Phenotype 4: Elderly with Severe Disease, Few Exacerbations
Age	Young	Elderly*	Elderly	Elderly
Sex	Women	Women	Men	Both
BMI[†]	Low	Overweight	Slightly low	Slightly high
Clinical severity[‡]	Mild	Mild	Moderate to severe	Moderate to severe
Airflow obstruction	No	Mild	Severe	Severe
Frequent exacerbations[§]	No	No	Yes	No
Chronic bronchial infection rate[‖]	Low	Low	High	Moderate
Etiology associated and respiratory comorbidities	Genetic/ID Postinfectious Idiopathic	Idiopathic Postinfectious Asthma	Postinfectious COPD	Postinfectious Idiopathic
Nonrespiratory comorbidities	Low	Low	Low	Cardiovascular Neoplasms
Death rate	Low	Low	High	High
Cause			Respiratory causes	Nonrespiratory causes

CONCLUSION

- Phenotype 1 i.e. genetic causes was associated with least mortality partly due to association with low mean age and effectiveness of substitutive treatments
- Phenotype 2 – included most of patients with asthma associated with bronchiectasis and has good prognosis
- Phenotype 3 – Significantly higher number of exacerbations, chronic bacterial infections (P. aeruginosa) and associated COPD

CONCLUSION

PRESCENCE OF BRONCHIECTASIS INCREASES SEVERITY AND MORTALITY WITH COPD

- Phenotype 4- Higher mortality likely due to associated comorbidities

THERAPEUTIC IMPLICATION FOR MANAGEMENT OF THESE COMORBIDITIES

Clinical phenotypes in adult patients with bronchiectasis

Stefano Aliberti[1], Sara Lonni[1], Simone Dore[2], Melissa J. McDonnell[3],

- Prospective analysis
- Multicentric, data from 5 European centres
- 1145 patients
- Cluster analysis

- Cluster 1 (n-179) – Patients with chronic infection with *P.aeruginosa*. Patients had most severe disease, worst radiological, highest inflammatory patterns and lowest functional status, highest no. of exacerbations and hospitalization. “PSEUDOMONAS”

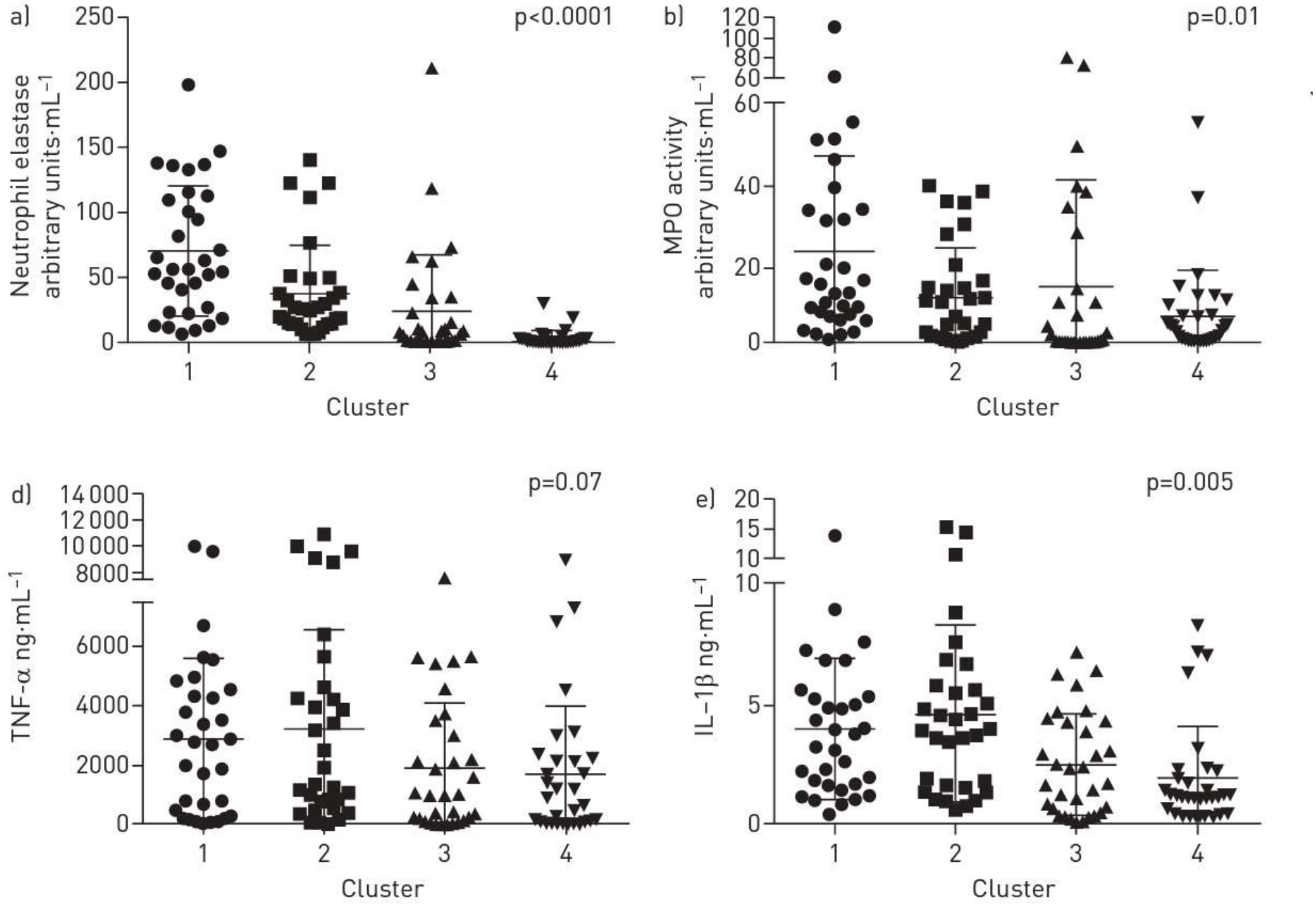
- Cluster 2 (n-273) – Presence of chronic infections with other pathogens other than *P.aeruginosa* "OTHER CHRONIC INFECTIONS"

- Cluster 3 (n-373) – No patient had chronic infection but almost daily sputum and slightly higher proportion were smokers or ex-smokers "DAILY SPUTUM"

- Cluster 4 (n-307) – None of the patient had chronic infection or daily sputum. These patients were of lower severity, lowest level of inflammatory markers, least severe radiological and less functional impairment "DRY BRONCHIECTASIS"

	Cluster 1: "*Pseudomonas*"	Cluster 2: "Other chronic infection"	Cluster 3: "Daily sputum"	Cluster 4: "Dry bronchiectasis"	Overall p-value
Patients	179 (100)	273 (100)	373 (100)	307 (100)	
Centre					<0.0001
Dundee, UK	44 (24)	128 (47)	90 (24)	24 (8)	
Leuven, Belgium	16 (9)	19 (7)	66 (18)	89 (29)	
Monza, Italy	23 (13)	24 (9)	87 (23)	96 (31)	
Galway, Ireland	39 (22)	78 (28)	74 (20)	89 (29)	
Athens, Greece	57 (32)	24 (9)	56 (15)	9 (3)	
Demographics and comorbidities					
Age years	67 (56–75)	65 (56–73)	67 (57–74)	66 (55–74)	0.52
Male	81 (45)	112 (41)	148 (40)	109 (36)	0.19
BMI $kg \cdot m^{-2}$	25 (21–27)	25 (22–28)	25 (22–28)	25 (21–28)	0.47
Smoker/ex-smoker	56 (31)	90 (33)	165 (44)	121 (39)	0.005
CCI >1	53 (30)	101 (37)	113 (30)	106 (35)	0.20
Disease severity					
BSI score	14 (11–17)	7 (5–10)	6 (3–9)	5 (3–7)	0.0001
FACED score	4 (2–5)	2 (1–3)	2 (1–3)	1 (0–3)	<0.001
Radiological status					
Reiff score	6 (4–9)	4 (2–6)	3 (2–6)	3 (2–6)	0.0001
Clinical status					
Daily cough	170 (95)	241 (88)	322 (86)	154 (50)	<0.0001
Daily sputum	166 (93)	204 (75)	362 (97)	0 (0)	<0.0001
Prior history of haemoptysis	42 (24)	36 (13)	80 (22)	43 (14)	0.002
MRC breathlessness scale	3 (2–5)	2 (1–3)	2 (1–3)	1 (1–2)	0.0001
Long-term oxygen therapy	34 (19)	14 (5.1)	36 (9.7)	0 (0)	<0.0001
Exacerbations in the previous year	3 (2–4)	2 (1–3)	2 (1–3)	2 (1–3)	0.0001
At least one hospitalisation in the previous year	109 (61)	63 (23)	90 (24)	36 (12)	<0.0001
Functional status					
FEV_1 % predicted	59 (46–78)	71 (55–93)	77 (57–95)	84 (68–101)	0.0001
Microbiology					
Chronic infection with *Pseudomonas aeruginosa*	179 (100)	0 (0)	0 (0)	0 (0)	<0.0001
Chronic infection with other pathogens	0 (0)	273 (100)	0 (0)	0 (0)	<0.0001
Laboratory findings					
C-reactive protein $mg \cdot L^{-1}$	10.7 (4.0–36.0)	5.0 (3.7–9.0)	4.5 (2.0–7.7)	3.0 (1.2–7.2)	0.0001
Long-term antibiotic treatment					
Either macrolide or inhaled antibiotics	120 (67)	105 (39)	122 (33)	38 (12)	<0.0001
Macrolide	97 (54)	103 (38)	119 (32)	37 (12)	<0.0001
Inhaled antibiotics	64 (36)	15 (5.5)	7 (1.9)	2 (0.7)	<0.0001
Both macrolide and inhaled	41 (23)	13 (4.8)	4 (1.1)	1 (0.3)	<0.0001

	Cluster 1: "*Pseudomonas*"	Cluster 2: "Other chronic infection"	Cluster 3: "Daily sputum"	Cluster 4: "Dry bronchiectasis"	Overall p-value
Patients	179 (100)	273 (100)	373 (100)	307 (100)	
Quality of life					
SGRQ	58 (34–72)	43 (27–61)	39 (27–55)	29 (12–40)	<0.001
Outcomes					
Exacerbations during 1-year follow-up	2 (1–3)	2 (1–2)	1 (0–2)	1 (0–2)	0.0001
At least one hospitalisation during 1-year follow-up	67 (42)	41 (16)	56 (16)	42 (14)	<0.0001
Mortality during 1-year follow-up	9 (5.1)	4 (1.5)	13 (3.6)	14 (4.9)	0.12
Mortality during 3-year follow-up	26 (17)	19 (7.6)	24 (8.2)	23 (11)	0.02


a)
p<0.0001
Neutrophil elastase arbitrary units·mL^{-1}
250
200
150
100
50
0
1
2
3
4
Cluster
b)
p=0.01
MPO activity arbitrary units·mL^{-1}
120
100
80
60
60
40
20
0
1
2
3
4
Cluster
d)
p=0.07
TNF-α ng·mL^{-1}
14 000
12 000
10 000
8000
6000
4000
2000
0
1
2
3
4
Cluster
e)
p=0.005
IL–1β ng·mL^{-1}
20
15
10
10
5
0
1
2
3
4
Cluster

CONCLUSION

- The study demonstrated these clusters represent clinical phenotypes as they exhibit difference in inflammatory markers, quality of life and long term clinical outcomes
- This study highlights importance of sputum surveillance for all patients of bronchiectasis
- Need better evidence on effectiveness and safety of eradication or long term suppressive therapy for *P.aeruginosa* infection

S. Aliberti et al. Eur Respir J 2016; 47: 1113-1122

SENSITIZED BRONCHIECTASIS

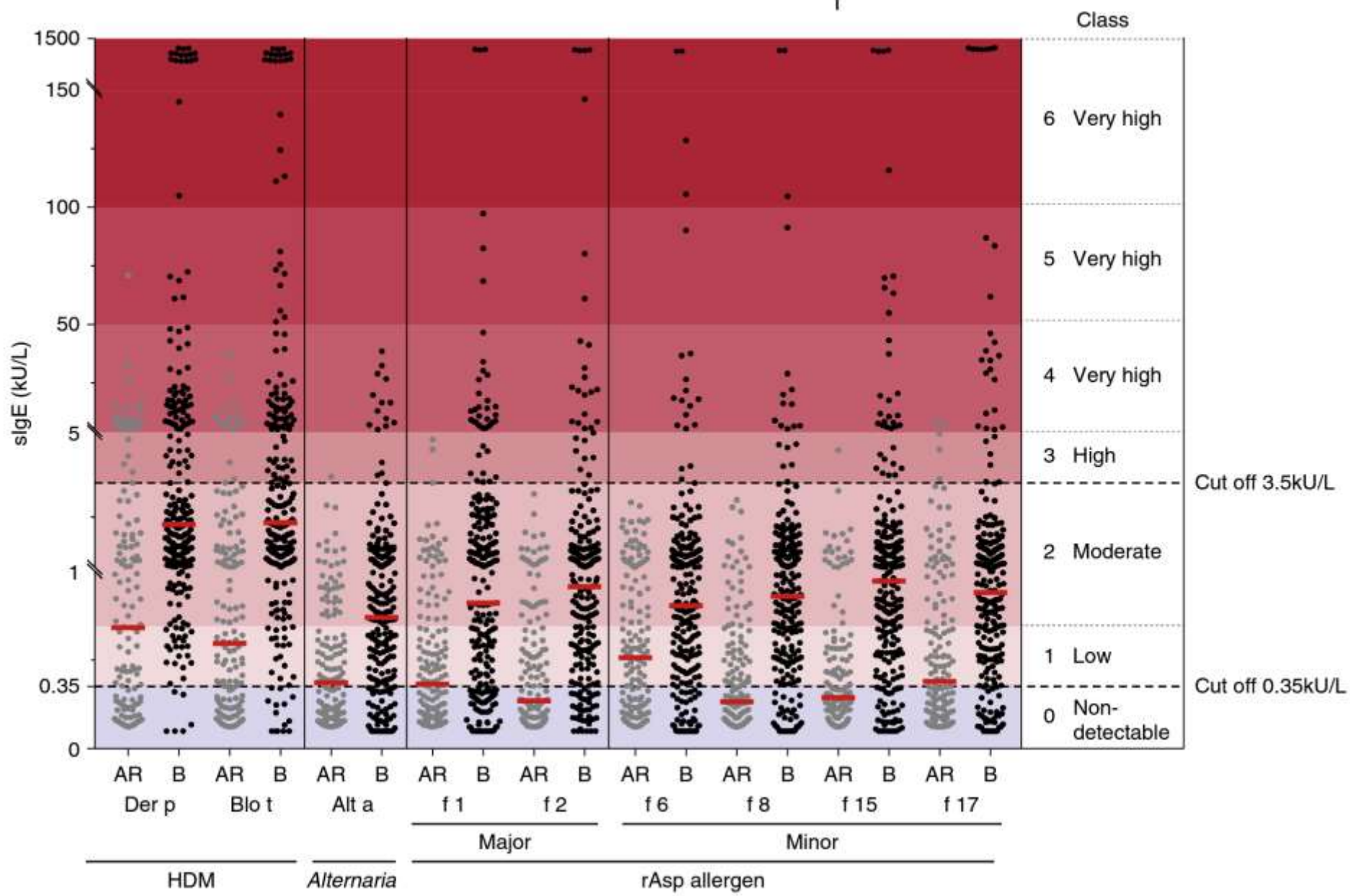
ORIGINAL ARTICLE

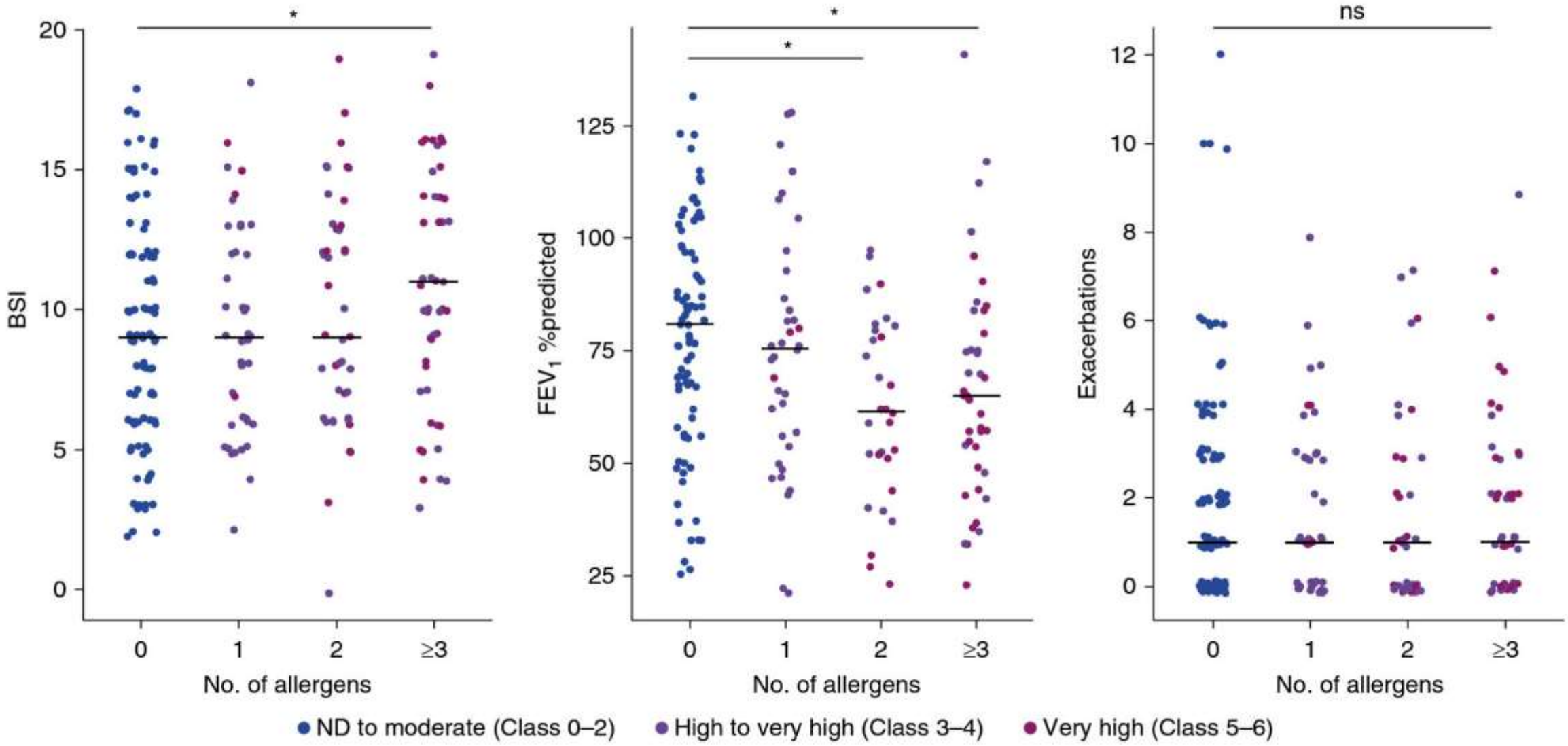
Distinct "Immunoallertypes" of Disease and High Frequencies of Sensitization in Non–Cystic Fibrosis Bronchiectasis

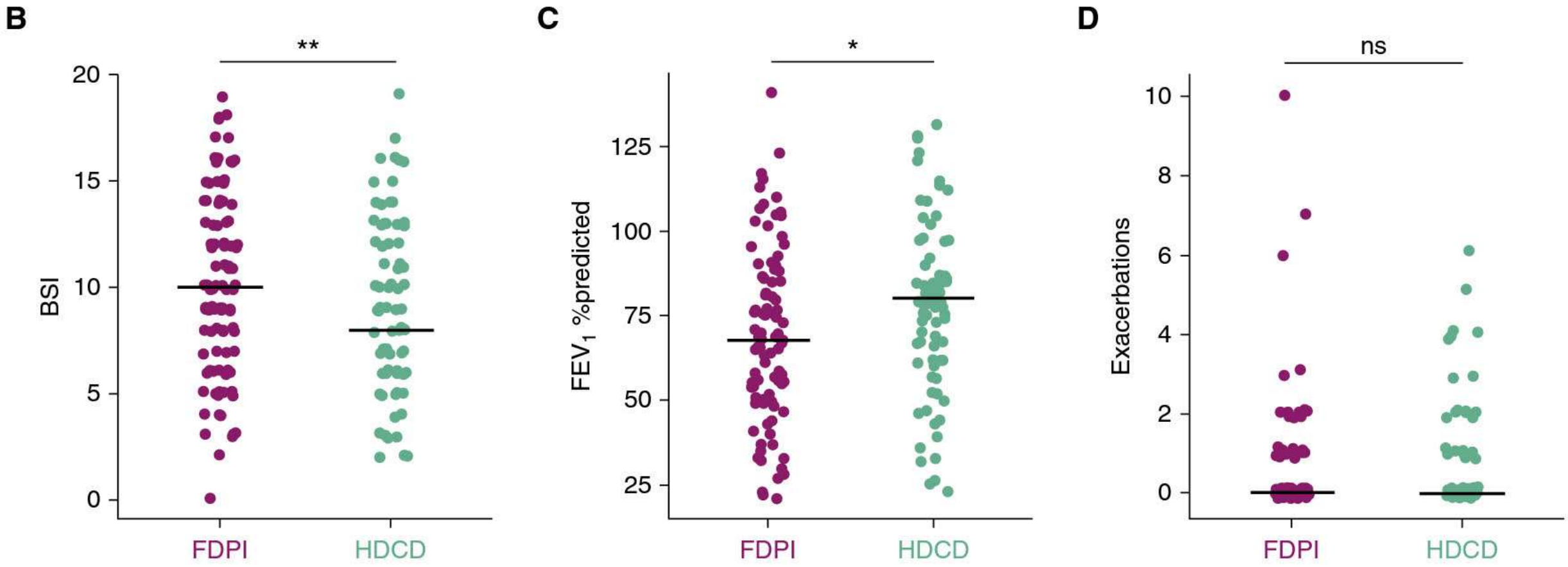
Micheál Mac Aogáin[1*], Pei Yee Tiew[1,2*], Albert Yick Hou Lim[3], Teck Boon Low[4], Gan Liang Tan[2], Tidi Hassan[5],

- CAMEB TRIAL (Cohort of Asian and Matched European Bronchiectasis
- Multicentric
- Cohort – 238, separate control of 149 patients of allergic rhinitis
- Study period – March 2016 and July 2017
- Tested sensitization for specific allergens i.e. house dust mite (Dermatophagoides pteronyssinus and Blomia tropicalis) and Aspergillus fumigatus

Lim et al Am J Respir Crit Care Med Vol 199, 2019


Class
1500
150
100
50
5
1
0.35
0
sIgE (kU/L)
6 Very high
5 Very high
4 Very high
3 High
2 Moderate
1 Low
0 Non-detectable
Cut off 3.5kU/L
Cut off 0.35kU/L
AR B AR B AR B AR B AR B AR B AR B AR B AR B
Der p Blo t Alt a f 1 f 2 f 6 f 8 f 15 f 17
Major
Minor
HDM
Alternaria
rAsp allergen


*
BSI
20
15
10
5
0
0
1
2
≥3
No. of allergens
*
*
FEV1 %predicted
125
100
75
50
25
0
1
2
≥3
No. of allergens
ns
Exacerbations
12
10
8
6
4
2
0
0
1
2
≥3
No. of allergens
ND to moderate (Class 0–2)
High to very high (Class 3–4)
Very high (Class 5–6)


B
**
20
15
10
5
0
BSI
FDPI
HDCD
C
*
125
100
75
50
25
FEV1 %predicted
FDPI
HDCD
D
ns
10
8
6
4
2
0
Exacerbations
FDPI
HDCD

CONCLUSION

- Each immunoallertype was defined by unique sensitization pattern and immune profile
- Patients in fungal driven proinflammatory (FDPI) group showed marked response to fungal allergen Alt a and rAsp coupled by proinflammatory profile – elevated airway TNF-alpha, IL-1 alpha and IL-1 beta

CONCLUSION

- Patients in HDM-driven, chemokine dominant (HDCD) accompanied by chemokine dominant response i.e. high CXCL1, CCL11 and CCL2
- FDPI immunoallertype has worse disease and poorer lung function but frequent exacerbators were equally observed in both groups
- The proinflammatory cytokines trigger release of ICAM-1 and VCAM-1 from endothelium leading to neutrophil and eosinophil airway recruitment. After cell recruitment, increased airway smooth muscle contractility and hyperresponsiveness can explain the poorer lung function
-

CONCLUSION

• THERAPEUTIC IMPLICATION:

- Targeted therapy for Th2 cytokine response including anti-inflammatories, corticosteroids or anti-Th2 cytokine

- Consideration to antifungal treatment

ORIGINAL ARTICLE

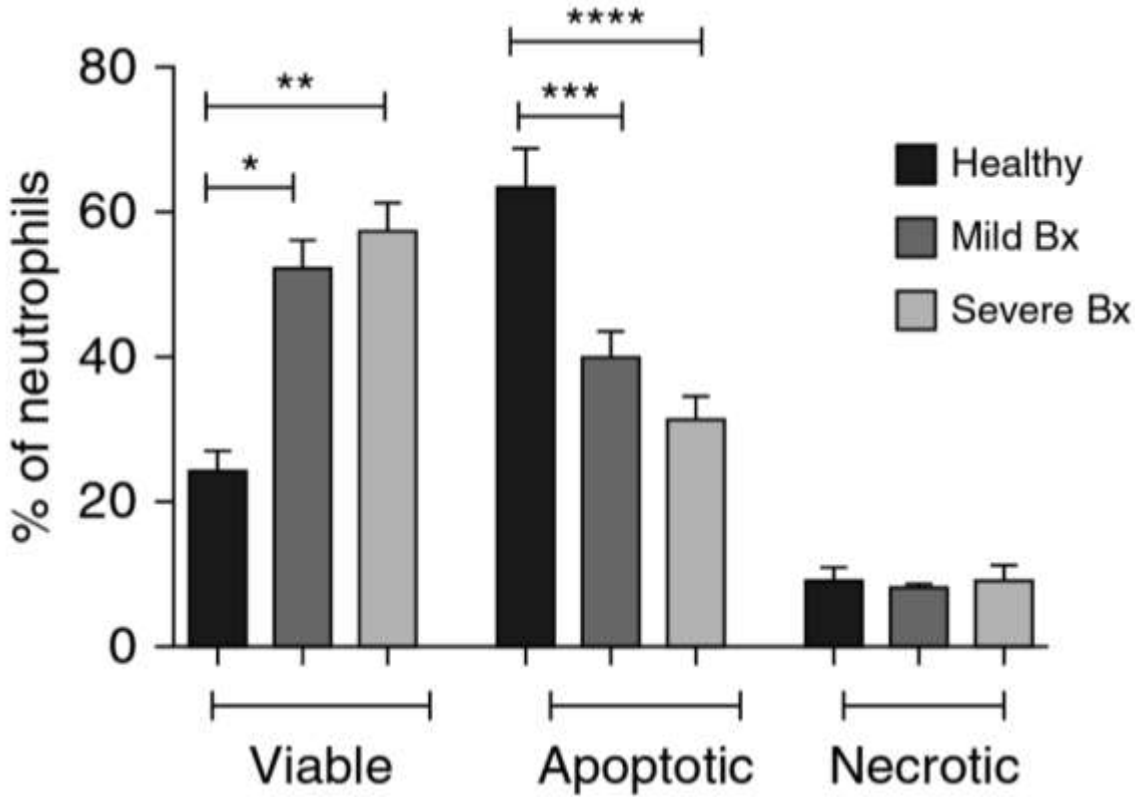
Blood Neutrophils Are Reprogrammed in Bronchiectasis

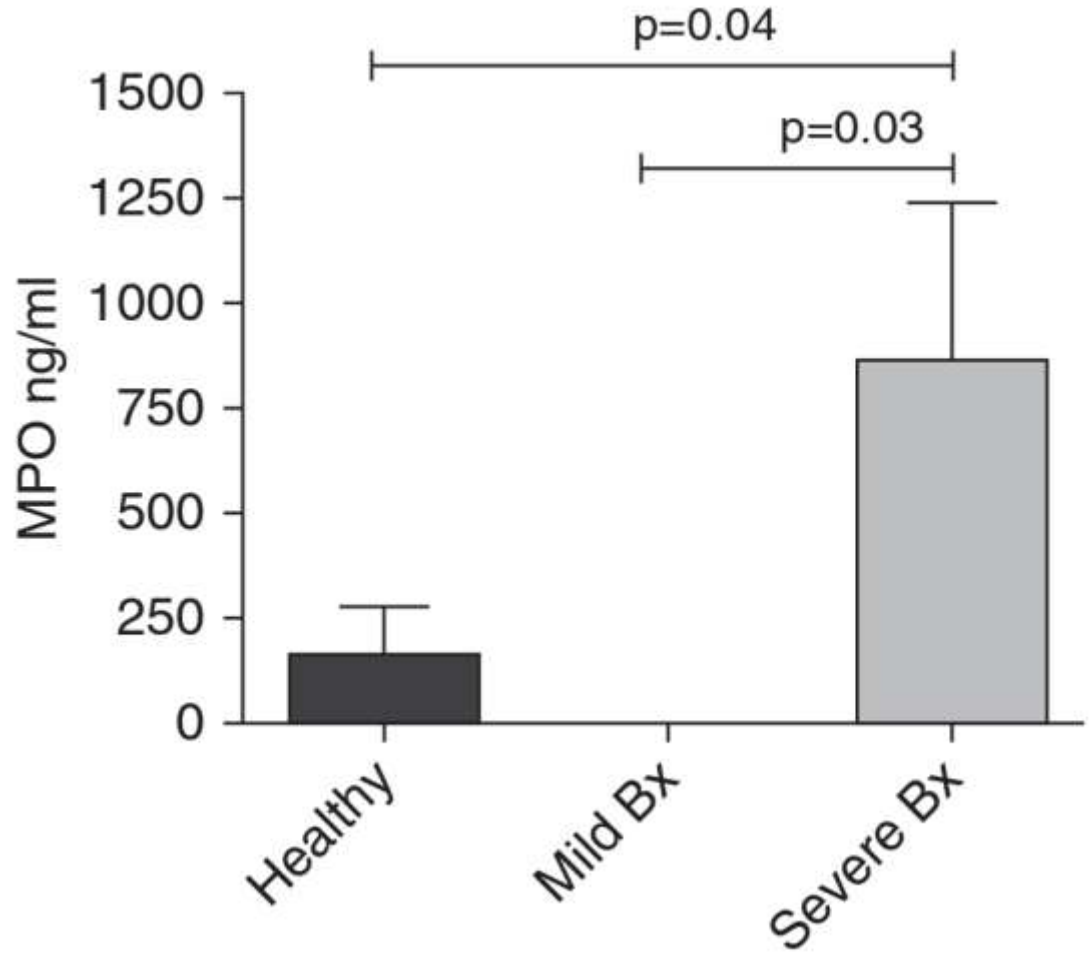
Pallavi Bedi[1], Donald J. Davidson[1], Brian J. McHugh[1], Adriano G. Rossi[1], and Adam T. Hill[1,2]

Methods: Included were 3 groups: 8 healthy volunteers, 8 patients with mild bronchiectasis and 8 patients with severe bronchiectasis

Eight patients with severe exacerbation were compared with 6 patients with community acquired pneumonia at start and end of exacerbation

Bedi et al. Am J Resp Crit Care Med Vol 198, 2018


80
60
40
20
0
% of neutrophils
*
**
***
****
Healthy
Mild Bx
Severe Bx
Viable
Apoptotic
Necrotic


p=0.04
p=0.03
1500
1250
1000
750
500
250
0
MPO ng/ml
Healthy
Mild Bx
Severe Bx

CONCLUSION

- In stable bronchiectasis compared with healthy volunteers, blood neutrophils had significantly prolonged viability, delayed apoptosis, increased myeloperoxidase release and impaired neutrophil phagocytosis and killing of *P.aeruginosa*

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

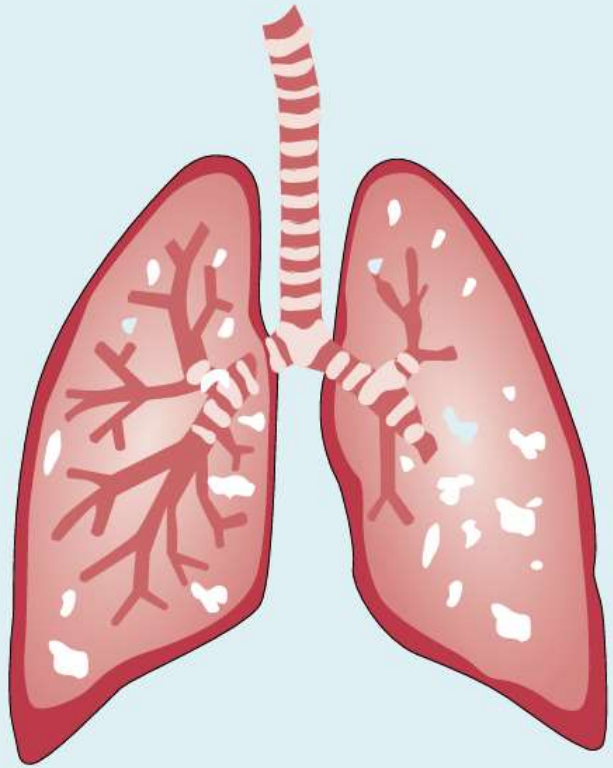
Sputum production
- Airway clearance
- Mucoactive drugs

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

TAKE HOME MESSAGE

- Broader understanding regarding definitive phenotypes of bronchiectasis
- A dedicated attempt should be made to have aetiological diagnosis as it can change the management
- Attempt should be made to control exacerbations as it is associated with worse prognosis