NTM & Bronchiectasis Physician/Patient Conference

Patient Phenotype - Bronchiectasis

NTM Info & Research (NTM ir)
Gaylord Texas Resort & Convention Center
Grapevine, TX

17 May 2019

TR Aksamit
Pulmonary Disease and Critical Care Medicine
Mayo Clinic
Rochester, MN USA

Patient Phenotype: Bronchiectasis

DISCLOSURE
(TR Aksamit)

Relevant Financial Relationship(s)
None

Chair: Bronchiectasis Research Registry
Research clinical study activity:
- **Bronchiectasis Research Registry**
- **Bayer, Cipro DPI, Global PI**
- **Aradigm/Grifols, Cipro liposomal**
- **Insmed, inhaled liposomal amikacin**
- **Zambon, inhaled colistin**
- **Astrazeneca**
- **Electromed, HillRom, RespiTech**

No personal funding or research support:
- **All funding directly made to the Mayo Foundation for Medical Research and Education**

Patient Phenotype: Bronchiectasis

- Background
- Phenotypes / endotypes
- Summary

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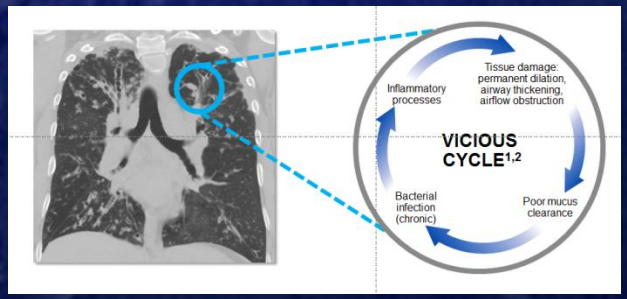
Inhaled Antibiotics for Bronchiectasis (NCFB – Non-cystic fibrosis bronchiectasis)

FDA approved inhaled antibiotics for NCFB bronchiectasis – 2019:

1.
2.
3.
4.
5.

Patient Phenotype: Bronchiectasis
Non-Cystic Fibrosis Bronchiectasis (NFCB)

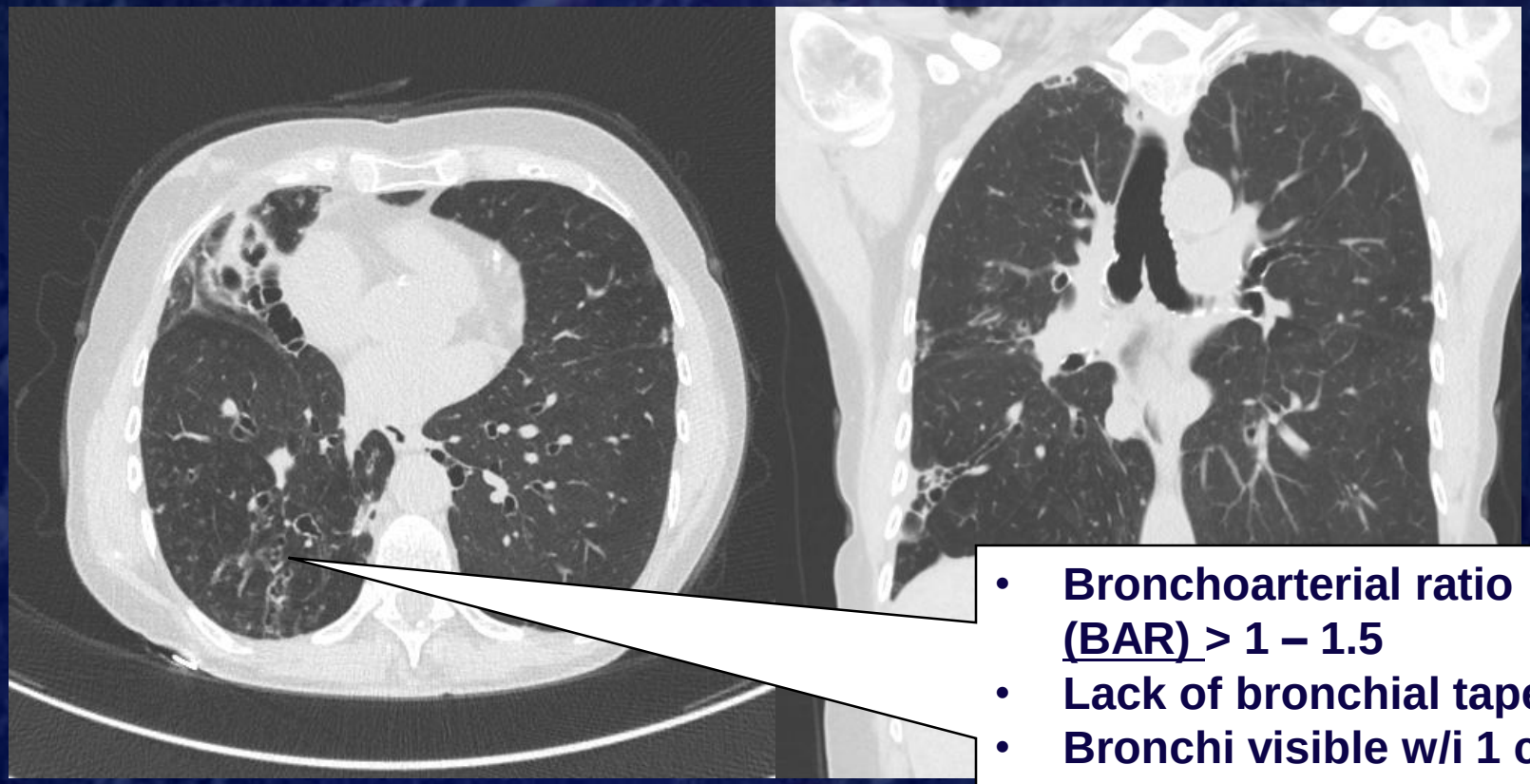
- **Bronchiectasis**
  - Abnormal, usually permanent dilation of the bronchial tubes
  - Impaired mucociliary clearance
  - Retention of secretions
  - Recurrent infection, inflammation and further airway damage



Courtesy: CT of the chest with coronal image, Dr. P.J. McShane; marking: mucus plug and dilated airways.

Eur Respir Dis 69: 6, 1986
Int J Chron Obstruct Pulm Dis 4: 411, 2009

Patient Phenotype: Bronchiectasis

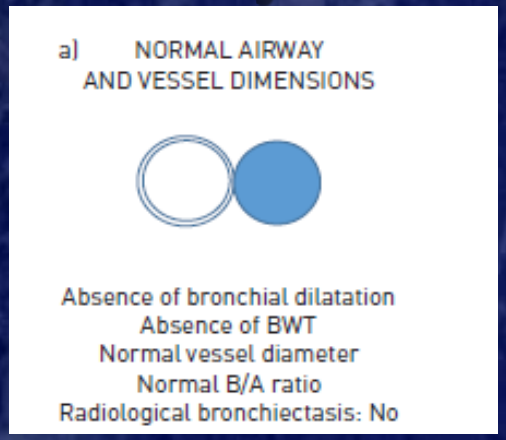


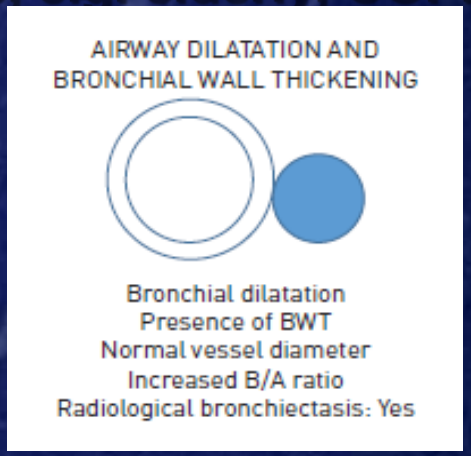
- Bronchoarterial ratio (BAR) > 1 – 1.5
- Lack of bronchial tapering
- Bronchi visible w/i 1 cm pleura

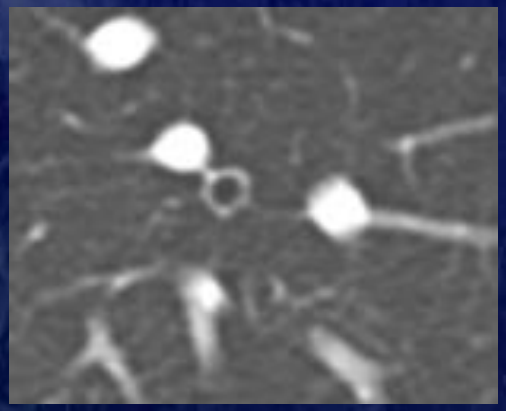
- Bronchial wall thickening
- Mucous plugging

Patient Phenotype: Bronchiectasis

- **Increased bronchoarterial ratio:**
  - Diameter of bronchus compared to adjacent artery (inner versus outer wall)
  - Normal may be between 1 and 1.5, e.g. elderly, COPD

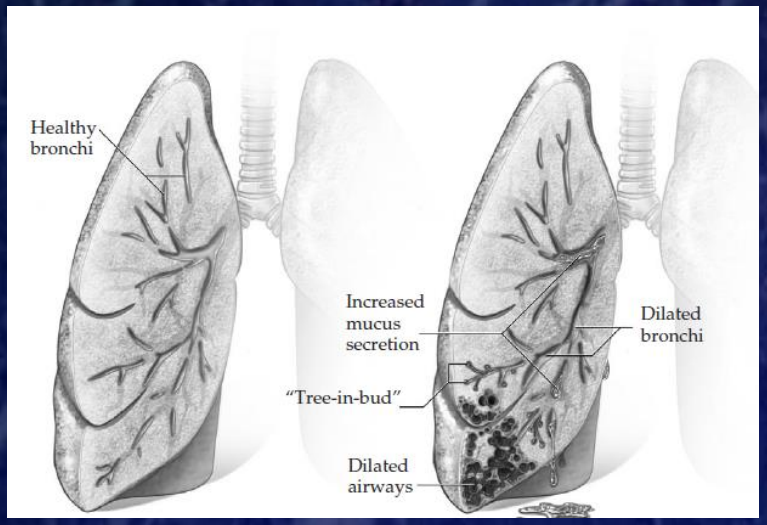


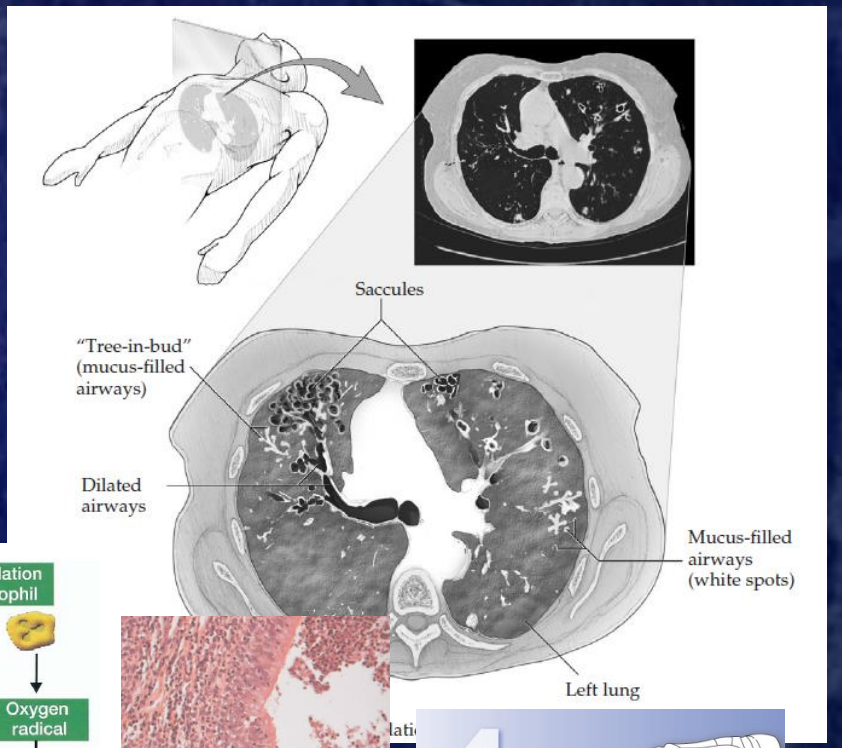


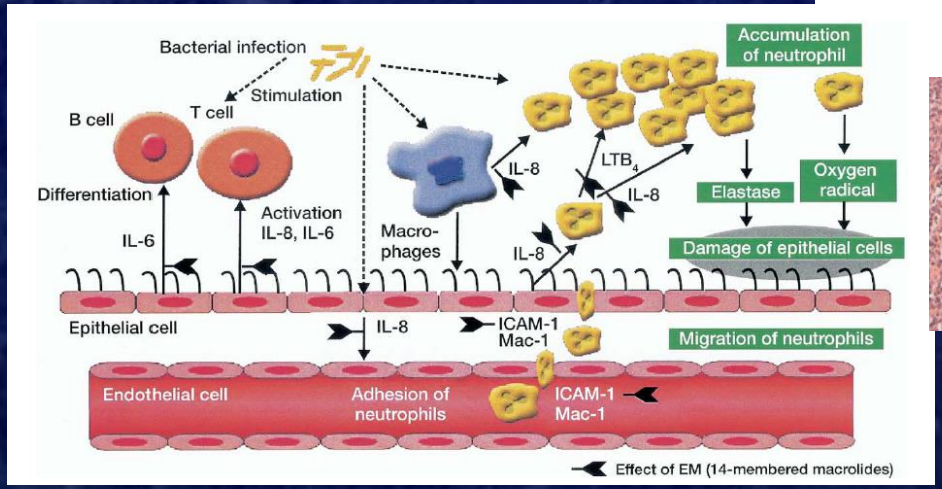


Polverino et al Eur Respir J 52: 1800328, 2018

Patient Phenotype: Bronchiectasis







Am J Med 117: 5S, 2004
ATS Breathing in America 2010
Eur Respir Mono 52, 22, 2011
AJRCCM 199: 842, 2019

Patient Phenotype: Bronchiectasis

Microbiome:

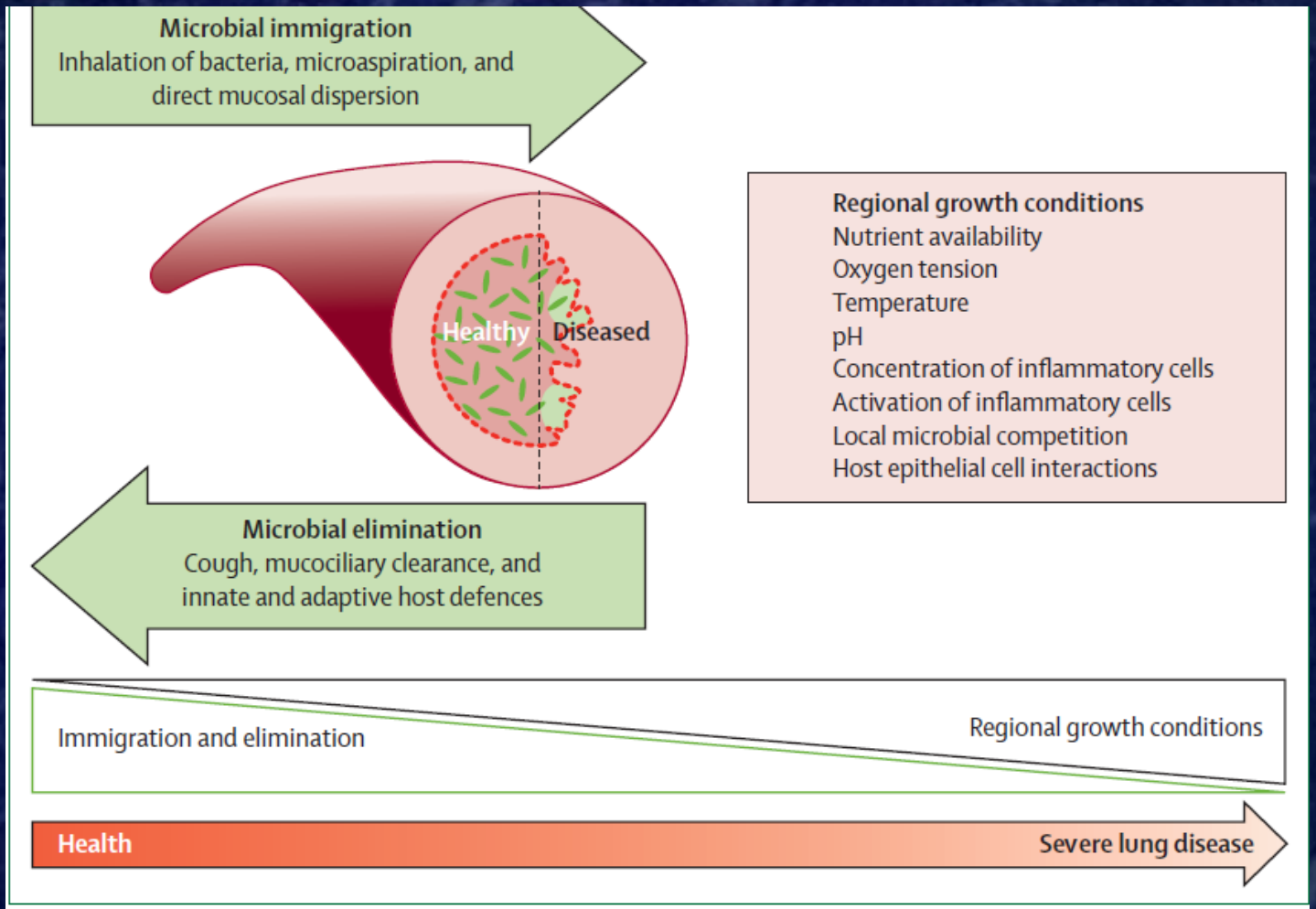
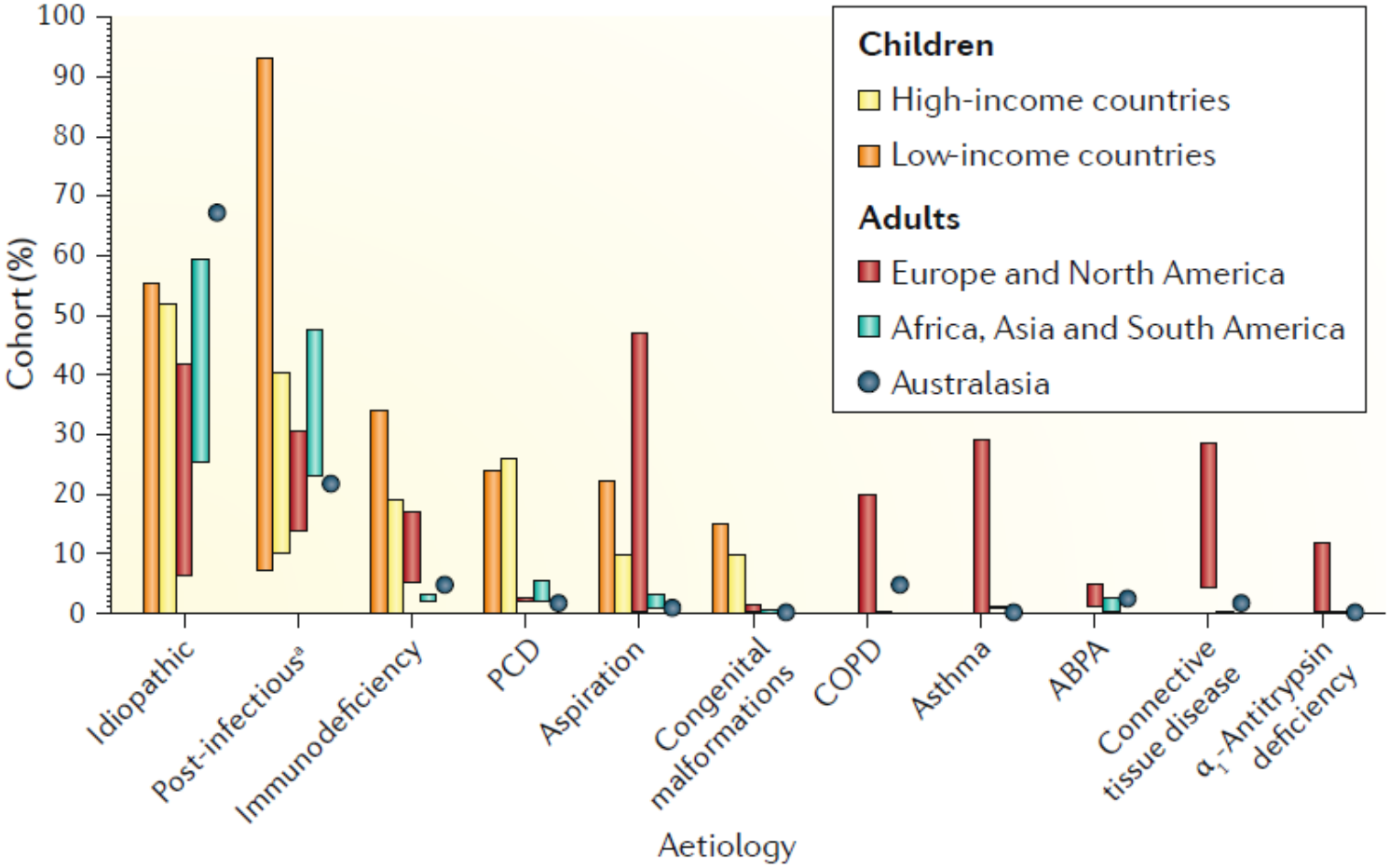


Figure 1: Determinants of the respiratory microbiome

Lancet 384: 691, 2014

Patient Phenotype: Bronchiectasis

Etiology and Associations



Chalmers, et al Nat Rev 4: 45, 2018

Patient Phenotype: Bronchiectasis

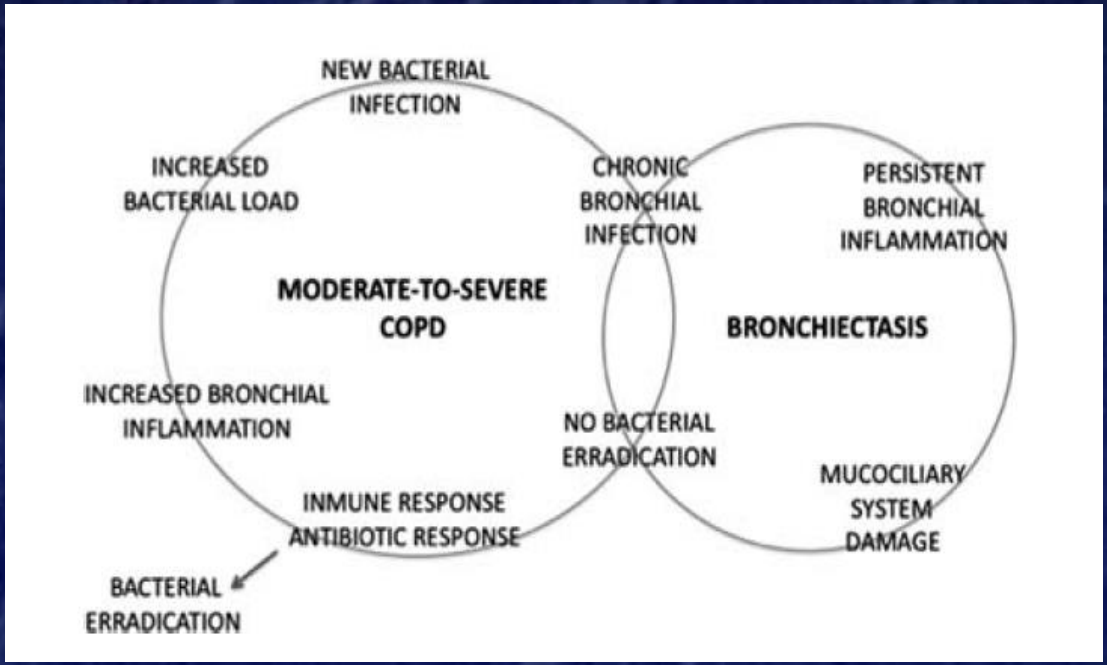
Bronchiectasis and Chronic Airway Disease

It Is Not Just About Asthma and COPD

Miguel Angel Martinez-Garcia, MD
Valencia, Spain
Eva Polverino, MD
Barcelona, Spain
Timothy Aksamit, MD, FCCP
Rochester, MN

Chest 154: 738, 2018

Patient Phenotype: Bronchiectasis



Bronchiectasis overlap with COPD and asthma: (SEVERE)

- **COPD: 8% - 58%**
- **Asthma: 12% - 68%**

Clin Pulm Med 22: 123, 2015
ERJ 52: 1800328, 2018
CHEST 154: 737, 2018

Patient Phenotype: Bronchiectasis

[Original Research **Bronchiectasis**]

CHEST

Adult Patients With Bronchiectasis

A First Look at the US Bronchiectasis Research Registry

CrossMark

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

BRONCHIECTASIS AND NTM RESEARCH REGISTRY
A COPD Foundation Initiative

CHEST 151: 982, 2017

Patient Phenotype: Bronchiectasis

Demographics

TABLE 1 Demographics and Clinical Characteristics of Patients With Bronchiectasis[a]

Characteristic	Data Available (No.)	Overall (N = 1,826)	NTM (n = 1,158)	No NTM (n = 668)	*P* Value[b]
Sex, No. (%)	1,826				
Female		1,439 (79)	964 (83)	475 (71)	< .01
Age, mean ± SD, y	1,823	64 ± 14	66 ± 12	61 ± 17	< .01
Age at diagnosis, mean ± SD, y	1,456	57 ± 17	59 ± 15	53 ± 19	< .01
Race/ethnicity, No. (%)	1,709				
Non-Hispanic white		1,514 (89)	1,003 (91)	511 (85)	< .01
Non-Hispanic black		34 (2)	7 (1)	27 (4)	
Hispanic		73 (4)	41 (4)	32 (5)	
Asian		60 (4)	41 (4)		
Other		28 (2)	16 (1)		
Primary insurance, No. (%)	1,684				
Commercial		794 (47)	504 (48)		
Medicaid and other state programs		49 (3)	24 (2)		
Medicare		749 (44)	485 (46)		
No insurance		18 (1)	9 (1)		
Other (including Tricare)		74 (4)	29 (3)		
BMI, mean ± SD, kg/m^2	1,812	23.2 ± 5.7	22.5 ± 5.5		
q1, q3,		19.9, 25.1	19.7, 24.3		
Smoking, No. (%)	1,815				
Never		1,094 (60)	686 (60)		
Former		693 (38)	447 (39)		
Current		28 (2)	18 (2)		
Chest wall deformity, No. (%)	1,731				
None		1,657 (96)			
Pectus excavatum		[illegible]			
Other					
Otitis or rhinosinusitis, No. (%)	1,562				
Yes		388 (25)	222 (23)		
Comorbidities, No. (%)					
History of pne[illegible]	1,745	1,187 (68)	758 (69)	429 (67)	.45
COPD	1,778	350 (20)	217 (19)	133 (20)	.60
Asthma	1,783	515 (29)	298 (26)	217 (33)	< .01
GERD	1,789	841 (47)	577 (51)	264 (40)	< .01
Rheumatologic disease	1,775	142 (8)	87 (8)	55 (8)	.60
Chronic ulcerative colitis or Crohn's disease	1,795	47 (3)	26 (2)	21 (3)	.25
Primary immunodeficiency	1,776	89 (5)	44 (4)	45 (7)	< .01
Primary ciliary dyskinesia	1,791	52 (3)	20 (2)	32 (5)	< .01
Prior tuberculosis, No. (%)	1,781				
Yes		70 (4)	50 (4)	20 (3)	.14

- **Age avg: 64**
- **Female: 79%**
- **Non-Hispanic white: 89%**
- **Smokers**
  - Never 60%
  - Former 38%
- **Any obstruction (PFT): 51%**
  - Mild-mod: 36%
  - Severe-v. sev: 15%

COPD 20%

BRONCHIECTASIS AND NTM RESEARCH REGISTRY
A COPD Foundation Initiative

Chest 151: 982, 2017

MAYO CLINIC

Patient Phenotype: Bronchiectasis

Characteristics and Health-care Utilization History of Patients With Bronchiectasis in US Medicare Enrollees With Prescription Drug Plans, 2006 to 2014

Emily Henkle, PhD, MPH; Benjamin Chan, MS; Jeffrey R. Curtis, MD, MPH; Timothy R. Aksamit, MD; Charles L. Daley, MD; and Kevin L. Winthrop, MD, MPH

2014, we identified patients ≥ 65 years of age with bronchiectasis by *International Classification of Diseases, Ninth Revision, Clinical Modification* claims (494.0 or 494.1) from a pulmonologist and no claim for cystic fibrosis. We calculated the prevalence from 2012 to 2014. Incident or newly diagnosed patients were those enrolled in Medicare at least 12 months prior to the first bronchiectasis diagnosis. We described clinical and health-care utilization characteristics for this cohort during the prior 12-month (baseline) period, and explored di[illegible]ences between those with and without a COPD diagnosis.

[illegible]s with bro[illegible]eeting all eligibility criteria. The [illegible]r 100,000 persons. Newly diagnosed [illegible]men (65%), and predominately white, non- [illegible]were hospitalized for respiratory infections. Fifty- [illegible]. Newly diagnosed patients with bronchiectasis and [illegible]cteristics and utilization, for example were more likely [illegible]ing the baseline period (16% vs 7%) and to have a smoking [illegible]se without a dual COPD diagnosis, respectively.

[illegible]prevalence of bronchiectasis in the United States and [illegible]th bronchiectasis with and without COPD that should

- **40% of Medicare enrollees w/ drug plan**
- **252,362 patients with bronchiectasis**
- **Avg annual prevalence 701/100k**
  - **51% COPD**
  - **COPD + BR:**
    - **More hospitalizations 16% vs 7%**

CHEST doi: 10.1016/j.chest.2018.07.014

Patient Phenotype: Bronchiectasis

- Background
- Phenotypes / endotypes
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Patient Phenotype: Bronchiectasis

PHENOTYPE

- Identified by relevant and common (clinical) features of the disease

ENDOTYPE

- Defined by a distinct functional or pathobiological ("biology") mechanism
- Closely related to GENOTYPE (genetics)

Flume et al Lancet 392: 880, 2018

Patient Phenotype: Bronchiectasis

Clinical phenotypes in adult patients with bronchiectasis

Stefano Aliberti[1], Sara Lonni[1], Simone Dore[2], Melissa J. McDonnell[3], Pieter C. Goeminne[4,5], Katerina Dimakou[6], Thomas C. Fardon[7], Robert Rutherford[3], Alberto Pesci[1], Marcos I. Restrepo[8], Giovanni Sotgiu[2] and James D. Chalmers[7]

Eur Respir J 47: 1113, 2016

Patient Phenotype: Bronchiectasis

Clinical phenotypes in adult patients with bronchi

Stefano Aliber
Pieter C. Goen
Robert Ruther
James D. Chal

...jiu[2] and

TABLE 2 Baseline characteristics in the four clusters

	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·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)		
FACED score	4 (2–5)	2 (1–3)	2 (1–3)		
Radiological status					
Reiff score			2 (2–6)		
Clinical status					
Daily cough	170 (95)				
Daily sputum	166 (93)	2			
Prior history of haemoptysis	42 (24)	36 (13)			
MRC breathlessness scale	3 (2–5)	2 (1–3)			
Long-term oxygen therapy	34 (19)	14 (5.1)	36 (9.7)		
Exacerbations in the previous year	3 (2–4)	2 (1–3)	2 (1–3)		
At least one hospitalisation in the previous year	109 (61)	63 (23)	90 (24)		
Functional status					
FEV1 % predicted	59 (46–78)	71 (55–93)	77 (57–95)		
Microbiology					
Chronic infection with *Pseudomonas aeruginosa*	179 (100)	0 (0)	0 (0)		
Chronic infection with other pathogens	0 (0)	273 (100)	0 (0)		
Laboratory findings					
C-reactive protein mg·L^{-1}	10.7 (4.0–36.0)	5.0 (3.7–9.0)	4.5 (2.0–7.7		
Long-term antibiotic treatment					
Either macrolide or inhaled antibiotics	120 (67)	105 (39)	122 (33)		
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

Data are presented as n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; CCI: Charlson Comorbidity Index; BSI: Bronchiectasis Severity Index; MRC: Medical Research Council; FEV1: forced expiratory volume in 1 s.

- **Demographics**
- **Comorbidities**
- **Disease severity**
- **Radiologic status**
- **Clinical status**
- **Functional status**
- **Microbiology**
- **Laboratory findings**
- **Long-term antibiotic treatment**

Eur Respir J 47: 1113, 2016

Patient Phenotype: Bronchiectasis

Clinical phenotypes in adult patients with bronchi

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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
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Functional status					
FEV_1 % predicted	59 (46–78)	71 (55–93)	77 (57–95)	84 (68–101)	0.0001
Microbiology					
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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
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Eur Respir J 47: 1113, 2016

Patient Phenotype: Bronchiectasis

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Eur Respir J 47: 1113, 2016

Patient Phenotype: Bronchiectasis

Clinical phenotypes in adult patients with bronchi

TABLE 2 Baseline characteristics in the four clusters

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TABLE 3 Aetiology of bronchiectasis in the four clusters

	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)	
Idiopathic	46 (26)	86 (33)	131 (36)	110 (36)	0.09
Post-infective	63 (36)	54 (21)	96 (26)	77 (25)	0.004
COPD	21 (12)	29 (11)	50 (14)	20 (6.6)	0.03
Connective tissue disease	10 (5.6)	26 (9.8)	26 (7.1)	27 (8.9)	0.377
Immunodeficiency	11 (6.2)	17 (6.4)	14 (3.8)	14 (4.6)	0.436
ABPA	10 (5.6)	20 (7.6)	12 (3.3)	12 (3.9)	0.083
Asthma	2 (1.1)	10 (3.8)	8 (2.2)	15 (4.9)	0.071
Inflammatory bowel disease	3 (1.7)	6 (2.3)	12 (3.3)	3 (1)	0.233
Ciliary dysfunction	7 (4)	6 (2.3)	5 (1.4)	2 (0.7)	0.055
Aspiration	2 (1.1)	6 (1.9)	3 (0.8)	3 (1)	0.419
α_1-antitrypsin deficiency	0 (0)	1 (0.4)	3 (0.8)	6 (2)	0.091
Congenital	0 (0)	2 (0.8)	3 (0.8)	0 (0)	0.284
Other	2 (1.1)	1 (0.4)	2 (0.5)	15 (4.9)	<0.001
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

Data are presented as n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; CCI: Charlson Comorbidity Index; BSI: Bronchiectasis Severity Index; MRC: Medical Research Council; FEV1: forced expiratory volume in 1 s.

Eur Respir J 47: 1113, 2016

Patient Phenotype: Bronchiectasis

Flume et al Lancet 392: 880, 2018

Patient Phenotype: Bronchiectasis

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Patrick A Flume, James D C

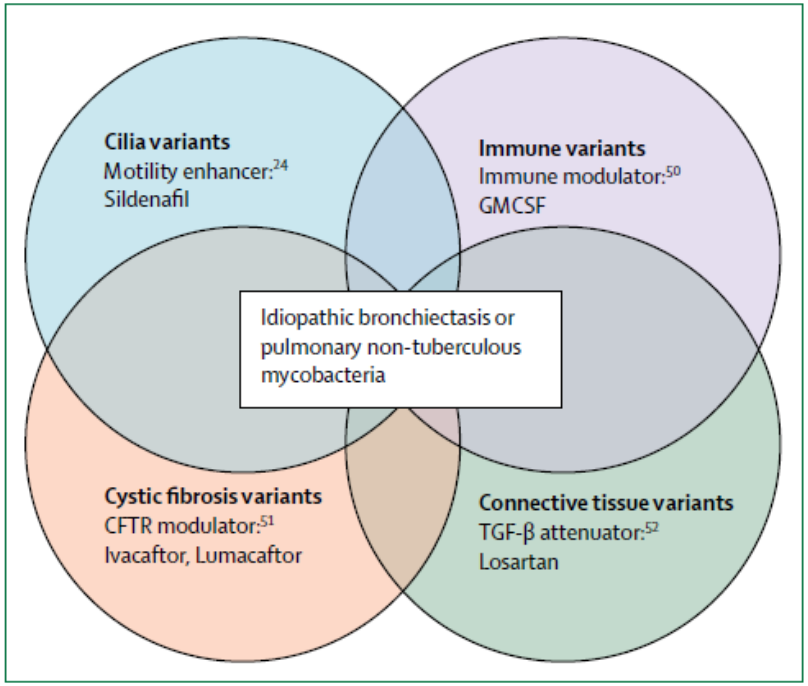

Figure 4: **Potential endotypes for patients with idiopathic bronchiectasis with pulmonary non-tuberculous mycobacteria infections**
Characterisation with biomarker measurements of sweat chloride, nasal nitric oxide, ciliary beat frequency, and body morphometrics coupled with the presence of relevant genetic variants could allow therapeutic targeting on the basis of the predominant endotype. CFTR=cystic fibrosis transmembrane conductance regulators. GMCSF=granulocyte-macrophage colony-stimulating factor. TGF-β=transforming growth factor-β.

MAYO CLINIC

Flume et al Lancet 392: 880, 2018

Patient Phenotype: Bronchiectasis

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

REVIEW

Treatable Traits: a new paradigm for 21st century management of chronic airway diseases

Vanessa M. McDonald, James Fingleton, Alvar Agusti, Sarah A. Hiles, Vanessa L. Clark, Anne E. Holland, Guy B. Marks, Philip P. Bardin, Richard Beasley, Ian D. Pavord, Peter A. B. Wark, Peter G. Gibson

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Patient Phenotype: Bronchiectasis

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Eur Respir J 53: 1802058, 2019

Patient Phenotype: Bronchiectasis

Bronchiectasis: a case-based approach to investigation and management

Martina Contarini[1,2], Simon Finch[3] and James D. Chalmers[3]

Eur Respir J 27: 180016, 2018

Patient Phenotype: Bronchiectasis

Bronchiectasis: a case-based approach to ir

Category	Cause/notes	Clinical phenotype	Specific treatment
Post-infection	Viral, bacterial, fungal, mycobacteria (usually classified separately)	Past history of severe infection; classically unilobar bronchiectasis	No specific treatment
NTM	*M. avium* and *M. abscessus* most frequent	Middle-aged or elderly; females with low BMI; middle lobe and lingual nodular bronchiectasis; cavitation; tree-in-bud	Antibiotic treatment
Post-TB	*M. tuberculosis*	Upper lobe most frequently	No specific therapy
ABPA	Hypersensitivity to *A. fumigatus*	History of asthma (not universal); thick sputum; *S. aureus* in sputum; central bronchiectasis; fleeting infiltrates	Steroids±antifungals
COPD	Smoking, biomass exposure	Fixed airflow obstruction; smoking history; bilateral lower lobe; tubular bronchiectasis	No specific therapy
Asthma	Not universally accepted as a cause of bronchiectasis	Long history of asthma; frequent exacerbations; neutrophilic airway inflammation	Inhaled corticosteroids, biologics *e.g.* anti-IgE and anti-IL5
Aspiration/ inhalation	Foreign body aspiration, gastric contents aspiration, inhalation of corrosive substances	Lower lobe bronchiectasis	Speech and language therapy, fundoplication, removal of exacerbating drugs
Adult CF	CFTR mutations	Upper lobe bronchiectasis; *P. aeruginosa* or *S. aureus* in sputum; non-respiratory manifestations	Specialist multidisciplinary care in adult CF centres, recognition and treatment of non-respiratory manifestations, CFTR modulator/corrector therapy
Diffuse panbronchiolitis	Idiopathic inflammatory disease	Mostly patients of Far Eastern ethnic origin	Macrolide antibiotics

Eur Respir J 27: 180016, 2018

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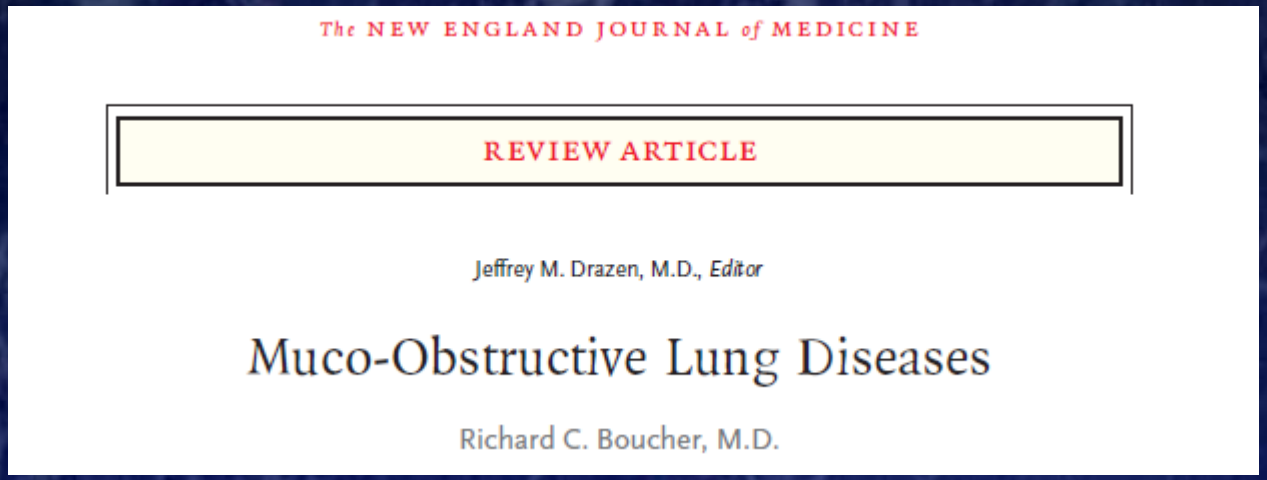
Eur Respir J 27: 180016, 2018

Patient Phenotype: Bronchiectasis



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

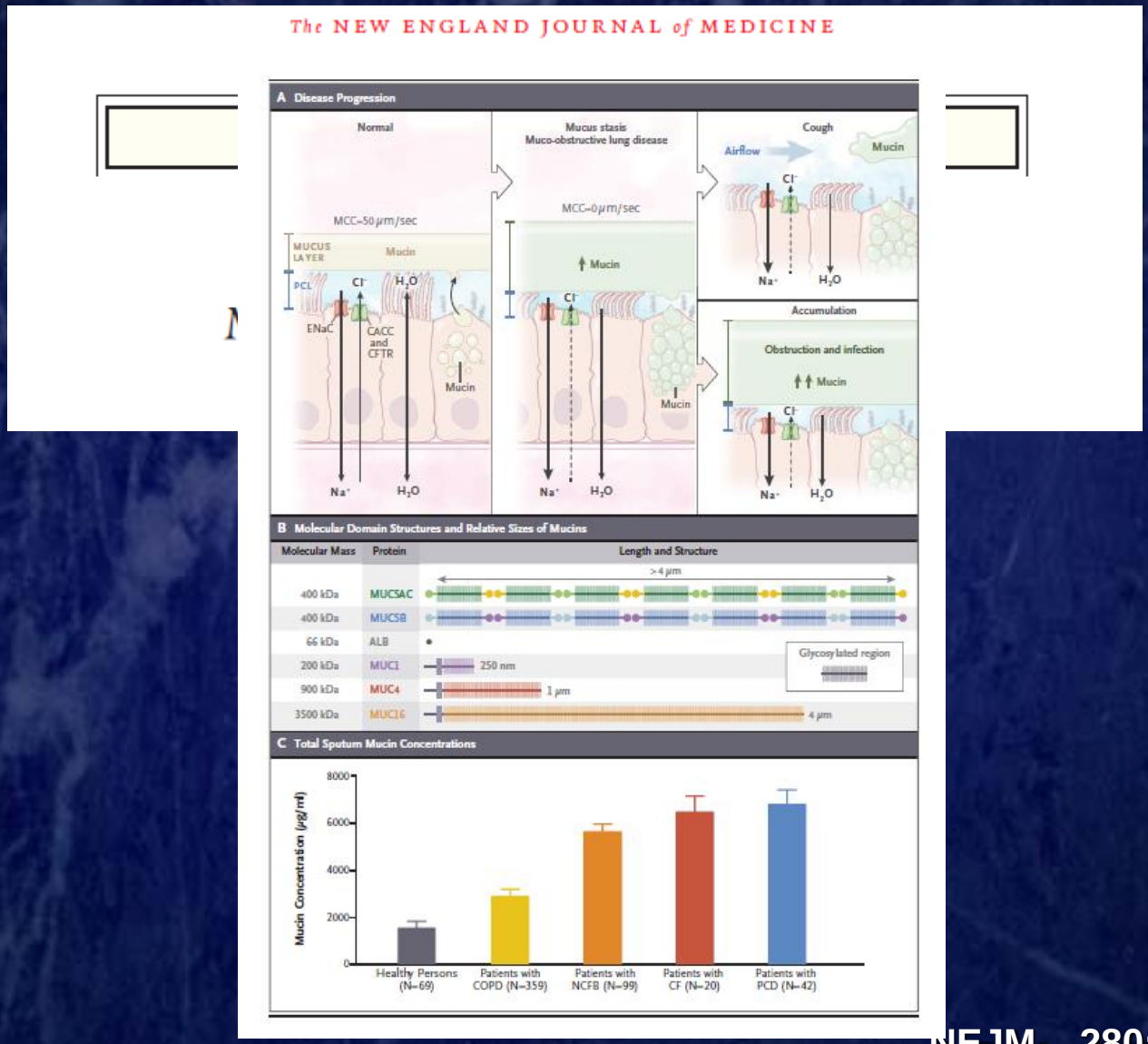
Jeffrey M. Drazen, M.D., *Editor*

Muco-Obstructive Lung Diseases

Richard C. Boucher, M.D.

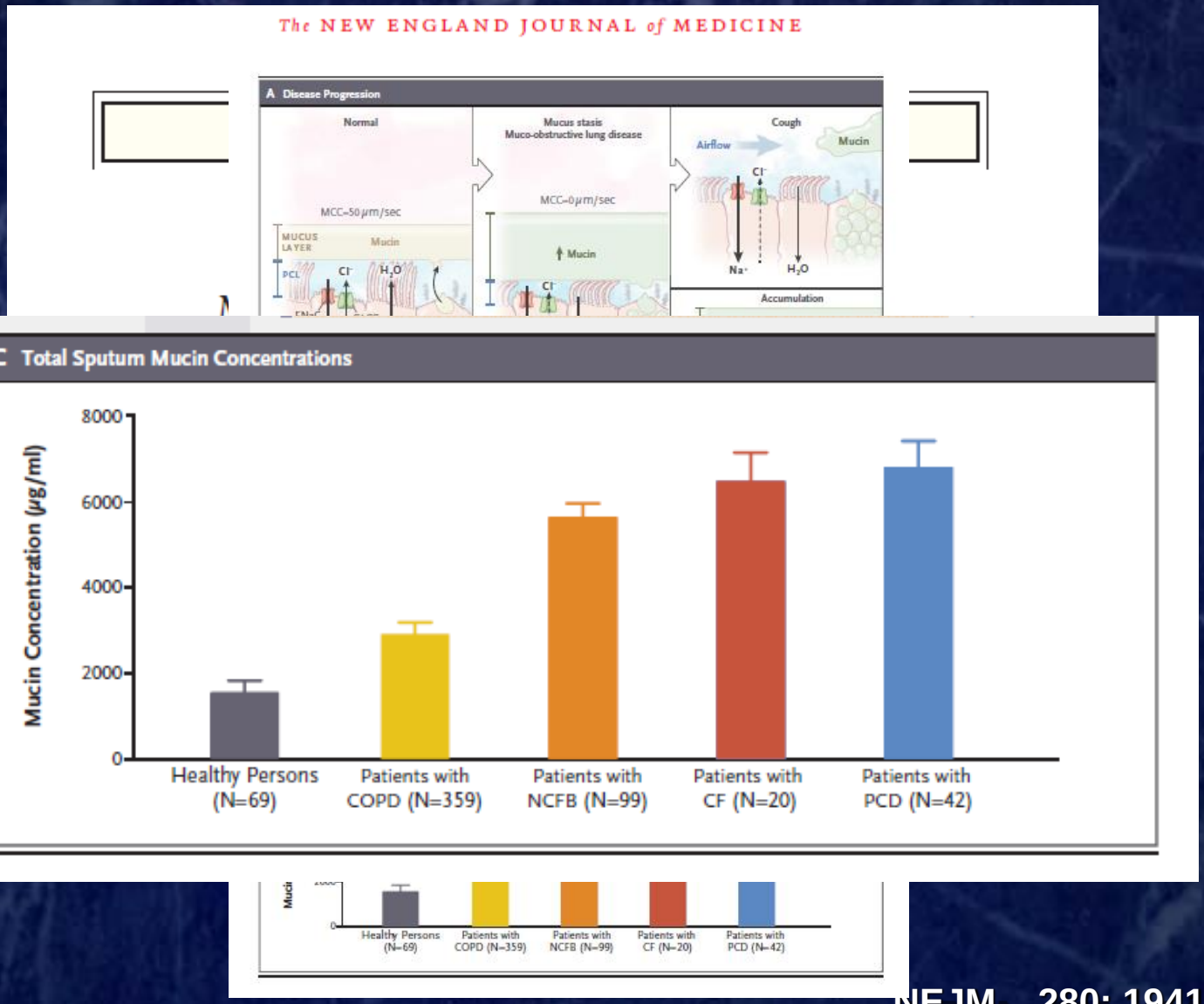
NEJM 280: 1941, 2019

Patient Phenotype: Bronchiectasis



NEJM 280: 1941, 2019

Patient Phenotype: Bronchiectasis



NEJM 280: 1941, 2019

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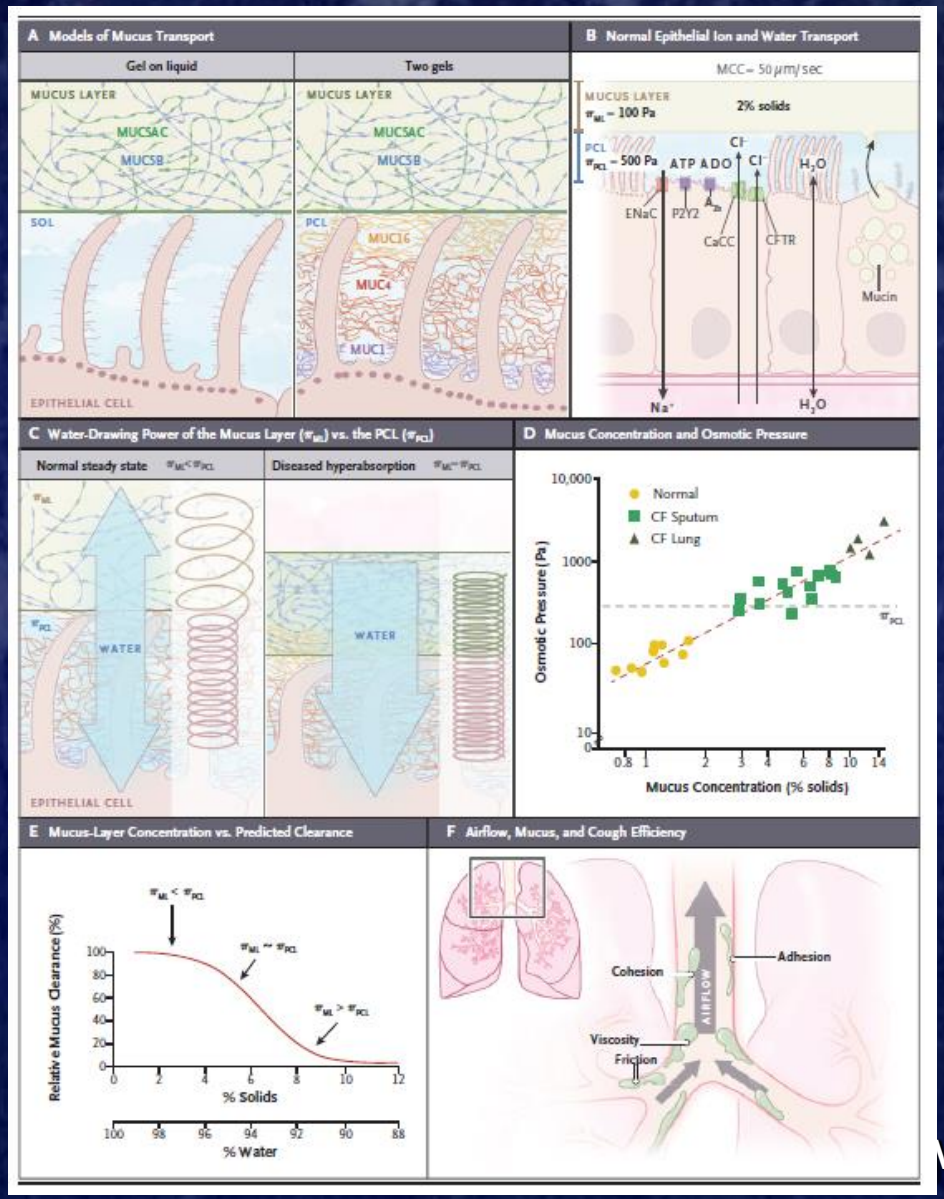
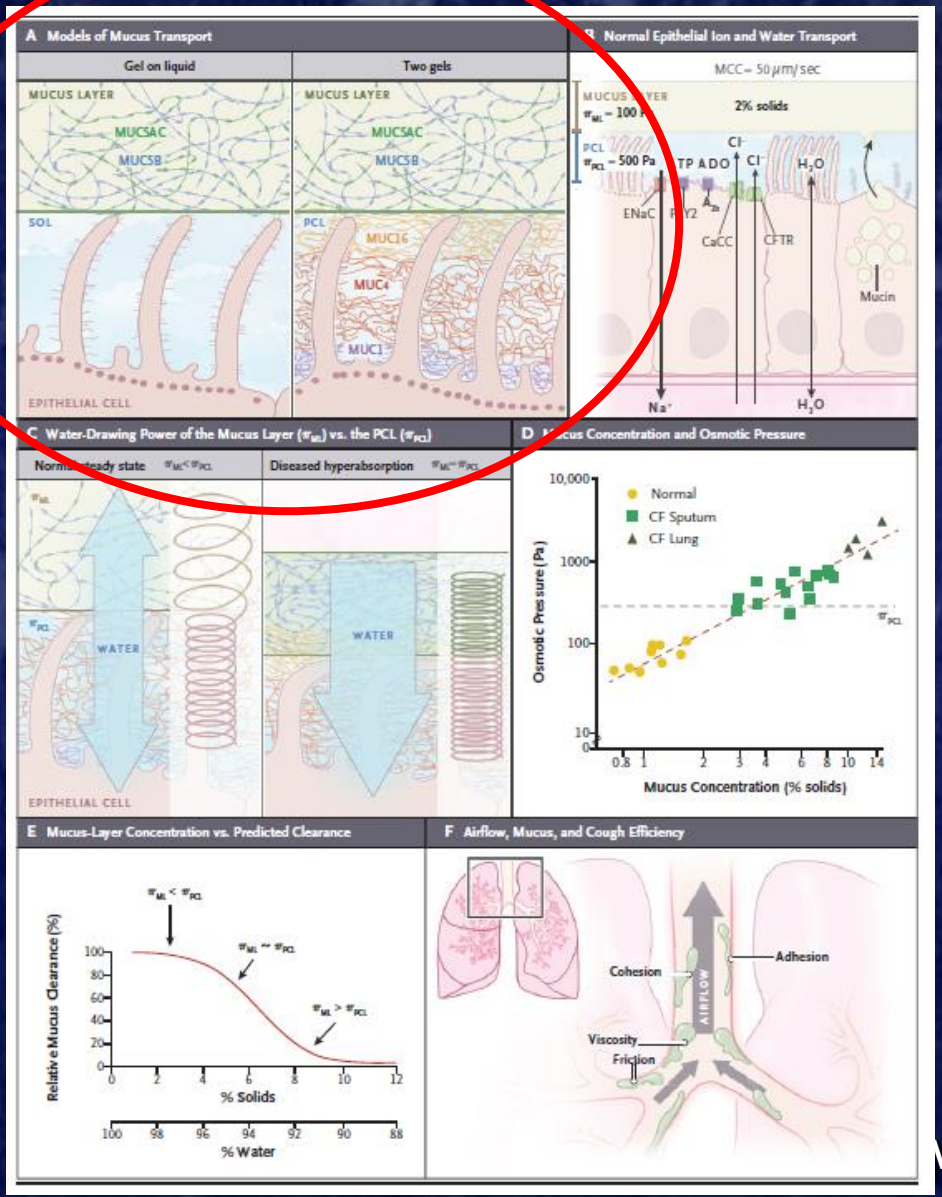


M 280: 1941, 2019

Patient Phenotype: Bronchiectasis



M 280: 1941, 2019

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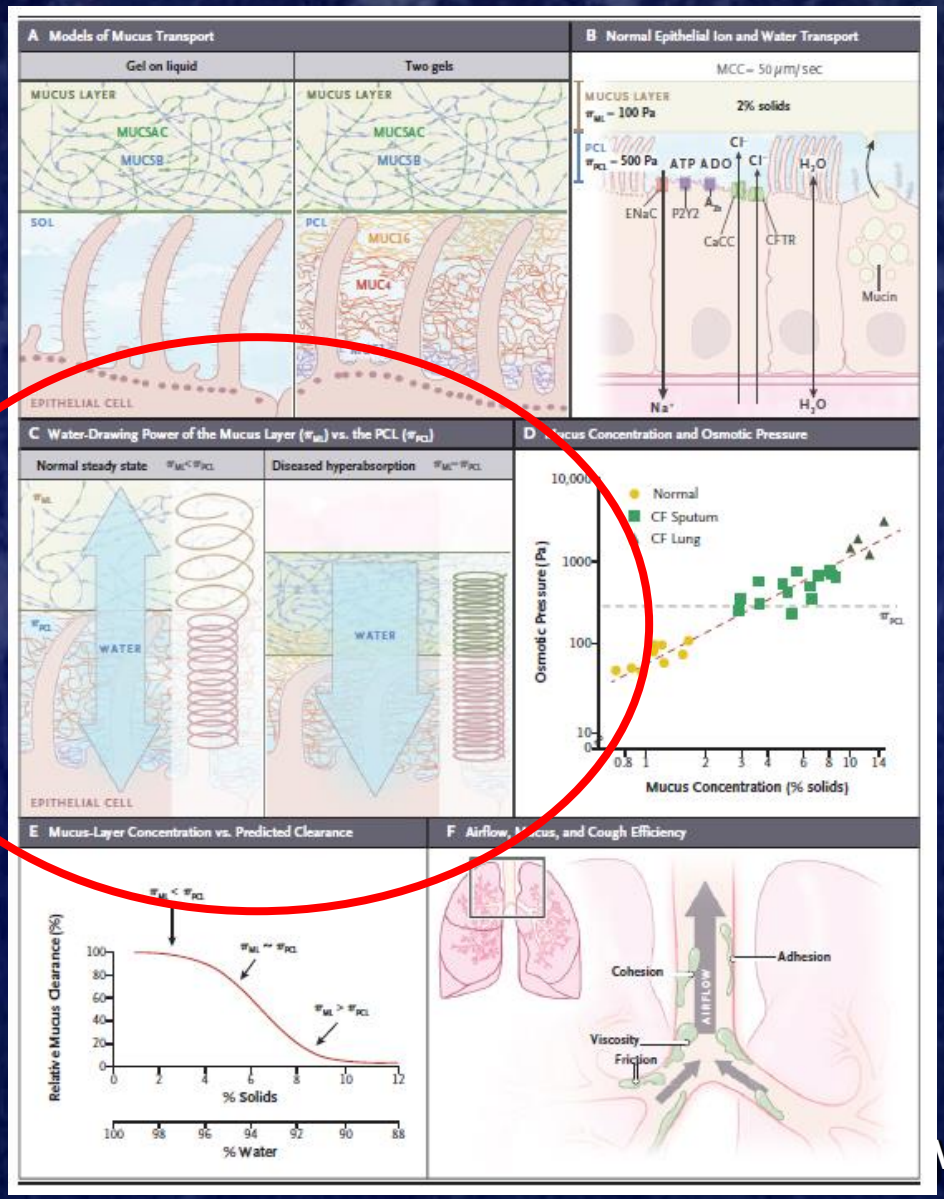
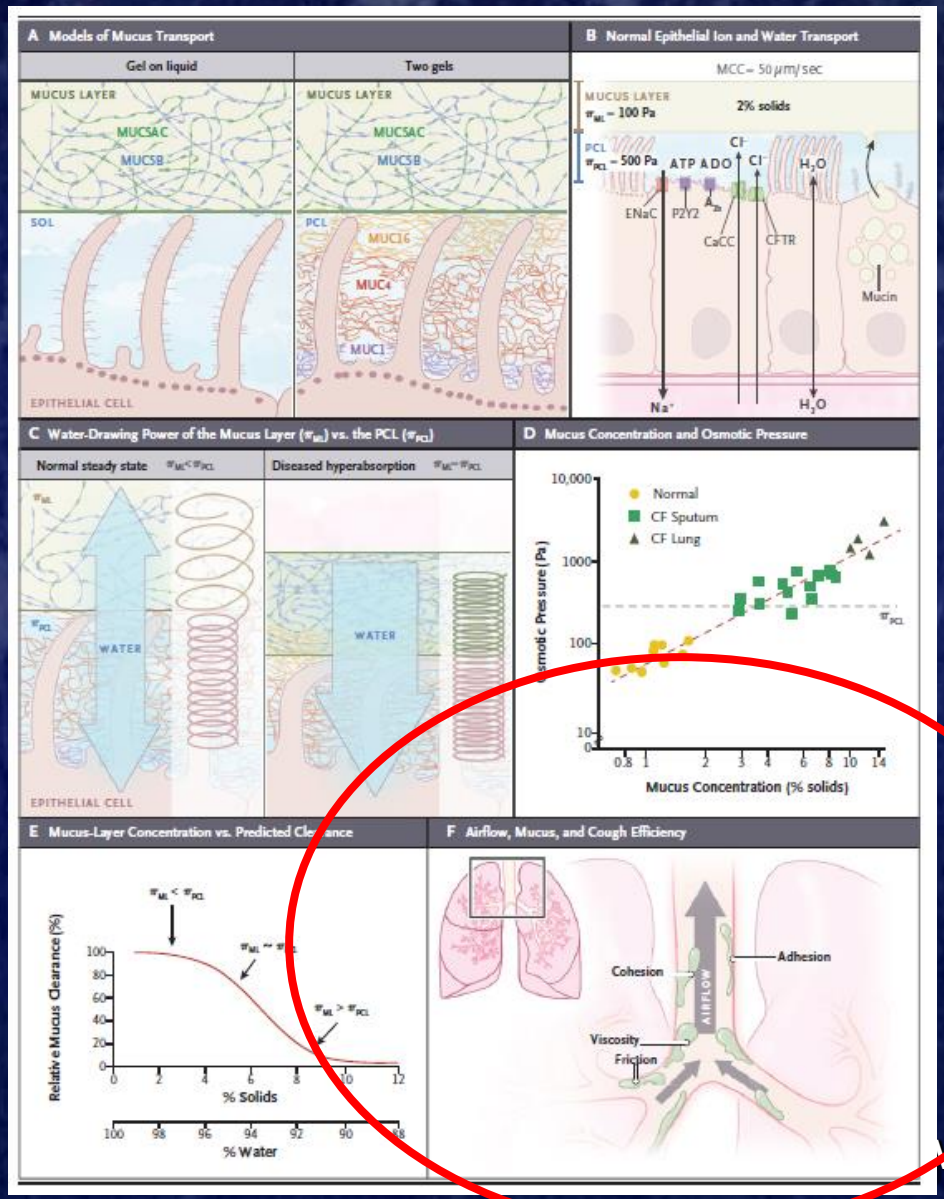


M 280: 1941, 2019

Patient Phenotype: Bronchiectasis



280: 1941, 2019

Patient Phenotype: Bronchiectasis

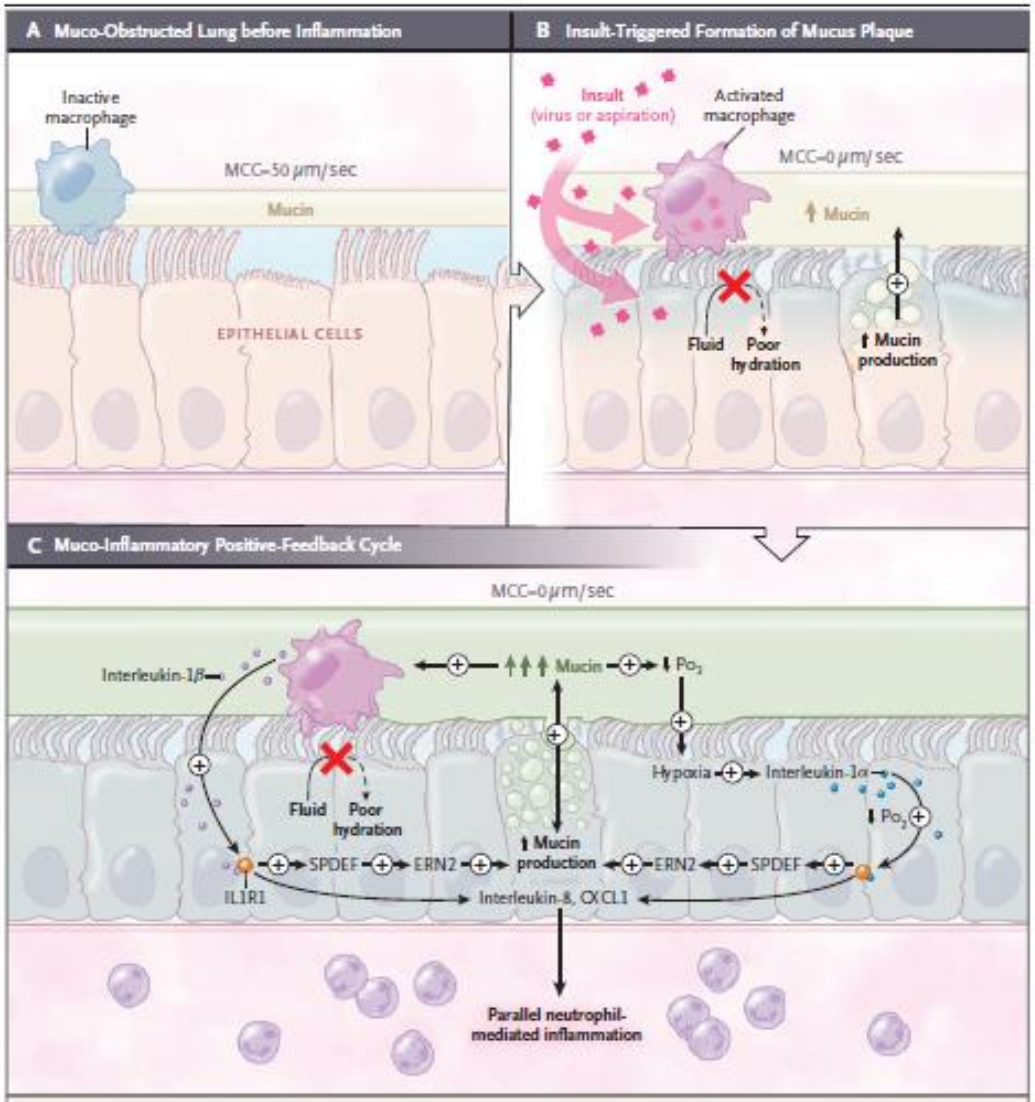
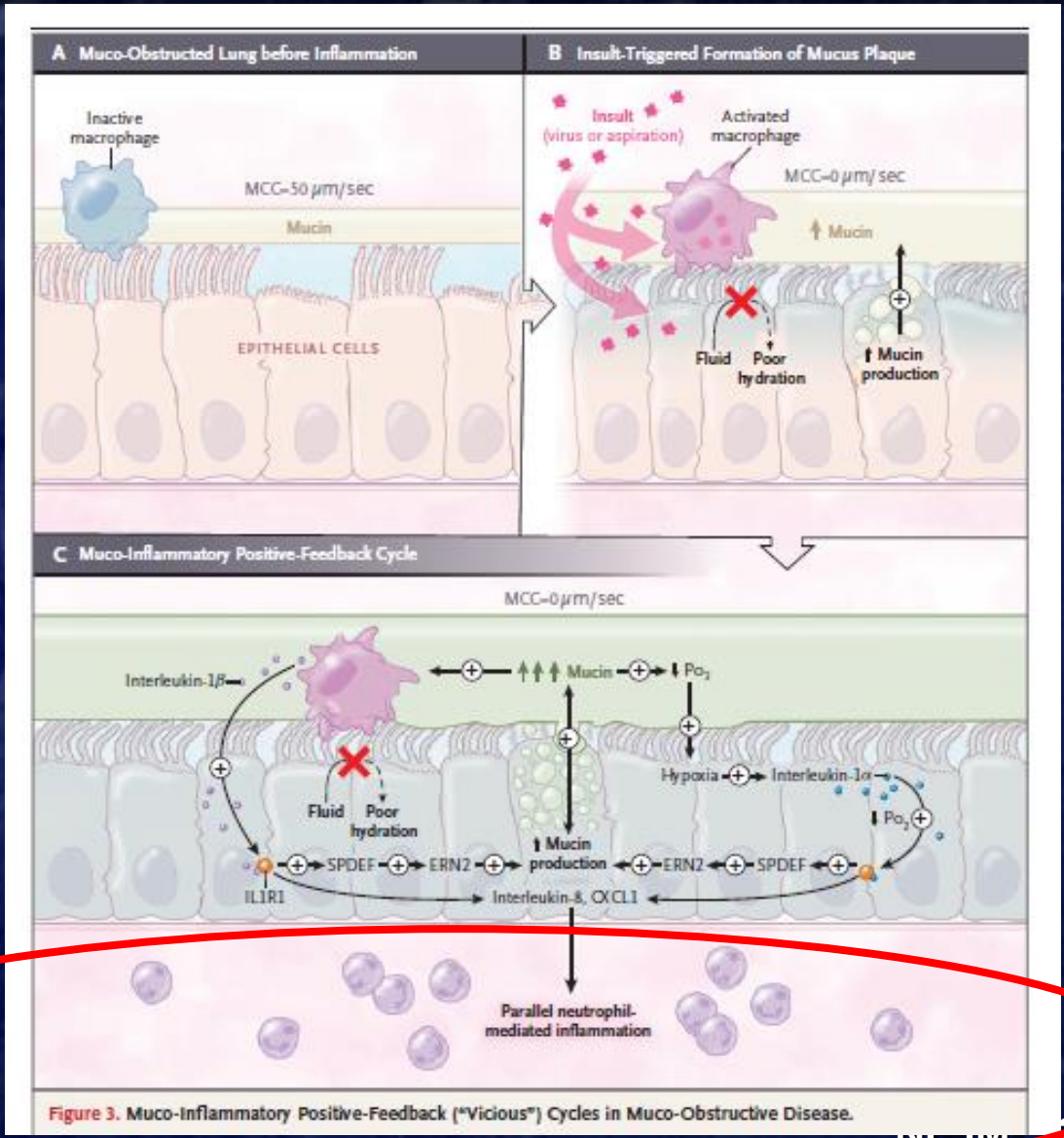


Figure 3. Muco-Inflammatory Positive-Feedback ("Vicious") Cycles in Muco-Obstructive Disease.

NEJM 280: 1941, 2019

Patient Phenotype: Bronchiectasis



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NEJM – 280: 1941, 2019

Patient Phenotype: Bronchiectasis

- Background
- Phenotypes / endotypes
- Summary

Patient Phenotype: Bronchiectasis

Summary

- Historical paradigms of bronchiectasis are insufficient and represent an unmet knowledge gap
- The relationships between different endotypes and resulting clinical phenotypic responses of (non-cystic fibrosis) patients with bronchiectasis are complex
- The role of other common airways diseases, including COPD, in the natural history of the disease process of bronchiectasis and response to therapeutic interventions represents opportunities in scope, numbers, and potential positive impact on advancing the science, closing the knowledge gap, and addressing the unmet needs of patients with bronchiectasis and healthcare systems