



臺北醫學大學・署立雙和醫院  
Taipei Medical University - Shuang Ho Hospital



# Airway Impairment and comorbidity of bronchiectasis

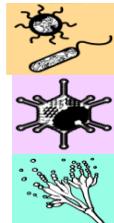
台北醫學大學-部立雙和醫院  
胸腔內科  
陳冠元 醫師

# Etiopathogenic of bronchoectasis

Initial insult



Susceptible host



Acute/Severe

Any severe past infection  
Tuberculosis



Repeated/Episodic

Gastroesophageal reflux  
Aspiration  
Toxin inhalation



Chronic/Persistent

Foreign body  
Airway tumor

~50% Idiopathic

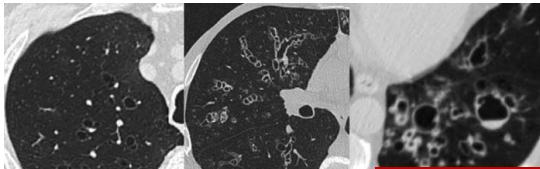
BMC Pulm Med. 2018 May 22;18(1):83



Mucociliary dysfunction



Primary ciliary dyskinesia  
Cystic fibrosis



Cylindrical

Varicoid

Saccular



Immune deficiency



Common variable immune deficiency  
X-linked agammaglobulinaemia  
Hyper-IgE syndrome  
Secondary immunodeficiencies



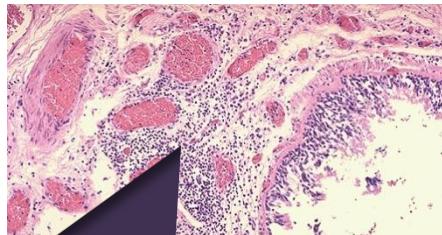
Systemic inflammation



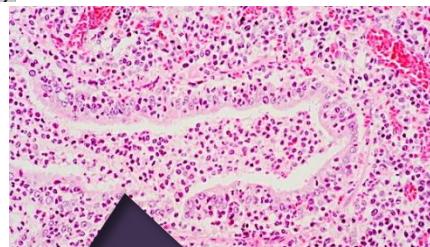
Rheumatoid arthritis  
Inflammatory bowel disease  
Other connective tissue disease

Geographic variation

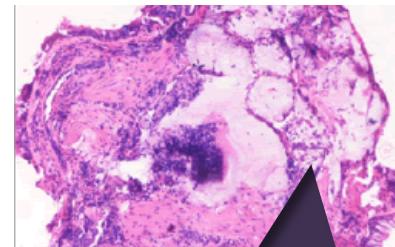
Common pathogenesis ?



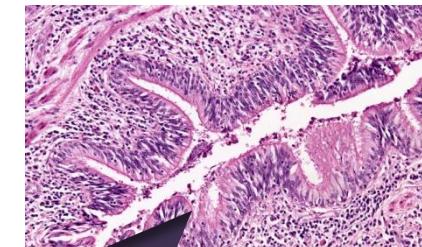
Inflammatory cell in the small airway and obstruction



Bronchial necrotizing inflammation and wall destruction



Disruption of elastic tissue and ASM



Loss of cartilage & bronchial dilation in the larger airways

# Pathogenesis of bronchoectasis

Initial insult

## Cycle theory

Eur J Respir Dis Suppl. 1986;147:6-15

Susceptible host

Impaired mucociliary clearance  
Mucus retention

Microbial infection/colonization

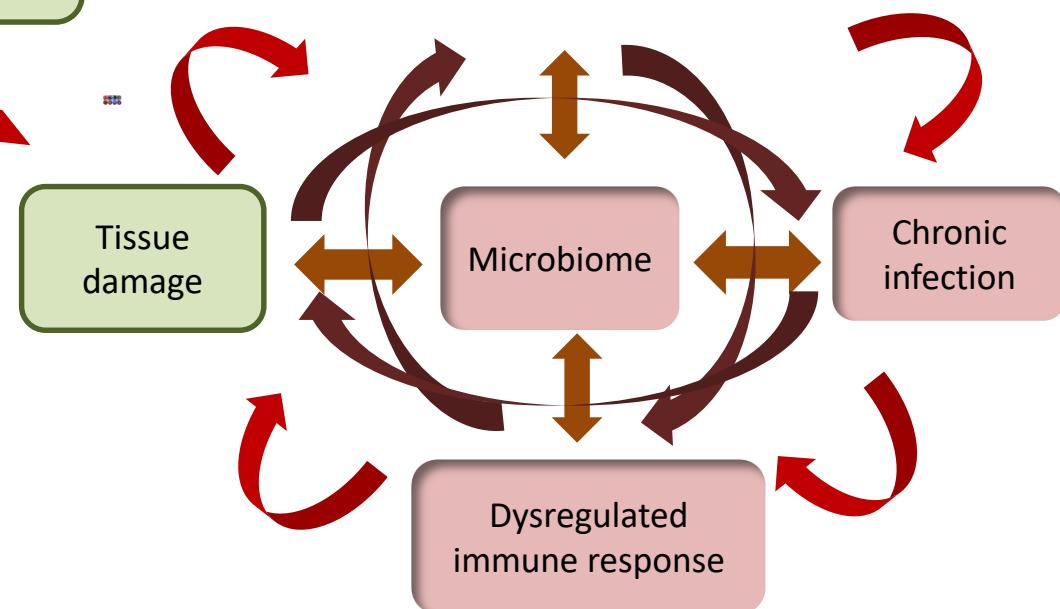
**Cole's vicious circle**

Chronic inflammation

## Vortex theory

Lancet. 2018 Sep 8;392(10150):880-890

**Mucus retention** (mucus hypersecretion , dehydrated mucus ,impaired mucociliary clearance )  
**Epithelial dysfunction**



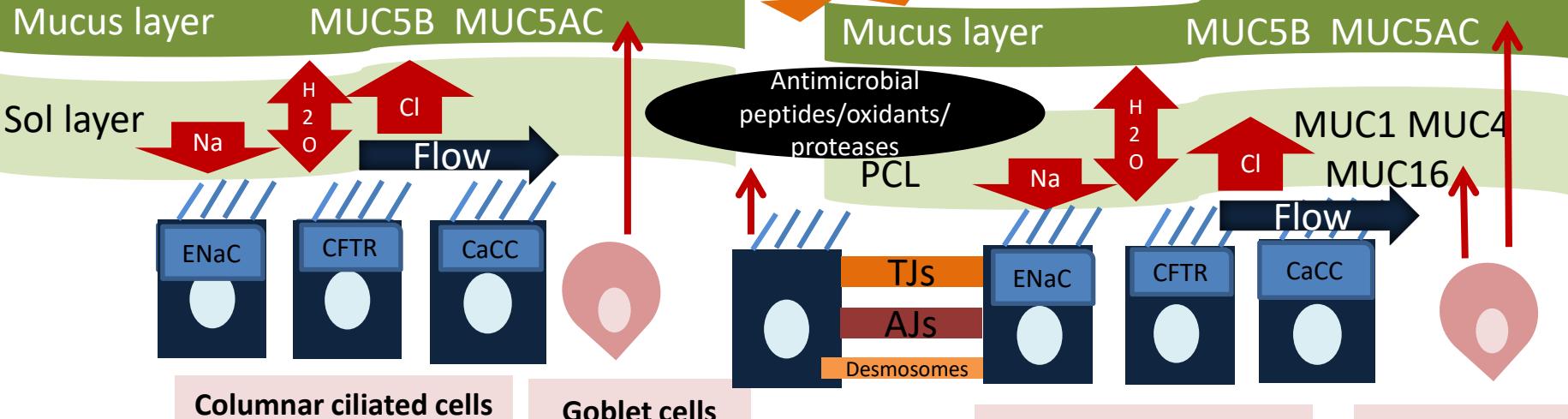
Airway destruction and distortion  
(Bronchiectasis)

# Epithelial function in normal airways

Gel on liquid

Two gel

N Engl J Med. 2019 May 16;380(20):1941-1953

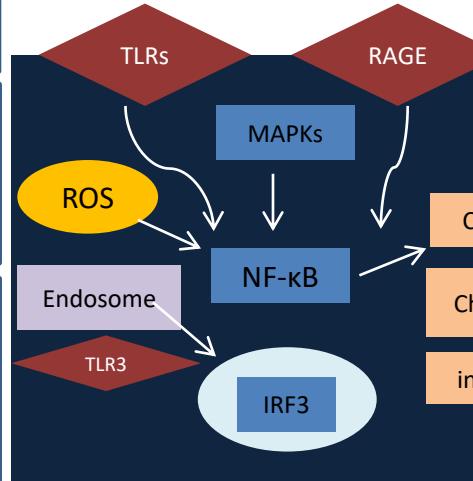


**Mucociliary clearance**  
Mucus production/secretion/  
rheology/Ciliary function

**Barrier function**  
Tight/Adherens  
junctions/desmosomes

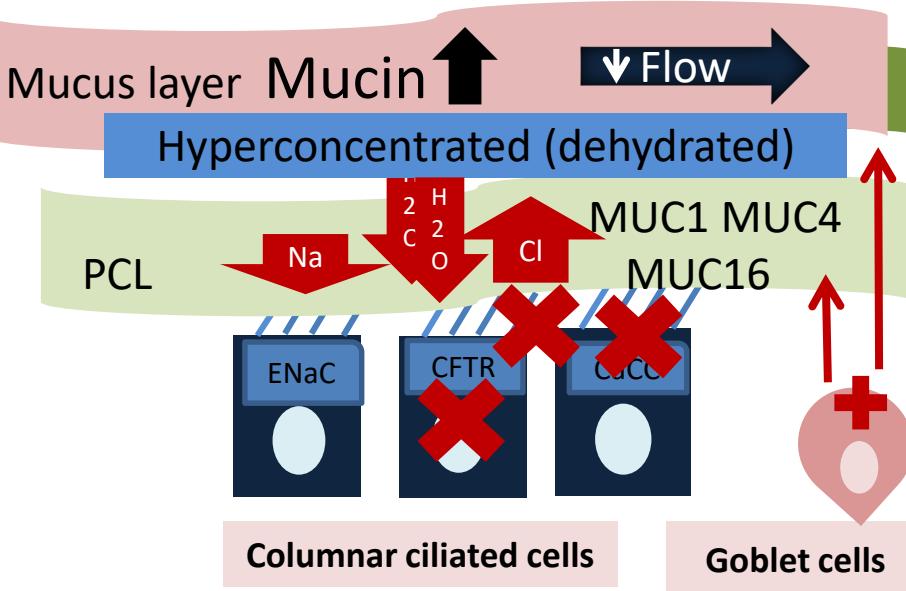
**Element of innate immunity  
and interface of adaptive  
immune response**

PAMPs & DAMPs



Clin Microbiol Rev. 2011 Jan; 24(1): 210–229

# Abnormal mucociliary clearance in bronchiectasis



## Muco-Obstructive Lung Disease

N Engl J Med. 2019 May 16;380(20):1941-1953

### COPD

### Bronchiectasis

### CYSTIC FIBROSIS

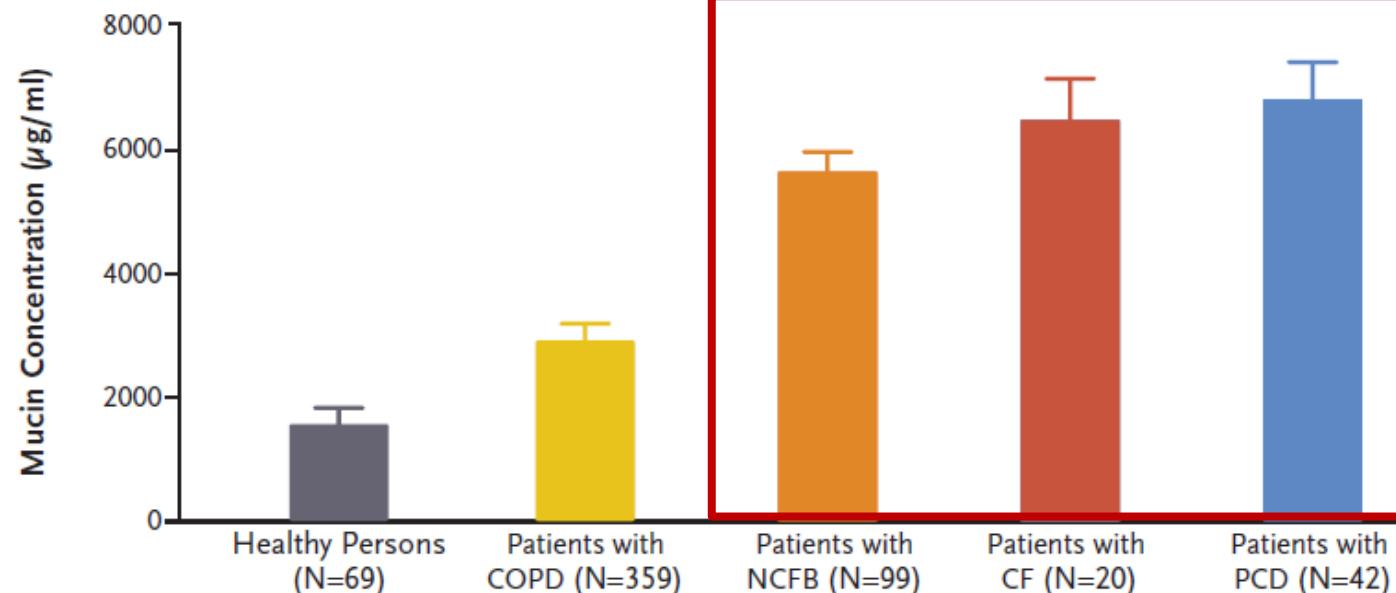
### Primary ciliary dyskinesia

### Non-cystic bronchiectasis

Defect in ion-fluid transport

Failed mucus transport

Mucus adhesion to airway surfaces



N Engl J Med. 2019 May 16;380(20):1941-1953

# Change of rheology of mucus

## Viscosity: mucus

## Cohesion: intra-mucus

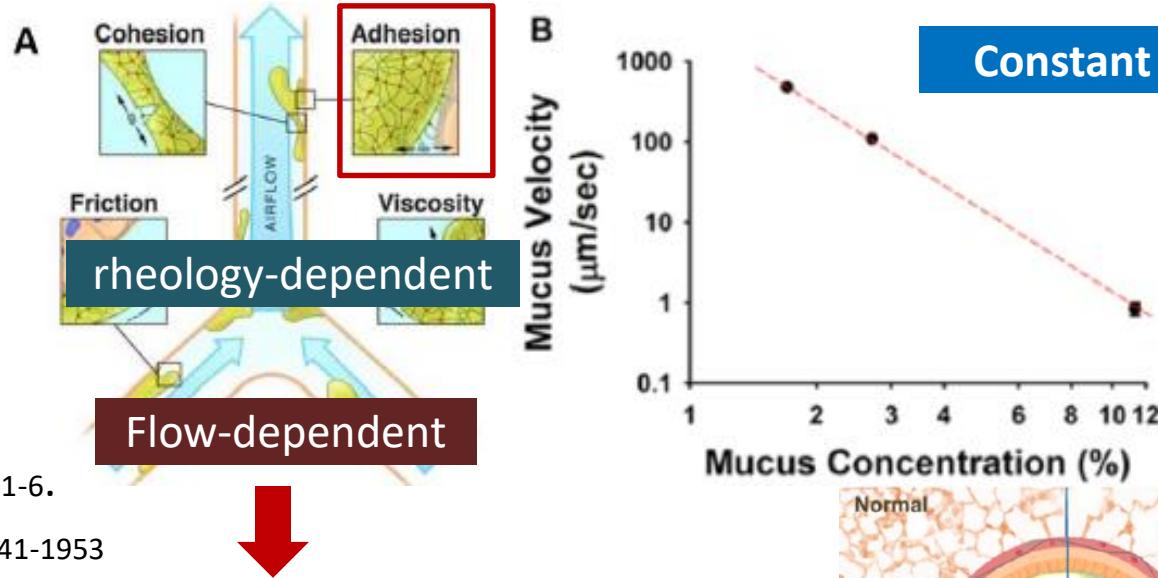
### **Adhesion: mucus-surface**

## Friction: mucus-surface

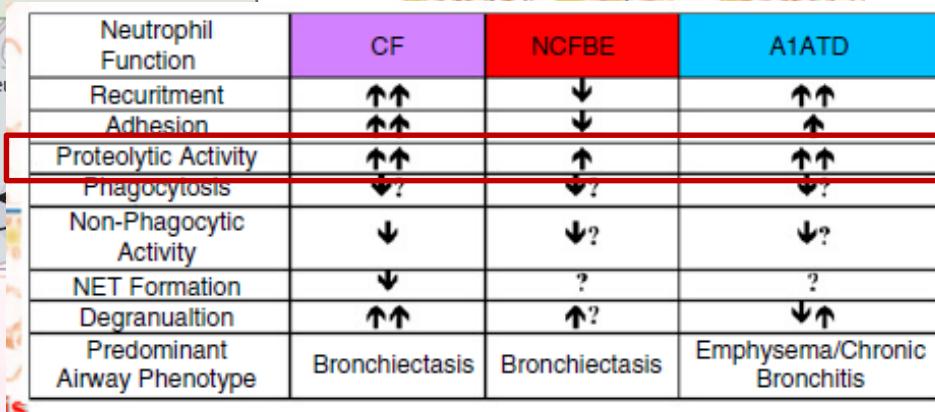
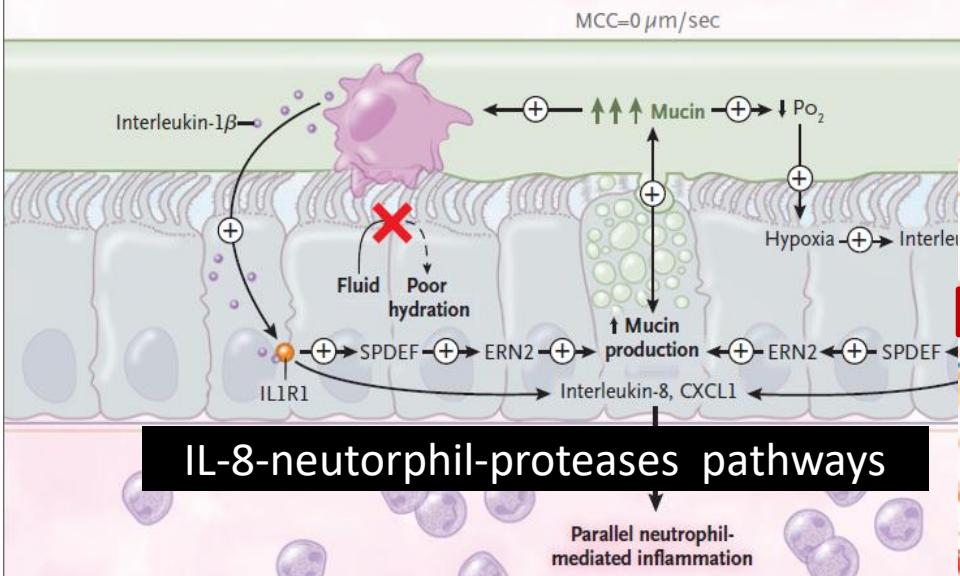
Pediatr Pulmonol 2016;51:251

Proc Natl Acad Sci U S A 2018;115:12501–6.

N Engl J Med. 2019 May 16;380(20):1941-1953

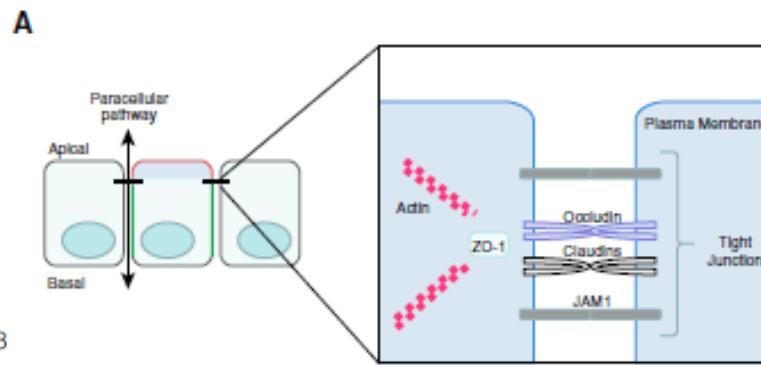


## **Mucostasis and muco-inflammatory positive Feed-back cycle**

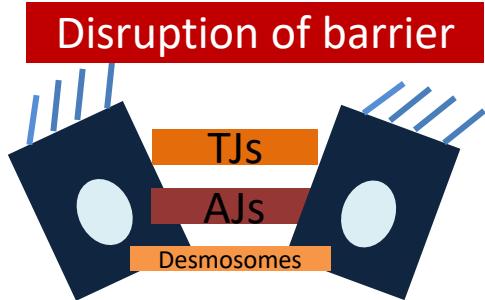
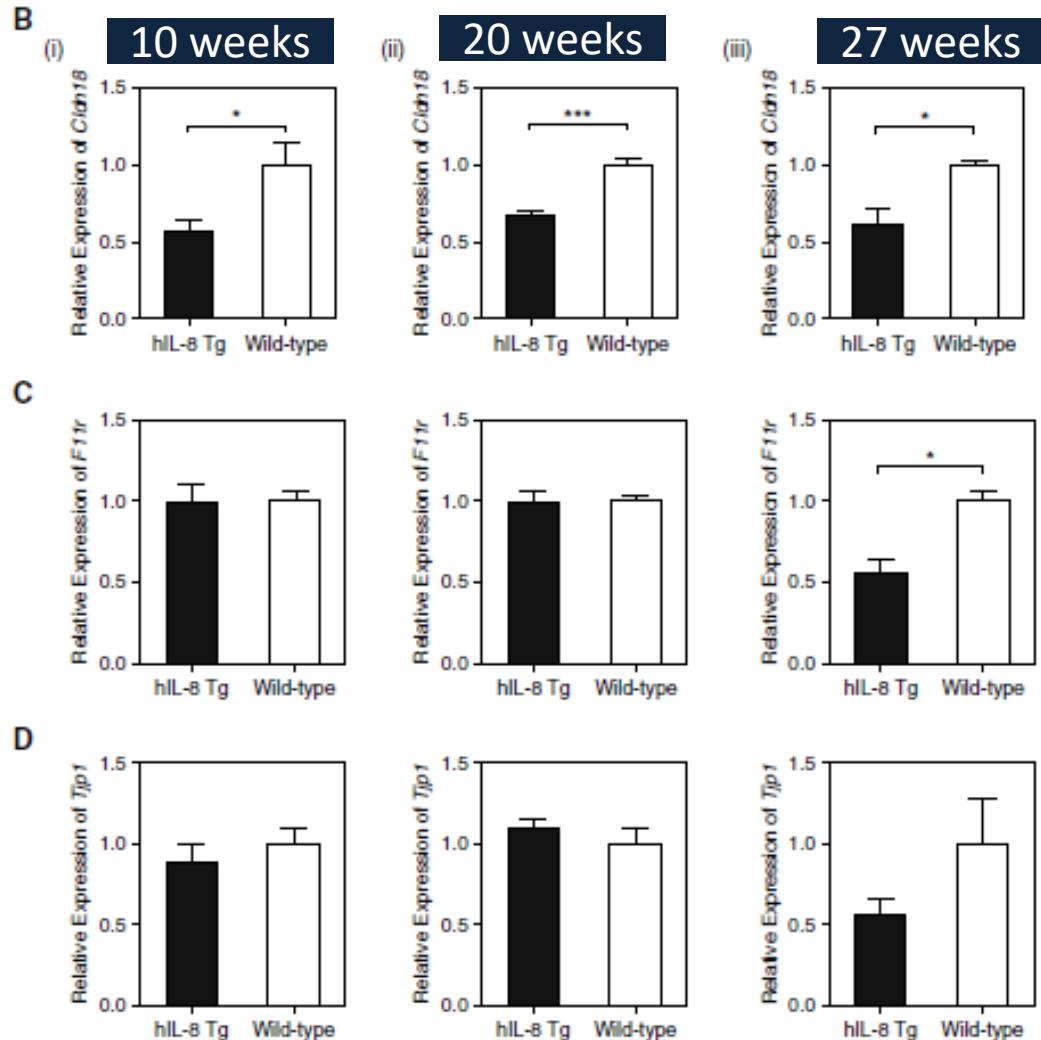


# IL-8-dependent inflammation mice model

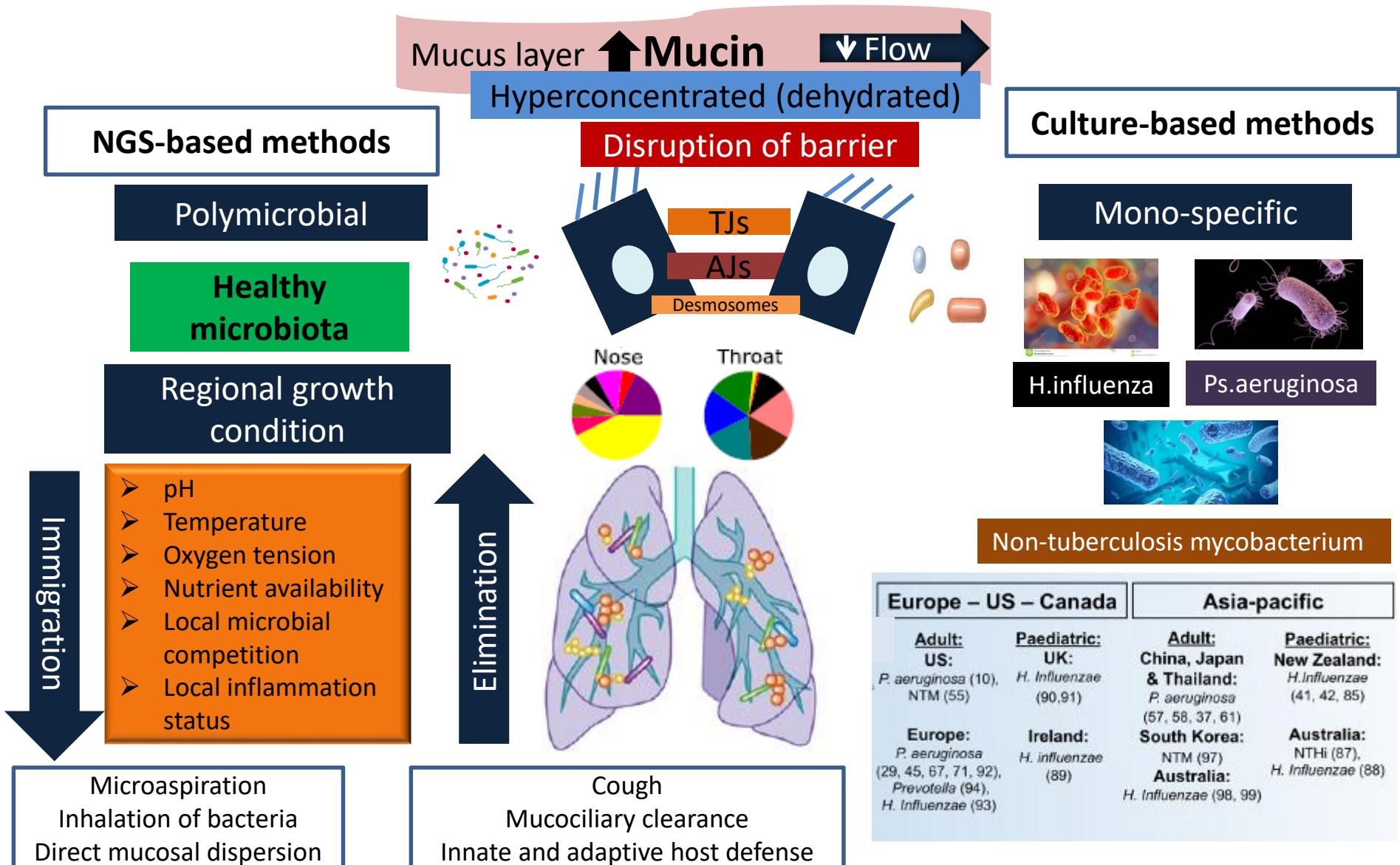
Am J Respir Cell Mol Biol Vol 59, Iss 5, pp 557–571, Nov 2018



- Reduced expression of Claudin 18 and F11r, with damage to epithelial organization leading to leaky tight junctions



# Microbiology and the microbiome in bronchiectasis



# Evolving microbiome in bronchiectasis

## Cystic fibrosis

1997-2000 (N=12)

2004-2007 (N=17)

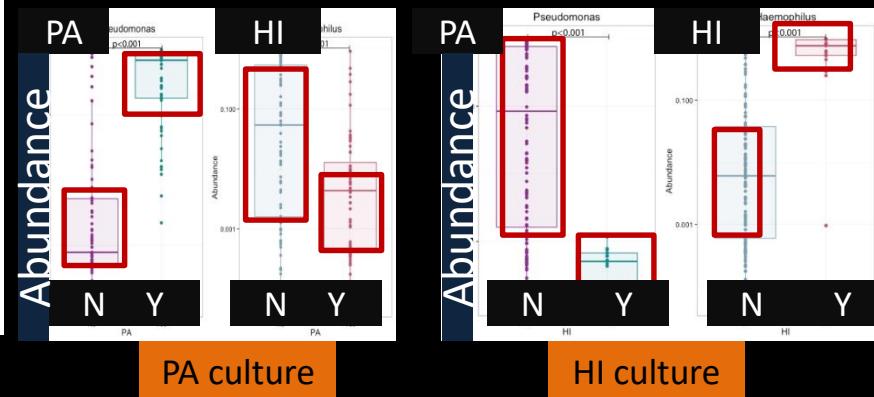
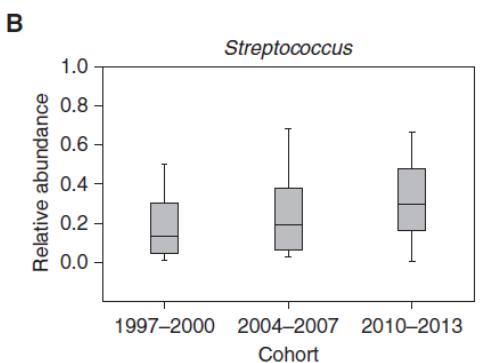
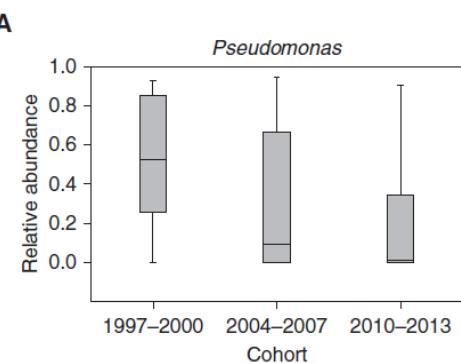
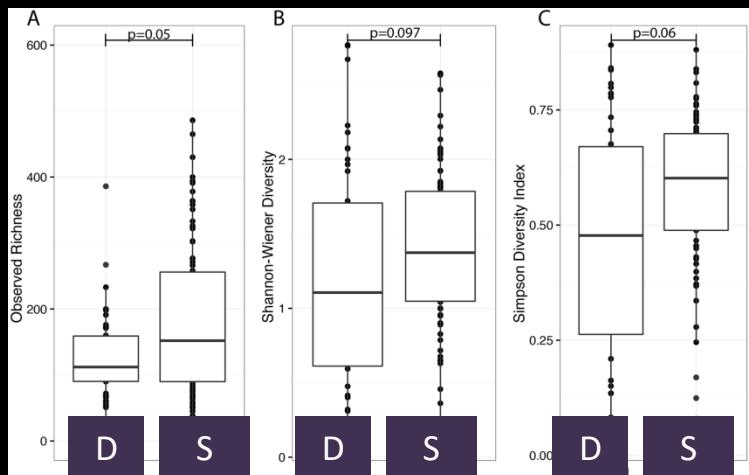
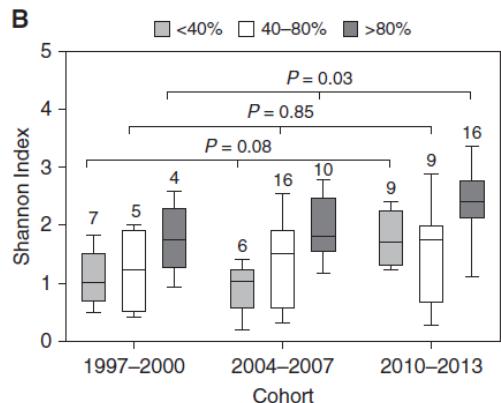
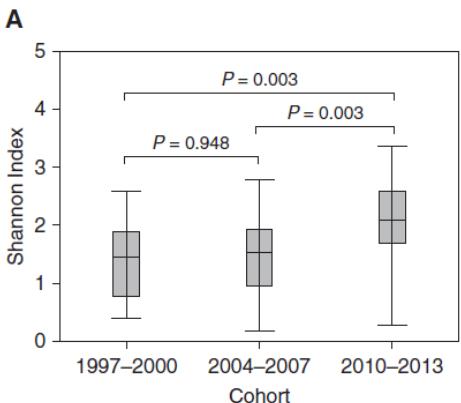
2010-2013 (N=16)

## Non-CF bronchiectasis

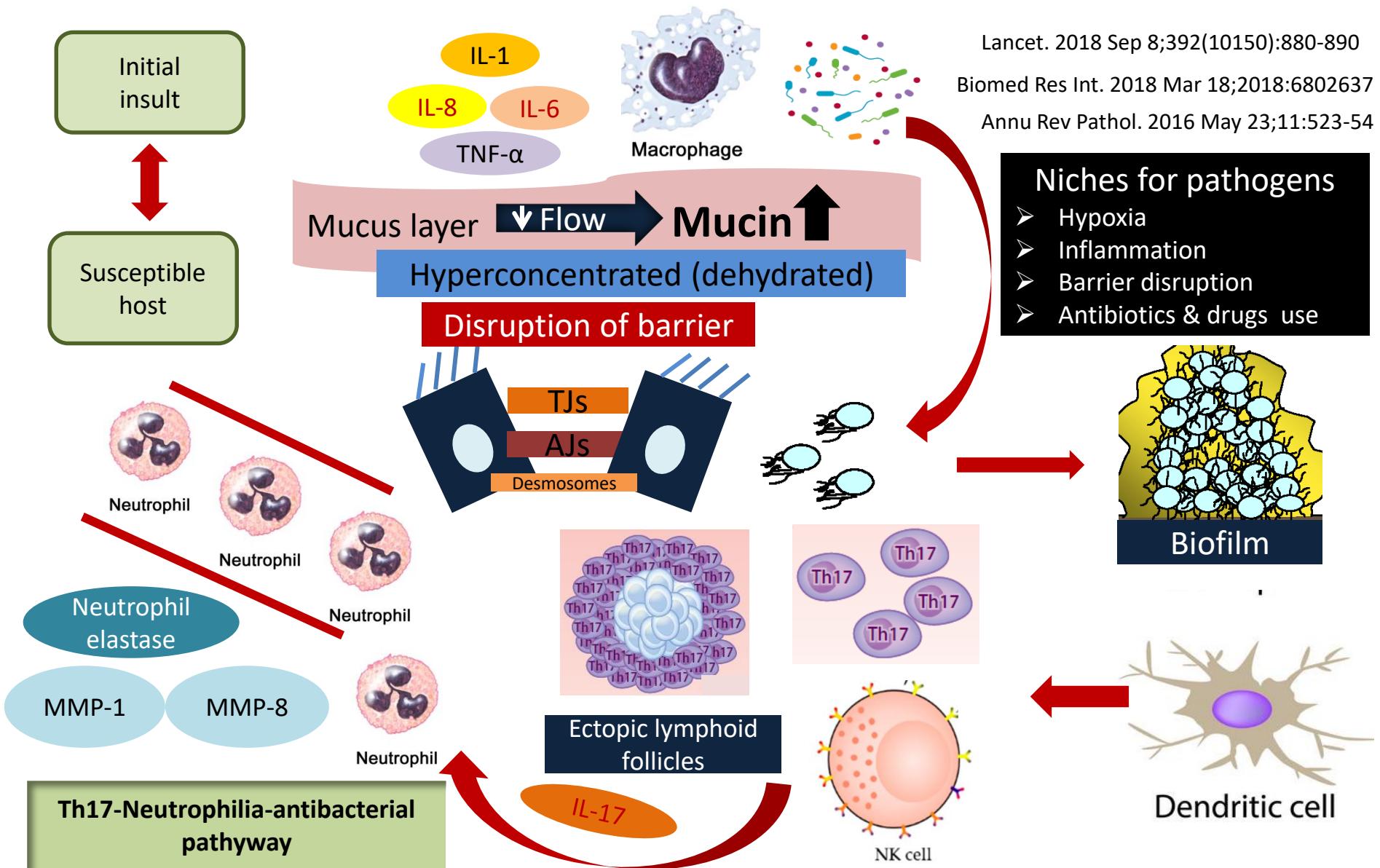
4-16 years

Decliners (N=11)

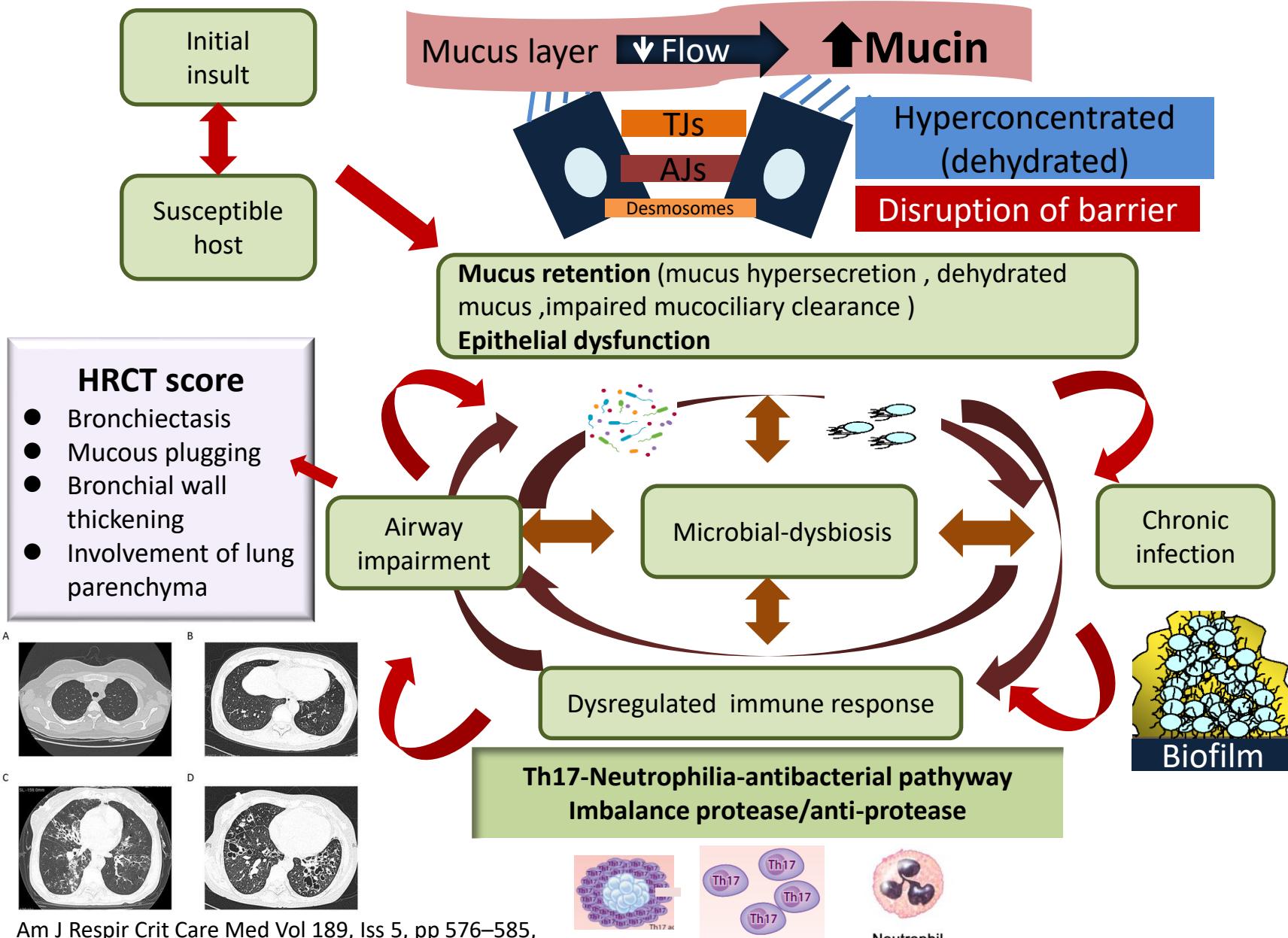
Stables(N=18)



# Chronic infection & immune response in bronchiectasis



# Airway impairment in bronchiectasis

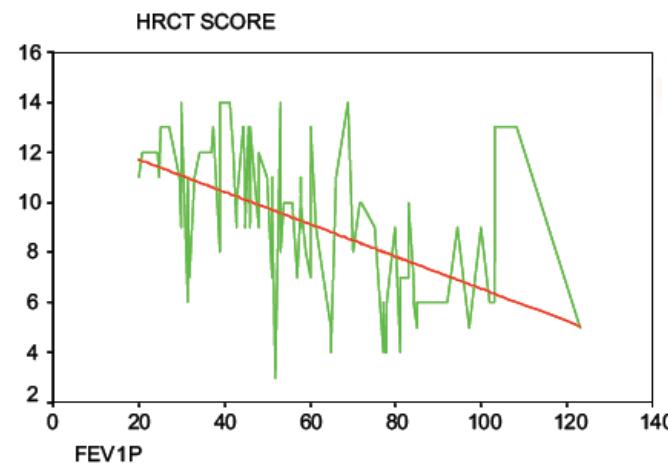


# Clinical impact of airway impairment in bronchiectasis

## Dyspnea

Parameter	Dyspnea (MRC)	Dyspnea (BDI)	Dyspnea (Borg)	HRCT score
FEV <sub>1</sub> (% pred.)	-0.26*	0.27*	-0.17	-0.19
FEV <sub>1</sub> /FVC	-0.23*	0.22*	-0.19	-0.20
PEF (L/min)	-0.17	0.19	-0.20	-0.14
RV/TLC	0.54†	-0.51†	0.45†	0.17
RV	0.46†	-0.41*	0.33†	0.12
HRCT score	0.27*	-0.09	0.15	-

## Pulmonary function



Respir Med. 2007 Nov;101(11):2248-53

## Microbiology

	Pa +ve group (n=22)	Pa -ve group (n=45)	p value
Extent of bronchiectasis	9.5 (3.5–14.0)	5.0 (1.5–15.5)	<0.0001
Bronchial wall dilatation	9.5 (2.5–17.5)	4.0 (1.0–17.5)	<0.0005
Bronchial wall thickening	6.0 (2.5–12)	3.5 (0–17.5)	<0.0001
Global decreased attenuation	5.5 (0–12)	2.0 (0–11)	<0.0005
Large plug score	0.5 (0–2.5)	0 (0–2.5)	0.07
Centrilobular plug score	0.5 (0–5)	0 (0–5)	0.33

Thorax. 1997 Mar;52(3):260-4

# Impact of airway impairment in bronchiectasis on prognosis

## Bronchiectasis Severity Index (BSI)

### Mortality

### Hospital admissions

### Exacerbations

- Age
- BMI
- **FEV1% predicted**
- Number of hospital admissions during the preceding year
- Number of exacerbations during the preceding year
- **Dyspnea**
- **P.aeruginosa colonization**
- **Others colonization**
- **Radiological extension**

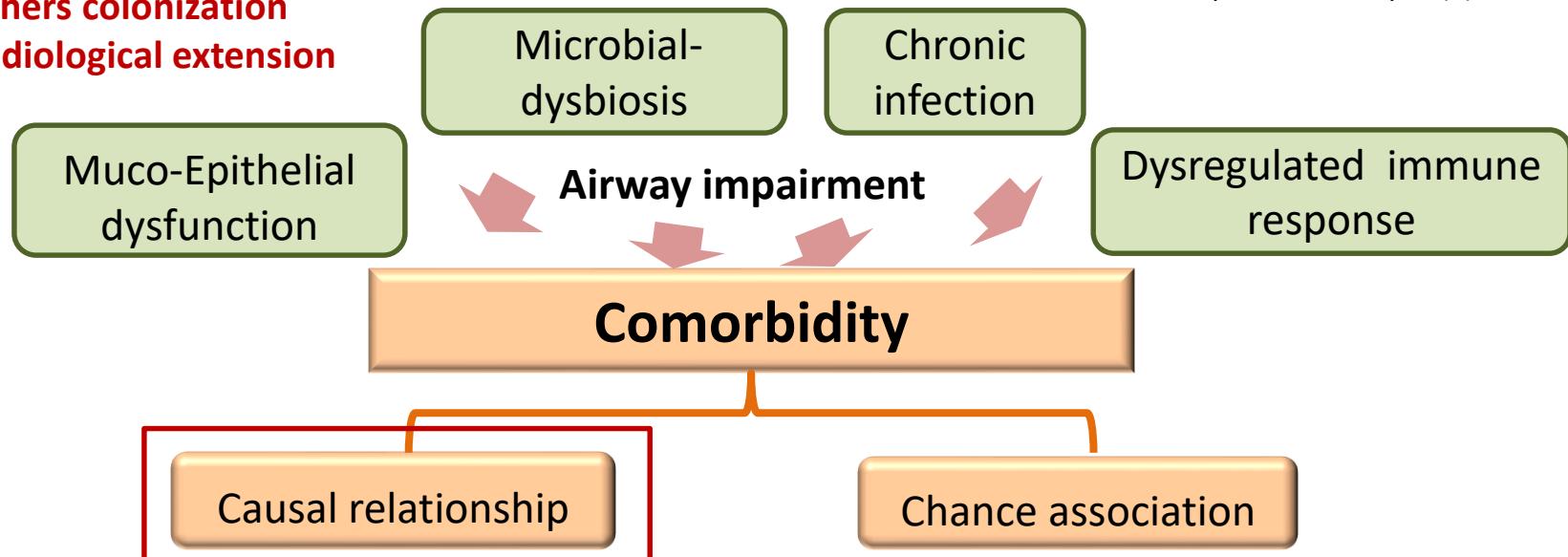
## FACED score

### All-cause 5-year mortality

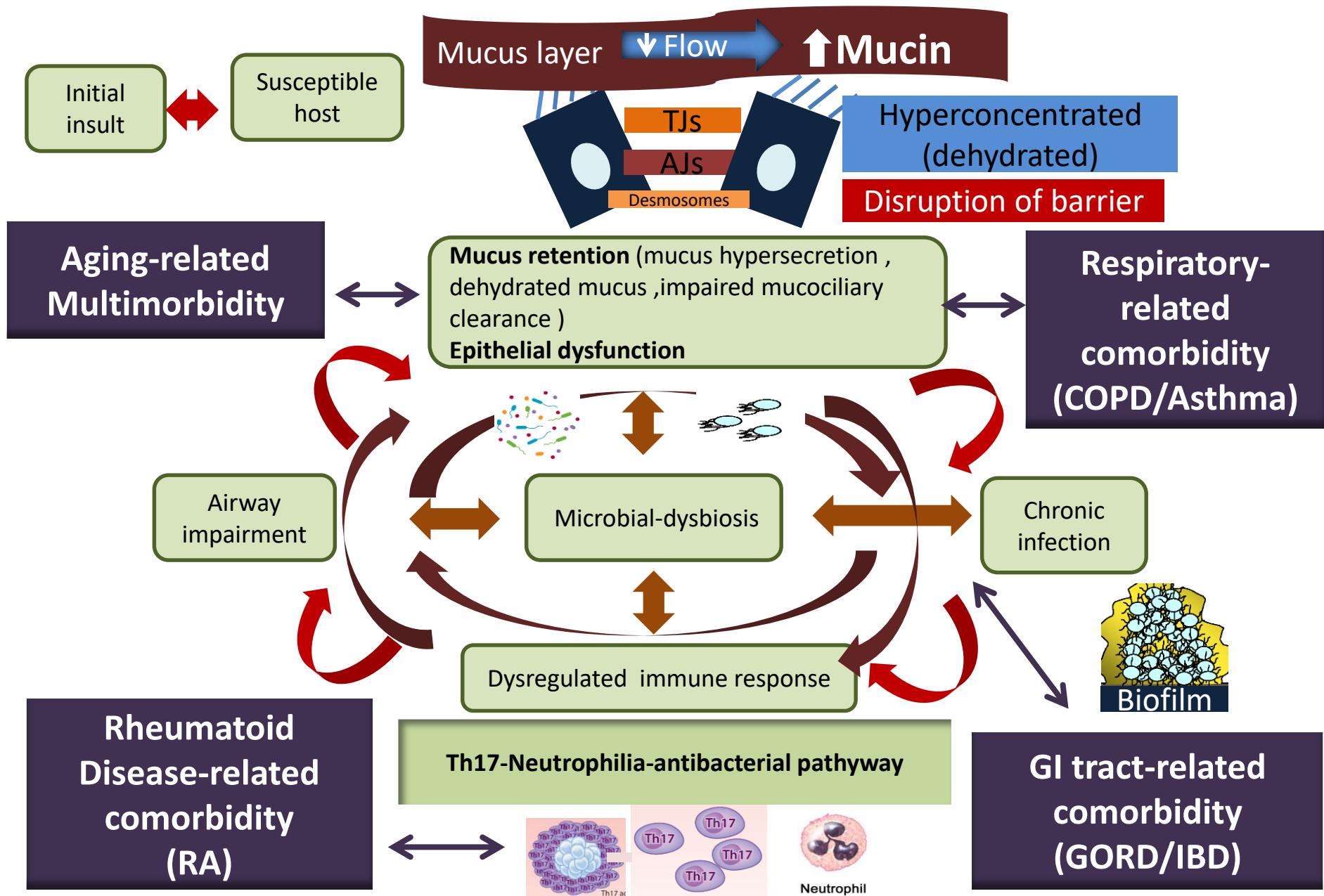
- **FEV1 % predicted**
- Age
- **P.aeruginosa colonization**
- **Radiological extension**
- **Dyspnea**

Am J Respir Crit Care Med. 2014 Mar 1; 189(5): 576–585

Eur Respir J. 2014 May;43(5):1357-67



# Co-morbidities in bronchiectasis



**Respiratory-related comorbidity  
(COPD/Asthma)**

# Bronchiectasis and chronic respiratory diseases

Pathogens

**Bronchiectasis**



Allergen

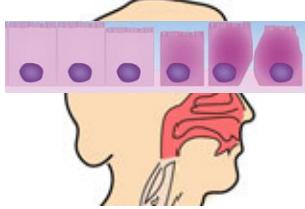
**Asthma**



Smoking

**COPD**

**Rhinosinusitis**

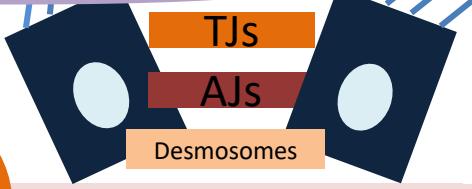


Mucus layer

↓ Flow

**Asthma**

Mucin ↑



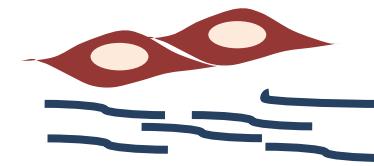
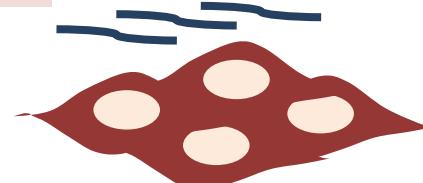
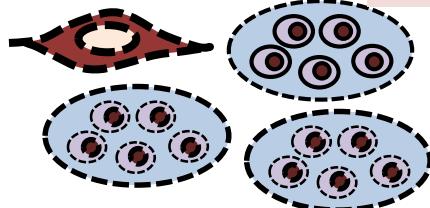
**COPD**

Mucus retention (mucus hypersecretion , dehydrated mucus ,impaired mucociliary clearance )  
Epithelial dysfunction

Submucosal gland

↑ BM

Basement membrane



**Loss of ASM and cartilage**

↑ Subepithelial fibrosis

↑ Peribronchial fibrosis

↑ ASM hypertrophy & hyperplasia

↑ ASM hypertrophy & hyperplasia

Neutrophil



Natural Killer Cell



T Cell

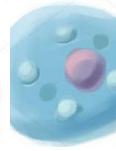
Th17



Eosinophil



Mast Cell



T Cell

Th2



B Cell



Neutrophil



Macrophag



T Cell



B Cell

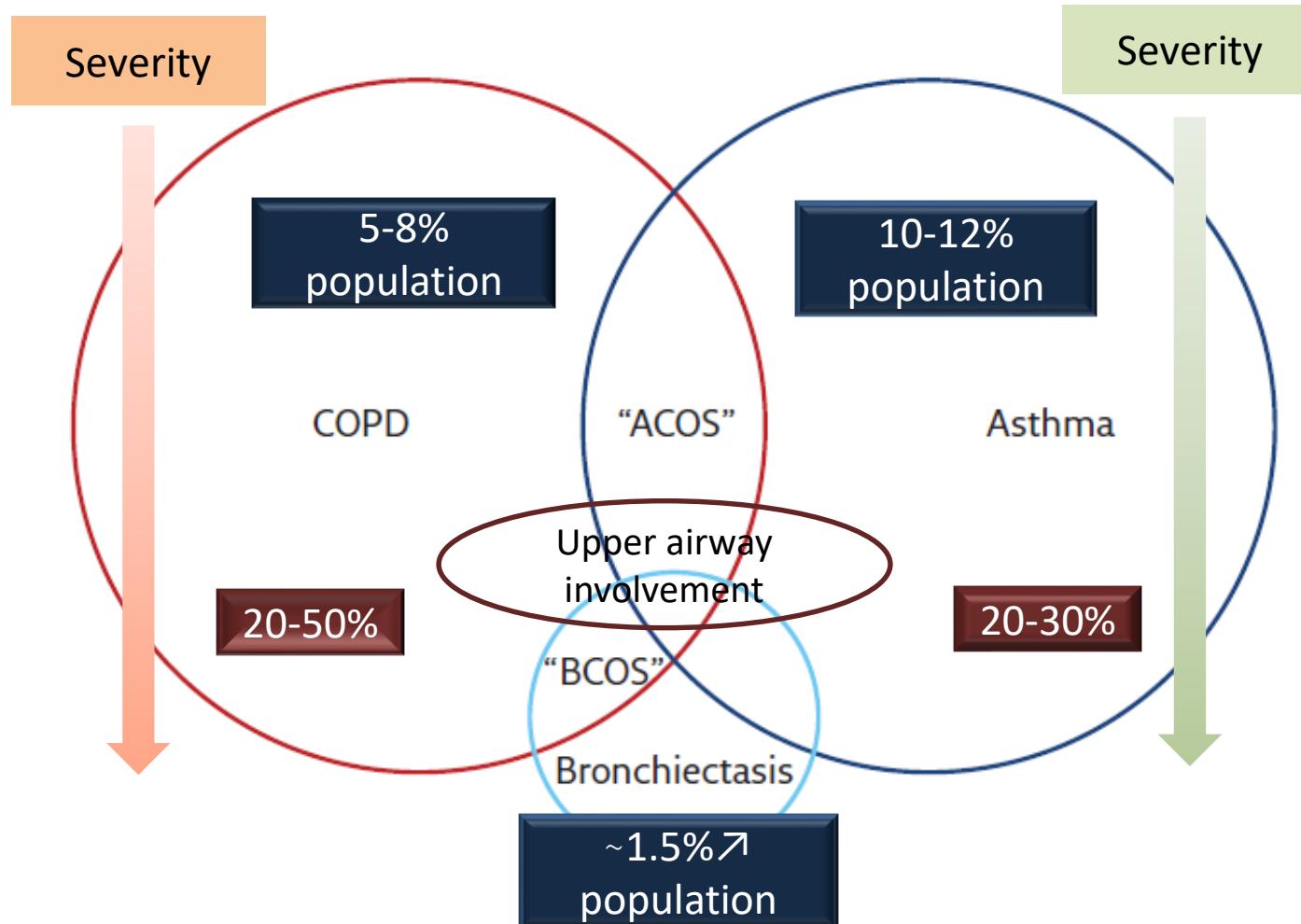


Th1  
Th17  
Tc1

Auto-antibody

# Mixed airway phenotype

## From upper airway to lower airway



# Overlap COPD and bronchiectasis

## Diagnosis

Normal airway & vessel



## Bronchiectasis

### Structure diagnosis

$B/A>1$  & wall thickness



## COPD

### Physiological diagnosis



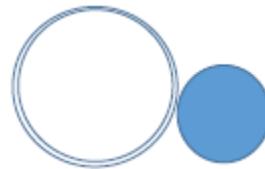
Cardiopulmonary diseases & elderly

## Over-diagnosis

Hypoxic vasoconstriction



20% healthy elderly

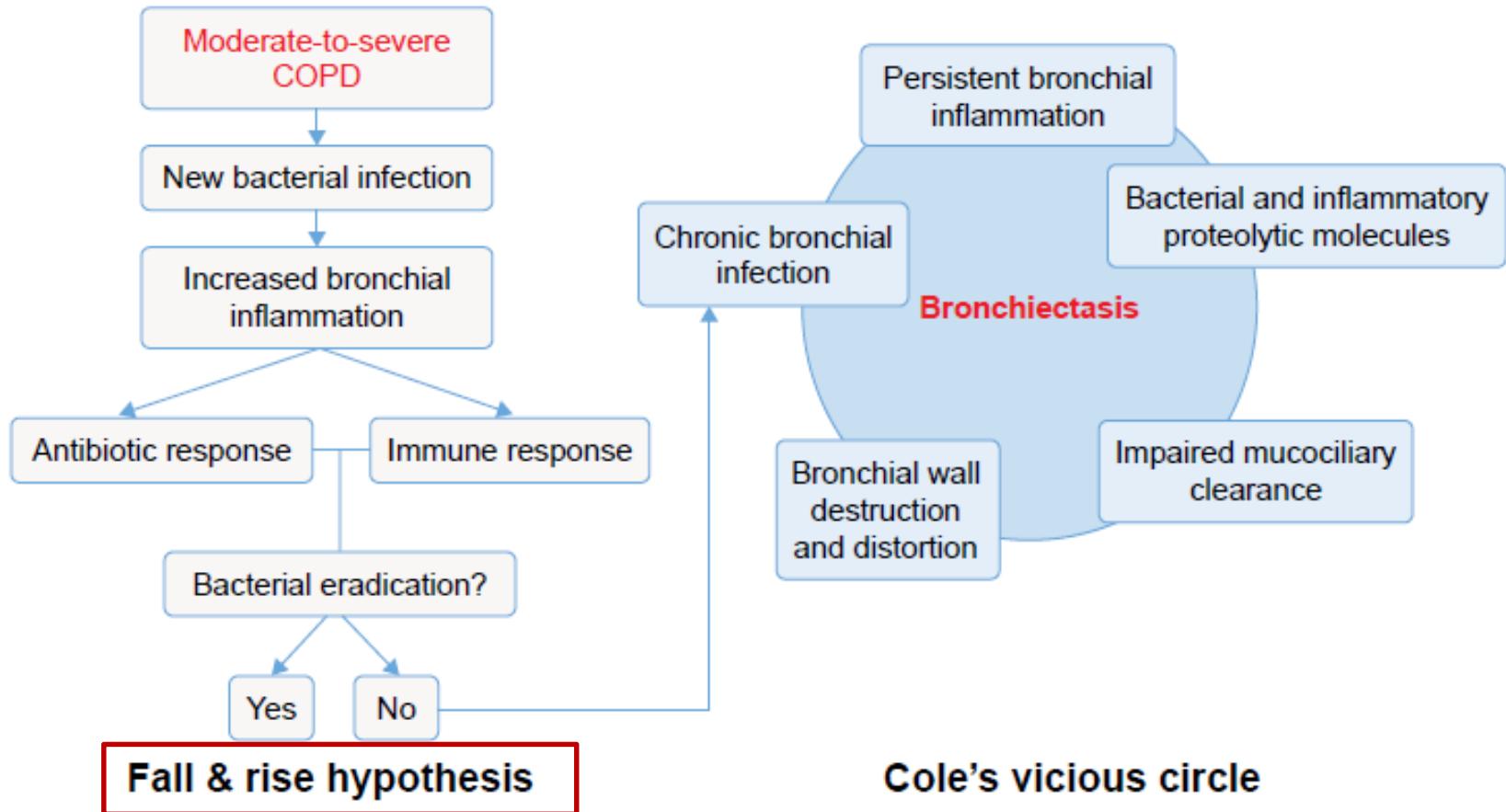


## Under-diagnosis

Vascular hypertension

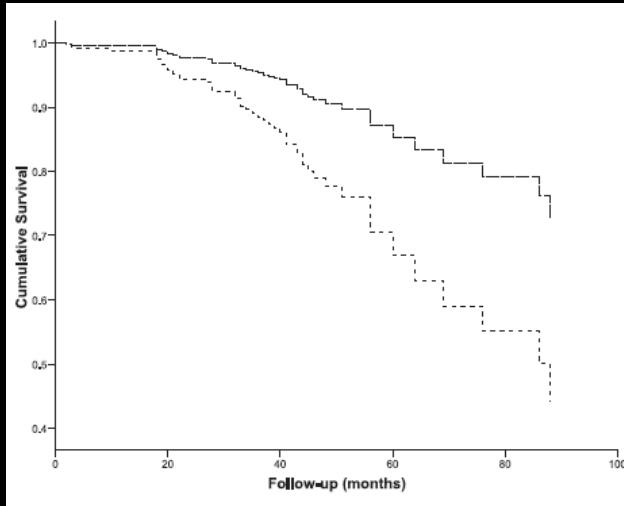


# Pathogenesis



# Clinical impact of overlap COPD and bronchiectasis

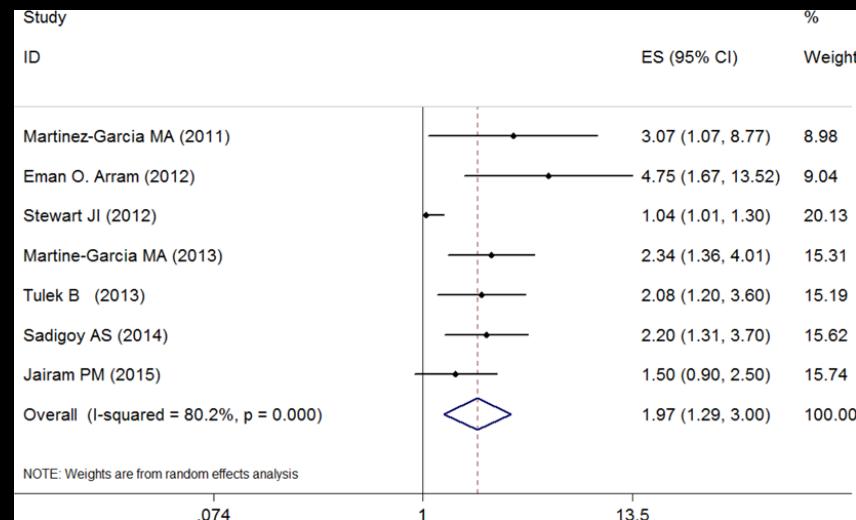
## Mortality



— COPD without bronchiectasis (n=86; 8 deaths)  
- - - COPD with bronchiectasis (n=115; 43 deaths)

Am J Respir Crit Care Med. 2013 Apr 15;187(8):823-31

## Exacerbation



PLoS One. 2016 Mar 15;11(3):e0150532

## Clinical features

- More severe airflow obstruction
- Greater sputum production
- Isolation of sputum pathogens (including *P.aeruginosa* )
- Greater systemic inflammation

Int J Chron Obstruct Pulmon Dis. 2015 Jul 28;10:1465-75

Therapeutic benefit from **macrolide** or avoid **ICS** use considering acute and chronic bacterial infection in COPD-bronchiectasis patients ?

# Overlap asthma and bronchiectasis



## Bronchiectasis in asthma

## Asthma in bronchiectasis



### Similarities : mucus hypersecretion

#### Asthma

Chronic respiratory disease with heterogeneous clinical manifestations  
Complex pathophysiology  
Chronic airway inflammation  
    Mostly eosinophilic  
Ventilatory disorder  
    Obstructive  
    Mostly reversible  
Exacerbations: marker of disease control  
    Infectious (viral?)  
    Non-infectious (allergens, treatment compliance, pollution)

#### Bronchiectasis

Eur Respir J. 2018 Sep 15;52(3). pii: 1800328

Chronic respiratory disease with heterogeneous clinical manifestations  
Complex pathophysiology  
Chronic airway inflammation  
    Mostly neutrophilic  
Ventilatory disorder  
    Mostly obstructive  
    Mostly non-reversible  
Exacerbations: marker of disease control  
    Infectious (bacterial, viral mixed, fungal)  
    Non-infectious (?)

#### Patients with Asthma or Cystic Fibrosis (2012 Criteria in JACI<sup>18</sup>)

Asthma or if Cystic Fibrosis, with deterioration of lung function  
Immediate skin reactivity to *Aspergillus* species  
Total serum IgE ≥ 1000 ng/mL (416 IU/mL)\*  
Increased *Aspergillus* species-specific IgE and IgG antibodies  
Chest roentgenographic infiltrates

\*Additional criteria might include peripheral blood eosinophilia, *Aspergillus* species serum precipitating antibodies, central bronchiectasis, and *Aspergillus* species-containing mucus plugs"

Therapeutic approach typical of bronchiectasis  
(long-term antibiotics, chest physiotherapy)

**Allergic bronchopulmonary aspergillosis (ABPA)**  
(systemic corticosteroids and selective antifungal therapy)

Biomarkers (FeNO, blood/sputum eosinophils) and long-term variability in pulmonary function over time may be relevant for personalized treatment

# **GI tract-related comorbidity (GORD/IBD)**

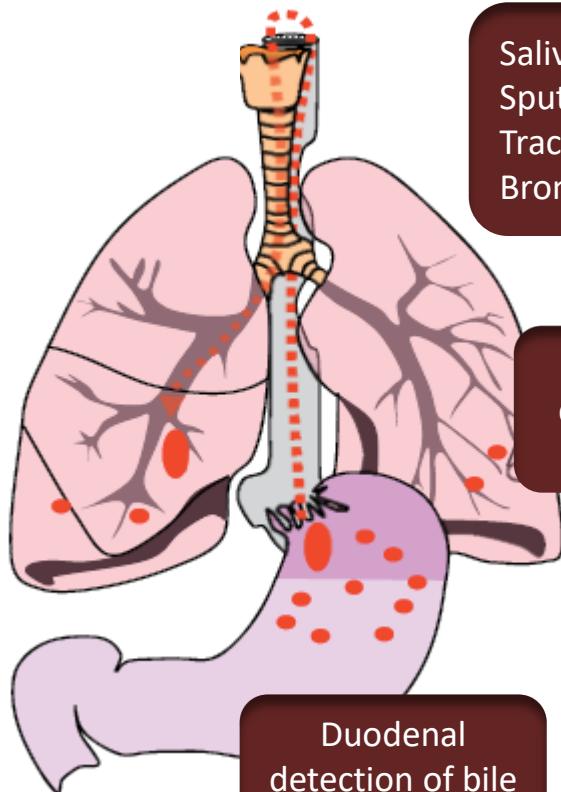
# Gastro-oesophageal reflux disease (GORD) in bronchiectasis

Anti-reflux impairment

(LOS, crural diaphragm & anatomical flap valve)

Ambulatory 24-h oesophageal pH monitoring

## Diagnosis of pulmonary microaspiration



Saliva  
Sputum  
Tracheal aspiration  
Bronchoalveolar lavage

Gastric  
detection of  
pepsin

Duodenal  
detection of bile  
salts

## Prevalence of GORD in bronchiectasis

Self-reported symptoms and questionnaires  
34-74%

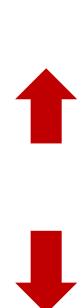
Oesophageal pH monitoring  
11-75%

## Risk factor of GORD in bronchiectasis

- Older age
- Female sex
- Larger BMI

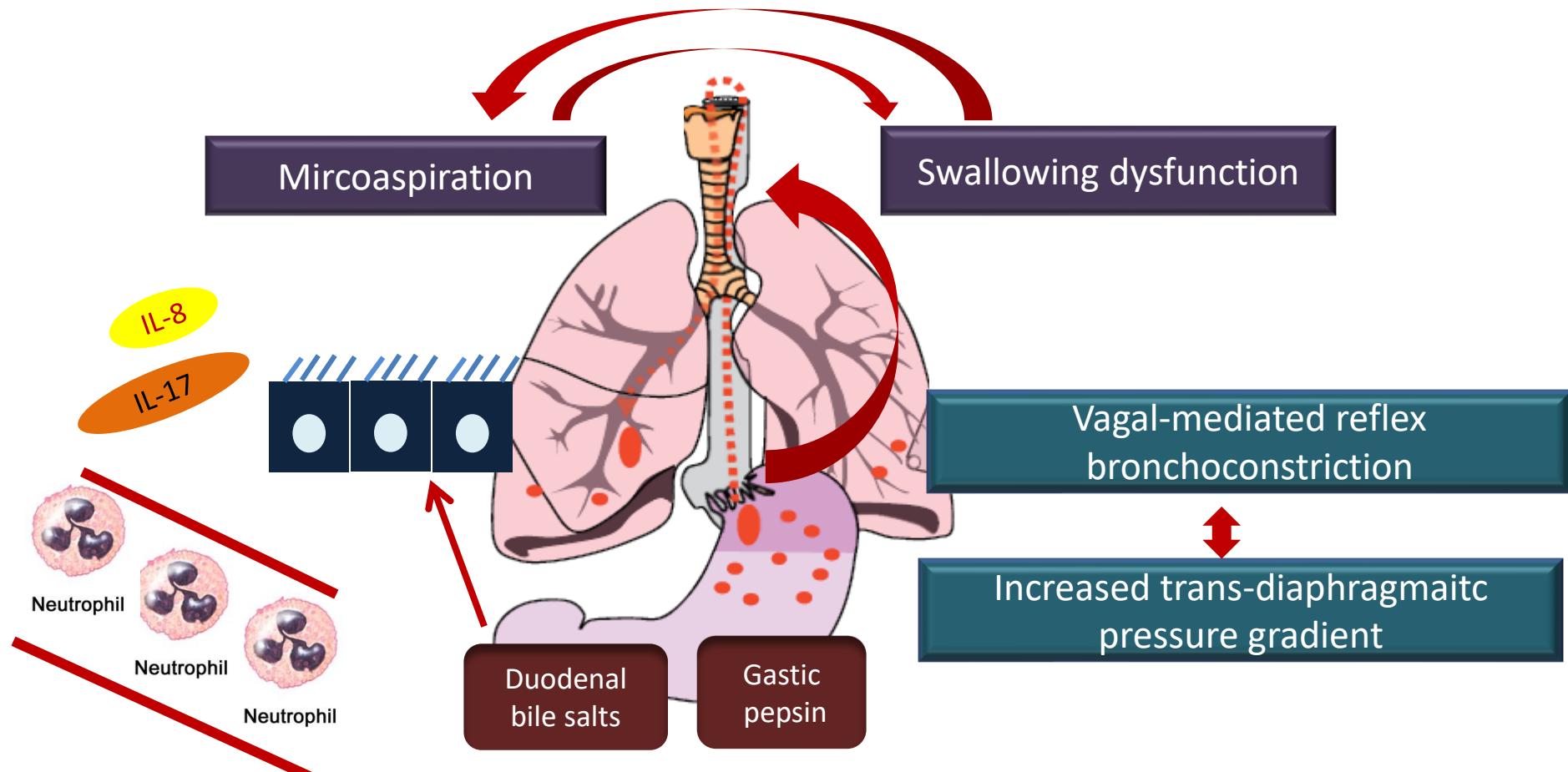
## Influence of GORD in bronchiectasis severity

Mortality  
Symptoms  
Exacerbations & hospitalizations  
Radiological severity  
Colonization rate  
Lung function  
HrQoL



# Mechanisms of GORD in the severity of bronchiectasis

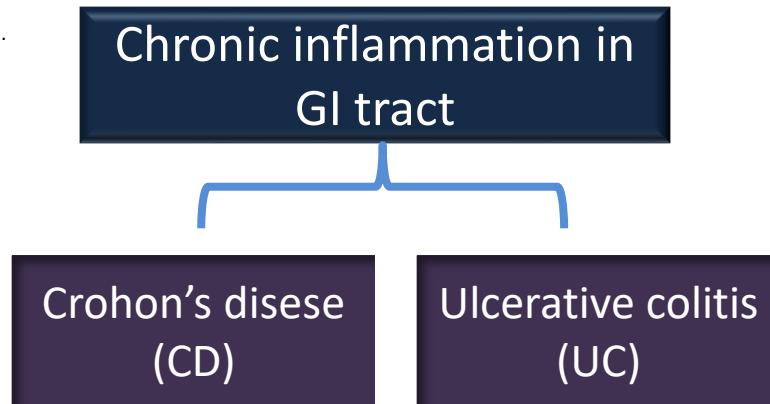
Gut-lung axis: horizontal transmission



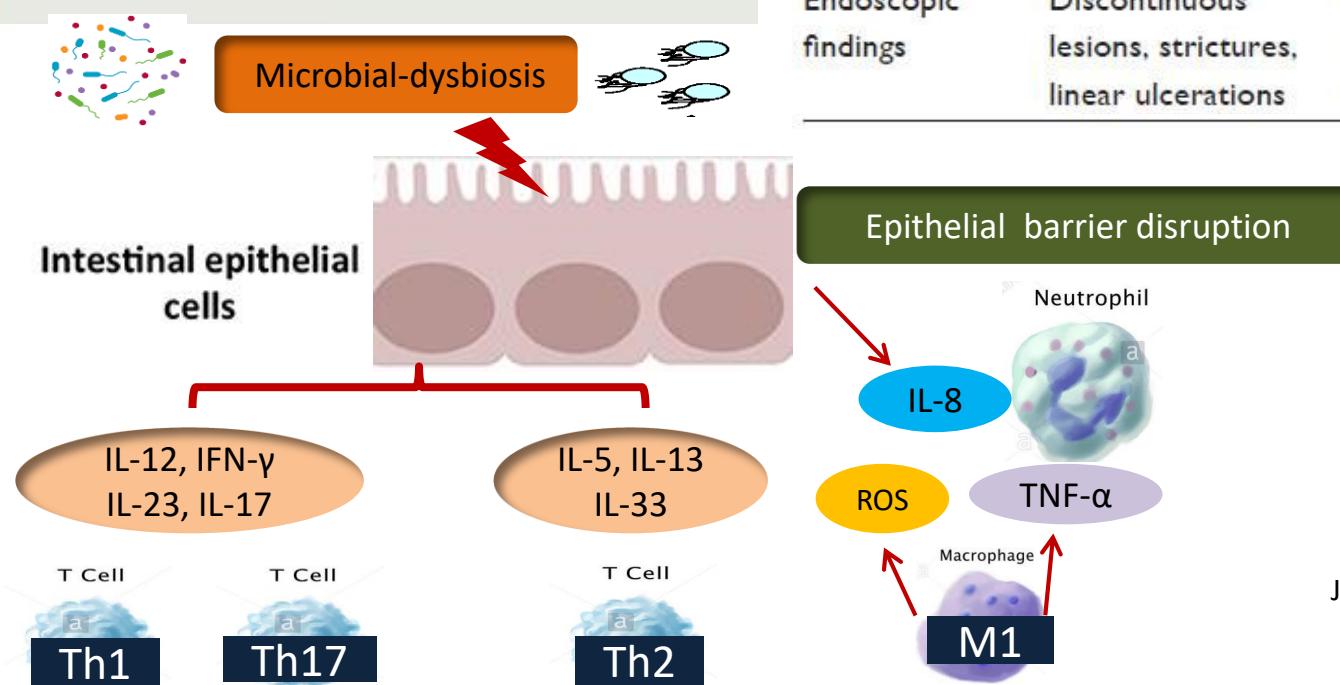
## Treatment

No significant differences were observed in lung function 6months after PPI therapy ; significant improvement in lung function with **higher BMI**

# Relationship to inflammatory bowel disease (IBD) & bronchiectasis



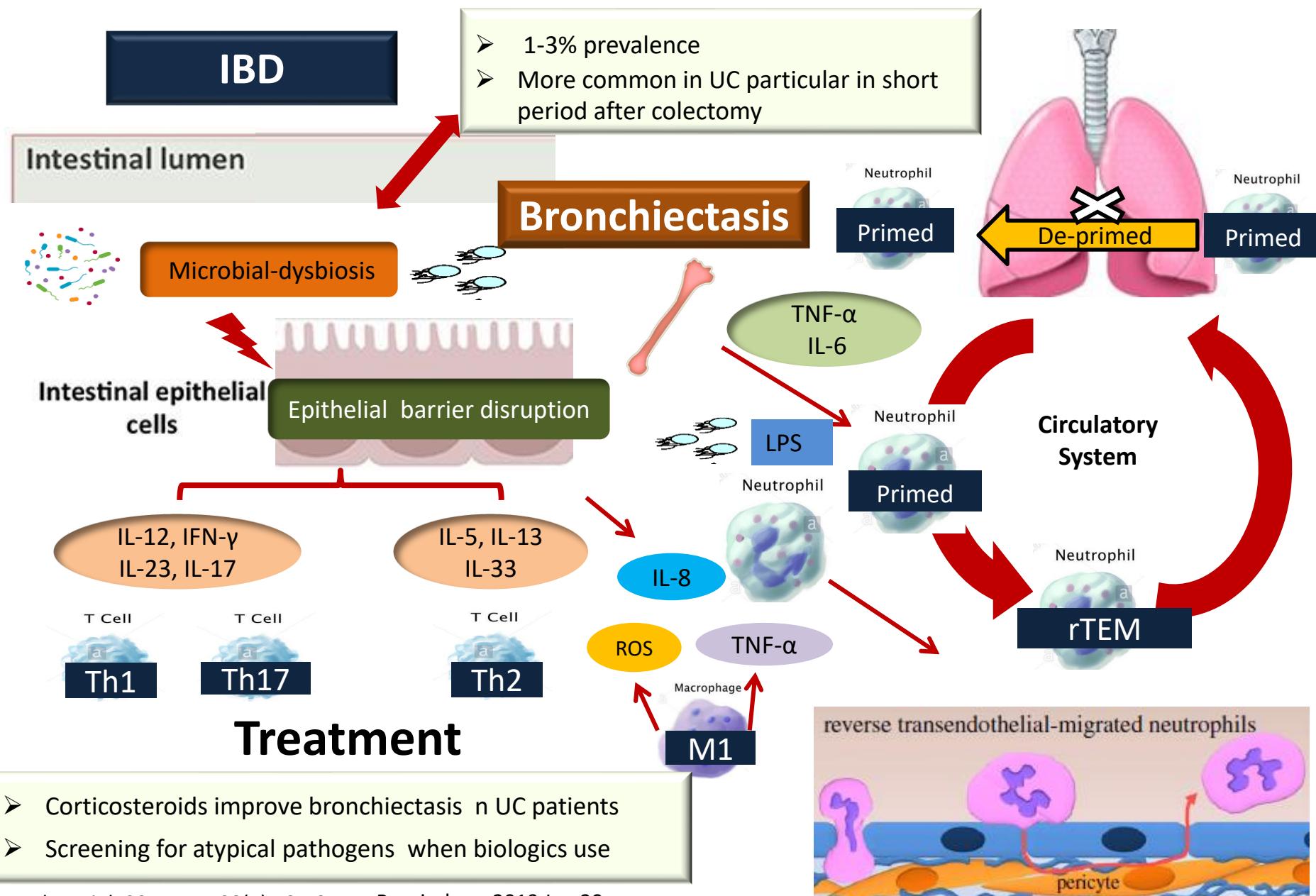
Key features	Crohn's disease	Ulcerative colitis
Histologic findings	Transmural inflammation, presence of granulomas	Mucosal and submucosal inflammation, polymorphonuclear cells aggregate
Endoscopic findings	Discontinuous lesions, strictures, linear ulcerations	Continuous lesions, presence of crypts, formation of residual mucosal tissue



J Leukoc Biol. 2015 Nov;98(5):727-37

J Inflamm Res. 2014; 7: 113–120

# Mechanisms of bronchiectasis in IBD

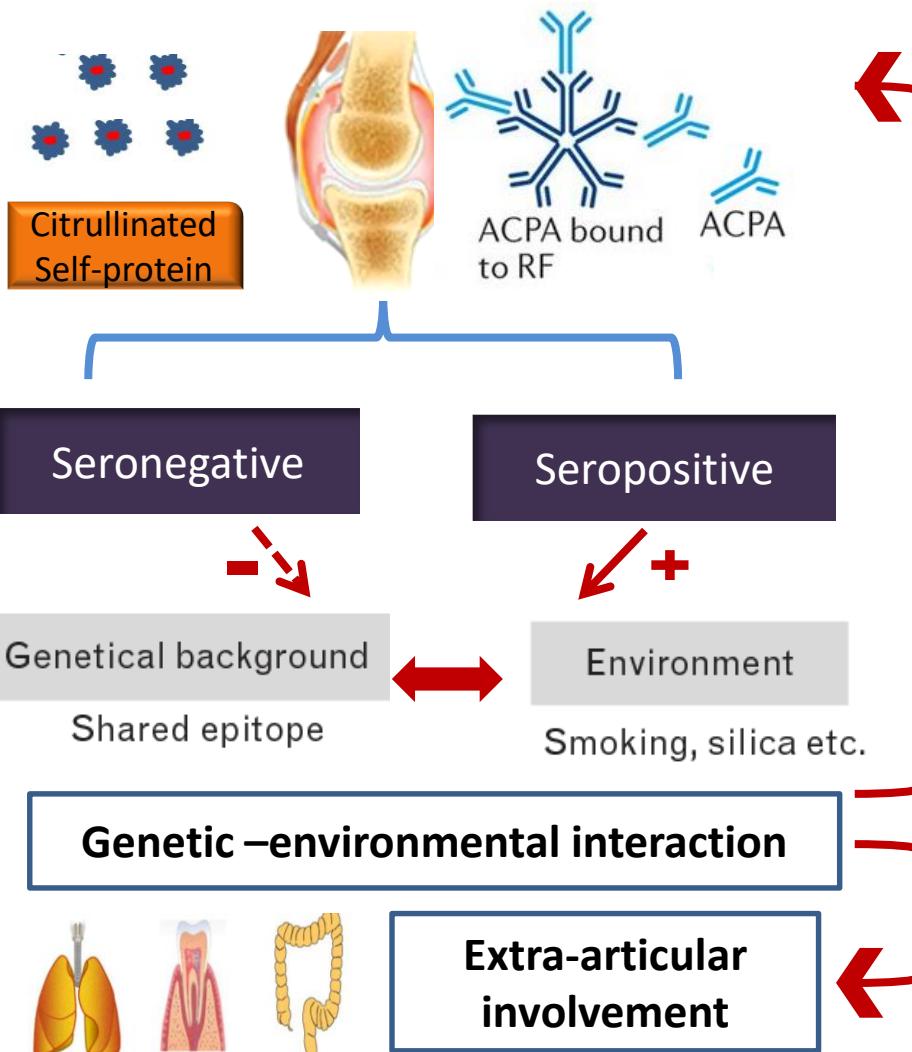


# **Rheumatoid Disease-related comorbidity**

## **Rheumatoid arthritis (RA)**

# Overlap rheumatoid arthritis and bronchiectasis

## Rheumatoid arthritis



Part of the respiratory tract affected	Clinical manifestation
Airways	Bronchiectasis Bronchiolitis COPD/emphysema
Pleura	Pleural effusion / pleuritis
Parenchyma	Interstitial lung disease (UIP, NSIP, COP) Rheumatoid nodules Fibrosis Drug-induced pneumonitis (synthetic, biologic DMARDs) Infections (pneumonitis), malignancies (lung cancer, lymphoma) Emphysema
Vasculature	Vasculitis Pulmonary hypertension Venous thromboembolism

Curr Opin Rheumatol. 2016 Jan;28(1):76-82

## Prevalence of bronchiectasis in RA

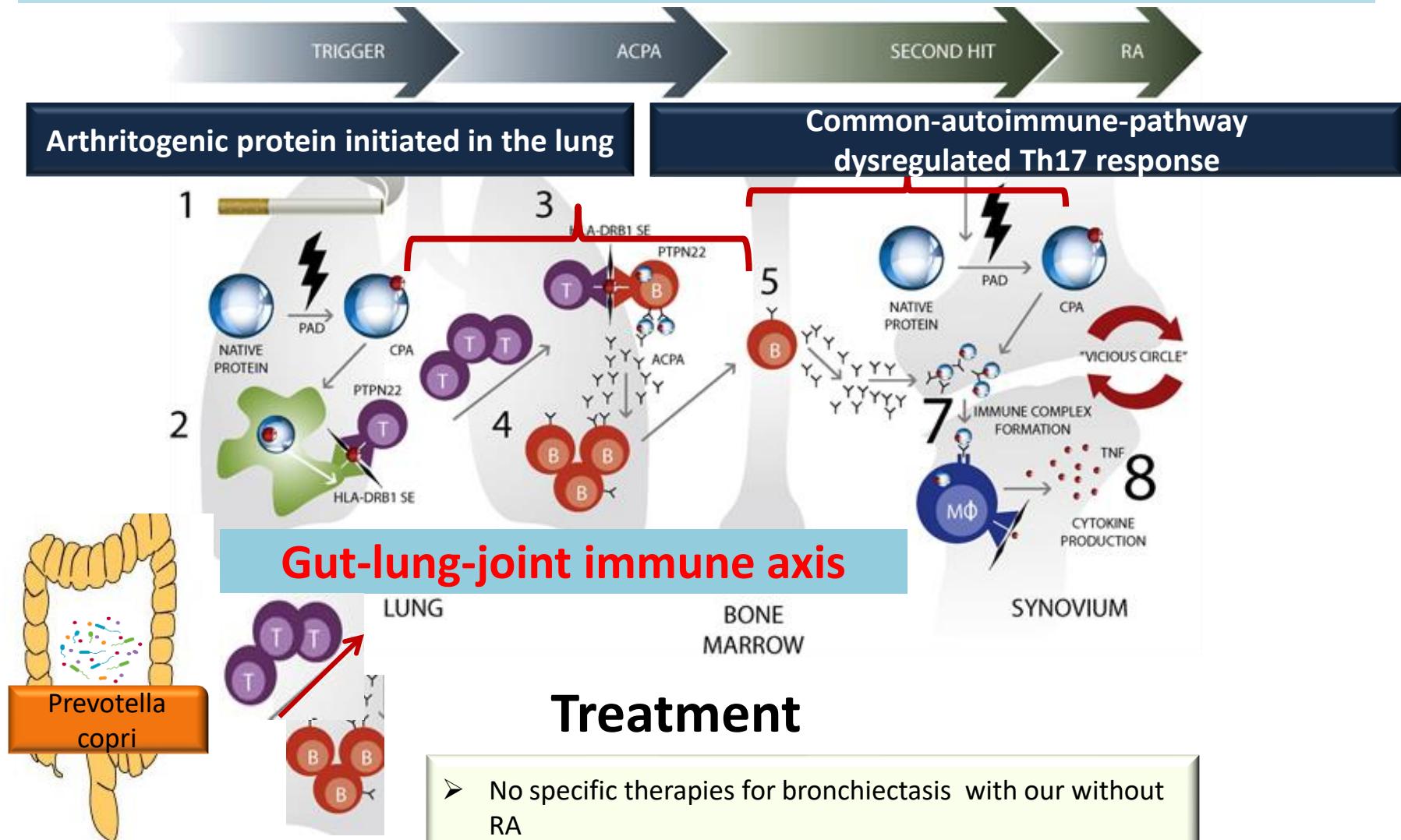
In the range of 1-23%

Pulmonary features tend to precede articular symptoms in RA-Bronchiectasis patients

Annu Rev Pathol. 2016 May 23;11:523-54

# Pathogenesis of RA-bronchiectasis

Causal association, cause or consequence ?





# Aging-related multimorbidity

## Bronchiectasis Severity Index (BSI)

### airway Impairment

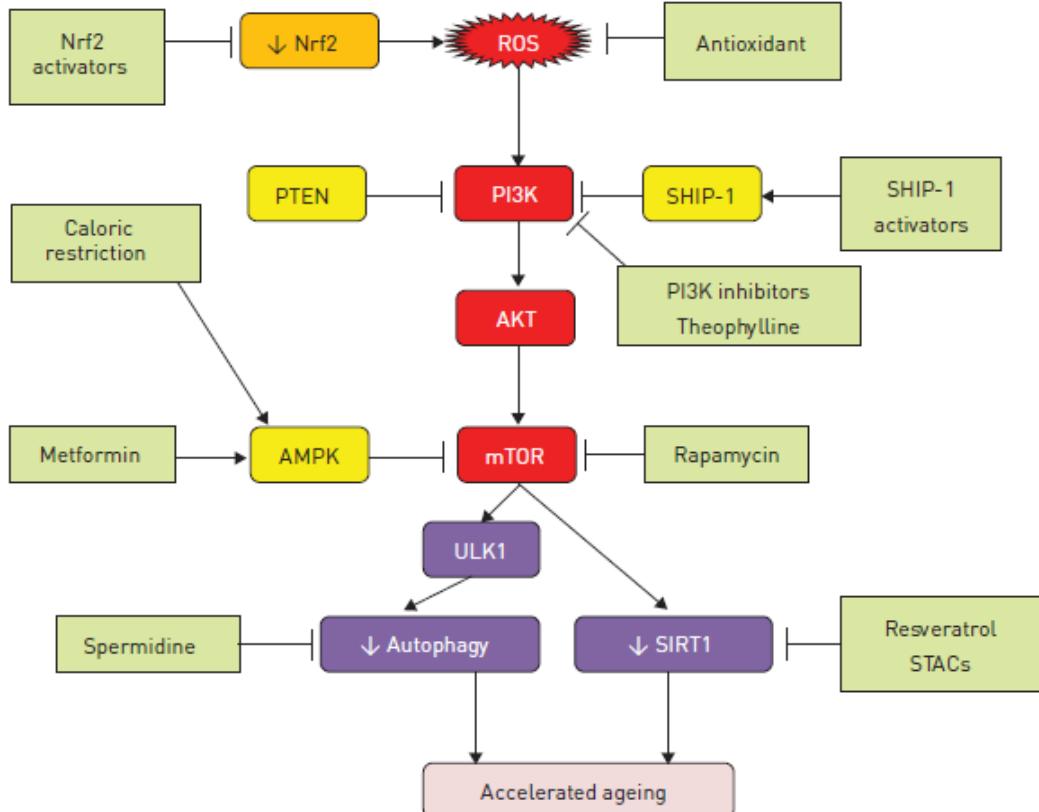
#### FACED score

Mortality

Hospital admissions

All-cause 5-year mortality

Exacerbations



## Bronchiectasis Aetiology Comorbidity Index (BACI)

### comorbidity

All-cause 5-year mortality

Exacerbations

Hospitalization

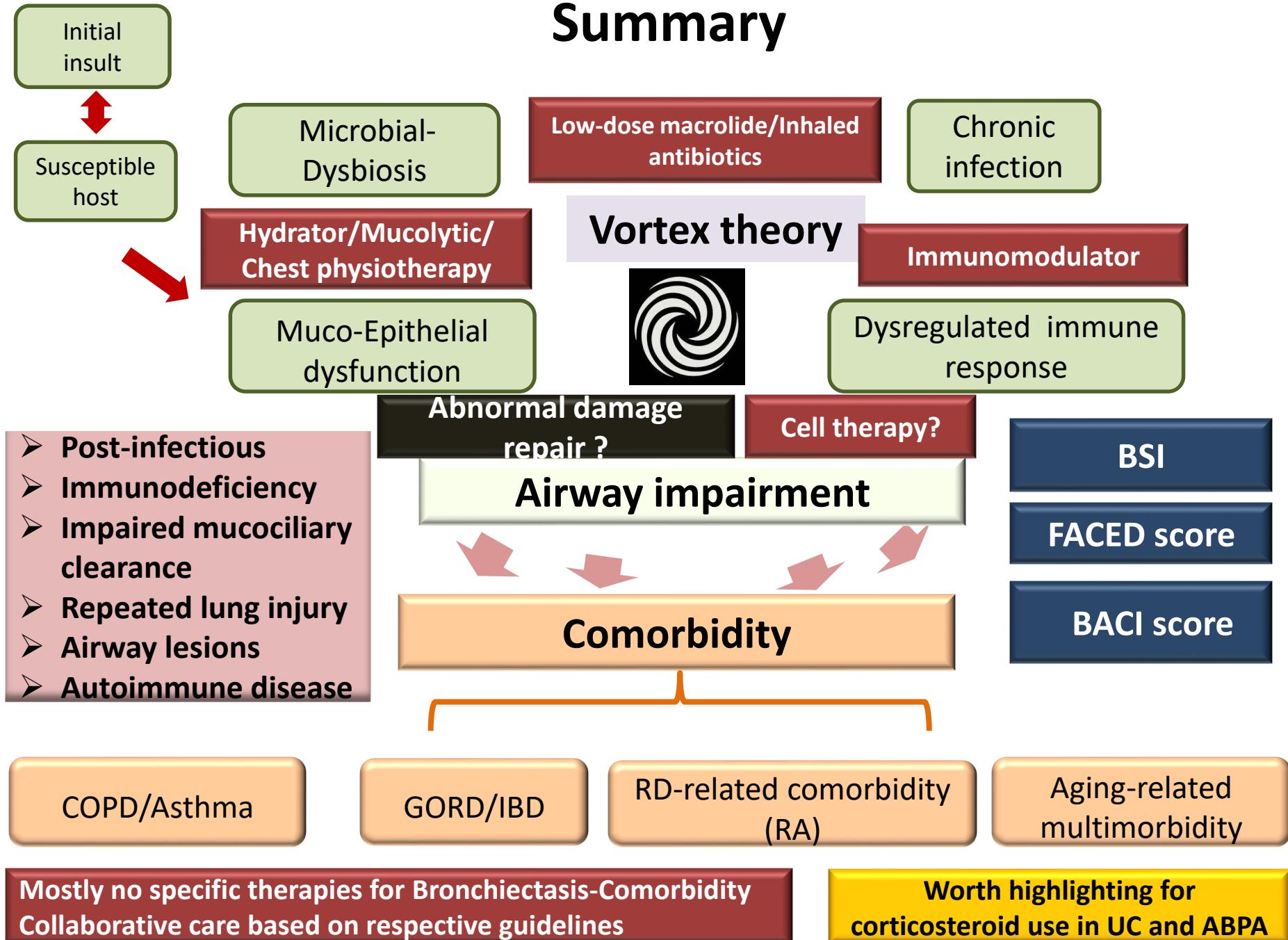
Exacerbations

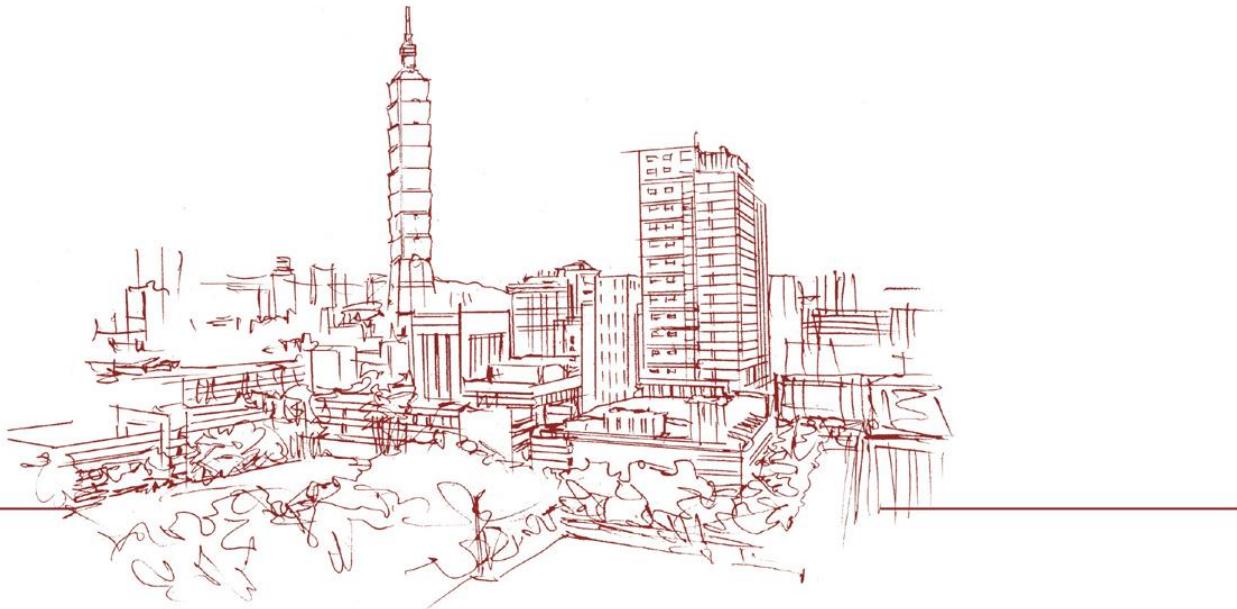
13 comorbidities

Hazard Ratio

- Metastatic malignancy
- Haematological malignancy
- COPD
- Cognitive impairment
- Inflammatory bowel disease
- Liver disease
- Connective tissue disease
- Iron deficiency anemia
- Diabetes
- Asthma
- Pulmonary hypertension
- Peripheral vascular disease
- Ischaemic heart disease

# Summary





# THANKS FOR YOUR ATTENTION



臺北醫學大學  
TAIPEI MEDICAL UNIVERSITY

