Evaluation of Patients with Diffuse Bronchiectasis

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Disclosures

- Advisory Board Member for Gilead in 2017

Objectives

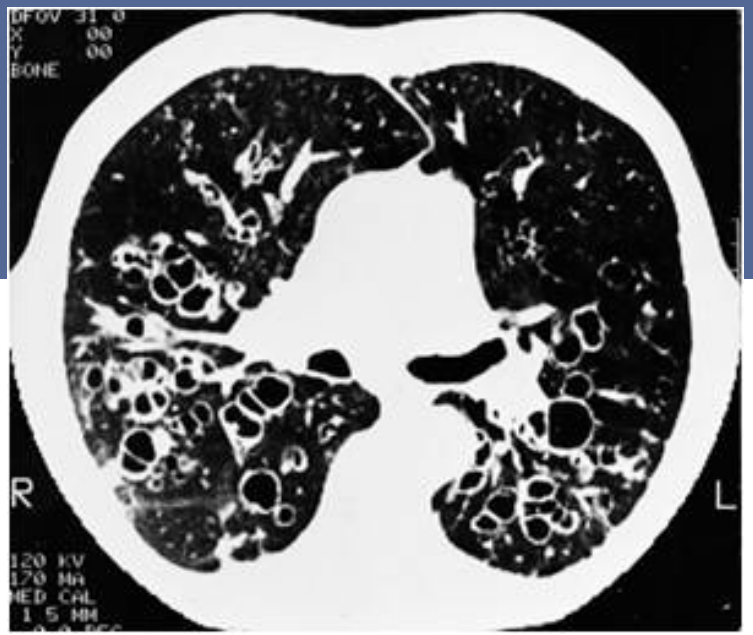
- Objectives for this lecture will include:
  - Understanding what bronchiectasis is
  - Learning the various etiologies of diffuse bronchiectasis in adult patients
  - Learning when to think of Cystic Fibrosis in an adult and how to evaluate a patient for Cystic Fibrosis
  - Learning a comprehensive evaluation of non-CF Bronchiectasis patients
  - Implementing these objectives into clinical practice to hopefully effect patient outcomes

Why investigate for the etiology of bronchiectasis?

- Finding the etiology can potentially change management in up to 37% of patients
  - A. Shoemark, L Ozerovitch, R. Wilson. *Respiratory Medicine* 2007; 101: p 1163-1170
  - PJ McShane, E Naureckas, M Strek. *CHEST* 2012; 142 (1): 159-167
- Patients want to know the cause
- Further our understanding of bronchiectasis

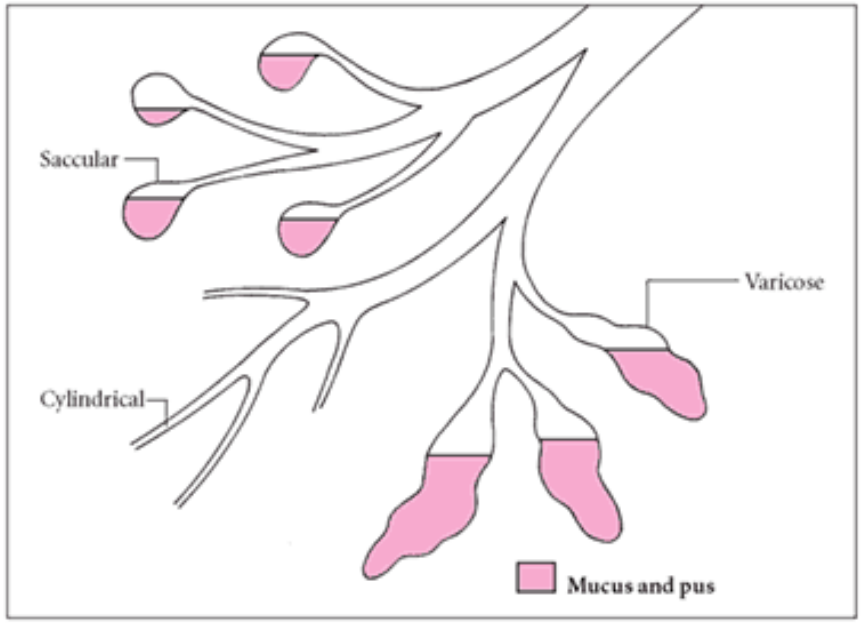
What is bronchiectasis?

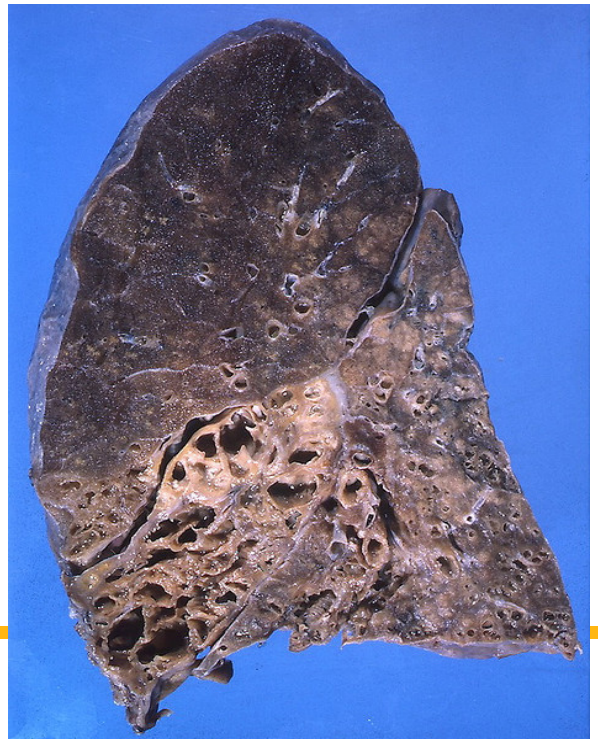
- Abnormal chronic dilation of one or more bronchi
- Irreversible
- The structural abnormality of the airway predisposes patients to bacterial infections, probably due to impaired mucus clearance
- Cycle of inflammation, infection >> further damage to airways
- Symptoms: chronic cough, sputum production, respiratory infections, progressive obstructive lung disease, chest pain, shortness of breath…..



FORMS OF BRONCHIAL DILATATION

Dilatations of the air sacs occur due to bronchiectasis, as depicted below.





Etiologies of Bronchiectasis

- Cystic Fibrosis
- Primary Ciliary Dyskinesia
- Immune Deficiency
- Autoimmunity/inflammatory (associated with RA, Sjogrens, IBD…)
- ABPA
- Aspiration
- Alpha-1 Antitrypsin
- Post-infectious
- Idiopathic
- Other rarer misc diseases (foreign body aspiration, Young's syndrome, congenital anatomical defects)

What is Cystic Fibrosis?

- Most common inherited life-shortening disease in Caucasians of Northern European ancestry
- Affects the lungs and digestive system of about 30,000 children and adults in the US (70,000 worldwide)
- About 1000 new cases of CF are diagnosed each year
- More than 50% of the CF patient population in the United States are ≥ 21 years old

History of Cystic Fibrosis

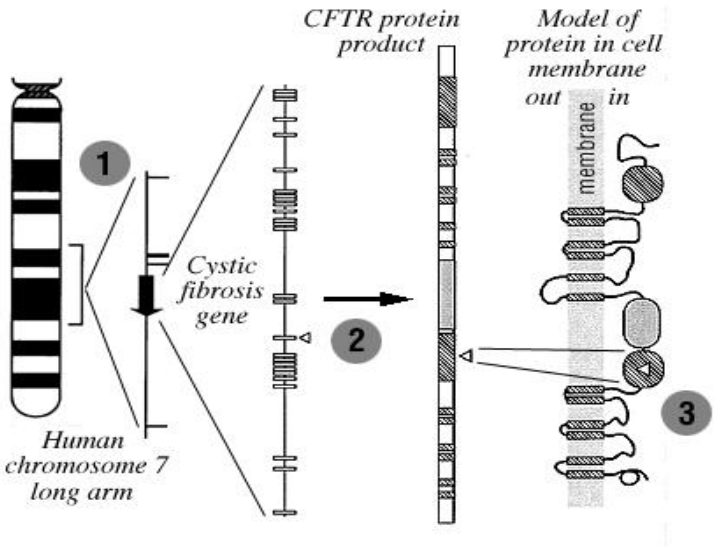
- 1938: clinical syndrome first described by Dr. Dorothy Anderson, severe malnutrition, hypochloremia, dehydration
- 1940s: autosomal recessive inheritance
- 1950-1960: life expectancy <1 year
- 1980s: CF epithelial cells characterized by abnormal ion transport. Chloride channel affected with exit blocked and sodium reabsorption accelerated
- 1989: CF gene located to long arm of chromosome 7

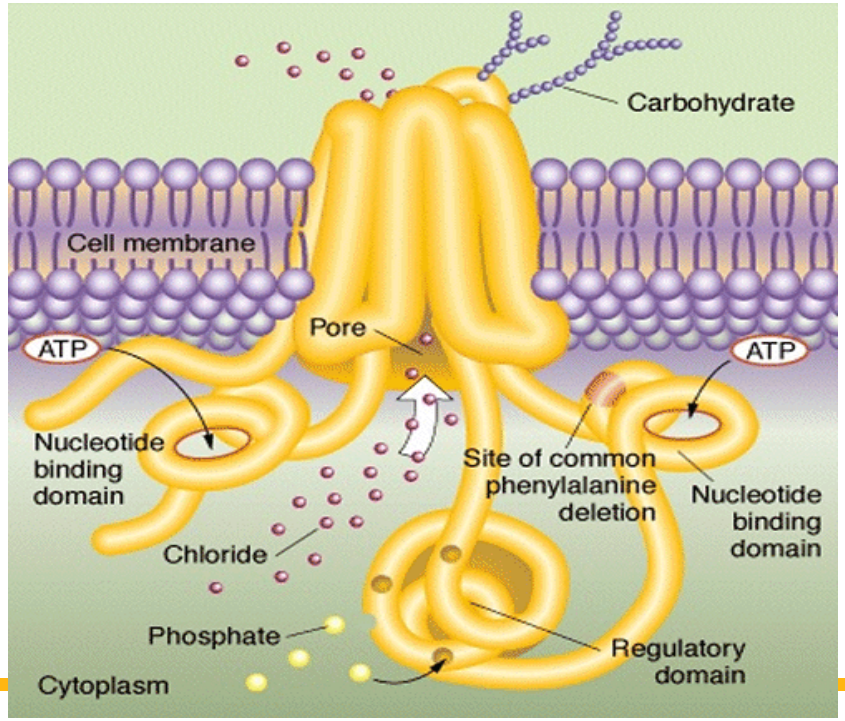
What is Cystic Fibrosis?

- Multisystem disease affecting the digestive system, sweat glands, reproductive tract, and lungs
- Autosomal recessive disorder caused by mutations in a gene on the long arm of chromosome 7 that encodes for the CFTR protein
- Most common mutation is a 3 base pair deletion that codes for phenylalanine at position 508 (ΔF508) accounting for 70% of CF alleles in Caucasians
- >1500 distinct sequence changes in the CFTR gene are associated with clinical disease
- Disease presentation may vary

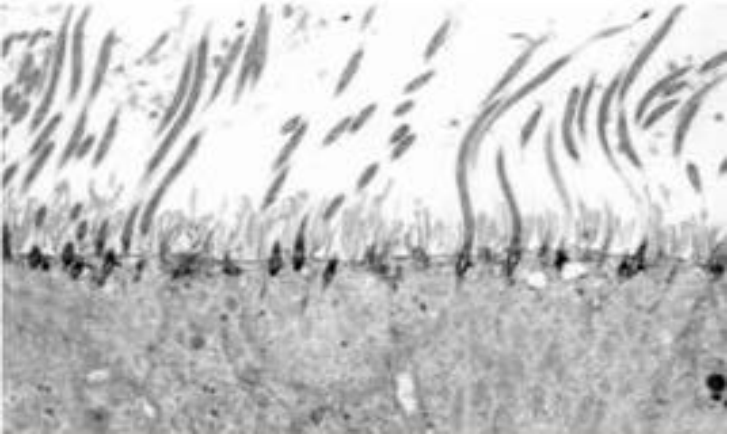
CFTR protein

- CFTR protein is a transmembrane protein that functions as a chloride channel



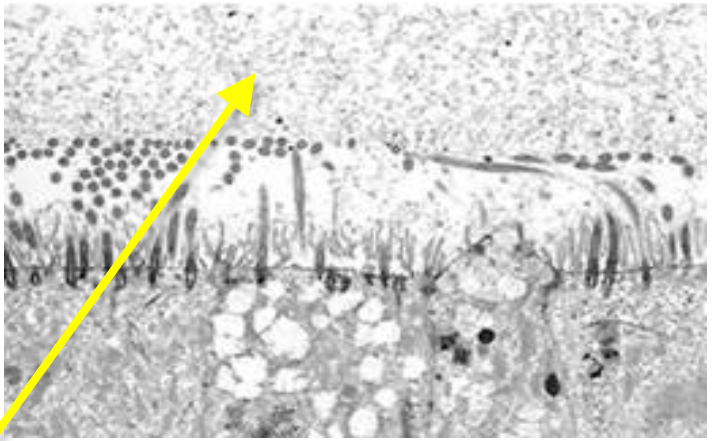


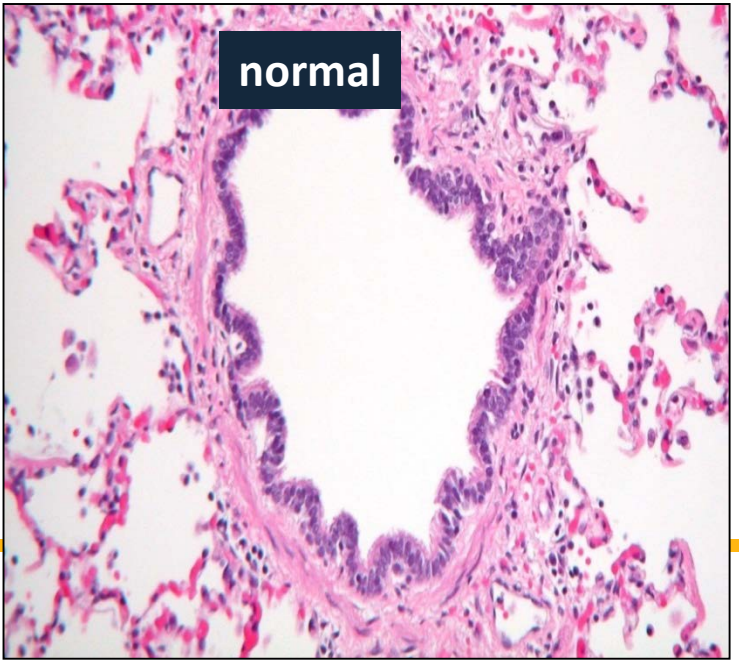
Mucociliary Clearance and Obstruction



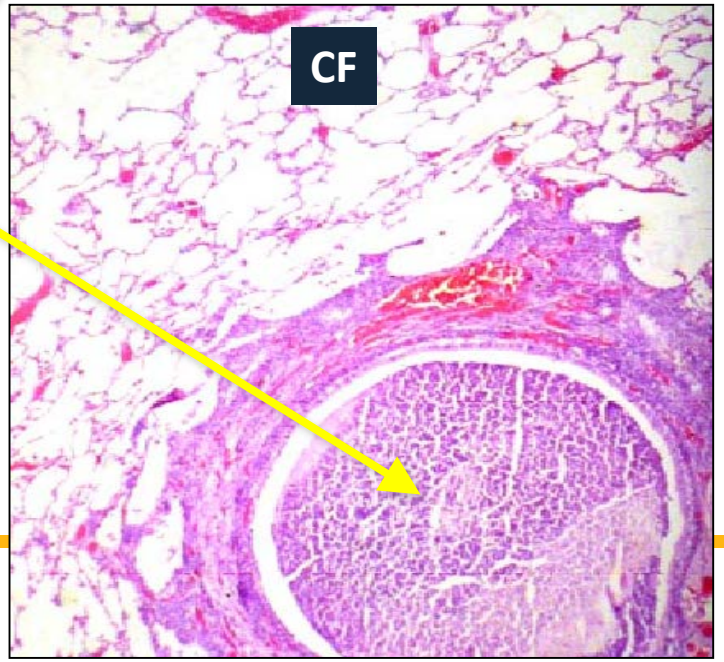
Periciliary Liquid (PCL)

Surface Epithelial Cells

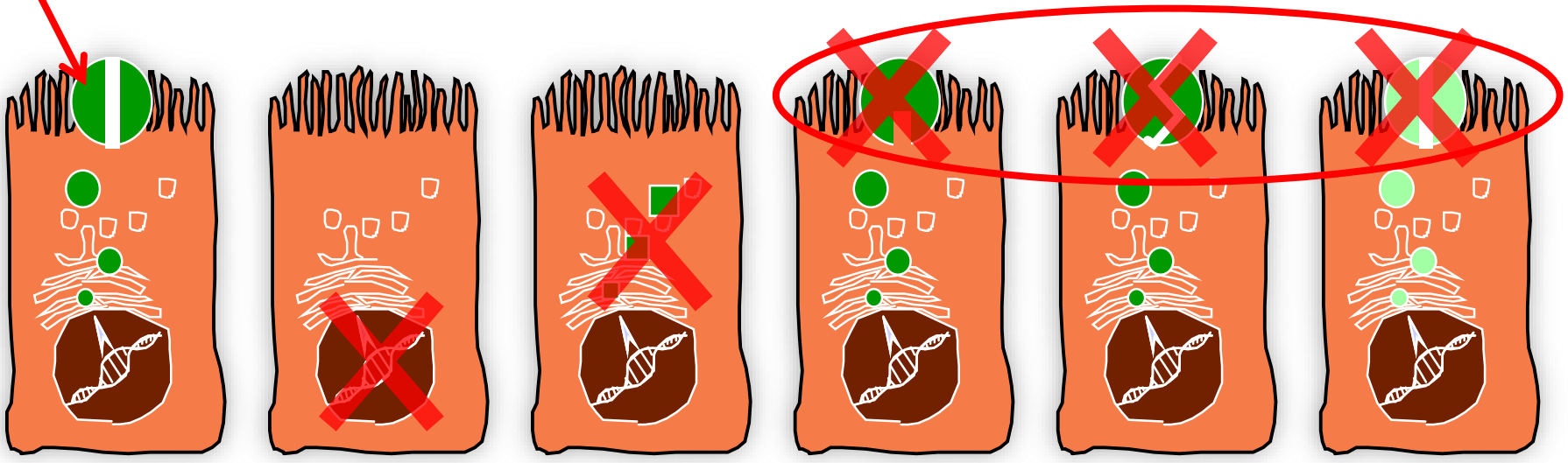




Tenacious Mucus



Understanding the Complexity of CFTR & the Classes of CFTR mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in gating	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	D1152H	3849+10kbC–>T
	12%	87%	5%	5%	5%

Does your patient have CF?

- 7% of adult CF patients are diagnosed during adulthood

Symptoms suggestive of CF

- Chronic Cough and sputum production
- Recurrent sinus infections
- Idiopathic chronic pancreatitis
- Inability to gain weight
- Clubbing
- Abnormal BMs suggestive of pancreatic insufficiency
- Diabetes or hepatobiliary disease
- Sputum cultures
  - S.aureua, S. maltophilia, P. Aeruginosa, B.cepacia, A. xylosoxidans
- Infertility
  - Male patients with congenital absence of the Vas Deferens

Sweat Chloride Test

- Positive test >60 mmol/L
- Borderline 30-60 mmol/L “possible CF”
- “Negative” <30 mmol/L
- But we now know that some patients with CF can have a “normal” or “negative” sweat test!

Testing….

- If a sweat test is intermediate/borderline: repeat it

- Send blood for molecular testing/DNA analysis
  - If you find 2 CFTR mutations => CF
  - Send expanded DNA analysis: In California blood can be sent Ambry Genetics for testing (need insurance auth). “508 first”
  - Send blood to Johns Hopkins for extended DNA analysis

  - Refer to an Adult CF Center

Nasal Potential Difference Measurement

- Must be done at an experienced center
- Not widely available

Primary Ciliary Dyskinesia

- Genetic disease rendering cilia immotile, dysmotile or missing
- Symptoms of Chronic cough and sputum production, presenting early in life
- Recurrent sinus infections/chronic congestion/rhinorrhea
- Chronic otitis media
- Infertility in both males and females
- Situs inversus
- Testing for CF being ruled out

PCD

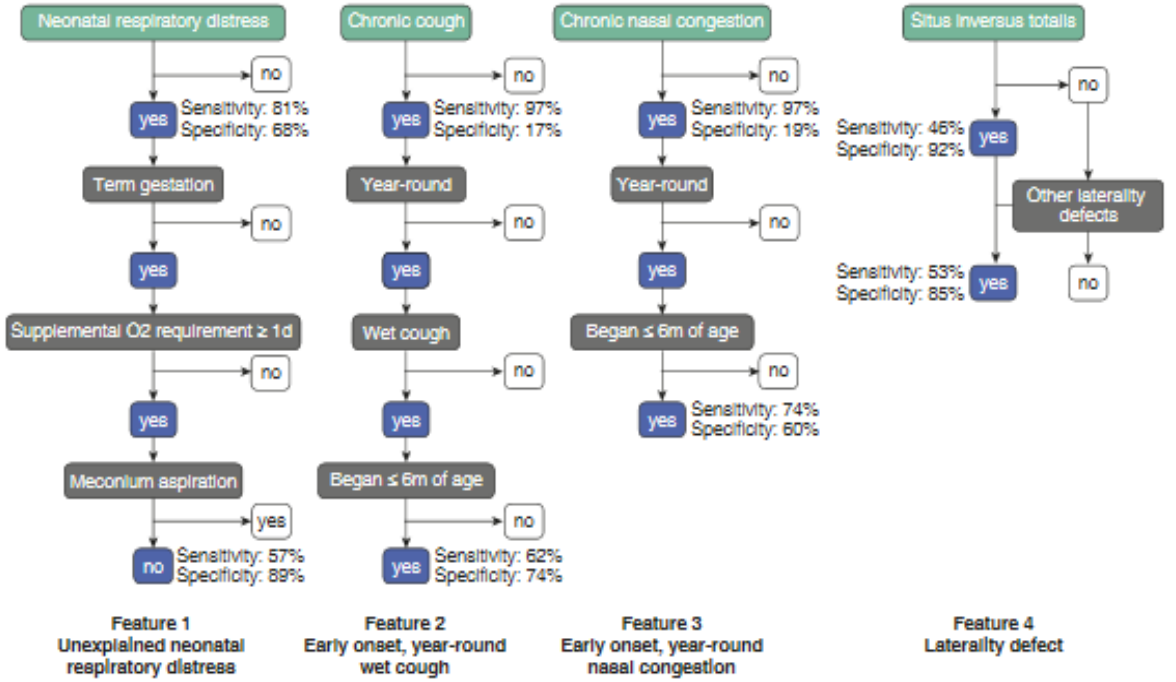


Figure 1. Schematic diagram showing general clinical features and series of questions to define criteria-defined clinical features. The four criteria-defined clinical features most predictive of primary ciliary dyskinesia were unexplained neonatal respiratory distress, early onset, year-round wet cough, early onset, year-round nasal congestion, and laterality defects. The sensitivity and specificity to identify children and adolescents with primary ciliary dyskinesia are shown for each general clinical feature and its respective criteria-defined clinical feature. Early onset is defined as onset before 6 months of age; year-round is defined as occurring in all 12 months of the year; and wet cough is defined as sounds productive even if unable to expectorate sputum.

Leigh, Ferkol, Davis, et al. *Annals Amer Thor Soc*, 2016; 13 : 1305

Diagnostic Tests for PCD

- Nasal Nitric Oxide is now the diagnostic test for PCD
  - Highly sensitive and specific
  - Noninvasive
  - Fast, inexpensive
- Electron Microscopy
- High Speed Video Microscopy
- Genetic Analysis (only 2/3 of patients will have this)

What evaluation should all non CF bronchiectasis patients have?

ERS Guidelines suggest a “minimal bundle”

- CBC with diff
- Serum Immunoglobulins (Total IgG, IgA, and IgM)
- Test for ABPA with total IgE and specific IgE to Aspergillus and IgG to Aspergillus or skin prick test
- Sputum Culture for Bacteria, AFB and fungus

Polverino, Goeminne, McDonnel, et al. Eur Resp Journal 2017; 50: 1700629

- Alpha 1 Antitrypsin Phenotype (not in the ERS Guideline)
- CT and PFT

Bronchiectasis evaluation

- Detailed history:
- Neonatal history/childhood symptoms
- Family history
- GI symptoms
- Fertility history
- Symptoms of aspiration
- Recurrent infections/pneumonias
- CTD disease symptoms

Bronchiectasis evaluation

- Consider based on history:
  - Swallow evaluation, pH probe study, GERD evaluation
  - CTD disease work up, rheumatoid factor, SSA-SSB
  - Do they need work up for IBD based on symptoms?

- Investigate for a treatable cause
- Identifying one etiology doesn't always rule out another etiology
  - 15% of patients can have more than 1 etiology

- Patients NEED to learn appropriate ACTs

- Bronchiectasis registries
- www.cff.org
- www.bronchiectasisandntminitiative.org
- www.bronchiectasis.au