Bronchiolitis and non-Cystic Fibrosis Bronchiectasis

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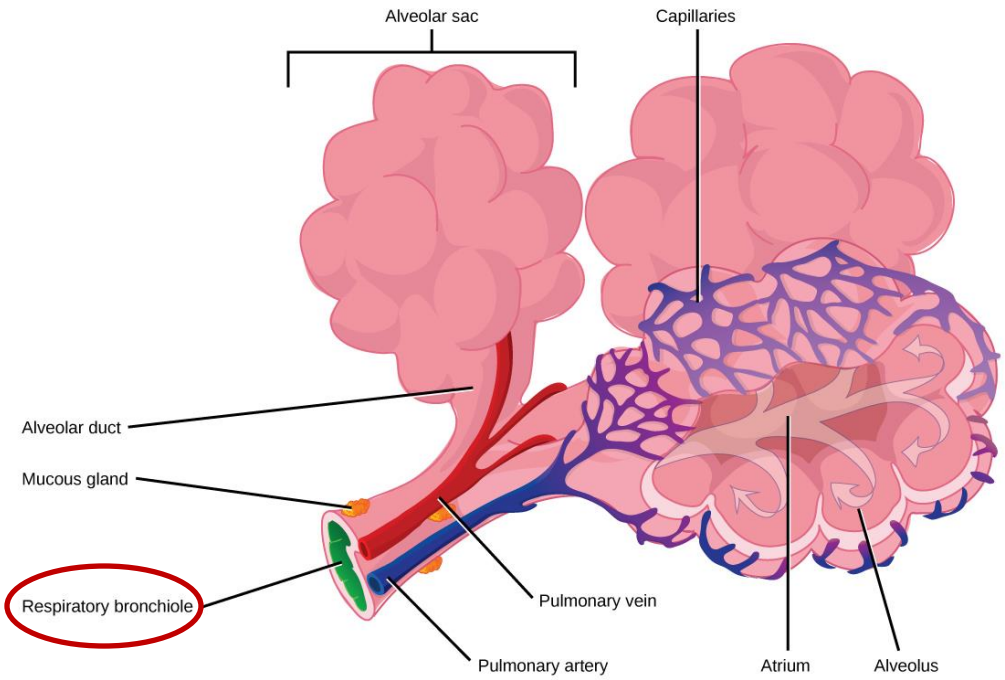
Clinical interests:
Inflammatory lung disease, asthma, bronchiectasis, cystic fibrosis, women's lung health

Conflicts of Interest/Disclosures

- I have no disclosures.

Bronchiolitis

- Bronchiolitis is an inflammatory and/or fibrotic reaction to injury of the bronchioles (small distal airways)
- Diagnosis is often delayed given non-specific symptoms
- Radiographic findings can be subtle.



Bronchiolitis

Radiographic features

- Bronchial wall thickening
- Bronchiolar dilatation (bronchiolectasis)
- Mosaic attenuation/air trapping on inspiratory and expiratory chest CT
- Luminal impaction
- Centrilobular nodules (observed in infectious and respiratory bronchiolitis)
- Subsegmental atelectasis

- Symptoms are often out of proportion to radiographic findings

Bronchiolitis

Primary bronchiolitis

- Acute bronchiolitis
- Constrictive/obliterative bronchiolitis/bronchiolitis obliterans
- Respiratory bronchiolitis
- Follicular bronchiolitis
- Diffuse panbronchiolitis
- Diffuse aspiration bronchiolitis
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
- Mineral dust airway disease

Swaminathan, AC et al. *Annals ATS* 17: 253-263 (2020)
Devakonda, A et al *Chest* 137: 938-951 (2010)

Primary Bronchiolitis

Acute bronchiolitis

- Common in infants and children (RSV most common pathogen)
- In adults, can develop in setting of bacterial and viral infections

Follicular bronchiolitis

- Typically develops in patients with autoimmune disease and immunodeficiencies (e.g. common variable immunodeficiency (CVID))
- COPA syndrome
- Hyperplastic lymphoid follicles are observed along bronchioles

Respiratory bronchiolitis

- Occurs primarily in smokers
- Characteristic finding is pigmented macrophages in respiratory bronchioles
- Ill-defined centrilobular nodules in upper lobe distribution are characteristic

Diffuse panbronchiolitis

- Most commonly seen in Japanese and Asian adults
- High volume of sputum is characteristic
- Chronic sinusitis is also common
- Treated with macrolides

Primary Bronchiolitis

Diffuse aspiration bronchiolitis

- Response to chronic inflammation due to recurrent aspiration

Mineral dust airway disease

- Small airway damage from inhalation exposure to mineral dusts including coal dust, silica, talc, aluminum oxide, mica and asbestos
- Inflammatory response to airway deposition likely contributory

Constrictive (obliterative) bronchiolitis/bronchiolitis obliterans

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)

Primary Bronchiolitis:
Constrictive (obliterative) bronchiolitis/ bronchiolitis obliterans

- Luminal narrowing due to extrinsic compression by peribronchial fibrosis and inflammation
- Imaging findings: mosaicism with air trapping (enhanced on expiratory views) on high resolution chest CT, can also see peripheral bronchiectasis
- Pulmonary function testing: Obstruction with air trapping
- Etiologies include:
  - Stem cell and lung transplant
  - Connective tissue disease, especially rheumatoid arthritis
  - Inflammatory bowel disease
  - Exposure to diacetyl (used in food flavoring, e.g. popcorn factory workers)
  - Inhalational injury
  - Post-infectious

Swaminathan, AC et al. *Annals ATS* 17: 253-263 (2020)
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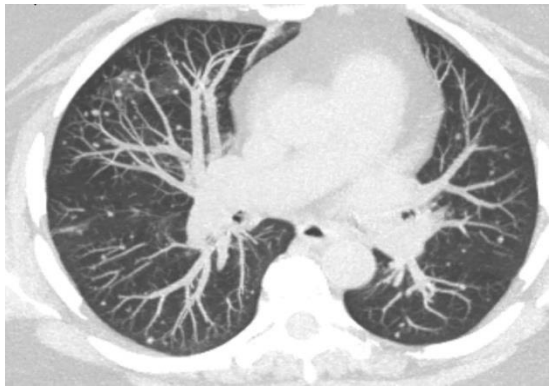
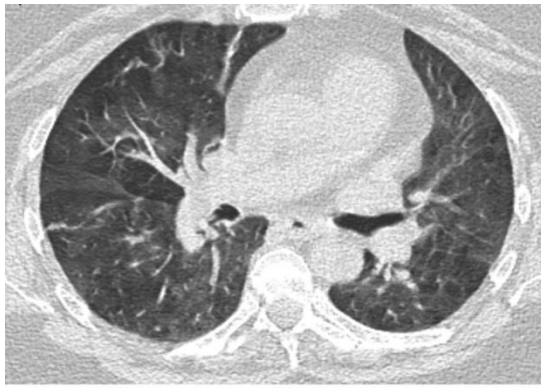
Primary Bronchiolitis:

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)



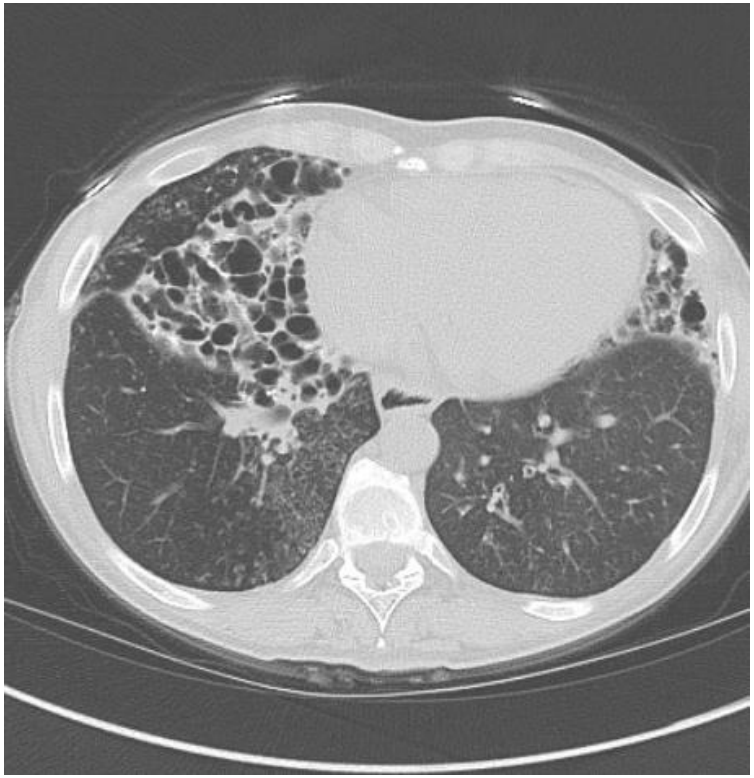


- Luminal narrowing of airways by proliferation of neuroendocrine cells +/- tumorlets
- Most commonly seen in middle aged women
- Imaging: mosaicism with air trapping (enhanced on expiratory views) on high resolution chest CT, small nodules and bronchial wall thickening
- PFTs: obstructive or mixed obstructive restrictive
- Slow progression is typical but can lead to respiratory insufficiency

Rossi, G et al. *ERJ* 47: 1829–1841 (2016)

Non-Cystic Fibrosis Bronchiectasis (NCFB)

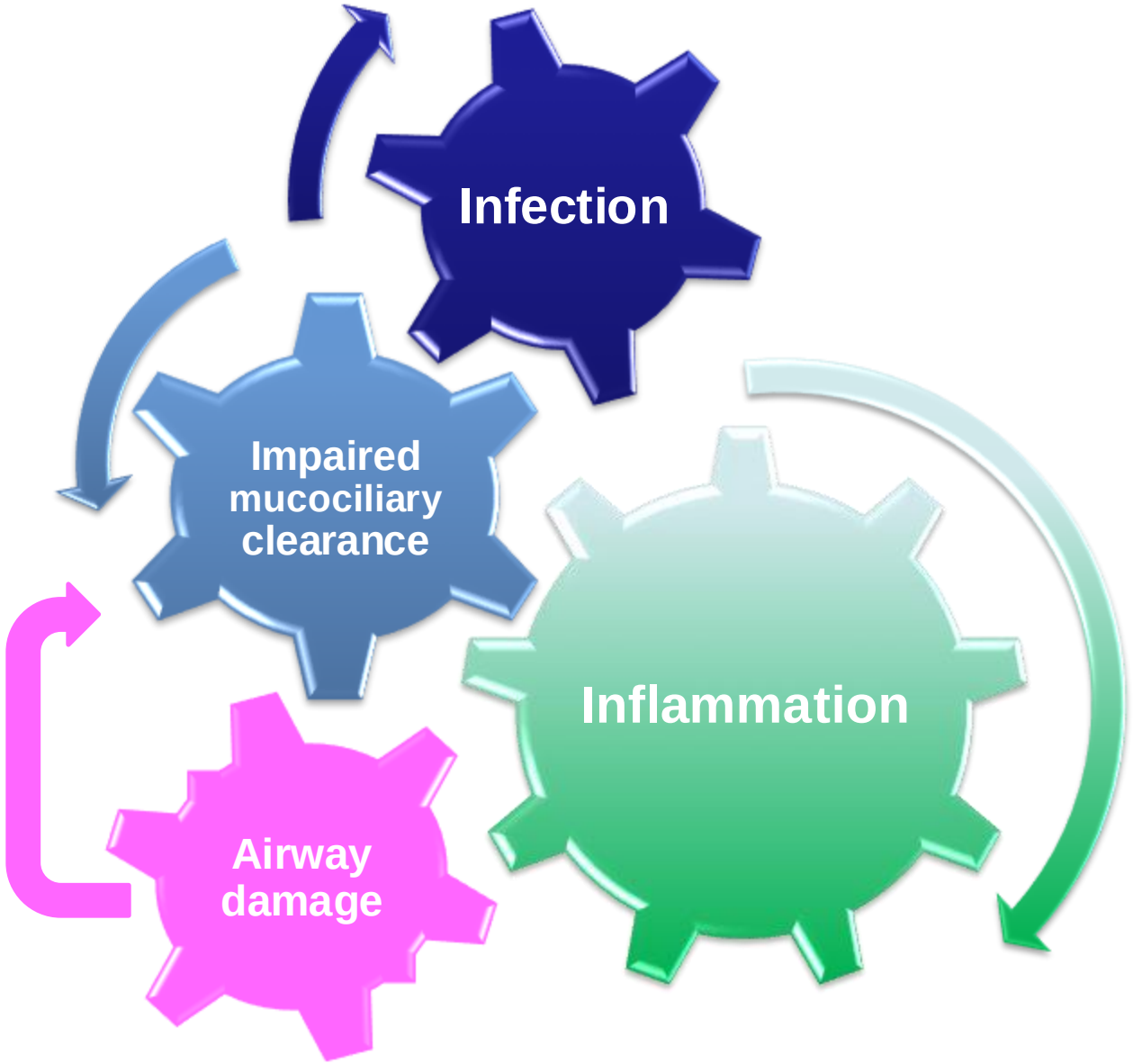
Non-CF Bronchiectasis



- Bronchiectasis is a disease characterized by permanent bronchial dilatation, impaired mucus clearance and recurrent infections
- It is a phenotypically and clinically heterogeneous disease
- Increasing in incidence
  - 139 patients/100,000
  - Incidence increases with age
- Chronic symptoms and therapy burden impact quality of life

Weycker, D. et al. *Chronic Resp Disease* (2017)

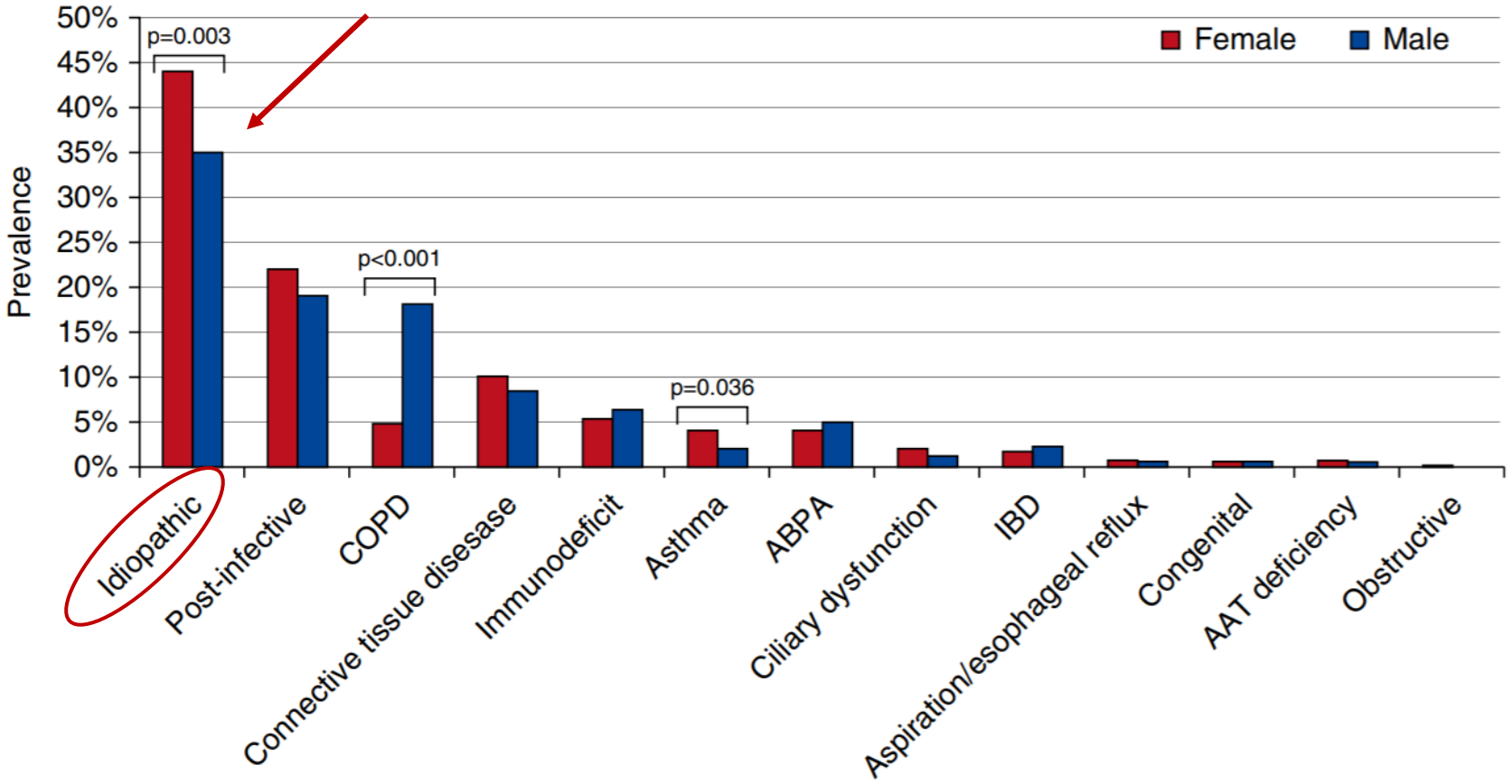
Pathophysiology of bronchiectasis



Etiologies of non-CF bronchiectasis

Idiopathic	Post-infectious	Genetic
Inflammatory	Ciliary Dysfunction	COPD/asthma
Congenital	Immune Disorders	Miscellaneous

Etiologies of non-CF bronchiectasis



Lonni, S. et al. *Annals of ATS* (2015)

Etiologies of non-CF bronchiectasis

Post-infectious

- Granulomatous infections
- Pneumonia
- Recurrent respiratory infections
- Viral/bacterial infections
  - Pertussis, measles, adeno

Genetic

- Cystic fibrosis
- Primary ciliary dyskinesia
- Alpha-1 anti-trypsin deficiency

Inflammatory

- Sarcoidosis
- Allergic bronchopulmonary aspergillosis (ABPA)
- Connective tissue diseases
- Inflammatory bowel disease

Immune disorders

- Common variable immunodeficiency
- Hypogammaglobulinemia
- Specific antibody deficiency
- Neutrophil function disorders
- HIV

Etiologies of non-CF Bronchiectasis

Congenital

- Mounier-Kuhn syndrome
- William Campbell syndrome
- Agenesis
- Sequestrations
- Hypoplasia

COPD/asthma

- COPD (more common in men)
- Asthma

Inhalational/injury

- GERD
- Aspiration pneumonia
- Toxic inhalation
- Thermal injury

Miscellaneous

- Radiation injury
- Traction bronchiectasis
- Post-obstructive
- Yellow nail syndrome
- Young syndrome

Bronchiectasis endotypes/phenotypes

- *Pseudomonas aeruginosa* colonization
  - Increased frequency of exacerbations
  - Increased risk of hospitalization
  - Decreased quality of life
  - *Pseudomonas aeruginosa* airway colonization is independently associated with mortality in non-CF bronchiectasis
- Eosinophilic bronchiectasis
  - Patients with ≥300 cells/μl blood eosinophils had higher sputum eosinophil counts
  - Patients with blood eosinophil counts of ≥300 cells/μl were associated with shorter time to exacerbation

King, PT et al. *Respiratory Medicine* (2007)
Mac Aogáin, M et al. *ERJ* (2018)
Goeminne, PC et al. *Resp Res* (2012)

Diagnostic evaluation

- **Recommend stepwise approach**
  - H&P, family history, exposure history
  - High resolution chest CT scan
  - Pulmonary function testing
  - Sputum microbial studies:
    - Respiratory culture
    - Atypical mycobacteria culture
    - Fungal culture
- Serologic testing
  - CBC/differential
  - Quantitative immunoglobulins (including IgG subclasses and IgE)
  - Rheumatoid factor, ANA, alpha-1 anti-trypsin
  - ESR/CRP

Diagnostic evaluation

- Additional studies:
  - Immunodeficiency evaluation
  - *Aspergillus* specific IgE
  - Additional connective tissue serologies
  - Barium swallow/pH probe/esophageal manometry
  - Sweat chloride
  - Cystic fibrosis transmembrane conductance regulator (CFTR) mutation analysis
  - Primary ciliary dyskinesia (PCD) mutation analysis
  - Nasal nitric oxide (low in patients with PCD)

"Adult onset" cystic fibrosis

- Although the majority of patients with CF are diagnosed in childhood, patients have been diagnosed as late as their 9th decade
- 9.0% of new diagnoses of CF between 2001 and 2005 were made in adults
- The availability of highly effective CFTR modulators has transformed the treatment of CF and highlights the importance of identifying these patients.

Keating, CL et al, *Chest* 2010; 137(5): 1157–1163

Consider testing for cystic fibrosis in bronchiectasis patients with:

- Nasal polyposis
- Male infertility/azoospermia/congenital absence of the vas deferens (CABVD)
- History of pancreatitis/pancreatic insufficiency
- ABPA in a non-asthmatic
- Aquagenic keratoderma (wrinkling)
- Age <40 at diagnosis

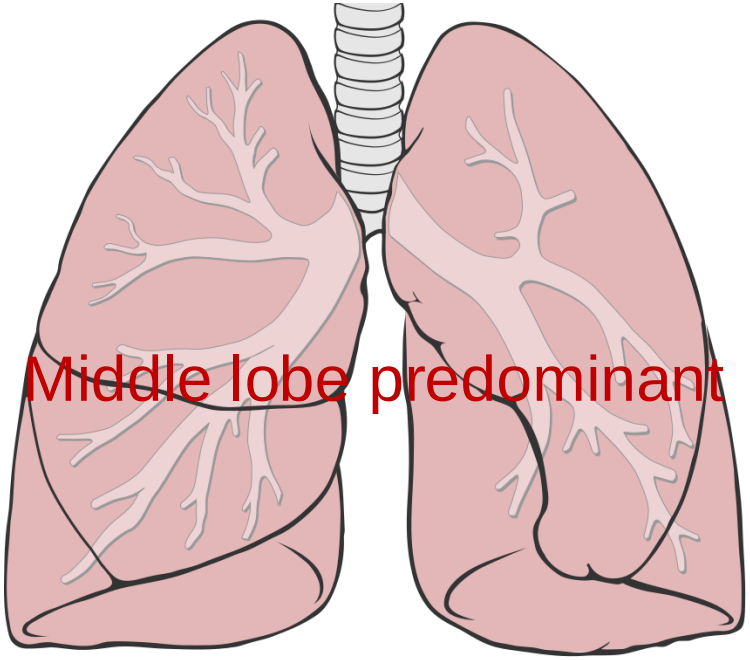
Barry, P et al, *Semin Respir Crit Care Med* 2023;44:242–251.

Radiographic features

- **Focal bronchiectasis**
  - Congenital (e.g. bronchial atresia)
  - Endobronchial lesion
  - Extrinsic compression
  - Foreign body
  - Airway stenosis
- **Diffuse bronchiectasis**
  - **Central**
    - Allergic bronchopulmonary aspergillosis (ABPA)
    - Mounier Kuhn syndrome
  - **Upper, middle and lower** lobe predominant

Radiographic features

Upper lobe predominant



Middle lobe predominant

Lower lobe predominant

Cystic fibrosis
Sarcoidosis
Tuberculosis
Post-radiation fibrosis
Allergic bronchopulmonary aspergillosis

- Non-tuberculous mycobacteria
- Primary ciliary dyskinesia

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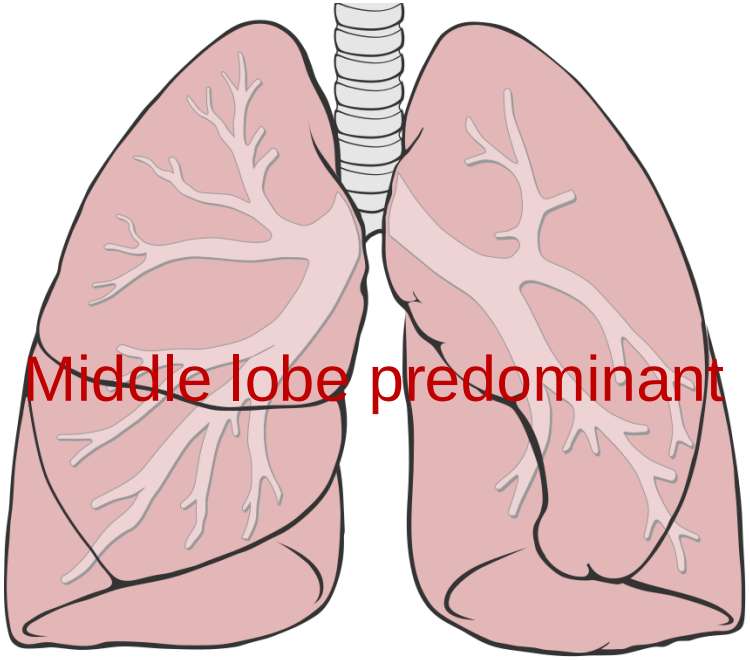
- Recurrent aspiration
- Hypogammaglobulinemia
- Common variable immunodeficiency (CVID)

Radiographic features

Upper lobe predominant



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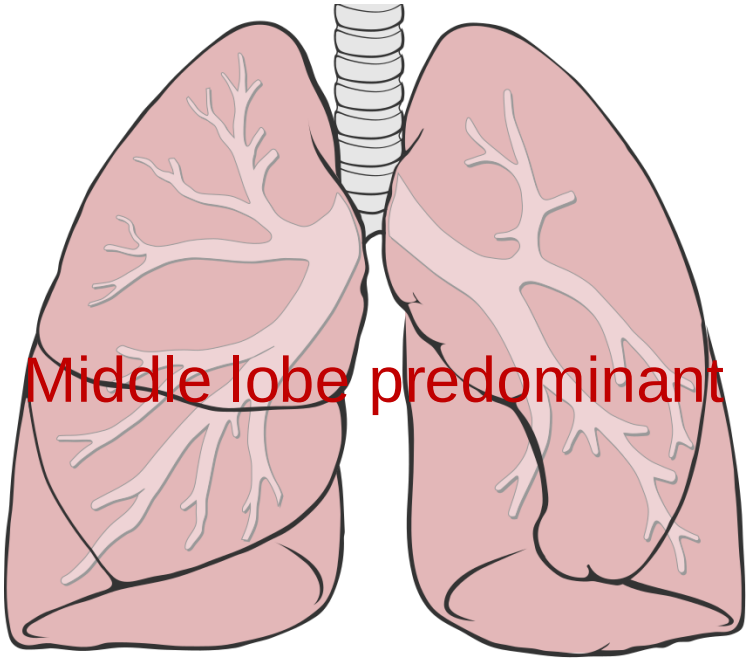

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Middle lobe predominant

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Lower lobe predominant

Primary ciliary dyskinesia

Recurrent aspiration

Hypogammaglobulinemia

Common variable immunodeficiency (CVID)

Non-tuberculous mycobacteria

- Common infection in patients with NCFB
- More common in women
- Increasing prevalence in US and worldwide
- Associated with significant morbidity and mortality
- Form biofilms and are hard to eradicate
- Associated with disease progression in NCFB
- Increased incidence of CFTR mutations

Don't forget to screen your patients with bronchiectasis for NTM.

Mac Aogáin, M et al. *EJR* (2019)
Goeminne, PC et al. *Resp Res* (2012)

Management

- Airway clearance
  - Positive expiratory pressure (PEP devices)
  - Mucolytics/hyperosmolar agents
  - Airway clearance vest, manual chest PT, drainage/breathing techniques
- Oral and IV antibiotics
  - Monitor sputum samples for airway colonization and new respiratory pathogens (bacterial and NTM)
  - Treatment is guided by culture data and resistance patterns
- Inhaled antibiotics
  - Inhaled antibiotics can deliver high doses of antibiotics locally
  - There is a direct correlation between bacterial load and inflammation
- Macrolides

Positive expiratory pressure devices

Airway clearance: other modalities

- Airway clearance vest
- Manual chest physiotherapy
- Postural drainage
- Huff coughing
- Autogenic drainage (breathing technique)

Hyperosmolar agents/Mucolytics

- Unlike cystic fibrosis, there only a few RCT for mucolytics or other inhalational therapies in NCFB.
- Nebulized hypertonic saline is a useful adjunct to enhance airway clearance by reducing osmolality. Small studies have reported decreased sputum burden and viscosity and QoL metrics. Kellett, F. *Resp Med* (2005 and 2011).
- The mucolytic dornase alpha (recombinant human DNase) was studied in NCFB and had no impact on lung function or exacerbations. In one study, it was found to be detrimental in NCFB. Wills, PJ et al., *AJRCCM* (1996).
- Inhaled mannitol had no effect on primary outcomes in NCFB. There was a reduction in time to first exacerbation and quality of life metrics. Bilton D, et al., *Thorax* (2014).
- The mucolytic N-acetylcysteine is an additional option although limited data in NCFB.

Anti-inflammatory therapy

- Inhaled and systemic corticosteroids have not been shown to alter the trajectory of NCFB.
- Macrolides
  - Exert immunomodulator effects that impact mucus production, biofilm formation and inhibit inflammatory mediators
    - EMBRACE trial
    - BAT trial
    - BLESS trial

Role of macrolides

- **EMBRACE** trial (Azithromycin 500 mg 3x/week vs placebo x 6 months) Wong, C. et al., *Lancet*, 2012.
- **BAT** trial (azithromycin 250 mg daily x 12 months vs placebo) Altenburg, J et al., *JAMA*, 2013.
- **BLESS** trial (erythromycin twice a day vs placebo x 48 weeks) Serisier, DJ et al., *JAMA*, 2013.
- All trials demonstrated reduction in the frequency of exacerbations and improvement in QoL metrics.
- Treatment option for patients with frequent exacerbations.
- Potential concerns:
  - Development of antimicrobial resistance
  - Hearing loss (should have screening audiogram), liver and GI toxicity
  - Should not be used in patients with prolonged QT
  - **Patients need to be appropriately screened for non-tuberculous mycobacteria**

Brensocatib

- Oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1)
- Prevents the activation of neutrophil serine proteases
- In phase II study (WILLOW), brensocatib prolonged time to first exacerbation and reduced the frequency of bronchiectasis exacerbations
- Phase III study (ASPEN) met the primary endpoint of reducing the annualized rate of pulmonary exacerbations
- Not yet available

Chalmers, JD et al. NEJM (2020)

Summary

- Bronchiolitis is characterized by narrowing of small airways due to inflammation/fibrosis and can have many etiologies.
- Symptoms in bronchiolitis are often out of proportion to imaging findings. Radiographic findings include mosaic attenuation, bronchial wall thickening, bronchiolar dilatation and centrilobular nodules.
- Non-CF bronchiectasis (NCFB) is a heterogeneous disease characterized by damaged airways, impaired mucus clearance and recurrent infection.
- Patients with bronchiectasis should undergo systematic evaluation to identify etiology. ~40% of patients have idiopathic bronchiectasis.
- The airway microbiome in NCFB is important in management and prognosis.
- *Pseudomonas aeruginosa* airway colonization is independently associated with mortality in non-CF bronchiectasis.
- Airway clearance, hyperosmolar/mucolytics, and appropriate use of inhaled and systemic antibiotics are important in the management of NCFB.
- Macrolide therapy in select patients can improve exacerbation rates.
- Additional advances in management of NCFB will require the identification of endotypes and phenotypes to guide development of precision medicine approaches.

References

Bronchiolitis:

- Swaminathan, AC et al. *Annals ATS* 17: 253-263 (2020)
- Devakonda, A et al. *Chest* 137: 938-951 (2010)

Bronchiectasis:

- O'Donnell, AE *N Engl J Med* 387: 533-545 (2022)
- Lonni, S et al. *Annals ATS* 12: 1764–1770 (2015)
- McShane, PJ et al. *AJRCCM* 188: 647–656 (2013)

Review Questions

1. 39-year-old woman with longstanding history of asthma that had been well controlled on moderate dose ICS/LABA inhaler presents with a two-month history of persistent dyspnea, cough, wheeze and sputum production. Her ICS/LABA dosing was increased with modest impact on her symptoms. She did not respond to empiric treatment with antibiotics. Her chest imaging is notable for interval development of mild bronchiectasis and mucus plugging. Her FEV1 has decreased by 22% compared to her prior testing.

What do you recommend as next step?

A. Montelukast
B. Mepolizumab
C. Immunoglobulin E level
D. CFTR mutation analysis

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Review Questions

Rationale:

- Allergic bronchopulmonary aspergillosis (ABPA) develops in ~2% of patients with asthma (higher incidence in corticosteroid dependent).
- Patients present with increased respiratory symptoms and sputum production and can report brown plugs.
- IgE is an excellent screening test and is part of diagnostic criteria for ABPA. IgE levels are typically > 500 IU/ml in patients with ABPA and peripheral eosinophilia is often observed.
- Characteristic radiographic findings include central bronchiectasis with mucus plugging although bronchiectasis is not always present.
- Although augmenting her asthma regimen may be appropriate, her symptoms and imaging findings merit evaluation for ABPA.
- Evaluation for cystic fibrosis should be considered in patients diagnosed with ABPA without history of asthma.

Review Questions

2. 46-year-old electrician with a history of hypertension, hyperlipidemia, GERD and active 2-pack a day smoker is involved in a car accident. He had a CT scan trauma series in the ED that was notable for bilateral upper lobe predominant ill-defined centrilobular nodules and tibia/fibula fractures. He denies any active respiratory symptoms other than an occasional cough. He is hemodynamically stable with oxygen saturation of 96%. He denies hemoptysis, environmental or inhalational exposures. His only medications are metoprolol, atorvastatin and famotidine.

What histologic features would you expect to find if he had a lung biopsy?

A. Interstitial inflammation and poorly formed interstitial granulomas
B. Diffuse alveolar hemorrhage
C. Lymphoid hyperplasia of bronchioles
D. Pigmented macrophages in respiratory bronchioles.

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Review Questions

Rationale:

- Pigmented macrophages in respiratory bronchioles is the histologic pattern observed in respiratory bronchiolitis (RB).
- Respiratory bronchiolitis is often asymptomatic and almost exclusively occurs in smokers.
- Respiratory bronchiolitis is suggested by smoking history and characteristic upper lobe predominant, ill-defined centrilobular nodules.
- Diagnosis can often be made based on characteristic radiographic appearance and smoking history.
- Smoking cessation is imperative to prevent progression to respiratory bronchiolitis-associated interstitial lung disease (RB-ILD).
- Option A (Interstitial inflammation and poorly formed interstitial granulomas) is pathology associated with hypersensitivity pneumonitis, which is also associated with upper lobe predominant centrilobular nodules. However, asymptomatic patient, lack of exposures and smoking history make RB more likely.
- Option B (Diffuse alveolar hemorrhage) unlikely in asymptomatic, healthy patient and is not limited to a specific lung zone.
- Option C (Lymphoid hyperplasia of bronchioles) is pathology associated with follicular bronchiolitis. Patient does not have typical risk factors. Follicular bronchiolitis would not have upper lobe distribution. In follicular bronchiolitis, small ground glass centrilobular nodules are often associated with peribronchial and ground glass nodules.

Thank you!

I have no disclosures.