The OTHER

Chronic Obstructive

Pulmonary Diseases

Expanding the Differential Diagnosis

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is the term used for describing pulmonary disorders with chronic and progressive airflow obstruction with little reversibility. The classic diseases that compose the definition of COPD are chronic bronchitis and emphysema.[1] Chronic bronchitis is a disease characterized by airflow obstruction and mucus hypersecretion. It is clinically defined by the presence of sputum production for at least 3 months for two successive years. Emphysema is characterized by airspace enlargement and alveolo-capillary destruction. Emphysema is a histological definition.[2] Both diseases are associated with cigarette smoking in greater than 90% of cases. It is estimated that 14 million people in the United States suffer from COPD. It is the fourth leading cause of death in the United States.[1,2] Although these diseases are not difficult to diagnose, chronic bronchitis and emphysema can present difficult therapeutic dilemmas for the clinician.

The main focus of this Program is to describe the OTHER chronic obstructive pulmonary diseases. These less common diseases pose interesting diagnostic and therapeutic challenges. Their presentation can mimic chronic bronchitis, emphysema, and even asthma. At the time of presentation, they can be easily misdiagnosed leading to either incorrect or inadequate treatment.[3,4] The study of these less common chronic obstructive pulmonary diseases provides a better understanding of the various sites of anatomical airflow obstruction in the lung.

This Protocol will review the various OTHER chronic obstructive pulmonary diseases by following an "upstream" route from the larynx to the alveoli. This approach will provide the physician with a broader differential diagnosis of chronic airflow obstruction leading to a heightened awareness for these less common diseases.

Review of airway anatomy:

The lung has over 300,000 airways branching out through more than 23 generations.[5] As an example, there are 25 bronchial/bronchiolar generations from the trachea and right mainstem bronchus to the acinar structures of the posterobasal segment of the lower lobe. Bronchi contain supporting cartilage in their walls and secrete mucus from submucosal glands.[6]

Further upstream, the lung's airways divide into the small airways, which are defined as those with a luminal diameter of less than 2-3 mm. These airways are comprised of small bronchi and bronchioles (1mm or less)[7]. The bronchioles can be distinguished from bronchi by their lack of supporting cartilage. The first branching bronchioles are the membranous bronchioles which in turn branch 5-10 times ending in the lobular bronchiole, the airway feeding the **secondary pulmonary lobule** or lobule of Miller. This structure is the smallest discrete unit of lung that is bound by visible connective tissue septae, the interlobular septae. The lobular bronchiole then divides into three or more terminal bronchioles that feed an acinar structure. The acinus contains two to five generations of respiratory bronchioles branching into alveolar ducts and alveoli[8]. Chronic obstructive disease can develop from obstruction or destruction of the large (central) and small (peripheral) airways. This will be discussed in the next section.

Anatomical sites of airflow obstruction:

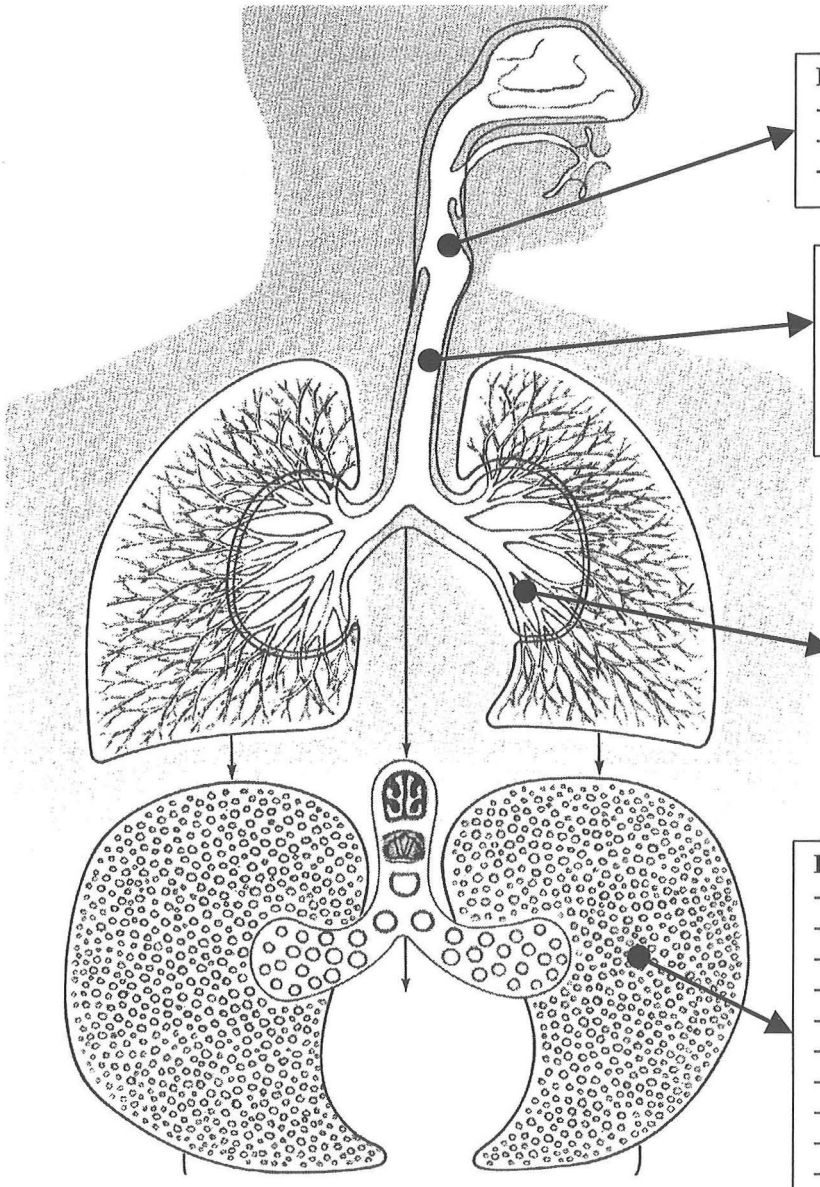
Airflow obstruction can occur at any generation of airway branching. The degree of impairment depends on the number and extent of obstruction of the involved airways. There are three major sites for airway obstruction in the lung: the upper airway, large (central) airways, and small (peripheral) airways.[6] In the normal lung, the greatest contribution to airway resistance (60-70%) occurs in the large (central) airways. This is explained by their relative small total cross-sectional area and association with turbulent air flow.[9] Therefore, a small decrease in luminal diameter can account for significant airflow limitation.

As the lung branches, the lumen of the airways progressively narrows to a diameter of less than 2 mm. Although these small airways are relatively narrow, they have branched through many subdivisions accounting for a cross-sectional area ranging from 53 to 186 cm^2.[10] Initial reports suggested that in the normal lung, these small airways contributed little (10-20%) to the overall airways resistance.[11] Therefore, these airways were given the name "silent airways".[12] This term suggested that significant small airway destruction or narrowing had to occur before airflow limitation could be detected by conventional pulmonary function testing or become clinically significant. Recent

reports demonstrate that the total contribution to airway resistance by the small airways was previously underestimated and is in the range of 30-40%.[6,13,14,15]

In emphysema, the site of airflow obstruction is primarily in the small airways. Utilizing lung obtained from autopsies or resections of advanced COPD patients, Hogg et al.[11] measured total peripheral airway resistance by wedging a peripheral catheter in the small airways (2-3 mm). In these emphysema patients, the small (peripheral) airways contributed up to 80% of the total airway resistance.

The best way to classify the OTHER chronic obstructive pulmonary diseases is by their location in the various anatomical sites of airflow obstruction in the respiratory tract (Figure 1).



Diseases of the Upper Airway:
- Vocal cord paralysis
- Laryngeal tumors
- Vocal cord dysfunction

Diseases of the trachea:
- Tracheal neoplasm
- Tracheal stenosis
- Tracheobronchopathia osteochondroplastica
- Amyloidosis
- Tracheobronchomegaly

Diseases of the large (central) airways:
- Bronchial tumors
- Bronchostenosis
- Bronchiectasis
- Cystic Fibrosis
- Amyloid
- Sarcoid
- Relapsing polychondritis

Diseases of the peripheral (small) airways:
- Sarcoid
- Hypersensitivity pneumonitis
- Mineral dust-induced small airways disease
- Bronchiolitis obliterans
- Respiratory bronchiolitis-ILD
- Lymphangiomyomatosis
- Eosinophilic granuloma
- Lymphocytic bronchiolitis
- Diffuse panbronchiolitis
- Recurrent pulmonary capillaritis

Figure 1: Diagram illustrating the cross-sectional area of the branching airways. The OTHER chronic obstructive pulmonary diseases are grouped by anatomical site of airflow obstruction. The diagram has been adapted from Netter FH. The Respiratory System. *In:* Divertie MB, Brass A, eds. The CIBA Collection of Medical Illustrations, Volume 7, 2nd edition. Summit, New Jersey: CIBA, 1980; Page 55. The disease categories were integrated by Dr. Carlos Girod based on the study of the references listed in the bibliography section.

When to suspect the diagnosis of one of the OTHER chronic obstructive pulmonary diseases?

These OTHER chronic pulmonary disorders are usually confused with the classic COPD diseases: chronic bronchitis, emphysema and bronchial asthma. The patients may be smokers or ex-smokers with dyspnea, cough, sputum production, and wheezing as seen in the COPD patient. The clinician may find that the physical exam, chest radiograph, and pulmonary function tests are consistent with COPD. A diagnosis is usually delayed and the patients are treated with COPD therapy.[3] Therefore, it is imperative to have a level of "healthy" skepticism when examining a patient with airflow obstruction that doesn't fit the usual COPD pattern or doesn't respond to therapy as expected.

The clinician should suspect one of the OTHER obstructive pulmonary diseases when dealing with a patient with chronic airflow obstruction and:

a) Little or no smoking history (<20 pack-year smoking)[1,3]
b) Onset of disease before the 4th decade or after the 7th decade of life
c) Rapid fall in FEV1 (> 75cc/year)[1,3,16]
d) Presence of connective tissue disease[17]
e) Presence of occupational or environmental exposures[14]
f) Unexplained systemic illness
g) Multi-system organ dysfunction

DISEASES OF THE UPPER AIRWAY: LARYNX AND TRACHEA

The "upper airway" corresponds to the airway passages from the nose to the main carina. These passages are usually divided into extra-thoracic or intra-thoracic airways depending on the location of the obstruction above or below the thoracic inlet, respectively. The larynx is extra-thoracic and is divided into the supraglottis, glottis, and subglottis. It normally accounts for 40% airflow resistance during quiet breathing. During increasing respiratory demands, the resistance is reduced by reflex dilatation of its lumen.[9] The trachea measures approximately 10-13 cm in length and is divided into extra- and intra-thoracic components.[18] Significant airflow limitation can occur when it is compressed, narrowed, or stenosed. The number of diseases leading to obstruction of the upper airway is extensive and a recent review lists more than fifty disorders.[19] This discussion will focus on upper airway lesions that present with **chronic** airflow limitation that can be easily mistaken for COPD. [3]

Chronic upper airway obstruction can present with cough (sometimes "barking"), recurrent infection, stridor, dyspnea, and hoarseness. It is important to ask the patient for a history of prior endotracheal intubation or tracheostomy. The presence of dyspnea with exertion and stridor is usually associated with critical airway narrowing ranging from 5-8 mm. Pulmonary function testing with spirometry is relatively insensitive until the airway narrowing becomes critical. At that point, reduced inspiratory or expiratory flow rates are seen.[3,19] Intrathoracic airway obstruction (predominantly tracheal lesions) is characterized by abnormalities in the flow-volume loop during exhalation. During forced exhalation, the pleural pressure becomes greater than the intraluminal tracheal pressure leading to further collapse and accentuation of the tracheal stenosis (Figure 2a). If the lesion is located extra-thoracic, a flattening or "serration" of the inspiratory flow volume loop is seen. This is related to magnification of the stenosis by

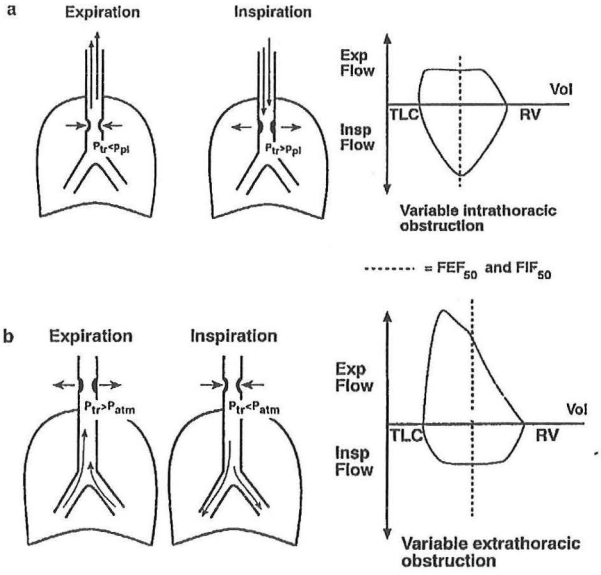


Figure 2: Flow-volume loops demonstrating intra- and extra-thoracic airway obstruction. Reference 3.

collapse during inspiration when the intraluminal tracheal pressures fall below atmospheric pressure (Figure 2b). If the lesion is fixed in the trachea, a fixed intra-thoracic obstruction develops affecting both inspiratory and expiratory flow loops.[3,19,20] All clinicians evaluating patients for chronic dyspnea and airflow obstruction, should learn to recognize these abnormal patterns of airflow obstruction.

The list of diseases of the upper airway that lead to obstruction is extensive and a complete discussion of these disorders is beyond the scope of this presentation. The reader is referred to an excellent review listed in reference 19. Of these diseases, a few present with a subacute or chronic picture that is at times difficult to differentiate from emphysema and chronic bronchitis (See Table 1)[3,21]. Of these diseases, the most important and elusive diagnoses include vocal cord paralysis or tumors, tracheal stenosis or tumors, tracheobronchopathia osteochondroplastica, tracheobronchial amyloidosis, and tracheobronchomegaly.

Table 1: Important causes of upper airway obstruction mimicking COPD:

Variable Intrathoracic Obstruction:	**Variable Extrathoracic Obstruction:**
Tracheal tumors	Vocal cord dysfunction
Tracheobronchomalacia	Glottic stricture
Tracheobronchomegaly (Mounier-Kuhn)	Laryngeal tumor

Fixed obstruction:
Bilateral vocal cord paralysis
Tracheal stenosis
Tracheal tumors
Extrinsic compression from goiter, lymphoadenopathy, or tumor
Fibrosing mediastinitis
Tracheobronchopathia chondroplastica
Tracheobronchial amyloidosis

Adapted from St. John RC, Gadek JE, Pacht ER. Journal of General Internal Medicine 1993 (Reference 3) and Braman SS and Gaissert HA. Upper airway obstruction. *In:* Fishman's Pulmonary Diseases and Disorders 1997 (Reference 21).

A- Vocal cord paralysis or tumors:

Vocal cord paralysis is the most common cause of a variable extra-thoracic airway obstruction[21] and may mimic COPD. The causes of vocal cord paralysis includes trauma, iatrogenic injury (intubation, endoscopy, damage to recurrent laryngeal nerve), or laryngeal or intra-thoracic tumors. Vocal cord paralysis can present with dyspnea, hoarseness, wheezing, and stridor. Of interest, a preserved voice can be seen with bilateral vocal cord paralysis or with gradual unilateral paralysis. This is related to equal bilateral vibration of the vocal cords allowing for preserved speech.[19] Vocal cord tumors can occur supraglottic and glottic demonstrating a flow-volume loop with a variable extra-thoracic airway obstruction (Figure 2b). The diagnosis of a vocal cord lesion is best made by direct laryngoscopy. Acute treatment may require the administration of helium-oxygen mixtures to decrease inhaled air viscosity and in emergencies, tracheostomy.

B- Vocal cord dysfunction:

In 1983, Cristopher et al. described vocal cord dysfunction (VCD) in five patients with a clinical presentation mimicking asthma.[22] The disease is believed to be a conversion disorder in which patients demonstrate paradoxical and involuntary closure of the true and false vocal cords during inspiration and at times, exhalation. The disease can be severe and require emergency room visits, hospitalization, and urgent endotracheal intubation.[23] VCD is more common in women and is associated with a high incidence of psychiatric disorders and prior physical or sexual abuse. The physical exam will reveal inspiratory and expiratory wheezing that is increased during auscultation of the neck. The flow volume loops will reveal a "classic" variable extra-thoracic airway obstruction (Figure 2b). A diagnosis of vocal cord dysfunction is confirmed by direct laryngoscopy during an attack.[21,23] The larynx will appear functionally normal if the patient is not wheezing or dyspneic. Treatment is difficult and requires the patient's acceptance of the diagnosis. Speech therapy and psychotherapy can be helpful in teaching relaxed throat breathing and relaxation techniques. The use of inhaled helium-oxygen (HeliOx) mixtures can abort an acute attack.

C- Tracheal compression, strictures, and tumors:

Tracheal narrowing from either extrinsic compression, post-intubation stenosis, and tumors can progress slowly with development of chronic obstructive symptoms suggestive of COPD.[3,19,21] The lumen of the trachea has to be significantly narrowed from its normal diameter of 13-25 mm to approximately 6-8 mm before symptoms or spirometric abnormalities develop. At that point, the flow-volume loops will demonstrate an inspiratory or expiratory "cut-off" depending on the location of the lesion in the intrathoracic or extrathoracic trachea.[19,20]

Mediastinal or esophageal tumors, lymphoadenopathy, fibrosing mediastinitis, vasculature anomalies, and goiters can cause extrinsic compression of the trachea. A tracheal stricture is usually congenital or develops post-intubation or tracheostomy. These patients can present months to years after the initial endotracheal intubation or tracheostomy with a fixed intrathoracic airway obstruction (Figure 3).[21] The mechanism for these strictures is believed to be necrosis of the tracheal mucosa by the inflated cuff of the endotracheal or tracheostomy tube. Prospective studies demonstrate a 10-19% incidence of tracheal stenosis after endotracheal intubation; most are clinically silent. Risk factors for the development of this serious complication includes diabetes, severe underlying respiratory failure, duration of intubation, female gender, increased endotracheal tube size, and overinflation of the balloon cuff.[19,21] The diagnosis is suggested by a fixed intra-thoracic airway obstruction in the flow-volume loops (Figure 3). The diagnosis is confirmed by either flexible laryngoscopy or ultrafast cine-CT scan with image reconstruction of the trachea and subglottic regions. Treatment of benign tracheal stenosis or strictures requires airway stenting, laser therapy, or surgical resection (Figure 4).[19,24,25]

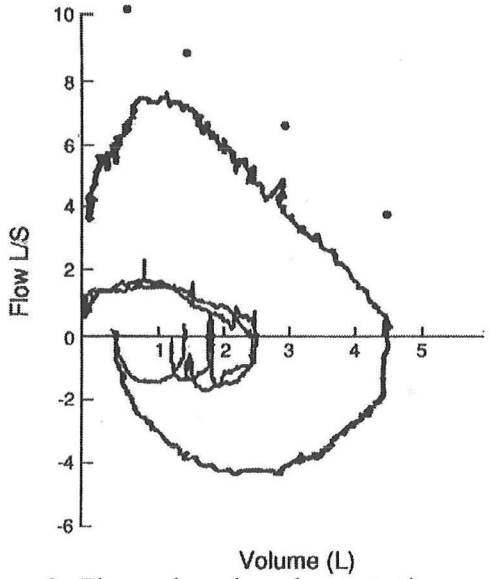


Figure 3: Flow-volume loop demonstrating a fixed-intrathoracic airway obstruction relieved with stenting. Adapted from reference 24.

Other important causes of tracheal obstruction that present with chronic airflow obstruction are benign and malignant tracheal tumors. These lesions can present with fixed or variable intra- and extra-thoracic airway obstruction. The most common tumors are squamous cell carcinoma, adenoid cystic carcinoma, Hodgkin's disease, and Kaposi's sarcoma.[19]

D- Tracheobronchopathia osteochondroplastica (TO):

TO is a rare benign disorder that affects the larynx, trachea, and major bronchi. The original descriptions were made in 1855-1857. This disease is usually asymptomatic and is found incidentally by CT scan or during post-mortem

examinations.[26] The striking feature is the endoscopic appearance of a deformed trachea with beaded, nodular, and "cobblestone" appearance. These submucosal nodules contain cartilage, bone structure, acellular proteinaceous material, calcifications, and hematopoetic cells. The nodules usually involve the cartilaginous trachea sparing the membranous trachea.[27] The pathogenesis of this disease is unknown. Various theories are reported including the possibility that TO is a congenital anomaly or sequelae of chronic infection, environmental exposures, metabolic abnormalities, or tracheal amyloidosis. Virchow postulated that the TO nodules develop from echondrosis and exostosis of tracheal cartilage. The current accepted hypothesis is that TO originates from elastic connective tissue undergoing cartilaginous and bony metaplasia.[26,27,28]

The true incidence of this disorder is unknown and is likely underdiagnosed based on the lack of radiographic abnormalities. Approximately 300 cases have been reported in the literature.[26] There is no sex predilection and is usually seen in patients aged 50 y/o or older. The disease can be quite symptomatic with non-productive and productive cough, recurrent bronchitis, dyspnea, and hemoptysis. It is difficult to distinguish from COPD.[26] Spirometric studies have demonstrated normal results to an obstructive pattern. Biopsy of the lesions by bronchoscopy is difficult due to forceps slippage. On follow-up, most patients demonstrate preservation of lung function suggesting a benign course. Nevertheless, there are reports of accelerated or progressive TO.[29,30] Treatment is primarily supportive with antibiotics for bronchitis or infections. Laser therapy or surgery resection may be required.

E- Tracheobronchial amyloidosis:

Amyloidosis can involve the respiratory system with three major presentations: interstitial infiltrates mimicking pulmonary fibrosis, pulmonary nodules or masses, and tracheobronchial amyloidosis. Tracheobronchial amyloidosis (TBA) is a rare disease with less than 100 cases reported in the literature. It represents a localized form of amyloidosis characterized by local clonal expansion of plasma cells producing light chain immunoglobulin fractions that accumulate in the trachea and bronchi. [31,32] It represents 10-25% of all cases of pulmonary amyloidosis.[31,33,34, 35]

The disease has no sex predilection and occurs in middle age patients. Symptoms of cough, hoarseness, hemoptysis, and dyspnea are reported with a delay in diagnosis of 1-2 years. Patients are misdiagnosed as having pneumonia, chronic bronchitis, and asthma. Unless atelectasis or lobar collapse develops, airway involvement is not detected by the chest radiograph. Fat pad biopsy, protein electrophoresis, and bone marrow biopsies are negative for systemic amyloidosis.[31,33] Pulmonary function studies demonstrate an obstructive pattern with air trapping in most cases. Depending on the degree and location of the luminal obstruction, a fixed airway obstruction may be seen in the flow-volume loop. TBA primarily involves the distal trachea, carina, and mainstem bronchi. The appearance of the TBA ranges from round, yellowish lesions to "cobblestoning" with diffuse inflammation of the tracheal mucosa. Despite a normal bronchoscopy, the chest CT scan may demonstrate tracheal and bronchial wall thickening and calcifications.[31]

O'Regan et al. demonstrated the stability of TBA even 12-24 months after diagnosis. But after long-term follow-up (average 8 years), a slowly progressive pattern of infiltration with airway narrowing and obstruction is noted.[31] Progression of TBA to diffuse systemic disease has not been described. Severe obstruction requires laser debridment with a rigid bronchoscope. Patients with upper airway disease may require tracheostomy. The lesions can recur after treatment.[31,33,35] Treatment with colchicine, melphalan, and prednisone has been reported but no study has confirmed their benefits. The role of radiation therapy for TBA has been reported and is supported by the well-known radiosensitivity of plasma cells.[31,35] 25% of patients with TBA die from respiratory failure, pneumonia, or post-tracheostomy bleeding.[36]

F- Tracheobronchomegaly: The Mounier-Kuhn Syndrome (MKS)

This syndrome was first described in 1932 by Mounier-Kuhn. It is characterized by flaccid dilatation and malacia of the trachea and major bronchi.[37] This syndrome is also a rare disorder with approximately 80 cases reported in the literature.[38] At UT Southwestern, two symptomatic cases have been identified in the last 2 years. It mimics chronic

bronchitis and emphysema. The diagnosis is elusive and is usually suspected after a patient undergoes a chest CT scan for other reasons. This disease usually presents in the third or fourth decade of life. Males with a smoking history are more commonly affected. Familial occurrence has been described.[37] It is unclear if MKS is an acquired or congenital tracheobronchial disease although most experts suspect that it is a congenital disorder.[38] A secondary tracheobronchomegaly can be associated with prolonged intubation or tracheostomy, chronic bronchiectasis, relapsing polychondritis, tracheal tumors, Ehler-Danlos syndrome, and congenital cutis laxa.[38,39]

Symptoms mimic those of chronic bronchitis and bronchiectasis. A deep "barky" cough and dyspnea are common but patients may be asymptomatic. Complications include pneumonia, bronchiectasis, emphysema, respiratory failure and even death. These complications are due to distal pooling of secretions caused by dynamic collapse of the trachea and mainstem bronchi during forceful cough. PFTs reveal decreased flow rates and air trapping. The diagnosis relies on CT-guided measurement of tracheal and bronchial diameters.[40] Bronchoscopy reveals enlargement and collapse of the trachea and mainstem bronchi with saccular dilatation, redundant folds, and pseudo-diverticuli. Histologically, the trachea and mainstem bronchi demonstrate decreased and atrophic longitudinal elastic fibers, enlarged cartilaginous rings, and thinning of the muscularis layer.[38] Treatment is supportive and focused on improving secretion clearance with rotating antibiotics, chest percussion, and use of CPAP to prevent collapse.[38,41]

DISEASES OF THE LARGE (CENTRAL) AIRWAYS:

The large (central) airways refer to the large bronchi with luminal diameters greater than 3 mm. The most prevalent diseases of the large (central) airways are asthma and chronic bronchitis. Chronic bronchitis is characterized by mucous gland hypertrophy, cartilage atrophy, smooth muscle hypertrophy, and mucosal thickening. These airway changes lead to the development of airflow obstruction.[1,6] There are OTHER important pulmonary disorders that involve the large (central) airways and present with chronic airflow obstruction mimicking COPD. Their correct diagnoses is usually delayed (Table 2).

Table 2: Important causes of large (central) airway obstruction that mimic COPD:

- Bronchial tumors
- Bronchostenosis
- Bronchiectasis
- Cystic Fibrosis
- Sarcoid
- Relapsing polychondritis

Adapted from St. John RC, Gadek JE, Pacht ER. Journal of General Internal Medicine 1993 (Reference 3) and Fishman's Pulmonary Diseases and Disorders. Reference 21.

Bronchial tumors can present with slow onset of airflow obstruction that can be confused with COPD. The most common benign bronchial tumors include adenomas, papillomas, hamartomas, and angiomas.[42] Malignant tumors include bronchogenic carcinoma, metastatic tumors, carcinoid tumors, and cylindromas.[43] **Bronchostenosis** is a benign stricture with stenosis of a major bronchus and is usually sequelae of endobronchial or lower-lung field tuberculosis.[44] Van den Brande et al. followed eleven elderly patients with endobronchial tuberculosis demonstrating that six developed bronchostenosis despite anti-tuberculous treatment. Bronchostenosis can present with chronic cough, wheezing (sometimes focal), and dyspnea.[45] The stenosis is treated with endoscopic dilatation or endobronchial stenting.[45,46]

A- Bronchiectasis:

Bronchiectasis is defined as a disorder characterized by irreversible bronchial wall dilatation. It is caused by a multitude of congenital, inflammatory, acquired, and obstructive disorders.[47,48,49,50] Because of the lack of interest in the research and treatment of this disease, it has been termed the "orphan" disease.[50] Its presentation with chronic airflow obstruction and symptoms easily confused with chronic bronchitis has earned bronchiectasis the name the "other" chronic obstructive pulmonary disease.[47,49]

Bronchiectasis primarily involves the medium-sized airways with bronchial distortion and dilatation. The exact mechanism causing airflow limitation in a disease associated with bronchial dilatation is unclear.[47] Possible causes include the presence of dynamic airway collapse and associated small airways disease. Utilizing high-resolution CT scans, Kang et al. demonstrated changes consistent with small airways involvement in greater than 50% of patients undergoing resection for bronchiectasis. Of the resected lobes, 85% demonstrated a bronchiolitis obliterans.[47,51]

Table 3: Conditions and disorders associated with bronchiectasis:*

Severe inflammation
Infection
- Mycobacterium species (tuberculosis, MAI)
- Bacterial (*S. aureus*, *Bordetella pertussis*)
- Viral (measles, influenza, rubeola, adenovirus, HIV)
- Fungal (histoplasmosis, coccidiomycosis)

Hypersensitivity
- Allergic bronchopulmonary aspergillosis (ABPA)

Inhalational injury
- Smoke
- Sulfur dioxide
- Ammonia

Other
- Gastric aspiration
- Diffuse panbronchiolitis

Autoimmune
Relapsing polychondritis
Behcet's
Sjogren's syndrome

Congenital syndromes
Cystic fibrosis
Alpha-1-antitrypsin
Primary ciliary dyskinesia
- Kartagener's (situs inversus, sinusitis, bronchiectasis)

Hypogammaglobulinemia
Chronic granulomatous disease
Young's syndrome (azoospermia and sinopulmonary syndrome)
Yellow-nail syndrome (lymphedema and pleural effusions)

Airway obstruction:
Foreign body
Bronchial stricture
Bronchial tumor
Bronchial nodule
- Sarcoidosis
- Amyloidosis
- Broncholith

Extrinsic bronchial compression
- Mediastinal mass or lymph node
- Lung cancer
- Vascular aneurysm
- Mediastinal fibrosis

Traction
Pulmonary fibrosis
Radiation
Sarcoid

Anatomical malformations or variants
Bronchomalacia
Williams-Campbell syndrome
Mounier-Kuhn syndrome
Swyer-James syndrome
Right middle lobe syndrome
Pulmonary sequestration

***Adapted from References 49 and 56.**

Development of bronchiectasis requires the presence of infection, obstruction, traction, and abnormal host factors. This process is sustained by either a congenital or acquired defect in mucociliary clearance leading to chronic infection and inflammation of the bronchial wall mucosa and lumen.

Reid classified bronchiectasis into three different morphological patterns: cylindrical, varicose, and saccular (cystic) bronchiectasis.[52] Reid's classification lacks clinical utility since there is no correlation between the pattern of bronchiectasis and the underlying pathogenesis or physiologic impairment. Nevertheless, the presence of saccular (cystic) bronchiectasis suggests a more severe and advanced disease.[47,49] Bronchiectasis is best classified by predisposing conditions as illustrated in Table 3. In approximately 40% of patients, the predisposing disorder is unknown.[47,56]

Post-infectious and infectious bronchiectasis is the most common cause of bronchiectasis. The incidence of infectious-related bronchiectasis has declined with the introduction of mass vaccination and antibiotics. Measles, pertussis, adenovirus, tuberculosis, and MAI are important pathogens.[56] Recently, *Mycobacterium avium-intracellulare* has been found to cause a syndrome of chronic bronchitis in immunocompetent, non-smoking, and elderly women. This disease is characterized by productive cough, night sweats, low-grade fever, malaise, weight loss, and airflow limitation. The chest radiograph can be rather unimpressive. High-resolution CT scan demonstrates nodular bronchiectasis with predominant involvement of the middle lobe and lingula. Treatment with rifabutin, ethambutol, and clarithromycin is successful in most patients.[53]

Hypogammaglobulinemia and bronchiectasis in adults is usually associated with common variable hypogammaglobulinemia. IgA, IgM, IgG, and IgG subclass deficiencies have been described with development of bronchiectasis.[50]

Allergic bronchopulmonary aspergillosis (ABPA) usually presents with upper-lobe and central bronchiectasis and a clinical picture of chronic, refractory asthma. It is characterized by intermittent wheezing, fever, cough, peripheral eosinophilia, transient pulmonary infiltrates, and bronchial plug expectoration. Patients usually have elevated *Aspergillus* serum precipitins and IgE levels and immediate skin test hypersensitivity to *Aspergillus* antigens.[56,58]

Yellow-Nail syndrome is a rare syndrome characterized by bronchiectasis, slow-growing yellow nails, lymphedema, and chylothorax. The etiology for this syndrome is unknown.[56]

Immotile cilia syndrome and Kartagener's syndrome are congenital abnormalities characterized by defective ciliary function due to deficiencies in the components of the microtubular system. These patients suffer from chronic rhinosinusitis, otitis, bronchiectasis (30%), sterility, olfactory defects, and corneal malformations. The diagnosis requires electron microscopy examination of a sinus or bronchial mucosal biopsy. Kartagener's syndrome accounts for 50% of the immotile cilia syndromes, an autosomal recessive trait characterized by the clinical triad of sinusitis, situs inversus, and bronchiectasis.[56]

Young's syndrome mimics the immotile cilia syndromes except for the absence of microtubular abnormalities. It is characterized by the presence of obstructive azoospermia, chronic sinusitis, and bronchiectasis (seen in 30-70% of cases). The pulmonary presentation is a mild form of bronchiectasis with cough, sputum, and airflow limitation. It can be differentiated from cystic fibrosis by lack of family history, pancreatic sufficiency, and normal sweat chloride test.[56] A recent report suggests that Young's syndrome may be a milder clinical phenotype of cystic fibrosis presenting with normal sweat chloride and lack of pancreatic insufficiency. Mutations in the cystic fibrosis *CFTR* gene, such as the Q1291H mutation, have been identified in Young's syndrome.[54,55]

Despite the variety of disorders predisposing to **bronchiectasis**, their clinical presentation, radiology, and pulmonary function tests are usually similar. In the past, bronchiectasis was primarily sequelae of severe viral, mycobacterial, or bacterial infection. It was characterized by severe bronchorrhea, hemoptysis, respiratory failure and death. Since the advent of immunization and antibiotics, bronchiectasis now presents with a more subtle clinical presentation easily confused with chronic bronchitis and COPD. Symptoms include chronic cough and sputum production that is usually worse in the mornings or after assuming a supine position. Sputum production as voluminous as 600cc has been quantified. A dry cough with intermittent exacerbations suggests "dry" bronchiectasis. With increases in the number of exacerbations, fever, dyspnea, wheezing, chest pain, hemoptysis, anorexia, and weight loss develop. The evaluation of bronchiectasis should include a full history focusing on childhood illnesses and prior history of pneumonia. Careful investigation for sinus disease and infertility is also important. The physical exam can reveal inspiratory coarse or "moist" crackles, rhonchi, and airway "popping" noises. Clubbing is seen in 7% of cases. Cor pulmonale is rare and suggests advanced and severe bronchiectasis.[56]

One of the main reasons why bronchiectasis is misdiagnosed as COPD is that 50% of patients lack abnormalities in the chest x-ray.[47,57] Radiographic findings that suggest bronchiectasis include bronchial wall thickening, volume loss at the lung bases, and parallel lines "tram tracks" that correlate with bronchial wall thickening and dilatation. Severe bronchiectasis can present with cystic or "ring" shadows and/or dilated bronchi with mucous plugging ("gloved finger" sign).

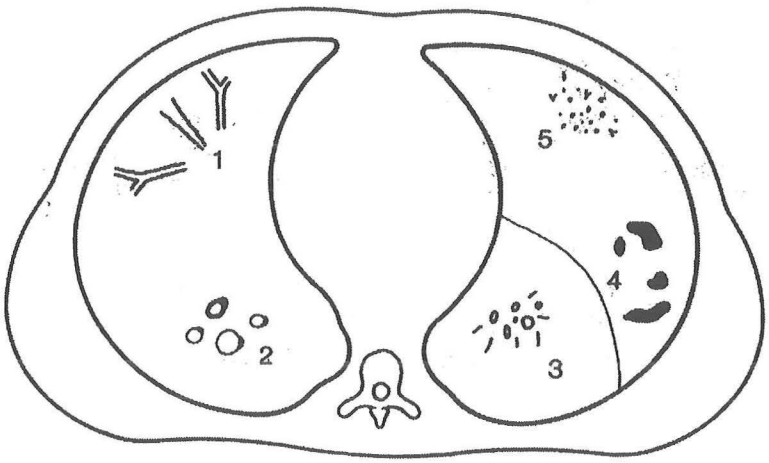


Figure 4: Diagram illustrating the different CT findings of bronchiectasis. 1) Non-tapering of bronchi, 2) Signet ring sign, 3) Crowding of bronchi with associated volume loss, 4) Mucous plugging of dilated bronchi, 5) Thickening and plugging of small airways leading to nodules and V- and Y- shaped opacities ("tree in bud"). From Reference 47, Page 114.

The diagnosis of bronchiectasis has recently improved with the introduction of the high-resolution CT scan. This technique allows for 1-1.5 mm sections every 10 mm from apex to base of the lung. CT scanning has made bronchography virtually obsolete. It is very sensitive in diagnosing early bronchiectasis and even suggesting a specific underlying disease.[47,58] HRCT is recommended for diagnosing difficult cases, determining the severity of disease, and mapping sites amenable for surgical resection. The different abnormalities seen in HRCT scan are summarized in Figure 4. Widespread bronchiectasis with symmetrical upper lobe predominance is associated with cystic fibrosis. Unilateral, mild upper lobe involvement is seen with tuberculosis. ABPA is characterized by central bronchiectasis. Hypogammaglobulinemia and immotile cilia syndrome typically involve the middle lobe.[58] MAI-associated bronchiectasis is characterized by nodular bronchiectasis of the middle lobe and lingula.[53]

Pulmonary function tests usually reveal airflow limitation and air trapping.[59] Bronchoscopy is performed when an obstructive cause is suspected in cases of focal bronchiectasis. Sputum should be obtained during the acute exacerbations of bronchiectasis. Based on clinical suspicion, sweat chloride, immunoglobulin levels and IgG subtypes, IgE levels, alpha-1 antitrypsin level, *Aspergillus* precipitins and skin testing, and mucosal biopsy for ciliary abnormalities may be indicated.[56]

Treatment should focus on the treatment of the predisposing condition. Adequate bronchial hygiene and secretion clearance can be achieved with chest percussion, postural drainage, mucolytics, and bronchodilators. Acute exacerbations of bronchiectasis require specific antibiotic therapy directed to the predominant organism isolated in sputum. Empiric therapy with ampicillin, amoxicillin, doxycycline, trimethoprim-sulfamethoxazole, or amoxicillin-clavulanate is usually adequate for mild bronchiectasis. Severe bronchiectasis with suspected *Pseudomonas aeruginosa* requires double anti-pseudomonal coverage. In cases of bronchiectasis with frequent exacerbations, chronic rotating antibiotic therapy is utilized. Surgery is reserved for localized bronchiectasis refractory to therapy or in patients with recurrent hemoptysis.[49,56,60]

B- Cystic Fibrosis:

Cystic fibrosis is the most prevalent lethal genetic disorder in the United States. It primarily affects Caucasians with an incidence of 1 in 2500 live births. CF is an autosomal recessive disorder with 1 in 25 Caucasians in the U.S. being asymptomatic carriers of the disease. It is a disease that is not only limited to Caucasians but is also seen in African-Americans with a much lower incidence at one out of 17,000 births.[61,62] The CF gene has been mapped to chromosome 7. The gene product is a protein essential in chloride transport, the *cystic fibrosis transmembrane conductance regulator* (CFTR).[63] The most common genetic mutation, seen in 70% of patients, is the deletion of three base pairs at codon 508 (delta F508) coding for phenylalanine. The defect in chloride transport is associated with increased sodium absorption with dissecation of mucus, infection, bronchial obliteration, and bronchiectasis (Figure 5).[64]

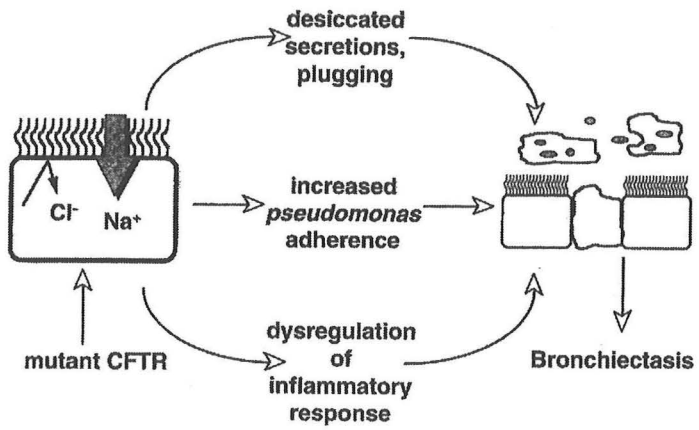


Figure 5: Pathogenesis of lung disease in cystic fibrosis. Mutant CFTR protein leads to increased sodium reabsorption leading to dissecated secretions and bronchial plugging. The association between the mutant CFTR and the dysregulation of the inflammatory response is still unexplained. From Davis PB, Drumm M, Konstan MW. Am J Respir Crit Care Med 1996; Reference 64.

CF is characterized by the development of chronic obstructive pulmonary disease, bronchiectasis, recurrent pulmonary infections, pancreatic insufficiency, and liver, gastrointestinal, and reproductive system dysfunction. The diagnosis involves recognition of characteristic clinical features, presence of an elevated sweat chloride (>60 mEq/L), PCR detection of a CFTR gene mutation, and measurement of abnormal nasal epithelial electrolyte ion transport.[65]

CF is usually diagnosed in early childhood (95% by the age of 8 y/o) and thus, treated by pediatricians and pediatric pulmunologists.[66] Recent developments in the treatment of cystic fibrosis have increased the mean life span to 30 years of age. Therefore, an increasing number of adult CF patients are currently under the care of internists and adult pulmonary specialists.[67,68] Increasing attention is now given to reports of adult with milder forms of cystic fibrosis that elude diagnosis until the ages of 60-70 years of age.[66,69,70] These older patients present with a clinical picture confused with chronic asthma, chronic bronchitis, and bronchiectasis. The diagnosis can be difficult to make since these patients may present with subtle clinical findings or have borderline or normal sweat chloride values.[71] The diagnosis of CF in adults is usually suspected when diffuse bronchiectasis is detected by high-resolution CT (HRCT) scan or a mucoid *Pseudomonas* strain is isolated in a routine sputum culture.[66] Older CF patients present with less pancreatic insufficiency, milder lung disease, unusual genetic mutations in the CFTR gene, and better overall clinical course.[72] The current hypothesis explaining this late manifestation of CF is that these patients have modifications of the cystic fibrosis phenotype by residual chloride airway secretion and other protective effects from genetic and environmental factors.[73]

The pulmonary course is characterized by progressive deterioration in lung function and increase in the frequency of acute exacerbations. The deterioration of lung function is associated with isolation of various airway colonizers beginning with *Staphylococcus aureus* and *Hemophilus influenza* and later with mucoid and non-mucoid strains of *Pseudomonas*. Greater than 90% of deaths in cystic fibrosis are due to lung disease.[64]

The pulmonary function tests demonstrate a predominant obstructive pattern with decreased expiratory flows and air trapping (increased RV/TLC ratio). The diffusion capacity (DLCO), a marker of pulmonary alveolo-capillary surface area, is usually preserved until late in the disease.[67] The radiograph in CF may be normal at initial presentation but later demonstrates hyperinflation, lobar collapse, peribronchial cuffing, and progressive bronchiectasis. In adult CF, the chest radiograph demonstrates features of bronchiectasis such as "tram-tracking", ring shadows, nodular opacities, and cysts with air-fluid levels. High-resolution CT scan is very sensitive for the detection of bronchial wall thickening and cylindrical, varicose, and cystic bronchiectasis.[62]

The diagnosis of CF in adults should be suspected in cases of unexplained diffuse bronchiectasis, recurrent pulmonary infections, or unexplained COPD. CFTR PCR mutation analysis may be necessary in patients with normal or borderline sweat chloride values.[64,66,73,74] The treatment of cystic fibrosis requires referral to a center of specialized care focusing on pulmonary, gastrointestinal, mineral metabolism, and dietary issues. Treatment is geared to the clearance and lysis of mucus secretions, bronchodilatation, antibiotics, anti-inflammatory therapy (corticosteroids, NSAID's), and the management of secondary complications, such as hypoxemia, hemoptysis, and pneumothorax. See diagram in Figure 6.[64]

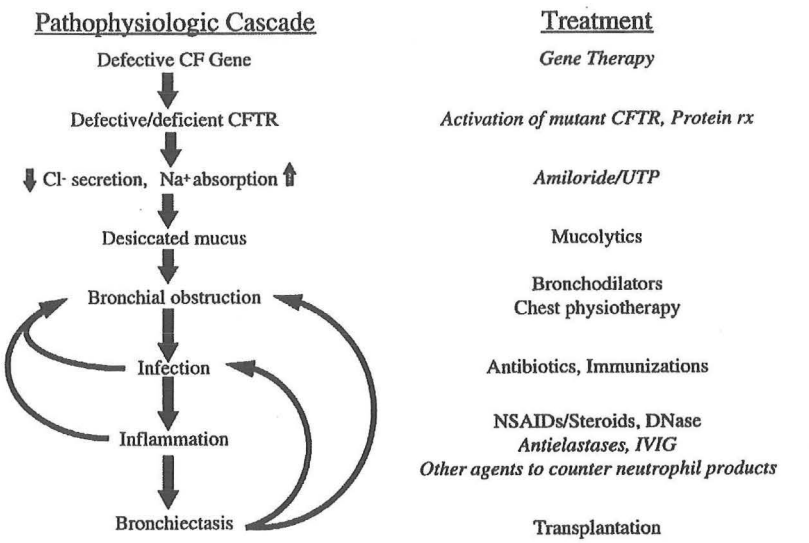


Figure 6: Therapeutic interventions in cystic fibrosis based on the pathophysiologic progress of the disease. Items in *Italics* represent agents waiting or undergoing clinical testing. From Davis PB, Drumm M, Konstan MW. Am J Respir Crit Care Med 1996; 154:1239. Reference 64.

C- Sarcoidosis:

Sarcoidosis is a common disorder usually associated with mediastinal and/or hilar lymphadenopathy and pulmonary parenchymal nodular or interstitial disease. Although sarcoid is considered an interstitial lung disease, airflow obstruction is the most common finding.[75,76,77] The anatomical site of airflow obstruction in sarcoid appears to be the small (peripheral) airways and it will be discussed later in the Protocol.[78,79] Of interest, a group of patients with sarcoidosis present with chronic airflow limitation due to granulomatous inflammation and nodules of the large (central) airways.[75,78,80] In fact, endobronchial sarcoid with some grade of bronchostenosis is seen in 2-26% of patients undergoing bronchoscopy. Endobronchial sarcoid can present even in the absence of involvement of the pulmonary parenchyma.[81] A far greater number of patients (38-64%) demonstrate non-occlusive large airway mucosal changes such as nodularity, increased vascularity, and edema.[75,80,82,83]

Bronchostenosis of the large (central) airways due to sarcoidosis presents with cough, focal wheezing, and stridor. Pulmonary function tests reveal moderate to severe airflow limitation. Bronchoscopy usually reveals multiple sites of segmental narrowing.[83] These lesions respond poorly to steroid therapy.[75,80] Successful balloon dilatation of the stenotic airways has been described.[84,85]

D- Relapsing Polychondritis:

Another interesting and important disease that presents with large (central) airway airflow limitation is relapsing polychondritis (RP). This disease was originally described by Jaksch-Watenhorst in 1923. It is an unusual disease with approximately 600 cases reported by the early 1990's. It is characterized by severe "relapsing" inflammation and destruction of cartilage and proteoglycan-rich tissues.[86] RP involves the ear, vestibular system, eye, nose, large joints, aortic root, chest wall, larynx and major airways. The clinical presentation can mimic rheumatoid arthritis, Wegener's granulomatosis, and systemic vasculitides.[87]

An autoimmune etiology for RP is suspected based on its frequent association with other connective tissue diseases and immunohistochemical demonstration of immunoglobulin and complement deposition in cartilage. Serum antibodies to type II collagen has been detected in 20% of patients.[87,88,89]

Respiratory system involvement may be the presenting manifestation in about 13-66% of patients with RP and portends a poor prognosis.[86,90] The leading cause of death in patients with RP is involvement of the respiratory

system with infection, pneumonia, respiratory failure, and loss of airway. The central airways (glottis, trachea and mainstem bronchi) are preferentially involved. Women are predominantly affected. These patients present with hoarseness, cough, pain over the anterior trachea, dyspnea, hemoptysis, wheezing, and even respiratory distress requiring intubation or emergent tracheostomy.[86,88,90] As reported by Tillie-Leblond et al., the pulmonary function tests reveal moderate to severe airflow limitation with FEV1/FVC ratios ranging from 16-81% (mean 48%).[86] Some patients may present with primary involvement of the trachea with either a variable extra-thoracic or fixed intra-thoracic airway obstruction. All patients had a normal D_LCO suggesting a preservation of lung parenchyma.[86,88]

Bronchoscopic examination of patients with airway obstruction reveals predominant involvement of the larynx and upper trachea. Rarely, patients present with isolated mainstem bronchi involvement. The airways reveal inflammation, dynamic collapse, and/or stenosis. The helical chest CT scans allows for airway reconstruction demonstrating more clearly the severity of airway involvement.[86,88]

Bronchoscopy-directed biopsy of RP lesion is usually non-diagnostic unless biopsy of the deep cartilage is performed. Since there is no reliable serologic test for RP, the diagnosis is usually delayed an average of 2-3 years from the onset of symptoms. Patients may present with elevation in ESR, anemia, leukocytosis, eosinophilia, and hypergammaglobulinemia.[87] The clinical criteria for diagnosing RP includes: 1) bilateral auricular cartilage involvement, 2) non-erosive polyarthritis, 3) nasal cartilage chondritis, 4) eye inflammation (episcleritis, scleritis), 5) airway involvement, and 6) cochlear or vestibular involvement.[91] A diagnosis of RP is made when 3 or more of these clinical features are present; or when 2 or more sites are involved and there is a response to steroids or biopsies demonstrating chondritis at one or more sites.[88]

The treatment of airway involvement with RP requires a multi-disciplinary approach involving otolaryngologists, pulmunologist, thoracic surgeons, and rheumatologists. For acute exacerbations with laryngeal or airway disease, high-dose prednisone at 0.75-1 mg/kg/d is recommended. Steroids should be tapered slowly with maintenance therapy continued during remissions. Cytotoxic therapy with azathioprine, cyclophosphamide, dapsone, penicillamine, and cyclosporine has been reported. Recent reports demonstrate excellent response to methotrexate at 17.5 mg/week.[87] Tracheostomy might be necessary in cases with upper airway compromise. For severe tracheo-bronchostenosis, surgical resection, airway stenting (Montgomery tube or collapsible metallic stents), and balloon dilatation have been attempted with response.[88] The 5- and 10-year survival rate for patients with airway strictures is 74 and 55%, respectively.[90,92] A recent series reported an improved survival rate of 94% at 8 years.[87]

DISEASES OF THE SMALL (PERIPHERAL) AIRWAYS:

A- Introduction: The association between airflow limitation and small airways disease.

The term "small airways" refers to peripheral airways with a lumen of 2 mm or less. These airways are comprised of small bronchi and bronchioles (1mm or less in diameter). The small airways are comprised of membranous bronchioles that are not supported by cartilage. The membranous bronchioles then branch into 8 to 14 different generations into lobular bronchioles feeding the secondary pulmonary lobule, or lobule of Miller. This lobule represents the smallest discrete unit of lung surrounded by visible interlobular septae. The lobular bronchiole then forms the acinus by dividing into various terminal bronchioles, which in turn branch into the respiratory bronchioles. The respiratory bronchiole divides into three further generations with increasing number of alveoli in their walls and end in the alveolar ducts and alveolar structures (Figure 7).

The cross sectional area of the membranous bronchioles and respiratory bronchioles is 53 and 186 cm^2, respectively. This is much larger than that of the major bronchi. Recent data suggest that in normal lung, the total contribution of the small airways to airflow obstruction is in the order of 30-40%.[13] Nevertheless, diseases that primarily affect the small airways can lead to significant airflow limitation with development of symptoms and signs consistent with COPD. In non-smokers, the small airways diseases are misdiagnosed as asthma, bronchitis, and congestive heart failure. As documented later in this Protocol, some interstitial lung diseases that are usually considered to be restrictive disorders involve the small bronchioles leading to a predominant chronic airflow obstruction.

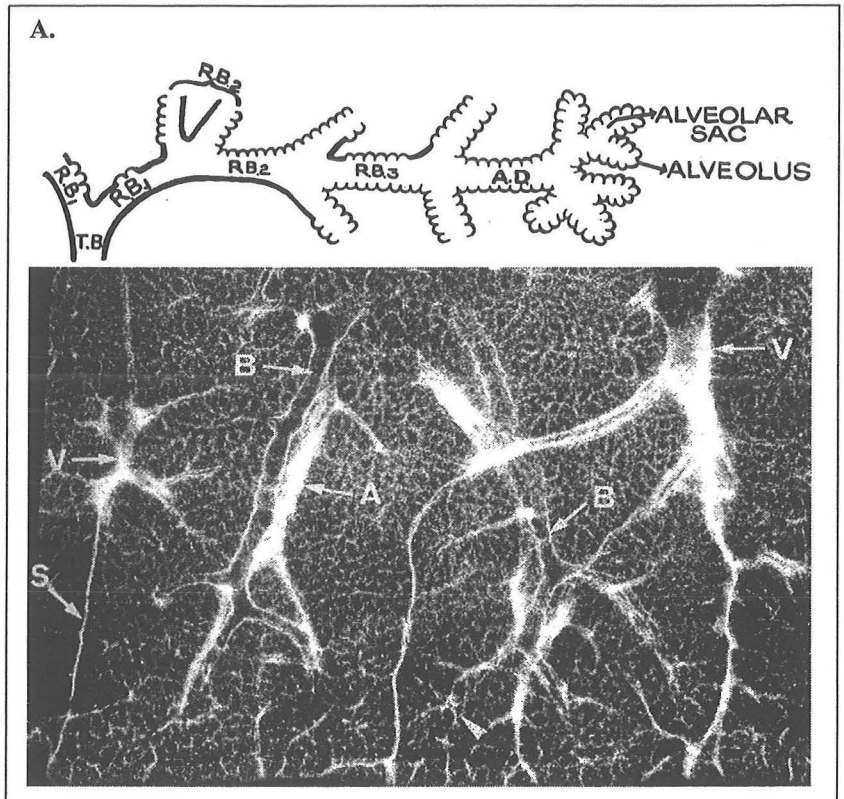


Figure 7: A) Illustration of small airways leading to the acinar structure, the gas exchange unit of the lung. Adapted from Thurlbeck WM. Pathology of chronic airflow obstruction. *In*: Cherniack NS, ed. Chronic Obstructive Pulmonary Disease. 1st ed. 1991, P. 10. Reference 6

B) Radiograph demonstrating the anatomy of the secondary pulmonary lobule or lobule of Miller. The lobule is demarcated by the interlobular septae (S). The lobular bronchiole (B) and artery (A) feed the pulmonary lobule. From Itoh H. J Thorac Imaging 1993; 8:176-188.

B- Use of the high-resolution CT (HRCT) scan in small airways disease:

The study of the small (peripheral) airways was previously hampered by a lack of reliable pulmonary function tests, sensitive radiographic imaging, or adequate lung biopsy specimens. The recent introduction of the high-resolution chest CT (HRCT) study has revolutionized the study of small airways disease. This technique allows for the detection of abnormalities in these small airways.[14,93,94]

The HRCT abnormalities that correlate with histological small airways disease are summarized in Table 4. Other abnormalities associated with bronchiolar obstruction include parenchymal cyst formation, secondary emphysema (airspace dilatation), and bronchiolectasis.

Table 4: CT and histological features and correlations of small airways disease that present with chronic airflow limitation.

Histological Feature:	**HRCT correlation:**
Bronchiolar wall thickening and inflammation	Centrilobular nodules
Partial or complete bronchiolar obstruction	Air trapping with "mosaic" pattern Parenchymal cysts

Adapted from Worthy SA, Muller NL. Radiologic Clinics of North America 1998; 36:163-173. (Reference 94)

For confusing or unexplained cases of chronic airflow limitation, the HRCT scan will not only suggest the presence of small airways disease but will also help rule out bronchiectasis and emphysema. This statement should not be misconstrued as a broad recommendation for the use of HRCT scanning in the evaluation of COPD.

C- Diseases of the small (peripheral) airways confused with COPD:

A variety of diseases of the small airways can present with symptoms, signs, and physiology of chronic airflow obstruction mimicking COPD (Table 5). These diseases may be difficult to diagnose and a high index of suspicion is essential.

Table 5: Important causes of small (peripheral) airway obstruction mimicking COPD:

- Sarcoid
- Hypersensitivity pneumonitis
- Mineral dust-induced small airways disease
- Bronchiolitis obliterans
- Respiratory bronchiolitis-ILD
- Lymphangiomyomatosis (LAM)
- Eosinophilic granuloma (EG)
- Diffuse panbronchiolitis
- Recurrent pulmonary capillaritis

Sarcoidosis

Sarcoidosis is usually classified as an interstitial lung disease with associated restrictive lung function. Nevertheless, it commonly presents with airflow limitation likely due to small airway inflammation (bronchiolitis) and obstruction. In one study of sarcoid patients undergoing open lung biopsy, 57% demonstrated granulomatous inflammation of the small airways.[81] The mechanisms suggested for bronchiolar obstruction in sarcoidosis include direct granulomatous inflammation of bronchiolar wall, extrusion of granulomas into the bronchiolar lumen, and proximal extension of alveolar fibrosis leading to concentric bronchiolar narrowing.[17,81]

Rarely, patients with sarcoidosis present with chest radiographs, HRCT and pulmonary function tests classic for advanced emphysema. Zar et al. reported a 39 y/o man with a 9 pack-year smoking history with symptoms of COPD and a chest CT scan with mediastinal adenopathy and changes consistent with emphysema. Transbronchial biopsies revealed non-caseating granulomas consistent with sarcoidosis.[95] Judson et al. reported 3 patients (2 mild smokers and one non-smoker) with a diagnosis of bullous sarcoidosis with severe airflow limitation. Sarcoidosis was suspected in all three after CT scans revealed mediastinal lymphoadenopathy. Open lung or thoracoscopic lung biopsies confirmed a diagnosis of sarcoidosis in all three patients. One patient required lung transplantation and another improved with corticosteroid therapy.[96] Although it is possible that these patients had both smoking-related emphysema and sarcoidosis, the pathology specimens revealed significant bronchiolar involvement with granulomatous inflammation and fibrosis. Of interest, Keller et al. reported a 9% incidence of occult sarcoidosis in patients undergoing lung volume reduction surgery for the treatment of emphysema.[97]

Hypersensitivity Pneumonitis (HP):

Hypersensitivity pneumonitis is a disorder characterized by the development of a local pulmonary immunological reaction in response to repeated inhalation of organic dusts.[98] This protocol will focus on the involvement of **small airways** with HP since a detailed description of this disease is beyond the scope of this presentation. In HP, the inflammatory reaction is primarily localized to the interstitium and alveolar structures with a clinical presentation

consistent with either acute pneumonia or an interstitial lung disease. Nevertheless, small airways disease with symptoms of airflow limitation can be seen in the acute, sub-acute, and chronic forms of HP.[99]

The list of organic dusts associated with the development of HP is extensive. The most common HP syndromes include bird fanciers' and farmer's lung. The inhaled antigens in bird fancier's lung are believed to originate from avian droppings, serum, feathers, and eggs. In farmer's lung, thermophilic actinomycetes or saprophytic fungi are the presumed inhaled antigen. The organic antigen must be an average of 0.3 to 5 micrometers in order to reach the terminal airways and alveolar structures. Upon repeated inhalation, the patient becomes sensitized with development of a Type II Arthrus-like reaction with antigen-antibody complex deposition in the early phases. This leads to an alveolitis characterized by lymphocyte and mononuclear cell infiltration. Upon persistent inhalation of the antigen, a T-cell mediated, Type IV-delayed hypersensitivity develops with lymphocyte and macrophage activation, granuloma formation, and development of fibrosis.[98,99,100,101]

Acute HP usually presents with a syndrome mimicking acute pneumonia and represents short-term, high-level antigen exposure in a previously primed host. Sub-acute HP is considered to be a more lengthy form of acute HP and has a more indolent course characterized by chronic respiratory complaints and a chest radiograph or HRCT with interstitial opacities and nodules. Chronic HP accounts for approximately 5% of HP patients. It is characterized by repeated exposure to low levels of inhaled antigen with a clinical picture consistent with chronic interstitial lung disease. Some of these patients may develop progressive respiratory failure and hypoxemia.[98,99,102]

A presentation of chronic airflow limitation consistent with small airway disease is seen in 10% of patients with HP. About 54-86% of patients with HP demonstrate evidence of small airways disease by HRCT with either air trapping ("mosaic" pattern) and/or centrilobular nodules.[94,103] In up to 60% of biopsy specimens in patients with either acute or chronic HP, mononuclear cell inflammation of the terminal and respiratory bronchioles is present.[99] The term "cellular bronchiolitis" has been utilized for this small airway inflammation.[94] Despite these findings, most patients with HP present with a restrictive lung disease rather than an obstructive pattern.[99] Pérez-Padilla et al. reviewed 36 open lung biopsies of patients with chronic pigeon's breeders disease focusing on the bronchiolar lesion. The severity of this bronchiolitis equaled and paralleled the degree of inflammation and fibrosis seen in the lung parenchyma and interstitium.[104] Thus, the contribution of the small airways disease in HP is shadowed by the widespread alveolar and interstitial inflammation.

A picture of chronic bronchitis is seen in approximately 20-50% of non-smoking patients with serum precipitins to avian or farmer's lung antigens. This presentation can mimic COPD with cough, sputum production, and dyspnea. It can be the sole presentation of exposure to the antigen in the absence of typical hypersensitivity pneumonitis.[99]

The clinician must be aware that some patients with HP can present with severe airflow limitation with symptoms indistinguishable from COPD. Some of these patients may demonstrate emphysematous changes by CT scan or lung biopsy.[99] A careful history for occupational and environmental exposures should be performed in all patients evaluated for chronic airflow limitation.

Bronchiolitis Obliterans (BO):

One of the most important diseases presenting with chronic airflow limitation is bronchiolitis obliterans (BO). It presents with rapidly progressive airflow limitation leading to significant exercise limitation and respiratory failure. Bronchiolitis obliterans was first described in 1901 by Lange in two patients who expired with advanced lung disease and demonstrated histological features of BO. It was not until the 1970's that the clinical, radiological, and histological manifestations of this disease were described and recognized.

Bronchiolitis obliterans is the "classic" small airways disease since it demonstrates the importance of the small airways as critical sites of airflow limitation. BO presents with profound dyspnea, severe airflow limitation, and hypoxemia despite a lack of parenchymal consolidation or significant interstitial disease.[14] The increase use of HRCT and video-assisted thoracoscopic lung biopsy (VATS) has led to an increased awareness of this disease. In some centers, BO has been identified as the cause of chronic obstructive lung disease in 5-7% of patients.[3] It is important to understand the pathogenesis, pathology, diagnosis, histology, and treatment of this disease.

Bronchiolitis obliterans is one of the various injury and repair pathways of the lung in response to an inhaled or blood-borne toxin. Thus, the term "bronchiolitis obliterans" is applied to the histological findings and warrants a careful search for the associated injury or predisposing illness.[14,94,105] The major histological and clinical classifications of bronchiolitis obliterans include constrictive bronchiolitis and proliferative bronchiolitis (with or without associated organizing pneumonia).[106] The definition, histology, clinical features, and response to treatment are summarized in Tables 6 and 7.

Table 6: Current definitions and terminology for bronchiolitis obliterans:

Current Definition:	**Previous definitions:**	**Histological features:**
Constrictive bronchiolitis	Bronchiolitis obliterans	Scarring and fibrosis with concentric narrowing of membranous bronchioles. Bronchial wall inflammation.
Proliferative bronchiolitis obliterans	"Polypoid" bronchiolitis BOOP	Intraluminal polyps of granulation tissue arising from or adherent to the bronchial walls at sites of mucosal ulceration. More prominent in alveolar ducts. With or w/o associated organizing pneumonia (OP). "Foamy" macrophages seen in the alveolar spaces.

Adapted from Colby TV, Myers JL. Seminars in Respiratory Medicine 1992; 13:119-133 and King TE. Bronchiolitis. *In*: Schwarz MI and King TE, eds. Interstitial Lung Disease. 3rd edition. Hamilton, Ontario: B.C. Decker Inc. 1998. Chapter 25:645-684.

Table 7: Clinical features of the different classifications of BO:

	Clinical features	**Radiology**	**Steroid response**
Constrictive bronchiolitis	Mimics COPD Obstructive PFTs	Normal CXR Mosaic pattern in HRCT	Poor
Proliferative BO or BOOP	Symptoms of pneumonia Restrictive PFTs	Parenchymal consolidation	Good

Adapted from References 79 and 105.

Constrictive bronchiolitis is the classic bronchiolitis obliterans presenting with progressive and irreversible airflow obstruction. These patients present with dyspnea, cough, and either unremarkable or hyperinflated lungs by chest radiograph. A diagnosis of constrictive bronchiolitis should be suspected in patients with an FEV1 <60% and no other cause of airflow limitation, chronic bronchitis, asthma, or emphysema. The diagnosis should also be considered in non-smokers with progressive respiratory dysfunction. A careful history should be obtained to identify possible associated conditions or injurious exposures as delineated in Table 8. In constrictive bronchiolitis, the physical examination may be normal or reveal wheezing, inspiratory "squeaks" or crackles. Pulmonary function tests usually demonstrate severe airflow limitation without a bronchodilator response. Of note, the DLCO may be normal or relatively preserved for the degree of expiratory flow impairment.

Table 8: Conditions associated with bronchiolitis obliterans (constrictive bronchiolitis)

Idiopathic (4%); called "cryptogenic" BO[107]
Post-infectious (Mycoplasma[108], HIV, viral)
Chronic asthma, bronchiectasis, Cystic fibrosis
Toxic agent or fume inhalation
Connective tissue disease (Rheumatoid arthritis, SLE, secondary Sjogren's)[17,109]
Bone marrow, heart/lung, and lung transplantation (may occur in 35-60% of patients)[14,110,111]
Drug reactions (penicillamine, gold, amiodarone, etc.)[105,]
Healed ARDS or diffuse alveolar damage (DAD)
Hypersensitivity pneumonitis
Inflammatory bowel disease
Mineral-dust airway disease
Idiopathic or "cryptogenic" bronchiolitis[107]
IgA nephropathy[112]

Adapted from Adapted from Wright JL et al. Am Rev Respir Dis 1992; 146:240-262. Reference 14 and references17,105,109,110,107,112, and 113.

The HRCT is essential in the diagnosis of constrictive BO since significant air trapping and a "mosaic" pattern are seen in a large majority of patients. The "mosaic" pattern represents patchy areas of decreased lung attenuation due to hyperinflated lung lobules with associated reflex vasoconstriction interposed with uninvolved lung.[78,94,114] The presence of this pattern is considered to be the "cardinal sign" for small airways disease.[78] Nevertheless, a normal HRCT scan does not exclude constrictive bronchiolitis.[114]

Histological evaluation of the lung in **constrictive bronchiolitis** reveals a patchy and nodular inflammation of the membranous and respiratory bronchioles with submucosal scarring and fibrosis leading to partial or complete luminal obstruction. Smooth muscle hypertrophy and associated bronchiolectasis is common.[14,106,115] This histology suggests that constrictive bronchiolitis represents a bronchiolar repair process after an inhalational or blood-borne injury. The repair is similar to that seen in idiopathic pulmonary fibrosis. Airway epithelial injury leads to a fibroproliferative repair response with proliferation and exudation of mesenchymal cells into the bronchial wall, airway lumen, and surrounding interstitium. Organization and fibrosis leads to constriction and obliteration of the small airways (See Figure 8).[106,107]

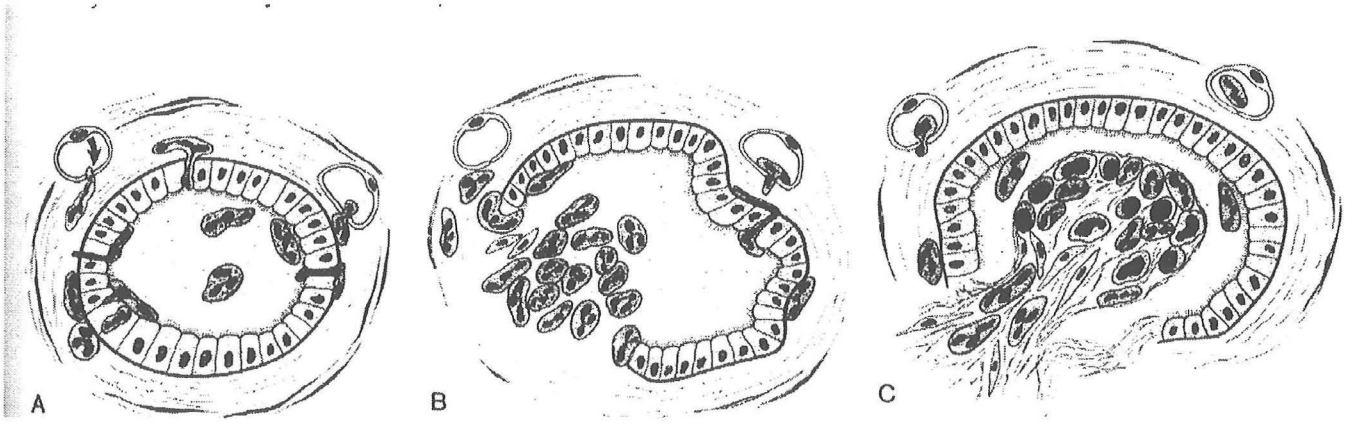


Figure 8: Proposed mechanism for development of bronchiolitis obliterans after airway injury. **A.** Neutrophil influx into the small airways. **B.** Injury to the airway with epithelial cell death and detachment. Further injury occurs from neutrophil products (proteases, oxygen-radicals, etc.). **C.** Airway obliteration with intraluminal and intramural fibroproliferation.

From Dorinsky PM, Gadek JE. Bronchiolitis obliterans. *In*: Cherniack NS, ed. Chronic Obstructive Pulmonary Disease. 1st ed. Philadelphia: W.B. Saunders Company, 1991, 338-343.

The diagnosis of **constrictive bronchiolitis** requires a high index of suspicion. Either open lung or video-assisted thoracoscopic lung biopsy is required for diagnostic confirmation based on the patchy nature of the disease even in advanced cases. Transbronchial lung biopsies commonly do not provide sufficient tissue for diagnosis. Some authors support the combination of clinical features and results of bronchoalveolar lavage (BAL) for a non-invasive diagnosis of constrictive bronchiolitis. The presence of a) non-smoking patient, b) dry cough and dyspnea, c) severe airflow limitation without response to bronchodilators, d) HRCT suggestive of BO, and e) greater than 25% neutrophils in bronchoalveolar lavage (BAL) is highly predictive of bronchiolitis obliterans.[107,116]

The clinical course of constrictive bronchiolitis is characterized by progressive dysfunction despite steroid therapy. Post-viral or cryptogenic bronchiolitis carries a better prognosis with a survival of 5 to 10 years. Rheumatoid arthritis and post-transplant related bronchiolitis is more rapidly progressive with survival measured in months.[78] Treatment with corticosteroids is supported by a number of small series and case reports. A suggested regimen is prednisone at 1 mg/kg/d for 12-16 weeks followed by a taper to 20 mg/day continued for several months. Then alternative day maintenance dosing should be continued for 2 years.[107]

Proliferative bronchiolitis is another clinical and histological form of bronchiolitis obliterans that is usually associated with an organizing pneumonia. It is more commonly known as "bronchiolitis obliterans organizing pneumonia" or BOOP. Another term for this form of BO is "bronchiolitis obliterans with intraluminal plugs". This disease presentation differs significantly from constrictive bronchiolitis by the presence of a **restrictive** pulmonary dysfunction and parenchymal consolidation. Rarely, proliferative bronchiolitis presents with an obstructive or mixed restrictive/obstructive pattern by pulmonary function testing.[117] This disease is associated with a variety of disorders and injuries (Table 9). As in constrictive bronchiolitis, proliferative bronchiolitis is a histological pattern representing an exuberant inflammatory response and repair during and after injury. Most cases of proliferative bronchiolitis are idiopathic (70-90%) and are associated with an organizing pneumonia. It is called "cryptogenic organizing pneumonia" or COP.[106,118,119] In contrast with constrictive BO, proliferative BO usually responds to steroid therapy.[106]

Table 9: Conditions associated with **proliferative bronchiolitis** with or without organizing pneumonia. NOTE: BOOP represents proliferative bronchiolitis with organizing pneumonia.

Idiopathic (70-90%), called cryptogenic organizing pneumonia (COP)
Collagen vascular disease (Rheumatoid arthritis, SLE, dermatomyositis)
Organizing acute infection
Organ transplantation
Radiation therapy
Drug-induced
Organizing diffuse alveolar damage or ARDS
Chronic eosinophilic pneumonia
Vasculitis (especially Wegener's granulomatosis)
Hypersensitivity pneumonitis
Aspiration pneumonitis

From King TE. Bronchiolitis. *In*: Schwarz MI and King TE, eds. Interstitial Lung Disease. 3rd edition. Hamilton, Ontario: B.C. Decker Inc. 1998. Chapter 25: P. 647.

Respiratory bronchiolitis-ILD:

Increased interest in respiratory bronchiolitis has been sparked by recent reports of a rare but fascinating clinical presentation of respiratory bronchiolitis with clinical features of interstitial lung disease (RB-ILD)[120,121,122,123]. These patients are young smokers with dyspnea and cough, mixed restrictive and obstructive pulmonary function tests, low DLCO, and hypoxemia. Open lung biopsies have demonstrated the accumulation of brown-pigmented

macrophages in respiratory bronchioles and proximal alveoli with accompanied interstitial fibrosis. Some patients with RB manifest premature emphysema. The initial description of RB-ILD was reported by Myers in 1987. He described six young smokers with progressive respiratory deterioration accompanied by restrictive PFTs, decreased DLCO, and hypoxemia[120]. This original description was followed by a report by Yousem (1989) of 18 smokers with similar clinical presentation and biopsy-proven RB-ILD[121].

The patients are usually young in presentation with age ranging from 22-53 y/o. It is a disease exclusively of smokers and mimics COPD. No specific sex or ethnic predilection has been described. The reported amount of cigarettes consumed ranged from 7-75 pack-years. Chronic symptoms consist of dyspnea (67%), sputum production (44%), cough (50%), and chest pain persisting for approximately five years prior to presentation. Rare asymptomatic patients have been reported in each series.

The physical examination can reveal late inspiratory bibasilar crackles, coarser than the "velcro-like" crackles of idiopathic pulmonary fibrosis. Laboratory data is unremarkable except for frequent hypoxemia at rest or with exercise[124]. The pulmonary function tests can present with normal flows or more commonly, demonstrate a mixed obstructive and restrictive pattern with characteristic low DLCO. An interesting feature reported in the literature is a case of respiratory bronchiolitis with dramatic reversal of a restrictive and obstructive pattern after bronchodilator administration. This phenomenon called "reversible restriction" is believed to be secondary to bronchodilation of small airways and alveolar ducts[125]. The chest radiographs can be normal or present with bilateral and diffuse reticulonodular infiltrates. High-resolution CT scan findings range from normal to ground-glass opacification, linear opacities, atelectasis, and even emphysema.[123,126]

The diagnosis should be suspected in a young smoker with unexplained dyspnea, cough, significant restrictive or mixed physiology, and low DLCO. Open lung biopsy specimens reveal an inflammatory lesion composed of mononuclear cells in the submucosa of membranous and respiratory bronchioles. The key feature that distinguishes this disease from the RB of smokers is the predominance of associated fibrosis extending in "stellate fashion." from the respiratory bronchioles to the surrounding alveolar walls.[122]

The small number of reported patients makes generalizations on treatment options impossible. Yet, most patients appear to respond to smoking cessation. Anecdotal response to corticosteroids has been published[121].

Lymphangioleiomyomatosis (LAM):

Lymphangioleiomyomatosis is an interesting but rare disease that affects non-smoking women in their childbearing years. The reported incidence is approximately one per million persons.[129] This syndrome is characterized by progressive airflow limitation leading to respiratory failure and ultimately death. It is a disease of unexplained etiology with hamartomatous smooth muscle proliferation involving the small airways, blood vessels, and lymphatics. The proliferation can extend into the interstitium and small airways leading to obstruction and distal formation of thin-walled cysts.[127,128,129,130] The disease is considered an interstitial lung disease. Nevertheless, it affects primarily the small (peripheral) airways leading to an obstructive disorder with lung hyperinflation.

LAM presents at a mean age of 34 years of age (range 9-50 years old) and primarily affects Caucasian women.[130] It rarely attacks post-menopausal women with one series reporting eight post-menopausal patients, six being on estrogen replacement therapy.[131] The patients usually present to medical care with dyspnea or spontaneous pneumothorax (occurring in 66% of patients).[129] Other symptoms include non-productive cough, hemoptysis, chylous effusion and ascites. Involvement of lymph nodes or obstruction of lymph flow in the chest and abdomen leads to chylothorax or chylous ascites. Hemoptysis is likely due to involvement of the pulmonary veins with pulmonary hemorrhage. LAM is easily confused with asthma, COPD, idiopathic pulmonary fibrosis, sarcoid, and tuberculosis. The diagnosis is usually delayed for 3-4 years from the onset of symptoms.[129,130]

The physical exam is usually normal or can present with crackles and/or rhonchi. Clubbing is rarely seen with LAM.[130] Approximately 33-57% of LAM patients present with renal angiomyolipomas and have a picture suggestive of tuberous sclerosis. Nevertheless, LAM patients lack the mental retardation, seizure disorder or facial angiofibromas seen in tuberous sclerosis (TS). Many experts refer to LAM as a *forma frustre* or part of the clinical spectrum of tuberous sclerosis.[129,130,132]

The pathogenesis of LAM is yet to be determined. The association between tuberous sclerosis and LAM suggests a similar genetic mutation. Recently, the genetic mutation in TS has been characterized as a germ cell mutation in either the TSC-1 and TSC-2 tumor suppressor genes mapped to chromosome 9 and 16, respectively.[133] TSC-1 codes for hamartin, a protein with tumor suppressor activity. The TSC-2 gene product is tuberin, a 180 kD protein that also has tumor suppressor activity through inhibition of rap 1. Rap 1 is a modulator of the ras pathway.[134] In LAM, a germ cell mutation is not seen but it is suspected that a spontaneous somatic cell mutation in combination with a loss of heterozygosity (LOH) leads to absent TSC-2 protein. It is suspected that this leads to decreased tumor suppressor activity and hamartomatous smooth-muscle growth in the lung.[129,135]

Progesterone treatment slows the progression of disease. Pregnancy and estrogen therapy are associated with either the onset of LAM or worsening of the clinical manifestations suggesting the importance of hormonal influences in this disease. Estrogen is believed to potentiate smooth muscle proliferation by downregulating tuberin, the TSC-2 gene product. Estrogen may also indirectly inhibit apoptosis of LAM cells.

The diagnosis of LAM should be suspected in women of childbearing age with dyspnea, spontaneous pneumothorax, hemoptysis, chylothorax, or unexplained airflow limitation. The chest radiograph may be normal or demonstrate a reticular or reticulo-nodular pattern. Pulmonary function tests range from normal early in disease to severe airflow obstruction, decreased DLCO, and hypoxemia. A very useful test for the diagnosis of LAM is the HRCT scan of the chest. This usually reveals the presence of numerous thin wall cysts (2mm - 5cm) diffusely in the lung parenchyma (Figure 9). As disease progresses, the cysts become more numerous and enlarged. Emphysematous cysts are distinguished from LAM cysts by the lack of walls and apical distribution. [127,130]

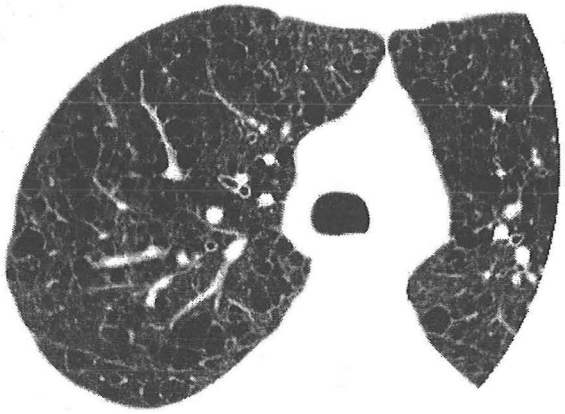


Figure 9: HRCT scan of LAM demonstrating the characteristic thin-walled cysts. These differ from emphysematous bullae by the presence of walls and diffuse distribution. From **www.uchsc.edu/uh/radiology**

The diagnosis of LAM is confirmed with a surgical lung biopsy. The histology of LAM reveals nodular proliferation of smooth muscle cells ("LAM cells") within the alveolar walls, lymphatics, and blood vessels. This smooth muscle cell proliferation obliterates bronchioles leading to distal cyst formation. The study of LAM cells suggests a smooth muscle origin. Nevertheless, these cells also contain estrogen and progesterone receptors (50% of cases) and stain positive with the melanoma HMB45 antibody.[129] There are increasing reports of diagnosis with the combination of transbronchial lung biopsy staining positive for the HMB45 melanoma antigen and a highly suggestive HRCT scan.[129,130,136]

The treatment of LAM is largely derived from small series or case reports. These patients may have a prolonged course or present with very rapid deterioration followed by respiratory failure and death. The best survival data comes from a series by Taylor et al. that reported that 78% of the patients were alive at 8.5 years from the onset of disease.[137] Ten percent of patients demonstrate a bronchodilator response by PFTs and thus, should be treated with inhaled beta-2 agonists.[129] Corticosteroids are not effective in the treatment of LAM. The treatment is primarily focused to hormonal manipulations. The literature reports variable results with progesterone therapy, oophorectomy, and tamoxifen. The data is strongest for progesterone therapy. Pregnancy should be avoided in order to prevent exacerbations.[129,130,138]

Eosinophilic granuloma (EG)

EG is an excellent mimicker of COPD. It presents in cigarette smokers with the usual symptoms of chronic airflow obstruction. It is an uncommon interstitial lung disease of unknown cause. The first cases of EG were reported in

1951 by Farinacci.[140] The term utilized for EG is "pulmonary Langerhans-cell histiocytosis" to allow distinction from other systemic histiocytosis.[139] This disease involves the small (peripheral) airways with granulomatous inflammation led by proliferating Langerhans cells.[3,4,140]

The incidence of disease is unknown. One review mentions a total of 200 cases reported in the literature in a 30-year period.[141] The patients are almost exclusively current or prior smokers (>95%) and present in their 3rd and 4th decade of life. Cough and dyspnea are present in 70% of cases. About one-third of the cases present with systemic symptoms including fever, weight loss, and generalized malaise. Spontaneous pneumothorax is seen in about 25% of cases and may be the presenting manifestation. In 15% of patients, EG can involve the bones, pituitary gland, skin, lymph nodes, liver, and spleen.[139,140,141] The physical examination is normal in most patients. Decreased breath sounds, rales, and wheezes are less common findings. Despite the name eosinophilic granuloma, peripheral blood eosinophilia is not seen.[141]

The pathogenesis of EG remains to be determined. The study of this disease has focused on the Langerhans' cell, a differentiated cell of monocyte-macrophage lineage with antigen-presenting capacity. These cells are characterized by the presence of Birbeck granules which are rod-shaped intracellular inclusions that by electron microscopy are pentalaminar.[142] The strong association between smoking and EG suggests direct effects of cigarette smoke on Langerhans' cell proliferation in the lung. Smoking leads to increased secretion of bombesin-like peptides in the lung that stimulate macrophage cytokine secretion and recruitment of Langerhans' cells with fibroblast proliferation (Figure 10). The pre-existing hypothesis suggesting that EG represented a local "malignant" proliferation of Langerhans' cells is no longer accepted.[139,140]

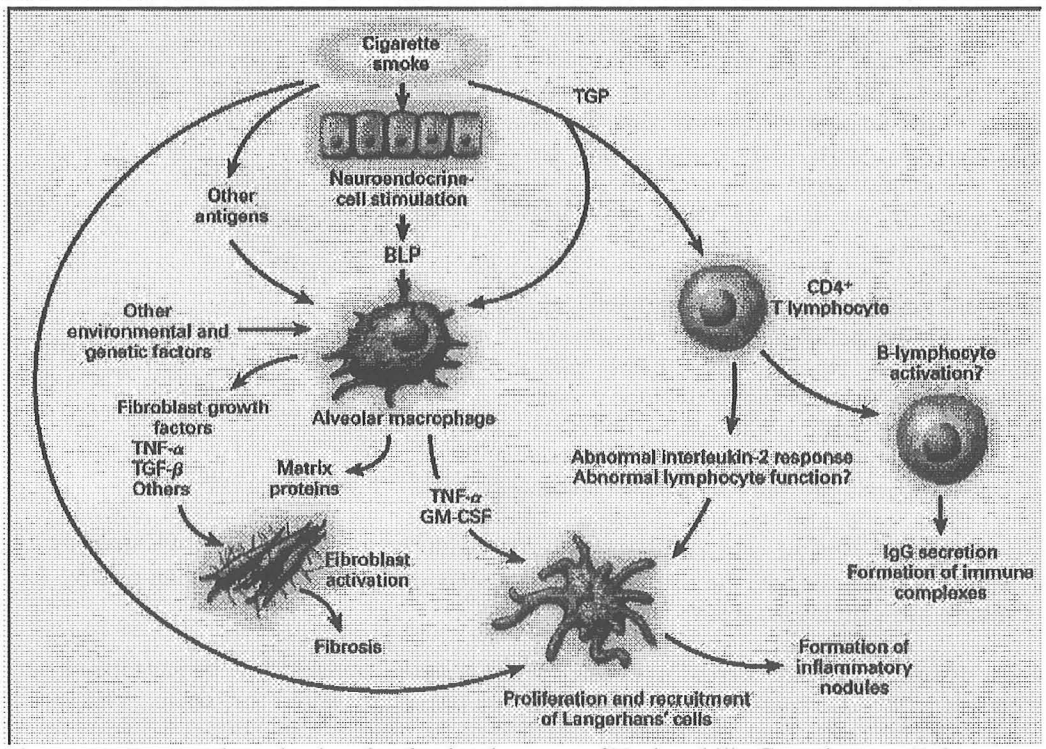


Figure 10: Proposed mechanism for the development of Eosinophilic Granuloma or Pulmonary Langerhans'-Cell Histiocytosis. From Vassallo et al. New Engl J Med 2000; 342:1969-1978. Reference 139.

The diagnosis of EG requires a high-index of suspicion. PFTs usually range from normal to an obstructive or mixed pattern. 60-90% of patients have a low DLCO. The degree of airflow obstruction correlates with the histology demonstrating peribronchiolar inflammation and fibrosis.[139,141] The chest radiographs are usually abnormal revealing bilateral upper-lobe nodular or reticulonodular infiltrates in association with cysts.[4,139,140] Lung volumes

are usually normal or increased differentiating EG from the other interstitial lung diseases. The HRCT scan can be virtually diagnostic for this disease.[4,127,143,144] Early on, the HRCT scan demonstrates nodular lesions and later, show an increase in the number and size of the cysts. In the right clinical context, the combination of upper lobe cysts and peribronchiolar nodules is highly suggestive and even diagnostic of EG.

The diagnosis is usually confirmed utilizing BAL, transbronchial biopsies or open lung biopsy. Recent reports have demonstrated that BAL with >5% Langerhans' cells (CD_{1a} positive cells) is highly suggestive of EG and may obviate the need for tissue diagnosis if the patient has a compatible clinical picture and HRCT scan.[139]

Histological abnormalities in EG follow a peribronchiolar distribution. Early in the disease, proliferating Langerhans' cells are seen in the peripheral airways. These proliferating cells form characteristic "stellate" nodules measuring 0.4-1.3 cm in size containing a variety of cells including LC, eosinophils, histiocytes, lymphocytes, plasma cells, and pigmented macrophages. The name "eosinophilic granuloma" comes from the abundance of eosinophils surrounding the histiocytic inflammation. Later in the disease, the stellate nodules may coalesce and cavitate with fibrotic transformation. Occlusion of the terminal and respiratory bronchioles by the expanding stellate nodules leads to airflow limitation and cyst formation.[139,141,145]

The natural history of EG is variable with most patients improving or stabilizing with smoking cessation. Less than 10% of cases progress to respiratory failure and death. Treatment with corticosteroids with stabilization of disease has been reported in various case studies. Current recommendations reserve corticosteroid use for patients with progressive disease despite smoking cessation.[139] Transplantation has been performed in severe cases and recurrences of EG in the transplanted lung have been reported.

Diffuse Panbronchiolitis (DPB)

Diffuse panbronchiolitis (DPB) is also a small airway disease of the respiratory bronchioles, the bridge between the conducting airways and the gas exchange parenchyma of the lung. DPB also highlights the important contribution of the small airways to the total airway resistance. These patients present with severe and chronic airflow obstruction indistinguishable from emphysema and chronic bronchitis in the setting of relatively quiescent lung histology.[7,146]

DPB is a disease of unclear etiology seen almost exclusively in Japanese and Korean adults.[147] In Japan, DPB has an incidence that approaches that of COPD. The increased incidence of DPB in the Japanese and Korean population is believed to be secondary to a high incidence (11-14%) of the HLA-Bw54 human leukocyte antigen. HLA-Bw54 is seen in 63% of DPB patients with a relative risk reported at 13.30.[146,147] Recent work by Keicho et al. has mapped the HLA-associated major susceptibility gene to 200 kb of the class I telomeric region of the HLA-B locus on chromosome 6p21.3.[148]

Recently, there have been reports of DPB in China, Latin America, and the United States.[149,150,151] Fitzgerald et al. reported five U.S. citizens (4 Caucasians and 1 Hispanic) with progressive obstructive pulmonary disease and biopsy-proven DPB. DPB may be grossly underdiagnosed in the U.S. as it is easily confused with chronic bronchitis. This disease should be suspected in patients with unexplained chronic obstructive pulmonary disease or bronchiolitis especially if sinusitis is present.[150]

DPB usually affects males in their 4th and 5th decade of life. Symptoms are commonly mistaken for chronic bronchitis, emphysema, bronchiolitis obliterans, or bronchiectasis. All patients report a history of paranasal sinusitis in their 2nd and 3rd decade of life. In the Japanese patients, smoking is seen in about two-thirds of patients.[147,150] The disease progresses with obstructive symptoms and bacterial superinfection with initial isolation of normal flora and *Haemophilus influenza* followed later by *Pseudomonas* sp. infection. Of note, these patients lack an immunoglobulin deficiency, connective tissue disease, or immunosuppresion.

The chest radiograph reveals hyperinflation and may demonstrate ill-defined <2mm nodules in the lung bases. In advanced disease, "tram lines" suggestive of bronchiectasis are seen. The HRCT scan is helpful in DPB by demonstrating centrilobular nodules or branching structures ("tree-in-bud") in the lung periphery consistent with bronchiolectasis. Bronchial wall thickening and diffuse bronchiectasis is observed in advanced disease.[114,147,150]

Pulmonary function tests reveal a severe obstructive pattern, air trapping (increased RV/TLC ratio), a reduced diffusion capacity, and hypoxemia.[147,150]

The diagnosis of DPB usually requires a lung biopsy either open or by VATS. The histology is highly characteristic with the gross pathology revealing gray-white to yellow inflammatory nodules with centrilobular distribution. By high power microscopy, there is inflammation centered at the terminal and respiratory bronchioles with dense peribronchiolar and luminal accumulation of neutrophils, lymphocytes, plasma cells, and histiocytes. There is associated proliferation of bronchial-associated lymphoid follicles and a characteristic accumulation of interstitial foamy macrophages.[115,147,150,152]

This disease is progressive and if untreated, the 5-year and 10-year survival is 42% and 25%, respectively. DPB has a high incidence of elevated cold agglutinin titers despite absent *Mycoplasma* antibodies. This led to empiric therapy with erythromycin and macrolides with an improvement in the 5-year survival to 91%. Patients are usually treated with low dose erythromycin at 400-600 mg/day for an average of 20 months.

DPB is a classic example of how the study of a rare disease can yield insight into the treatment of common disorders. The recent observed impact of chronic macrolide therapy in DPB has fire-started research into the anti-inflammatory properties of macrolides on the bronchial and bronchiolar mucosa. These anti-inflammatory effects go beyond the antimicrobial properties of these agents and are likely related to the inhibition of local cytokine and chemokine production. Abe et al. recently demonstrated the inhibition of IL-8 secretion in human bronchial epithelial cell lines by clarithromycin (CAM) (Figure 11).[153] These effects of clarithromycin were mediated through the activator protein (AP)-1 promotor binding sites of the IL-8 gene. The effects of macrolides on other large and small airways diseases, such a bronchiectasis, cystic fibrosis, chronic bronchitis, and bronchiolitis remain to be proven.

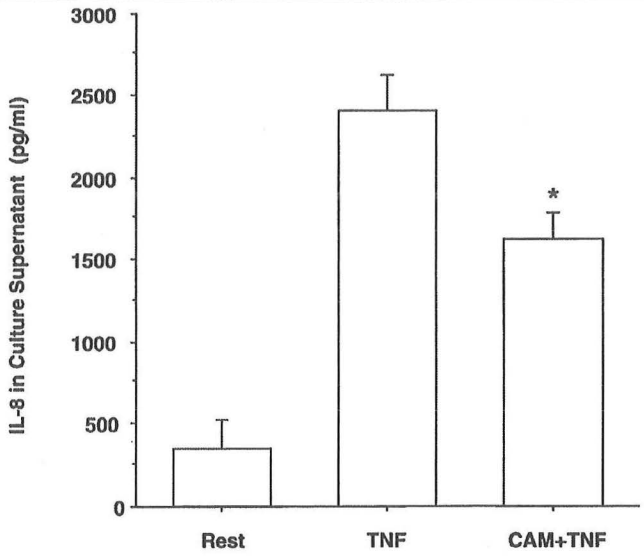


Figure 11: Clarithromycin (CAM) inhibits TNF-alpha mediated IL-8 protein release from human bronchial epithelial cell line (BET-1A). *p<0.05. From Abe S, Nakamura H, Inoue S, et al. Am J Respir Cell Mol Biol 2000; 22:51-60. Reference 153

SUMMARY

The OTHER chronic obstructive pulmonary diseases have been reviewed by following the predominant site of airway involvement: larynx, trachea and major bronchi, large (central airways) and peripheral (small) airways. These diseases vary in their incidence, clinical presentation, radiographs, histology, diagnosis, and treatment. Nevertheless, they are all characterized by chronic and progressive obstructive lung disease. These diseases can mimic COPD confusing even the most astute clinicians.

The laryngeal and tracheal diseases present with a more abrupt presentation with critical airway stenosis leading to expiratory and inspiratory limitations. A chronic bronchitis or asthmatic picture characterizes the diseases of the large (central) airways. The small (peripheral) airways diseases usually present with significant obstruction and hypoxemia with rather unimpressive chest radiographs and histological abnormalities.

These OTHER chronic obstructive pulmonary diseases should be considered in patients with chronic airflow obstruction with either too rapid a fall in spirometric values, minimal or absent smoking history, or young age. A

systematic approach to the diagnosis of these diseases should include the use of chest radiographs and complete pulmonary function testing including examination of flow-volume loops, spirometric values, lung volumes, and DLCO. In patients with atypical presentations and unrevealing radiographs, a high-resolution CT scan of the chest with inspiratory and expiratory cuts may provide evidence for either large airway or small airway disease. When suspected, these patients should be referred to a pulmonary disease specialist for further evaluation and possible lung biopsy.

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