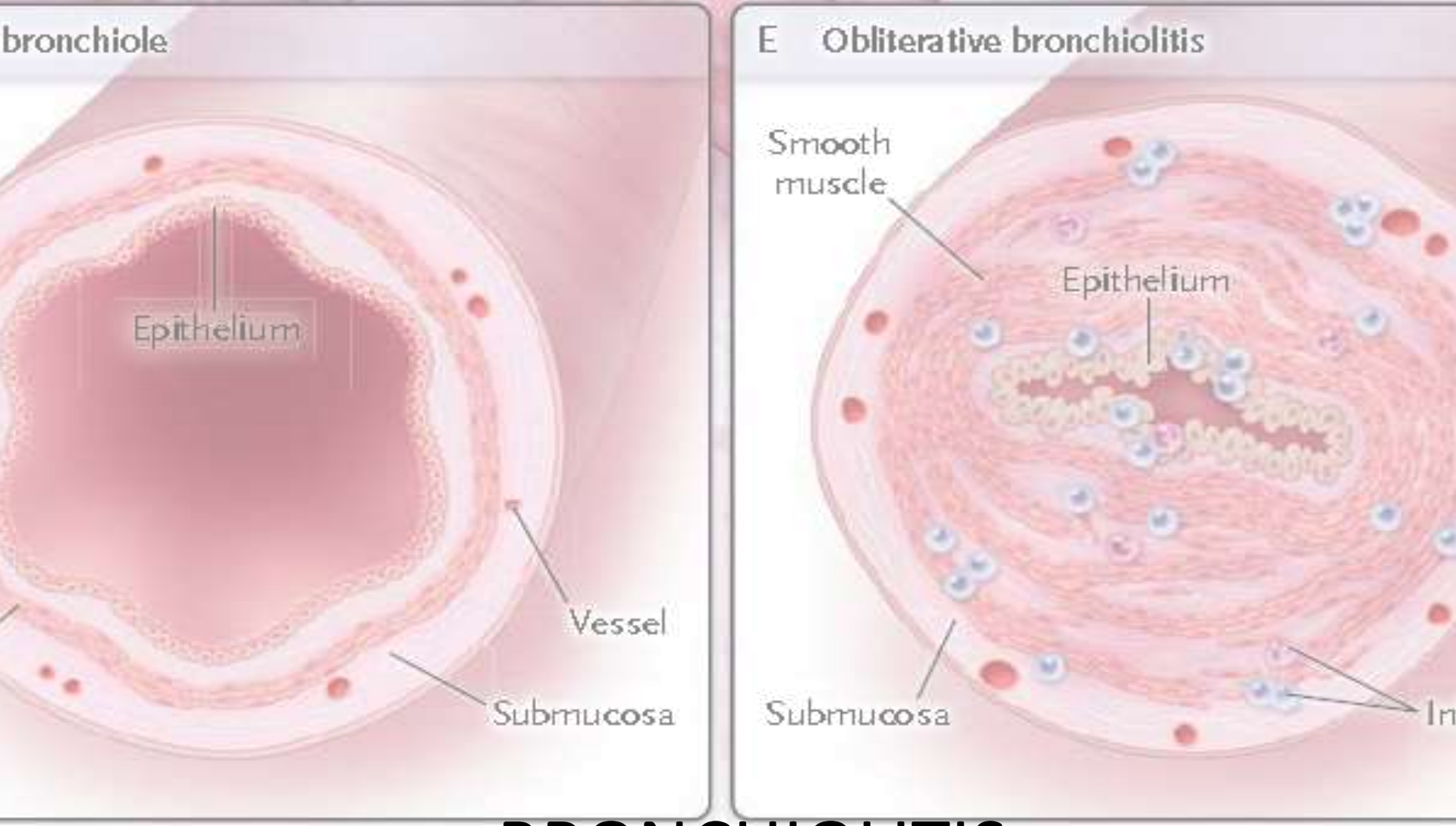


BRONCHIOLITIS
Diagnosis and Management

Milind Baldi

Overview

- Introduction: Why a puzzling subject ?
- Relevant anatomy
- Physiological assessment
- Radiological assessment
- Individual disorders

Why a puzzling subject ?

- Terminology
  - Synonyms
  - Similar terms, different meanings
  - Different terms, similar meaning
  - Modifications in literature
- Classification
  - Classification of classifications
  - Diverse approaches to classify
- Diverse insults
- Diverse presentations
- Silent zone
- Evidence

Terminology: Synonyms

- Bronchiolitis
- Bronchiolar diseases
- Small airway diseases
- Peripheral airway diseases
- Bronchiolar syndromes

Terminology

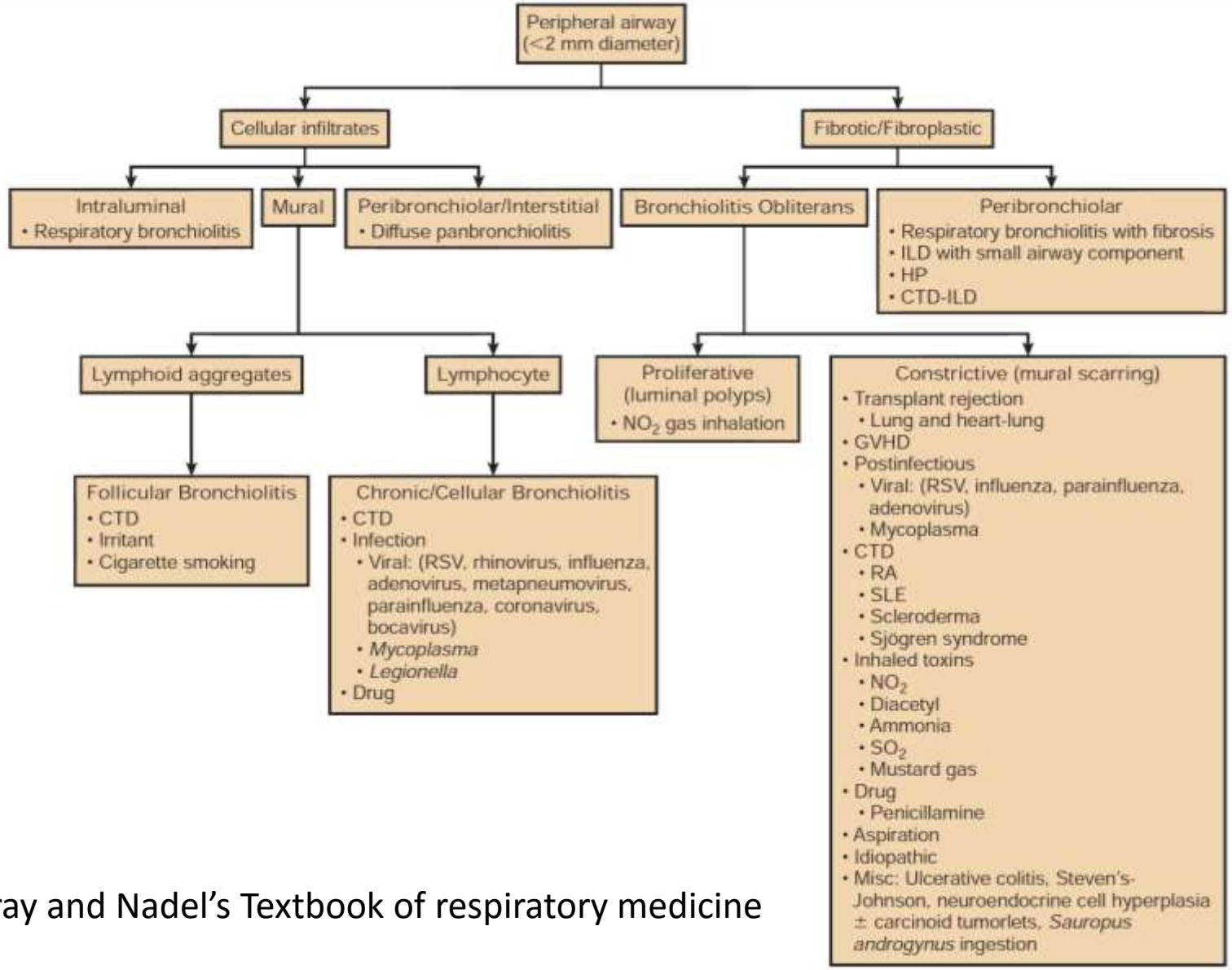
Similar terms, different meanings

- Bronchiolitis obliterans and Bronchiolitis obliterans syndrome

Different terms, similar meaning

- Bronchiolitis obliterans and obliterative bronchiolitis
- Bronchiolitis obliterans and constrcitive bronchiolitis

Modifications in literature



Murray and Nadel's Textbook of respiratory medicine

Classifications: predominant involvement

- Primary Bronchiolar Disorders
  - Constrictive Bronchiolitis (Obliterative Bronchiolitis, Bronchiolitis Obliterans)
  - Acute Bronchiolitis
  - Diffuse Panbronchiolitis
  - Respiratory Bronchiolitis
  - Mineral Dust Airway Disease
  - Follicular Bronchiolitis
  - Other Forms of Primary Bronchiolitis
- Interstitial Lung Diseases with a Prominent Bronchiolar Component
  - Hypersensitivity Pneumonitis
  - RB-ILD and DIP
  - Cryptogenic Organizing Pneumonia
  - Other Interstitial Lung Diseases
- Bronchiolar Involvement in Large Airway Diseases

Am J Respir Crit Care Med Vol 168. pp 1277–1292, 2003

Secondary

Infections

Hypersensitivity disorders:

- Bronchial asthma
- Allergic bronchopulmonary aspergillosis
- Bronchocentric granulomatosis
- Hypersensitivity pneumonitis
- Chronic eosinophilic pneumonia
- Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)

Smoking-related disorders:

- Bronchiolitis in COPD
- Respiratory bronchiolitis
- RB-ILD
- Pulmonary Langerhans cell histiocytosis

Toxic fumes and gases inhalation

Diffuse chronic aspiration

Inhaled particle-induced small airways disease

Drug-induced bronchiolar toxicities

Sarcoidosis

Neoplasms

Idiopathic/primary

Cryptogenic constrictive bronchiolitis

Diffuse panbronchiolitis

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Neuroendocrine hyperplasia in infants

Bronchiolitis obliterans syndrome

Connective tissue disorders:

- Primary Sjögren's syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyositis–dermatomyositis
- Mixed connective tissue disease
- Ankylosing spondylitis

Inflammatory bowel disease

Bronchiolitis obliterans organizing pneumonia – cryptogenic organizing pneumonia

Expert Rev. Respir. Med. 7(3), 289–306 (2013)

Classifications: Radiolgical

Table 3—*Causes and/or Underlying Disorders Associated With Constrictive Bronchiolitis*

	Char Clinica
Hypersensitivity pneumonitis	Subacute dyspne malaise
RB/RB-ILD	Inspirato digital
Follicular bronchiolitis	Progressi cough
Mineral dust airway disease	Progressi
Pulmonary Langerhans cell histiocytosis	Dyspnea, chest p

RB = respiratory bronchiolitis; RI

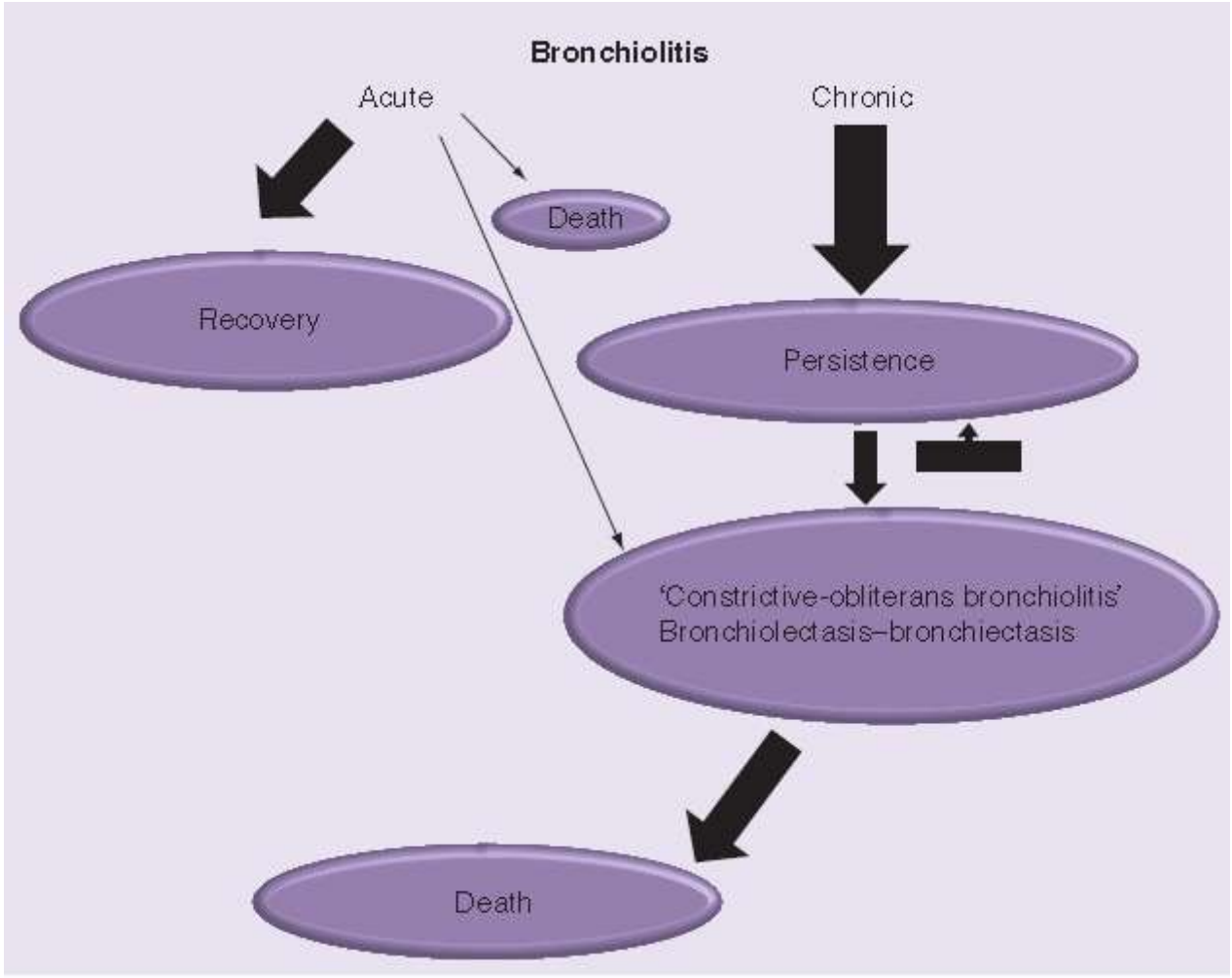
	Histopathologic Features
Postinfectious	
Viral (adenovirus, respiratory *syncytial* virus, influenza, parainfluenza)	
Mycoplasma	
Collagen vascular diseases	Patchy peribronchiolar lymphocytic infiltration, poorly formed granulomas
Rheumatoid arthritis	
Systemic lupus erythematosus	
Eosinophilic fasciitis	
Transplant related	Pigmented macrophages and interstitial inflammation around respiratory bronchioles
Graft vs host disease	
Allograft recipients	
Bone marrow transplant	
Heart-lung transplant	Peribronchiolar lymphoid aggregates
Toxic fume exposure	
Nitrogen dioxide	
Sulfur dioxide	
Ammonia	Peribronchial infiltration of dust laden macrophages
Chlorine	
Phosgene	
Diacetyl (popcorn workers)	
Ingested toxins	Cellular interstitial infiltrates composed of Langerhans cells, lymphocytes, macrophages, and fibroblasts
Sauropus androgynus	
Drugs	
D-penicillamine	
Gold	
Cocaine	
Carmustine	
Cryptogenic constrictive bronchiolitis	

sion of other abbreviations.

CHEST 2010; 137(4): 938 – 951

Why a puzzling subject ?
Diverse insults

- Infections
- Connective tissue diseases
- Drug reactions
- Inhalational injuries
- Post-transplant patients


Bronchiolitis
Acute
Chronic
Death
Recovery
Persistence
'Constrictive-obliterans bronchiolitis'
Bronchiolectasis–bronchiectasis
Death

Silent zone

- Significant percentage of bronchioles must be damaged before the disease manifests clinically
- Radiological imaging may not resolve to the level of bronchioles
- Bronchoscopy is unable to reach upto bronchioles
- TBLB is usually not of help, as the disease is patchy

Why a puzzling subject ?
Diverse presentations

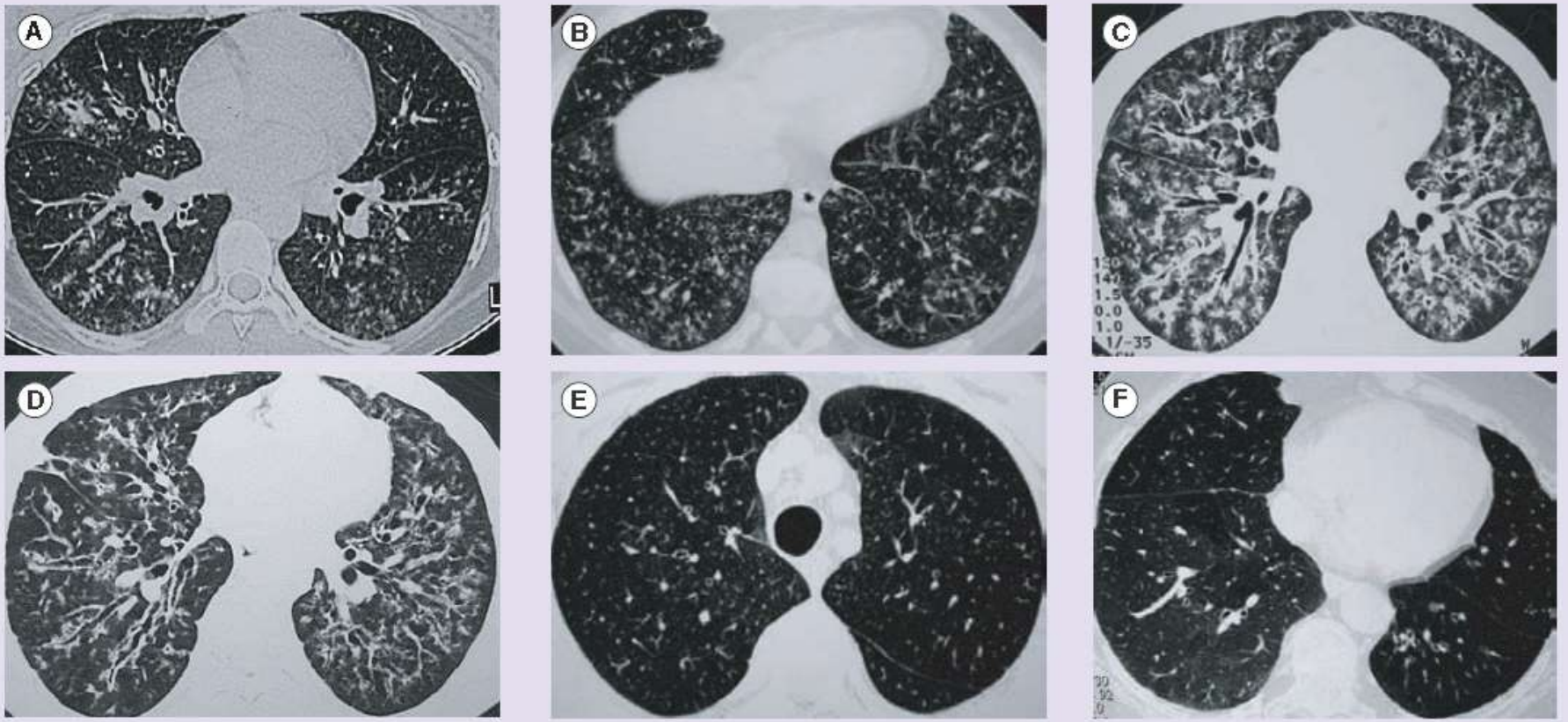


Figure 5. High-resolution computed tomography pictures of various forms of bronchiolitis.

Expert Rev. Respir. Med. 7(3), 289–306 (2013)

Why a puzzling subject ?
Diverse presentations

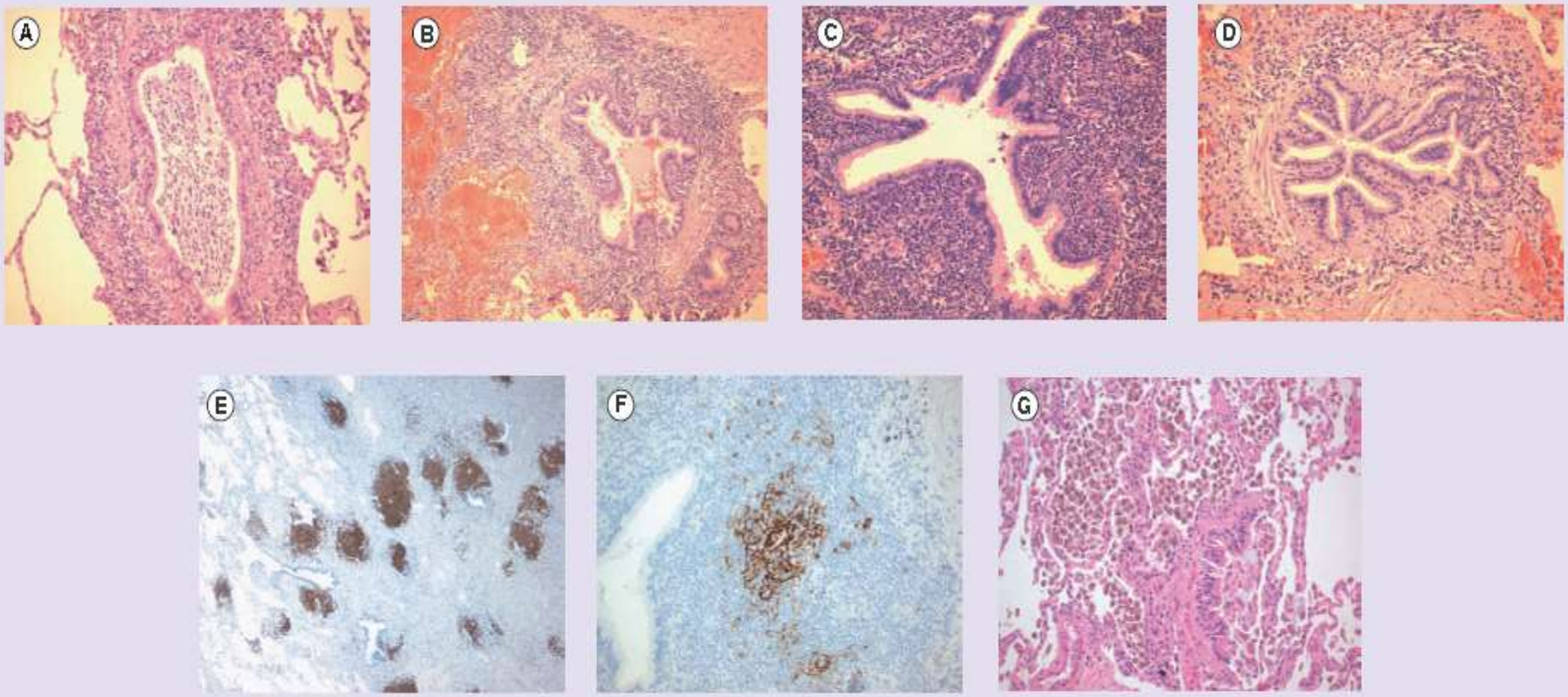


Figure 4. Histopathological pictures of various forms of bronchiolitis

Expert Rev. Respir. Med. 7(3), 289–306 (2013)

respect to either etiology or pathogenesis (1, 2).

A confusing array of terms has been used in referring to bronchiolar disorders. Some of these descriptive terms are synonymous, whereas others overlap in their intended meaning. For example, the term "bronchiolitis obliterans" has been applied to

Am J Respir Crit Care Med Vol 168. pp 1277–1292

The term "bronchiolitis" has been historically confusing to clinicians and pathologists alike. Bronchiolitis is inconsistently applied as both a descriptive and a formal diagnostic term in part

Proc Am Thorac Soc Vol 3. pp 41–47, 2006

Confusing terminology has hampered correlation of bronchiolar disease with clinical, physiologic, and imaging features. For example, the term 'bronchiolitis oblit-

Curr Opin Pulm Med 12:145–151

clear understanding of pathogenesis is lacking.

The nomenclature applied to the bronchiolar syndromes has been confusing. The following terms have been used: bronchiolitis obliterans, bronchiolitis fibrosa

Fishman's pulmonary diseases and disorders

Overview

- Introduction: Why a puzzling subject ?
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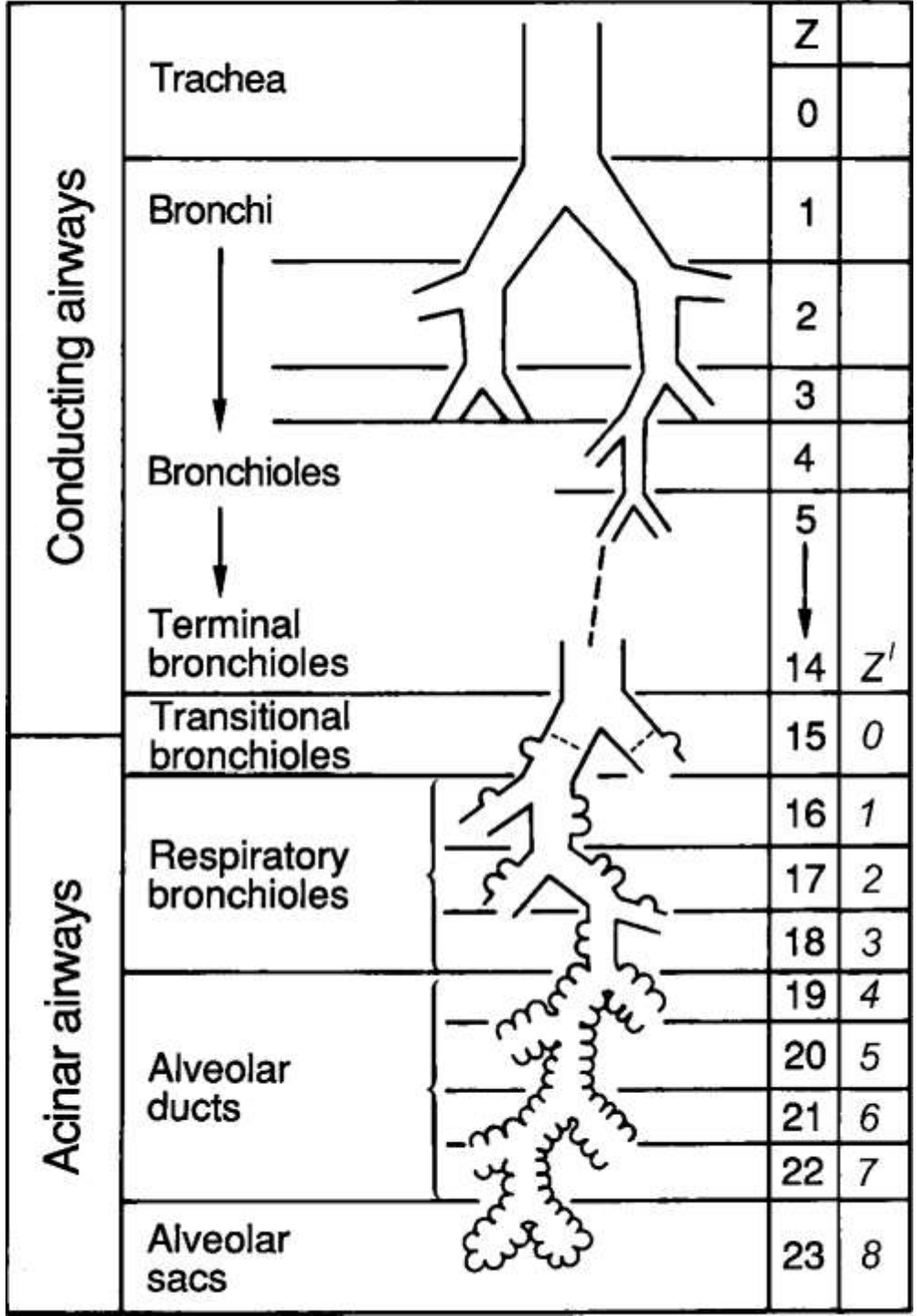
- Radiological assessment
- Individual disorders


Conducting airways
Acinar airways
Trachea
Bronchi
Bronchioles
Terminal bronchioles
Transitional bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
Z
0
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Relevant Anatomy

- **Bronchi**: characterized by incomplete cartilaginous rings, ciliated epithelium, goblet cells, sub mucosal glands and are innervated by muscarinic output via vagus
- **Bronchioles**: sparsely ciliated simple columnar epithelium and secretory club cells but lack cartilage, goblet cells and glands and are not innervated by vagus

Relevant Anatomy

- The **pulmonary acinus** is defined as the lung unit distal to a terminal bronchiole, which is the last purely conducting airway
- Acini measure 6–10 mm in diameter
- **Secondary pulmonary lobules** are made up of three to 24 acini

Murray and Nadel's Textbook of Respiratory Medicine

Relevant Anatomy

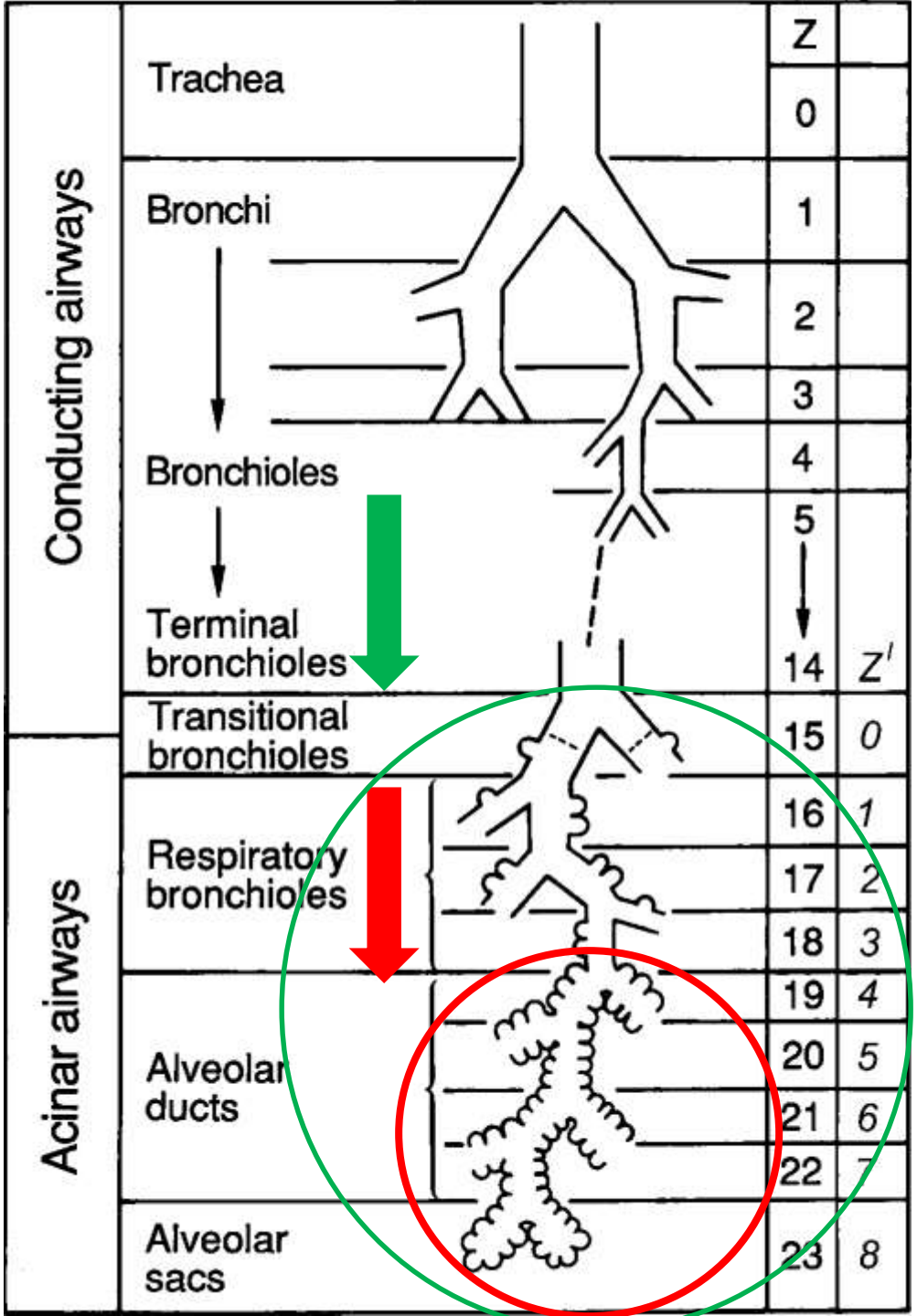
- The **secondary pulmonary lobule**, as defined by Miller, refers to the smallest unit of lung structure marginated by connective tissue septa
- It has a polyhedral shape
- Measures from 1 to 2.5 cm in diameter

Murray and Nadel's Textbook of Respiratory Medicine

Relevant Anatomy

- The secondary lobule is important, pathologically, because disease processes are intrenched by the connective tissue septa marginating the lobules.
- The alveolar ducts, alveolar sacs and alveoli distal to the last respiratory bronchiole make up the **primary pulmonary lobule**

Murray and Nadel's Textbook of Respiratory Medicine


Conducting airways
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Terminal bronchioles
Transitional bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
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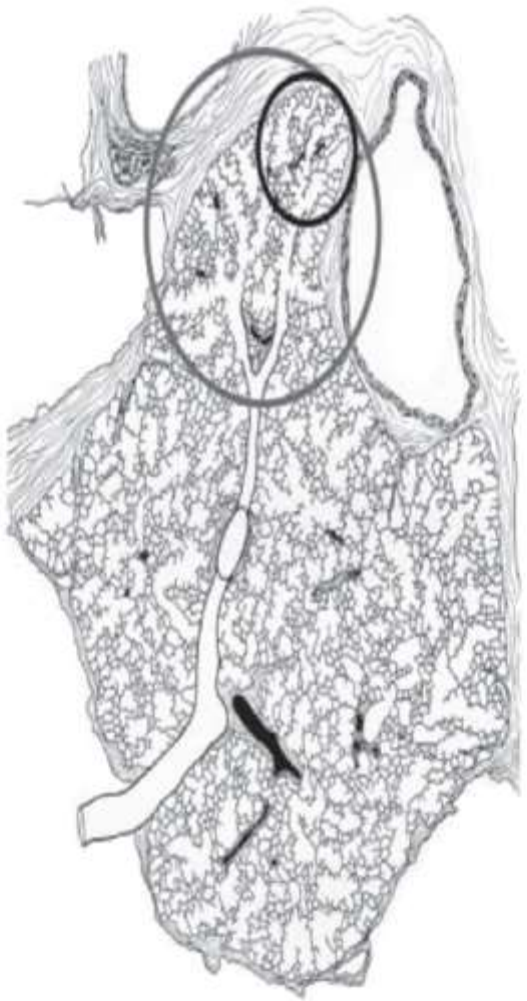

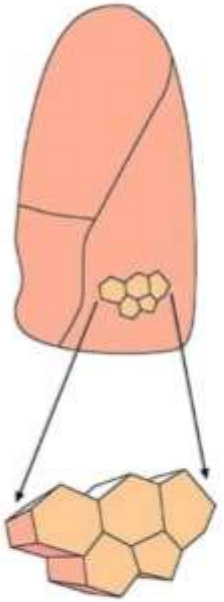

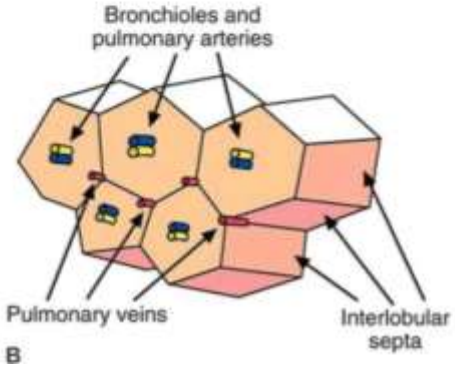

Secondary pulmonary lobule, as shown by Miller

Acinus: large circle

Primary pulmonary lobule of Miller: small circle

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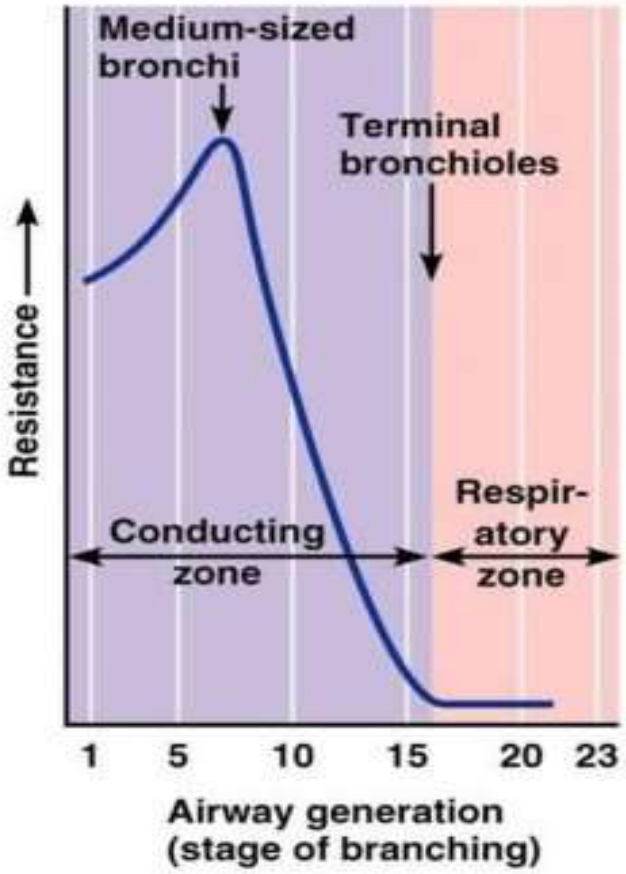
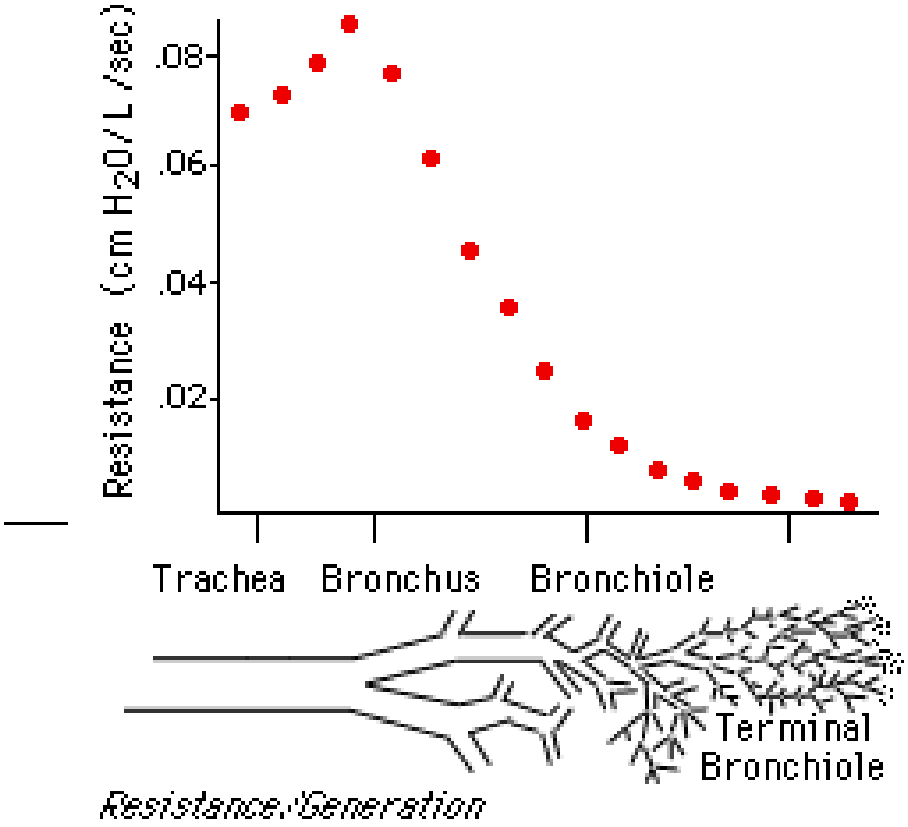
Small airway diseases: physiological assessment





Physiological assessment of the small airways

- Spirometry
- Plethysmography
- Impulse oscillometry
- Nitrogen washout test

Basis

- Airflow limitation during expiration
- Abnormal distribution of ventilation to peripheral lung units

Spirometry: FEV1 and curve

- FEV1 largely reflects large airways obstruction, and a significant amount of small airways disease must accumulate before FEV1 becomes abnormal
- The shape of the forced expiratory flow–volume curve on spirometry can be used as it depends on
  - regional heterogeneity of flow time constants
  - progressive increases of resistance with lung deflation
  - premature airway closure
  - (all characteristics of small airways disease)
- together create upper concavity of the curve relative to normal

Eur Clin Respir J. 2014; 1:10.3402/ecrj.v1.25898

Spirometry: FEF 25-75

- It was postulated that the latter part of the vital capacity was affected by increased resistance in small airways
- Pathology in these airways causes excessive airway narrowing and collapse at an earlier time and closer to the alveolus during exhalation

Am J Med. 1972; 52: 72537

Spirometry: FEF 25-75

- However, FEF25-75 is dependent on the FVC and therefore changes in FVC will affect the portion of the flow-volume curve examined
- Hence spirometric parameters are not useful in identifying small airway dysfunction

European Respiratory Journal 2014 43: 1051-1058

Plethysmography

- Provides a sensitive measure of gas trapping
- The residual volume (RV) is an important measure of small airways dysfunction and may be raised before the onset of abnormal spirometry
- Since TLC is frequently raised in obstructive lung disease RV/TLC ratio is a useful marker of gas trapping
- Not specific for small airway obstruction

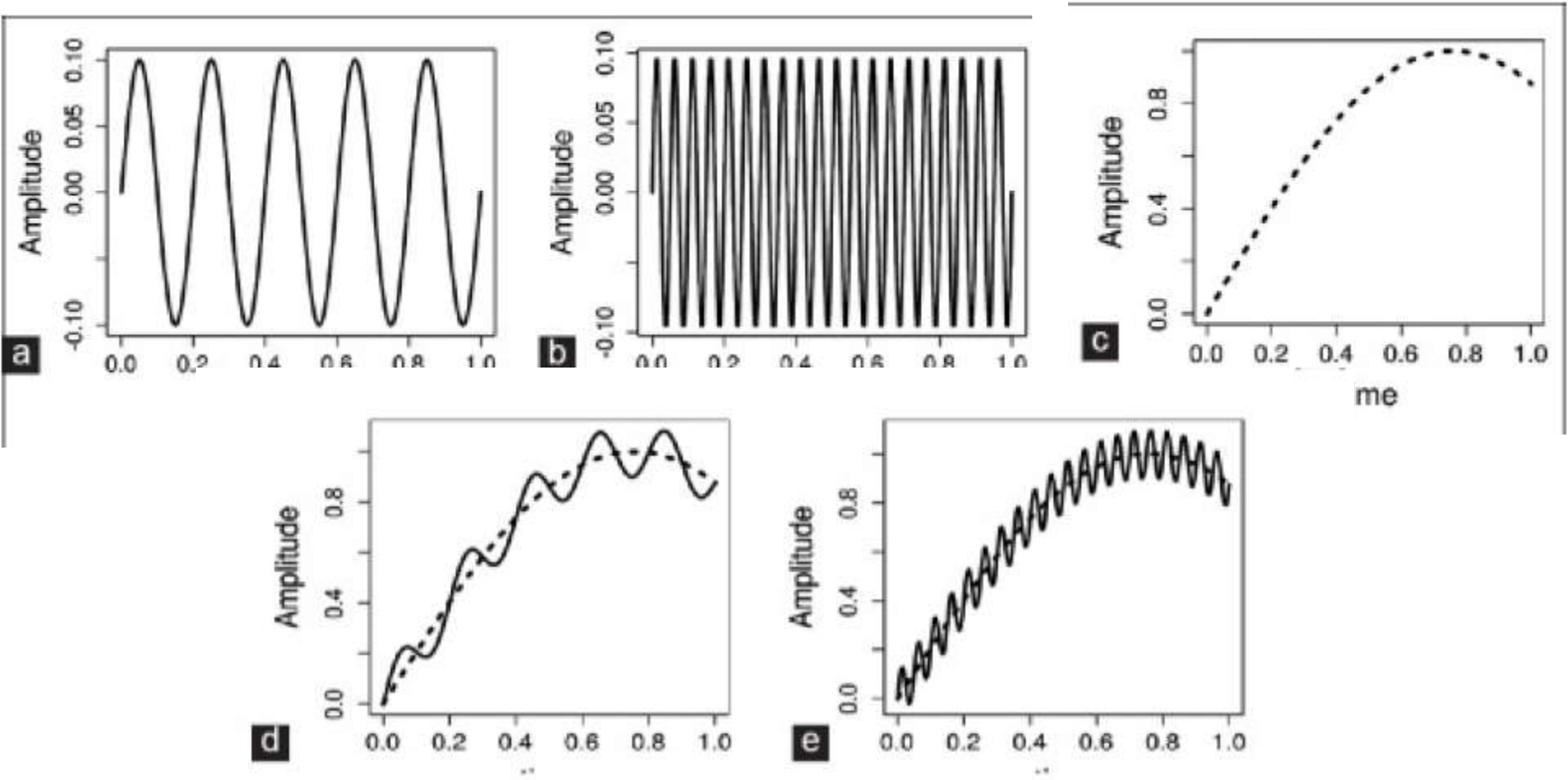
Impulse oscillometry

- Permits passive measurement of lung mechanics
- Sound waves are superimposed on normal tidal breathing, and the disturbances in flow and pressure caused by the external waves are used to calculate parameters describing the resistance to airflow

IMPULSE OSCILLOMETRY : Principle

- Sound waves, generated with the help of a loudspeaker are transmitted into the lungs of the subject.
- These sound waves, which are essentially pressure waves, cause changes in the pressure and this change in pressure drives changes in airflow.
- By measuring the magnitude of change in the pressure and flow, one can determine the mechanical properties of the lung.

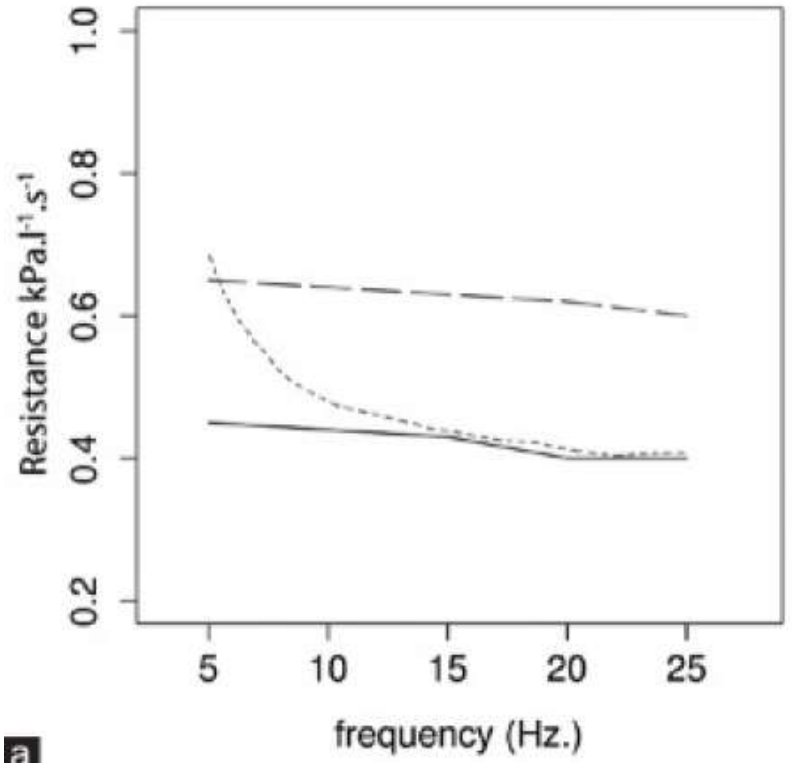
Lung India. 2016 JulAug; 33(4): 410–416.



When the sound waves are overlapped on the tidal breathing, they result in a change in the flow and now flow recording shows a complex signal consisting of both respiratory and sound wave induced components

Impulse oscillometry

- Resistance is independent of the frequency in healthy subjects.
- In central airway obstruction, the resistance at all frequency increases
- In small airway obstruction, the resistance at lower frequencies increases but is unchanged at higher frequencies that do not reach the small airways



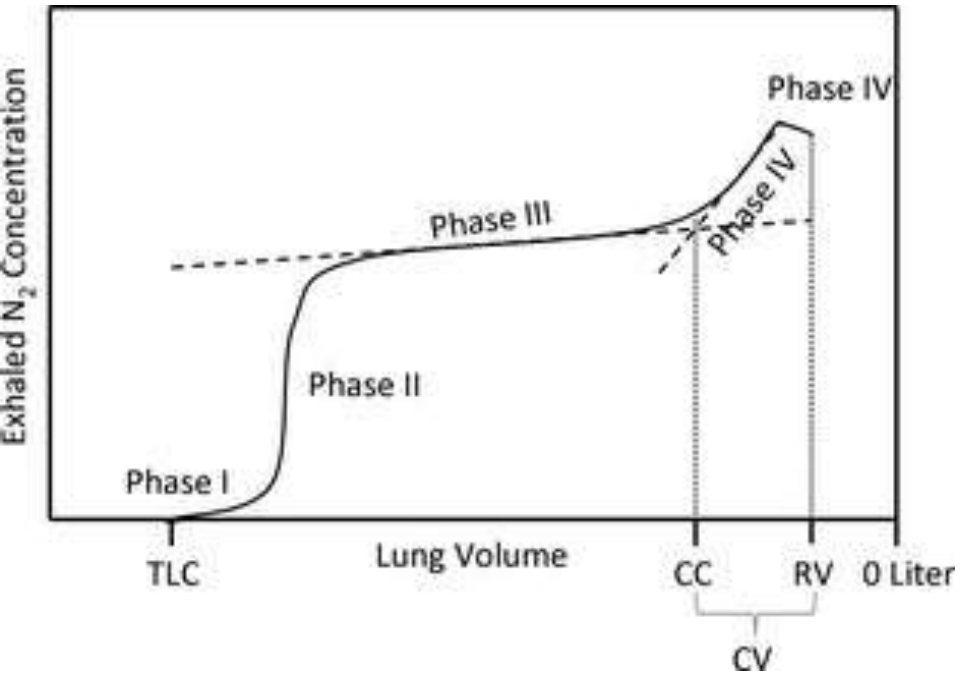
Bold, long dash and short dash lines represent normal, central airway obstruction and peripheral airway obstruction respectively

Lung India. 2016 JulAug; 33(4): 410–416.

Single breath nitrogen washout

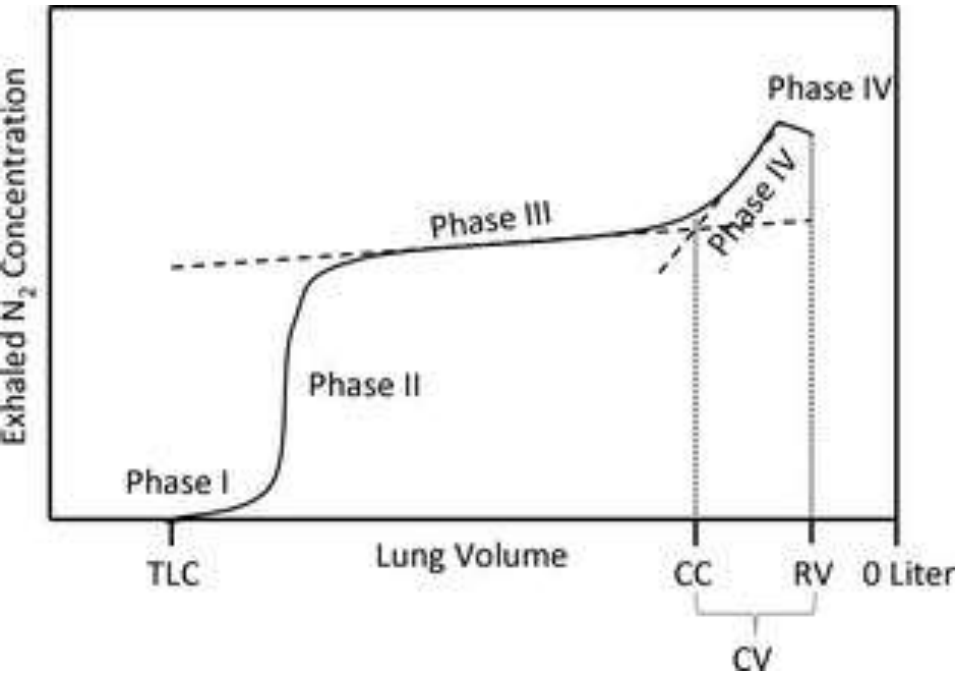
- The SBNW is performed by inhaling 100% oxygen from RV to TLC followed by a SVC exhalation. The exhaled volume and nitrogen concentration is measured and the resulting trace can be broken down into four distinct phases

Single breath nitrogen washout



- In phase I, the nitrogen concentration is close to 0% as this represents anatomical dead space where there is no gas mixing.
- During phase II, there is a sharp rise in the expired nitrogen concentration as dead space gas mixes with resident alveolar gas

Single breath nitrogen washout



- Phase III represents alveolar gas and the expired nitrogen concentration begins to plateau, although there is a slight rise from the start to finish of this phase due to ventilation heterogeneity
- In phase IV, there is a steep rise in expired N2 concentration as the most poorly ventilated areas (with little O2 mixing) empty.
- This is also the point at which the small airways start to close as a result of gravity-dependent collapse and is known as the closing volume (CV)

Single breath nitrogen washout

- Normally, small airways closure occurs close to RV. However, small airways disease may cause premature airway collapse resulting in an increased CV and gas trapping. CV may be expressed as a ratio of VC and should not exceed 25%
- Where airways disease occurs, those affected lung units mix less well with the inspired oxygen (and thus have a higher nitrogen concentration) and empty more slowly. This causes an increase in Slope of phase III.

Single breath nitrogen washout

- No evidence for use of SBNW method in patients with bronchiolitis
- However, ample evidence in asthma where slope of phase III has been shown to correlate with frequency of exacerbation, inflammatory markers and normalization with treatment.
- Despite its sensitivity, the SBNW is not specific to bronchiolitis

Allergy. 2006; 61: 85-9
Thorax. 2005; 60: 639-44.
Eur Respir J. 2006; 27: 951-6.

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Imaging of small airway disorders

- The three components of secondary pulmonary lobule are
  - Interlobular septa
  - Centrilobular structures
  - Lobular parenchyma
- The visibility of bronchioles depend on their thickness
- The wall of a terminal bronchiole measures around 0.1 mm, which is below the resolution limit of HRCT
- When there is increased soft tissue in or around the bronchioles, they can become visible at the center of the secondary pulmonary lobule

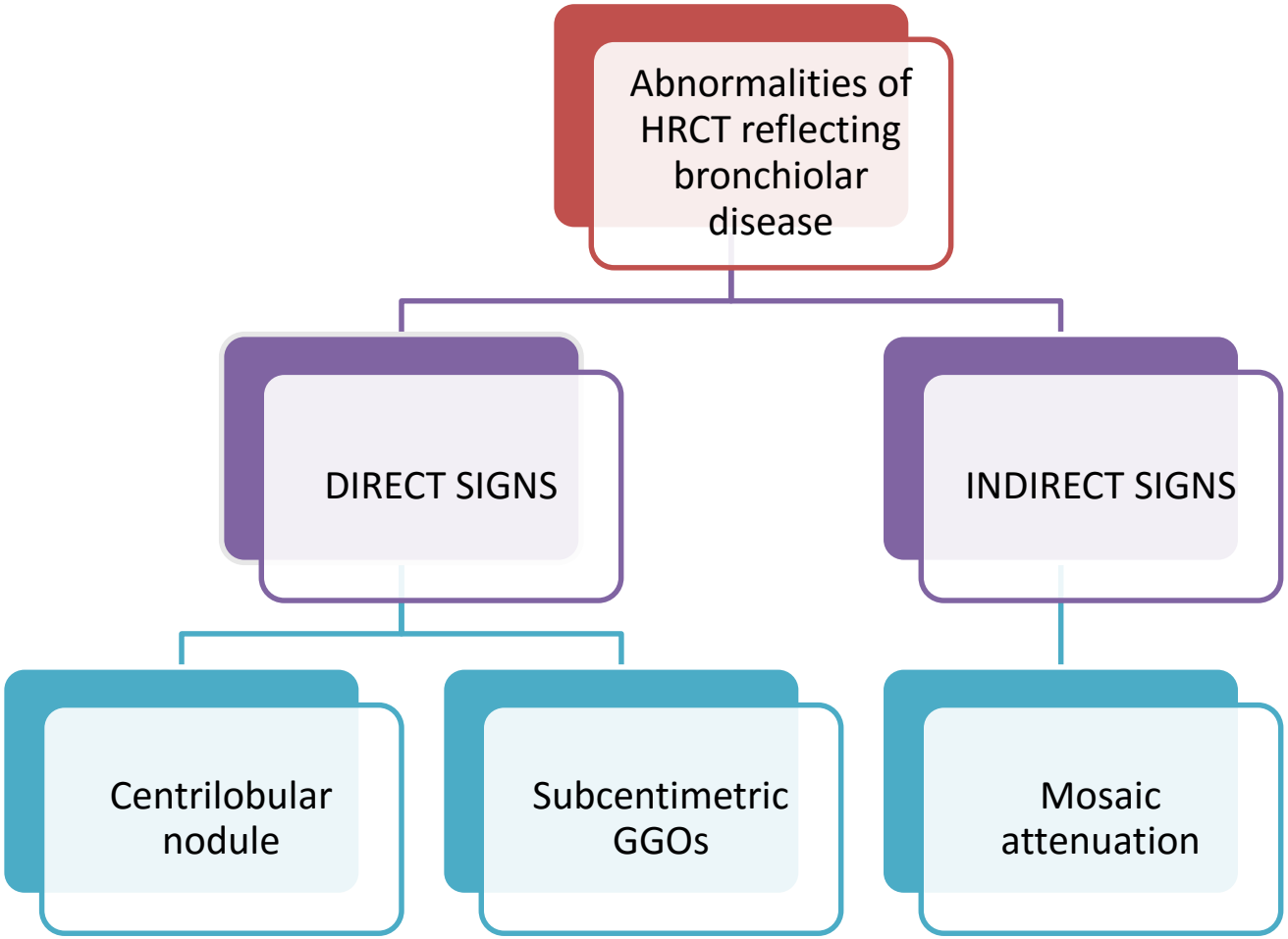
Radiology 1995; 196:3–12

Imaging of small airway disorders

- Optimal evaluation of small airways requires HRCT protocols that use thin (0.63-1.25 mm) collimation with images reconstructed contiguously or at most at 10-mm intervals from the apices to costophrenic angles in the supine position
- HRCT scanning at full exhalation should be obtained routinely when small airways disease is suspected
- In most cases, there is little indication for the routine use of iv contrast

Am J Respir Crit Care Med . 2003 ; 168 (11): 1277 - 1292 .

Imaging of small airway disorders



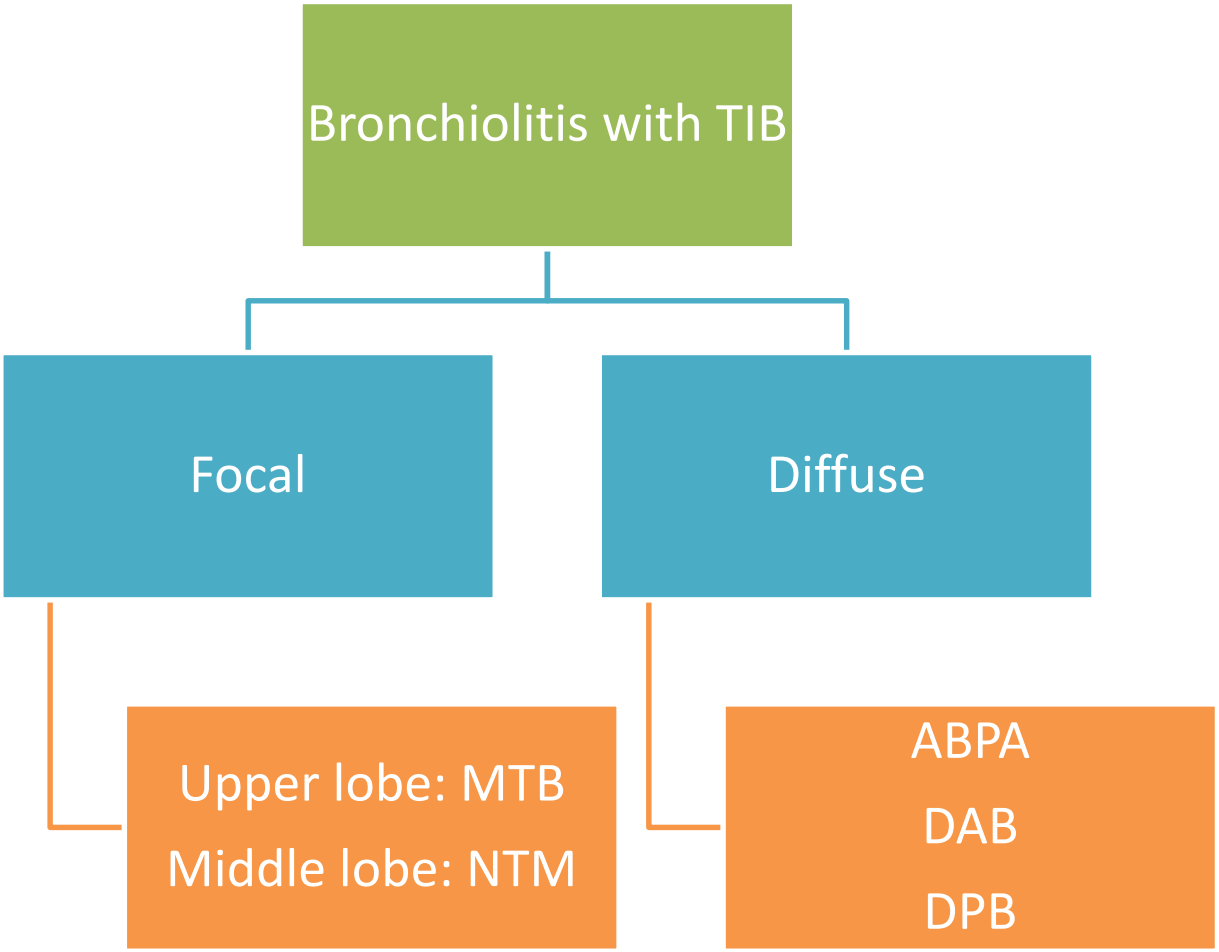
Imaging of small airway disorders

- Centrilobular nodules are caused by **inspissation of secretions in the lumen of bronchioles** resulting in clustered, sharply delineated, centrilobular opacities typically demonstrating a tree-in-bud pattern
- When abnormalities are primarily localized to inflammation in the **centrilobular, peribronchiolar or perivascular space in the absence of bronchiolar impaction**, the result is poorly defined subcentimeter ground-glass nodules and typically absent branching or tree-in-bud configuration.

Bronchiolar Diseases With Predominantly Tree-in-Bud Opacities

	Clinical feature	Cause/ass with	HRCT features	Histopathology
Infection	Wheezing with signs of Infection	Viral, bacterial, parasitic, mycobacterial, fungal	TIB, dense consolidation	inflammation of bronchioles with epithelial necrosis and sloughing
Immunologic disorders (ABPA)	Cough, fever, wheezing	Asthma	TIB,CB HAM	eosinophilic infiltration
Diffuse aspiration bronchiolitis	Nonspecific	Elderly, bed bound	TIB	Foreign body giant cell Reaction
Diffuse panbronchiolitis	Japanese; sub acute onset of cough,	HLABw54 antigen	TIB, thickened ecstatic bronchi	Infiltration of plasma cells & foamy macrophages in RB

Bronchiolar Diseases With Predominantly Tree-in-Bud Opacities



Poorly Defined Centrilobular Ground-Glass Nodules

- If HRCT scan discloses centrilobular opacities appearing as ill-defined ground-glass nodules in the absence of a tree-in-bud pattern, the differential diagnosis is distinctly different than if tree-in-bud opacities are present

Bronchiolar Diseases With GG Centrilobular Nodules

	Clinical feature	Cause/ass with	HRCT features	Histopathology
Hypersensitivity pneumonitis	Subacute onset of dyspnea, fever, malaise	Organic dust exposure	GGCLN, mosaic perfusion	poorly formed granulomas
RB/ RB-ILD	Inspiratory crackles	Cigarette smoke	Ill-defined GGCLN, upper lobe predominance	Pigmented macrophages around RB
Follicular bronchiolitis	Progressive dyspnea	CTD (Sjögren, RA) Immunodefi ciency	GGCLN, diffuse and bilateral	Peribronchiolar lymphoid aggregates

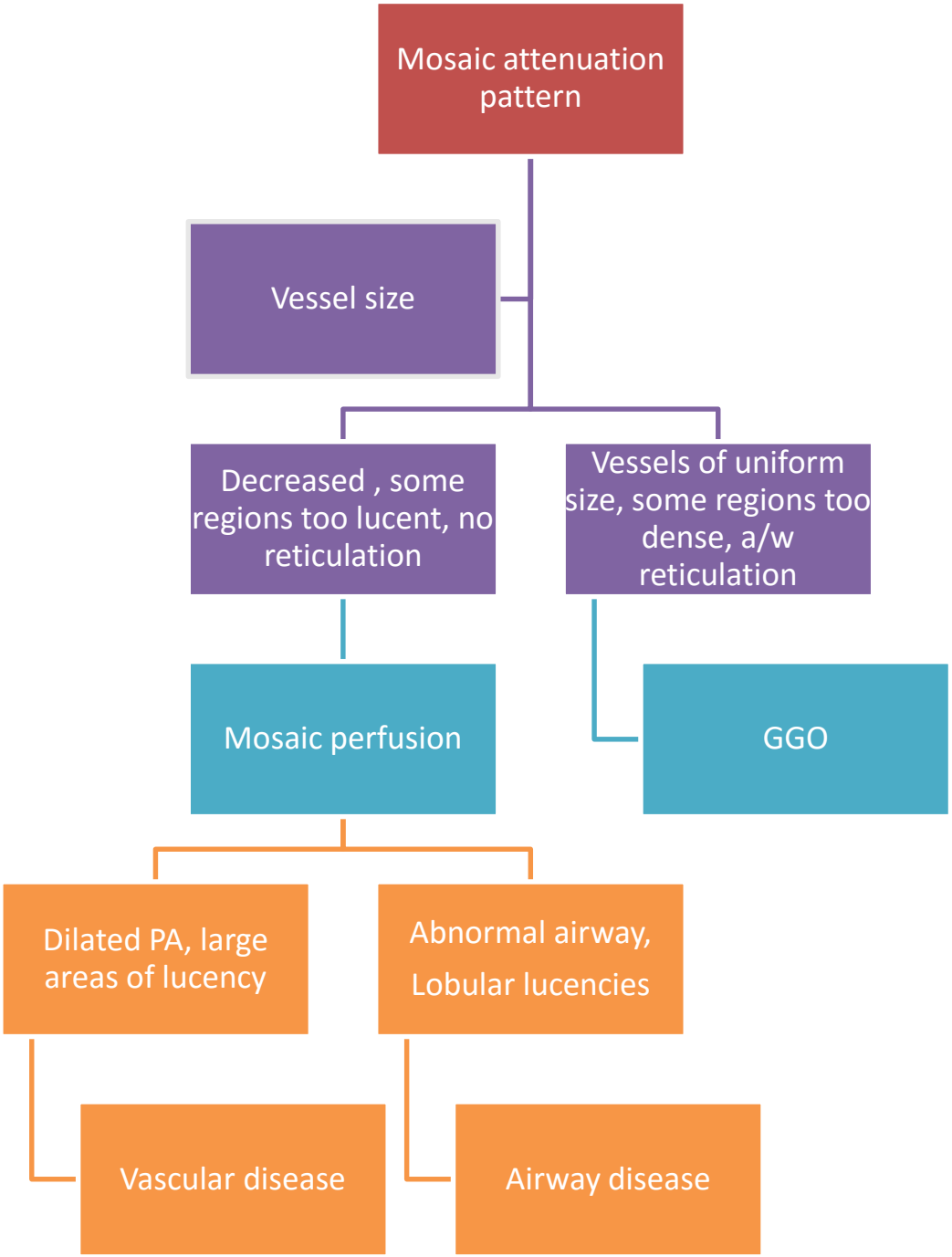
Expiratory scans

- Normally lung attenuation changes with expiration
- Retention of gas within lung or part of a lung as a result of airway obstruction or abnormalities in lung compliance is termed as air trapping
- Air trapping is said to be present if lung parenchyma remains lucent or shows less than normal increase in attenuation after expiration

Mosaic Lung Attenuation

Alternate foci of relatively increased lung density with foci of decreased lung density, frequently resulting in a geographic appearance to the lung parenchyma

Lower-density lung being abnormal because of decreased perfusion (vasoconstriction) and commonly, an element of air trapping


Mosaic attenuation pattern
Vessel size
Decreased , some regions too lucent, no reticulation
Vessels of uniform size, some regions too dense, a/w reticulation
Mosaic perfusion
GGO
Dilated PA, large areas of lucency
Abnormal airway,
Lobular lucencies
Vascular disease
Airway disease

Bronchiolar disorders associated with mosaic perfusion

- Postinfectious
  - Viral (adenovirus, respiratory syncytial virus, influenza, parainfluenza)
  - *Mycoplasma*
- Collagen vascular diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
- Transplant related
  - Graft vs host disease
  - Bone marrow transplant
  - Heart-lung transplant
- Toxic fume exposure
  - Nitrogen dioxide
  - Sulfur dioxide
  - Chlorine
  - Phosgene
  - Diacetyl (popcorn workers)
- Ingested toxins
  - *Sauropus androgynus*
- Drugs
  - D-penicillamine
  - Gold
  - Cocaine
- Cryptogenic constrictive bronchiolitis

Individual disorders

- Obliterative bronchiolitis
  - Idiopathic
  - Exposure to inhaled toxins
  - Autoimmune disorder
  - Post infective
  - After HSCT
  - After lung transplant
- Respiratory bronchiolitis
- Diffuse panbronchiolitis
- Follicular bronchiolitis
- Diffuse aspiration bronchiolitis

Obliterative bronchiolitis

- Confusion over terminology still prevails
- What is for sure is that OB and BO are used synonymously
- CB and OB are very closely related
- CB and OB are very different from PB or BOOP

Pathogenesis

- injury and inflammation of small-airway epithelial cells and subepithelial structures lead to excessive fibroproliferation, which is due to aberrant tissue repair, including ineffective epithelial regeneration, in response to tissue injury

N Engl J Med. 2014 May 8;370(19):1820-8

Idiopathic (primary) bronchiolitis

- Cryptogenic constrictive bronchiolitis:
  - extremely rare
  - purely bronchiolar disorder
  - Increased frequency of transplant associated bronchiolitis has helped in understanding this entity

Exposure to inhaled toxins

- The inhalation of fumes, gases, mists, mineral dusts, or organic material
- Exposure can result in subtle or severe clinical illness, usually associated with immediate development of pulmonary edema and late development of constrictive bronchiolitis with airflow limitation

Toxic Exposures Associated with Bronchiolitis

- Nitrogen dioxide
- Spillage of nitric acid (component of jet and missile fuels)
- Silo gas
- Chemical manufacturing (explosives and dyes)
- Electric arc or acetylene gas welding
- Contamination of anesthetic gases (nitrous oxide gas cylinder)
- Fire smoke (firemen, astronauts, others exposed to burning materials)
- Burning of sulfur-containing fossil fuels
- Sugar refining, fruit preserving
- Fungicides
- Refrigerants
- Bleaching, disinfectant and plastic making
- Phosgene∗
- Chemical industry, dye and insecticide manufacturing
- Ozone
- Arc welding and air, sewage, and water treatment
- Natural gas retrieval, paper pulp, sewage treatment,
- tannery work
- Hydrogen fluoride
- Talcum powder (hydrous magnesium silicate)
- Iron oxide
- Aluminum oxide
- Silica
- Sheet silicates (talc, mica, etc.)

Toxic exposure

Toxin	Comment
Sulfur mustard	Used in chemical warfare; one of the earliest associations of an agent with the condition
Nitrogen oxides	Used in fertilizer production; probably involved in silo-filler's disease
Diacetyl and alpha-diketone substitutes	Used in the manufacture of popcorn, roasted and flavored coffee, cookie dough, and food flavorings
Multiple chemicals and incinerator fly ash released during combustion	Often produced by uncontrolled fires
Papaverine, found in juice extracted from *Sauropus androgynus*	Juice extracted from this leafy plant may assist in weight loss
Fiberglass	Used in the fabrication of certain structural materials (e.g., for boats or automobile bodies)

Curr Opin Allergy Clin Immunol. 2013 April ; 13(2): 167–172

Toxic exposure

- The distribution and extent of the lung injury depend on
  - concentration of the agent
  - duration of exposure
  - route and pattern of breathing
  - solubility
  - biologic reactivity of the agent
  - biologic susceptibility of the individual

Autoimmune disorders

- the frequency of obliterative bronchiolitis is the highest in patients with rheumatoid arthritis
- Initially was thought to be due to medications (penicillamine and gold), however, persistance even now has led to the hypothesis that it is related to disease

Am J Respir Crit Care Med 1998;157:1658-65

Post infective

- Primarily described in children
- Infection with RSV, rhino virus, adeno virus, measles virus or mycoplasma
- In view of the high incidence of these infections, the development of permanent airway obstruction can be assumed to be quite unusual.

Pediatr Radiol 1998;28:23-9.

After HSCT

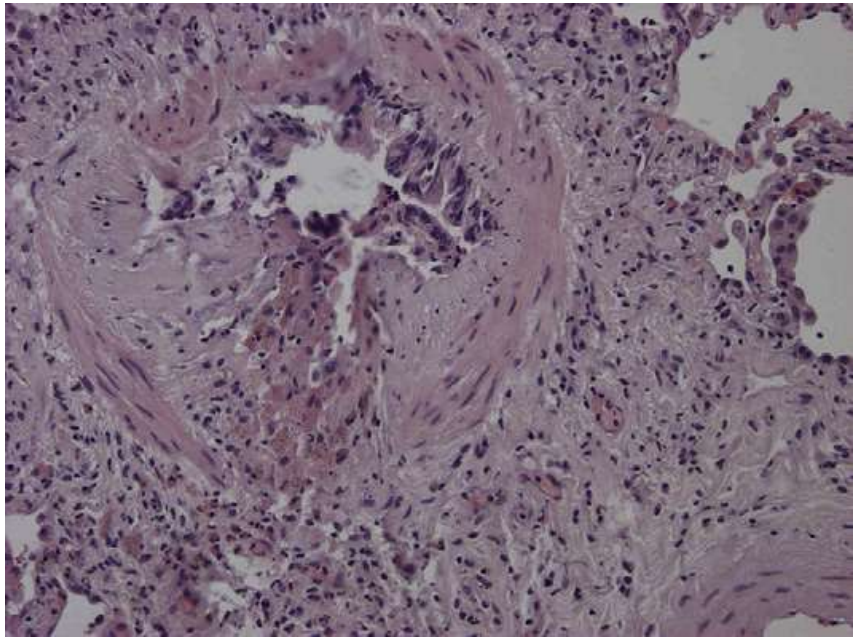
- The primary noninfectious pulmonary complication in patients who undergo allogeneic HSCT.
- develops within 2 years after transplantation
- Incidence ranges from 5.5% - 14 %
- Clinical risk factors
  - Older age of donor or recipient
  - Greater degree of HLA mismatch
  - Presence of gastroesophageal reflux
  - Decreased gamma globulin levels
  - Busulfan-based conditioning regimen
  - Tobacco use
  - Acute GVHD
  - RSV or parainfluenza infection within first 100 days

Biol Blood Marrow Transplant 2011;17:1072-8.

J Infect Dis 2006;193:1619-25

After LT

- first described in 1984
- Lung biopsy: intraluminal polyps of fibromyxoid granulation tissue, which tends to obliterate the lumen of terminal bronchioles, and dense submucosal eosinophilic fibrous scars



After LT

- The small airway lesions have a patchy distribution,
- can hardly be demonstrated by TBB
- As a result, in order to establish the diagnosis of BO without the need for open lung biopsy, in 1993, the ISHLT proposed a clinical definition based on pulmonary function criteria.

Updated classification

Table 1
Bronchiolitis obliterans syndrome classification system

	1993 Classification	2002 Classification	
	FEV_1 80% or more of baseline	FEV_1 >90% of baseline *and* FEF_{25-75} >75% of baseline	BOS 0
		FEV_1 81% to 90% of baseline *and/or* FEF_{25-75} = or <75% of baseline	BOS 0-p
BOS 1	FEV_1 66% to 80% of baseline	FEV_1 66% to 80% of baseline	BOS 1
BOS 2	FEV_1 51% to 65% of baseline	FEV_1 51% to 65% of baseline	BOS 2
BOS 3	FEV_1 50% or less of baseline	FEV_1 50% or less of baseline	BOS 3

J Heart Lung Transplant 2002;21:297–310

Management: BO after LT

- The current treatment consists primarily of increasing immunosuppression by changing medications within therapeutic classes, adding medications, or administering other immune-modulating therapies
- The disease probably has various clinical phenotypes, as was suggested by the different responses to therapy among patients in whom obliterative bronchiolitis developed after lung transplantation

Management: BO after LT

- Azithromycin has resulted in improved pulmonary function in approximately 50% of lung-transplant recipients with obliterative bronchiolitis
- For end-stage obliterative bronchiolitis, lung transplantation is accepted as a therapeutic option

Management: BO

- Treatment of CB is often ineffective
- No proper evidence base due to the confusion in terminology (case series have also included case of BOOP , hence mixed results)
- It is intuitive to immunosupress patients as
  - Histopathologic identification of lymphocytic infiltrates
  - The association with diseases such as rheumatoid arthritis
  - The effectiveness of glucocorticoids in proliferative bronchiolitis

Management: BO

- However, the role of systemic glucocorticoid therapy in nontransplant-related bronchiolitis obliterans is unclear.
- Most case series of the constrictive type of bronchiolitis obliterans have not shown improvement with systemic glucocorticoid

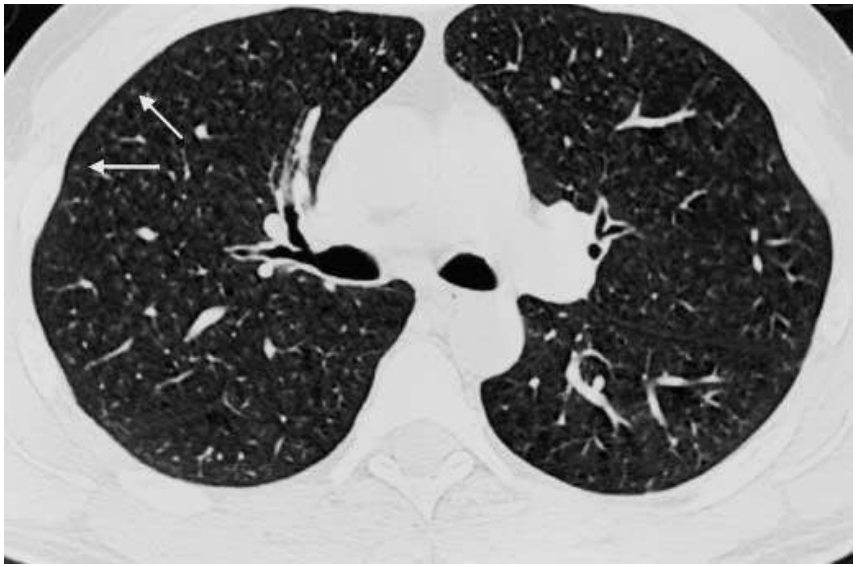
Respirology 2009; 14:443-452
J Korean Med Sci 2001; 16:150-158
Am Rev Respir Dis 1993; 148:1093-101

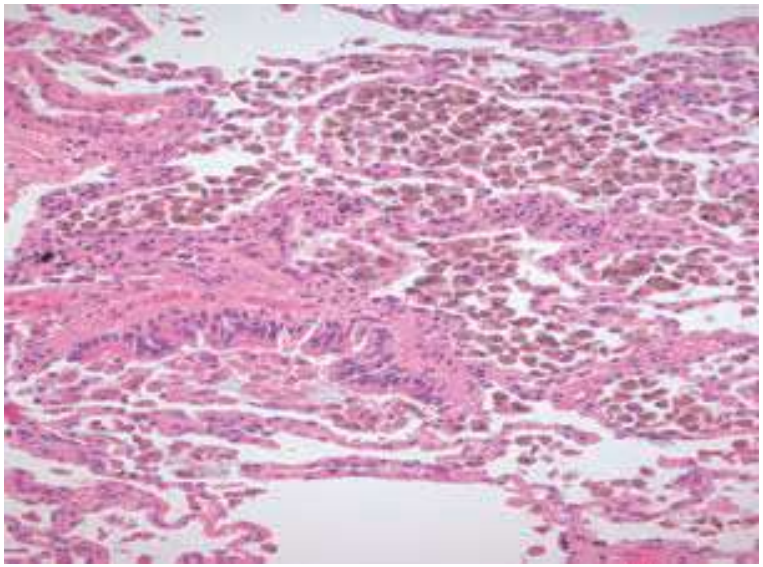
Respiratory Bronchiolitis

- Related to cigarette smoking
- Asymptomatic
- Normal chest radiograph
- Centrilobular nodules are seen on HRCT
- RB is a highly sensitive and relatively specific morphological marker of cigarette smoking
- Characterized by prominent accumulation of pigmented macrophages in the lumen of respiratory bronchioles and the adjacent alveoli

Am J Surg Pathol 2002; 26:647–653

RB





Ill-defined centrilobular nodules,

Submucosal inflammation and fibrosis of the respiratory bronchioles

Pigmented macrophages are present in the bronchiolar lumen

RB- treatment

- No treatment required other than smoking cessation

The main difference between respiratory bronchiolitis, RBILD, and DIP is the extent and distribution of interstitial involvement

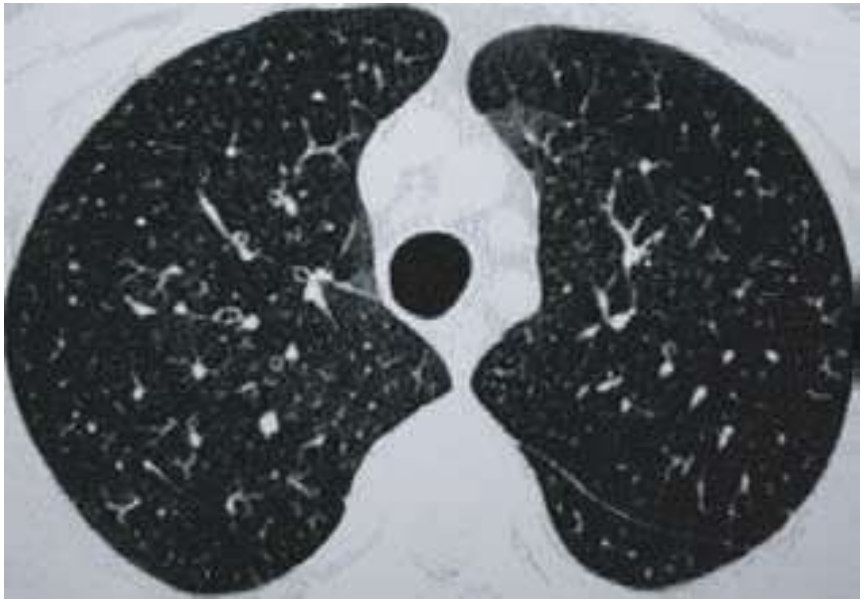
Semin Respir Crit Care Med. 2003 Oct;24(5):585-94

RB-ILD

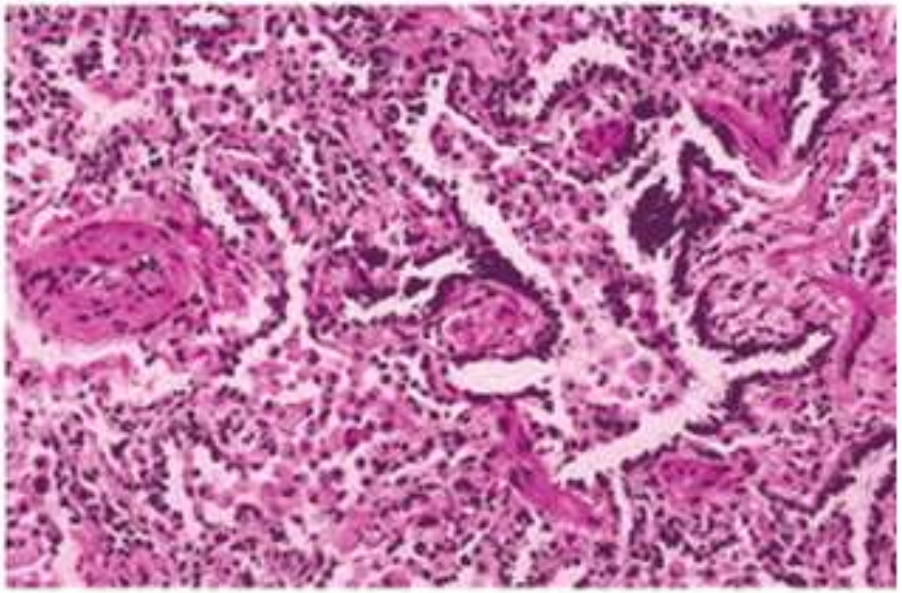
- In RB, when inflammation is severe enough to cause symptomatic parenchymal lung infiltrates, it is referred to as respiratory bronchiolitis associated ILD
- smoking cessation is imperative to arrest progression
- Corticosteroid therapy offers modest clinical benefit

Semin Respir Crit Care Med. 2003 Oct;24(5):585-94

RB-ILD



mild bronchiolar wall thickening and minimal centrilobular nodules associated with subtle ground-glass opacities.



High-power view showing marked increase in alveolar macrophages and mild alveolar septal thickening and fibrosis

RB-ILD - treatment

- Usually the disease responds to smoking cessation in majority of patients
- For patients who have progressive RB-ILD despite smoking cessation, glucocorticoid therapy and other immunosuppressive agents are sometimes used, but data supporting their efficacy are conflicting

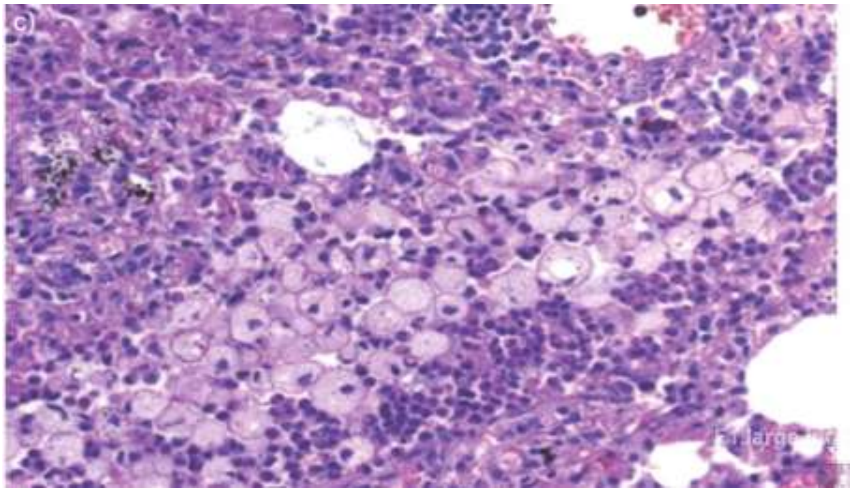
Diffuse panbronchiolitis

- Diffuse: distribution of the lesions throughout both lungs
- Pan: pathologic finding that the inflammation involves all layers of the respiratory bronchioles

Sarcoidosis Vasc Diffuse Lung Dis 2004; 21:94

DPB: pathology

- Infiltration of walls of respiratory bronchioles with lymphocyte, macrophages and foamy histiocyte
- Inflammation extend into peribronchiolar space but not alveolar walls



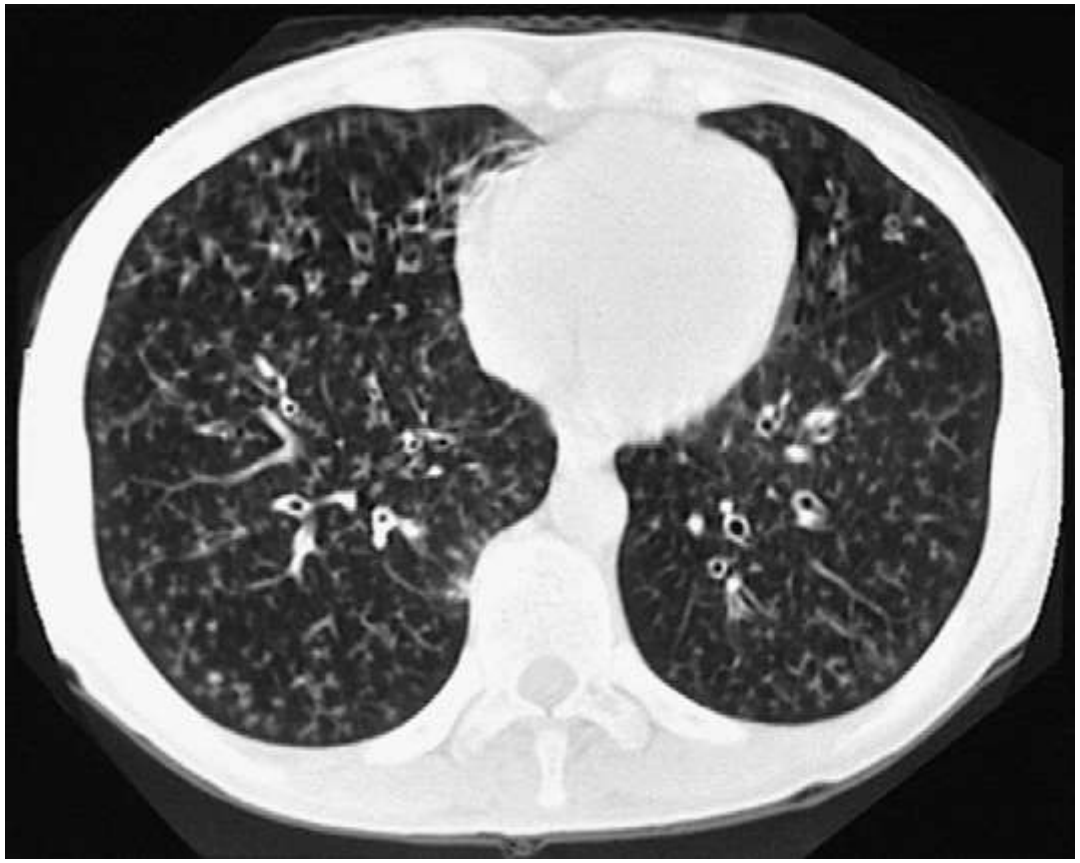
Sarcoidosis Vasc Diffuse Lung Dis 2004; 21:94

DPB: diagnosis

- unique to Asians
- HLA-B54
- >80% have history of or coexisting paranasal sinusitis
- Present with cough with copious expectoration
- Followed by exertional dyspnea

Clin Chest Med 33 (2012) 297–305

DPB: imaging



Centrilobular nodular shadows (tree in bud) are diffusely distributed with bronchiectasis.

Diagnostic criteria

1. Persistent cough, sputum, and exertional dyspnea
2. History of, or current, chronic sinusitis
3. Bilateral, diffuse, centrilobular micronodules on chest CT images
4. Coarse crackles
5. FEV1/FVC less than 70% and PaO2 less than 80 mm Hg
6. Titer of cold hemagglutinin equal to or greater than 64.

- Definite cases should fulfill the first 3 criteria(1–3) and at least 2 other remaining criteria (4–5).

Ministry of Health and Welfare of Japan; 1999. p. 109–111

DPB: treatment

- The 5-year survival rate for DPB improved from 62.9 to 91.4% after implementation of macrolide therapy
- “There is little evidence for macrolides in the treatment of DPB. It may be reasonable to use low-dose macrolides soon after diagnosis is made and to continue this treatment for at least six months”

Auris Nasus Larynx. 2016 Apr;43(2):131-6 Cochrane Database Syst Rev. 2015 Jan 25;1

- In the treatment of DPB, the serum and sputum erythromycin levels are below the minimum inhibitory concentrations of the common superinfecting organisms, suggesting that antimicrobial effects may be less important than anti-inflammatory effects
- First choice: erythromycin 400–600 mg/d, orally (6 months to 2 years)

Clin Chest Med. 2012 Jun;33(2):297-305

Follicular Bronchiolitis

Lymphoproliferative Pulmonary Diseases (LPDs)
Reactive/non-neoplastic lymphoid lesions: classified based on the pattern of pulmonary involvement • Nodular lymphoid hyperplasia (NLH): focal • Follicular bronchiolitis (FB): peribronchial • Lymphoid interstitial pneumonia (LIP): diffuse with pulmonary cyst
Malignant parenchymal lymphoproliferative lesions **Primary (0.5% of all primary lung neoplasms)** • Extranodal marginal zone lymphoma of MALT origin (MALT lymphoma) • Diffuse large B-cell lymphoma (DLBCL) • lymphomatoid granulomatosis (LYG)
Secondary • Non-Hodgkin lymphoma (NHL) • Hodgkin lymphoma (HL)
Lymphoproliferative disorders in the immunocompromised • Acquired immune deficiency syndrome (AIDS)- related lymphoma (ARL) • Post-transplantation lymphoproliferative disorder (PTLD)

FB is characterized by the presence of hyperplastic lymphoid follicles that are prominent and well-defined reactive germinal centers distributed along bronchovascular bundles and associated with minimal interstitial disease

FB: classification

- **Connective tissue disease**
  - Sjögren's syndrome
  - Rheumatoid arthritis
  - Systemic lupus erythematosis
- **Immunodeficiency**
  - AIDS
  - Common variable immunodeficiency (CVID)
- **Infections**
  - *Pneumocystis Jirovicci pneumonia*
  - *Legionella pneumonia*
  - Active hepatitis

Interstitial lung diseases

LIP
Respiratory bronchiolitis-ILD (RB-ILD)
Desquamative interstitial pneumonia (DIP)
Hypersensitivity pneumonitis (HP)
Cryptogenic organizing pneumonia (COP)

Airway inflammatory diseases

Bronchiectasis
Asthma
COPD

Idiopathic (primary)

Journal of Clinical and Diagnostic Research. 2015 Sep, Vol-9(9):1-5

Clinical presentation

- Gradually worsening dyspnea in a predisposed individual

FB: histopathology

- two fundamental features
  - the presence of well formed lymphoid follicles in the walls of bronchioles
  - narrowing or complete obliteration of the bronchiolar lumen

Arch Bronconeumol. 2013;49(4):166-68.

FB: Radiology

- Bilateral 1–3 mm nodules—centrilobular/peribronchial distribution
- Bilateral patchy ground-glass opacities (mosaic pattern)
- Fluffy tree-in-bud “Cotton-in-bud” peribronchiolar opacities
- Disease is limited to the airways (i.e. no diffuse interstitial involvement

Am J Roentgenol. 2005;185:354–63.

FB: treatment

- In secondary FB, management is usually aimed at treating the underlying condition.
- FB associated with HIV has been shown to improve with the initiation of anti-retroviral therapy
- When associated with a connective tissue disease, FB is generally approached with the same treatment modalities of the primary disease

Journal of Clinical and Diagnostic Research 2015 Sep, Vol-9(9): 1-5

Diffuse aspiration bronchiolitis

Aspiration related lung disorders
Diffuse aspiration bronchiolitis
Aspiration pneumonitis and Mendelson syndrome
Aspiration pneumonia
Lung abscess
Foreign body aspiration
Exogenous lipoid pneumonia
Chronic aspiration changes

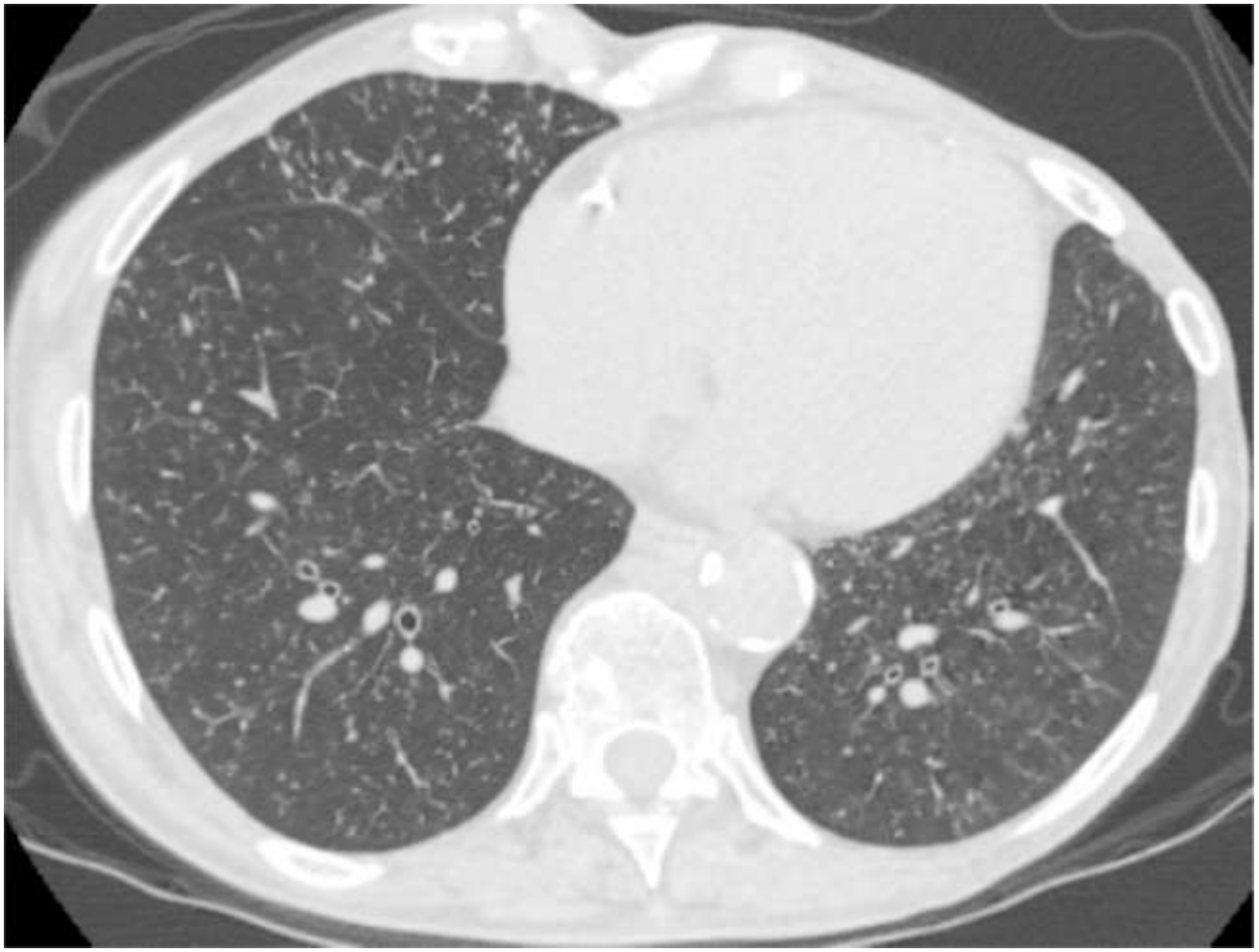
DAB: clinical presentation

- DAB describes the resultant inflammation of bronchioles secondary to aspiration
- there is a high association of DAB with
  - oropharyngeal dysphagia
  - Bedridden status
  - Dementia
  - neurological disorders
- characterized by persistent cough, dyspnea and recurrent pneumonias

DAB: histopathology

- Histopathologically, a bronchiolocentric organizing pneumonia process is apparent with giant cells granulomas containing material compatible with food

DAB: Radiology



HRCT scan of the chest, showing diffuse micronodules and tree-in-bud opacities

DAB: management

- Management of patients with DAB focuses on prevention of recurrent aspiration by addressing the underlying risk factors, such as GERD

Take home message

- OB = BO ~ CB
- BOOP = PB
- BO ≠ CB + PB
- Bronchiolitis is an intellectual challenge to clinicians and pathologists
- Think of bronchiolitis in a patient with disproportionate symptoms and imaging

Take home message

- Routine spirometry may not identify bronchiolitis
- Routine chest radiography not identify bronchiolitis
- The “gold standard” approach is a multidisciplinary one, including clinical, radiological, and histopathological expertise, to establish the final diagnosis