Interstitial Lung Disease

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Interstitial lung disease

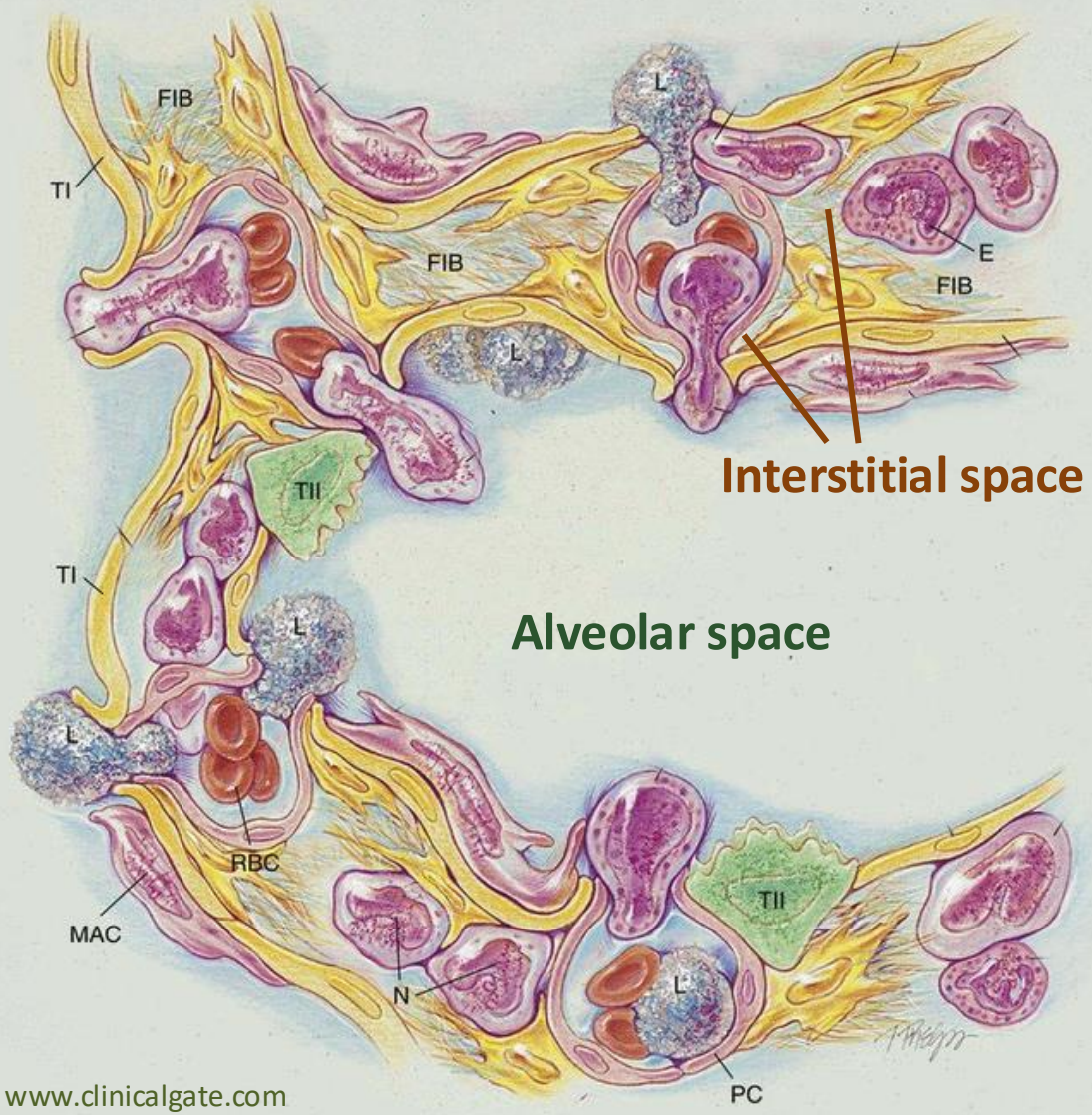
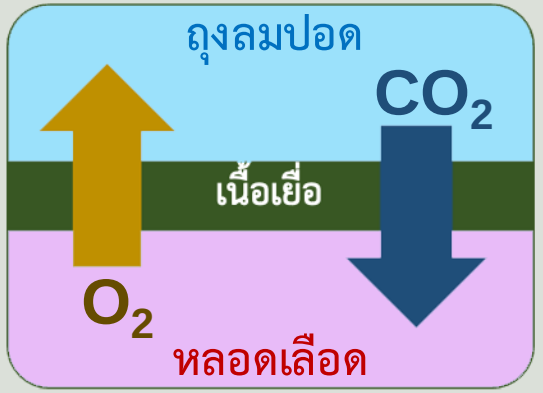
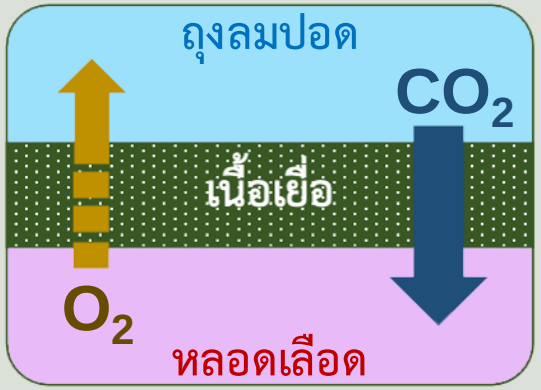


Photo: www.clinicalgate.com

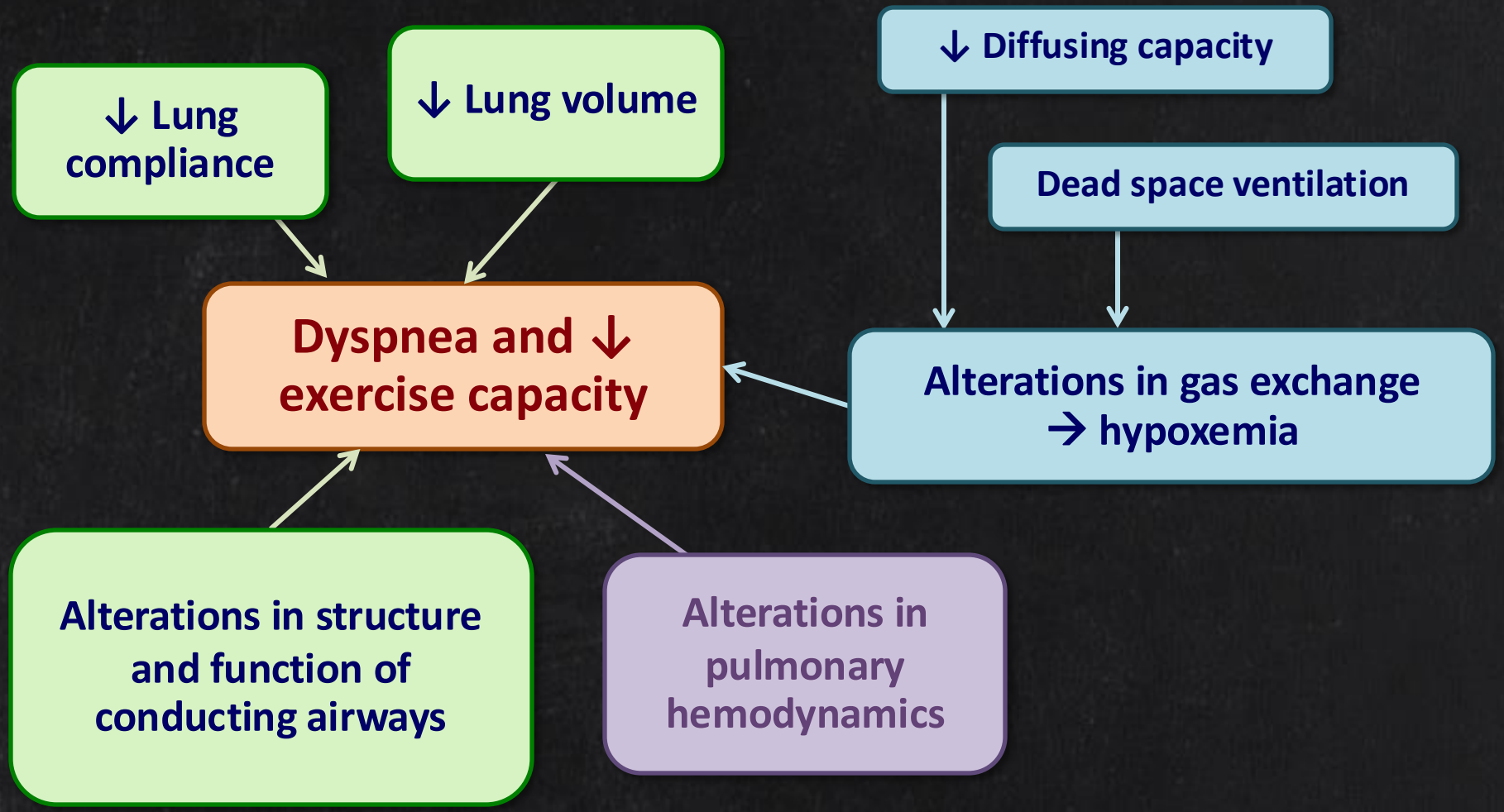


Normal

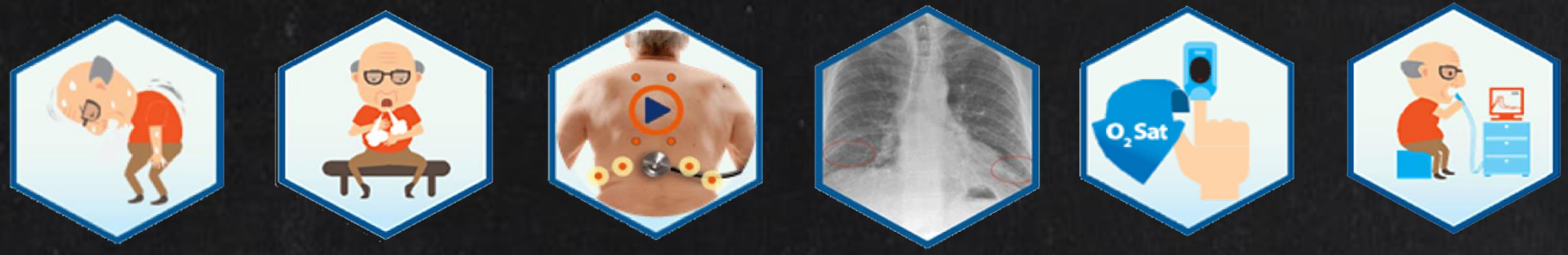


ILD

Interstitial lung disease

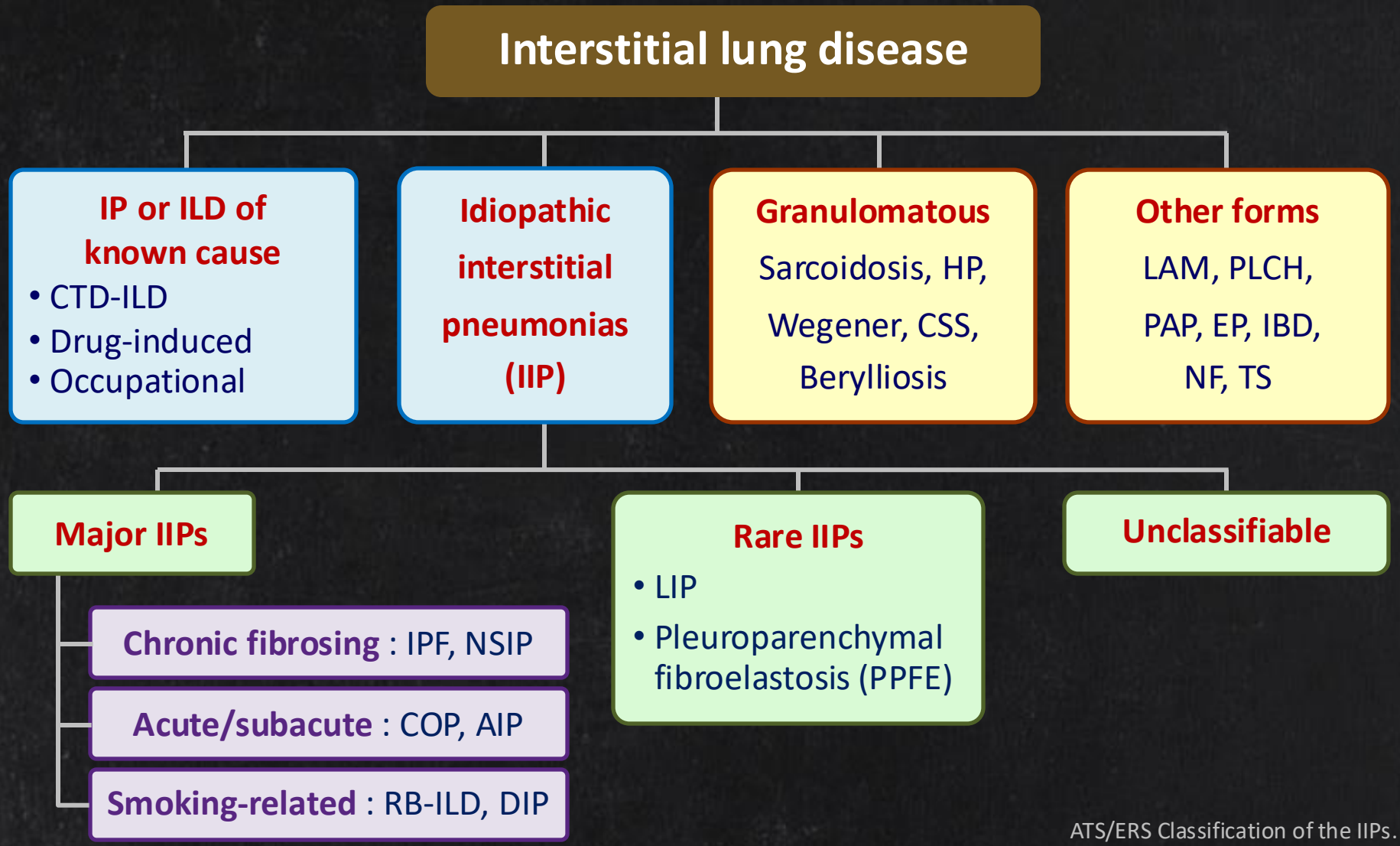


Interstitial lung disease



ILD
IPF
COP
DIP
NSIP
RB-ILD
LAM
CSS
PLCH
PAP
AIP
WG
IIP
LIP
PPFE
IPAF
DAH
AEP
HP
CTD-ILD

ILD classification



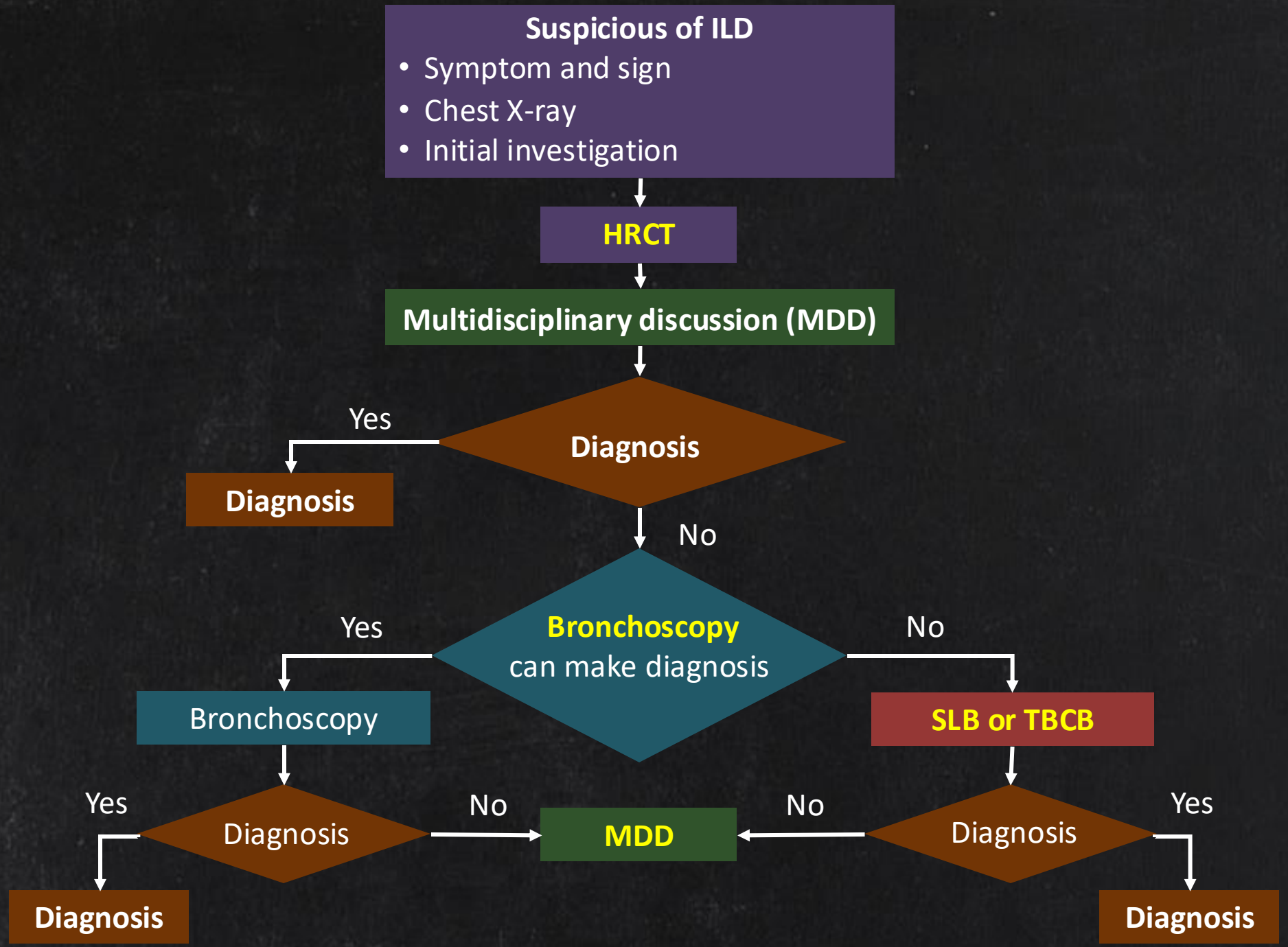
ATS/ERS Classification of the IIPs. AJRCCM 2002;165:277-304.
ATS/ERS Statement. AJRCCM 2013;188:733-48.

Diagnostic approach

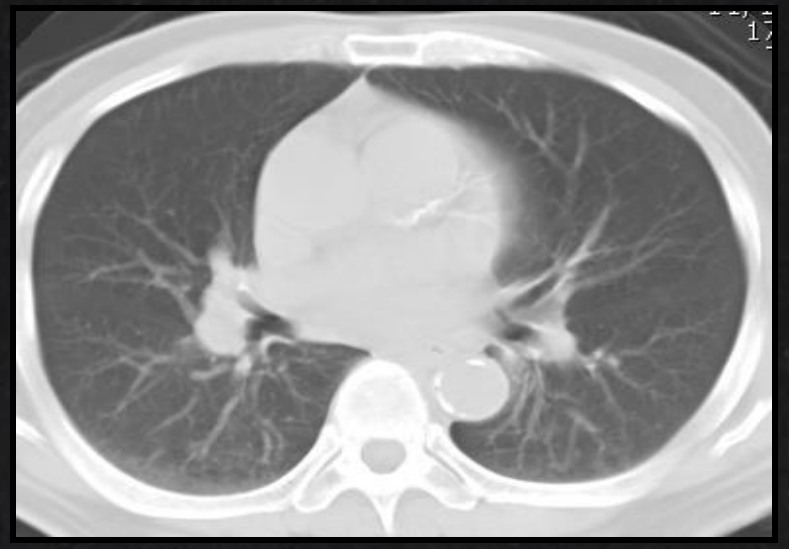
- Clinical data
- HRCT
- Tissue diagnosis
- Serology and other lab tests

Multidisciplinary discussion

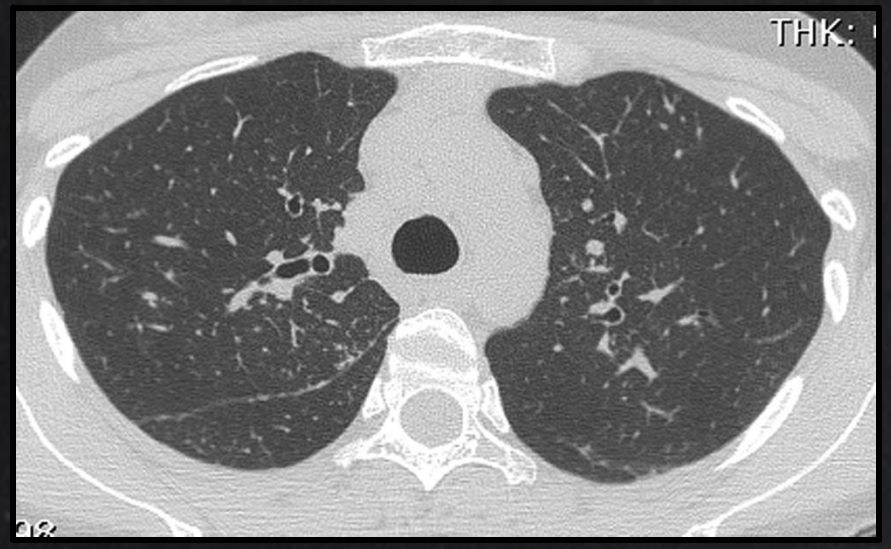
- Primary care physician/internal medicine
- Pulmonologist
- Radiologist
- Pathologist
- Thoracic surgeon
- Rheumatologist


Suspicious of ILD
• Symptom and sign
• Chest X-ray
• Initial investigation
HRCT
Multidisciplinary discussion (MDD)
Diagnosis
Yes
Diagnosis
No
Bronchoscopy
can make diagnosis
Yes
Bronchoscopy
Yes
Diagnosis
No
MDD
No
SLB or TBCB
Diagnosis
Yes
Diagnosis
Yes
Diagnosis

CT chest



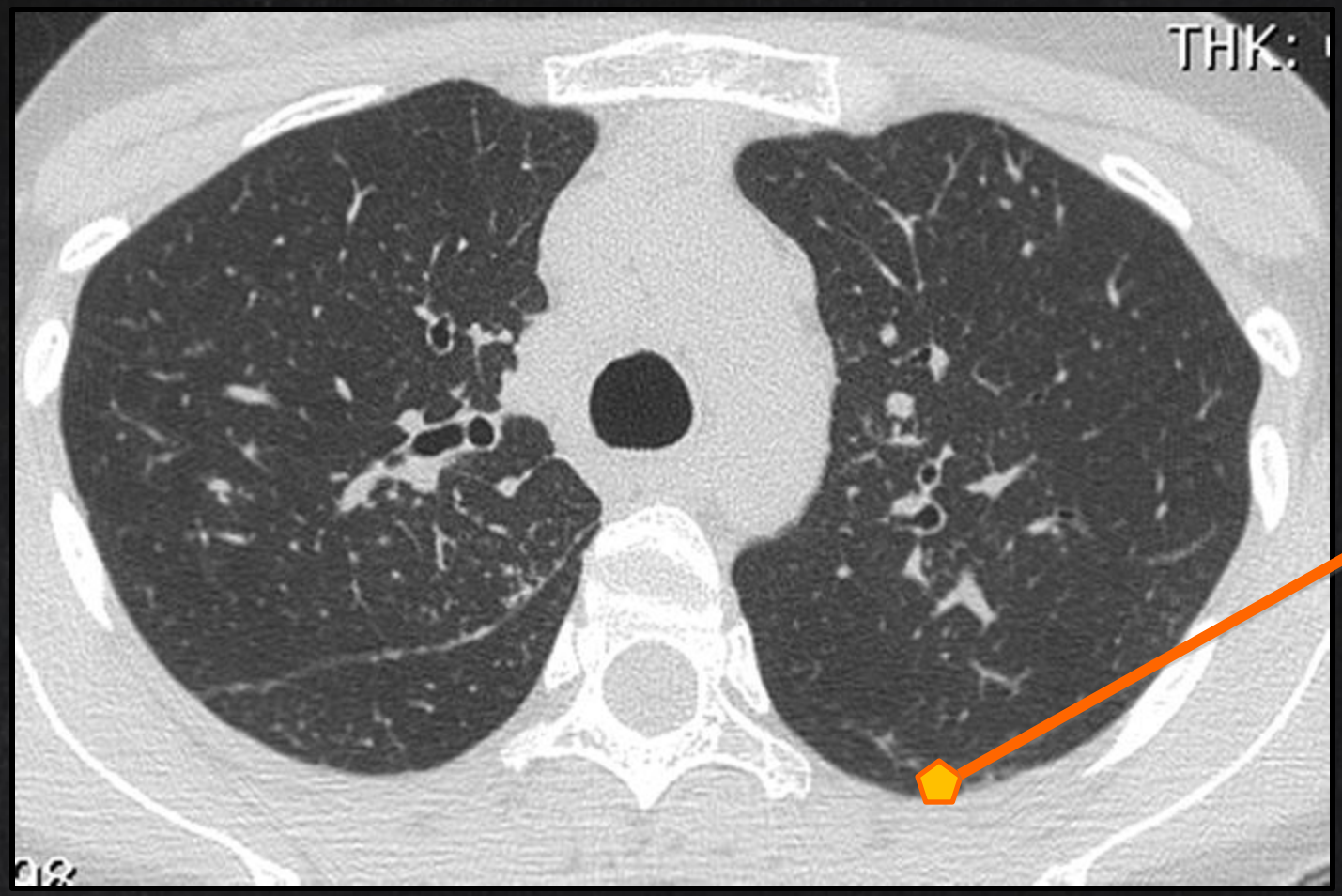
CT chest

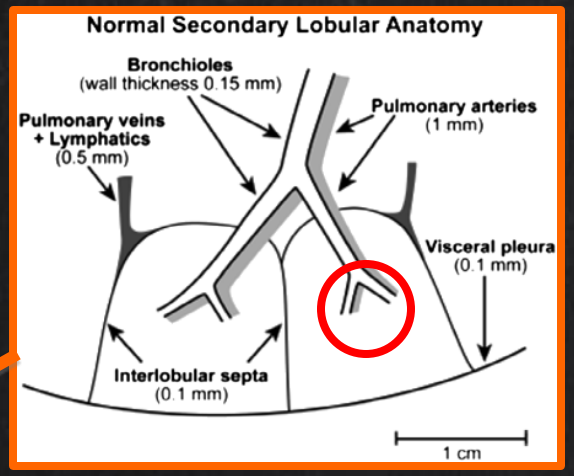


HRCT

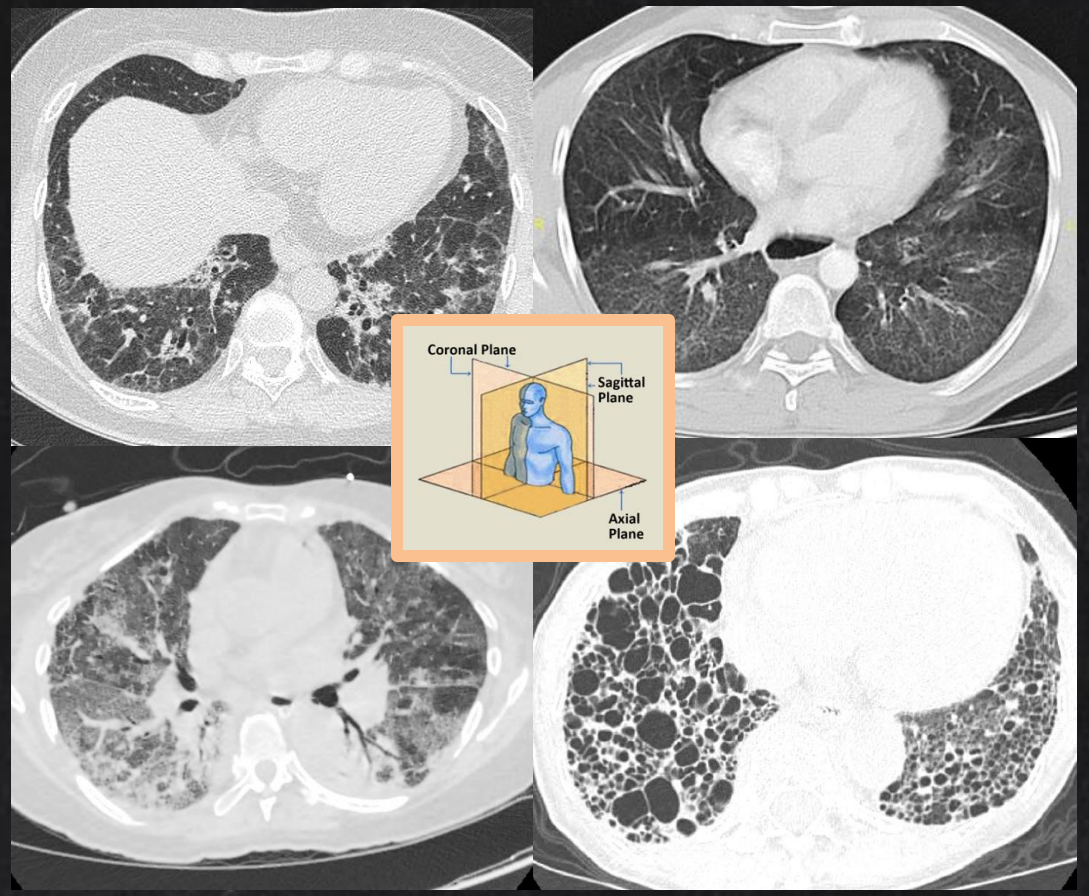
- Thin collimation → 1-1.5 mm.
- Indication :
  - Interstitial lung disease
  - Bronchiolitis
- Non contrast

Secondary lobule





HRCT



Abnormalities

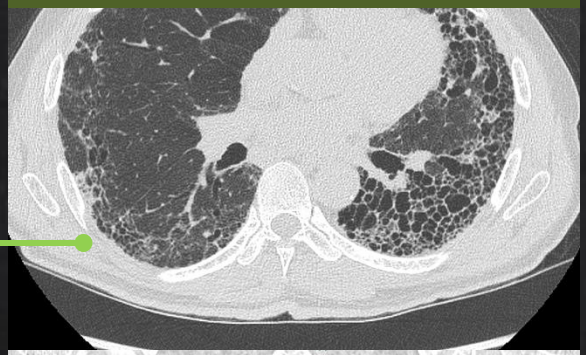
- Interstitial / alveolar process
- Pattern
- Distribution

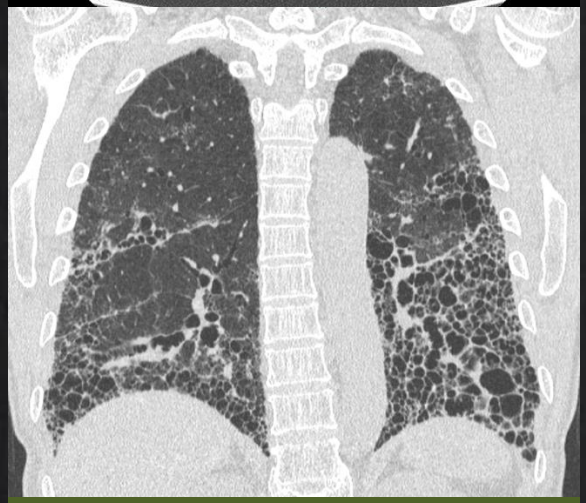
Lung volume

Associated finding

- Sign of PHT
- Pleural effusion
- Mediastinal lymph node
- Esophagus
- Subcutaneous emphysema

Axial distribution



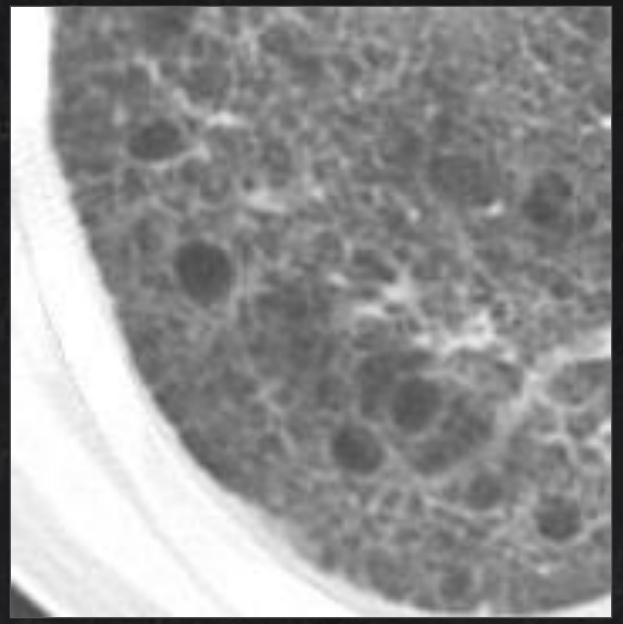


Craniocaudal distribution

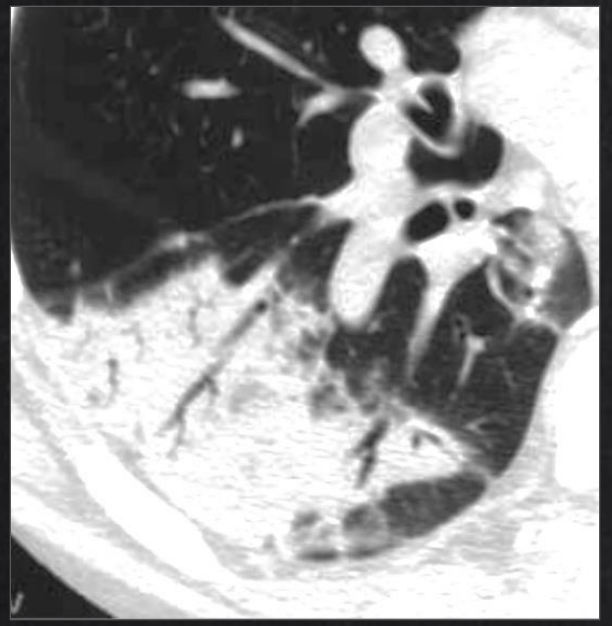
HRCT findings

Micronodules	• Centrilobular distribution • Perilymphatic distribution • Random distribution
Reticulation	• Interlobular septal thickening • Intralobular septal thickening
High attenuation	• Ground-glass opacity • Consolidation • Mosaic attenuation
Low attenuation	• Honeycombing • Traction bronchiectasis • Cysts

GGO vs consolidation

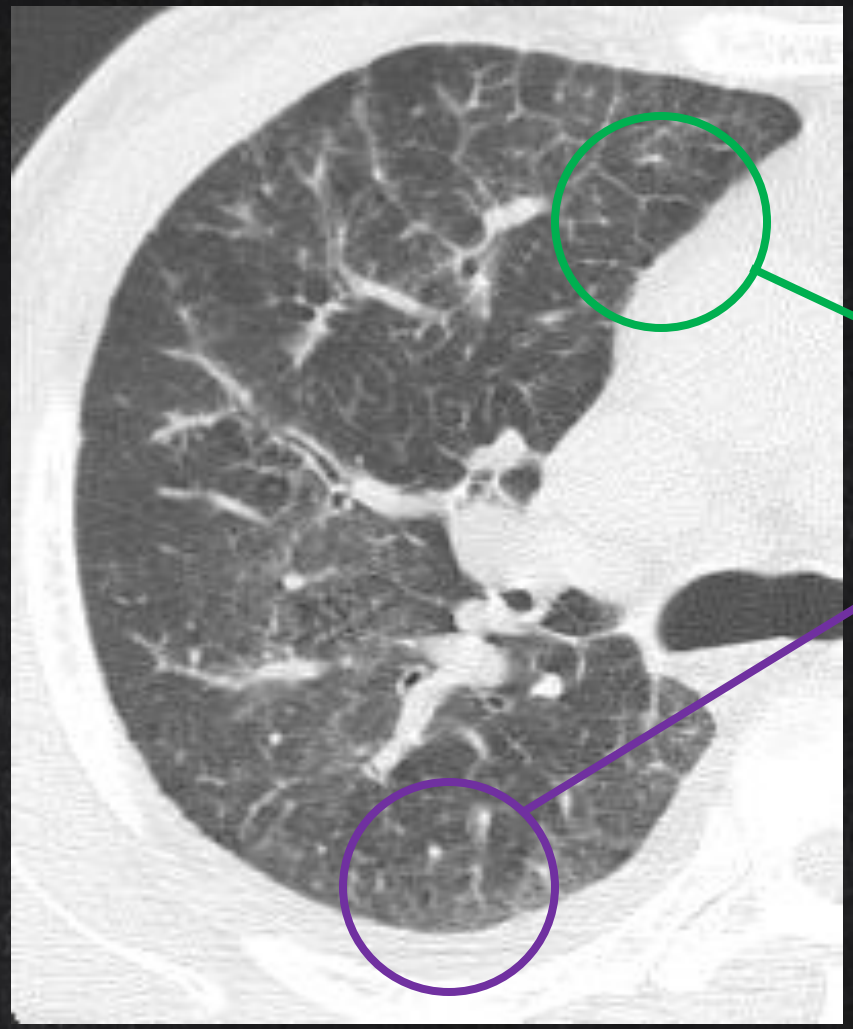


Ground-glass opacity (GGO)



Consolidation

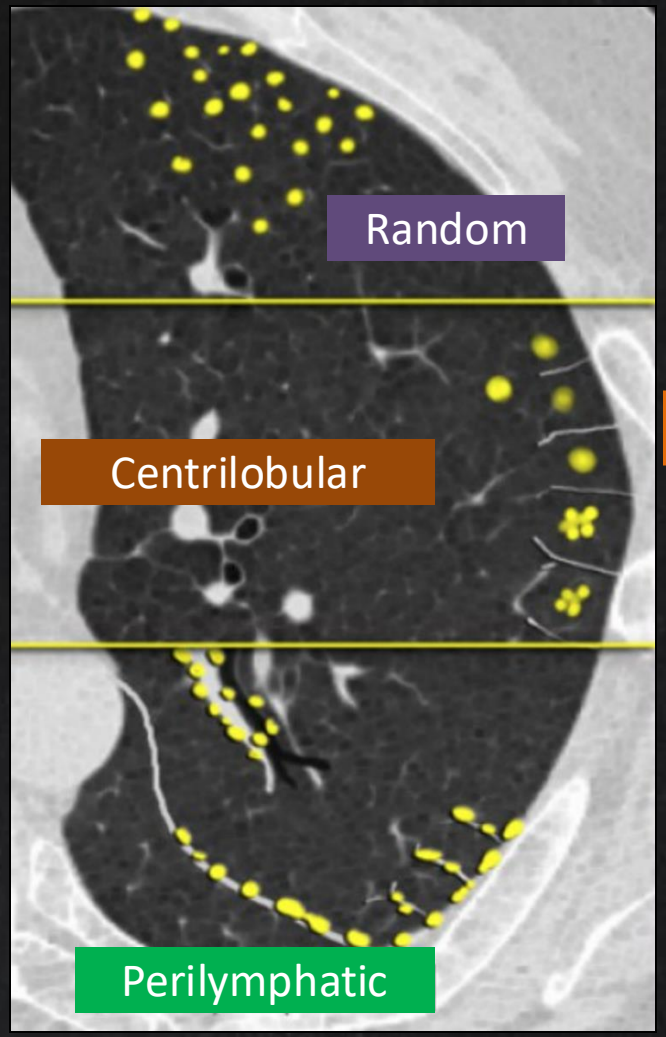
Reticular lines

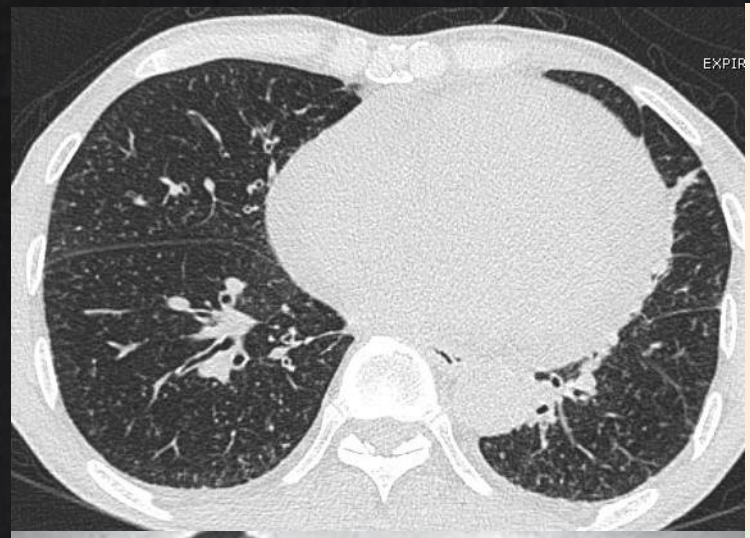


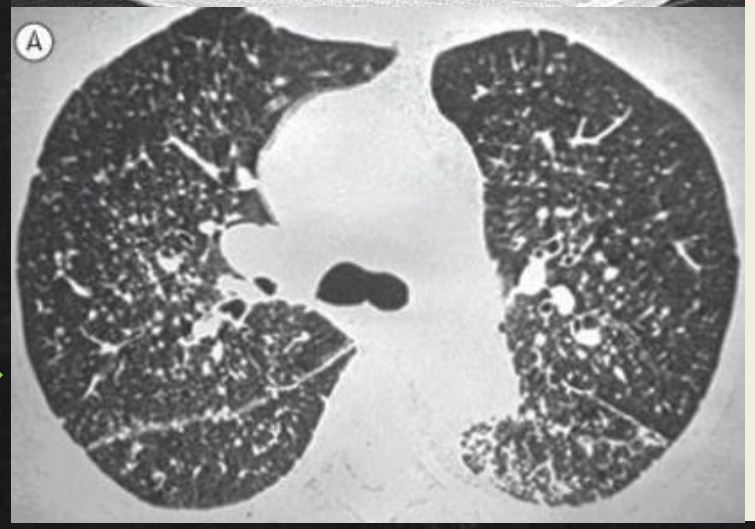
Interlobular septal thickening

Intralobular septal thickening

Nodular pattern



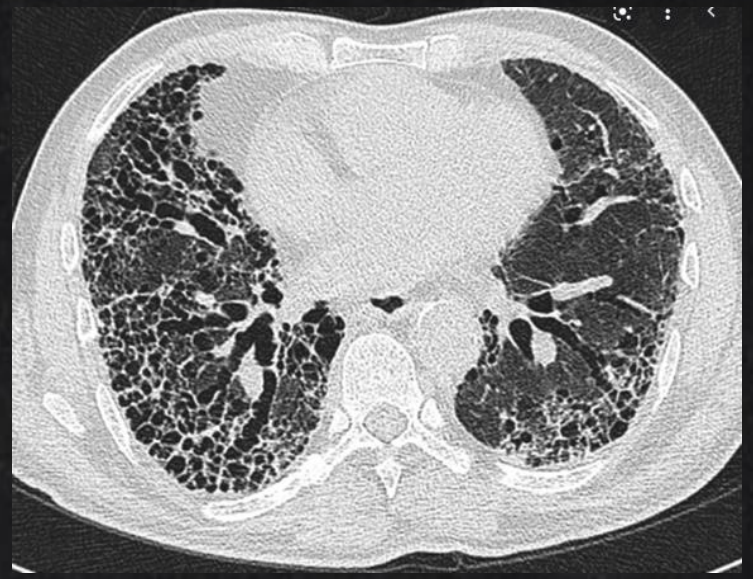


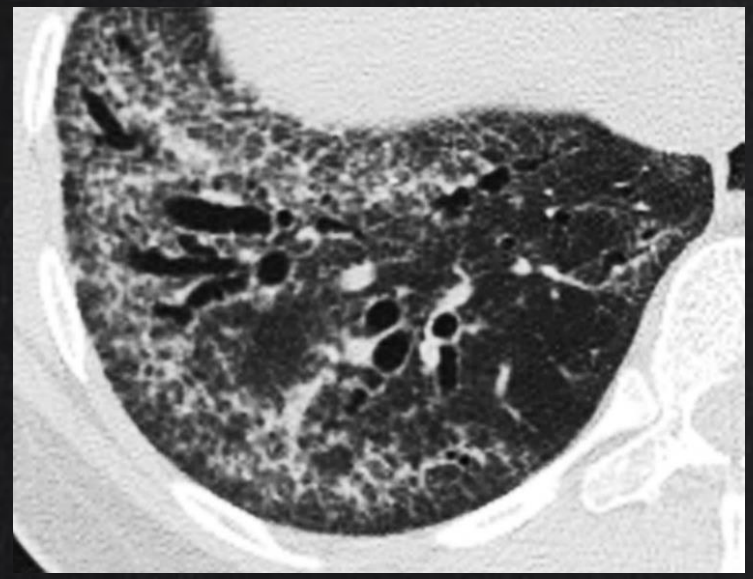


- Infection
  (bacteria, virus, TB, NTM, fungus)
- Bronchiolitis of any causes
- Aspiration pneumonitis
- Vascular causes e.g. tumor micro-embolism, cholesterol granuloma
- Hypersensitivity pneumonitis

- Lymphangitis carcinomatosis
- Sarcoidosis
- Pneumoconiosis (silicosis, coal worker's, berylliosis)

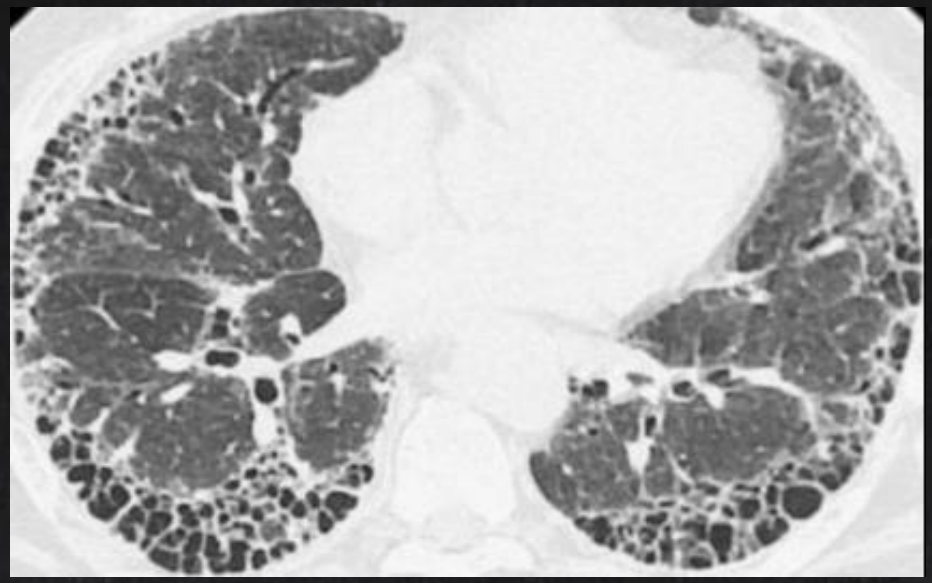
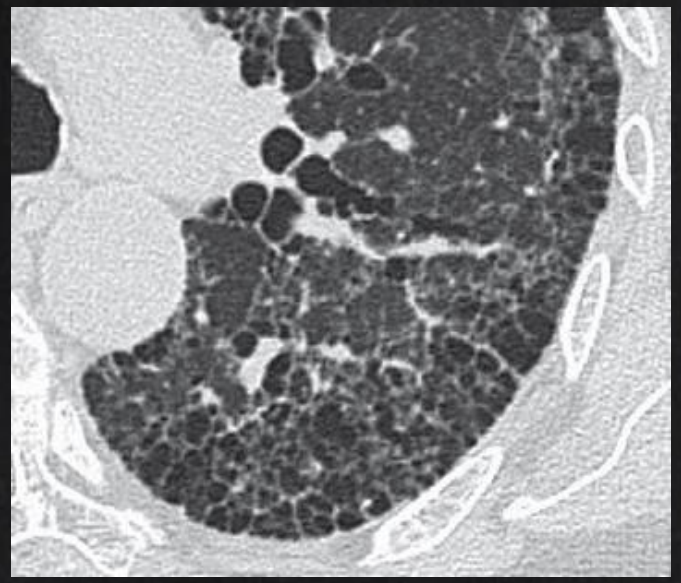
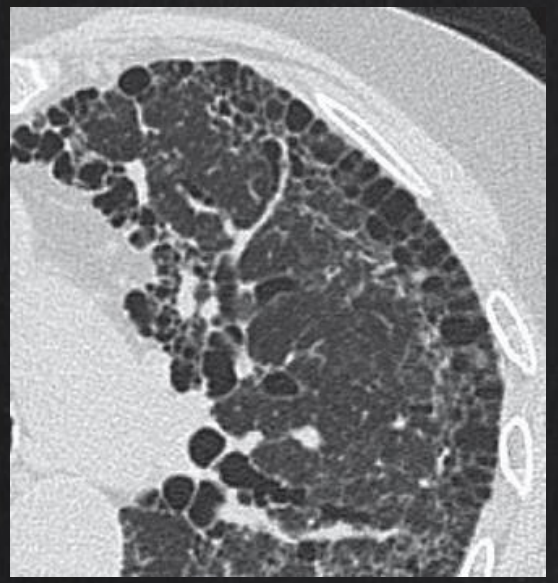
Traction bronchiectasis





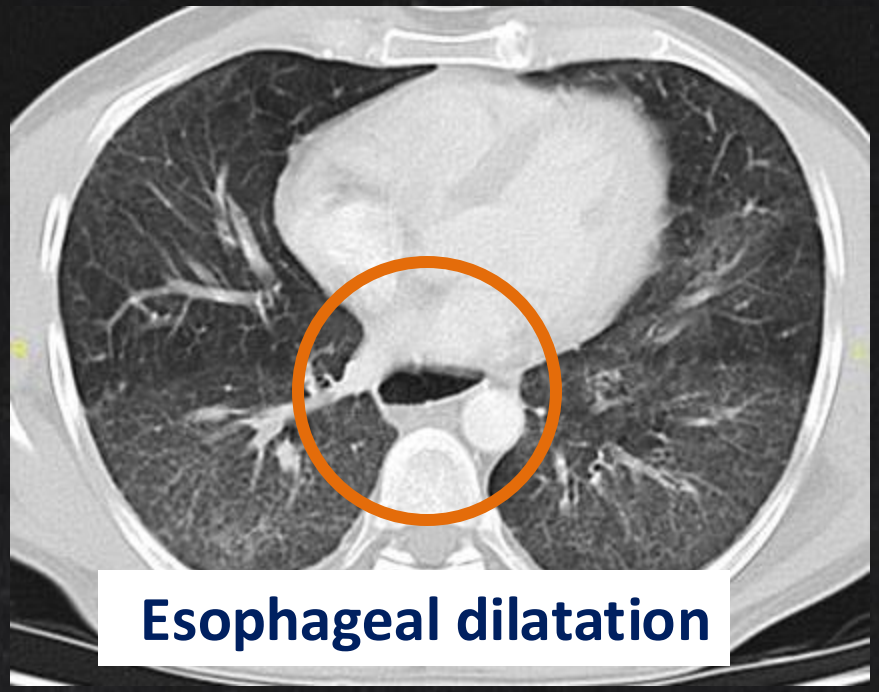
Dilatation of bronchi and bronchioles within areas of pulmonary fibrosis or distorted lung parenchymal architecture

Honeycombing

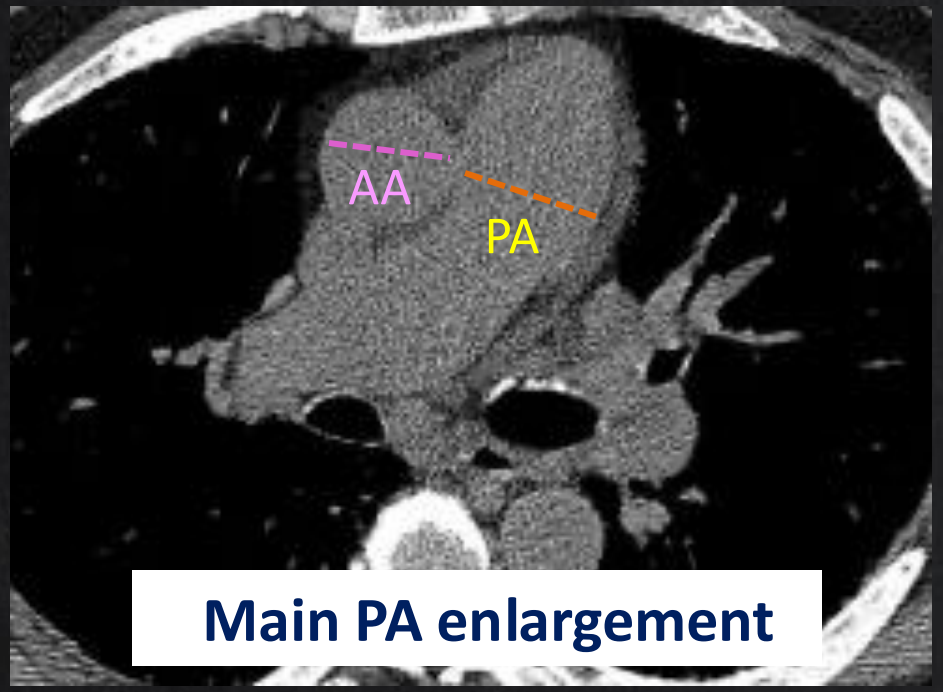
Layers of small cystic spaces
with irregularly thickened walls composed of fibrous tissue

Suggestive of CTD



Esophageal dilatation

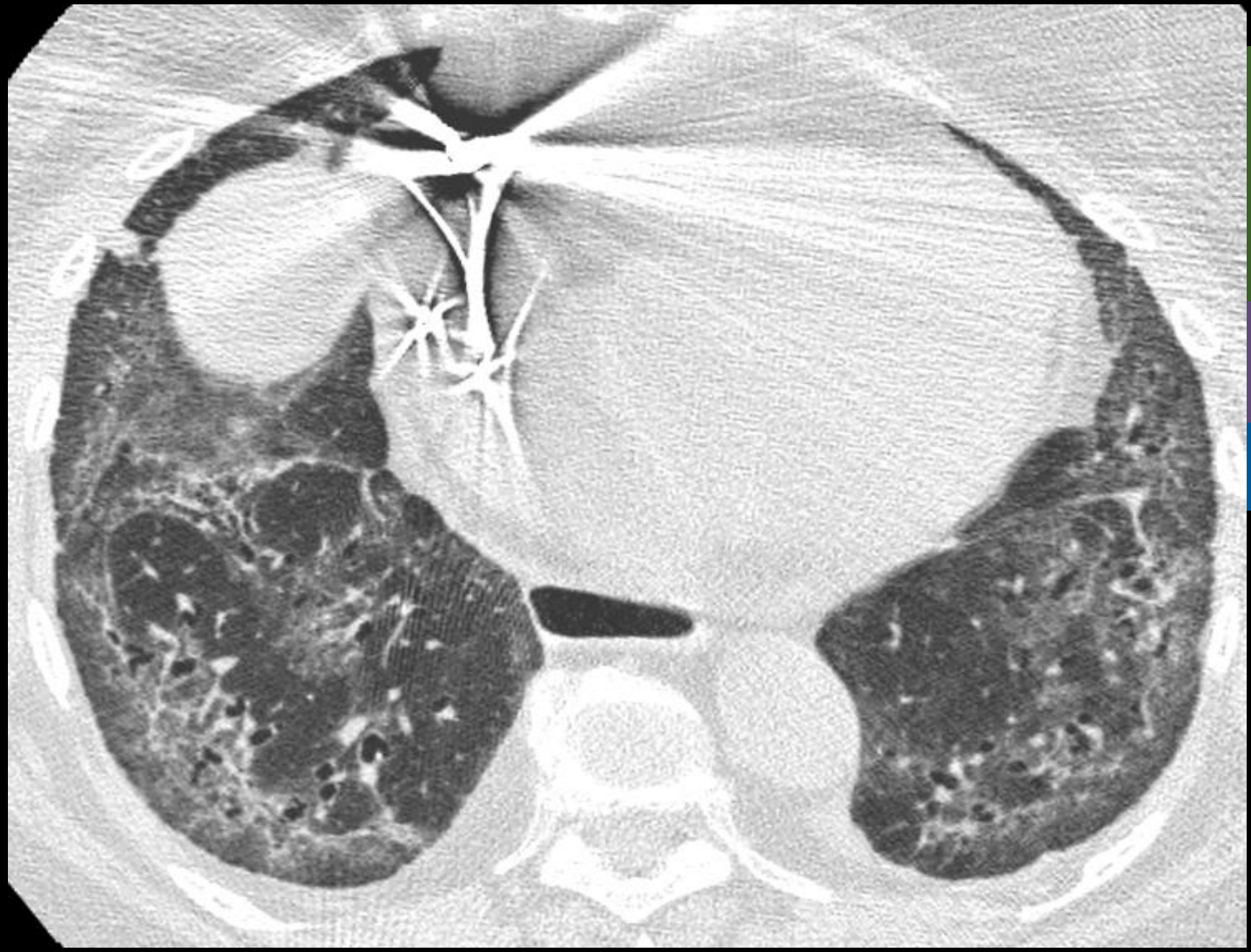
- NSIP pattern
- LIP, OP, UIP, DIP pattern
- Esophageal dilatation
- Pleural or pericardial effusion



Main PA enlargement

- PA:AA ratio > 0.9
- Differential diagnosis of the causes of PH

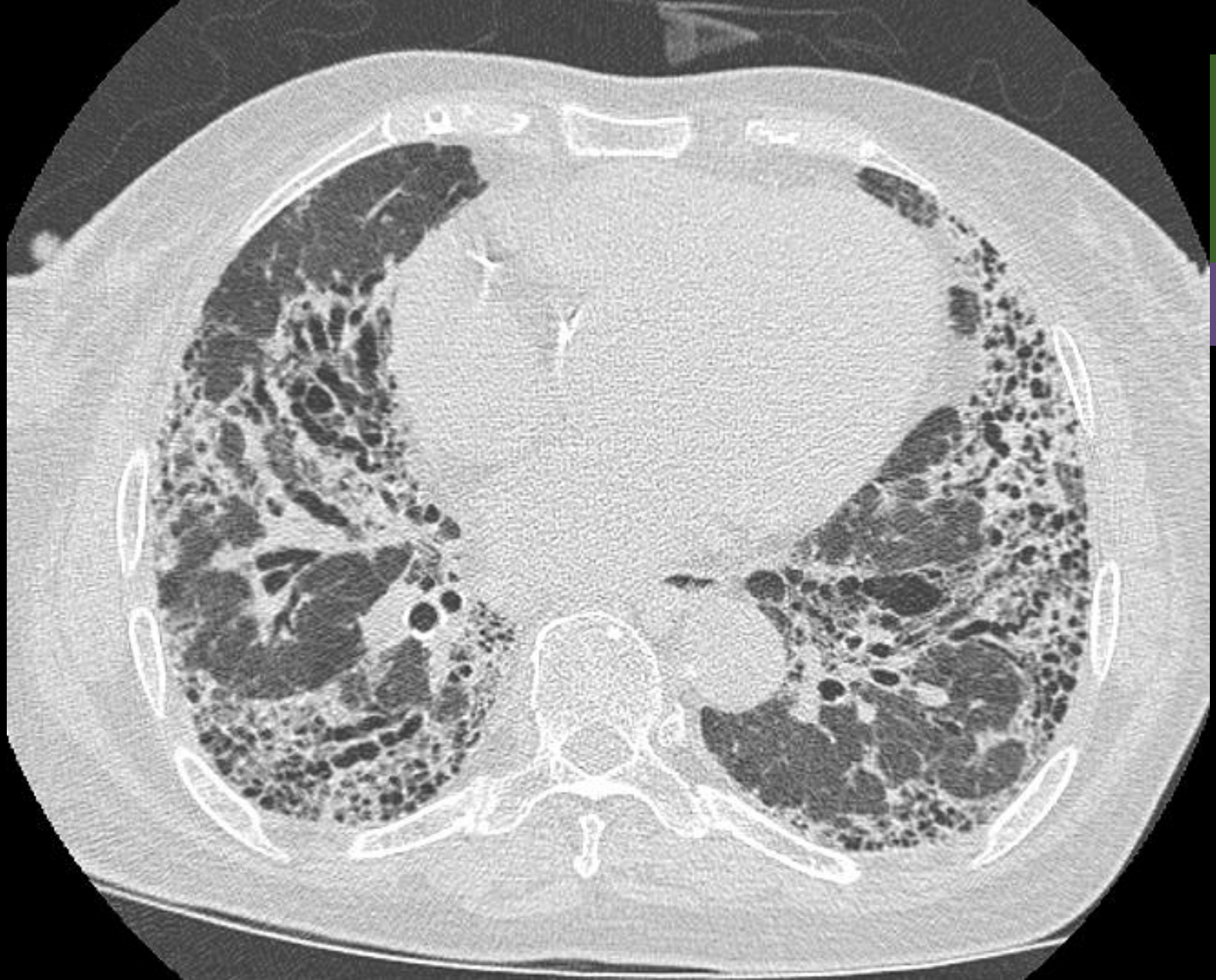
HRCT patterns	UIP	NSIP	OP
GGO	+/-	+++	+
Consolidation	-	-	+++
Reticulation	++	++	Perilobular pattern with linear opacities
Traction bronchiectasis	+++	+	-
Honeycombing	+++	+/-	-
Cystic lesion	-	+ (bronchiolectasis)	-
Nodule	-	-	+/- Small, ill-defined peribronchial nodules
Distribution and associated findings	• Subpleural area • Basal lungs	• Subpleural area • Basal lungs • +/- Immediate subpleural sparing (20%)	• Focal or multi-focal • Subpleural or peribronchial distribution • Reverse halo (20%)



- Ground glass opacities
- Reticulation
- Traction bronchiectasis
- No honeycombing

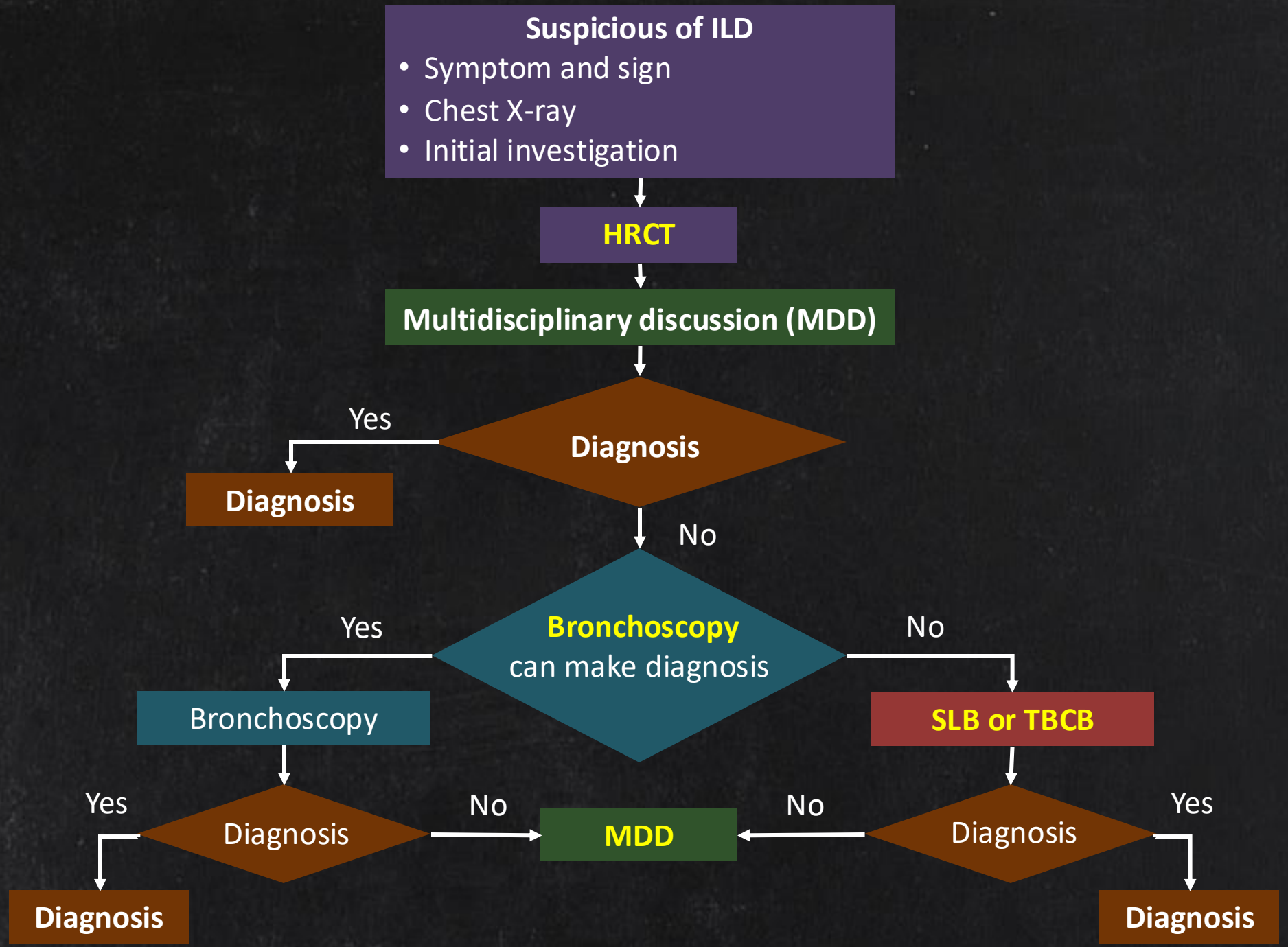
- Basal lung, bilateral
- Immediate subpleural sparing

- Esophageal dilatation



- Reticulation
- Traction bronchiectasis
- Honeycombing
- No GGO

- Basal lung, bilateral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HRCT
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Diagnosis
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Diagnosis
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Bronchoscopy
can make diagnosis
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Bronchoscopy
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Diagnosis
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MDD
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SLB or TBCB
Diagnosis
Yes
Diagnosis
Yes
Diagnosis

Interstitial pneumonia

HRCT patterns or histopathology → **Disease**

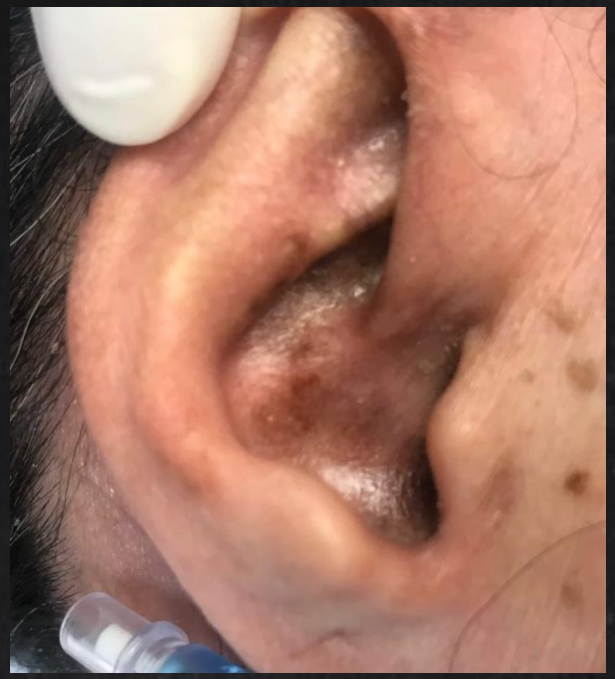
Identify causes and associated disease

- Symptoms and signs
- Autoantibody testings

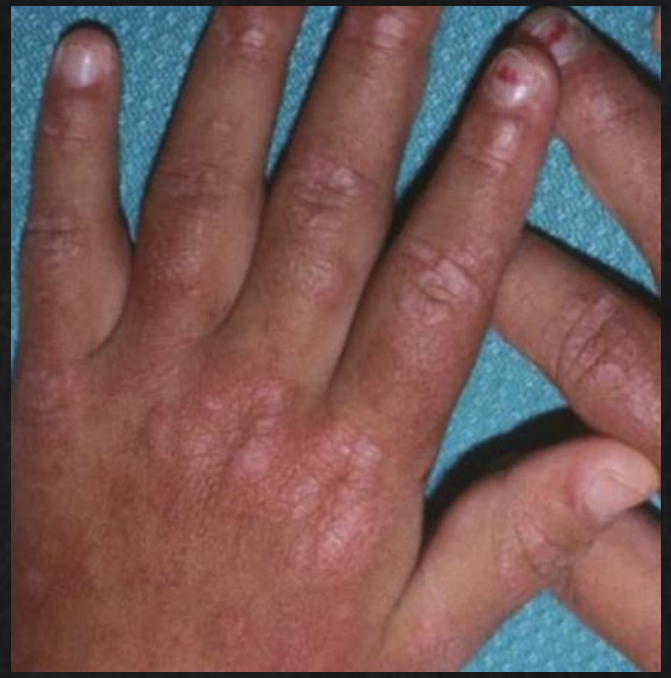
Connective tissue diseases

- ปวดข้อ, ข้ออักเสบ
- ผิวหนัง เช่น ผิวหนังตึงแข็ง, ผื่นที่ใบหน้า, ผื่นแพ้แสง, ผื่นที่นิ้วมือ, Raynaud’s phenomenon
- สำลักบ่อยหรือกรดไหลย้อน
- กล้ามเนื้อส่วนต้นอ่อนแรง
- ตาแห้ง, ปากแห้ง

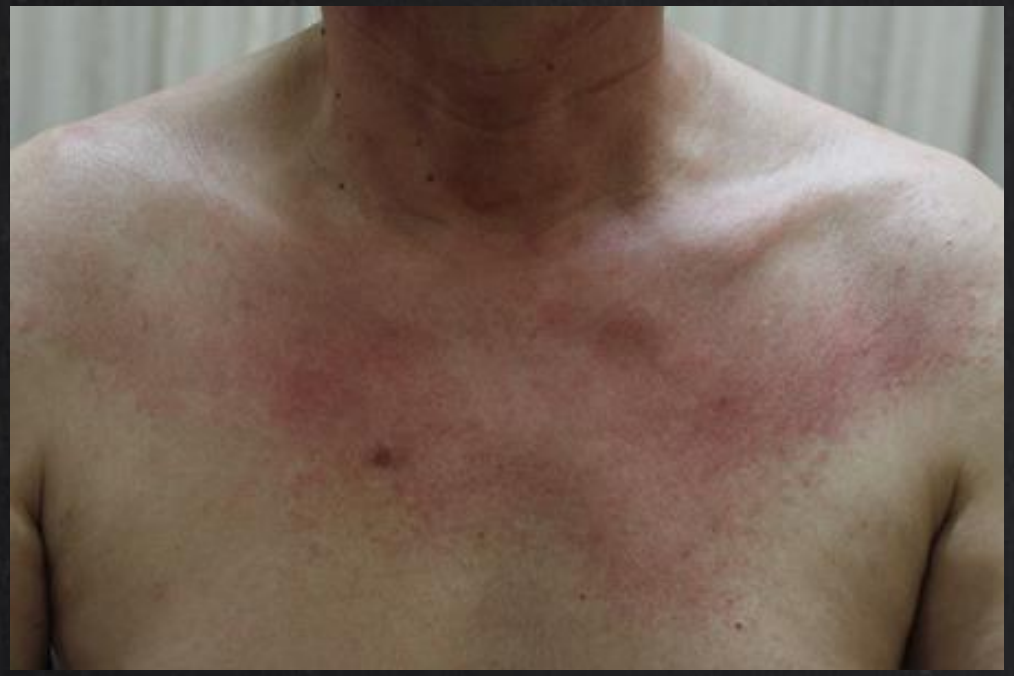
Connective tissue diseases



Discoid rash

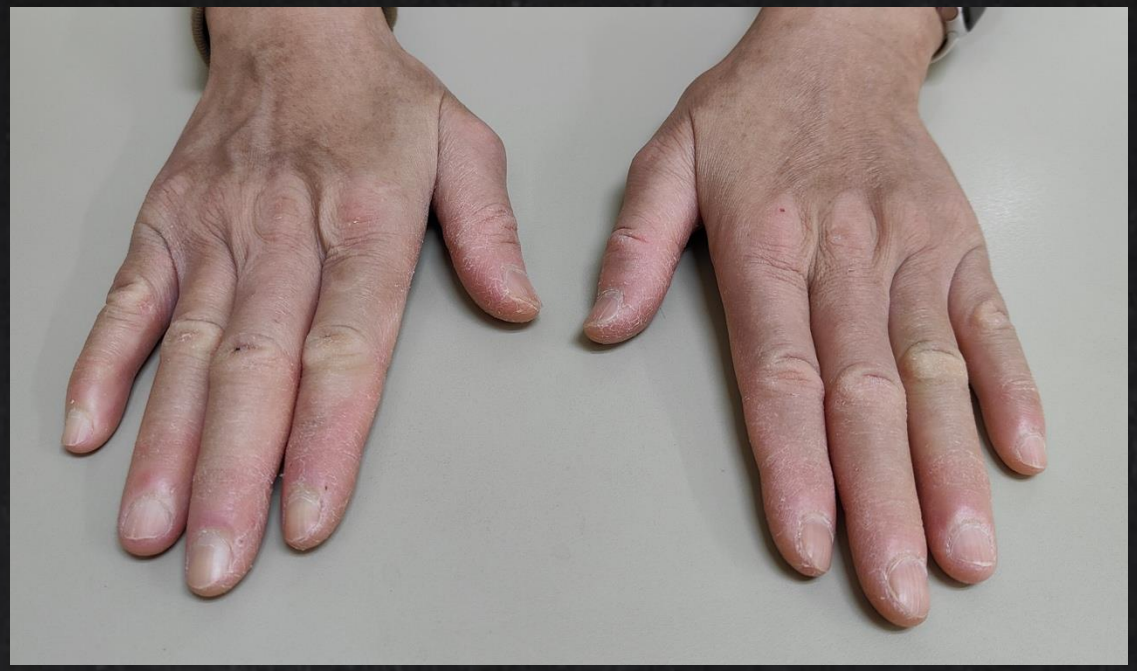


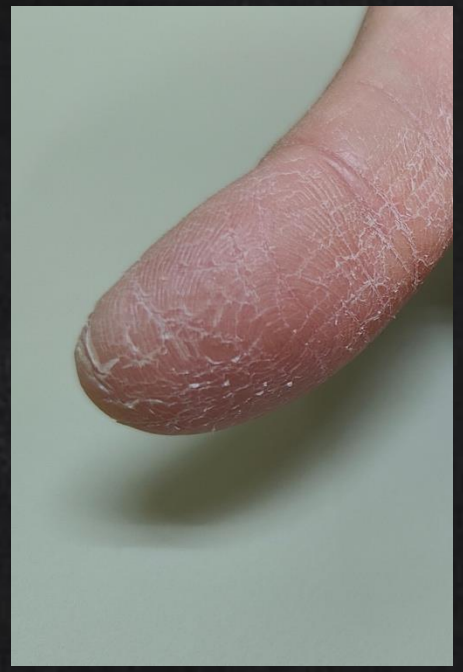
Grotton’s papule

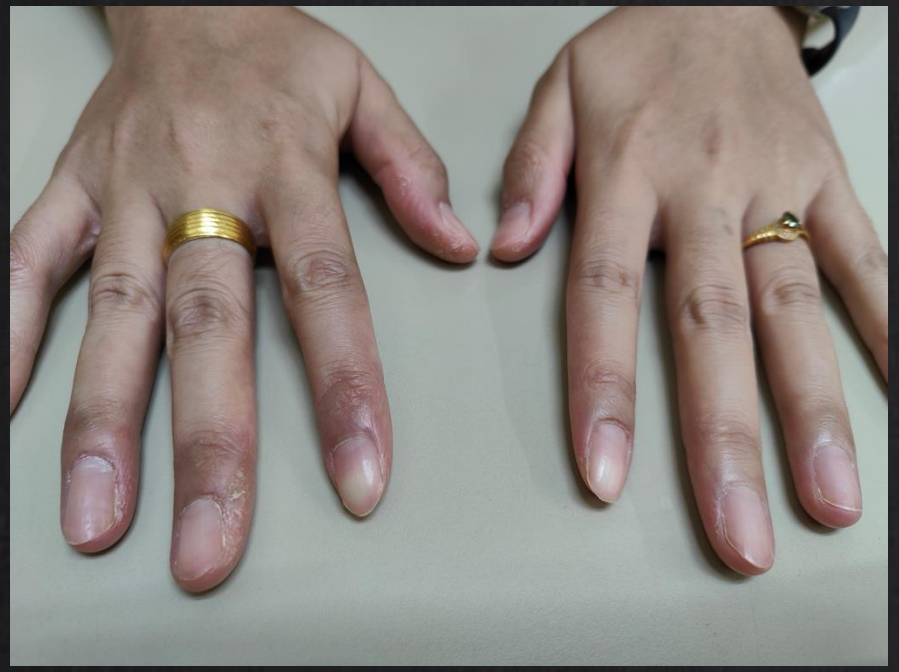


Heliotroph rash

Connective tissue diseases







Autoantibodies

Autoantibodies	Diseases
ANA	• Low titer → non-specific
RF	• Rheumatoid arthritis
Scl-70	• Systemic sclerosis
RNP	• Mixed connective tissue disease
Jo-1	• Myositis
Ro/SSA, La/SSB	• Sjogren's syndrome
CCP	• Rheumatoid arthritis
Myositis panel	
• **Antisynthetase**	• PL-7, PL-12, EJ, OJ : all associated with presence of ILD
• **MDA-5**	• Associated with aggressive ILD
• **PMScl**	• Overlapping features of PM and Scleroderma
• **Ro-52**	• Associated with aggressive ILD

SLE	90-100%
SSc	97%
MCTD	100%
PM/DM	40-80%
RA	30-50%

Pulmonary function tests

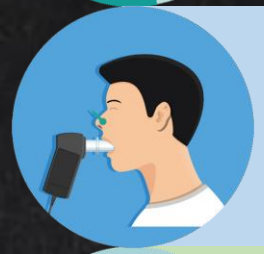
Diagnosis

Follow-up

- Spirometry
- Total lung capacity (TLC)
- Diffusing capacity (DLCO)
- 6-minute walk test (6MWT)

Follow-up and monitoring

- Dyspnea
- Exertional desaturation
- Exclude other causes



- FVC % predicted decline ≥ 10%
- DLCO % predicted decline ≥ 15%
- 6MWT: distance, exertional desaturation

- Progression of HRCT abnormalities

ILD Progression

Treatment

Specific treatment

- **Treat specific disease**
  - Corticosteroids
  - Immunosuppressants
  - Antifibrotics
- Lung transplantation

Other treatment

- Treat comorbid diseases
- Smoking cessation
- Improve nutrition
- Vaccination
- Long-term oxygen
- Pulmonary rehabilitation
- Psychosocial support
- Palliative care

CTD and lung involvment

Disease	Airway	Pleura	ILD	PAH	Muscle
SSc	+/-	+/-	+++++	+++	-
RA	++++	+++	++	+/-	-
Myositis	+/-	-	++++	+/-	+++
Sjogren's	+++	+/-	++	+	+/-
SLE	+/-	++++	+	++	+

Lauretis A, et al. Chronic Respiratory Disease 2011; 8:53-82.

CTD-ILD

Disease	UIP	NSIP	DAD	OP	LIP	DAH	Airway
SSc	++	++++	+	+	-	-	-
RA	++	+	+	-	-	-	++
Myositis	++	++++	+	++	-	-	-
Sjogren's	++	+++	-	+	++	-	++
SLE	+	+	++	+	-	+++	-
MCTD	++	+++	-	-	+	-	-

CTD-ILD

Disease	Type of ILD	Prevalence of ILD	Occult CTD	Progressive
SSc	**NSIP** UIP	> 50%	Less often	++
RA	**UIP** NSIP OP, DIP	10%	Less often	++
Myositis	**NSIP**, OP UIP, DAD	20-70%	**Often**	++
Sjogren's	**NSIP** UIP, LIP	10-40%	**Less often**	?
MCTD	**NSIP**, OP UIP	40-50%	**Often**	+/-

Fretheim, et al. Rheumatology 2020; Hoffmann-Vold, et al. J Respir Crit Care Med 2019; Am Qin, et al. Ann Rheum Dis 2015; Ramos-Calrsas, et al. Rheumatology 2015; Gunnarsson, et al. Ann Rheum Dis 2011; Reiseter, et al. Rheumatology 2018; Dobloug et al. Ann Rheum Dis 2015;Lilleker et al. Ann Rheum Dis 2018; Cross, et al. Ann Rheum Dis 2014; Hyldgard C, et al. Ann Rheum Dis 2017; Wijsenbeek, et al. Curr Med Res Opin 2019.

Treatment of CTD-ILD

Pharmacological

Non-pharmacological

Specific treatment

- Corticosteroids
- Immunosuppressants
- Biologic agents

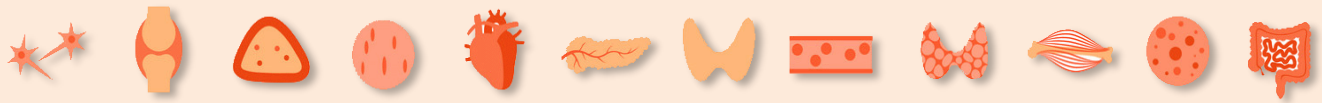
Pre-treatment evaluation

- Precaution
- Infection screening
- Education (drugs, goal, self-care)

Monitoring

- Adverse event
- Treatment response

Specific treatment of CTD-ILD

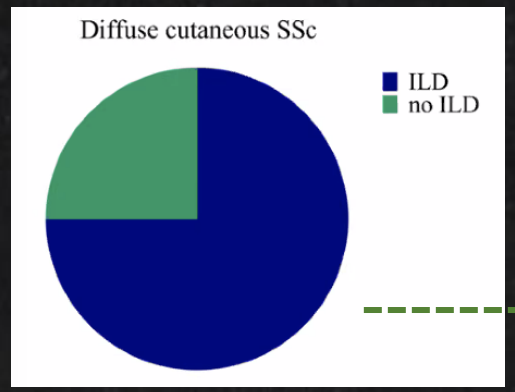
Diagnosis	• Classification criteria of specific CTD • Onset and disease behavior (chronic, subacute, RP-ILD)
ILD subtypes	• HRCT (+/- histopathologic) pattern
Disease severity and risk of progression	• Clinical, imaging, PFTs • Demographic data, serology (individual basis)
Extrapulmonary organs	
Patient factors	• Precaution/contraindication • Patient's preference and healthcare rights
Physicians	• Experience and hospital resources

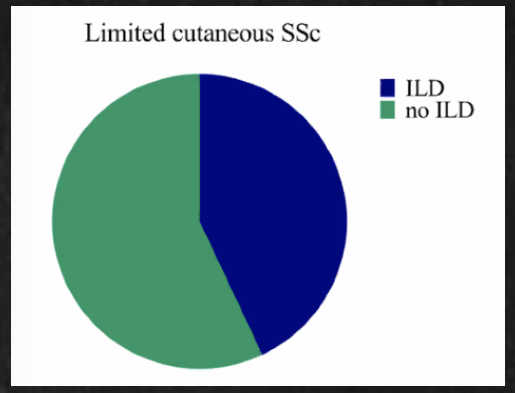
Pre-treatment evaluation

Drugs	CBC	LFT	Cr	FBS	Lipid	HBsAg	Anti-HBc	Anti-HCV	UA	Stool parasite
Corticosteroids	✓		✓	✓		✓	✓	✓		✓
Azathioprine	✓	✓	✓							✓
Cyclophosphamide	✓	✓	✓						✓	✓
Cyclosporine	✓	✓	✓							✓
Mycophenolate	✓	✓	✓							✓
Tacrolimus	✓	✓	✓							✓
Rituximab	✓					✓	✓	✓		✓
Tocilizumab	✓	✓			✓	✓	✓	✓		✓

สมาคมอุรเวชช์แห่งประเทศไทยฯ. แนวเวชปฏิบัติการรักษาด้วยยาในโรคปอดอินเตอร์สติเชียลจากโรคกล้ามเนื้ออักเสบไม่ทราบสาเหตุในผู้ใหญ่ พ.ศ. 2565

Systemic sclerosis

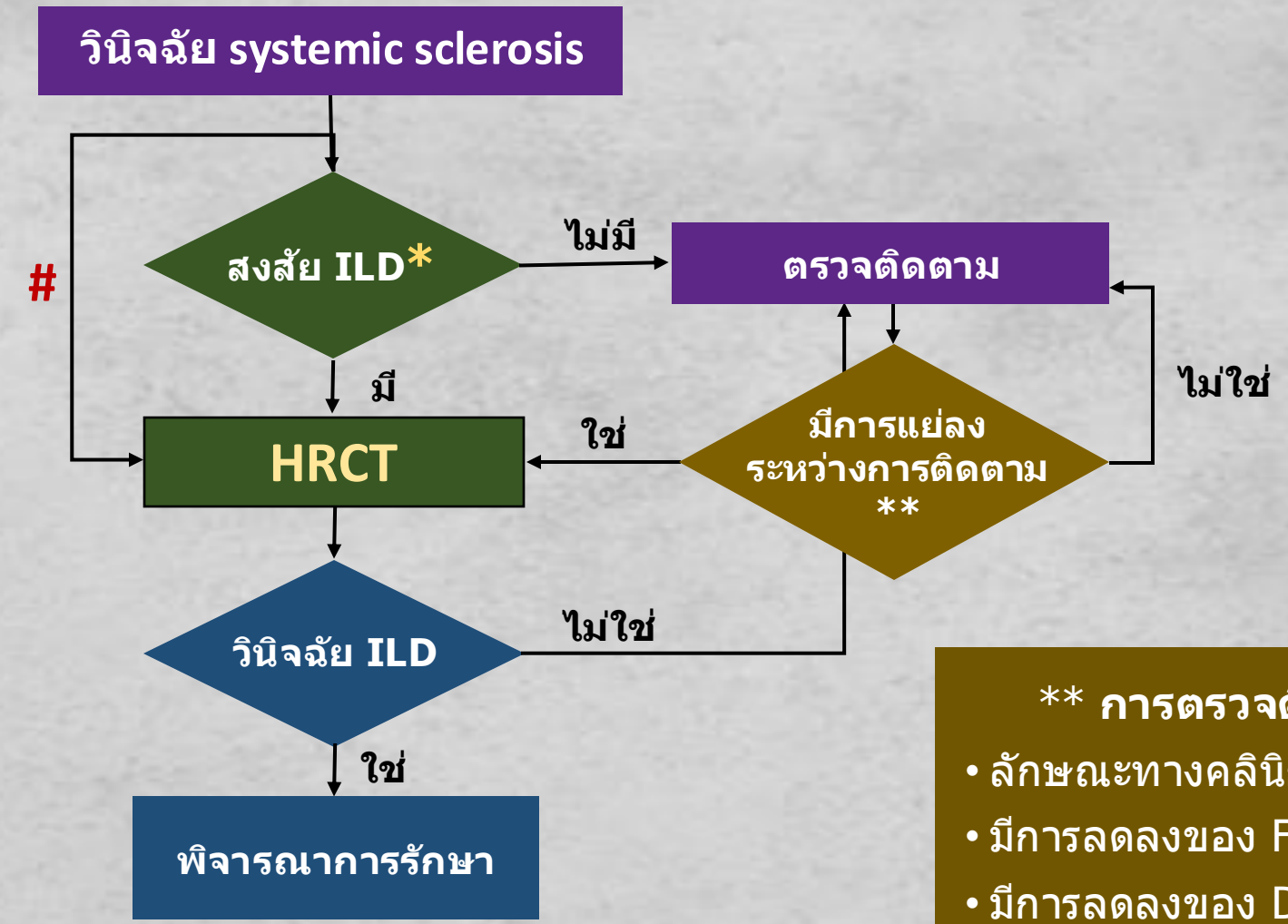




Lungs in SSc	ILD	PAH
Prevalence	40-75% by PFT 90% by CT	13-35% by echo 7-13% by RHC
Associated with	Diffuse SSc	Limited SSc
Serology	Anti-Scl-70	Anticentromere
Cause of death	35%	30%

Fretheim, et al. Rheumatology 2020;59:2920-29.
Hoffmann-Void AM, et al. Am J Respir Crit Care Med 2019;200:1258-66.

Screening ILD



*ลักษณะที่สงสัย ILD

- ลักษณะทางคลินิก เช่น เหนื่อย ไอ และ velcro crackles
- FVC < 80% predicted
- TLC < 80% predicted
- DL_{CO} < 80% predicted
- Desaturation (resting/exertion)

Predictors of ILD

- Male
- Diffuse scleroderma
- Anti-topoisomerase I Ab (anti-Scl-70)
- Esophageal dysmotility / GERD
- African American

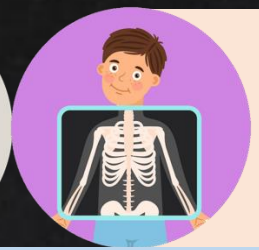
ผู้ป่วยที่มีปัจจัยเสี่ยงในการเกิด ILD ทั้งนี้ ขึ้นกับแพทย์ผู้ดูแล ทีมแพทย์สหสาขา และบริบทของแต่ละ รพ.

** การตรวจติดตาม

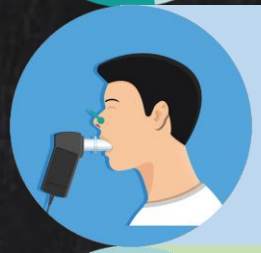
- ลักษณะทางคลินิก
- มีการลดลงของ FVC
- มีการลดลงของ DL_{CO}
- ระดับออกซิเจนปลายนิ้ว

แนวทาง
การดูแลรักษา SSc-ILD

Follow-up and monitoring



- Dyspnea
- Exertional desaturation
- Exclude other causes



- FVC % predicted decline ≥ 10%
- DLCO % predicted decline ≥ 15%
- 6MWT: distance, exertional desaturation

- Progression of HRCT abnormalities

ILD Progression

SSc-ILD treatment

SSc-ILD

Clinical data	HRCT and/or histopathologic pattern	Extent of disease	Risk of progression
• Symptoms and O_2 sat • Extrapulmonary involvement	• NSIP • UIP • OP	• Limited • Extensive ↓ • HRCT extent > 20% • FVC < 70% predicted Mortality 4x	• Low risk • High risk ↓ • Disease extent (severity) • Exertional desaturation • FVC decline ≥ 10% • DLCO decline ≥ 15%

Goh NS, et al. Am J Respir Crit Care Med 2008;177:1248-54.
Jung E, et al. Arch Rheumatol 2018;33:322-7.
Distler O, et al. Eur Respir J 2020;55: 1902026.
Goh NS, Arthritis Rheumatol 2017;69:1670-8.

SSc-ILD treatment

Specific treatment

- **Treat specific disease**
  - Immunosuppressants
  - Biologic treatment
  - HSCT
  - Antifibrotics
- Lung transplantation

Other treatment

- Treat comorbid diseases
- Smoking cessation
- Improve nutrition
- Vaccination
- Long-term oxygen
- Pulmonary rehabilitation
- Psychosocial support
- Palliative care

HSCT, Hematopoietic stem cell transplantation

2023 ATS treatment recommendation

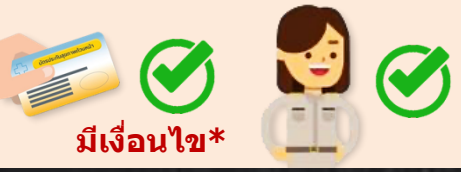
Strong in favor	Mycophenolate				
Conditional in favor	Cyclophosphamide	Rituximab	Tocilizumab	Nintedanib, Nintedanib + MMF	
Research recommendation	Pirfenidone, Pirfenidone + MMF				

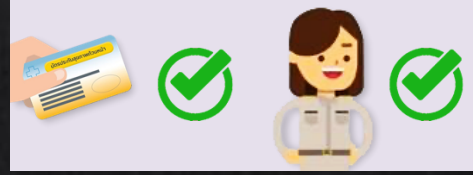
Raghu, G, et al. Am J Respir Crit Care Med 2023 Sep 29. doi: 10.1164/rccm.202306-1113ST.

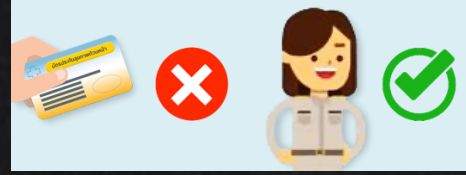
SSc-ILD treatment

Faculty of Medicine Siriraj Hospital Mahidol University

• Improve and stabilize FVC • Safety	• Improve and stabilize FVC • Higher adverse events comparing to MMF • Pulse regimen is preferred over oral daily regimen	• Stabilize FVC • Use only for maintenance Rx	• Improve FVC • Data from meta-analysis: study in patients who failed first-line Rx • iv drip over 4-6 hr	• Stabilize FVC • Secondary outcome • Safety • Recommend in inflammatory phenotype (↑CRP, skin) and early/dSSc
18-26 THB (500 mg)	7 THB (50 mg)	7 THB (50 mg)	4,800 THB (500 mg)	• iv → not approve in SSc-ILD • iv form cannot be used for SC inject.







ราคาอ้างอิง ของโรงพยาบาลศิริราช เมื่อ ก.ค. 2567.

Immunosuppressants

Drugs	Dose and duration	Note
Prednisolone	• Dose < 10 mg/day	• Do not use as monotherapy • Awareness of renal crisis
CYC	• **Oral daily**: 1-2 MKD (1 year) • **Pulse regimen** • IVCY: monthly 600 mg/m2 (6 months) • Oral pulse: 400 mg twice a month (1 year)	• **First line treatment for SSc-ILD** • Awareness of adverse event and drug toxicity (neutropenia, cystits, cancer risk) • Mesna might be considered in patients who received pulse regimen • PJP prophylaxis should be considered (TMP/SMZ (80/400) once a day or (160/800) 3 times a week)
MMF	• 2,000-3,000 mg/day (2 years)	• **First line treatment for SSc-ILD** with less adverse event compared to CYC
AZA	• 1-2 MKD	• Only used as **maintenance treatment**

แนวทาง
การดูแลรักษา SSc-ILD

การรักษา SSc-ILD

วัคซีนและการรักษาที่ไม่ใช่ยา
- เลิกบุหรี่
- รักษาโรคร่วม
- วัคซีน
- การฟื้นฟูสมรรถภาพปอด
- ปรับภาวะโภชนาการ
- การให้ออกซิเจนระยะยาว
- Palliative และ end-of-life care

พิจารณาการรักษาด้วยยา
- ไม่ใช่ → ตรวจติดตาม *
- ใช่ → พิจารณาให้ immunosuppressive drugs ได้แก่ cyclophosphamide หรือ mycophenolate mofetil → ตรวจติดตาม *

ตรวจติดตาม *
- ไม่ใช่ → มีการลุกลามของโรค
- ใช่ → พิจารณาให้ immunosuppressive drugs

ตรวจติดตาม *
- ไม่ใช่ → ไม่ตอบสนองหรือมีการลุกลามของโรค
- ใช่ → ปรับการรักษา

ปรับการรักษา
- ปรับขนาดยาหรือพิจารณายากลุ่มอื่น เช่น tocilizumab, rituximab เป็นต้น
- ประเมินการปลูกถ่ายปอด
- Autologous hematopoietic stem cell transplantation
- Antifibrotics

*** การตรวจติดตาม**
- Clinical data
- O_2 saturation
- FVC decline
- DLCO decline
- HRCT extent

การพิจารณาการรักษา
- FVC < 70% predicted
- HRCT extent > 20%
- Symptoms and O_2 saturation
- Some HRCT features e.g. OP
- Extrapulmonary organ

Risk of progression
- Age
- Male
- Shorter onset of SSc
- Lower baseline FVC and DLCO
- Rapid decline of FVC, DLCO
- HRCT extent

Idiopathic inflammatory myositis

Onset	Frequency
Asymptomatic	25%
Subacute / chronic	58%
Rapidly progressive	17%

More frequently seen in

- DM
- CADM
- Positive anti-MDA5
- Hypomyopathic DM

DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis

Marie I, Hachulla E, Cherin P, et al. Arthritis and rheumatism 2002;47:614-22.
Kalluri M, Oddis CV. Clinic in Chest Medicine 2010;31:501-12.

Antisynthetase syndrome

- Presence of one of antisynthetase antibodies

• Anti-Jo-1 and anti-PL	60-80%
• Anti-PL7	10-15%
• Anti-PL12	5-10%
• Anti-EJ, -OJ, -KS	5-15%

- Combination with

One of major involvement	
• Polyarthritis	62%
• Myositis	57%
• ILD	70%

OR two minor	
• Fever	43%
• Mechanic's hands	28%
• Raynaud's	47%

Labirua A, et al. Current Opinion in Rhurmatology 2010;22:633-8.

Anti-MDA5-related ILD

- Anti-MDA5 was found in 7-13% of DM patients
- ANA may be negative
- Significant myositis could be found only 20%
- Other manifestations
  - Skin (digital ulcer, DM rash)
  - Arthritis (80%)
  - Raynaud's phenomenon (45%)
  - Mechanic's hands (80%)
  - Panniculitis

Anti-MDA5-related ILD

- Anti-MDA5 → associated with rapidly progressive ILD
- Survival rate → 54% at 6 months
- Autoantibodies titer level > 500 U/mL → associated with
  - Treatment resistance
  - Higher risk of short-term death from respiratory failure

Treatment of IIM-ILD

Specific treatment

- Pharmacological treatment
  - **Corticosteroids**
  - **Immunosuppressants**
  - Biologic treatment
  - Other rescue treatment
  - Antifibrotics

Other treatment

- Treat comorbid diseases
- Smoking cessation
- Improve nutrition
- Vaccination
- Long-term oxygen
- Pulmonary rehabilitation
- Psychosocial support
- Palliative care

Causes of secondary OP

Infection

- Bacteria: *Burkholderia cepacia*, *Nocardia asteroides*, *Legionella pneumoniae*, *P. aeruginosa*, *S. pneumoniae*, *S. aereus*, *Mycoplasma pneumoniae*
- Viruses: SARS-CoV-2, HPV, CMV, HIV, influenza, parainfluenza, HHV-7, RSV
- Parasites: *Plasmodium vivax*, *Dirofilaria imitis*
- Fungi: *Cryptococcus neoformans*, *Penicillium janthinellum*, PJP

Connective tissue disease

- IIM: PM/DM, ASS, anti-MDA5
- Sjogren's syndrome
- RA
- SSc
- Granulomatosis with polyangiitis

Drugs

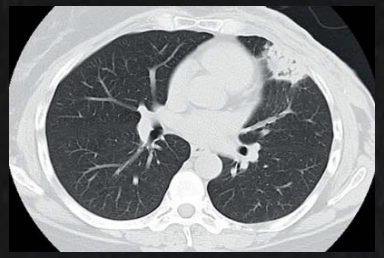
- Amiodarone
- Nitrofurantioin
- Methotrexate
- Bleomycin
- Freebase cocaine

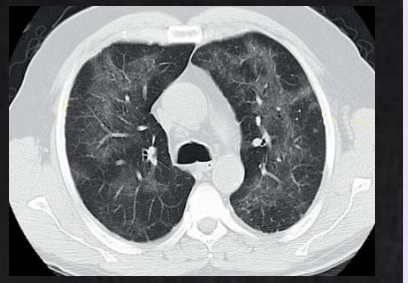
Others

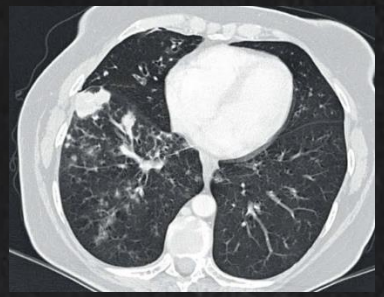
- Hematologic malignancy: leukemia, lymphoma
- BM/stem cell or solid organ transplantation
- Radiation therapy
- Immunodeficiency syndrome
- Associated with other ILDs: CEP, HP, organizing DAD
- IBD: Crohn's disease, UC
- Others: inhalation injury, aspiration

Cherian SV, et al. Chest 2022;162(1):156-78.

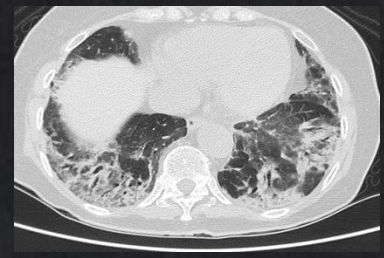
Radiographic features

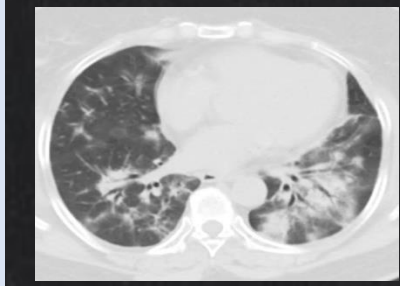


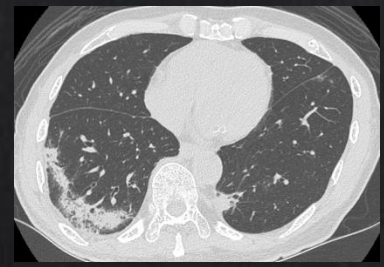




Findings	Distribution
• Consolidation • Ground-glass opacities • Crazy-paving pattern • Reverse halo (Atoll) sign • Nodules (solitary or multiple): subtle, poorly defined pattern	• Multifocal, bilateral • Peripheral (subpleural) • Peribronchovascular pattern • Linear and band-like pattern • Perilobular pattern: poorly defined, bowed or polygonal opacities • Recurrent or migratory

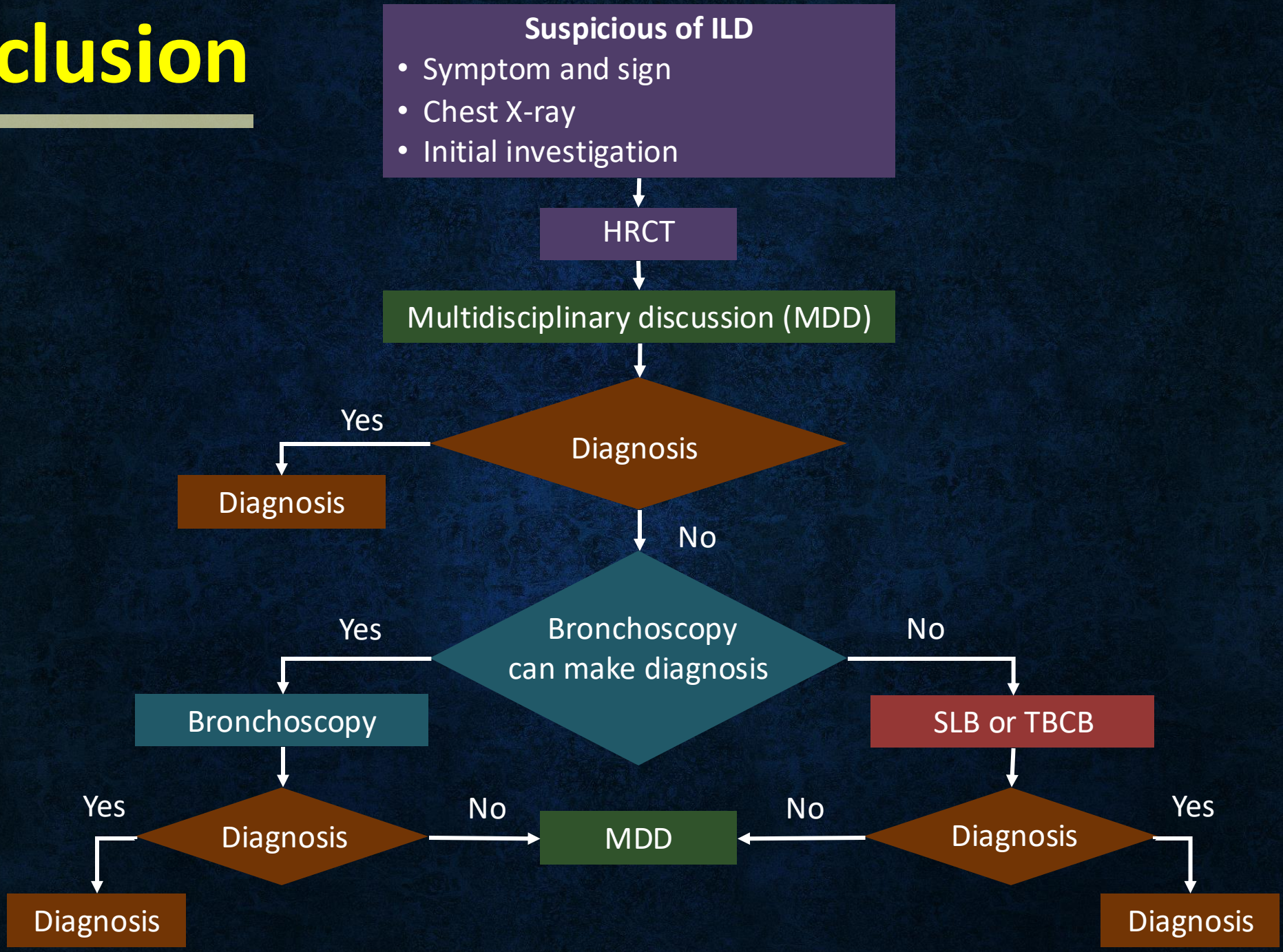






Cherian SV, et al. Chest 2022;162(1):156-78.
Feinstein MB, et al. J Clin Pathol 2015;68:441-7.

Conclusion


Suspicious of ILD
• Symptom and sign
• Chest X-ray
• Initial investigation
HRCT
Multidisciplinary discussion (MDD)
Diagnosis
Yes
Diagnosis
No
Bronchoscopy can make diagnosis
Yes
Bronchoscopy
No
SLB or TBCB
Yes
Diagnosis
No
MDD
No
Diagnosis
Yes
Diagnosis
Diagnosis

Conclusion

EARLY

- Detection
- Diagnosis
- Treatment
- Referral

Multidisciplinary discussion

If worsening