Hypersensitivity Pneumonitis

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AT THE FOREFRONT
UChicago
Medicine

Goals

- Understand the role of imaging in HP diagnosis
- Stratify HP cases using the new guidelines
- Be able to recognize high confidence imaging patterns in HP
- List different categories of HP patterns based on diagnostic confidence

Hypersensitivity pneumonitis

- Hypersensitivity pneumonitis is an allergic reaction to inhaled organic dusts or chemicals.
- More than 300 substances.
    - Molds (farming, humidifiers, old homes/water damage)
    - Birds
    - Hot tub lung (GNR and NTM species)
- Imaging (HRCT) central to the diagnosis of HP

Diagnosis of Hypersensitivity Pneumonitis in Adults
An Official ATS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson, Jeffrey L. Myers, Michael Kreuter, Martina Vasakova, Elena Bargagli, Jonathan H. Chung, Bridget F. Collins, Elisabeth Bendstrup, Hassan A. Chami, Abigail T. Chua, Tamera J. Corte, Jean-Charles Dalphin[†], Sonye K. Danoff, Javier Diaz-Mendoza, Abhijit Duggal, Ryoko Egashira, Thomas Ewing, Mridu Gulati, Yoshikazu Inoue, Alex R. Jenkins, Kerri A. Johannson, Takeshi Johkoh, Maximiliano Tamae-Kakazu, Masanori Kitaichi, Shandra L. Knight, Dirk Koschel, David J. Lederer, Yolanda Mageto, Lisa A. Maier, Carlos Matiz, Ferran Morell, Andrew G. Nicholson, Setu Patolia, Carlos A. Pereira, Elisabetta A. Renzoni, Margaret L. Salisbury, Moises Selman, Simon L. F. Walsh, Wim A. Wuyts, and Kevin C. Wilson; on behalf of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin[†] (June 2, 1956–October 17, 2019)

Diagnosis and Evaluation of Hypersensitivity Pneumonitis

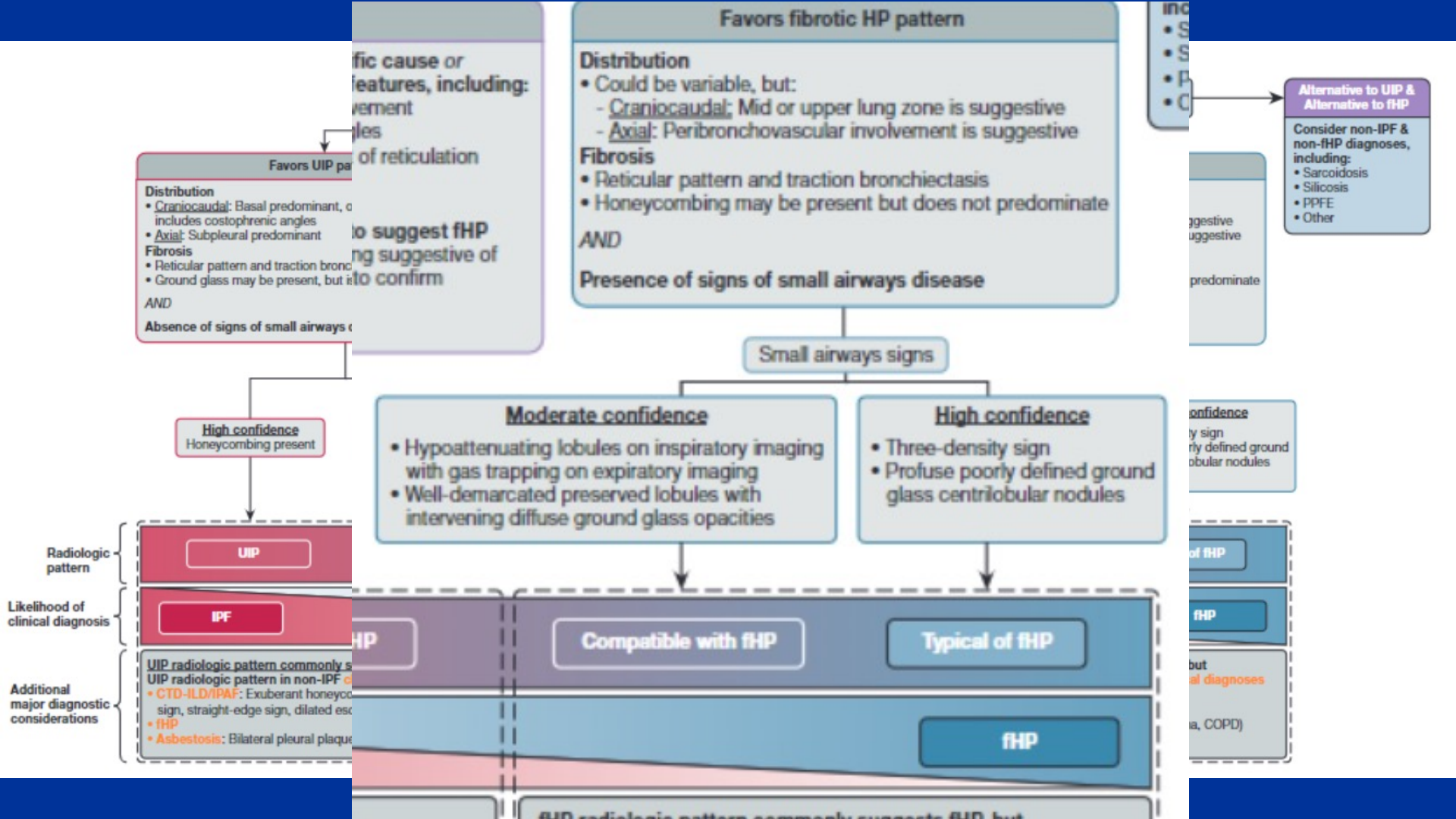## CHEST Guideline and Expert Panel Report

Check for updates

Evans R. Fernández Pérez, MD, FCCP; William D. Travis, MD, FCCP; David A. Lynch, MB, BCh; Kevin K. Brown, MD, FCCP; Kerri A. Johannson, MD, MPH; Moisés Selman, MD; Jay H. Ryu, MD, FCCP; Athol U. Wells, MD; Yuh-Chin Tony Huang, MD, MHS, FCCP; Carlos A. C. Pereira, MD, FCCP; Mary-Beth Scholand, MD, FCCP; Ana Villar, MD, PhD; Naohiko Inase, MD, PhD; Richard B. Evans, MD, MPH, FCCP; Stephen A. Mette, MD, FCCP; and Lindsy Frazer-Green, PhD

Check for updates

Integration and Application of Clinical Practice Guidelines for the Diagnosis of Idiopathic Pulmonary Fibrosis and Fibrotic Hypersensitivity Pneumonitis

Daniel-Costin Marinescu, MD; Ganesh Raghu, MD; Martine Remy-Jardin, MD; William D. Travis, MD;
Ayodeji Adegunsoye, MD; Mary Beth Beasley, MD; Jonathan H. Chung, MD; Andrew Churg, MD; Vincent Cottin, MD;
Ryoko Egashira, MD; Evans R. Fernández Pérez, MD; Yoshikazu Inoue, MD; Kerri A. Johannson, MD;
Ella A. Kazerooni, MD; Yet H. Khor, MD; David A. Lynch, MD; Nestor L. Müller, MD; Jeffrey L. Myers, MD;
Andrew G. Nicholson, MD; Sujeet Rajan, MD; Ryoko Saito-Koyama, MD; Lauren Troy, MD; Simon L. F. Walsh, MD;
Athol U. Wells, MD; Marlies S. Wijsenbeek, MD; Joanne L. Wright, MD; and Christopher J. Ryerson, MD

Favors fibrotic HP pattern

Distribution
- Could be variable, but:
  - Craniocaudal: Mid or upper lung zone is suggestive
  - Axial: Peribronchovascular involvement is suggestive

Fibrosis
- Reticular pattern and traction bronchiectasis
- Honeycombing may be present but does not predominate

AND

Presence of signs of small airways disease

Alternative to UIP & Alternative to fHP

Consider non-IPF & non-fHP diagnoses, including:
- Sarcoidosis
- Silicosis
- PPFE
- Other

Favors UIP pattern

Distribution
- Craniocaudal: Basal predominant, includes costophrenic angles
- Axial: Subpleural predominant

Fibrosis
- Reticular pattern and traction bronchiectasis
- Ground glass may be present, but is

AND

Absence of signs of small airways disease

High confidence
Honeycombing present

Small airways signs

Moderate confidence
- Hypoattenuating lobules on inspiratory imaging with gas trapping on expiratory imaging
- Well-demarcated preserved lobules with intervening diffuse ground glass opacities

High confidence
- Three-density sign
- Profuse poorly defined ground glass centrilobular nodules

Radiologic pattern: **UIP**

Likelihood of clinical diagnosis: **IPF**

Compatible with fHP

Typical of fHP

fHP

Additional major diagnostic considerations:

UIP radiologic pattern commonly suggests
UIP radiologic pattern in non-IPF
- CTD-ILD/IPAF: Exuberant honeycombing sign, straight-edge sign, dilated esophagus
- fHP
- Asbestosis: Bilateral pleural plaques

Prevalence	Guidelines	Accuracy (%)	[1]NPV(%)	[2]PPV(%)
Low (10%)	ATS/JRS/ ALAT	92.3	96	60.7
	ACCP	87.6	96.9	43
High (50%)	ATS/JRS/ ALAT	79.7	72.6	93.3
	ACCP	81.7	77.7	87.1

Table 4. Comparison of diagnostic performance accounting for prevalence.

[1]Negative predictive prevalence

[2]Positive predictive prevalence

Under peer review currently. Unpublished date from UCM.

Notable Changes to HP Imaging pre 2020

- First, HP imaging patterns are separated into two main patterns of fibrotic and non-fibrotic rather than the previous three-tier system (acute, subacute, chronic)

Notable Changes to HP Imaging pre 2020

- Confidence of CT patterns is essential (as you will soon see): "Typical," "Compatible with," and "Indeterminate" in fibrotic disease

Notable Changes to HP Imaging pre 2020

- In non-fibrotic disease, only "Typical" and "Compatible with" are defined. "Indeterminate" too broad to define.

- Truly, HP can present with simple air-trapping or even be near-normal on CT in NF HP.

Notable Changes to HP Imaging pre 2020

- "Three-density sign" was coined to replace "headcheese sign." Though used often in the US, it is not commonly used worldwide.
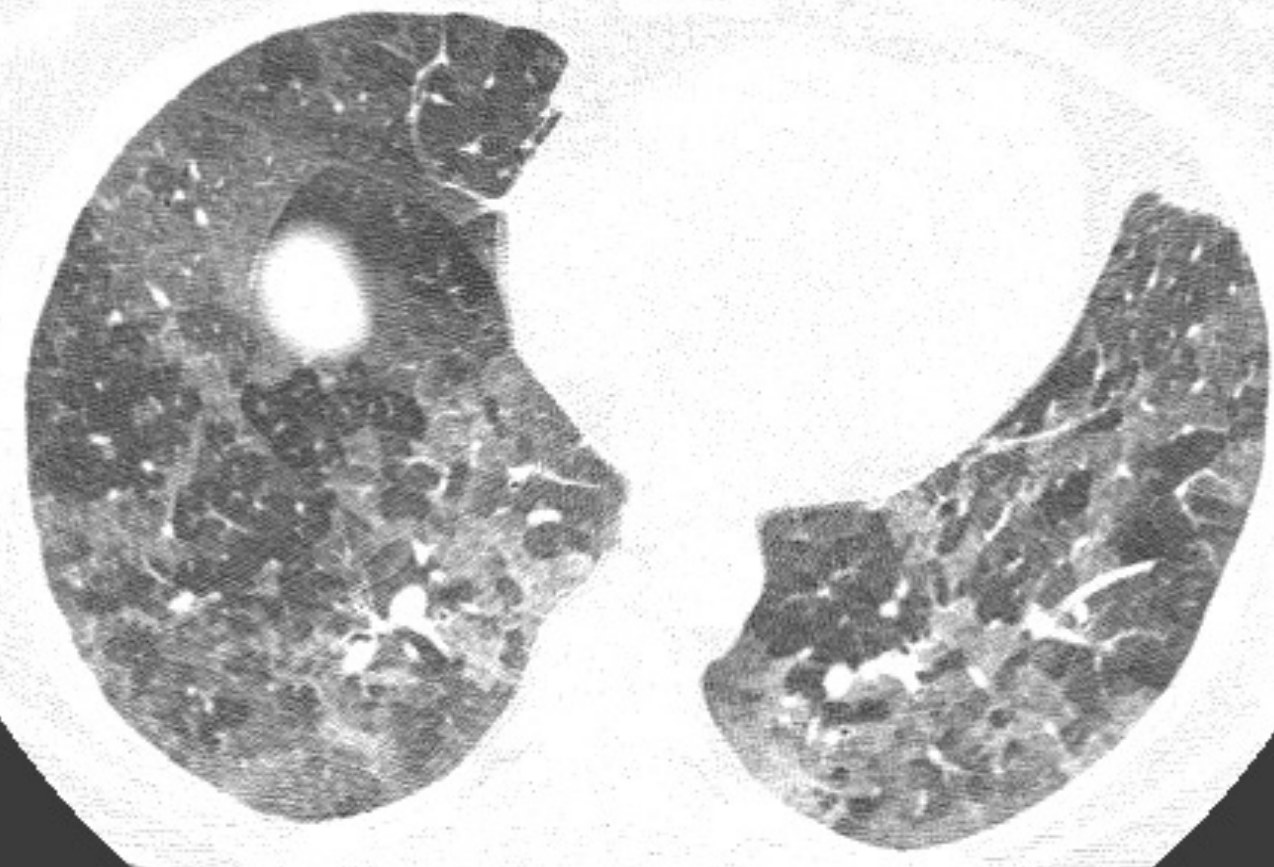
Imaging Patterns

Imaging of NF HP

- Non-fibrotic: Almost always diffuse distribution (70-90%)
  - Ground-glass opacity (GGO): >90%
  - Centrilobluar nodularity (almost always of GGO): 50%
  - Mosaic attenuation/air-trapping (headcheese sign): 80%
  - Highest likelihood of diagnosing HP based purely on imaging pattern.

1: Chung JH, Montner SM, Adegunsoye A, Oldham JM, Husain AN, Vij R, Noth I, Strek ME. Eur Radiol. 2017 Jul 7.
2: Chung JH, Zhan X, Cao M, Koelsch TL, Gomez DC, Brown KK, Lynch DA, Russell G, Fernández Pérez ER. Ann Am Thorac Soc. 2017 May 17.
3: Magee AL, Montner SM, Husain A, Adegunsoye A, Vij R, Chung JH. Radiol Clin North Am. 2016 Nov;54(6):1033-1046.

Table 5. Chest HRCT Scan Features of the Nonfibrotic HP Pattern

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a*) at least one HRCT abnormality indicative of parenchymal infiltration and *b*) at least one HRCT abnormality indicative of small airway disease, both in a diffuse distribution	"Compatible-with-HP" patterns are nonspecific patterns that have been described in HP	N/A
Relevant radiological findings	HRCT abnormalities indicative of parenchymal infiltration: • GGOs • Mosaic attenuation* HRCT abnormalities indicative of small airway disease: • Ill-defined, centrilobular nodules • Air trapping Distribution of parenchymal abnormalities: • Craniocaudal: diffuse (with or without some basal sparing) • Axial: diffuse	Parenchymal abnormalities: • Uniform and subtle GGOs • Airspace consolidation • Lung cysts Distribution of parenchymal abnormalities: • Craniocaudal: diffuse (variant: lower lobe predominance) • Axial: diffuse (variant: peribronchovascular)	N/A

Definition of abbreviations: GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; N/A = not applicable.
*Mosaic attenuation corresponding to parenchymal infiltration is created by GGOs adjacent to normal-appearing lung.

Imaging Patterns

Typical Non-fibrotic HP

1. At least one HRCT abnormality indicative of parenchymal infiltration: GGO or mosaic attenuation
2. And at least one HRCT abnormality indicative of small airway disease: CLO nodules or air-trapping
3. Both in a diffuse distribution

TABLE 4] Diagnostic CT Categories of Nonfibrotic HP Based on CT Patterns

HRCT	Typical Nonfibrotic HP	Compatible With Nonfibrotic HP
Features	Any of the following: • Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones • Inspiratory mosaic attenuation with three-density sign • Inspiratory mosaic attenuation and air-trapping associated with centrilobular nodules ***And*** • Lack of features suggesting an alternative diagnosis	Any of the following: • Centrilobular nodules of ground-glass attenuation that are not profuse or diffuse, and not associated with mosaic attenuation or lobular air-trapping • Patchy or diffuse ground-glass opacity • Mosaic attenuation and lobular air-trapping without centrilobular nodules or ground-glass abnormality ***And*** • Lack of features suggesting an alternative diagnosis

In a nonsmoker, the presence of diffuse, profuse, poorly defined ground-glass centrilobular nodules is highly suggestive of the diagnosis of hypersensitivity pneumonitis (HP); similar findings may occasionally occur, for example in infections, pulmonary hemorrhage, metastatic pulmonary calcification, or severe Group 1 pulmonary hypertension, but the clinical context will usually identify these rare causes. The distribution alone is not pathognomonic of HP. HRCT = high-resolution CT.

Imaging Patterns

Main difference between ATS and ACCP:

1. No distribution requirement in ACCP
2. Much more weight given to CLO nodularity and three density sign in ACCP
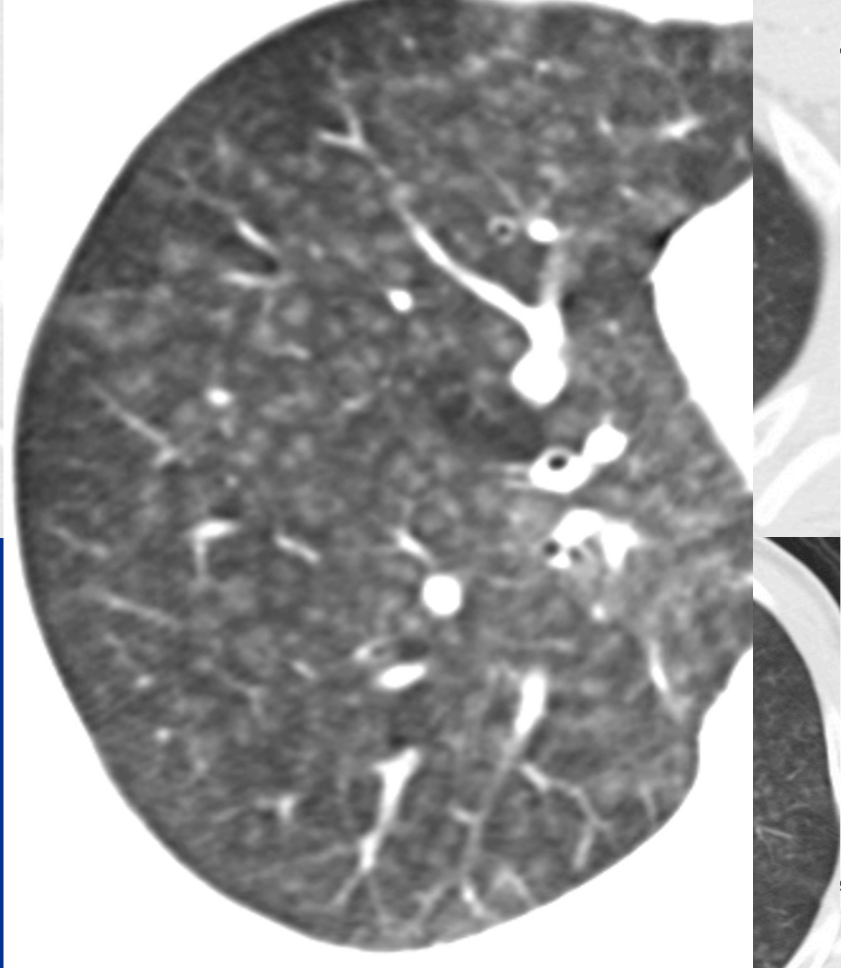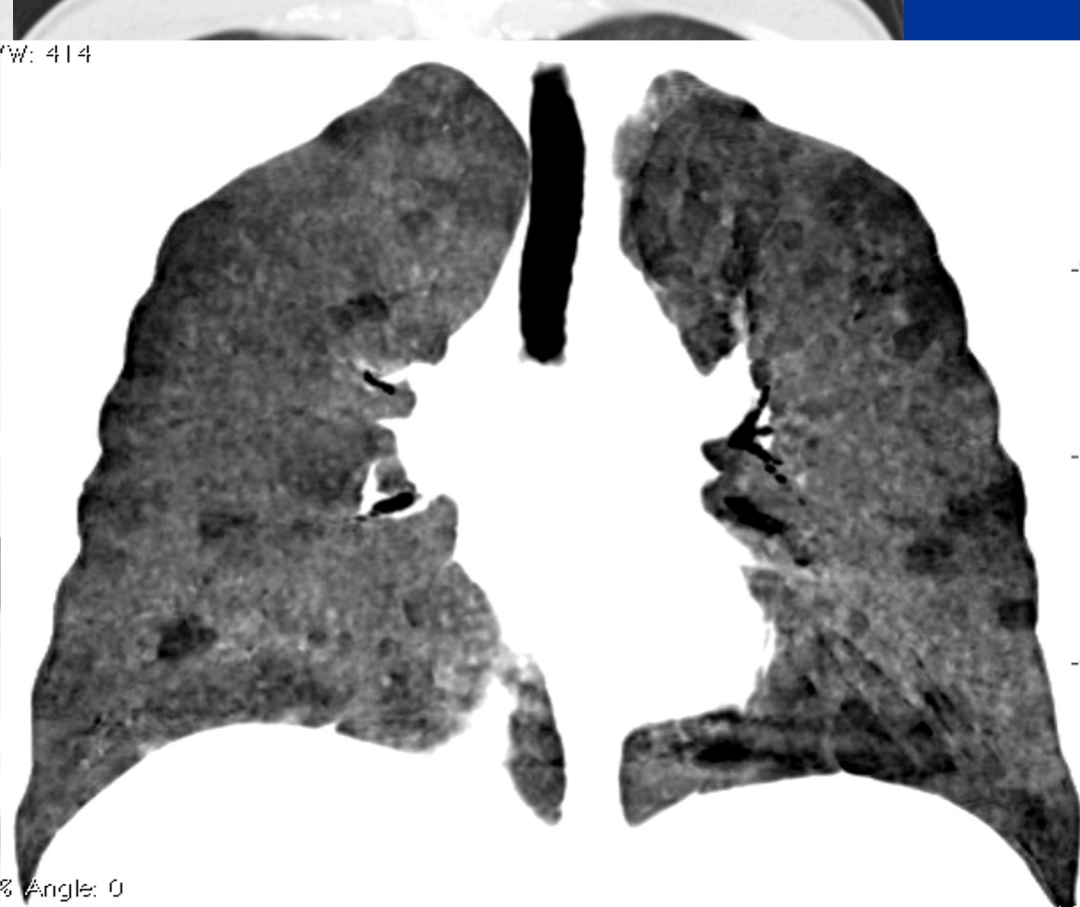
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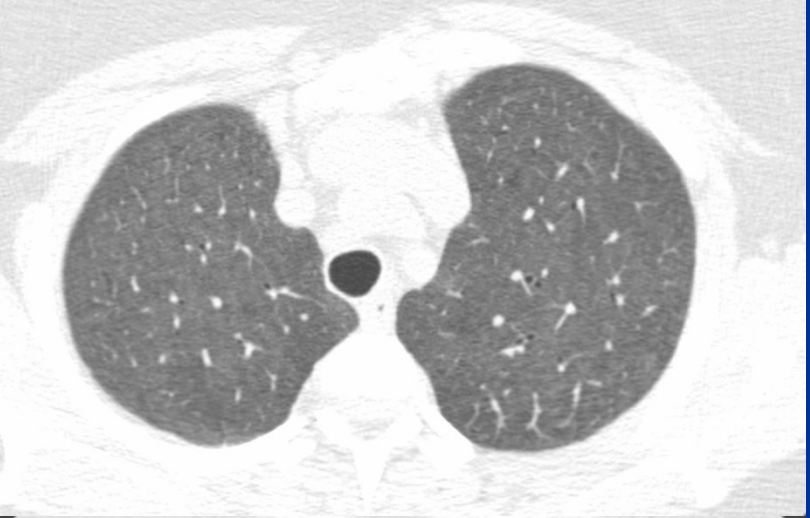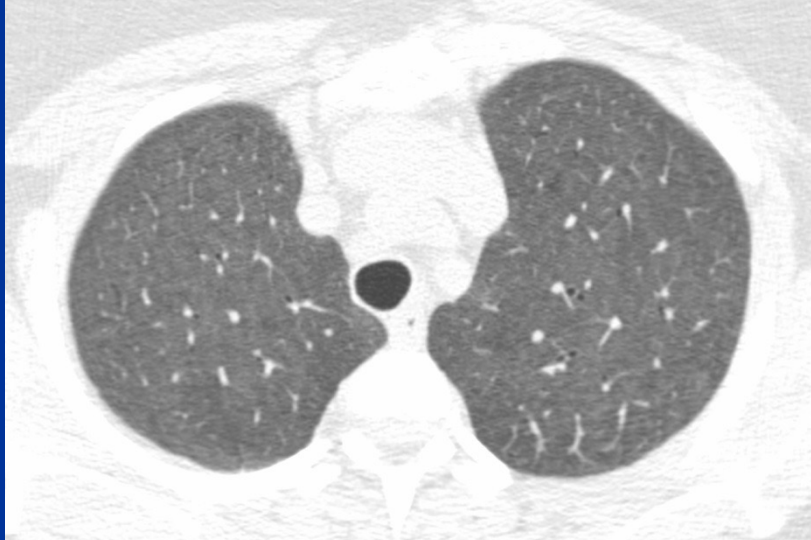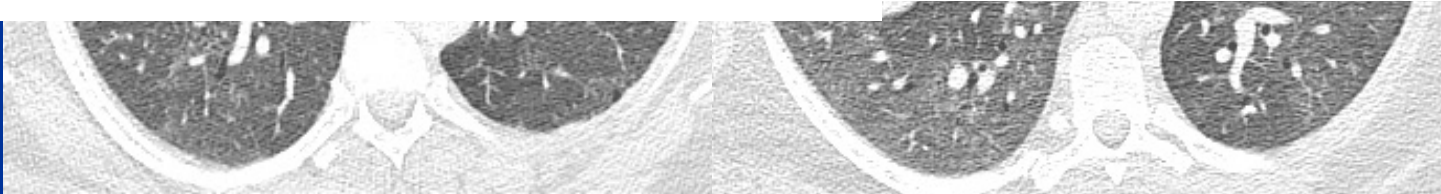
Imaging Patterns

- **Fibrotic HP imaging**
- Distribution: more variable
  - Slight majority lower and peripheral
  - However, upper lung distribution most helpful
    - Different from UIP and NSIP (usually basilar)
      Silva CI, Müller NL, Lynch DA, et al. Radiology. 2008 Jan;246(1):288-97.
  - Findings of pulmonary fibrosis
  - Mosaic attenuation/air-trapping less common (40-60%)
  - Lower likelihood of diagnosing HP based purely on imaging pattern compared to non-fibrotic disease (45-65%); often mimics UIP pattern in 25-35% of cases.

1: Chung JH, Montner SM, Adegunsoye A, Oldham JM, Husain AN, Vij R, Noth I, Strek ME. Eur Radiol. 2017 Jul 7.
2: Chung JH, Zhan X, Cao M, Koelsch TL, Gomez DC, Brown KK, Lynch DA, Russell G, Fernández Pérez ER. Ann Am Thorac Soc. 2017 May 17.
3: Magee AL, Montner SM, Husain A, Adegunsoye A, Vij R, Chung JH. Radiol Clin North Am. 2016 Nov;54(6):1033-1046.

Table 6. Chest HRCT Scan Features of the Fibrotic HP Pattern

HRCT Pattern	Typical HP	Compatible with HP	Indeterminate for HP
Description	The "typical HP" pattern is suggestive of a diagnosis of HP. It requires *a)* an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b)* at least one abnormality that is indicative of small airway disease	"Compatible-with-HP" patterns exist when the HRCT pattern and/or distribution of lung fibrosis varies from that of the typical HP pattern; the variant fibrosis should be accompanied by signs of small airway disease	The "indeterminate-for-HP" pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined, centrilobular nodules and/or GGOs • Mosaic attenuation, three-density pattern,* and/or air trapping (*often in a lobular distribution*)	Variant patterns of lung fibrosis: • UIP pattern: basal and subpleural distribution of honeycombing with/without traction bronchiectasis (*per 2018 diagnosis of IPF guidelines* [20]) • Extensive GGOs with superimposed subtle features of lung fibrosis Variant (predominant) distributions of lung fibrosis: • Axial: peribronchovascular, subpleural areas • Craniocaudal: upper lung zones HRCT abnormalities indicative of small airway disease: • Ill-defined centrilobular nodules, or • Three-density pattern* and/or air trapping	Lone patterns (i.e., not accompanied by other findings suggestive of HP) of: • UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Probable UIP pattern (*as per 2018 IPF diagnosis guidelines* [20]) • Indeterminate pattern for UIP (*as per 2018 IPF diagnosis guidelines* [20]) • Fibrotic NSIP pattern • Organizing pneumonia–like pattern • Truly indeterminate HRCT pattern

Definition of abbreviations: GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Rarely, fibrotic HP may be seen *1)* as a component of combined pulmonary fibrosis and emphysema or pleuroparenchymal fibroelastosis with emphysema, *2)* as a pure emphysematous form of HP, or *3)* in acute exacerbation.

*The three-density pattern was formerly called the "headcheese sign." It is described in detail in Table 4.

Imaging Patterns

Typical Fibrotic HP

1. Lung fibrosis on HRCT
2. At least one abnormality indicative of small airway disease: Ill-defined CLO nodules (often GGO), mosaic attenuation, three-density pattern, or air trapping
3. Typical distribution of fibrotic HP: diffuse (random, both planes), mid lung, or basal sparing (mid/upper lung)

**TABLE 5]** Diagnostic CT Categories of Fibrotic HP Based on CT Patterns

HRCT	Typical Fibrotic HP	Compatible With Fibrotic HP	Indeterminate for Fibrotic HP
Features	CT signs of fibrosis with either of the following: • Profuse poorly defined centrilobular nodules of ground-glass opacity affecting all lung zones • Inspiratory mosaic attenuation with three-density sign **And** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis with any of the following: • Patchy or diffuse ground-glass opacity • Patchy, nonprofuse centrilobular nodules of ground-glass attenuation • Mosaic attenuation and lobular air-trapping that do not meet criteria for typical fibrotic HP **And** • Lack of features suggesting an alternative diagnosis	CT signs of fibrosis without other features suggestive of HP

CT signs of fibrosis include any of the following: reticular or ground-glass abnormality with traction bronchiectasis or bronchiolectasis; lobar volume loss; honeycombing. The distribution of fibrotic hypersensitivity pneumonitis (HP) is quite variable and often not diagnostically helpful. However, a mid-lung predominant distribution of fibrosis is suggestive of fibrotic HP, and an upper lobe predominance is much more common in fibrotic HP than in idiopathic pulmonary fibrosis. HRCT = high-resolution CT.

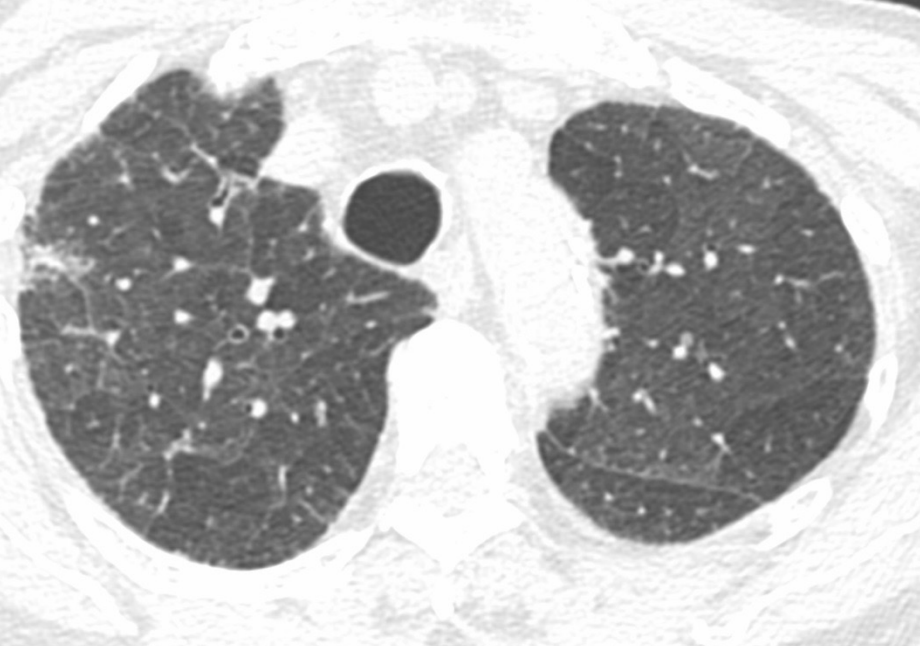# Imaging Patterns

Main difference between ATS and ACCP:

1. No distribution requirement in ACCP

2. Much more weight given to CLO nodularity and three density sign in ACCP
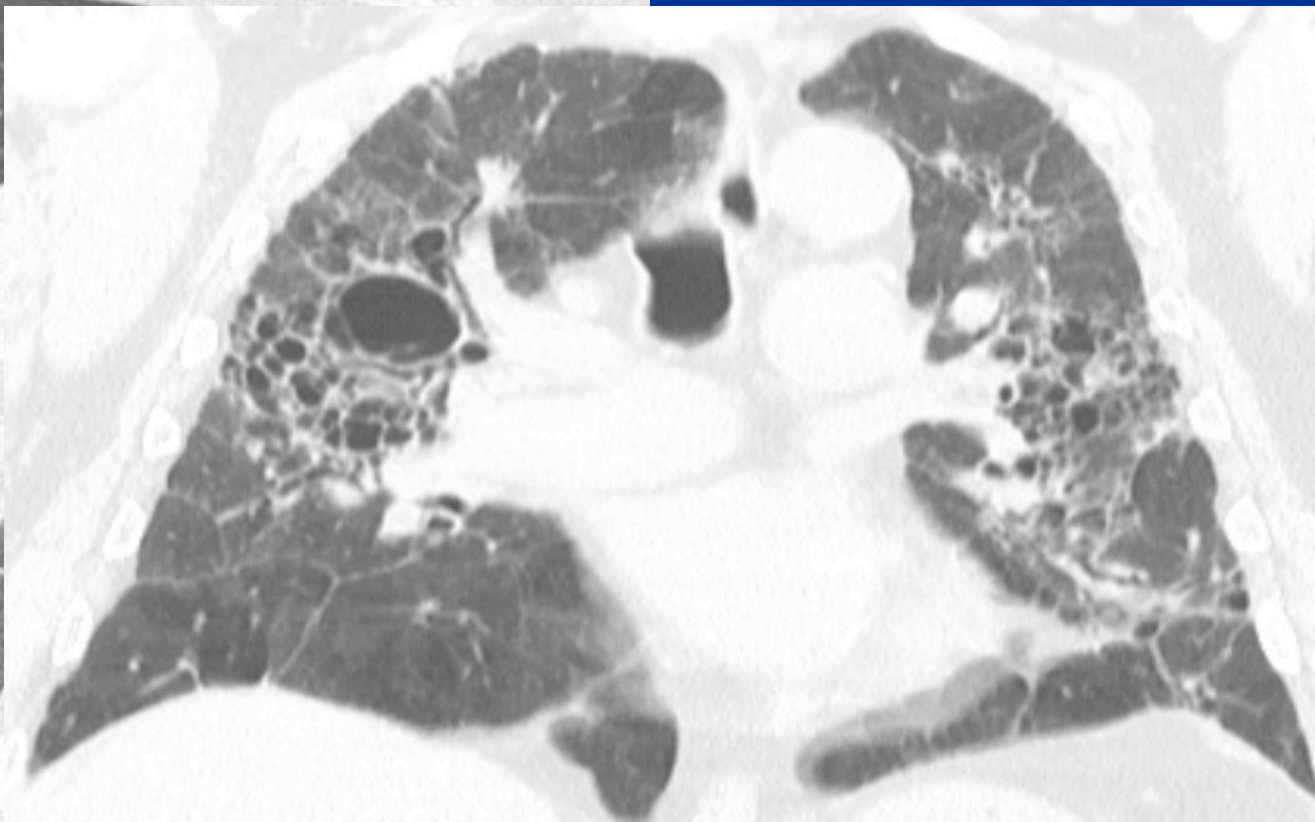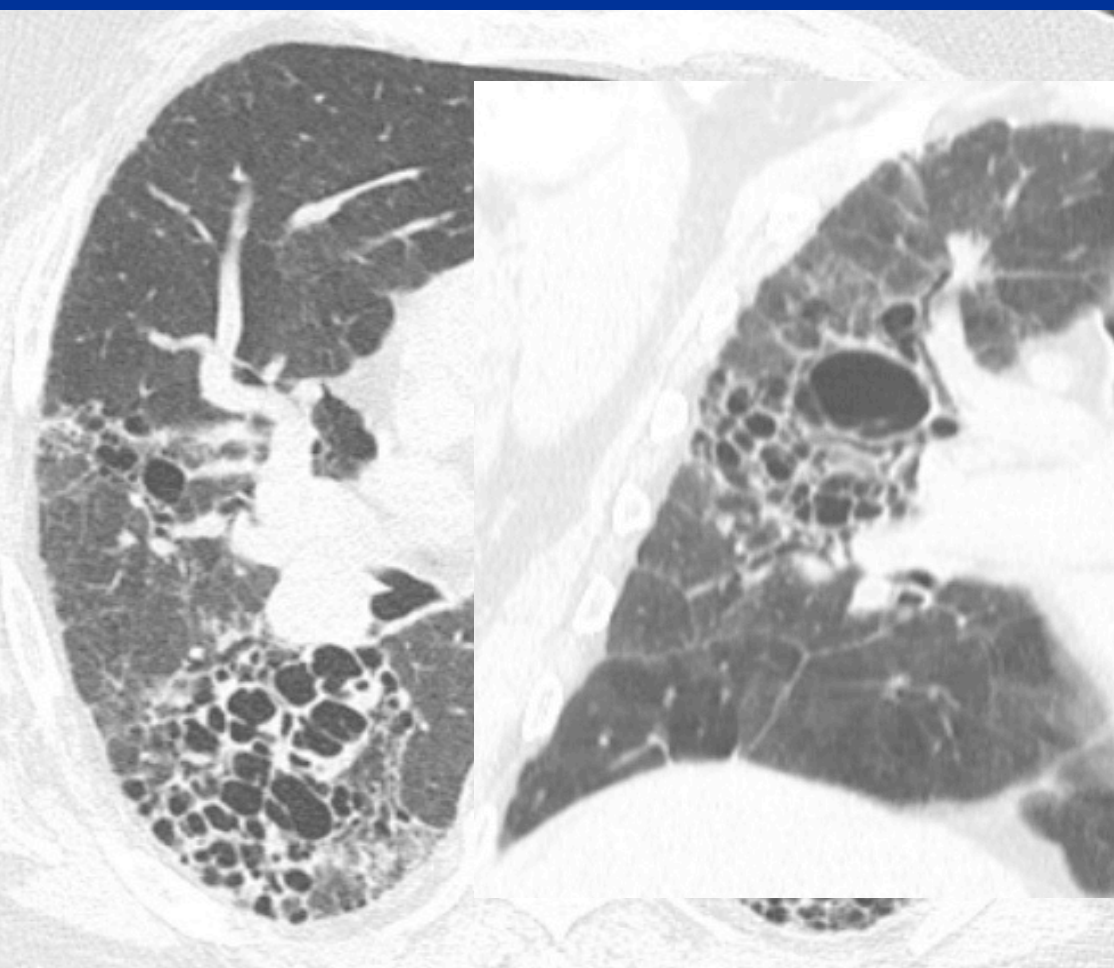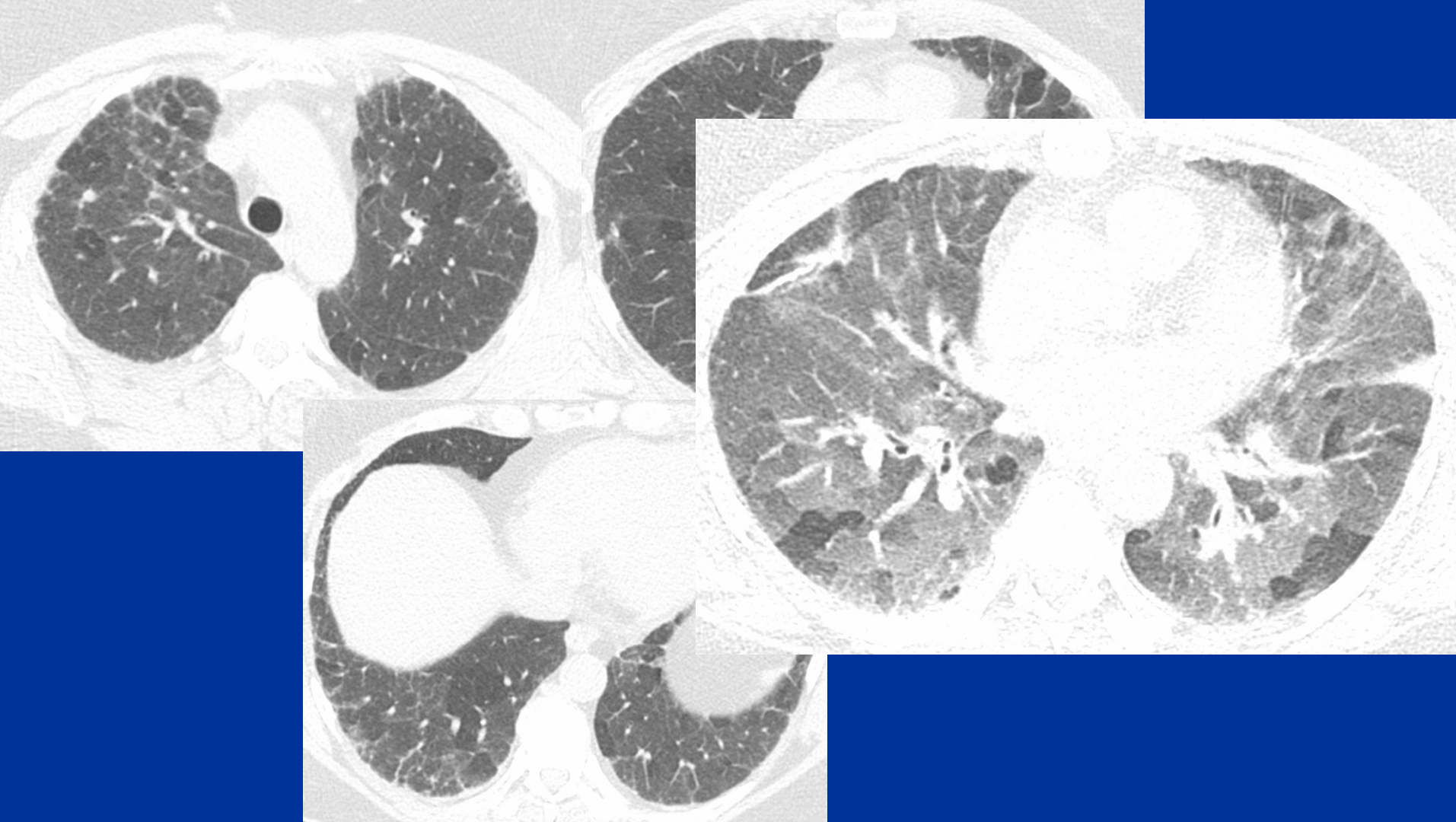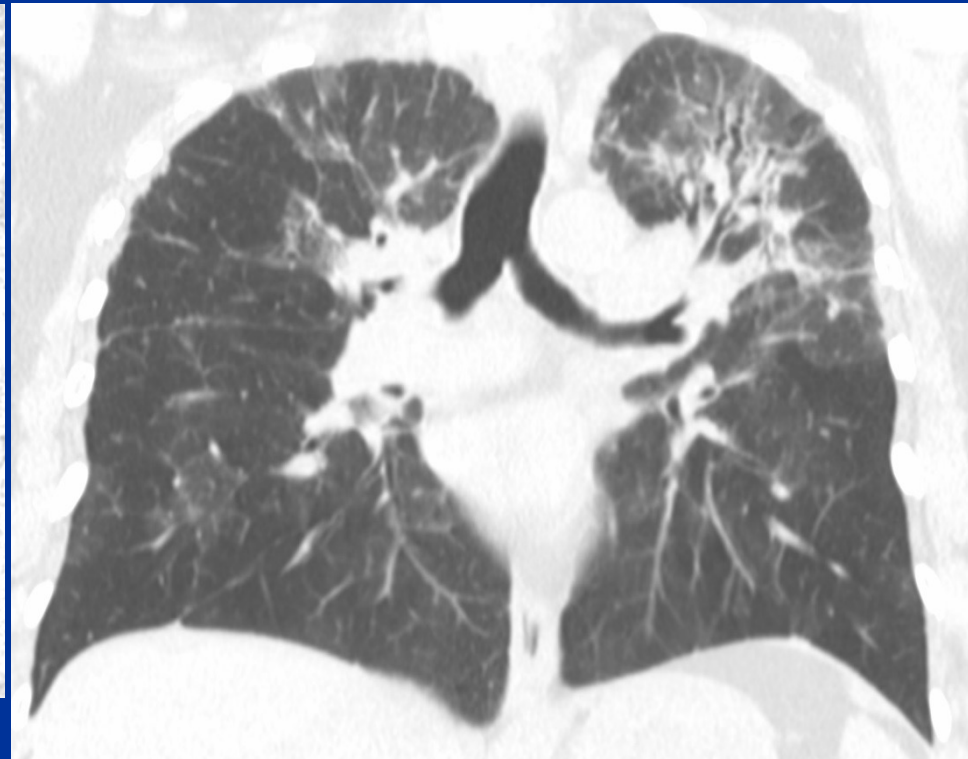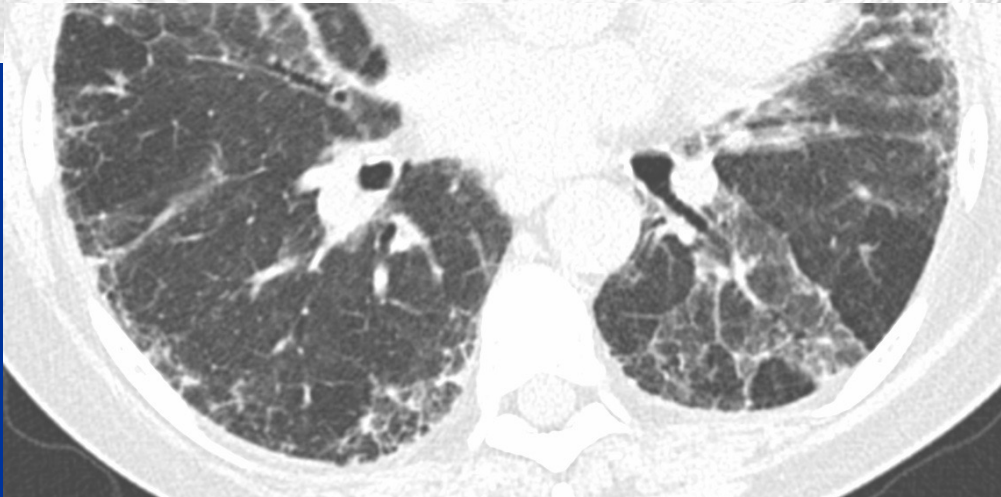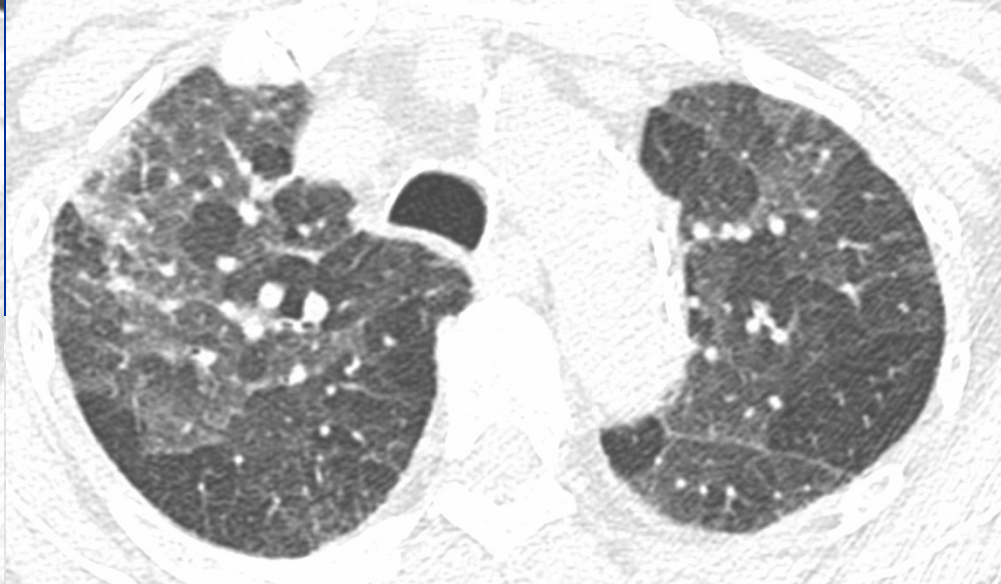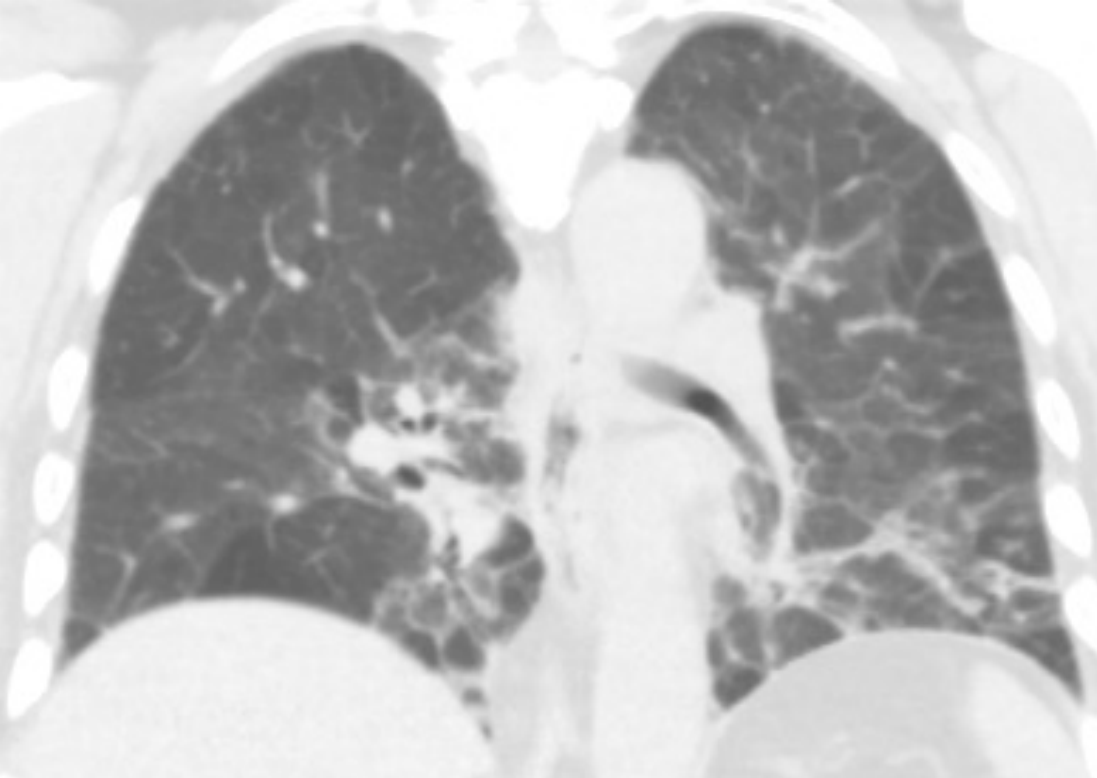
Summary

- New HP diagnostic guidelines
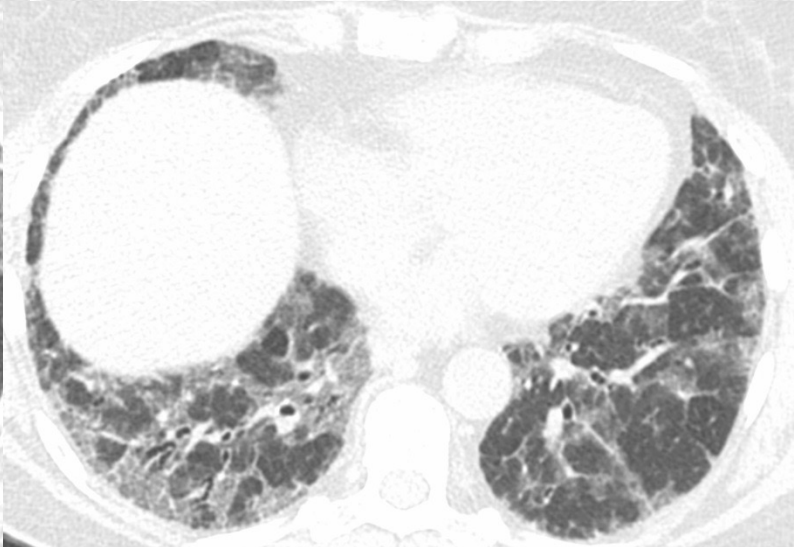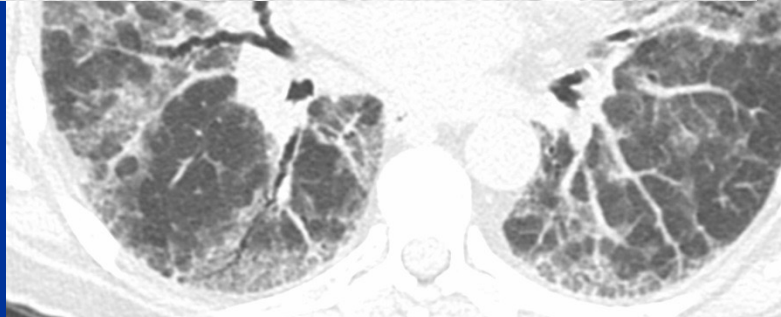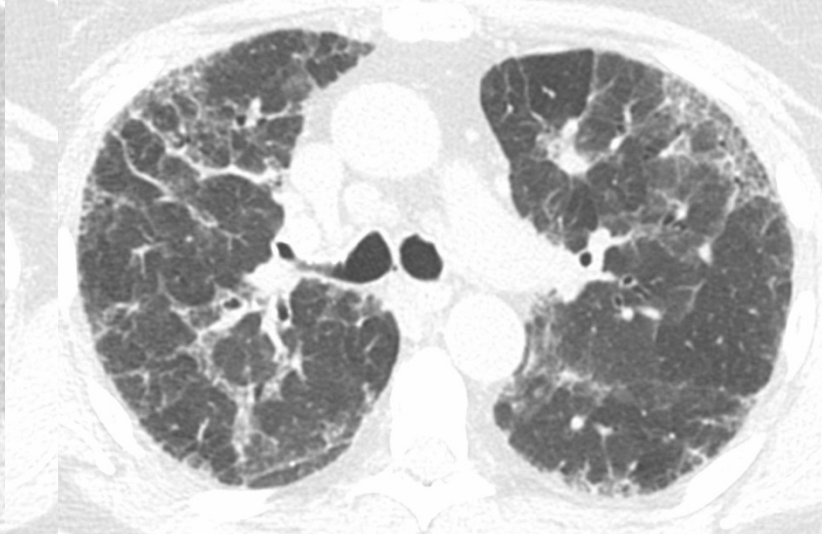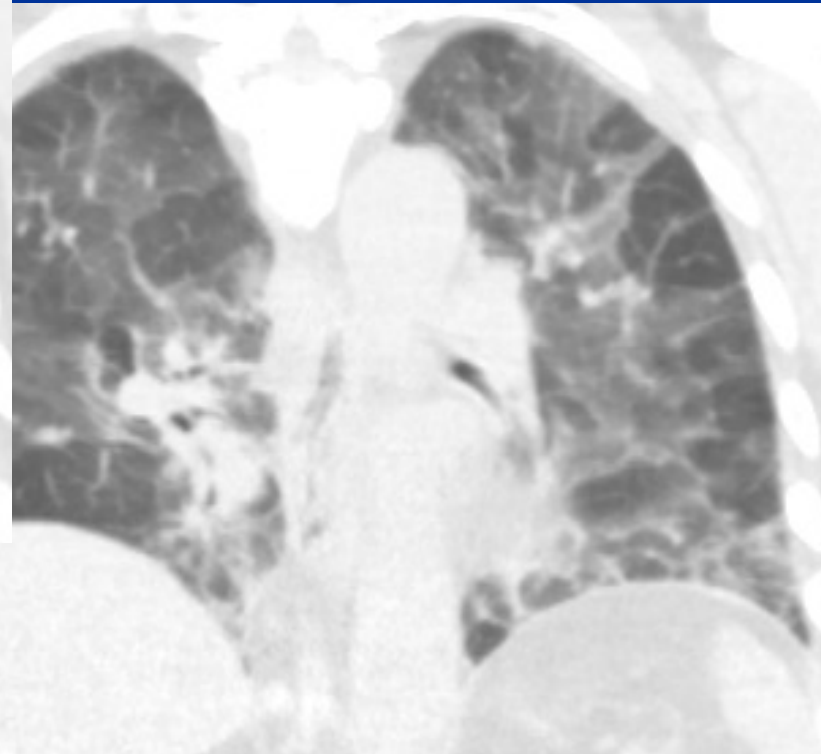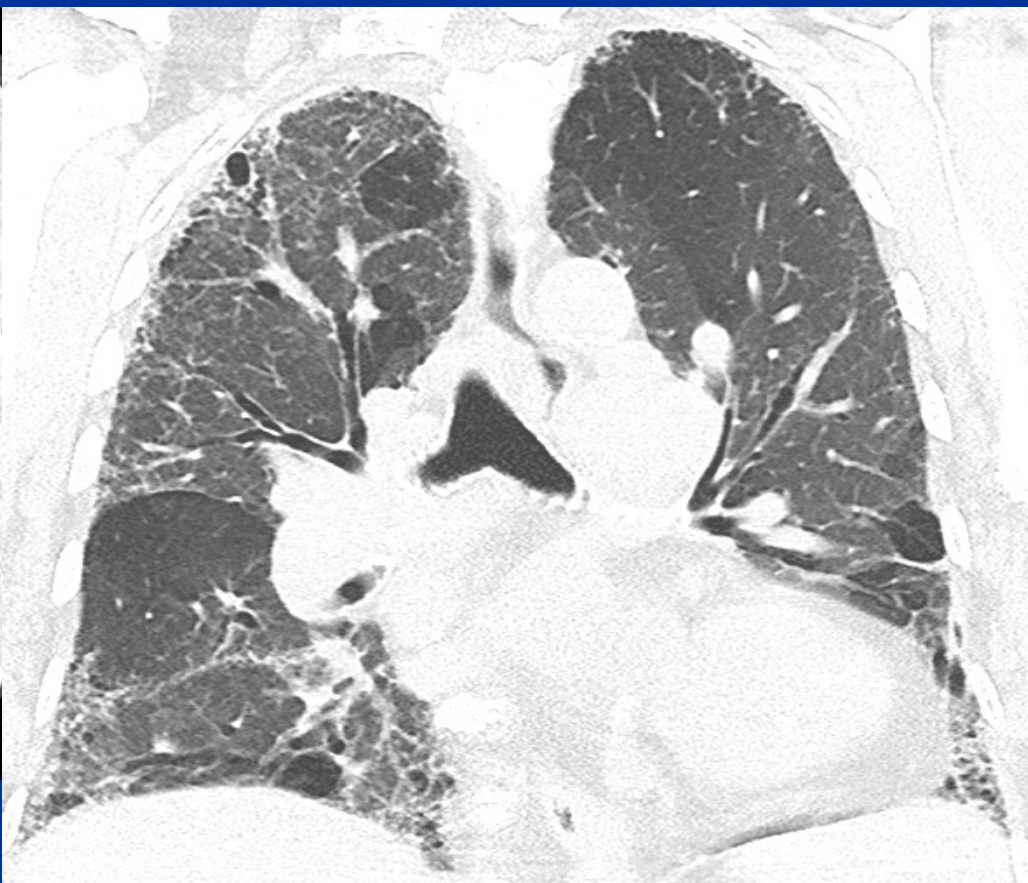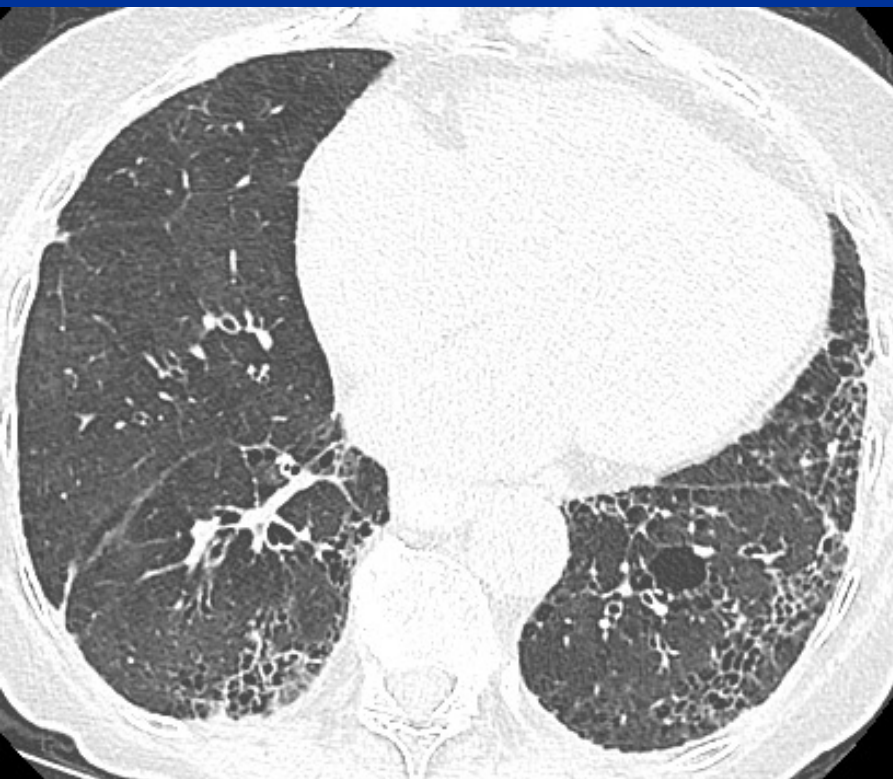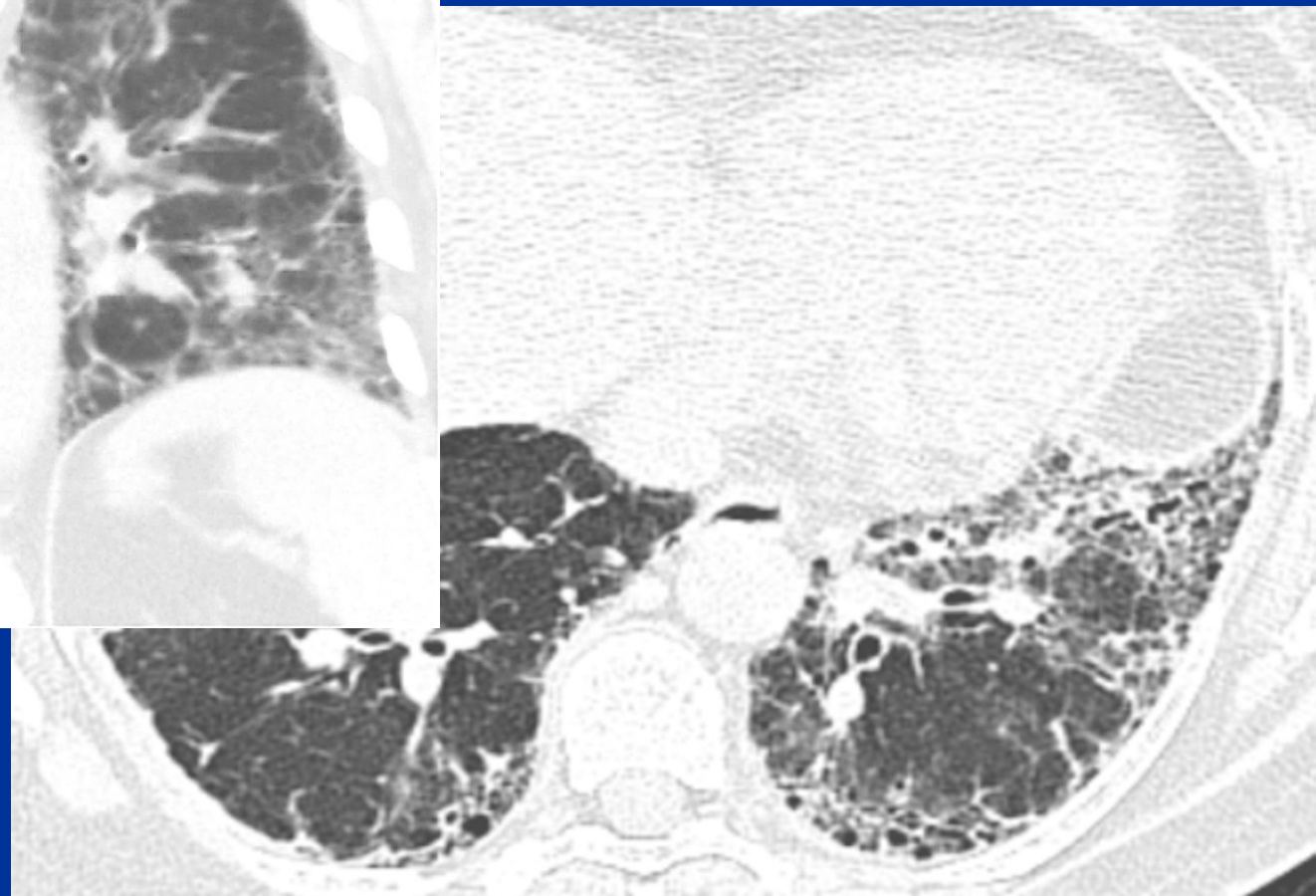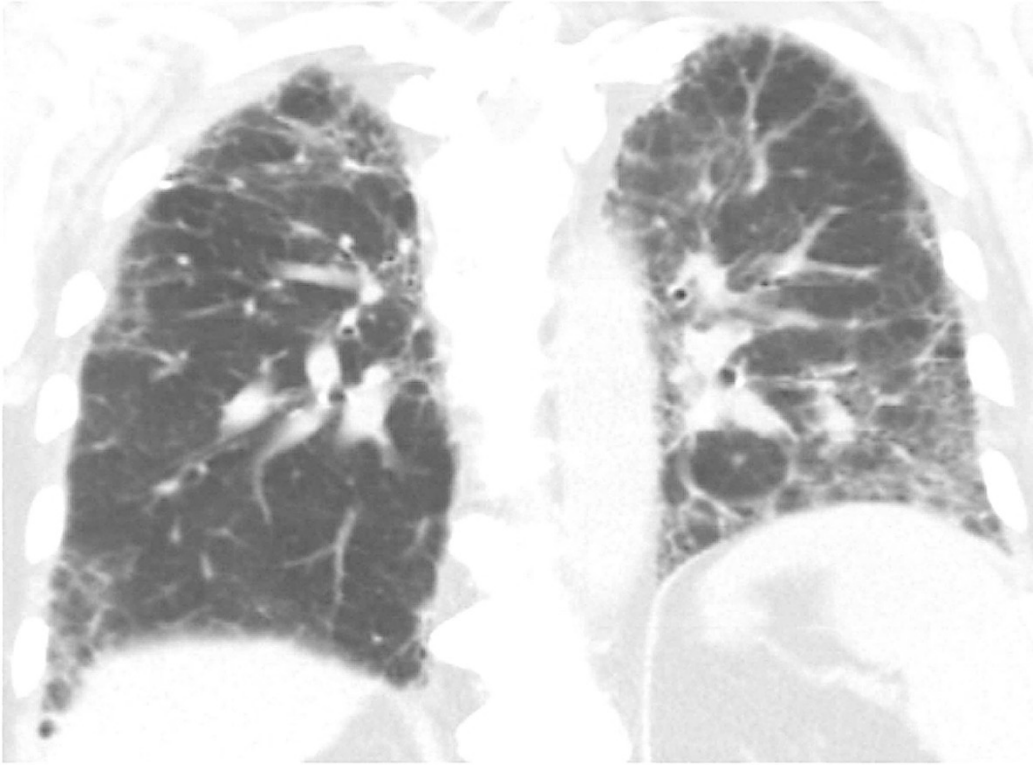 - Fibrotic vs Non-fibrotic
  - Level of confidence
  - "Three-density sign" (aka headcheese sign)
  - High confidence patterns combine lung infiltration and small airways disease +/- typical distribution.
  - ATS vs ACCP
    - ATS likely slightly more accurate in most western countries but ACCP simpler to employ

Thank You

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@jonherochung