ACUTE EXACERBATIONS OF PROGRESSIVE PULMONARY FIBROSIS

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What is Progressive Pulmonary Fibrosis?

What is Exacerbations?
How to diagnose AE
Epidemiology & Risk factors
Management
Prognosis

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WHAT IS “PROGRESSIVE PULMONARY FIBROSIS”?

- **New concept** in the field of ILD
- Following the approval of Nintedanib and Pirfenidone to treat IPF === Could it have an effect in other types of ILD?
- IPF progress in most cases to fibrosis
- Other individual types of ILD could be more heterogeneous
  - Good response to immunomodulatory or nonpharmacologic interventions
  - Progressive fibrosis **despite treatment**, as IPF
- Phenotype of progressive fibrosis : Why not to treat it regardless of the cause/diagnosis
- The concept **does not replace the initial clinical diagnosis** which stay as critical as ever to assigning initial therapy. It would complement or serve as a modifier of the initial diagnosis, **when the treatment is ineffective** and/or there is progressive fibrosis.

Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381:1718– 1727.

Definition of PPF

In a patient with ILD of known or unknown etiology other than IPF who has radiological evidence of pulmonary fibrosis, PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation*:

1 Worsening respiratory symptoms

2 Physiological evidence of disease progression (either of the following):
   a. Absolute decline in FVC ⩾5% predicted within 1 yr of follow-up
   b. Absolute decline in D_{LCO} (corrected for Hb) ⩾10% predicted within 1 yr of follow-up

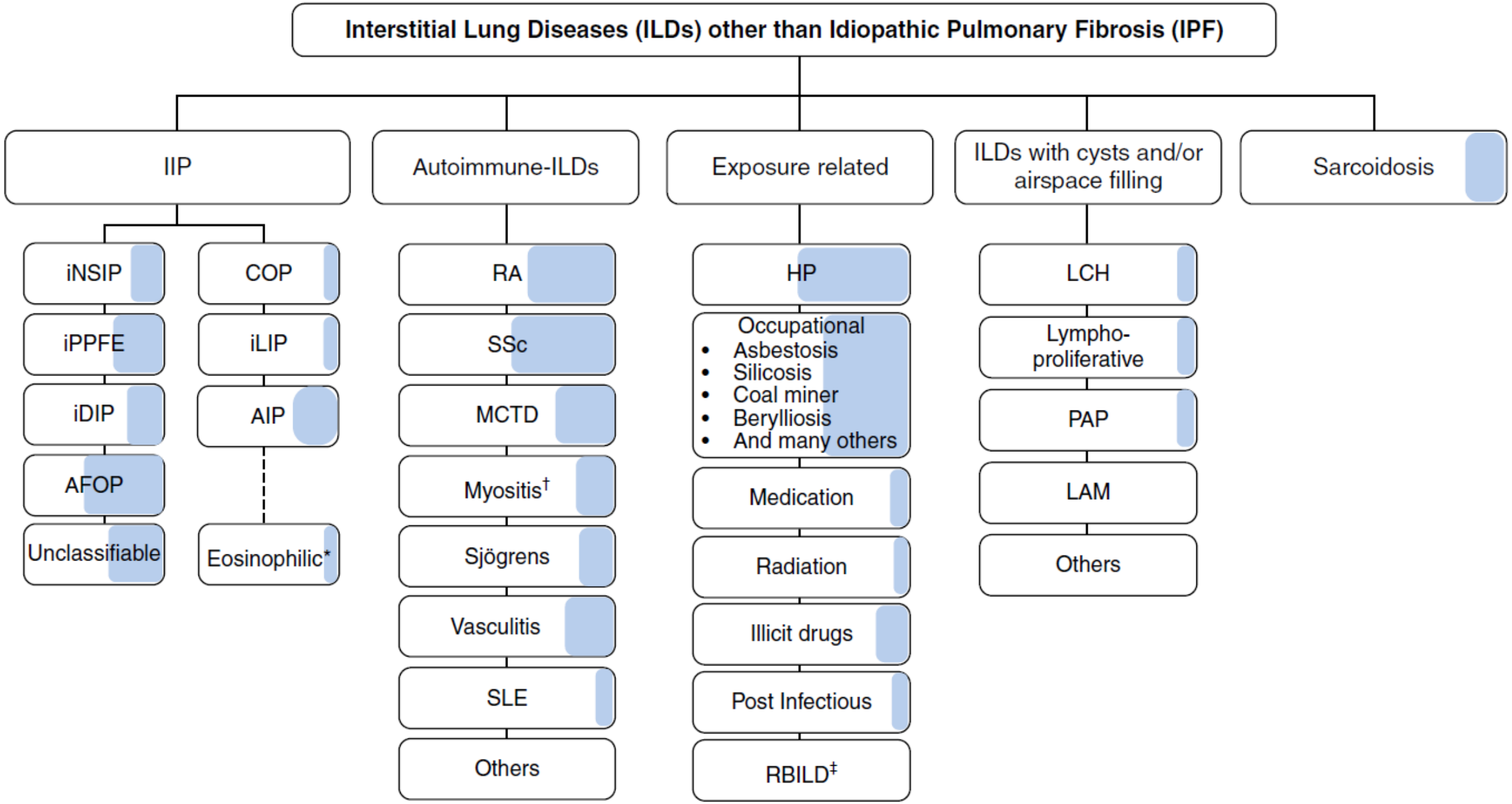
3 Radiological evidence of disease progression (one or more of the following):
   a. Increased extent or severity of traction bronchiectasis and bronchiolectasis
   b. New ground-glass opacity with traction bronchiectasis
   c. New fine reticulation
   d. Increased extent or increased coarseness of reticular abnormality
   e. New or increased honeycombing
   f. Increased lobar volume loss

Am J Respir Crit Care Med Vol 205, Iss 9, pp e18–e47, May 1, 2022

TABLE 2 Risk factors for the progression of non-idiopathic pulmonary fibrosis interstitial lung diseases (ILDs)

Risk factor	First author (year) [ref.]	Hazard ratio (95% CI)	p-value
General risk factors			
UIP	Flaherty (2019) [2]	1.53 (−0.68–3.74)	NA
BMI	Alakhras (2007) [19]	0.93 (0.89–0.97)	0.002
Oxygen desaturation during 6MWT[#]	Alfieri (2020) [20]	OR[¶] 8.7 (4.42–17.3)	NA
Disease			
Fibrotic hypersensitivity pneumonitis	Gimenez (2018) [21]		
Decline in FVC by ⩾10%	Gimenez (2018) [21]	4.13 (1.96–8.70)	0.005
Lower baseline FVC %	Gimenez (2018) [21]	1.03 (1.01–1.05)	0.003
Antigen identification	Gimenez (2018) [21]	0.18 (0.04–0.77)	0.021
MUC5B$^+$/*TLD*$^+$ (gene variants)	Ley (2019) [22]	3.52 (1.87–6.62)	0.00009
Rheumatoid arthritis-ILD	Zamora-Legoff (2017) [9]		
UIP *versus* NSIP	Zamora-Legoff (2017) [9]	3.29 (1.28–8.41)	0.013
High levels of CCP antibody/anti-CCP2 titres$^+$	Khan (2021) [23]	1.05 (1.01–1.10)	0.01
Smoking, 30 pack-years	Kronzer (2021) [24]	OR[¶] 6.06 (2.72–13.5)	NA
Fibrotic score on HRCT	Solomon (2016) [25]	1.02 (1.01–1.03)	0.0002
Extent of fibrosis on HRCT	Solomon (2016) [25]	1.12 (1.08–1.17)	<0.000006
Systemic sclerosis	Goh (2017) [26]		
Low baseline FVC <65% and low baseline D_{LCO} ⩽55%	Sánchez-Cano (2018) [27]; Hoffmann-Vold (2019) [28]	OR[¶] 1.02 (1.01–1.03)	<0.001
Decline in D_{LCO} >15%	Le Gouellec (2017) [29]	2.03 (1.25–3.29)	<0.005
Decline in K_{CO} >10%	Goh (2017) [26]	2.35 (1.40–3.95)	<0.001
Fibrotic score on HRCT	Ibrahim (2020) [30]	2.52 (1.16–5.49)	0.02
Extent of fibrosis on HRCT (HRCT extent 10–30% and FVC <70%)	Goh (2008) [31]	3.46 (2.19–5.46)	<0.0005

Rajan SK, Cottin V, Dhar R, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J 2023; 61: 2103187



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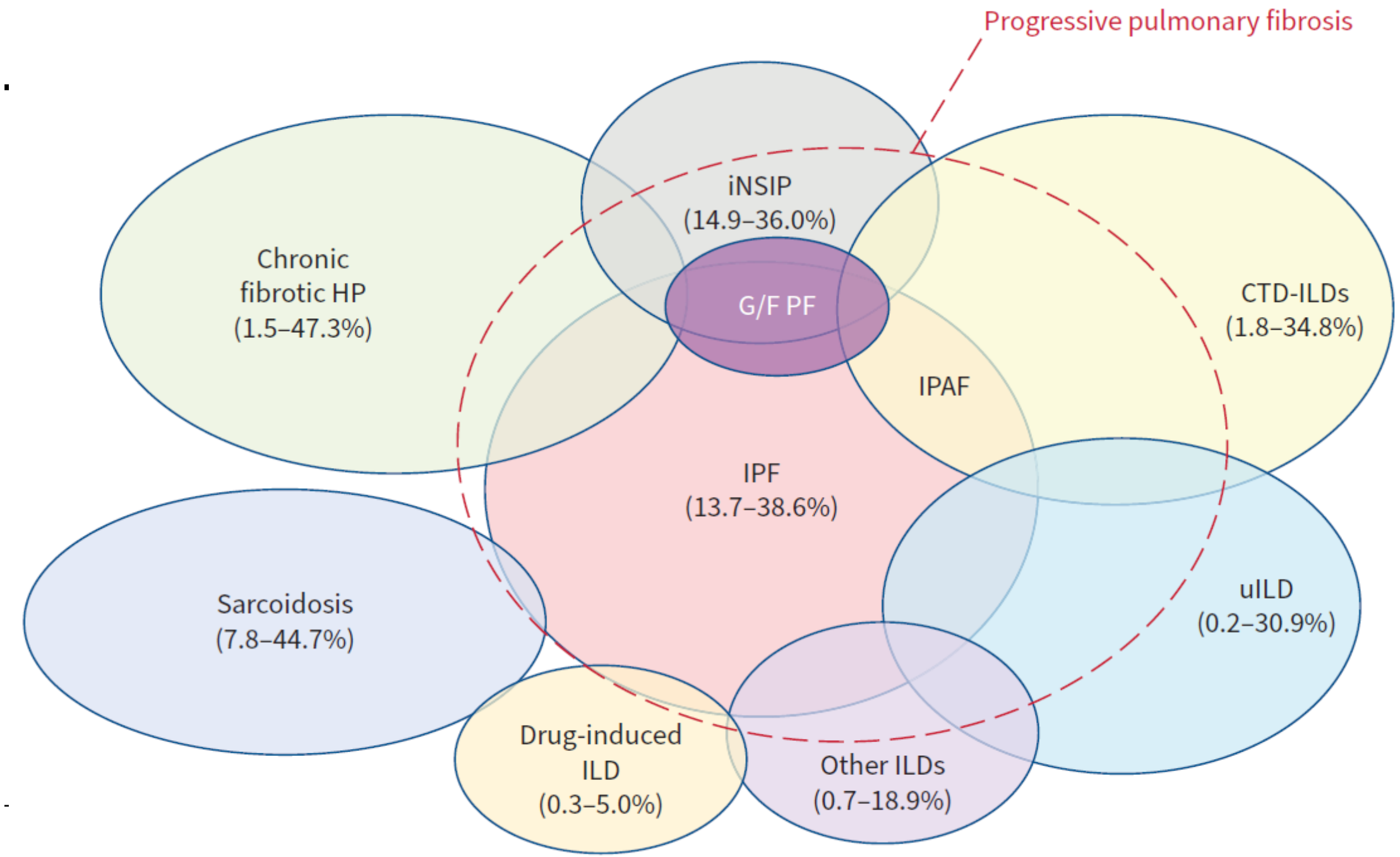

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WHAT ABOUT EXACERBATIONS?

Exacerbation of IPF
Acute, clinically significant deterioration characterized by evidence of new widespread alveolar abnormality

Exacerbation of non-IPF ILD
Acute, clinically significant deterioration characterized by evidence of new widespread alveolar abnormality

Respir Med. 2021 July ; 183: 106400. doi:10.1016/j.rmed.2021.106400

WHAT ABOUT EXACERBATIONS?

Diagnostic criteria

Exacerbation of IPF	Exacerbation of non-IPF ILD
Previous or concurrent dx of IPF	Previous or concurrent dx of a non-IPF fibrosing ILD
Acute worsening of dyspnea typically < 1 month duration	Acute worsening of dyspnea typically < 1 month duration
HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on UIP pattern	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a fibrosing ILD pattern (with or without honeycombing)
Deterioration not fully explained by cardiac failure or fluid overload	Deterioration not fully explained by cardiac failure or fluid overload

Respir Med. 2021 July ; 183: 106400. doi:10.1016/j.rmed.2021.106400

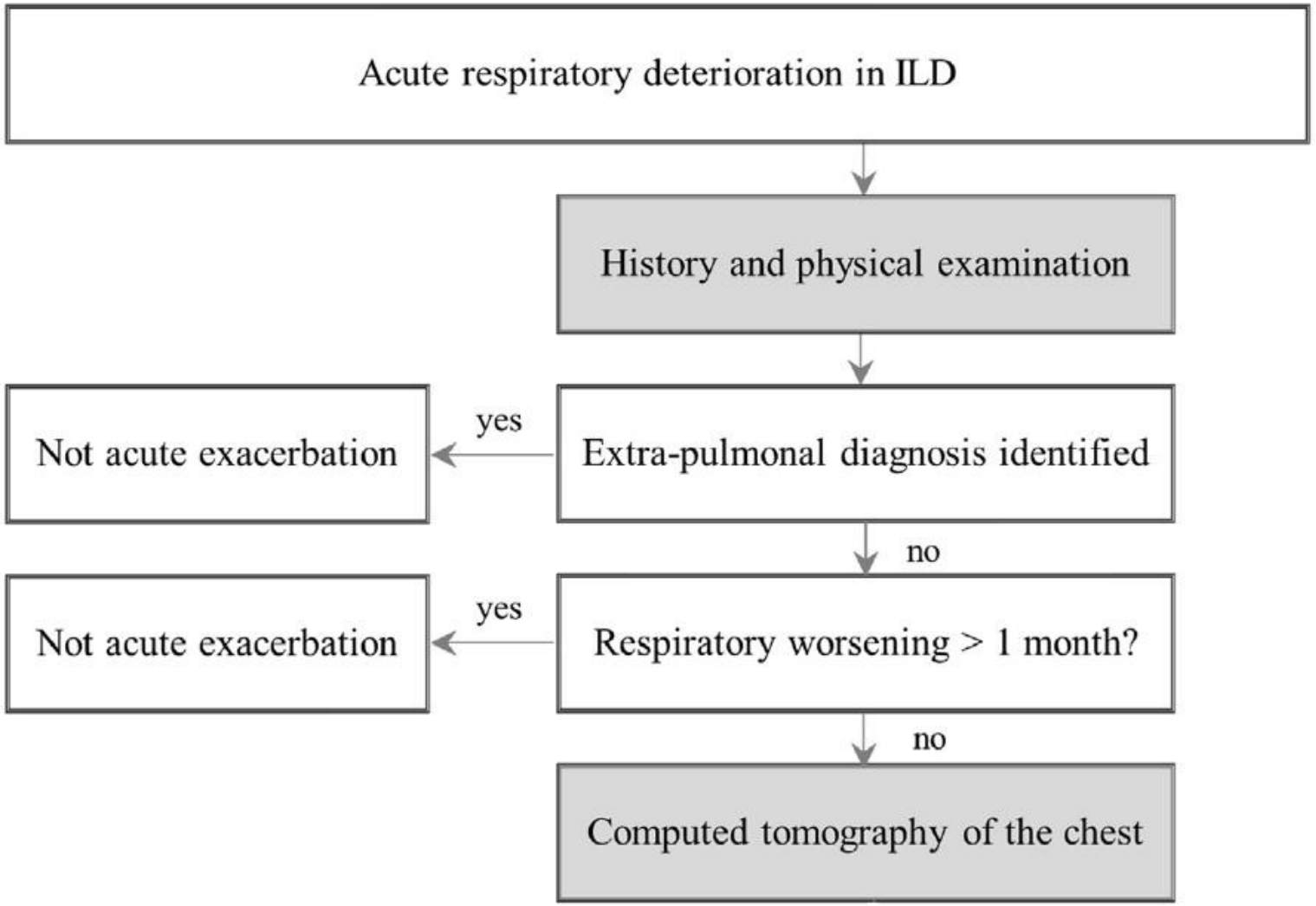
WHAT ABOUT EXACERBATIONS?

Most AE-ILDs are characterized by “Diffuse Alveolar Damage”

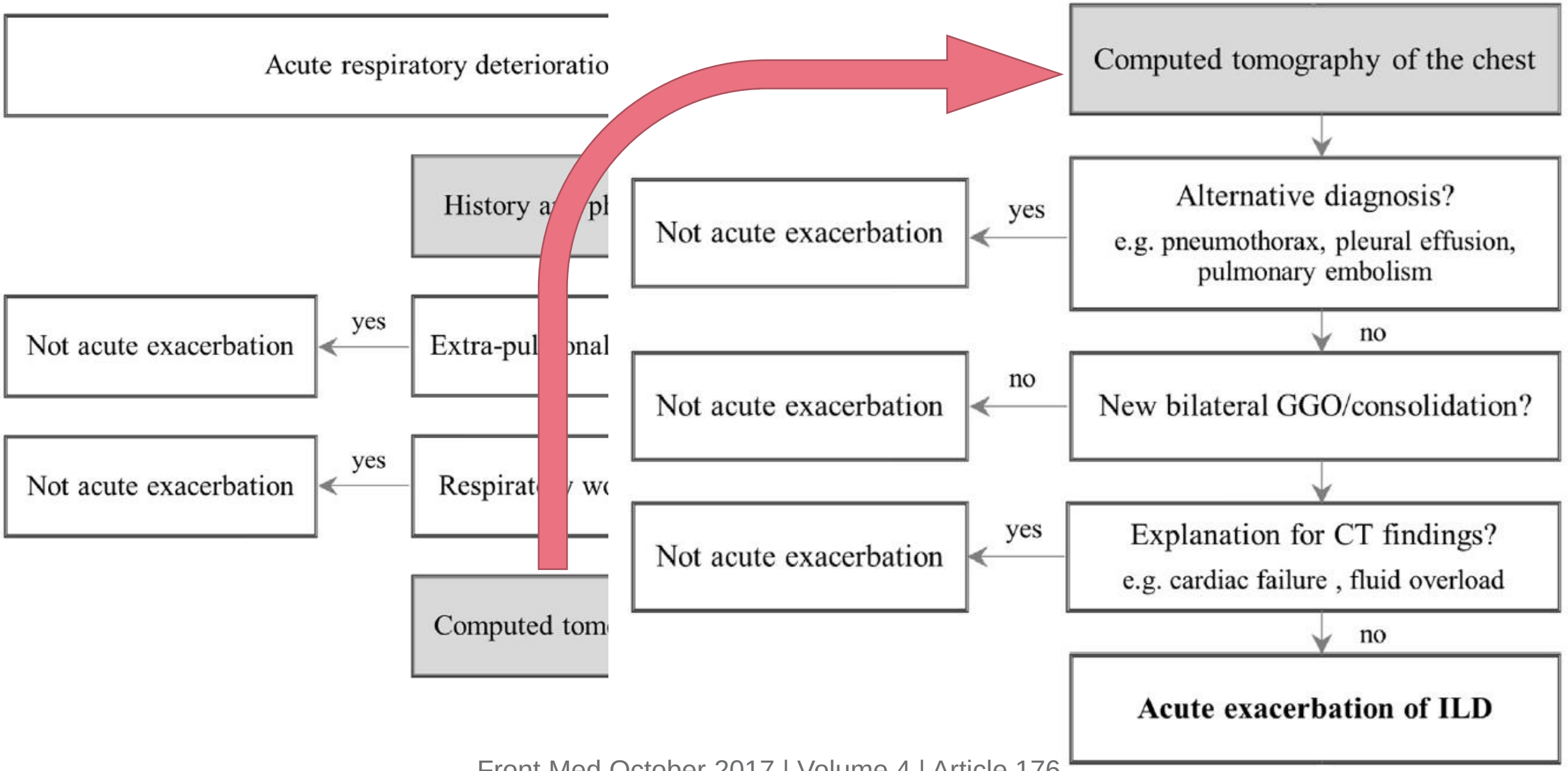
Other histological features : Organizing pneumonia
Alveolar haemorrhage
Unspecific inflammatory changes

In early stages, we have an interstitial oedema and hyaline membranes
Type II pneumocyte hyperplasia, fibroblast foci, squamous metaplasia and honeycombing have also been reported

HOW TO DIAGNOSE AN AE OF ILD-PPF?



HOW TO DIAGNOSE AN AE OF ILD-PPF?



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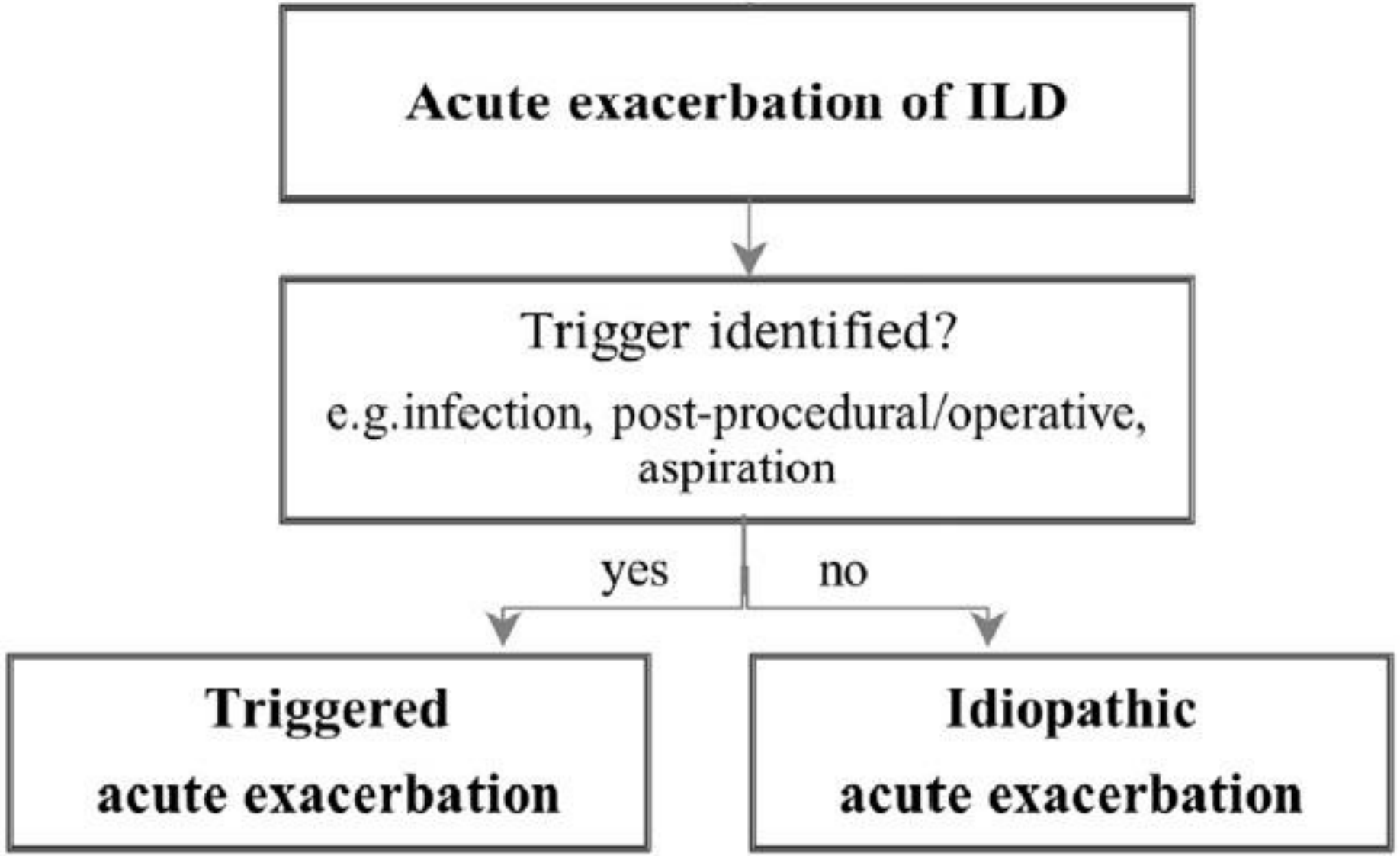

WHY AN ACUTE EXACERBATION?

The onset and development of an AE-ILD is **unpredictable**

It is uncertain whether an AE-ILD is triggered by

an **intrinsic factor** causing a progression of the underlying disease

and/or a response to an **external factor** (e.g., infection, aspiration, pulmonary emboli, mechanical stretch)

Little is understood regarding the triggers and pathogenic aspects of AE-ILDs

Nevertheless, same clinical, radiographic, and histologic features exist across exacerbations of **different ILD backgrounds**.

This suggest that acute exacerbations of various ILDs may lie on a **common pathologic spectrum** that reflects their clinical course.

Front Med October 2017 | Volume 4 | Article 176 / Respir Med. 2021 July ; 183: 106400. doi:10.1016/j.rmed.2021.106400

EPIDEMIOLOGY AND RISK FACTORS

Incidence of **IPF-AE** is higher in cohort studies than in randomized trials : 1.9 - 11.7 - 14.2 % per year.
Incidence of **non IPF-AE** more difficult to determine : 3.2 - 4.2 - 5.7 - 6.3% in one year.
In non IPF-AE younger / Males = Females

In the majority of studies : IPF patients have higher risk for AE than non-IPF ILD

Risk factors for AE in IPF
Low FVC, low DLCO, baseline hypoxemia
Severe disease - Advanced age - Never smoking - Higher BMI - Recent worsening

Risk factors for AE in non IPF ILD (Chronic HP and CTD-associated ILD)
UIP pattern / RA – Advanced age

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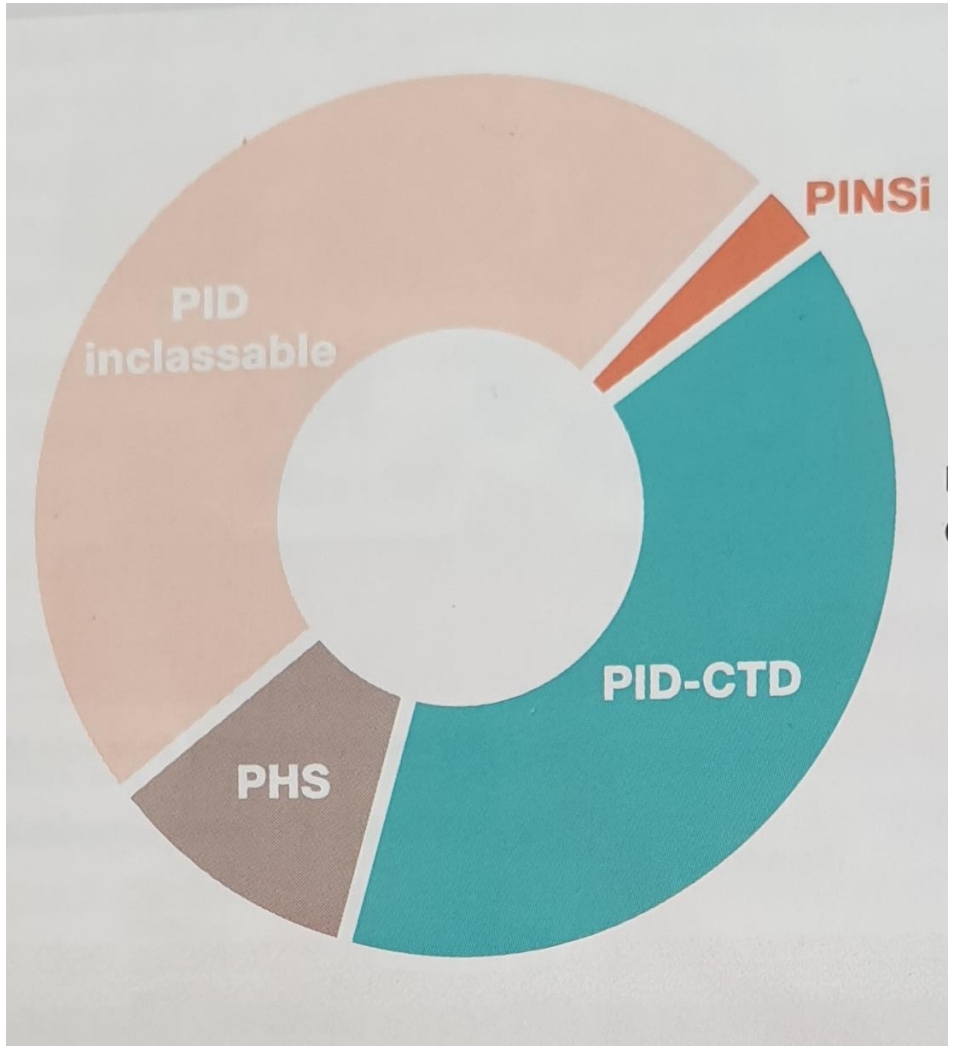
ACUTE EXACERBATIONS IN “NON IPF PPF”

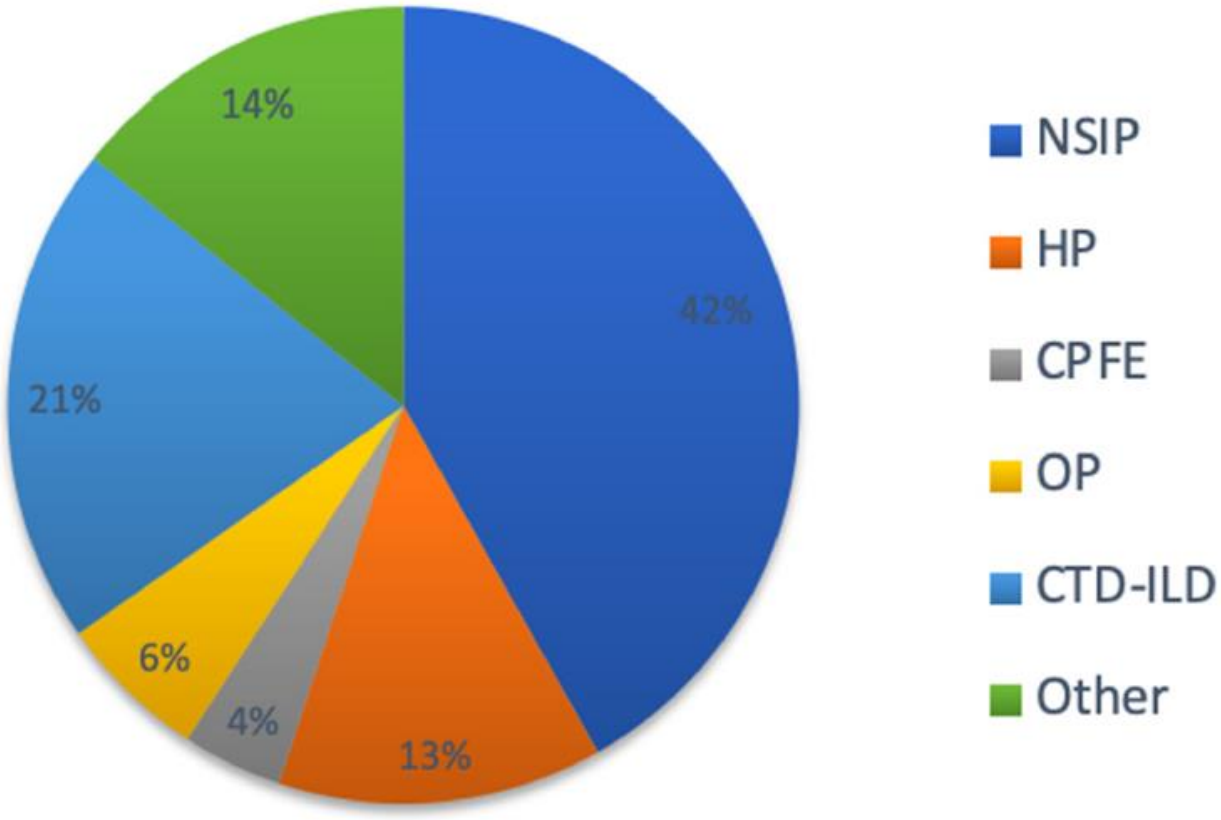


1019 consecutive ILD patients (01-2008 and 07-2015)
IPF (n 462) and other FILD [NSIP (n 22), CHP (n 29), CTD-ILD (n 205) and unclassifiable ILD (n 209)].
193 patients with 1st AE **(AE-FILD n 69, AE-IPF n 124).**

Time to first AE in FILD > IPF (log-rank test, $P < 0.001$).
Baseline disease severity was closely associated with the incidence of AE-ILD.
AE had a **negative impact on overall survival**. AE-FILD and AE-IPF showed **similar poor short-term outcomes.**

Suzuki A, et al. Respirology. 2020. PMID: 31426125

ACUTE EXACERBATIONS IN “NON IPF PPF”



158 consecutive adult patients hospitalized for AE-ILD (2009 to 2016) : IPF (38%) and non-IPF (62%) [NSIP (42%) & CTD-ILD (21%)]

Mortality during hospitalization : 19% non-IPF vs 43% IPF

Negative prognostic factors

Neutrophilia (HR 1.02 (CI 1.01–1.04)),

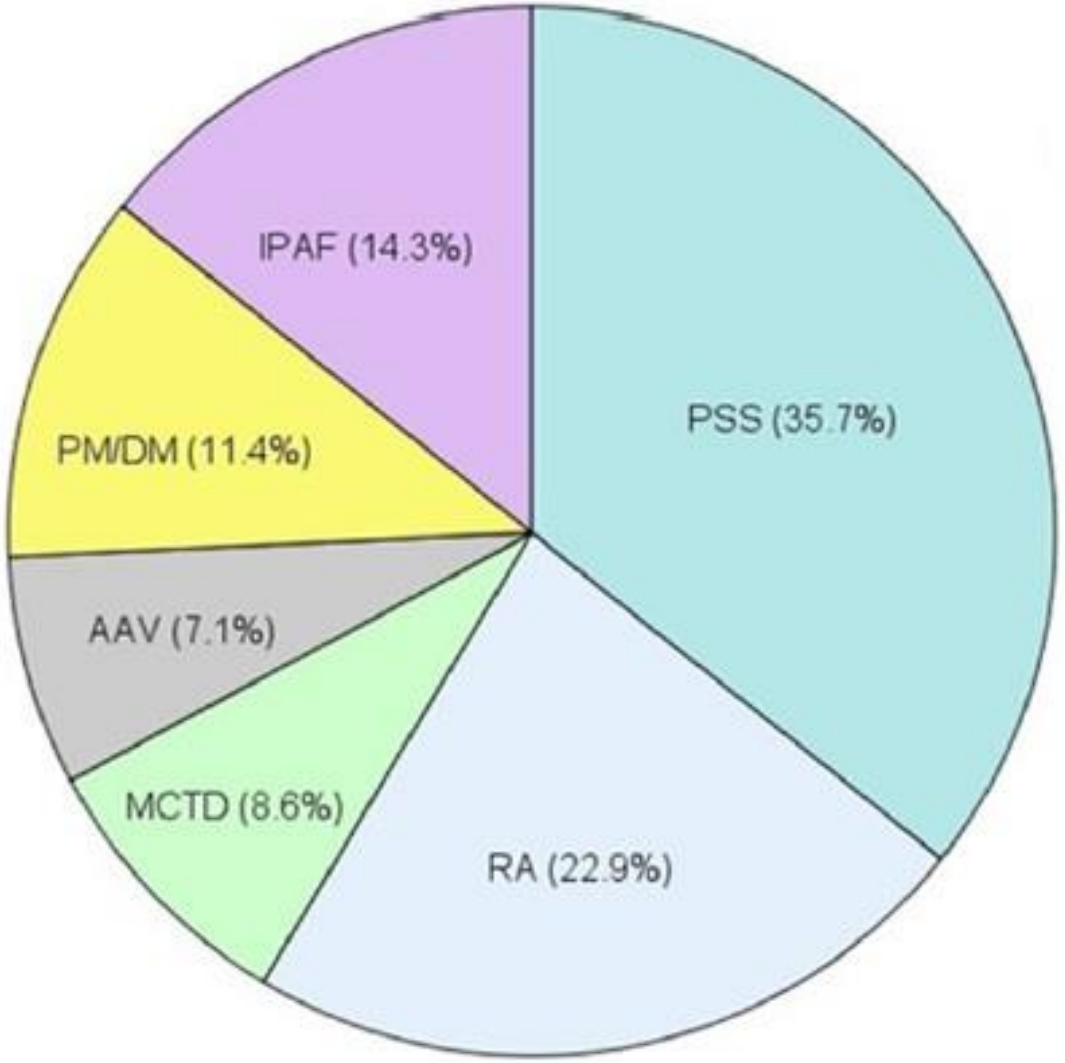
Pulmonary hypertension (HR 1.85 (CI 1.17–2.92))

IPF diagnosis (HR 2.31 (CI 1.55–3.46))

Lymphocytosis might act as a **protective** prognostic factor (OR 0.938 (CI 0.884–0.995)).

Differences between Acute Exacerbations of Idiopathic Pulmonary Fibrosis and Other Interstitial Lung Diseases. Diagnostics **2021**, 11, 1623.

ACUTE EXACERBATIONS IN “CTD PPF”



107 AE-IPF and 70 AE-CTD-ILD.
Same incidence (p = 0.526).
Risk factor for AE-CTD = TLC% pred (p = 0.018).

Lower mortality rate following AE-CTD-ILD than AE-IPF(p = 0.029). No difference in survival among CTD subgroups (p = 0.353).

WBC count and PO2/FiO2 ratio = independent predictors for survival (p=0.038 & p< 0.001).

Cao et al. BMC Pulmonary Medicine (2019) 19:215

MANAGEMENT OF ACUTE EXACERBATIONS

No randomised studies on which to base optimal management of AE in ILDs.

In IPF : **supportive care and long-term oxygen therapy** . Corticosteroids = anecdotal evidence of benefit (organising pneumonia) + high mortality rate

In other PF-ILDs : **limited evidence for corticosteroids** benefit in AE of IIP, CTD-ILDs, sarcoidosis and hypersensitivity pneumonitis. Mortality rates remain high and the optimal dose is not known.

Identify and eliminate potential exposure to causative toxic agents (hypersensitivity pneumonitis).

Empiric broad-spectrum antibiotics to rule out difficult-to-identify infectious agents / **antiviral therapy** during periods of heightened risk (seasonal)

Immunosuppressive agents (cyclosporine A, cyclophosphamide, tacrolimus or azathioprine) can be used with corticosteroids, but, without conclusive evidence.

Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018; 27: 180071

MANAGEMENT OF ACUTE EXACERBATIONS

Severe hypoxic respiratory failure : **Mechanical ventilation** but high mortality rate (assess risk vs the benefit)/ **Nasal cannula oxygen, conventional or high-flow** / **Non-invasive ventilation** as a bridge to **transplantation** in eligible patients = last resort in a minority of patients

ECMO is emerging as an effective management method. It Minimises the risk of "triggering" underlying chronic processes that can lead to fatal deterioration of the lungs, and reduces the invasiveness of ventilation. It could be used as a **bridge to transplantation**.

This management approaches are likely to be applicable with AE-PF ILDs. **Further controlled studies are required**, especially because PF-ILDs may be more likely to have inflammatory process during an AE (i.e. organising pneumonia with dense fibrosis) and therefore may benefit from acute immunomodulatory therapy much more than in AE-IPF.

Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018; 27: 180071

PREVENTION OF ACUTE EXACERBATIONS

No formal recommendations for a treatment preventing AE in ILDs.
In **IPF**, data suggest that **antifibrotic drugs could have a role in preventing AE**

Contrasting results in phase II trials with pirfenidone : one showing a benefit and one failing to show an effect
Meta-analysis of 5 RCT: pirfenidone was associated with decreases in all-cause & IPF-related mortality, but **no significant decrease in the incidence of AEs** .

In a phase II study, **nintedanib appeared to delay the time to first AE**
One/two pivotal INPULSIS phase III trials : nintedanib **reduce AE** vs placebo (p=0.02)
Pooled analyses of phase II and III data suggest a **longer time to first AE**

Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018; 27: 180071

PREVENTION OF ACUTE EXACERBATIONS

In **other ILDs**, **less evidence** for pirfenidone and nintedanib versus placebo decreasing incidence of AEs in patients with PF-ILD

Other potential preventive measures in AE of IPF and other ILDs may include:

- Influenza and pneumococcal vaccination,
- Hand washing and avoidance of sick contacts,
- Avoidance of airborne irritants and pollutants,
- Strategies to minimise mechanical ventilator-induced lung injury
- Anti-acid treatment ??? conflicting data

Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018; 27: 180071

PROGNOSIS OF ACUTE EXACERBATIONS

AE in IPF and other PF-ILDs is associated with a high economic burden from a high rate of hospitalisation with a poor prognosis and a **high rate of mortality**!

Post-exacerbation mortality in ILDs : 33 to 83%

Hospital mortality rates in CTD-ILD : 50–100% / In HP : 75–100% .

High mortality associated with :

- Lower baseline lung function parameters
- Impaired oxygenation
- Higher fibrosis score/more extensive radiological disease

Front Med October 2017 | Volume 4 | Article 176

Kolb M, Bondue B, Pesci A, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018; 27: 180071

PROGNOSIS OF ACUTE EXACERBATIONS

AE-IPF cause 35 to 46% of deaths in IPF with in-hospital mortality estimated over 50%
Median survival after AE-IPF = 1 to 4 m : 1m mortality = 37-53% / 3m mortality = 3.8-73.7%
The overall survival after admission for AE-ILD = 67% at 1 month and 40% at 3 months.
The highest overall mortality rate is seen in AE-HP = 75–100% . In other AE-ILD = 34 to 83%
Potential prognostic factors :

Lower baseline FVC and DLCO AND more impaired O2 = worse outcome in AE-IPF
Higher fibrosis score / More extensive disease on HRCT seems to be of prognostic relevance
Markers in the blood : lactate dehydrogenase, C-reactive protein, Krebs von den Lungen-6 (KL-6), circulating fibrocytes, and anti-HSP70 autoantibodies.

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CONCLUSIONS

Progressive Pulmonary Fibrosis is a phenotype found in severe forms of various ILD (HP, CTD, NSIP...) and is associated with a higher mortality.
It could improve with the ususal treament of the underlying disease; **if not,** there is increasing evidence to support the early use of antifibrotics.

Concerning Acute Exacerbation, more research is needed to clarify its epidemiology, risk factors, optimal management and prognosis, especially that it appears in numerous and various interstitial lung disease.