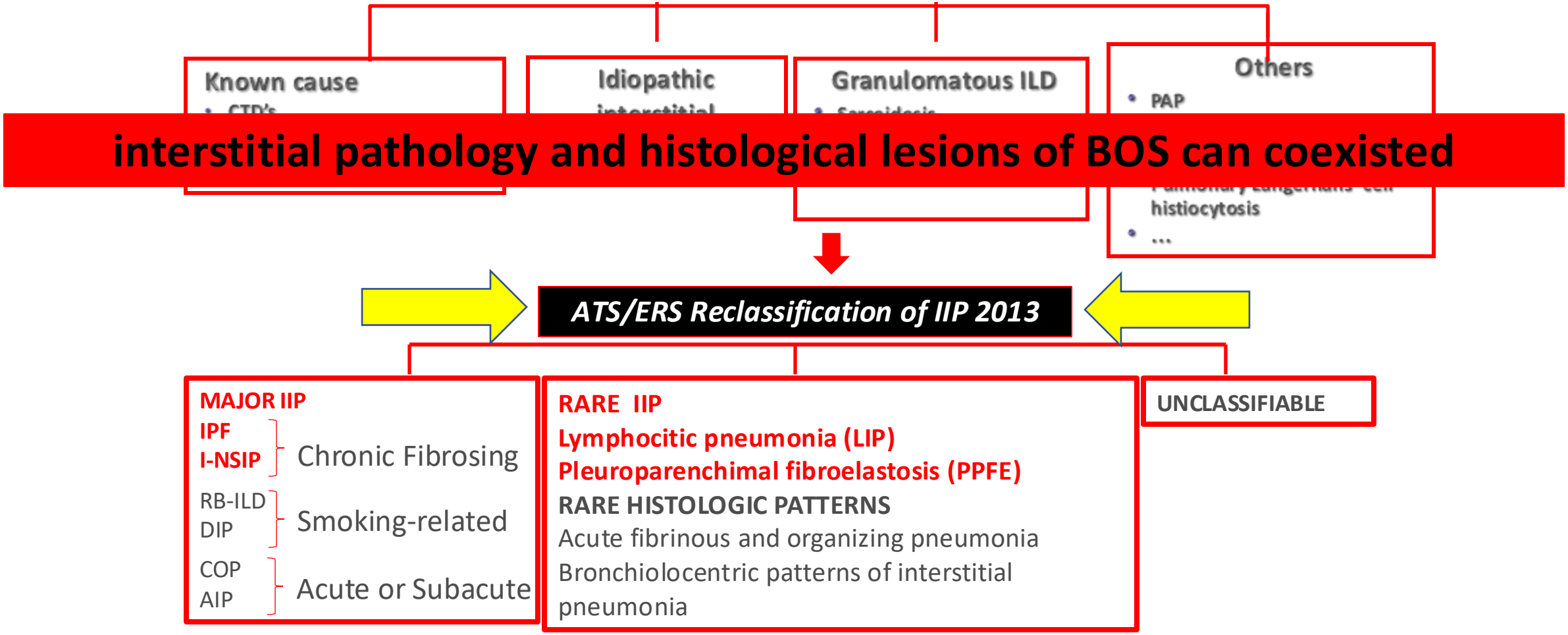
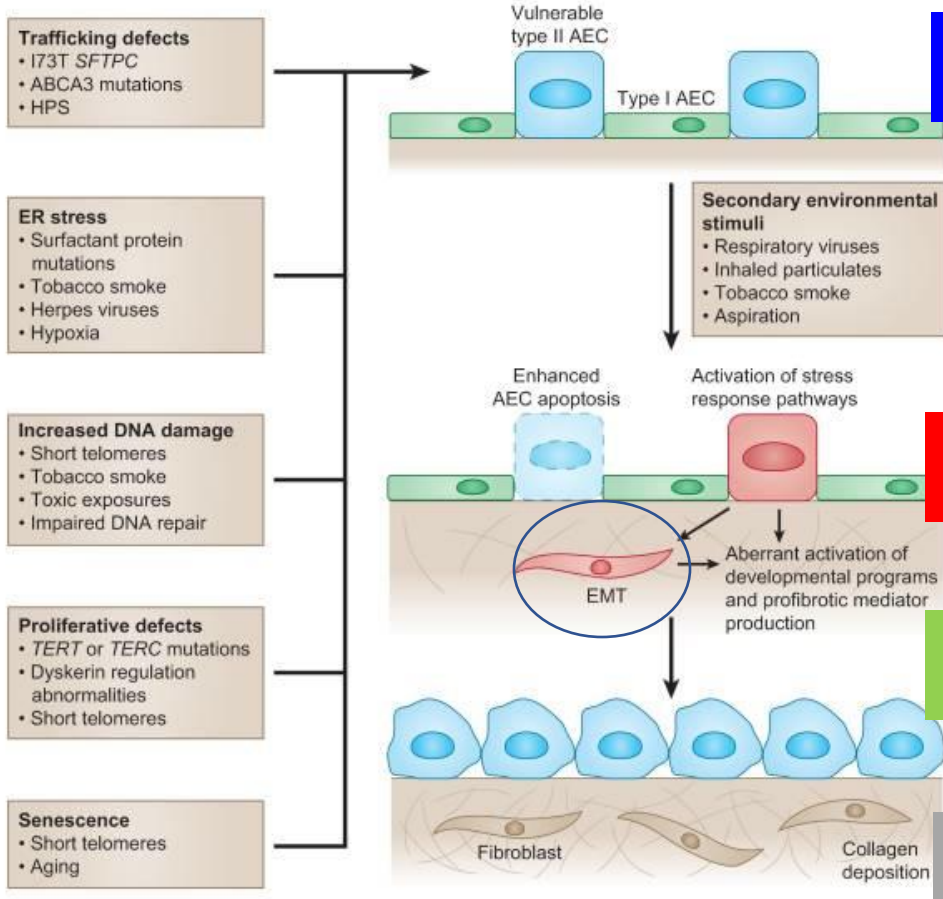
Interstitial lung diseases encompass a large heterogeneous group of diffuse parenchymal lung diseases, characterised **by varying degrees of inflammation and fibrosis**

Post- HSCT ILDs may correspond to several histological patterns, such as organizing pneumonia (OP) and nonspecific interstitial pneumonia (NSIP), predominantly, as well as diffuse alveolar damage, lymphocytic interstitial pneumonia, and pleuroparenchymal fibroelastosis (PPFE)



Insights in IPF pathogenesis

IPF ≠ Other «inflammatory» ILDs



1)Alveolar loss/senescence

~~Inflammation~~

2)Aberrant signaling

3)Remodelling

4)Fibrosis

injured epithelial cells promote fibroblast recruitment, proliferation, and differentiation to invasive myofibroblasts

PPFE: definition and classification

- A rare interstitial lung disease, characterized by fibrosis and fibroelastosis involving both visceral pleura and the subjacent subpleural lung parenchyma with an upper-lobe predominance
- Firstly described in 1992 by Amitani et al under the name of «upper lobe pulmonary fibrosis» (PULF) and defined in 2004 by Frankel et al as «pleuroparenchymal fibroelastosis»
- Idiopathic PPFE (IPPFE) is included as a distinct clinicopathological entity in the updated ATS/ERS classification (2013)
- However it was later observed in a number of other conditions, including patients who had undergone a hematopoietic stem cell transplant (HSCT) and is now considered to be a long-term non-infectious pulmonary complication (LTNIPC) after HSCT.

Etiology

Idiopathic : 10- 30 %

Familial history of pulmonary fibrosis: 10%

Secondary or associated with underlying conditions:

- Radiation/chemotherapy
- **Bone marrow- or stem cell-transplantation**
- **Lung transplantation**
- Occupational dust exposure
- Recurrent infections
- Autoimmune diseases **(SSc, RA)**
- Other ILDs such as **IPF, HP**

Pleuroparenchymal fibroelastosis: a pattern of chronic lung injury☆,☆☆

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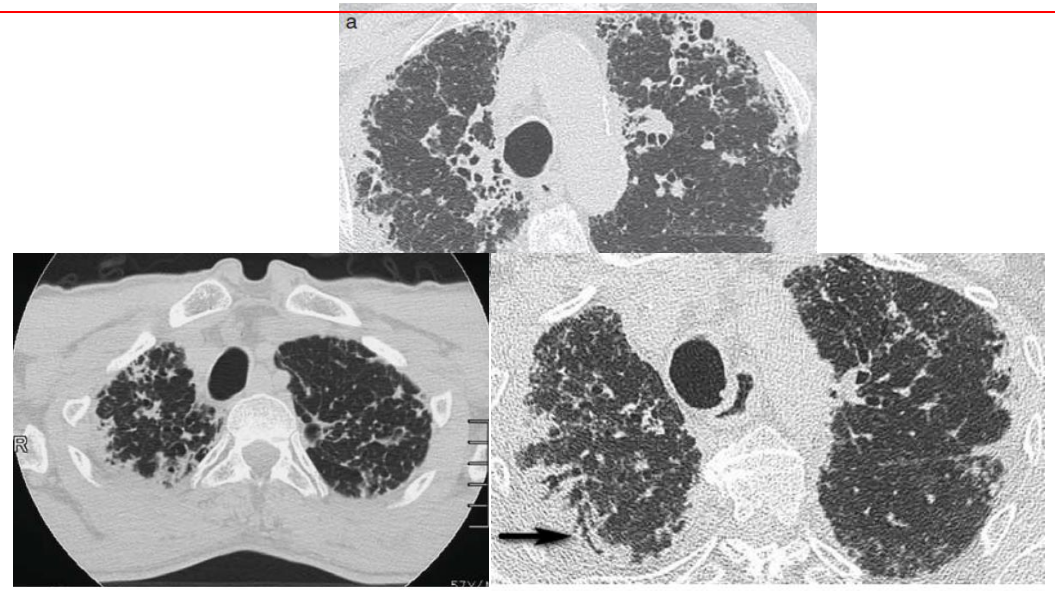
PPFE may actually represent a pattern of chronic lung injury rather than a specific entity

Overall prevalence of PPFE after HSCT of 0.28–3.3%, while after lung transplantation is 7.54%

PPFE: clinical and radiological characteristics

- No gender predilection
- Mostly in non-smokers
- Clinical findings: spontaneous pneumothorax (30%), exertional dyspnea, dry cough, pleuritic chest pain due to pneumothorax and weight loss
- Physical signs: slender status, platythorax
- Restrictive ventilatory pattern: FVC ⇩ TLC ⇩ RV/TLC ⇧(due to compensatory overinflation of lower lobes), Gas exchange impairment: DLCO , KCO normal
- Hypoxemia and hypercapnia in advanced disease

- Irregular pleuroparenchymal thickening with **upper lobe predominance**
- Wedge-shaped densities and hila tend to be retracted
- Small foci of consolidation away from sub-pleural lesion
- Significant volume loss
- Interlobular septal thickening



EUROPEAN RESPIRATORY *journal*

Pleuroparenchymal fibroelastosis in systemic sclerosis: prevalence and prognostic impact

Characteristics	Whole cohort (n=359)	RBH cohort (n=228)	Ancona cohort (n=131)	*P*
PPFE	65 (18.1)	42 (18.4)	23 (17.5)	0.8
Limited	24 (6.7)	16 (7.0)	8 (6.1)	
Extensive	41 (11.4)	26 (11.4)	15 (11.4)	

Table 2. PPFE prevalence and extent in the whole cohort and by center

The overall prevalence of PPFE in the combined SSc population was 18%

PPFE was significantly linked to free-standing bronchial abnormalities (61% vs 25% in PPFE vs no PPFE; p<0.0001) and **to worse survival**, independently of ILD severity or short-term lung function changes (HR 1.89, 95% CI 1.10-3.25; p=0.005).

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PPFE & AIRWAY DISEASES & INFECTIONS?

A significant association between PPFE and bronchial abnormalities (including freestanding bronchiectasis) is reported for SSC, IPF and hypersensitivity pneumonitis

A potential association of atypical Mycobacteria infection and PPF has been recently suggested as an etiology for PPFE in non-HSCT patients

Various studies have shown that post-HSCT patients who develop PPFE also have established lung-associated cGvHD (i.e., bronchiolitis obliterans syndrome (BOS)
The co-existence of BOS in patients diagnosed with PPFE has been shown to be high (47–100%)

ANTIFIBROTICS & LTX IN PF

Two antifibrotics, pirfenidone and nintedanib, both proved to be effective in reducing functional decline and disease progression in IPF

Nintedanib has been approved for patients with SSC-ILD and chronic fibrosing non-IPF ILD with a progressive phenotype (HP, **PPFE**, autoimmune ILDs, occupational ILDs)

Idiopathic interstitial pneumonia, of which IPF is the most prevalent form, has become the most frequent indication for LTx

Antifibrotic effect on peri-transplant outcome has been debated, due to the supposed higher risk of complications (bronchial anastomotic complications, such as bronchial dehiscence,and perioperative bleeding). However, In clinical practice, no evidence of increased risk has been reported

No consensus exists for use of **antifibrotics post-LTx** and most centres advocate discontinuation. However, one might suggest that patients with IPF undergoing single LTx might benefit from continuation to attenuate fibrosis progression in the native lung

ANY POTENTIAL ROLE FOR ANTIFIBROTICS IN CLAD/cGVHD?

Antifibrotics in the pathophysiological processes after LTx and in CLAD development

- Both phenotypes of CLAD, BOS and RAS, are associated with fibroproliferative features
- **Results from randomized trial of pirfenidone in patients with chronic rejection (STOP-CLAD study)** could not demonstrate a significant beneficial effect
- A multicentre, randomised, double-blind placebo-controlled trial of nintedanib in LTx recipients with BOS grade 1–2 is ongoing (INFINITx-BOS)

Antifibrotics in pulmonary chronic graft-versus-host disease

- Pirfenidone has shown to be effective in a murine model of cGvHD by reducing macrophage infiltration, transforming growth factor-β production and T-cell reaction
- A recent case report noted a remarkable improvement of respiratory symptoms and pulmonary function after starting nintedanib in a patient with BOS post-alloHCT
- Two patients treated with nintedanib, of whom one had beneficial effect on fibrotic pulmonary cGvHD; the other patient had persistent fibrotic changes after alloHCT due to disease-related diffuse alveolar haemorrhage, but also improved with nintedanib