Spectrum of Fibrotic Lung Diseases

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N Engl J Med. 2020 Sep 3;383(10):958-968

Study Design

- The New England Journal of Medicine
- September 2, 2020
- Review article
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Interstitial lung disease (ILD)

= a group of respiratory diseases affecting the interstitium (the tissue and space around the alveoli (air sacs)) of the lungs.

- Pulmonary alveolar walls are infiltrated by various combinations of inflammatory cells, fibrosis, and proliferations of certain cells

- Most common fibrotic ILD = **Idiopathic pulmonary fibrosis (IPF)**

IPF

Characterized:

Imaging and pathological pattern of usual interstitial pneumonia (UIP)

without

an identifiable cause or association with a disease known to be associated with pulmonary fibrosis

- Chronic irreversible disease – progressing to respiratory failure and death (median interval between diagnosis and death = 3y)

IPF vs other ILDs

IPF

- Men:women ratio = 7:3
- Age: >60y
- Pathological features: severe outcome
- Progressive IPF: Respiratory symptoms, limited exercise capacity, impaired quality of life, organ failure

Other ILDs

- Men:women ratio = balanced
- Age: 20-60y
- Pathological features: more heterogenous and often less severe

Epidemiology

- Overall prevalence of ILD: 76 cases per 100.000 people in Europe, 74.3 cases per 100.000 people in the US

- Sarcoidosis, IPF and connective-tissue disease (CTD)-associated ILDs = most common fibrotic ILDs
  - Prevalence: 30.2, 8.2 and 12.1 cases per 100.000

Clinical characteristics of selected broad categories of pulmonary fibrosis

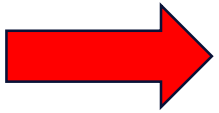
Condition	Clinical Features	Findings on Chest Imaging	Other Features Not Characteristic of IPF	Management	Prognosis	Risk Factors for Progressive Fibrosis or Death	Relative Prevalence†	Fibrosing Phenotype
IPF[3]	Velcro-like crackles; finger clubbing (30–50% of patients); male: female ratio, 3:1; age >50 yr	Definite or probable UIP pattern, indeterminate pattern for UIP (and biopsy findings or clinical course suggestive of IPF)	NA	Antifibrotic therapy (pirfenidone, nintedanib)	Median survival, 3–4 yr; potential for slowing progression	Older age, male sex, honeycombing or UIP pattern on CT, FVC <70%	12	90–100
SSc–ILD[8,10]	Raynaud's phenomenon, skin thickening, fingertip lesions, telangiectasia, gastroesophageal reflux, vasculopathy	More common fibrotic NSIP than UIP pattern	Younger age, more women than men affected, multisystemic involvement, autoimmune serologic findings (anti–Scl-70, anticentromere, and anti–RNA polymerase III antibodies), abnormal nailfold capillaroscopy	Immunosuppressive therapy: mycophenolate; alternatively, IV cyclophosphamide, azathioprine, rituximab, tocilizumab Antifibrotic therapy (nintedanib) Stem-cell transplantation or lung transplantation in select patients	10-Yr mortality, 40%; 35% of SSc-related deaths due to ILD; possible stabilization with treatment	Diffuse cutaneous SSc, <7 yr since diagnosis, male sex, Black race, anti–Scl-70 antibodies, disease extent on CT >20%, reduced FVC and DLco	9	40
Rheumatoid arthritis–ILD[11,12]	Morning stiffness, symmetric arthritis, synovitis, joint erosions, rheumatoid nodules	Predominance of UIP pattern over NSIP or indeterminate pattern, multicompartment involvement (association of airways or pleural involvement)	Autoimmune serologic features (ACPAs, but rheumatoid factor less specific)	Lack of evidence for immunosuppressive therapy; rituximab, abatacept, or mycophenolate occasionally used; antifibrotic therapy (nintedanib) used in cases of progressive fibrosis; pirfenidone is under investigation‡	Median survival, 3 yr (UIP pattern) or longer (other patterns); effect of treatment on lung disease unknown	Older age, male sex, disease extent on CT >20%, honeycombing or UIP pattern on CT, FVC < 70%	8	32
Sarcoidosis, fibrotic (stage IV)[13]	Multisystem disease in any organ, especially skin, eye, heart, liver, and lymph nodes; pulmonary involvement in 90% of cases; wide range of clinical phenotypes	Upper-lobe, peribronchovascular, and lymphatic distribution; dense perihilar fibrotic or cavitated masses; bronchial distortion, reticular opacities, and traction bronchiectasis; UIP-like pattern rare	Younger age; Female: male ratio, 1:1; multiorgan involvement; absence of bibasilar crackles and clubbing; noncaseating epithelioid-cell granulomas with giant cells on pathological evaluation	Monitoring alone or treatment with glucocorticoids; methotrexate or azathioprine as glucocorticoid-sparing agent or second-line therapy; infliximab or adalimumab as third-line therapy; lack of evidence for leflunomide and hydroxychloroquine for lung disease; benefit of antifibrotic therapy unclear	10-Yr mortality, about 10%; 75% of sarcoidosis-related deaths due to lung disease; generally responsive to immunomodulation	Black race, disease extent on CT >20%, pulmonary hypertension, female sex	45	13
Chronic fibrotic hypersensitivity pneumonitis[14–16]	Prolonged exposure to inhaled particles, predominantly organic antigens; onset of symptoms over a period of 6 mo or more§	Reticulation and honeycombing, with peribronchovascular, upper- and middle-zone distribution; ground-glass attenuation with mosaicism and air trapping	Offending inhaled antigen not always identified; recurrent episodes of symptoms; BAL lymphocytosis (>20% of cases); positive precipitins; biopsy, if performed showing airway-centric lymphocytic infiltration, loose granulomas, and giant cells	Exposure avoidance; limited evidence for glucocorticoids and immunosuppressive therapy (mycophenolate or azathioprine); antifibrotic therapy (nintedanib) for progressive fibrosis; lung transplantation in rare cases	5-Yr survival, 50–80%; potential for improvement or stabilization with treatment	Persistent exposure to offending antigen, honeycombing or UIP pattern on CT	3	21
Unclassifiable fibrotic ILD[16,17]	Demographic features vary; median age, 60–65 yr; nonspecific symptoms with dyspnea and cough; no first-choice diagnosis; often subtle autoimmune features	Nonspecific features generally not meeting criteria for main patterns	Major discrepancy among clinical, imaging, and histologic features; nondiagnostic CT findings and no biopsy performed or biopsy results noncontributory	Limited evidence for glucocorticoids; immunosuppressive therapy often first-line; antifibrotic therapy (pirfenidone or nintedanib) in progressive fibrosis	5-Yr survival, 45–70%; variable disease course	Honeycombing on imaging, progressive decline in lung function	8	53

- IPF
- Systemic sclerosis (SSc)-ILD
- Rheumatoid arthritis- ILD
- Sarcoidosis fibrotic (stage IV)
- Chronic fibrotic hypersensitivity pneumonitis
- Unclassifiable fibrotic ILD

- Main clinical features
- Findings on chest imaging
- Other features
- Management
- Prognosis
- Risk factors for progressive fibrosis and death
- Relative Prevalence
- Progressive fibrosing phenotypes

Pathophysiology

- Much is still unknown about pathophysiology of specific disease entities
- Formation of fibrosis = essential response against pathogens
- In pulmonary fibrosis: various, often disease-specific triggers set off exaggerated cascades of inflammatory and fibrotic responses



downstream fibrotic tissue remodeling and extracellular-matrix deposition

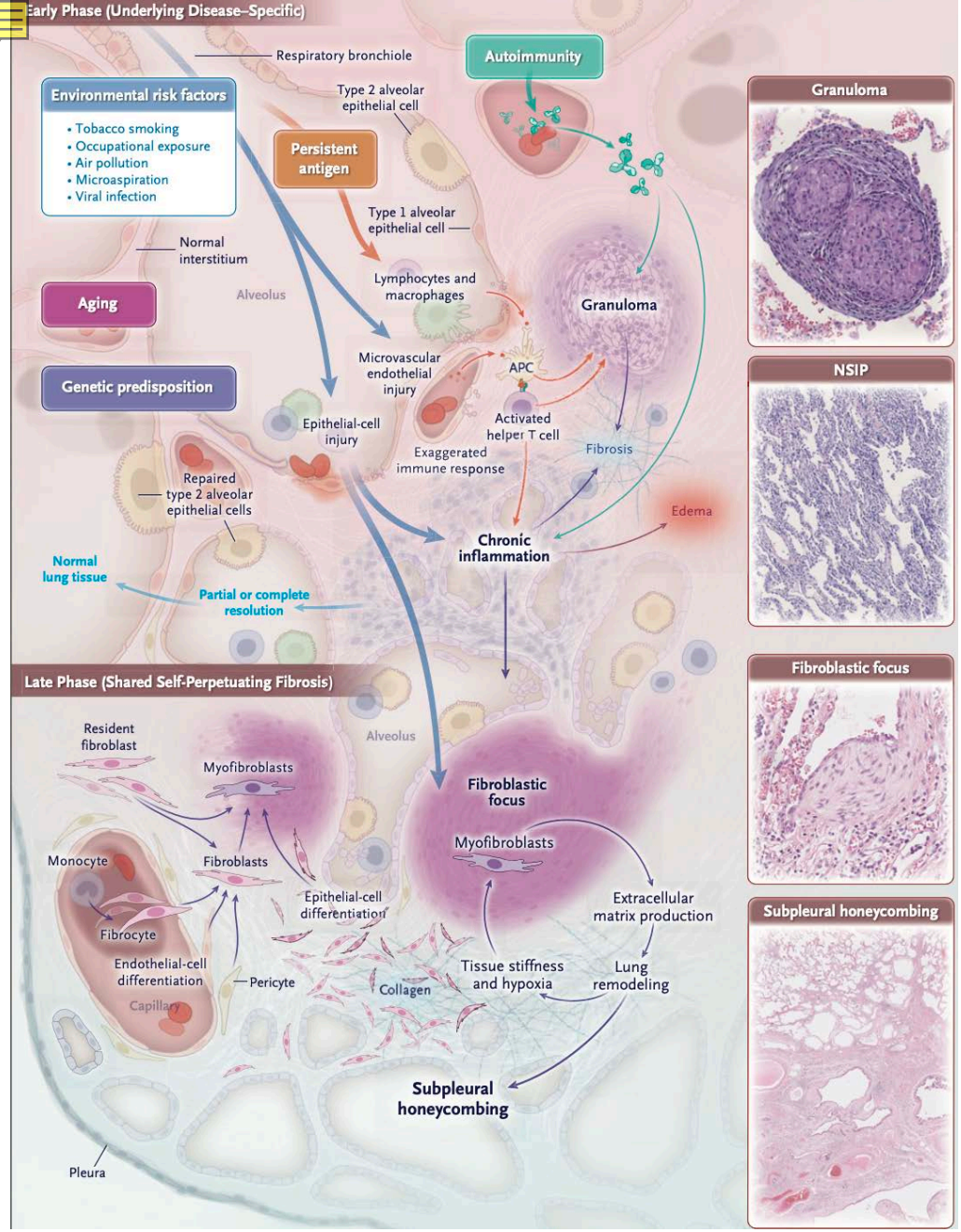
Genetic studies

- Frequent polymorphism in the ***MUC5B*** – associated with increased risks of IPF, rheumatoid arthritis with ILD, chronic hypersensitivity pneumonitis (CHP)

but NOT

with sarcoidosis, or antisynthetase syndrome

- Telomere shortening and telomere-related gene mutations (***TERT, TERC, RTEL1, PARN***): IPF, RA-ILD, CHP



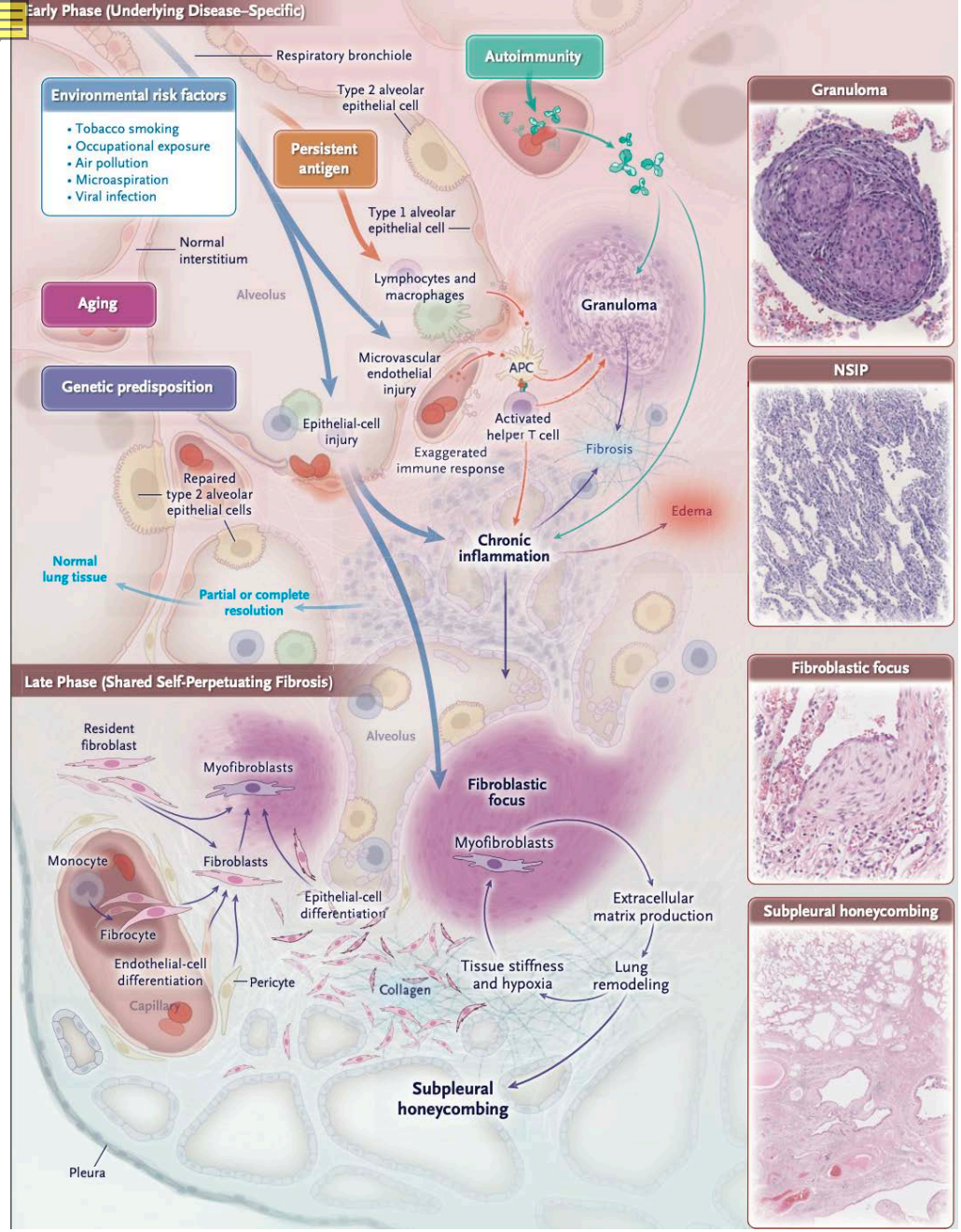
Early Phase = disease specific:

- Lymphocyte activation and differentiation, autoimmunity and exaggerated immune response in immune mediated conditions (connective-tissue disease – associated ILD, chronic granulomatous inflammation)

Environmental risk factors: repeated injury to the pulmonary alveolar cell

Aging, genetic background, epigenetic modifications

After repeated alveolar or endothelial-cell injury or immune activation and inflammation, fibroblasts can be active by profibrotic cytokines -> proliferation and differentiate into myofibroblast -> migration to alveolar interstitium and represents “active front” of fibrogenesis



<u>Later Phase of fibrogensis:</u>

Lung tissue remodeling and subpleural microscopic honeycombing

Tissue stiffness and hypoxia

Up-regulation of profibrotic cytokines pathways and myofibroblast activation

Disease entities with pulmonary fibrosis

- **5 broad clinical categories:**

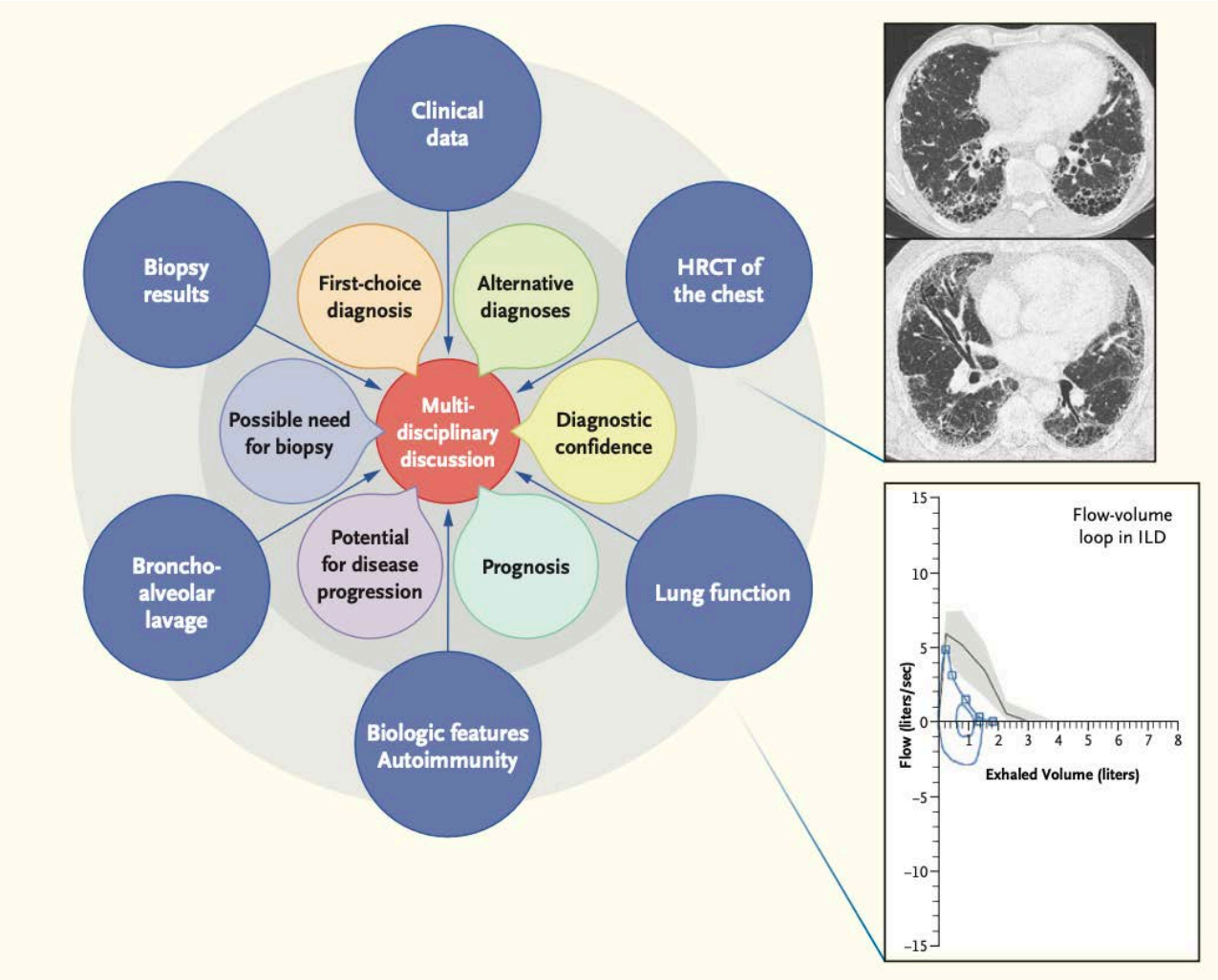
1. ILDs related to distinct primary diseases: sarcoidosis, Langerhans-cell granulomatosis, eosinophilic pneumonia, lymphangioleiomyomatosis, pulmonary alveolar proteinosis
2. ILDs related to environmental exposures: pneumoconiosis due to inhalation of organic particles (mold or birds or others)
3. ILDs induces by drugs, illicit drugs or irradiation
4. ILDs associated with CTDs
5. Idiopathic interstitial pneumonias: IPF, idiopathic nonspecific interstitial pneumonia, and others

Current specific interest

Development of fibrosis after coronavirus disease 2019 (Covid-19)

- Pulmonary fibrosis = complication of ARDS

Diagnostic approach



Disease specific symptoms: cough, progressive exertional dyspnea, exercise limitations

Medical history: environment, job, drugs, medication

Examination of hands, joints, skin

Serological testing

HRCT:

- UIP pattern = hallmark of pulmonary fibrosis (IPF, RA-ILD)
- Nonspecific interstitial pneumonia (SSc-ILD): mixed reticulation, GGO, bronchiectasis, central axial distribution, sparing subpleural area

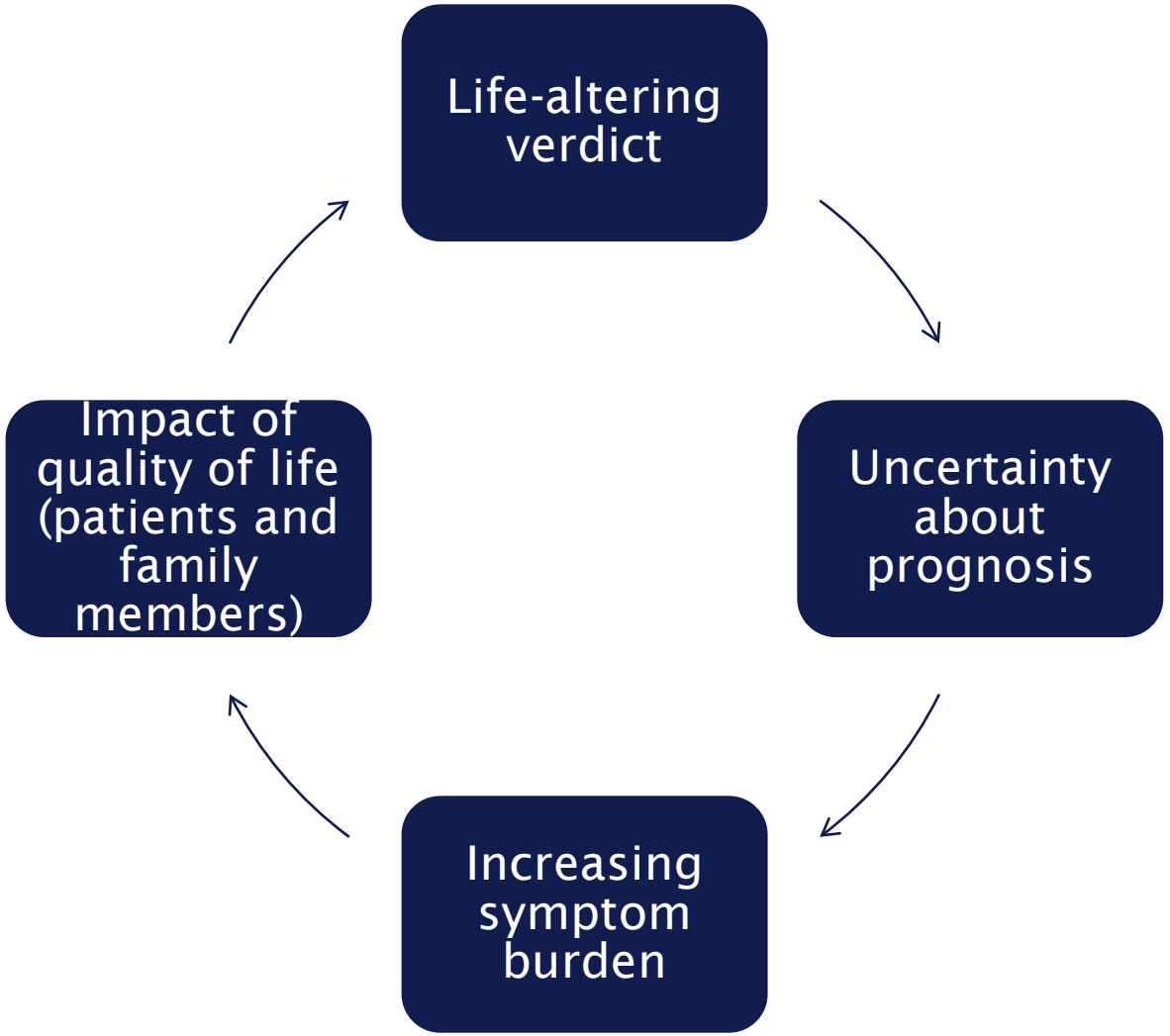
Lung function: restrictive lung-function

- ↓ FVC
- Normal or ↑ FEV1
- ↓ TLC
- Low RV
- ↓ DLCO

Progressive pulmonary fibrosis

- **Untreated IPF** = progression and respiratory failure
- > 50% of all pts with pulmonary fibrosis (other than IPF): stable, chronic disease or improvement with immunomodulatory therapy
- No serum biomarker for monitoring disease progression
- Predictors of disease progression: sex, age, FVC, DLCO

Management of pulmonary fibrosis



Cave: off-label treatment with potential serious side effects

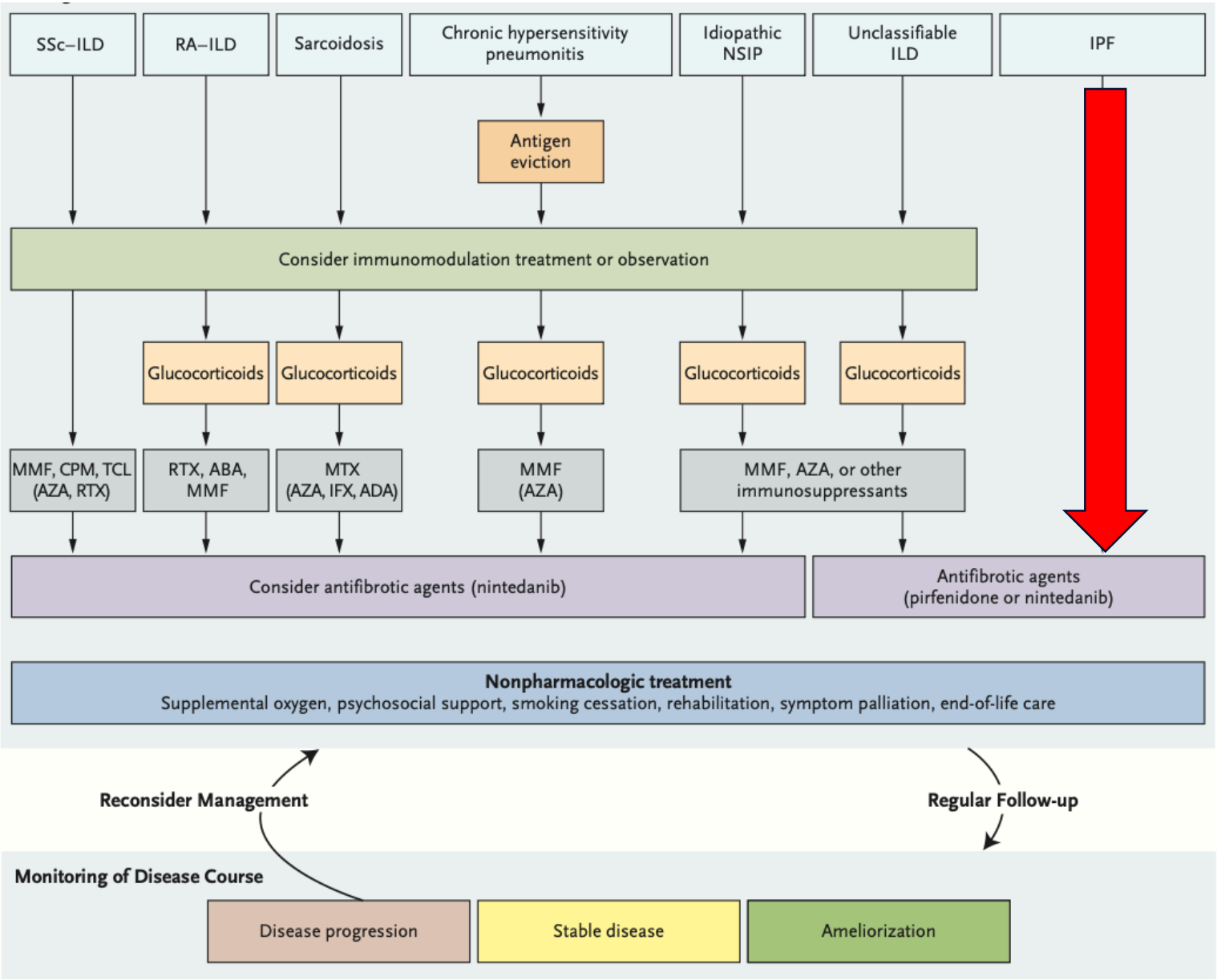
Prevention of exposures

Avoidance offending antigen

Cessation of tobacco smoking

Pneumococcal and influenza vaccinations

Supplemental oxygen:
- Resting hypoxemia (PaO_2 <55mmHg, oxygen saturation <89%, Cor pulmonale or polycythemia



1. line therapy: treatment of underlying disease -> immunomodulatory therapy

Nintedanib and Pirfenidone

- **Nintedanib:**
  - Approved bei FDA und EMA
  - For patients with SSC-ILD and chronic fibrosing ILDs with progressive phenotype
  - Not associated with an improvement in function BUT reduces the decline in FVC by about half
- **Pirfenidone:**
  - Reduces disease progression in patients with progressive, unclassifiable, fibrotic ILD

Benefit – risk of side effects

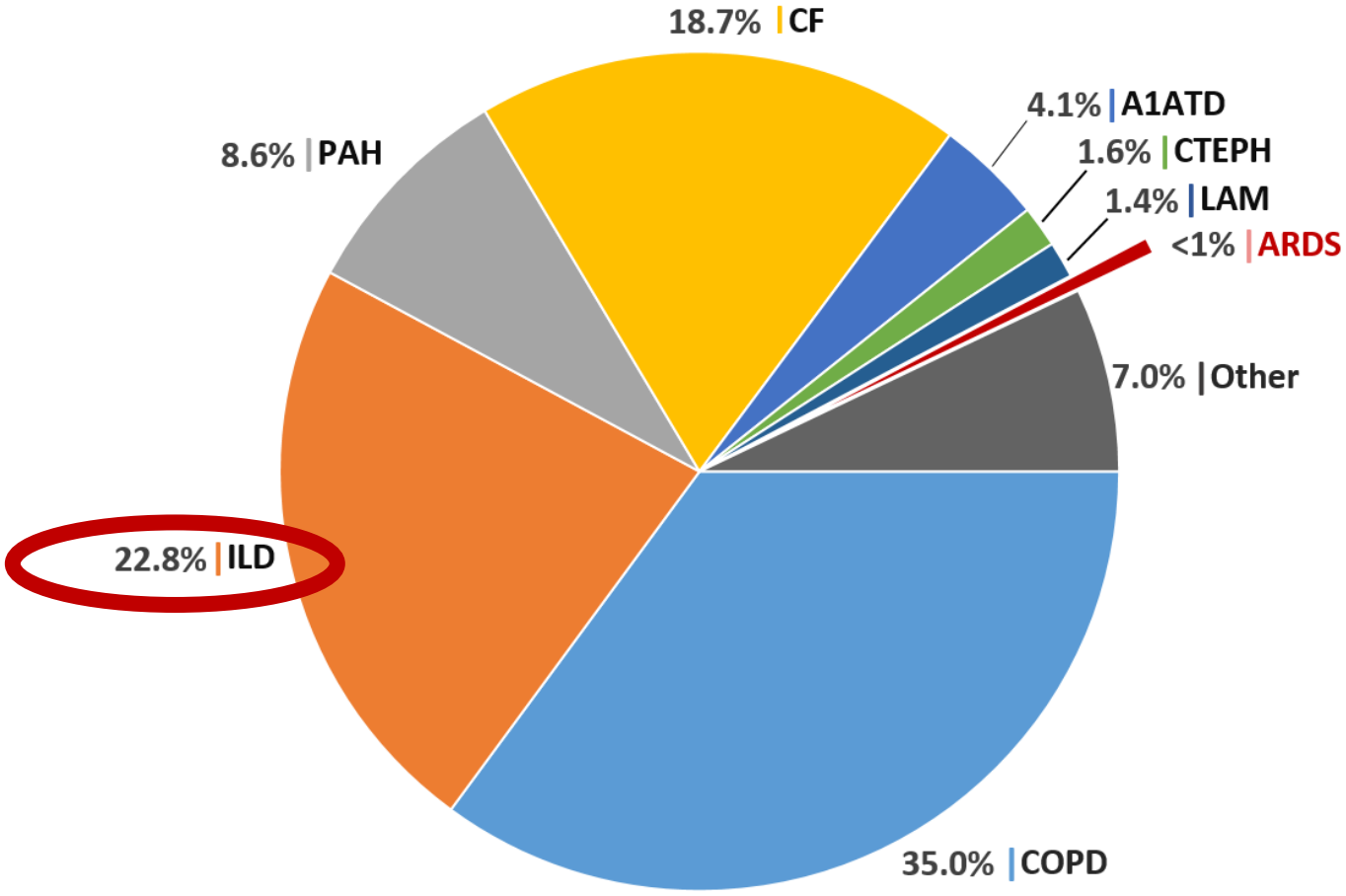
Future directions

- Identification of biomarkers
- Novel techniques such as molecular classifiers – gain more insights

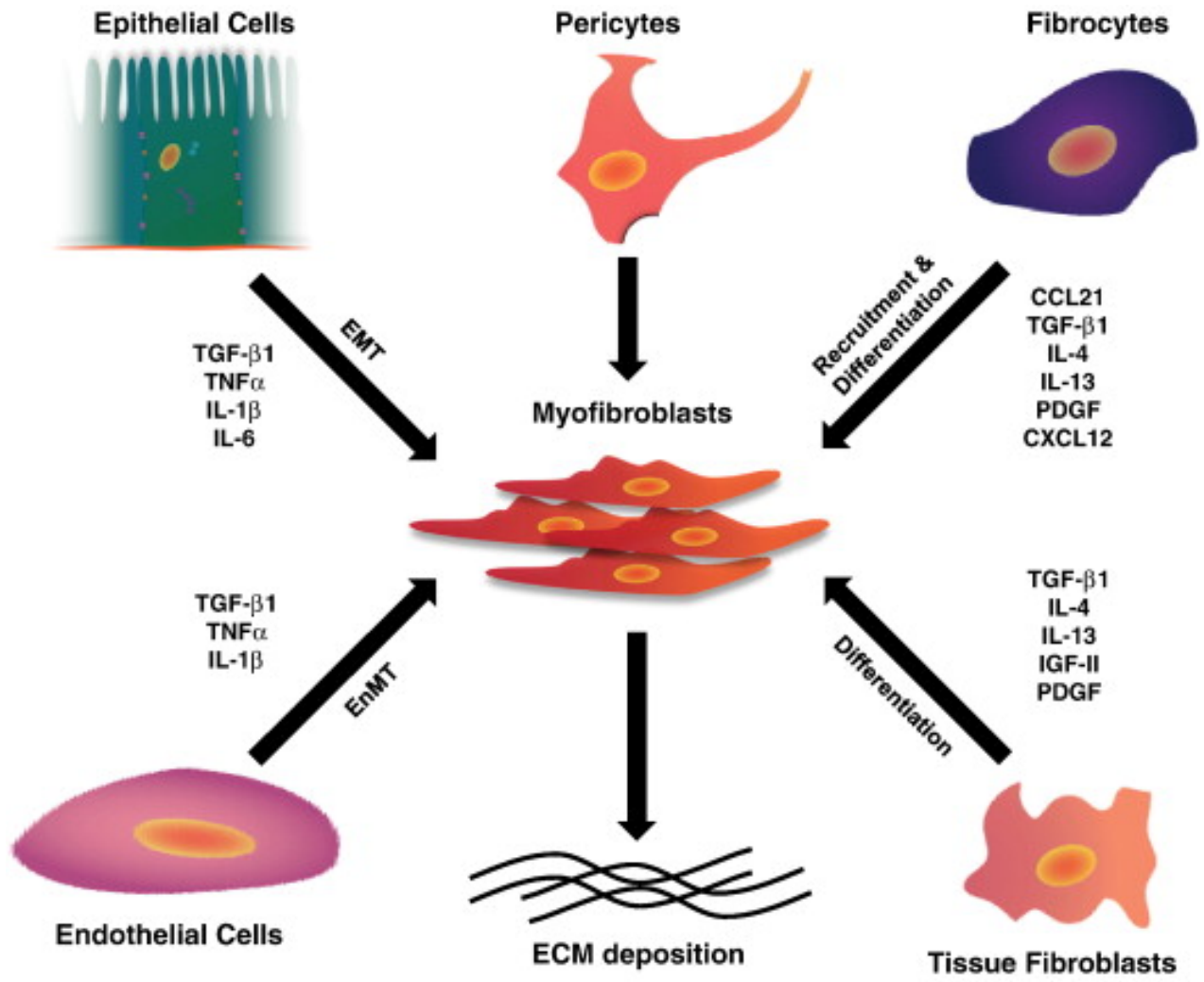
Limitation of the review article

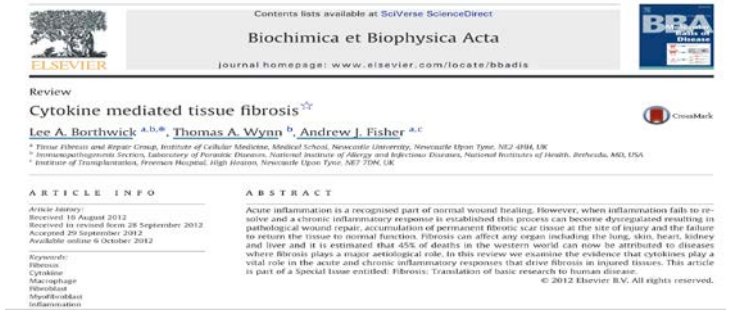
- Off-label treatment – side effects
- Meaning of lung transplantation
- Side effect of Nintedanib and Pirfenidone

ILD: Indication for lung transplantation



Source: Vienna LTx program data 1989-2021





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Review

Cytokine mediated tissue fibrosis☆

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ARTICLE INFO

Article history:
Received 16 August 2012
Received in revised form 28 September 2012
Accepted 29 September 2012
Available online 6 October 2012

Keywords:
Fibrosis
Cytokine
Macrophage
Fibroblast
Myofibroblast
Inflammation

ABSTRACT

Acute inflammation is a recognised part of normal wound healing. However, when inflammation fails to resolve and a chronic inflammatory response is established this process can become dysregulated resulting in pathological wound repair, accumulation of permanent fibrotic scar tissue at the site of injury and the failure to return the tissue to normal function. Fibrosis can affect any organ including the lung, skin, heart, kidney and liver and it is estimated that 45% of deaths in the western world can now be attributed to diseases where fibrosis plays a major aetiological role. In this review we examine the evidence that cytokines play a vital role in the acute and chronic inflammatory responses that drive fibrosis in injured tissues. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.