IPF for Healthcare Professionals

What is IPF?

Idiopathic Pulmonary Fibrosis (IPF)

Just as the name implies, idiopathic pulmonary fibrosis is the scarring (fibrosis) of lung tissue (pulmonary) from an unknown cause (idiopathic).

I	**Idiopathic**	**Of unknown aetiology**
P	**Pulmonary**	**Of, or relating to, the lung(s)**
F	**Fibrosis**	**An increase of interstitial fibrous tissue**

TERMINOLOGY

Many different terms and acronyms are related to IPF

DPLD
Diffuse parenchymal lung disease

ILD
Interstitial lung disease

UIP
Usual interstitial pneumonia

IIP
Idiopathic interstitial pneumonia

CFA
Cryptogenic fibrosing alveolitis

The relationship among the terms is explained on the following slides and throughout the slide kit

DISTINGUISHING the Terms

Diffuse parenchymal lung disease (DPLD) is also referred to as interstitial lung disease (ILD)

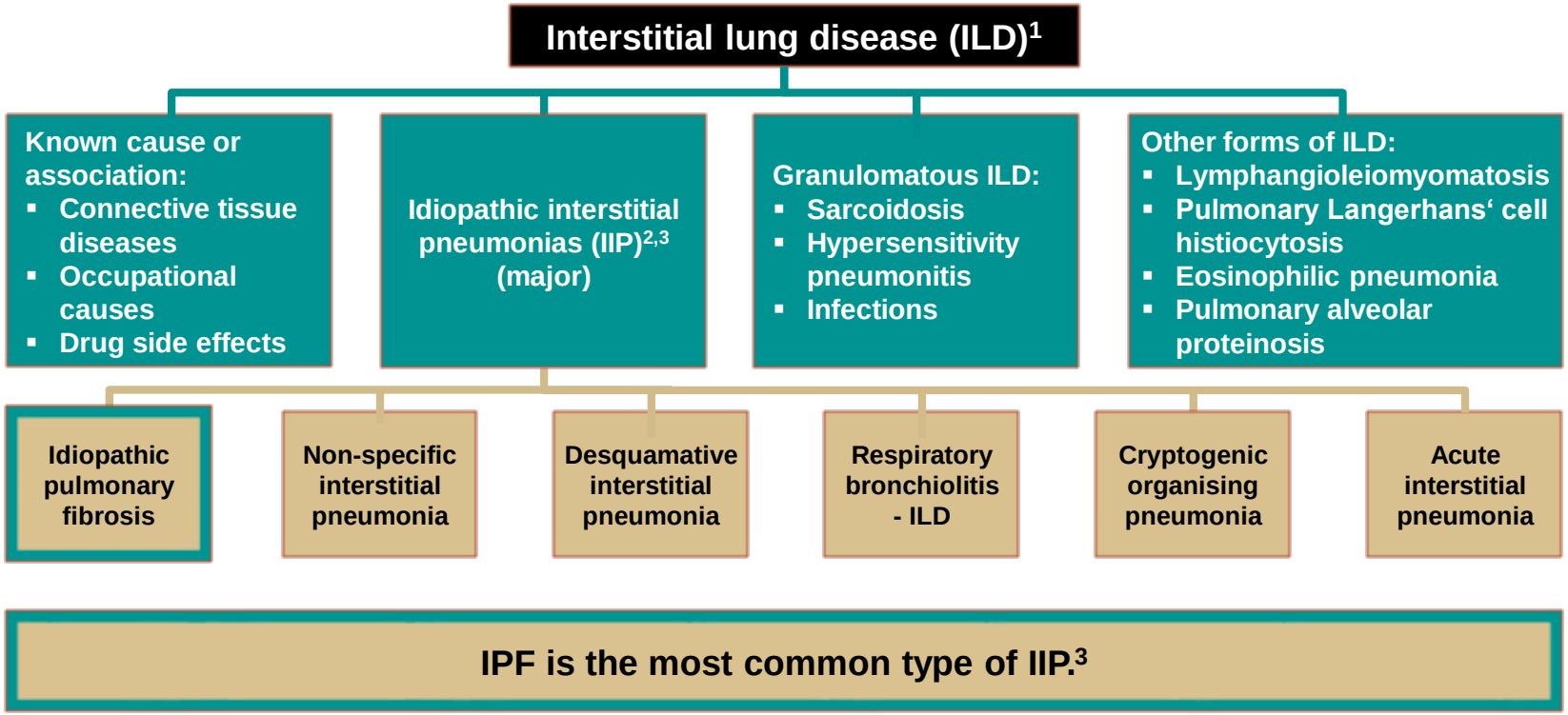
Idiopathic interstitial pneumonias (IIP) is a subgroup of DPLD[1]

Idiopathic pulmonary fibrosis (IPF) is classified under the sub-group IIP[2,3]

- The histology is that of usual interstitial pneumonia (UIP)
- Clinicopathological diagnosis also sometimes refers to cryptogenic fibrosing alveolitis (CFA)

1. Du Bois RM. Nature Reviews: Drug Discovery 2010;9(2):129-140.
2. Du Bois RM & Wells AU. Eur Respir J 2001;18(Suppl 32):43s-55s.
3. Travis D, et al. Am J Respir Crit Care Med 2013;Vol 188, Iss. 6, pp 733–748.

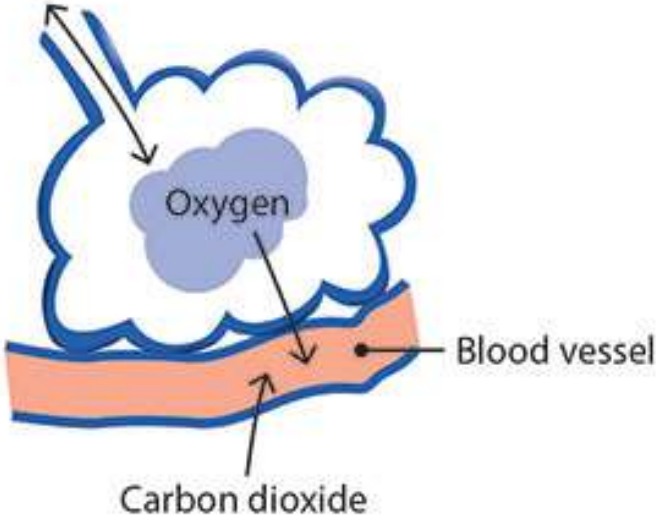
IPF in relation to other DPLDs



1. Am J Respir Crit Care Med 2002;Vol 165. pp 277–304.
2. Travis D, et al. Am J Respir Crit Care Med 2013; Vol 188, Iss. 6, pp 733–748.
3. Prasad et al. Intractable and Rare Diseases Research 2015; 4(2):65-69.

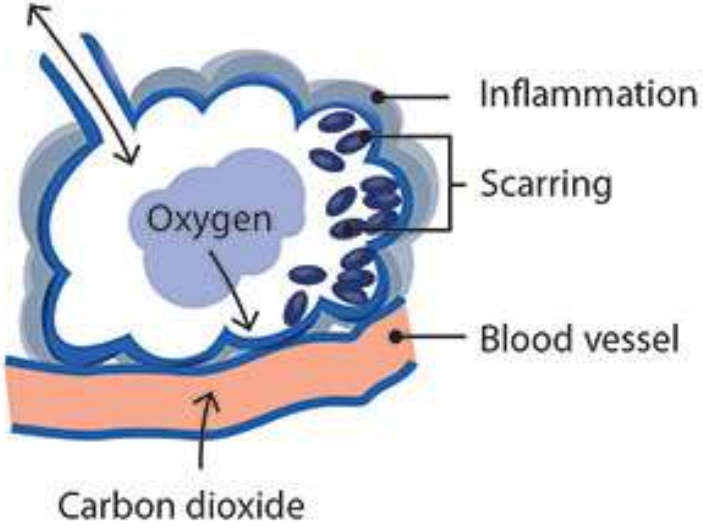
Normal air sac

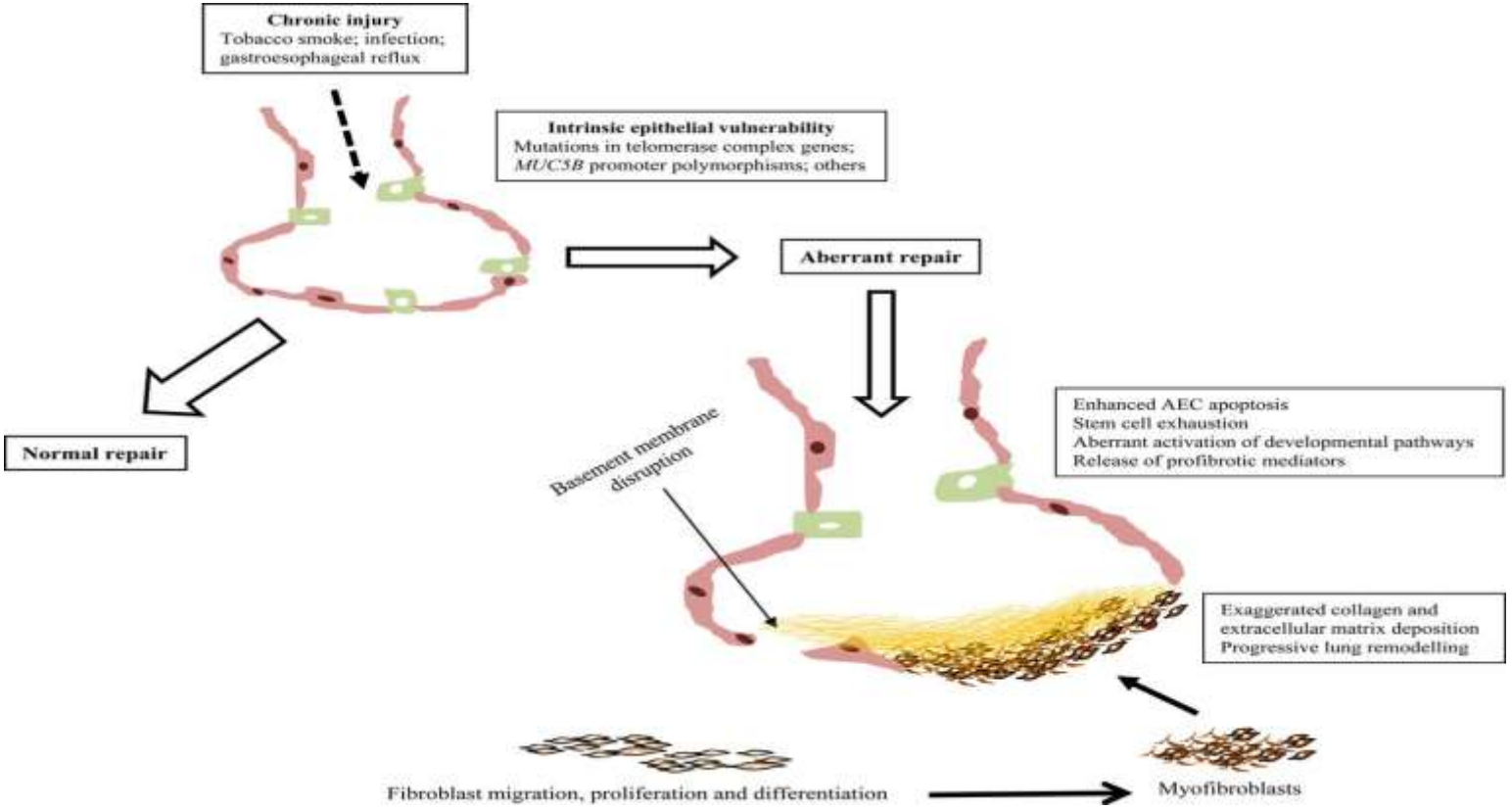
Air to and from mouth/nose

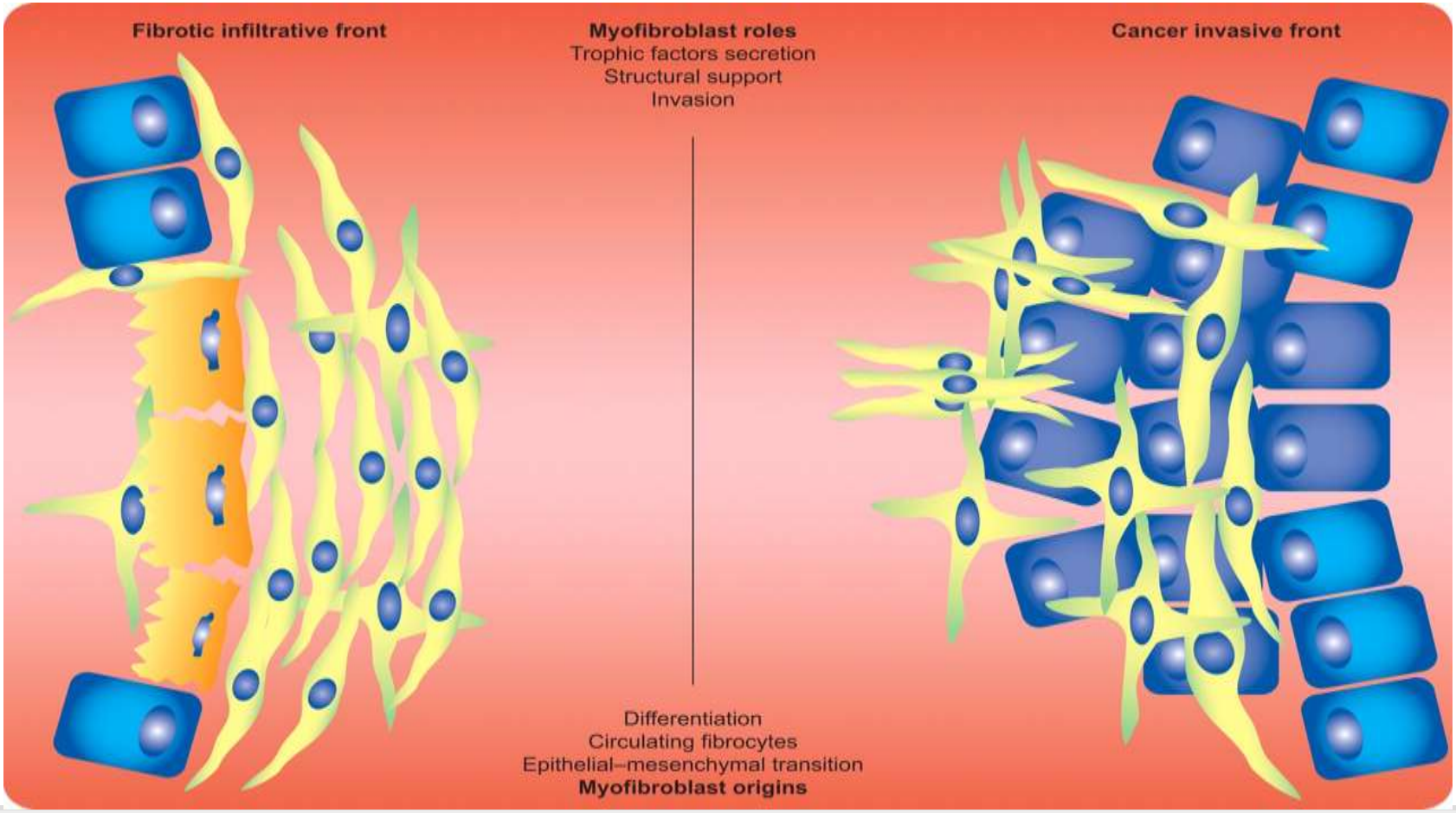


Air sac damaged by IPF

Air to and from mouth/nose

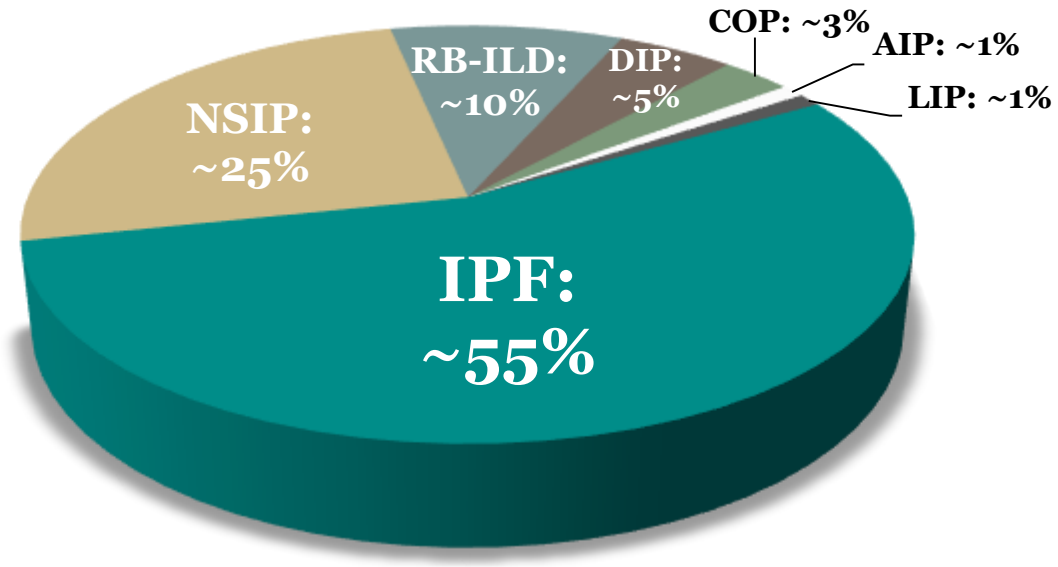



Chronic injury
Tobacco smoke; infection; gastroesophageal reflux
Intrinsic epithelial vulnerability
Mutations in telomerase complex genes; *MUC5B* promoter polymorphisms; others
Aberrant repair
Normal repair
Basement membrane disruption
Enhanced AEC apoptosis
Stem cell exhaustion
Aberrant activation of developmental pathways
Release of profibrotic mediators
Exaggerated collagen and extracellular matrix deposition
Progressive lung remodelling
Fibroblast migration, proliferation and differentiation
Myofibroblasts


Fibrotic infiltrative front
Myofibroblast roles
Trophic factors secretion
Structural support
Invasion
Cancer invasive front
Differentiation
Circulating fibrocytes
Epithelial–mesenchymal transition
Myofibroblast origins

Ipf is the most common type of IIP

IPF occurs on more than half of IIP cases



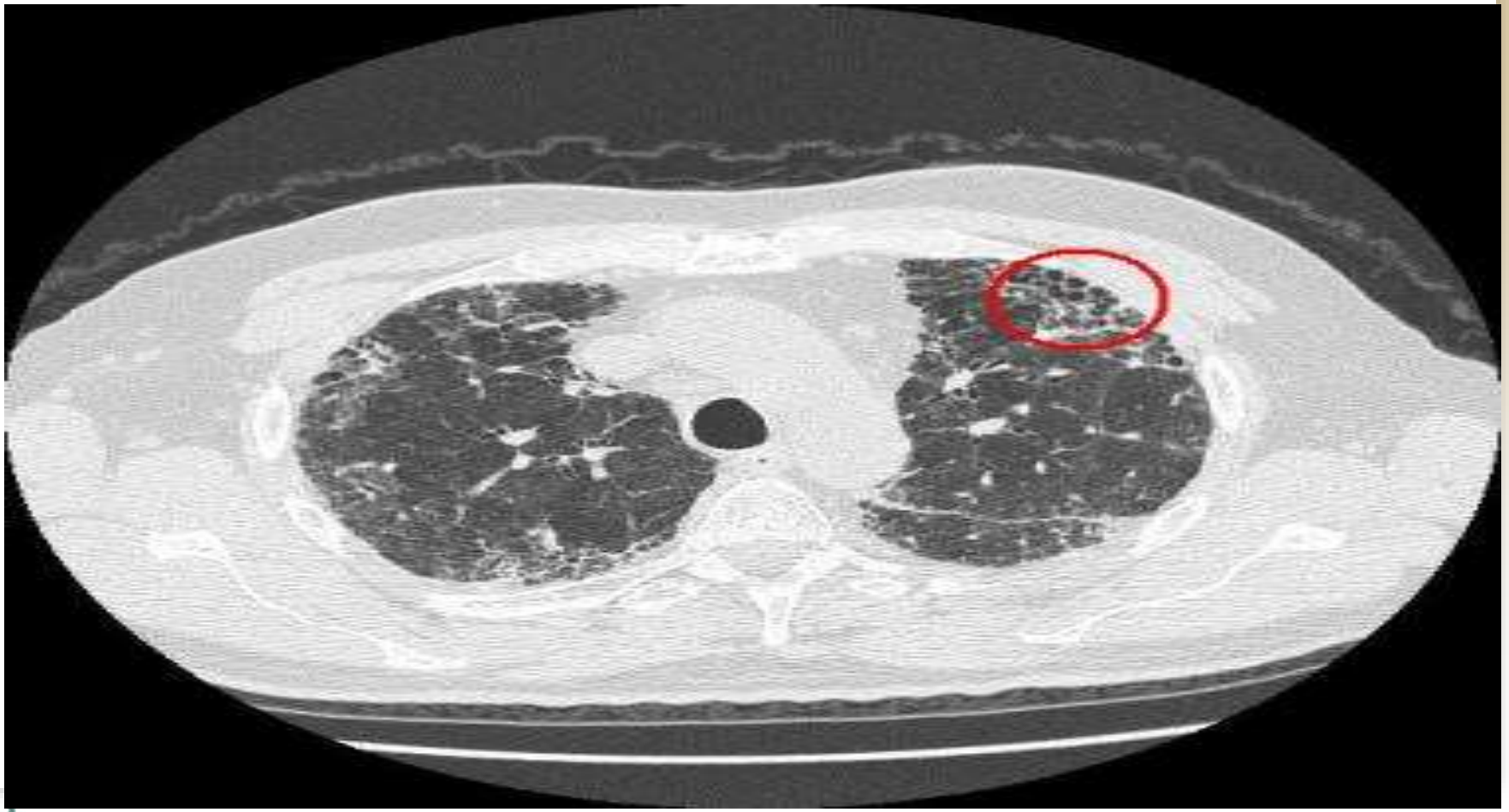
AIP, acute interstitial pneumonia; COPD, cryptogenic organising pneumonia; DIP, desquamative interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; RB-ILD, respiratory bronchiolitis interstitial lung disease

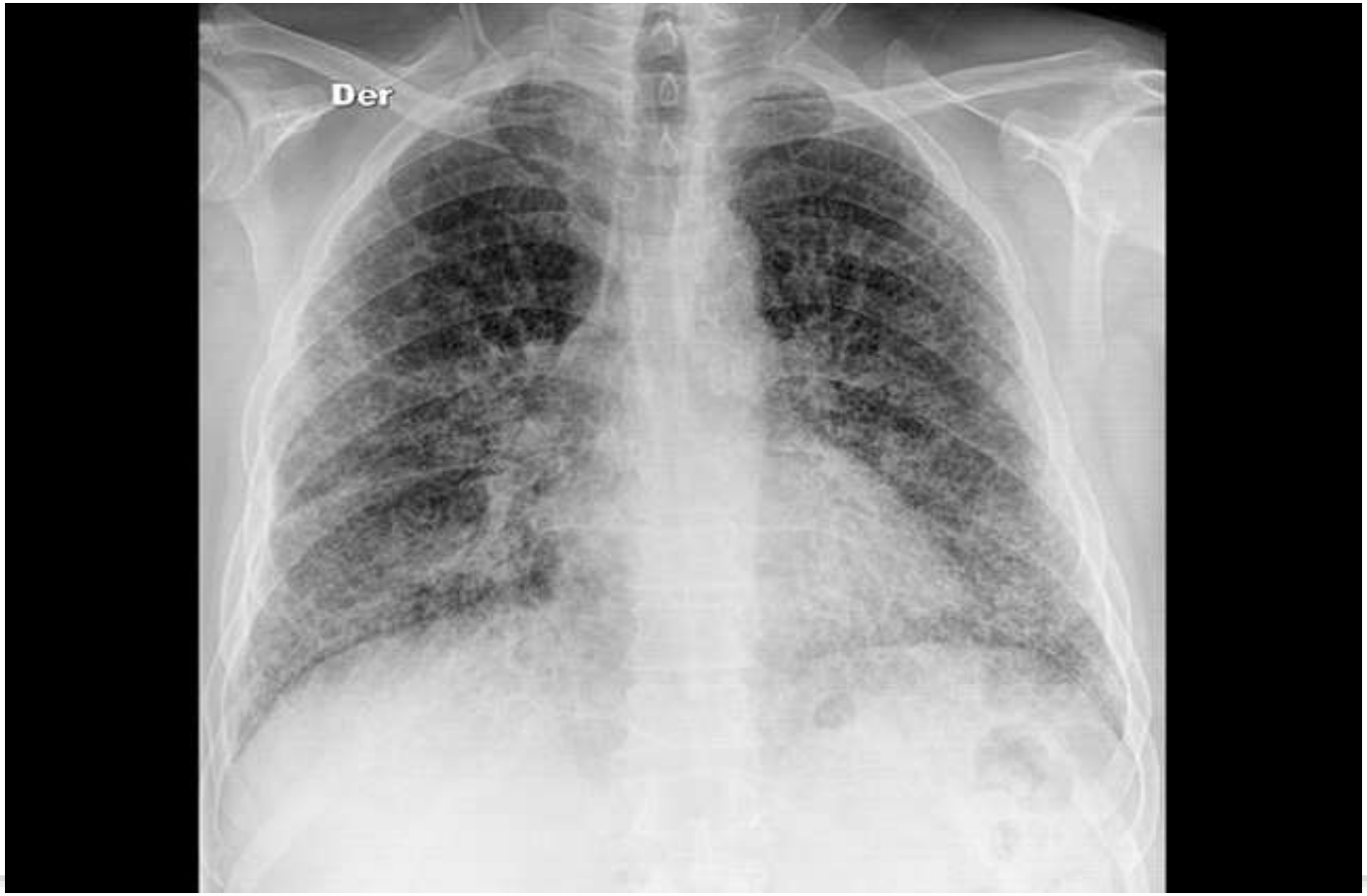
European Lung White Book. Chapter 22: Interstitial lung diseases. Accessed 14th Jan 2014 from: http://www.erswhitebook.org/chapters/interstitial-lung-diseases

Diagnosis

Diagnostic Value of Bronchoalveolar Lavage in Interstitial Lung Disease

Condition	BAL findings
Alveolar proteinosis	Milky effluent, foamy macrophages and lipoproteinaceous intraalveolar material (periodic acid–Schiff stain–positive)
Lipoid pneumonia	Fat globules in macrophages
Pulmonary Langerhans Cell Histiocytosis	Increased CD1+ Langerhans cells, electron microscopy demonstrating Birbeck granule in lavaged macrophage (expensive and difficult to perform)
Asbestos-related pulmonary disease	Dust particles, ferruginous bodies
Berrylliosis	Positive lymphocyte transformation test to beryllium
Silicosis	Dust particles by polarized light microscopy
Lipoidosis	Accumulation of specific lipopigment in alveolar macrophages

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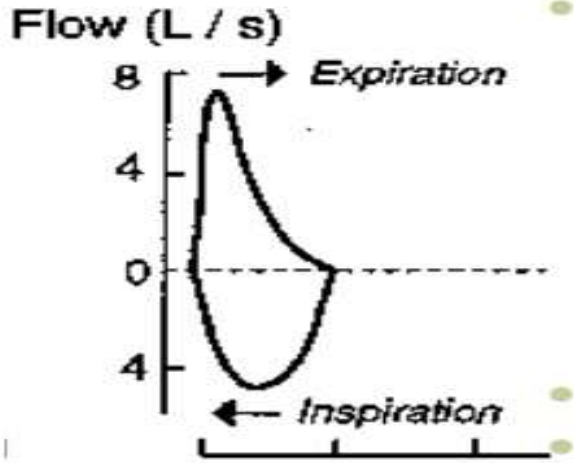
PFT

Restrictive Lung Disease



- Characterized by diminished lung volume due to:
  - change in alteration in lung parenchyma (interstitial lung disease)
  - disease of pleura, chest wall (e.g. scoliosis), or neuromuscular apparatus (e.g. muscular dystrophy)
- Decreased TLC, FVC
- Normal or increased: FEV_1/FVC ratio

IPF EPIDEMIOLOGY

Burden of disease

It is estimated that up to

3 million people worldwide

have IPF

1. Raghu G, et al. Am J Respir Crit Care Med. 2006;174(7):810-816.
3. Nalysnyk L, et al. Eur Respir Rev. 2012;21(126):355-361.

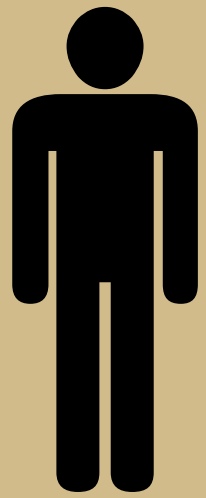
Prevalence

Prevalence of IPF is estimated as

14-42.7

100,000

Persons



Nalysnyk L, et al. Eur Respir Rev. 2012;21(126):355-361.

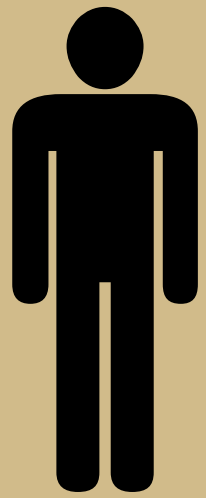
Incidence

Incidence of IPF is estimated as

6.8-16.3

100,000

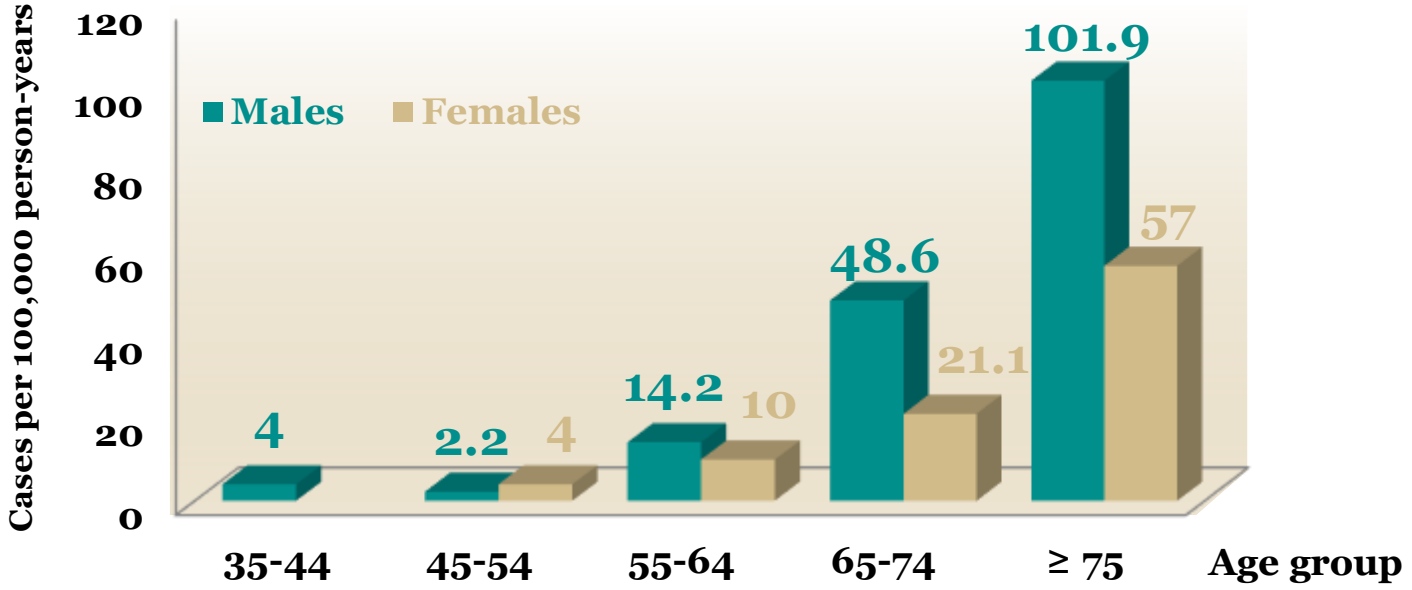
Person-Years



Nalysnyk L, et al. Eur Respir Rev. 2012;21(126):355-361.

Incidence varies according to age and gender

Incidence rates

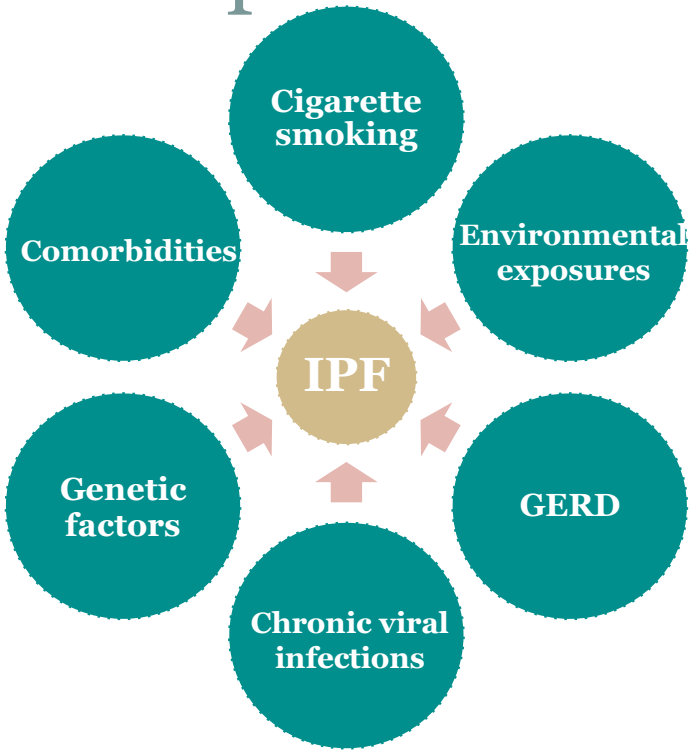


Coultas DB, Zumwalt RE, Black WC, Sobonya RE. Am J Resp Crit Care Med 1994;150(4):967-972.

IPF Risk Factors

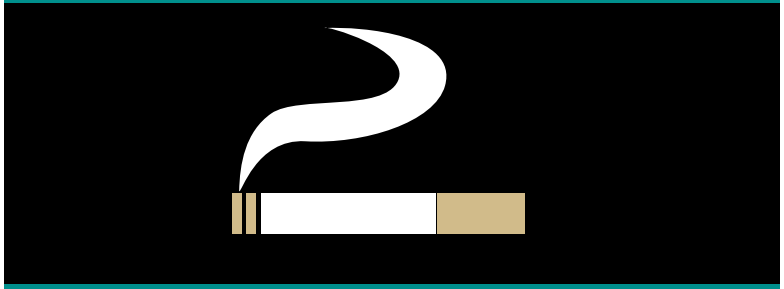
Risk Factors of ipf

Several potential risk factors for developing IPF have been identified:



risk factors of ipf

Cigarette Smoking



A history of smoking (>20 pack-years) is strongly associated with an increased risk for IPF

Environmental and occupational exposure

A variety of environmental exposures is associated with an increased risk for IPF:

- Exposure to metal dusts or wood dusts
- Agriculture exposures
- Hairdressing
- Stone cutting and polishing

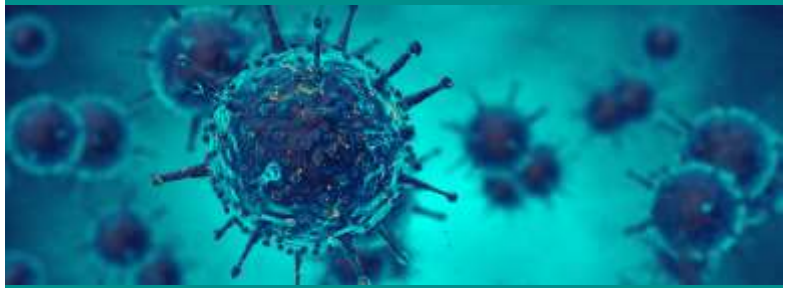
Raghu G. Am J Respir Crit Care Med 2011;183:788-824.

Risk factors of IPF

GERD

- GERD is associated with **microaspiration**
- 66%-87% of IPF patients suffer from GERD
- 33%-53% of patients are **asymptomatic**

Chronic viral infection



- In face of several studies, definite conclusions about the role of chronic viral infections in IPF cannot yet be made
- **Epstein-Barr virus** and **hepatitis C** have been a common focus of research

Raghu G. Am J Respir Crit Care Med 2011;183:788-824.

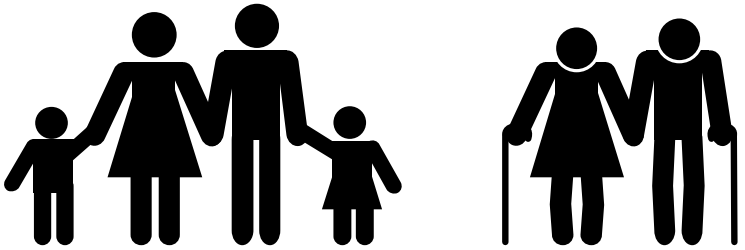
Risk factors of IPF

Genetic factors are suggested to increase the risk of developing IPF

Sporadic IPF

- IPF occurs in only **one person** of a family
- Genetic components linked to the development of sporadic IPF include **polymorphisms** of genes encoding for enzymes, cytokines, profibrotic molecules, coagulation pathway genes and genes for surfactant proteins

Familial IPF

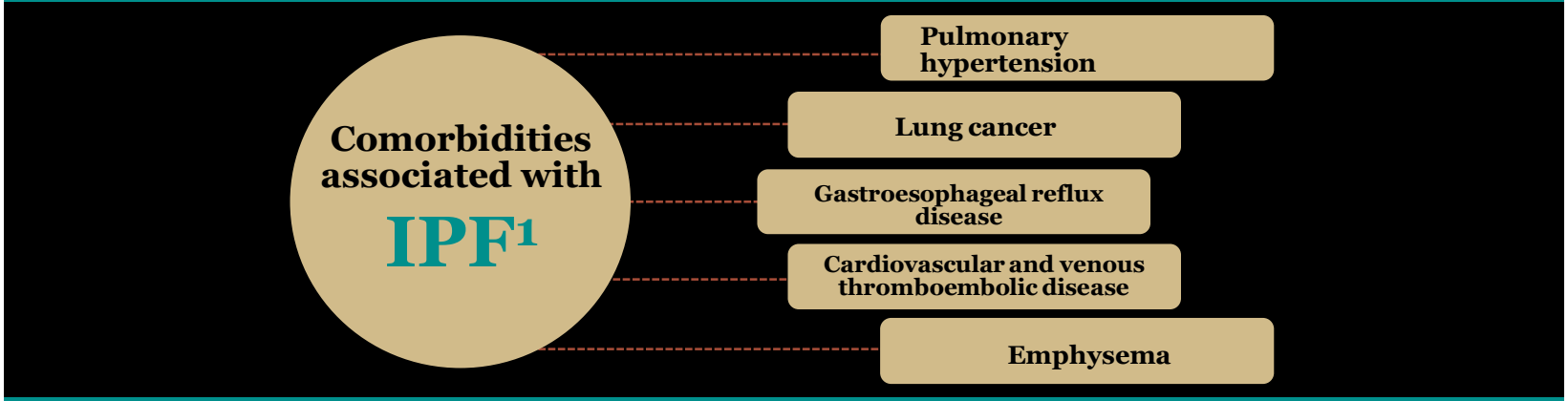


- Disease affects **two or more members** of the same family
- Accounting for <5% of total IPF patient population
- Recent studies identified **genetic mutations** in genes related to familial pulmonary fibrosis including SFTPC, SFTPA2, TERT and TERC

Raghu G. Am J Respir Crit Care Med 2011;183:788-824.

Risk factors of IPF

Comorbidities



- Comorbidities may have a **negative impact** on patients' quality of life[1]
- **Identification** and **management** of comorbidities may improve patients' well-being and their quality of life[1,2]
- **Vaccination** may help prevent unnecessary complications[2]

1. Fell CD. Clin Chest Med. 2012; 33(1): 51-57.
2. Lee JS, McLaughlin S, Collard HR. Curr Opin Pulm Med. 2011; 17(5):348-354

IPF – CLINICAL FEATURES & PRESENTATION

Clinical presentation

IPF is recognised as a distinct disease entity since 2008[1]

Current ATS/ERS guidelines define IPF as[2]:

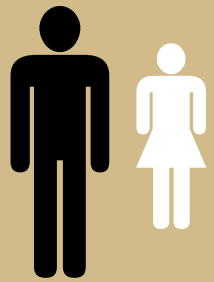
- A type of chronic progressive fibrosing interstitial pneumonia
- Having no known cause
- Occurring primarily in older adults
- Limited to the lungs
- Associated with a radiological or histological pattern of UIP

ATS/ERS, American Thoracic Society/European Respiratory Society.

1. Travis WD, Hunninghake G, King TE Jr, et al. Am J Respir Crit Care Med 2008;177(12):1338-1347.
2. Raghu G. Am J Respir Crit Care Med 2011;183:788-824.

Patient Profile[1,2]

Sex



IPF affects more males than females.

Age

IPF is rarely seen in those under 50 years of age. Diagnosis typically occurs in the 6th to 7th decade of life.

Smoking Status

History of smoking is associated with an increased risk for IPF.

1. Raghu G. Am J Respir Crit Care Med 2011;183:788-824.
2. Meltzer EB & Noble PW. Orphanet J Rare Dis 2008;3:8.

Clinical presentation

IPF is recognised as a distinct disease entity since 2008[1]

Clinical presentation of IPF[2,3]

- Non-productive cough
- Exertional dyspnoea
- Inspiratory crackles
- Compromised pulmonary function
- Finger clubbing

1. Travis WD, Hunninghake G, King TE Jr, et al. Am J Respir Crit Care Med 2008;177(12):1338-1347.
2. Raghu G. Am J Respir Crit Care Med 2011;183:788-824.
3. NHLBI. What are the signs and symptoms of IPF?
Accessed 17th Jan 2014: www.nhlbi.nih.gov/health/health-topics/topics/ipf/signs.html

Patient-reported Symptoms[1,2]

Non-productive cough

In later stages of the disease, the cough may expel mucoid sputum.

Exertional dyspnoea

- Breathlessness upon exertion
- Slow onset, but worsens with time as the disease progresses

1. Meltzer EB & Noble PW. *Orphanet J Rare Dis* 2008;3:8.
2. Du Bois RM & Wells AU. *Eur Respir J* 2001;18(Suppl. 32):43s-55s.

Clinical Respiratory Signs[1,2]

Inspiratory crackles

Also known as:

- Bibasilar end-inspiratory crackles
- Velcro rales

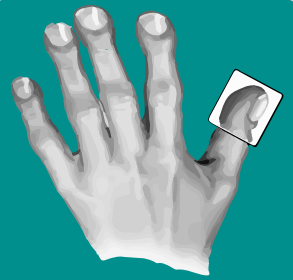
Compromised pulmonary function

- Reduced spirometric volumes (forced vital capacity (FVC))
- Impaired carbon monoxide diffusing capacity of the lung (DL_{CO})

1. Meltzer EB & Noble PW. *Orphanet J Rare Dis* 2008;3:8.
2. Du Bois RM & Wells AU. *Eur Respir J* 2001;18(Suppl. 32):43s-55s.

Physical Indicators

Finger clubbing[1,2]



Digital clubbing

is characterised by bulbous swelling of the ends of the fingers and loss of the angle between the nail bed and the proximal nail fold

50-70% of patients with IPF have clubbing

Other associated indicators

Cor pulmonale may be present at the end-stage of IPF[2]

≈ 90% of patients with IPF have symptoms of **GERD** (gastro-oesophageal reflux disease)[2]

1. Sarkar M, et al. Lung India 2012;29(4):354-362.
2. Meltzer EB & Noble PW. Orphanet J Rare Dis 2008;3:8.

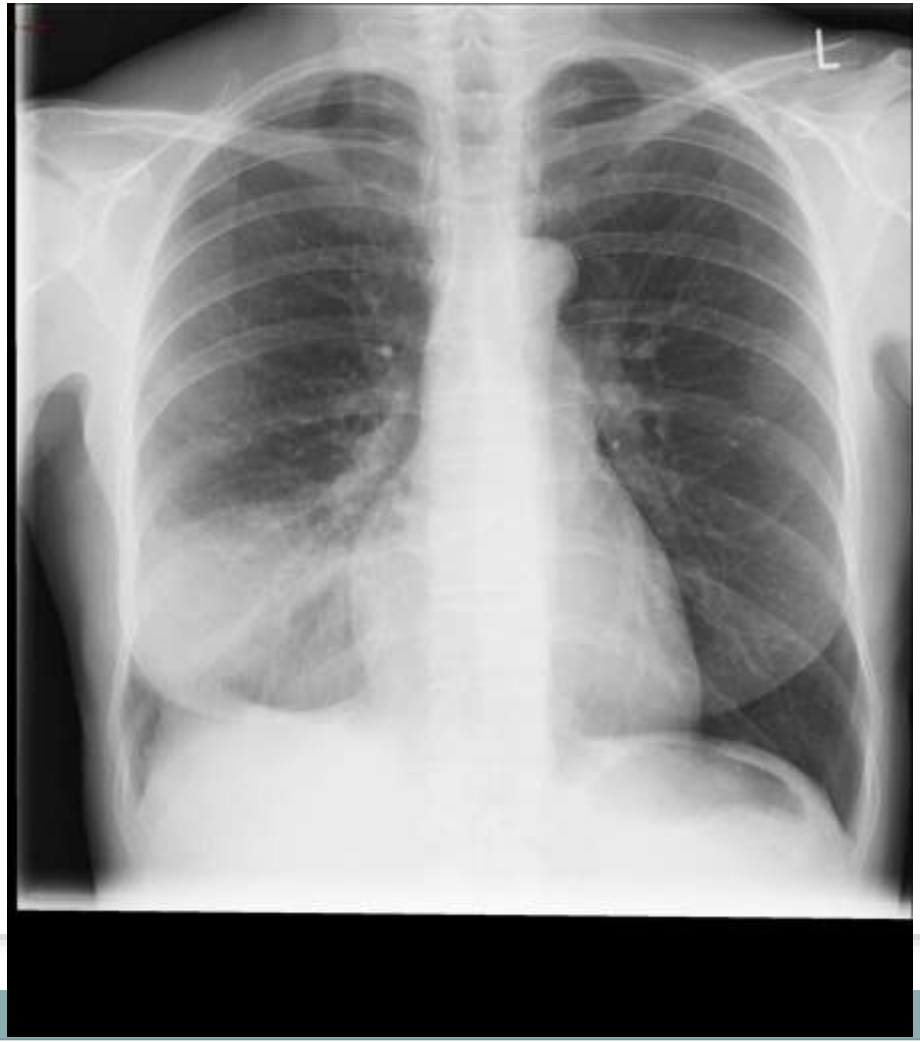
Agent	2015 Guideline	2011 Guideline
New and revised recommendations		
Anticoagulation (warfarin)	Strong recommendation against use*	Conditional recommendation against use‡
Combination prednisone + azathioprine + *N*-acetylcysteine	Strong recommendation against use†	Conditional recommendation against use†
Selective endothelin receptor antagonist (ambrisentan)	Strong recommendation against use†	Not addressed
Imatinib, a tyrosine kinase inhibitor with one target	Strong recommendation against use*	Not addressed
Nintedanib, a tyrosine kinase inhibitor with multiple targets	Conditional recommendation for use*	Not addressed
Pirfenidone	Conditional recommendation for use*	Conditional recommendation against use†
Dual endothelin receptor antagonists (macitentan, bosentan)	Conditional recommendation against use†	Strong recommendation against use*
Phosphodiesterase-5 inhibitor (Sildenafil)	Conditional recommendation against use*	Not addressed
Unchanged recommendations		
Antiacid therapy	Conditional recommendation for use‡	Conditional recommendation for use‡
N-acetylcysteine monotherapy	Conditional recommendation against use†	Conditional recommendation against use†
Anti–pulmonary hypertension therapy for idiopathic pulmonary fibrosis-associated pulmonary hypertension	Reassessment of the previous recommendation was deferred	Conditional recommendation against use‡
Lung transplantation: single vs. bilateral lung transplantation	Formulation of a recommendation for single vs. bilateral lung transplantation was deferred	Not addressed

Case studies

Patient 56 year old female with history of smoking 1 ppd, for 30 years.

Had routine gallbladder surgery, she did well post operatively until day 5

She presented to clinic with dyspnea shortness of breath. Diagnosed with PNA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Readmitted abx and nebs, increased dyspnea on day 10 post

Worsening xray

6 months post surgery had lung biposy, UIP dx