SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2011; 28; 3-17

Interstitial lung disease in the elderly: pathogenesis, diagnosis and management

K.C. Meyer
Section of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health

Abstract. Advancing age is associated with increased risk for some forms of interstitial lung disease (ILD), and this risk is especially reflected by the considerably increased incidence of idiopathic pulmonary fibrosis (IPF) in the elderly. Although the causes of this increased risk are not well-defined, both ageing and IPF have been associated with shortening of telomeres due to telomerase deficiency. Thoracic imaging with high-resolution computed tomographic (HRCT) scanning plays a key role in the diagnosis of ILD in the elderly, and a characteristic appearance of the lung parenchymal changes on HRCT may provide a confident diagnosis and obviate the need for invasive testing such as surgical lung biopsy. An effective treatment for IPF remains elusive, but many patients will benefit from supportive care and treatment of various co-morbid conditions that are often found in patients with IPF.*(Sarcoidosis Vasc Diffuse Lung Dis 2011; 28: 3-17)*

Key words: interstitial lung disease, idiopathic pulmonary fibrosis, aging, elderly patient

Introduction

Infiltrative lung diseases, which are collectively termed interstitial lung disease (ILD), characteristically affect the lung parenchyma in a diffuse fashion (1). Many forms of ILD (Table 1), especially idiopathic pulmonary fibrosis (IPF), can lead to progressive loss of lung function and death. Interstitial lung diseases can affect patients of all ages, but ILD is uncommon in children. Certain forms of the more than 100 different, currently recognized ILD entities tend to occur in young to middle-aged adults (e.g. sarcoidosis), while the most commonly diagnosed form of idiopathic interstitial pneumonia (IIP), IPF, is highly prevalent in the elderly (2-4). Other disorders (pulmonary vasculitis, rheumatoid arthritis-related ILD) tend to be more prevalent in the elderly, and ILD linked to occupational exposures, especially asbestosis, tend to become clinically apparent in older individuals. Lastly, elderly patients often receive prescription drugs that are potentially pneumotoxic, and drug-induced pneumonitis is not uncommon in elderly patients.

The clinical approach to elderly patients with ILD should focus on sparing patients potential harm from complications of procedures and providing reasonable therapies that minimize risk of adverse reactions to pharmacologic or other interventions. Advanced age may modify severity and progression of lung disorders such as pulmonary vasculitis, radia-

Received: 13 August 2010
Accepted: 14 September 2010
Correspondence: Keith C. Meyer, MD, MS, FACP, FCCP
Section of Allergy, Pulmonary and Critical Care Medicine
Department of Medicine
University of Wisconsin School of Medicine and Public Health
Tel. 608 263-6363 (office); 608 263-3035 (secretary)
Fax 608 263-3104
E-mail: kcm@medicine.wisc.edu

Support: The George and Julie Mosher Pulmonary Research Fund

Table 1. The spectrum of interstitial lung diseases

Major category	Specific disorders
Idiopathic interstitial pneumonias	▪ Idiopathic pulmonary fibrosis (IPF) ▪ Non-specific interstitial pneumonia (NSIP) ▪ Cryptogenic organizing pneumonia (COP) ▪ Desquamative interstitial pneumonia (DIP) ▪ Respiratory bronchiolitis with ILD (RBILD) ▪ Acute interstitial pneumonia (AIP) ▪ Lymphoid interstitial pneumonia (LIP)
Granulomatous disorders	▪ Sarcoidosis ▪ Hypersensitivity pneumonitis (pathology can overlap with NSIP or organizing pneumonia) ▪ Chronic beryllium disease (CBD)
Iatrogenic lung disease	▪ Drug-induced pneumotoxicity ▪ Radiation pneumonitis and/or fibrosis
Connective tissue disorders (aka collagen-vascular disease) that may cause ILD	▪ Vasculitis (pulmonary capillaritis, lung involvement in systemic vasculitis) ▪ Systemic sclerosis ▪ Rheumatoid arthritis ▪ Systemic lupus erythematosus ▪ Dermatopolymyositis ▪ Sjögren's syndrome ▪ Mixed connective tissue disease ▪ Undifferentiated connective tissue disease
Eosinophilic pneumonias	▪ Acute eosinophilic pneumonia ▪ Chronic eosinophilic pneumonia ▪ Eosinophilic pneumonia in systemic disease - Churg-Strauss syndrome - Idiopathic hypereosinophilic syndrome ▪ Eosinophilic pneumonia of known cause - Infection - Drug-induced
Inherited disorders	▪ Hermansky-Pudlak syndrome ▪ Familial idiopathic interstitial pneumonia ▪ Neurofibromatosis/tuberous sclerosis ▪ Metabolic storage diseases ▪ Pulmonary alveolar microlithiasis
Occupational/environmental disorders	▪ Asbestosis ▪ Silicosis ▪ Coal-worker's pneumoconiosis ▪ Chronic beryllium disease
Primary/unique disorders	▪ Pulmonary Langerhans cell histiocytosis ▪ Alveolar proteinosis ▪ Lymphangioleiomyomatosis ▪ Amyloidosis ▪ Lipoid pneumonia
Other disorders	▪ Diffuse alveolar damage (DAD): associated with numerous causes (drug reactions, inhalational injury, AIP, etc.) ▪ Diffuse alveolar hemorrhage (DAH) : numerous causes including capillaritis, other pulmonary microvascular disorders, DAD, drug effects, bland hemorrhage

tion-induced pneumonitis and fibrosis, or pneumotoxic drug reactions. This has been demonstrated for ANCA-associated vasculitis (5-6), but these disorders can occur at any age. Because IPF truly appears to be an ageing-related form of ILD, this article will focus extensively on the pathogenesis, natural history, and treatment of IPF.

Susceptibility to lung injury and fibrosis associated with advanced age

Ongoing research in animal models and in human subjects are providing substantial insights into the pathogenesis of pulmonary fibrosis (PF). Mesenchymal cells derived from epithelial to mesenchymal transition and bone marrow-derived fibrocytes that traffic to the lung are hypothesized to contribute to the populations of (myo)fibroblasts that respond to fibrogenic cytokines and growth factors that have been implicated in PF pathogenesis, and arrays of genes are being uncovered that are differentially expressed in fibrotic lungs versus control lungs (7). Advancing age may modulate pro-inflammatory and fibrotic responses, as shown by recent findings that inflammatory responses to bleomycin are exaggerated in senescence-accelerated mice and a greater degree of fibrosis correlates with mobilization of bone marrow-derived fibrocytes and higher levels of the profibrotic cytokine, transforming growth factor- 1 (8). Additionally, defects in cellular homeostasis associated with advanced age, such as decline in the ability to repair damaged cellular components via autophagy (9) may increase susceptibility to oxidative stress and injury that can lead to PF.

Various genetic abnormalities or disorders have been linked to PF (Table 2), and some specific gene mutations and polymorphisms have now been associated with PF. These include surfactant-associated protein gene mutations and certain gene polymorphisms (e.g. IL-1 receptor antagonist, TNF-α, complement receptor-1, TGF-β1, and plasminogen activator inhibitor-1) (10). Such associations indicate that genetic factors undoubtedly play a key role in disease susceptibility, although gene-gene and/or gene-environment interactions as well as epigenetic factors undoubtedly influence susceptibility to PF (11, 12). Two endogenous gene products that may be particularly crucial mediators of PF are endothelin-1 and TGF-β1, which may have synergistic effects in inducing PF (13, 14). Other observations that support a genetic predisposition to PF include the differential responses of inbred mouse strains to fibrogenic agents as well as the considerable variation in susceptibility to developing pneumoconioses that occurs in humans with sustained exposure to fibrogenic dusts. Interestingly, aged Fischer 344 rats display increased interstitial matrix volume with advanced age that appears to be caused by progressive thickening of basement membranes combined with continuous deposition of mature, cross-linked collagen, but such changes are not observed in the mouse and do not result in visible change in the overall gross architecture of lung matrix for old versus young animals (15).

Table 2. Genetic abnormalities linked to pulmonary fibrosis

Clinical disorders associated with PF
- Tuberous sclerosis
- Neurofibromatosis
- Niemann-Pick disease
- Gaucher disease
- Hermansky-Pudlak syndrome
- Familial hypocalciuric hypercalcemia
- Familial idiopathic interstitial pneumonia
  - Surfactant protein C
  - ELMOD-2

Gene polymorphisms associated with PF
- IL-1 receptor antagonist
- TNF-α
- Complement receptor-1
- Surfactant associated proteins (SP-A, SP-B)
- ACE
- TGF-β1
- Plasminogen activator inhibitor-1

Impaired gene function associated with PF
- reduced telomerase function (telomere shortening)

Factors that are inherent to advancing age may come into play with advancing age and explain the greatly increased susceptibility of older individuals to pulmonary fibrosis. Of particular interest is the recently identified, age-associated reduction in telomerase activity in human somatic cells (16). A reduction in telomerase activity can decrease its inhibitory effect on the differentiation of fibroblasts into myofibroblasts (17). Additionally, senescent fibroblasts have been shown to display altered expression of plasminogen activator inhibitor-1, which has been associated with fibrosis (18). Insufficiency of stem cell responses as a consequence of advanced age may also play a significant role in susceptibility to lung injury and fibrosis, both in responding to injurious events or stimuli as well as in maintaining the integrity of well-functioning lung tissues (19, 20).

Because PF displays a considerably increased prevalence in humans who are in their sixth decade of life or beyond, telomerase mutations that are associated with adult-onset PF are of particular interest. Telomeres are shorter in older versus younger in-

dividuals, and this shortening has been linked to human aging. Telomerase antagonizes or reverses telomere shortening, and cultured cells display replicative senescence as telomeres shorten. Mutations in the reverse transcriptase protein component (hTERT) of the telomerase ribonucleoprotein complex have been linked to dyskeratosis congenita as well as sporadic bone marrow failure (21), and hTERT mutations have recently been linked to familial PF (22, 23). Examination of cultured fibroblasts and other cell types from patients with IPF associated with telomerase complex gene mutations has revealed reduced telomere lengths versus age-matched controls (24). Short, dysfunctional telomeres can lead to cell death or cell cycle arrest if damage to DNA occurs However, the observation that hTERT mutations and telomere shortening occur in family members without pulmonary fibrosis indicate that other factors (e.g. environmental effects, other genes) likely modulate clinical expression of disease. Nonetheless, the interconnected pathways of telomere dysfunction and DNA damage appear to be activated as a consequence of ageing and tissue fibrosis (25). Another pathway that may prove to be very important in ageing and pulmonary fibrosis is the WNT signaling pathway, which has been associated with accelerated stem cell ageing and with pulmonary fibrosis (26, 27).

Other observations suggest that the aging lung may be more susceptible to injury and fibrosis with exposure to certain environmental agents such as sustained inhalation of cigarette smoke or fibrogenic agents earlier in life. The relative incidence of asbestosis increases significantly as exposed individuals age for those exposed to significant amounts of asbestos (28). Interestingly, animal models have shown that lung fibroblasts from aged mice are more susceptible to DNA damage when subjected to oxidative stress (29), and animal studies suggest that antagonizing oxidative stress in aged rats may prevent cellular injury (30). Cigarette smoking is a risk factor for the development of IPF, and other exposures have also been associated with susceptibility to develop IPF (31, 32).

Although little data exists for the role of age in susceptibility to the pneumotoxic effects of drugs, advancing age may increase susceptibility to drug-induced diffuse lung disease and fibrosis. However, there are no data to support this possibility, and multiple complex metabolic and genetic factors have been linked to drug-induced lung injury (33). Nonetheless, elderly patients are more likely to be receiving drugs that are known causes of interstitial pneumonitis/fibrosis, and pneumotoxic reactions must be ruled out in all elderly patients who present with diffuse lung disease. Lastly, the elderly are more susceptible to tuberculosis (34), which is especially prevalent in less developed and third-world countries and may present with a diffuse infiltrative lung disease pattern.

Epidemiology of IPF

Because most of the available studies were performed before the current definition of IPF was adopted and did not exclude other forms of IIP, a relative lack of studies based on population screening combined with a lack of uniform diagnostic criteria have made it difficult to establish a truly accurate estimate of the incidence and prevalence of IPF. Despite these problems, IPF does not appear to have a biased expression on the basis of race or ethnic background. However, males are more frequently affected than females. Coultas et al. (2) reported the incidence and prevalence of IPF in the desert southwestern region of the U.S. as 11 and 20 per 100,000 per year respectively for men and 7 and 13 per 100,000 per year for women. A study in the United Kingdom that examined data from a longitudinal computerized general practice database estimated the incidence of IPF at 4.6 per 100,000 person-years and observed a progressive increase in the incidence for the periods of 1991-1995 to 2000-2003 (35).

A more recent study by Raghu and colleagues (3) using relatively narrow criteria (diagnostic code for IPF plus procedure code for lung biopsy, transbronchial biopsy, or thoracic CT scan) found the incidence and prevalence of IPF in the U.S. to be 6.8 and 14 per 100,000/year. When broader diagnostic criteria were used (diagnostic code only), the incidence and prevalence were 16.3 and 42.7 per 100,000/year. Both Coultas et al. and Raghu et al. found a dramatic increase in the incidence and prevalence of IPF with advancing age. Coultas et al. reported that the incidence and prevalence of IPF in persons age 75 and older were 102 and 175 for men

Table 3. Criteria for the clinical diagnosis of IPF (35)

Major (all 4 required)
• Typical HRCT appearance
• Exclude other diseases
• PFTs showing parenchymal restriction and impaired gas exchange
• BAL or transbronchial lung biopsy not showing alternative diagnosis
Minor (3 of 4 required)
• Bibasilar velcro-like crackles
• Age>50
• Duration of illness > 3 months
• Insidious onset

and 57 and 73 per 100,000 for women. Similarly, Raghu et al. estimated an incidence and prevalence of 71 and 271 per 100,000/year for elderly men and 67 and 266 per 100,000/yr for elderly women. A recently published population-based study in Minnesota also found a relatively high incidence of IPF in elderly patients aged 70-79 years (4). In comparison, the incidence of IPF approaches that of primary lung cancer in the elderly (36), and the incidence of colorectal cancer is estimated at 15-18 per 1000,000/yr (37). Increased death rates from IPF have also been recently reported all across the USA, and fatal respiratory exacerbations are common (4, 38).

Pathobiology and natural history of IPF

IPF is characterized by radiological and/or histopathological patterns of usual interstitial pneumonia (UIP) on surgical lung biopsy or by a constellation of clinical criteria that predict a confident diagnosis of IPF in the absence of a surgical lung biopsy (39-43). When the diagnosis of IPF is made, it infers that patients lack other explanations for the presence of a UIP lesion, such as an associated connective tissue disorder or an iatrogenic /environmental exposure that can cause pulmonary fibrosis with a UIP histopathological pattern. Lung histopathology in UIP demonstrates areas of essentially normal lung interspersed with fibrotic lesions that are characterized by temporal heterogeneity. Architectural distortion of the lung parenchyma is a hallmark characteristic of UIP, and other histopathologic findings that are characteristic of UIP include the presence of fibroblast foci (discrete collections of fibroblasts, myofibroblasts, and newly formed collagen), smooth muscle hyperplasia, and honeycomb cysts (dilated airspaces lined with bronchiolar epithelium and usually filled with inspissated mucus and inflammatory cells). Examination of native lung explants from patients with a pre-transplant diagnosis of IPF who received a transplanted lung are highly likely to show areas consistent with changes of NSIP as well as desquamative interstitial pneumonia (DIP) (44). Additionally, Flaherty et al. (45) found that surgical lung biopsies from different lung regions in a given patient often show discordant histopathology, with one regional biopsy showing UIP but another showing NSIP. Survival was observed to be better for patients with concordant NSIP/NSIP and worst for those with concordant UIP/UIP, while that for patients with UIP/NSIP was similar to that for UIP/UIP.

Abnormal wound healing and tissue remodeling may account for the progressive nature of the lung lesions in IPF (or other progressive forms of PF) and the inability of the injured lung to return to normal structure and function (Figure 1). Increased levels of proinflammatory cytokines and chemokines that promote inflammation and fibroproliferation support a role for inflammation and polarization of immune responses in the IPF lung, even though conventional anti-inflammatory/immunosuppressive therapies appear to have little effect on disease progression (46). Key cytokines that have been implicated as promoting fibrotic responses include TGF-beta, IL-13, and CC chemokines) (46). Other abnormalities that have been identified include epithelial injury associated with apoptosis and loss of type I alveolar cells accompanied by a proliferation of type II cells and basement membrane disruption, and reactive oxygen intermediates are released as inflammatory cells are recruited to the lungs and fibrosis progresses.

Another aspect of damage and remodeling of the lung parenchyma consists of microvascular changes that include evidence of endothelial cell death accompanied by recruitment of endothelial cells and fibroblasts, activation of the coagulation cascade, and deposition of excessive extracellular matrix. Turner-Warwick (47) described extensive microvascular remodeling that was characterized by neovascular changes in areas of fibrosis and in areas where anastomoses between systemic and pul-

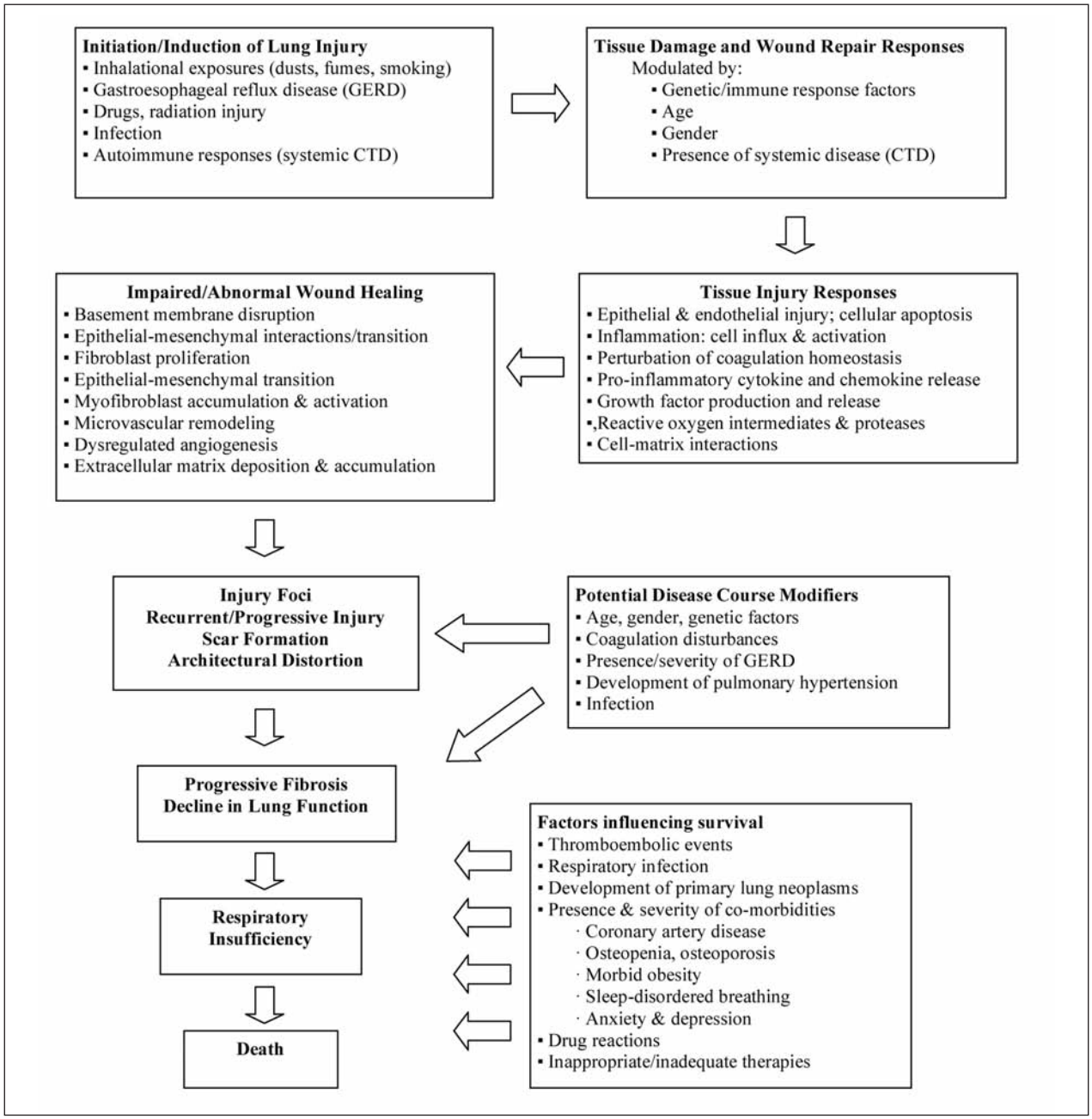


Fig. 1. Pathobiology and natural history of progressive pulmonary fibrosis (e.g. IPF)

monary microvasculature were identified. Aberrant vascular remodeling has also been described in animal models of pulmonary fibrosis (48), and communications between the systemic and pulmonary microvasculature may promote right-to-left shunting and hypoxemia, especially during physical exertion. Additionally, more extensive microvascular changes may predispose patients to develop secondary pulmonary hypertension (PH) and further exacerbate gas exchange in patients who develop this complication. Vascular remodeling in IPF has been associated with an imbalance of angiogenic and angiostatic

CXC chemokines with net augmentation of angiogenic activity (49), but a relative lack of the potent angiogenic factor, vascular endothelial growth factor (VEGF) (50), as well as enhanced expression of angiostatic factors such as pigment epithelial-derived factor have also been described in IPF (51). One interesting distinction between granulation tissue seen in organizing pneumonia and the fibroblast foci of UIP is a relative paucity of pro-angiogenic cytokines in the fibroblast foci of UIP (52).

Pulmonary hypertension (PH) is a frequent complication of IPF. Lettieri et al. (53) identified PH (defined as mean pulmonary artery pressure >25 mm Hg) in 31.6% of patients undergoing pre-transplant evaluation with cardiac catheterization. Higher pulmonary arterial pressures correlated with increased risk of death, and patients with PH had a lower DL_{CO}, lower walk distance and greater oxyhemoglobin desaturation on a six minute walk test (6-MWT), and patients with secondary PH were more likely to require supplemental oxygen therapy. Nadrous et al. (54) found that systolic pulmonary artery pressure that was estimated via echocardiography correlated inversely with DL_{CO}, and patients with systolic pulmonary artery pressure (sPAP) greater than 50 mm Hg had a significantly worse survival than patients with milder pressure elevation. When a cohort of lung transplant candidates with IPF were re-evaluated with right heart catheterization just prior to undergoing lung transplant, the prevalence of PH had increased from 33% to 85% of patients (55), suggesting that the risk of developing secondary PH gradually increases as lung function becomes progressively impaired. Additionally, examination of the United Network for Organ Sharing (UNOS) database identified PH in 46.1% of patients with IPF who had undergone right heart catherization (56), and 6-MWT distance was significantly lower in recently listed patients with IPF who had PH vs. those who did not have PH (57).

Median survival in IPF has been shown by various investigators to range between 2 and 5 years (58), and survival of patients with IPF is clearly worse than that for patients with other forms of IIP such as cellular NSIP. However, survival varies according to various factors such as age, extent of fibrosis, the presence of secondary hypertension, or other specific features of the clinical presentation. Flaherty et al. (59) found that patients who had an indeterminate HRCT combined with a surgical lung biopsy that showed UIP had a median survival of 5.8 yrs, while those with typical HRCT findings had a median survival of 2.1 years. One explanation for this considerable difference in survival may be that individuals with indeterminate HRCT findings were diagnosed much earlier in the course of their disease than if HRCT showed typical changes that provide a confident diagnosis of IPF. Interestingly, survival with collagen-vascular disease-associated UIP has been observed to be better than that for patients with idiopathic UIP/IPF (60).

Various clinical findings, measures of lung function, and the extent of fibrosis on HRCT have been linked to disease progression and survival, but the clinical course of IPF can be quite variable. Some patients can have sustained and relatively rapid decline in lung function that leads to respiratory failure versus others with fairly stable and relatively gradual decline in lung function over prolonged periods of time. The trigger(s) and determinants for acute and/or rapid decline in respiratory status are largely unknown. Acute exacerbations can occur in patients who are otherwise stable and result in a precipitous decline and death (61, 62). Although the exact incidence and prevalence of acute exacerbation in IPF (AEIPF) is unknown, it is apparent that such rapid decline may occur in at least 5-15% of patients with IPF. A recent perspective implicates occult infection, GER and microvascular coagulation as potential risks and/or causative factors for AEIPF (63). Some of the most useful measures (Table 4) that correlate with disease severity and/or progression are subjective dyspnea, change in FVC over time, baseline DLCO and change over time, and degree of oxyhemoglobin desaturation or change in walk distance during a six-minute walk test (6-MWT), or a modified 6-MWT (64-69). Patients with severe reduction in DLCO are more likely to have secondary pulmonary hypertension (PH) as a complication of their disease (53). Although most patients succumb to respiratory complications of their disease, many die of other causes such as cardiac events or malignancy (70). Patients with IPF are at increased risk to develop primary lung cancer, even when smoking is not a factor (71). They are also at risk for pulmonary infection, venous thromboembolism, and adverse drug reactions.

Table 4. Clinical correlates of disease progression and survival in IPF

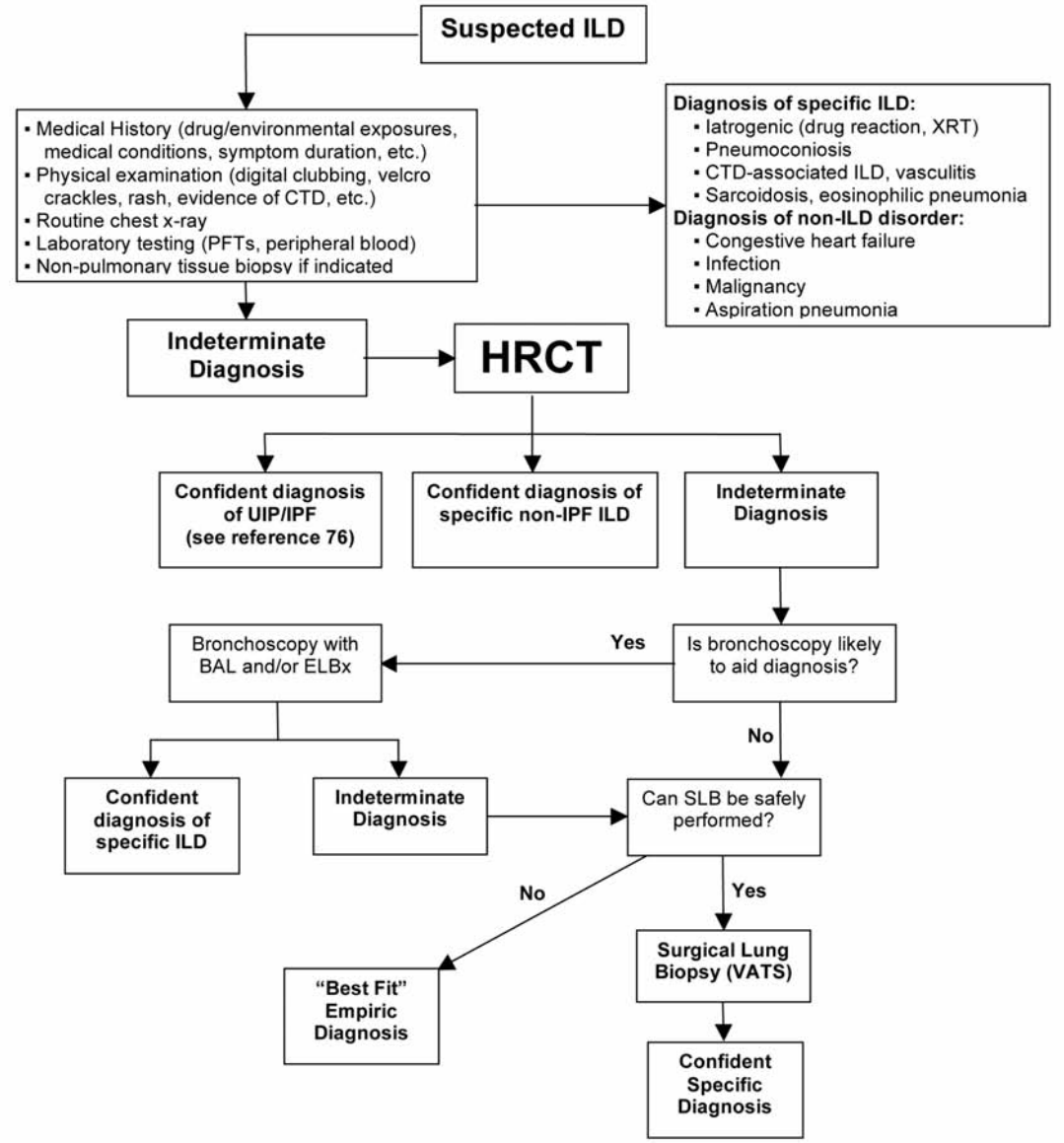
Clinical variable	Predictive characteristics
FVC	▪ >10% decline in serial values indicates progressive disease ▪ Decline on serial testing correlates with disease progression and mortality risk
DLCO% predicted	▪ Worse survival if <35% predicted ▪ ≈40% predicted = breakpoint for severe disease and increased risk of PH ▪ ≥15% decline in serial measurements correlates with progressive disease
6-MWT	▪ Desaturation to ≤88% correlates with increased mortality risk ▪ Walk distance correlates with mortality risk ▪ Decline in distance (≥200 ft) on serial testing indicates progressive disease
Dyspnea score	Changes over time correlate well with stability/progression
Respiratory event	Hospitalization for a respiratory complication predicts accelerated progression
HRCT	▪ Extent of reticulation and honeycombing correlates with mortality ▪ Worsening (↑ honeycomb change) detected over longer time periods (≥2 yrs) correlates with decline in clinical status
Lung histopathology	▪ Extent of fibrosis correlates with progression and mortality
PAP - Echocardiogram - RH catheterization	▪ PH (e.g. mean pulmonary artery pressure ≥35 mm Hg) correlates with increased risk of progression and mortality ▪ Echocardiographic estimates of PAP are less reliable than RH catheterization and may be misleading

Abbreviations Used: DLCO=diffusion capacity for carbon monoxide; 6-MWT=6-minute walk test; FVC=forced vital capacity; PAP=pulmonary artery pressure; PH=pulmonary hypertension

Diagnostic approach to ILD in the elderly patient

An elderly patient with symptoms and signs that are suggestive of possible ILD must be carefully evaluated to determine whether ILD is present and to identify its cause if the suspicion of ILD is confirmed (Figure 2). Most patients with ILD present with progressive dyspnea, and many have cough. Most forms of ILD are characterized by a subacute or chronic course and presentation, but some may develop quite rapidly over the course of a few days to weeks. These include acute interstitial pneumonia (AIP), acute eosinophilic pneumonia (EP), acute hypersensitivity pneumonitis (HP), drug reactions, and organizing pneumonia (OP). Additionally, acute exacerbations of idiopathic pulmonary fibrosis (IPF) can occur in patients with pre-existent but unrecognized disease. Some conditions, such as congestive heart failure, aspiration pneumonitis, or lymphangitic carcinoma, can masquerade as ILD. Exposures in the workplace as well as other settings may be the cause of ILD, and a careful and comprehensive exposure history must always be obtained including remote and even transient exposures. Cigarette smoking is a risk factor for IPF, but other forms of ILD (pulmonary Langerhans histiocytosis, desquamative interstitial pneumonia, and respiratory bronchiolitis with ILD) are also strongly linked to smoking. The elderly patient can also present with a connective tissue disorder or vasculitis. Therefore, extrapulmonary symptoms and signs should be sought to identify clues that suggest the presence of a connective tissue disorder (CTD). Lastly, a large number of prescription drugs can cause interstitial pneumonitis that can progress to pulmonary fibrosis, and elderly patients are often taking many drugs. Commonly used medications that are particularly notorious for causing pulmonary toxicity include methotrexate, amiodarone, and nitrofurantoin. The number of drugs that are associated with acute and chronic lung inflammation that can progress to irreversible fibrosis is quite formidable, and the website, www.pneumotox.com, provides an invaluable resource that provides key information concerning specific drugs and their potential to cause adverse pulmonary reactions.

Patients with IPF are usually in their sixth to eighth decade of life, and they tend to have relatively advanced disease and HRCT findings that are typical for IPF when they are evaluated. Because UIP can be associated with certain exposures (e.g. pneumotoxic drugs) or various rheumatologic disorders (e.g. rheumatoid arthritis), a detailed clinical history should help to exclude environmental expo-



Abbreviations: CTD=connective tissue disease; HRCT=High-resolution computed tomography of the thorax; ILD=Interstitial lung disease; UIP=Usual interstitial pneumonia; IPF=Idiopathic pulmonary fibrosis; BAL=bronchoalveolar lavage; ELBx=endoscopic lung biopsy (transbronchial or endobronchial); SLB=surgical lung biopsy; VATS=Video-assisted thorascopic surgery; XRT=radiotherapy

Fig. 2. Diagnostic approach to suspected ILD in the elderly patient

sures associated with pulmonary fibrosis, to identify medications that can induce a pneumotoxic reaction, or to detect a collagen-vascular disorder that may be present. Physical examination usually reveals bilateral rales at the lung bases on chest auscultation, and many patients have digital clubbing. A restrictive ventilatory defect on pulmonary function testing and a reduction in the diffusion capacity for carbon monoxide (DL_{CO}) are typically found. Arterial hypoxemia is usually present with advanced disease, and oxyhemoglobin desaturation can often be brought out with exercise when milder disease is present by performing cardiopulmonary exercise testing or a 6-minute walk test (6-MWT). It should

be kept in mind that arterial oxygen tension and oxyhemoglobin saturation values can be lower in elderly patients than the usual values for younger individuals due to age-related decline in lung function and do not necessarily indicate the presence of a lung parenchymal abnormality.

Chest radiographs typically reveal bilateral interstitial opacities that are most prominent at the lung bases and in peripheral subpleural locations, but such changes can be seen with other forms of ILD, such as other forms of idiopathic interstitial pneumonia (IIP), asbestosis, or hypersensitivity pneumonitis. Occasionally, the routine chest radiograph may not reveal any significant abnormalities, and the disease is detected only when HRCT is performed. HRCT is a key tool for evaluating patients with diffuse parenchymal lung disease, and typical HRCT changes in UIP include a predilection for basilar and peripheral lung zones with patchy involvement and relative sparing of more central areas (72). Linear opacities, which represent thickened intralobular and interlobular septae, are observed, and more advanced disease is characterized by honeycomb cysts (representing bronchiolectasis) and traction bronchiectasis. Ground-glass opacities (GGO) should be minimal or absent, and the finding of prominent GGO on HRCT would suggest an alternative diagnosis such as NSIP or cryptogenic OP (COP).

Although bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial lung biopsy (TBLB) can provide useful information that may establish the diagnosis of a specific form of ILD or at least substantially narrow the differential diagnosis, adequate sampling from two or more geographic lung regions (e.g. upper and lower lobes) via a surgical lung biopsy (SLB) is required to definitively characterize the histological pattern as UIP or other forms of IIP and thereby the definitive and most confident diagnosis of IPF, especially in patients who have clinical and imaging features that are atypical for IPF. Bronchoalveolar lavage (BAL) from patients with IPF typically reveals a differential cell count that shows a non-specific, modest increase in neutrophils and/or eosinophils (73). The presence of a prominent BAL cell lymphocytosis pattern or the finding of a marked increase in eosinophils is not consistent with UIP/IPF and suggests an alternative diagnosis. While transbronchial lung biopsies may occasionally show changes consistent with IPF (74), the likelihood of retrieving adequate alveolar tissue and the ability to characterize the histological pattern of UIP in TBLB specimens is relatively low. However, bronchoscopy with performance of a BAL or TBLBx was incorporated into the 2000 expert consensus statement on making a clinical diagnosis of IPF in the absence of a surgical lung biopsy as a means of assisting in the exclusion of other diagnoses (40). The recommendation to utilize bronchoscopy for diagnosis will, however, be removed from a revised, American Thoracic Society-sponsored guideline document on IPF that will be published in the near future (personal communication, Ganesh Raghu), as TBLB and BAL specimens do not appear to assist significantly in making a diagnosis of IPF. Bronchoscopy can still be useful, however, in establishing other diagnoses in patients with HRCT and clinical characteristics that are atypical for IPF.

With increasing awareness of typical clinical features and of a highly consistent HRCT pattern of UIP for a substantial number of patients with IPF (42, 43) the trend in accepting a diagnosis of IPF without the need for subjecting patients to bronchoscopy and /or confirmation of the UIP pattern via the surgical lung biopsy (SLB) has become increasingly accepted. However, in the presence of atypical clinical and/or HRCT feaures, especially in new onset ILD, the diagnosis of IPF can only be ascertained by recognition of UIP pattern in the SLB (39). When SLB is performed, the likelihood of the accuracy of the diagnosis of IPF is higher when the clinician interacts with an experienced pathologist(s) and radiologist(s) familiar with ILD/IIP (75).

Fell et al. (76) have observed that patients with advanced age (especially ≥70 yrs) were highly likely to have a diagnosis of UIP/IPF vs. NSIP when SLBs were performed for patients that had HRCT imaging that was consistent with IIP but could not be considered diagnostic of UIP/IPF. This group has created a clinical scoring system that incorporates the combination of age plus HRCT interstitial scoring that has considerable power to predict the presence of IPF vs. other forms of IIP (76). Indeed, this scoring system has been reported to have a positive predictive value of 100% for IPF for patients 55 years of age or older with relatively modest amounts of fibrosis on HRCT (average HRCT scores of 0.8-1.0) (76). Because SLB is not risk-free and can cause

significant morbidity and possible mortality (77, 78) the risks and benefits of the procedure and the necessity of establishing an accurate and confident diagnosis should be carefully weighed prior to subjecting the elderly patient to SLB, especially for those who or frail or have risk factors for complications. New methods of diagnosis and differentiation of certain forms of ILD from others are currently evolving (79), and these may offer additional non-invasive means that allow caregivers to make specific diagnoses without resorting to surgical lung biopsy in the future. The study by Fell and colleagues (76) is a landmark observation that needs to be validated but has the potential to save elderly patients from surgical lung biopsy with its attendant risks.

Treatment

If ILD linked to ongoing drug or environmental exposures is identified, such exposures must be promptly curtailed. Some forms of ILD such as silicosis or asbestosis are refractory to pharmacologic therapies. However, disorders characterized by lung inflammation (e.g. EP, COP, cellular NSIP, sarcoidosis) may respond well to immunosuppressive therapies, and CTD-associated ILD tends to stabilize if systemic immunosuppressive/anti-inflammatory therapies achieve remission of the systemic disease. Additionally, other therapeutic interventions such as providing supplemental oxygen and pulmonary rehabilitation can benefit the patient. Comorbid conditions such as gastroesophageal reflux disease (GERD) may contribute substantially to symptoms and may even be important in disease pathogenesis (80), and effective control of GERD, if present, may help to stabilize ILD (81). Other comorbidities such as coronary artery disease, sleep-disordered breathing, osteoporosis, anxiety, and depression should be identified and treated appropriately.

The diagnosis of IPF is often made relatively late in the course of the disease when patients have fairly impaired lung function. Older studies that suggested that a beneficial response to immunosuppressive therapy may occur probably included some patients with non-IPF forms of IIP. Non-IPF forms of IIP, such as NSIP or COP, can respond to immunosuppressive pharmacologic agents (e.g. corticosteroids, cytotoxic drugs). Over the past decade it has become clear that anti-inflammatory and immunosuppressive pharmacologic therapies have had relatively little efficacy in the treatment of the majority of patients with IPF, as acknowledged by a National Institutes of Health expert panel (82) as well as the international consensus statement on IPF (39). Recent clinical trials have focused on anti-fibrotic therapies (e.g. interferon-γ, pirfenidone, bosentan, and etanercept) as potential treatments for IPF (Table 5). A recent prospective, randomized, placebo-controlled, 2-year multicenter trial examining recombinant human interferon-γ, which has been shown experimentally to downregulate TGF-β production, was prematurely terminated due to lack of efficacy. A post hoc subgroup analysis of a prior Phase III trial of one year duration had suggested that patients with less severe derangement in lung function may benefit from treatment with interferon-γ (83), but this observation was not supported by the subsequent 2-year trial (84). Phase II trials with etanercept, bosentan, and pirfenidone as well as Phase III trials with pirfenidone and bosentan have been completed. However, although clinical trials with pirfenidone (85) and bosentan (86) have suggested that these drugs could have some benefit for patients with IPF, clinical trial results to date have not been perceived by the US Food and Drug Administration to have a sufficiently compelling impact on survival or disease progression that would allow approval of these drugs for the indication of IPF in the United States. However, pirfenidone has been approved as a treatment for IPF in Japan, and it may receive approval in Europe. Although immunomodulatory therapies have shown little benefit for clinically stable patients with IPF, corticosteroids may have a role in the treatment and stabilization of patients who develop an acute exacerbation of IPF.

Interventions other than immunomodulatory or anti-fibrotic pharmacologic therapies may benefit patients with IPF (Table 6) (87). Lung transplantation is an option for those who meet criteria for listing at a transplant center, and survival following listing for lung transplantation is decreased for waitlisted patients who do not undergo lung transplantation in comparison to those who receive transplants. In addition to survival, quality of life can improve considerably for those who undergo successful lung transplantation. Because the diagnosis of IPF con-

Table 5. Pharmacologic therapy: potential pharmacologic agents and their targets

Agent(s)	Target	Rationale
▪ Pirfenidone ▪ Anti-TGF-β	TGF-β	Down-regulation of TGF-β-stimulated collagen synthesis and extracellular matrix accumulation
Bosentan	Endothelin-I	Suppress TGF-β production and fibroblast/myofibroblast stimulation via Endothelin-I antagonism
Etanercept	TNF-α	Antagonize the mitogenic effects of TNF-α on fibroblasts and suppress collagen synthesis
N-acetylcysteine	ROI (oxidant-antioxidant imbalance)	Replenish pulmonary glutathione stores and thereby antagonize signaling and tissue damaging effects of oxygen radicals (e.g. stimulatory effects of ROI on myofibroblasts)
Imatinib mesylate	Protein kinases	Inhibition of protein kinase-mediated fibroblast proliferation
Anti-CTGF	CTGF	Suppress fibroblast stimulation by CTGF
▪ Corticosteroids ▪ Azathioprine ▪ Cyclophosphamide	Inflammation	Suppression of any inflammatory component responsive to immunosuppressive therapy
▪ Sildenafil ▪ Inhaled epoprostenol	Vasoconstriction	Relieve PH

Abbreviations: TGF-β=transforming growth factor-β; TNF-α=tumor necrosis factor-α; ROI=reactive oxygen intermediates; CTGF=connective tissue growth factor; PH=pulmonary hypertension

fers a relatively poor prognosis, an expert panel convened under the auspices of the International Society for Heart and Lung Transplantation recommended referral of eligible patients to a transplant center at the time that a radiographic or histologic diagnosis of IPF is made (88). However, post-transplant survival is significantly lower for elderly patients (89), and lung transplantation is generally not offered to patients who are older that 65 years. Patients who undergo lung transplantation must comply with a complex medical treatment plan and have frequent monitoring to detect graft rejection or infection, and 5-year survival for single lung transplant (Kaplan-Meier) is only 43%. Other interventions, including those that target co-morbidities, may improve quality of life and relieve symptoms of IPF. Supplemental oxygen is generally given when evidence of resting hypoxemia or significant exercise-induced or nocturnal hypoxemia is detected.

Summary and Perspective

Advanced age places individuals at increased risk to develop certain disorders (IPF) or to more readily sustain lung injury and/or more aggressive loss of lung function in certain settings (e.g. thoracic radiation pneumonitis/fibrosis, ANCA-associated vasculitis, drug reactions). We are beginning to understand underlying genetic abnormalities and mechanisms that may especially predispose the elderly to pulmonary fibrosis (e.g. telomerase dysfunction), and much more research is needed to understand predisposition of the elderly to diseases such as IPF, which may well be linked to poorly understood factors, such as an inability to suppress and/or appropriately regulate injury and/or immune responses that can be triggered by endogenous or environmental factors as well as inappropriate or inadequate stem cell responses that may appear with advancing age and/or onset of lung injury.

A millennia-honored dictum of good medical practice that has been passed down from the time of Hippocrates is *primum non nocere* – "first do no harm!" In our desire to reach an ultimate, confident diagnosis of which specific form of ILD an elderly patient has developed, one can do harm. An overly aggressive pursuit of invasive modalities has the potential to lead to a patient's death. Additionally, if we do not understand disease pathogenesis of a disorder such as IPF, treatments and assumptions concerning therapeutic efficacy of well-intentioned treatments for IPF may cause more harm than good. Can apparent responses from clinical trials be extrapolated

Table 6. Management of the (Elderly) patient with IPF

- Present patients with treatment options accompanied by thoughtful counseling
  - Enrollment in clinical trials
  - Off-label therapies (e.g. corticosteroids, cytoxic drugs, other agents)
  - Lung transplantation
  - Best supportive care
- Disease-specific monitoring (for prognosis and treatment decisions)
  - Pulmonary function testing (FVC, DL_{CO}, 6-MWT)
  - Thoracic imaging
  - Dyspnea score
- Supplemental oxygen if indicated (keep SpO_2 ≥90%)
  - Exertion
  - Nocturnal with sleep
  - Continuous
- Maintain ideal body-mass index
  - Weight reduction if obese
  - Improved nutrition if cachectic
- Pulmonary rehabilitation
  - Optimal exercise program
  - Patient education
- Vaccinations
  - Pneumoccal vaccine
  - Seasonal influenza
  - Others as indicated (e.g. H1N1)
- Detect and treat co-morbidities and complications
  - Gastroesophageal reflux disease
  - Cardiovascular disease
  - Drug toxicity (if treated)
  - Sleep-disordered breathing
  - Metabolic bone disease (osteopenia, osteoporosis)
  - Anemia
  - Secondary PH
  - Anxiety
  - Depression

to patients whose disease is more advanced as a consequence of depressed physiologic parameters or other issues that would not allow them to meet the criteria for clinical trial inclusion? Do apparent responses in clinical trials apply to the subset group of elderly patients? Lastly, do marginal but statistically significant responses in adequately-powered clinical trials indicate that all patients should receive a specific treatment despite cost, when such costs, especially for treatment of entities such as secondary PH associated with IPF as an example, can be astronomical and only provide marginal benefit? (90). Conclusions drawn from inadequately-powered studies and/or post hoc analyses of phase III trials can lead to the off-label prescription of agents that may actually be ineffectual or cause physical and/or economic harm (91). Hopefully, these issues will be more clearly resolved as our understanding of the pathogenesis of IPF improves.

Although principles of diagnosis and treatment as concerns ILD in the elderly patient are similar to those for younger patients, elderly individuals can be more frail and more readily harmed by overly aggressive diagnostic and therapeutic interventions. Nonetheless, aggressive interventions should be undertaken for the diagnosis and treatment of disorders that may respond well to appropriate therapies, such as vasculitis, non-IPF ILD such as HP or EP, or drug reactions.

References

1. Schwarz MI, King TE Jr. Interstitial Lung Diseases. 4th Edition. Hamilton, ON, Canada, BC Decker, 2003.
2. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am JRespir Crit Care Med 1994; 150: 967-72.
3. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006; 174: 810-6.
4. Fernandez Perez ER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis : a population-based study. Chest 2010; 137: 129-37.
5. Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century – a disease of older patients. Rheumatology (Oxford) 2005; 44: 495-501.
6. Chen M, Yu F, Zhang Y, et al. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. Medicine (Baltimore) 2008; 87: 203-9.
7. Eickelberg O, Selman M. Update in diffuse parenchymal lung disease 2009. Am J Respir Crit Care Med 2010; 181: 883-8.
8. Xu J, Gonzalez ET, Iyer SS, et al. Use of senescence-accelerated mouse model in bleomycin-iniduced lung injury suggests that bone marrow-derived cells can alter the outcome of lung injury in aged mice. J Gerontol 2009; 64A: 731-9.
9. Cuervo AM. Autophagy and aging: keeping that old broom working. Trends Genet 2008; 24: 604-12.
10. Lawson WE, Loyd JE. The genetic approach in pulmonary fibrosis: can it provide clues to this complex disease? Proc Am Thorac Soc 2006; 3: 345-9.
11. Garcia CK, Raghu,G. Inherited interstitial Lung Disease. Clin Chest Med 2004; 25: 421-33.
12. Kottmann RM, Hogan CM, Phipps RP, et al. Determinants of initiation and progression of idiopathic pulmonary fibrosis. Respirology 2009; 14: 917-33.
13. Hocher B, Schwarz A, Fagan KA, et al. Pulmonary fibrosis and chronic lung inflammation in ET-1 transgenic mice. Am J Respir Cell Mol Biol 2000; 23: 19-26.
14. Kulasekaran P, Scavone CA, Rogers DS, et al. Endothelin-1 and transforming growth factor- 1 independently induce fibroblast resistance to apoptosis via AKT activation. Am J Respir Cell Mol Biol 2009; 41: 484-93.
15. Pinkerton KE, Barry BE, O'Neil JJ, et al. Morphologic changes in the

lung during the life span of Fischer 344 rats. Am J Anat 1982; 164: 155-74.
16. Collins K, Mitchell JR. Telomerase in the human organism. Oncogene 2002; 21: 564-79.
17. Liu T, Hu B, Chung MJ, Ullenbruch M, Jin H, Phan SH. Telomerase regulation of myofibroblast differentiation. Am J Respir Cell Mol Biol 2006; 34: 625-33.
18. Mu XC, Staiano-Coico L, Higgine PJ. Increased transcription and modified growth state-dependent expression of the plasminogen activator inhibitor type-1 gene characterize the senescent phenotype in human diploid fibroblasts. J Cell Physiol 1998; 174: 90-8.
19. Mora AL, Rojas M. Aging and lung injury repair: a role for bone marrow derived mesenchymal stem cells. J Cell Biochem 2008; 105: 641-7.
20. Ruzankina Y, Asare A, Brown EJ. Replicative stress, stem cells and aging. Mech Ageing Dev 2008; 129: 460-6.
21. Garcia CK, Wright WE, Shay JW. Human diseases of telomerase dysfunction: insights into tissue aging. Nucleic Acids Research 2007; 1-11.
22. Armanios MY, Chen JJ, Cogan JD, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. New Engl J Med 2007; 356: 1317-26.
23. Tsakiri K, Cronkhite JT, Kuan PJ, et al. Adult-onset pulmonary fibrosis caused by mutations in telomerase. PNAS 2007; 104: 7552-7.
24. Alder JK, Chen JJ, Lancaster L, et al. Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci USA 2008; 105: 13051-6.
25. Jiang H, Schiffer E, Song Z, et al. Proteins induced by telomere dysfunction and DNA damage represent biomarkers of human aging and disease. Proc Natl Acad Sci USA 2008; 105: 11299-304.
26. Brack AS, Conboy MJ, Roy S, et al. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science 2007; 317: 807-10.
27. Königshoff M, Eickelberg O. WNT signaling in lung disease: a failure or a regeneration signal? Am J Respir Cell Mol Biol 2010; 42: 21-31.
28. Kilburn KH, Lilis R, Anderson HA, et al. Interaction of asbestos, age, and cigarette smoking in producing radiographic evidence of diffuse pulmonary fibrosis. Am J Med 1986; 80: 377-81.
29. Lopez-Diazguerrero NE, Luna-Lopez A, Gutierrez-Ruiz MC, et al. Susceptibility of DNA to oxidative stressors in young and aging mice. Life Sci 2005; 77: 2840-54.
30. Zhang HJ, Doctrow SR, Oberley LW, Kregel KC. Chronic antioxidant enzyme mimetic treatment differentially modulates hyperthermia-induced liver HSP70 expression with aging. J Apl Physiol 2006; 100: 1385-91.
31. Garantziotis S, Schwartz DA. Host-environment interactions in pulmonary fibrosis. Semin Respir Crit Care Med 2006; 27: 574-80.
32. Taskar VS, Coultas DB. Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc 2006; 3: 293-8.
33. Delaunois LM. Mechanisms in pulmonary toxicology. Clin Chest Med 2004; 25: 1-14.
34. Iademarco MF, Castro KG. Epidemiology of tuberculosis. Semin Respir Infect 2003; 18: 225-40.
35. Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006; 61: 980-5.
36. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003: 123; 21S-49s.
37. Jermal A, Murrray T, Samuels A, et al. Cancer statistics 2003. CA Cancer J Clin 2003; 53: 5-26.
38. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007; 176: 277-84.
39. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. Amercan Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646-64.
40. ATS/ERS. International Multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir and Crit Care Med 2002; 165: 277-304.
41. Diette GB, Scatarige JC, Haponik EF, et al. Do high-resolution CT findings of usual interstitial pneumonitis obviate lung biopsy? Respiration 2005; 72: 134-41.
42. Schmidt SL, Sundaram B, Flaherty KR. Diagnosing fibrotic lung disease: when is high-resolution computed tomography sufficient to make a diagnosis of idiopathic pulmonary fibrosis? Respirology 2009; 14: 934-9.
43. Kanne JP. Idiopathic interstitial pneumonias. Semin Roentgenol 2010; 45: 8-21.
44. Katzenstein AL, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol 2002; 26: 1567-77.
45. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 2001; 164: 1722-7.
46. Keane MP, Strieter RM, Lynch JP III, Belperio JA. Inflammation and angiogenesis in fibrotic lung disease. Semin Respir Crit Care Med 2006; 27: 589-99.
47. Turner-Warwick M. Precapillary systemic pulmonary anastomoses. Thorax 1963; 18: 225-37.
48. Peao MNDA, Aguas AP, DeSa CM, Grande NR. Neoformation of blood vessels in association with rat lung fibrosis induced by bleomycin. Anat Rec 1994; 238: 57-67.
49. Keane MP, Arenberg DA, Lynch JP III, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. J Immunol 1997; 159: 1437-43.
50. Meyer KC, Cardoni A, Xiang Z. Vascular endothelial growth factor in bronchoalveolar lavage from normal subjects and patients with diffuse parenchymal lung disease. J Lab Clin Med 2000; 135: 332-8.
51. Cosgrove GP, Brown KK, Schliemann WP, et al. Pigment epithelial-derived factor in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2004; 170: 242-51.
52. Lappi-Blanco E, Soini Y, Kinnula V, et al. VEGF and bFGF are highly expressed in intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia. J Pathol 2002; 196: 220-7.
53. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-52.
54. Nadrous HF, Pellikka PA, Krowka MUJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 2393-9.
55. Nathan SD, Ahmad S, Koch J, Barnett S, Ad N, Burton N. Serial measures of pulmonary artery pressures in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 168S.
56. Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 2007; 30: 715-21.
57. Lederer DJ, Caplan-Shaw CE, O'Shea MK, et al. Racial and ethnic disparities in survival in lung transplant candidates with idiopathic pulmonary fibrosis. Am J Transplant 2006; 6: 398-403.
58. Collard HR, King TE Jr. Demystifying idiopathic interstitial pneumonia. Arch Intern Med 2003; 163: 17-29.
59. Flaherty KR, Thwaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003; 58: 143-8.
60. Park JH, Kim DS, Part I-N, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 2007; 175: 705-11.

61. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 2005; 142: 963-7.
62. Brown KK, Raghu G. Medical treatment for pulmonary fibrosis: current trends, concepts, and prospects. Clin Chest Med 2004; 25: 759-72.
63. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007; 176: 636-43.
64. Collard HR, King TE Jr, Bartelson BB, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003; 168: 538-42.
65. King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. Chest 2005; 127: 171-7.
66. Wells AU, Desai SR, Rubens MB, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med 2003; 167: 962-9.
67. Lama RN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2005; 168: 1084-90.
68. Flaherty KR, Adin-Cristian A, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006; 174: 803-9.
69. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005; 25: 96-103.
70. Panos RJ, Mortenson RL, Niccoli SA, King TE Jr. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. Am J Med 1990; 88: 396-404.
71. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study. Am J Respir Crit Care Med 2000; 161: 5-8.
72. Wells A. Clinical usefulness of high resolution computed tomography in cryptogenic fibrosing alveolitis. Thorax 1998; 53: 1080-7.
73. Meyer KC. The role of bronchoalveolar lavage in interstitial lung disease. Clin Chest Med 2004; 25: 637-49.
74. Barbescu EA, Katzenstein AL, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. Chest 2006; 1129: 1126-31.
75. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004; 170: 904-10.
76. Fell CD, Martinez FJ, Liu LX, et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2010; 181: 832-7.
77. Kreider ME, Hansen-Flaschen J, Ahmad NN, et al. Coomplications of video-assisted thoracoscopic lung biopsy in patients with interstitial lung disease. Ann Thorac Surg 2007; 83: 1140-5.
78. Lettieri CJ, Veerappan GR, Helman DL, et al. Outcomes and safety of surgical lung biopsy for interstitial lung disease. Chest 2005; 127: 1600-5.
79. Selman M, Pardo A, Barrera L, et al. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 2006; 173: 188-98.
80. Tobin RW, Pope CE II, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 158: 1804-8.
81. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J 2006; 27: 136-42.
82. Mason RJ, Schwartz MI, Hunninghake GW, Musson RA. NHLBI Workshop Summary. Pharmacological therapy for idiopathic pulmonary fibrosis. Past, present, and future. Am J Respir Crit Care Med 1999; 160: 1771-7.
83. Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004; 350: 125-33.
84. King TE Jr, Albera C, Bradford WZ, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009; 374: 222-8.
85. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2009 Dec 8. [Epub ahead of print].
86. Ross B, D'Orleans-Juste P, Giaid A. Potential role of endothelin-1 in pulmonary fibrosis: from the bench to the clinic. Am J Respir Cell Mol Biol 2010; 42: 16-20.
87. Frankel SK, Schwarz MI. Update in idiopathic pulmonary fibrosis. Curr Opin Pulm Med 2009; 15: 463-9.
88. Orens JB, et al. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006; 25: 745-55.
89. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis. Ann Intern Med 2009; 151: 767-74.
90. Polomis D, Runo J, Meyer KC. Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med 2008; 14: 462-9.
91. Meyer KC. Interferon gamma-1b therapy for idiopathic pulmonary fibrosis: is the cart before the horse? Mayo Clin Proc 2003; 78: 1073-5.