

Review article

Idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is the most common of the interstitial pneumonias of unknown etiology and the most aggressive interstitial lung disease. IPF is confirmed by the identification of usual interstitial pneumonia (UIP) on surgical lung biopsy (1–5).

The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases (DPLDs) also described as interstitial lung diseases. The IIPs are a heterogeneous group of nonneoplastic disorders resulting from damage to the lung parenchyma by varying patterns of inflammation and fibrosis (1). The IIPs include the entities of IPF, nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamate interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP).

It is important to emphasize that IPF is a progressive and irreversible illness and, until now, there has been no available drug that has been able to modify the progressive natural course of IPF and its usual terminal outcome (1, 2, 6). It is characterized by radiographically evident interstitial infiltrates predominantly affecting the lung bases and by progressive dyspnea and worsening of pulmonary function, pathologically by fibroblast proliferation and extracellular matrix accumulation resulting in irreversible distortion of the architecture of the lung (1). The current strict definition of IPF provides a new focus for basic and clinical research that will improve insight into the pathogenesis of this disorder and stimulate the development of novel therapies (7).

Definition

IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histologic appearance of UIP on surgical (thoracoscopic or open) lung biopsy (1). Many older studies included several forms of IIP under the term 'IPF', but today the clinical label 'IPF' should be reserved for patients with a specific form of fibrosing interstitial pneumonia referred to as UIP (1, 2, 8). Historical grouping of disparate disorders under the heading of IPF makes it difficult to compare current and older studies. This observation also explains the discrepancies between older and newer investigations of IPF in reported natural history and response to therapy (7). The definite diagnosis of IPF in the presence of a surgical biopsy showing UIP includes the following: 1) exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases; 2) abnormal pulmonary function studies that include evidence of restriction [reduced VC often with an increased forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio] and/or impaired gas exchange; and 3) abnormalities on conventional chest radiographs or high-resolution computed tomography (HRCT) scans (1).

In the absence of a surgical lung biopsy, the diagnosis of IPF remains uncertain. However, in the immunocompetent adult, the presence of all of the following major diagnostic criteria as well as at least three of the four minor criteria increases the likelihood of a correct clinical diagnosis of IPF (1):

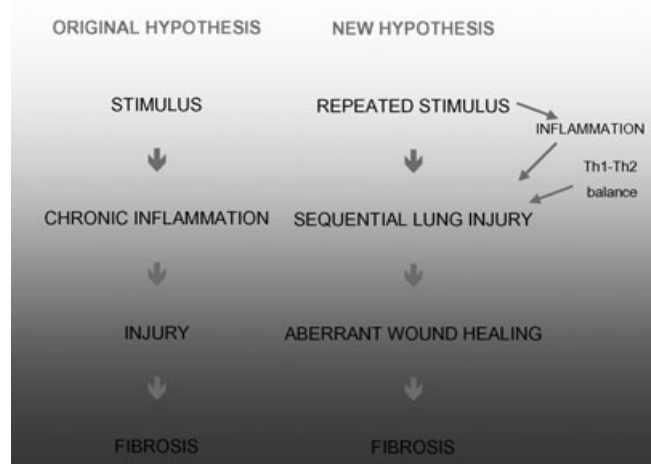


Figure 1. Original and new hypothesis for the pathogenesis of IPF [adapted from Ref. (7)].

Major criteria

- Exclusion of other known causes of interstitial lung disease such as drug toxicities, environmental exposures, and collagen vascular diseases.
- Abnormal pulmonary function studies that include evidence of restriction (reduced VC often with an increased FEV1/FVC ratio) and/or impaired gas exchange.
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans.
- Transbronchial lung biopsy (TBB) or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.

Minor criteria

- Age > 50 years.
- Insidious onset of otherwise unexplained dyspnea on exertion.
- Duration of illness ≥ 3 months.
- Bibasilar, inspiratory crackles (dry or 'velcro' type in quality).

Epidemiology of IPF

Idiopathic pulmonary fibrosis has been reported worldwide and does not have predilection by race or ethnicity. Incidence of IPF is estimated to be around seven cases per 100 000 per year in women and 10 cases per 100 000 per year in men (9), but it increases with older age (10). The disease occurs primarily in individuals between 50 and 70 years of age, and it appears to be infrequent in young

people and extremely rare in children (1, 11, 12). The prevalence of IPF ranges from 13 cases per 100 000 for women to 20 cases per 100 000 for men (9), although these figures may underestimate the problem. The etiology is unknown.

Pathogenesis

Recognition of IPF as a distinct entity with lesions that vary in age and location raised important questions about the established view that IPF was a disease in which parenchymal fibrosis was directly caused by chronic inflammation (6–8). Although the pathogenetic mechanisms remain to be determined, the prevailing hypothesis holds that fibrosis is preceded and provoked by a chronic inflammatory process that injures the lung and modulates lung fibrogenesis, leading to the end-stage fibrotic scar. An important assumption was that if the inflammatory cascade was interrupted before irreversible tissue injury occurred, fibrosis might be avoided. Thus, this theory explains the initial enthusiasm for corticosteroid and cytotoxic therapy for IPF (7). However, there is little evidence that inflammation is prominent in early disease, and it is unclear whether inflammation is relevant to the development of the fibrotic process. Evidence suggests that inflammation does not play a pivotal role. Inflammation is not a prominent histopathologic finding, and epithelial injury in the absence of ongoing inflammation is sufficient to stimulate the development of fibrosis (Fig. 1). In addition, the inflammatory response to a lung fibrogenic insult is not necessarily related to the fibrotic response (13). Clinical measurements of inflammation fail to correlate with stage or outcome and it is now clear that potent anti-inflammatory therapy does not improve outcome. A growing body of evidence suggesting that IPF involves abnormal wound healing in response to multiple, microscopic sites of ongoing alveolar epithelial injury and activation associated with the formation of patchy fibroblast–myofibroblast foci, which evolve to fibrosis (13). In addition to emerging evidence that inflammation is not more prominent in early stages of UIP (8), it is becoming clear that the primary sites of ongoing injury and repair are the regions of fibroblastic proliferation, so-called fibroblast foci (8, 13, 14). These small aggregates of actively proliferating myofibroblasts and fibroblasts constitute many microscopic sites of ongoing alveolar epithelial injury and activation associated with evolving fibrosis (8, 14, 15). After injury, the alveolar epithelium must initiate a wound healing process to restore its barrier integrity. One important step is the rapid reepithelialization of the denuded area through epithelial cell migration, proliferation, and differentiation. In IPF, this response seems slow and inadequate. The alveolar epithelium shows a marked loss of or damage to type I cells, hyperplasia of type II cells, and altered expression of adhesion molecules and MHC

antigens (16–19). Where the basement membrane remains intact, type II cells attempt to recover the epithelial surface; these cells express several enzymes, cytokines, and growth factors (16). In UIP, the capacity of type II alveolar cells to restore damaged type I cells is seriously altered, resulting in epithelial cuboidalization and the presence of transitional reactive phenotypes (16), abnormalities in pulmonary surfactant (20, 21), and alveolar collapse (22). In IPF, epithelial cells express several cytokines and growth factors that may promote fibroblast migration and proliferation and extracellular matrix accumulation. Alveolar epithelial cells may initiate the pathologic process, producing most of the factors [e.g. transforming growth factor (TGF)- β 1, tumor necrosis factor (TNF)- α] (23–25) inducing the phenotypic changes seen among fibroblasts during the progression to end-stage fibrosis. Present evidence suggests that the earliest, and possibly the only, morphologic change associated with subsequent progression to dense fibrosis is the presence and extent of fibroblastic foci in the injured lung (8, 14, 15).

After an initial insult or injury, the normal physiologic response of inflammation leads to matrix stimulation with proliferation and altered phenotype of mesenchymal cells (fibrogenesis) to stop the injury and provide temporary repair. This is usually followed by matrix mobilization (fibrolysis) and apoptosis of repair cells, both mesenchymal and inflammatory, and return to normal organ function. In the case of IPF, this normal process is diverted, with retention of altered mesenchymal cell phenotype (fibroblasts and myofibroblasts) through avoidance of apoptosis, with continued matrix production and reduced matrix mobilization. In addition, the altered stromal cell population and activated epithelium release a series of profibrogenic factors, such as TGF- β and platelet-derived growth factor, which interact with the deposited matrix at the site of abnormal repair (26), thus creating a new microenvironment in patchy areas of the lung. Other areas remain in normal structure and environment. The ability of matrix to sequester many growth and differentiation factors to create a 'fibrogenic' microenvironment is well established (26, 27). Many of these factors act on inflammatory cells in normal passage through the tissue modulating susceptibility to normal apoptosis, resulting in accumulation of these cells and apparent 'inflammation.' Thus, 'inflammation' is a result of a new microenvironment caused by abnormal interaction between mesenchyme and epithelium (28, 29). Nevertheless, the centrality of fibroblasts/myofibroblasts in IPF/UIP still remains controversial and unproven (13, 30–32). However, the type of inflammatory response may modulate tissue injury, fibrosis or both during the evolution of IPF. The inflammatory response in IPF is thought to resemble closely a Th2-type immune response. There are eosinophils, mast cells and increased amounts of the Th2 cytokines interleukin-4 and interleukin-13 (33–37). In murine models of lung disease, animals whose

response to tissue injury is predominantly of the Th2-type are more prone to pulmonary fibrosis after lung injury than those with a predominantly Th1 response (35). Although the Th2 and Th1 phenotypes are not as well defined in IPF as they are in asthma and animal models, their potential importance is one rationale for undertaking trials of immunomodulators such as interferon- γ in an attempt to switch the inflammatory response to a more Th1-like phenotype (38).

Diagnosis

IPF begins insidiously, with the gradual onset of dyspnea or nonproductive cough. Dyspnea is usually progressive and is the most prominent and disabling symptom (39–42). In general, patients have symptoms for >6 months before seeking medical attention and, unfortunately, most of them are assisted by lung specialists 1 or 2 years after the beginning of symptoms. The disorder generally presents in the fifth and sixth decades. Associated systemic symptoms, such as low-grade fever and myalgia, may be present but are not common. A detailed occupational history, with attention to exposure to asbestos, silica, or other respirable toxins, is critical to rule out a pneumoconiosis that may mimic IPF (7). The physical examination in most patients (more than 80%) reveals fine bibasilar inspiratory crackles (velcro rales). With progression of the disease, rales extend toward the upper lung zones. Clubbing is noted in 25–50% of patients (11, 40, 43). The rest of the physical examination is unremarkable until late in the course of the disease, when severe pulmonary hypertension and cor pulmonale may become apparent (11, 44). Franck findings of collagen vascular disease (such as rashes, inflammatory arthritis, myositis, dry eyes, dry mouth, Raynaud's phenomenon, etc.) suggest an alternative diagnosis (1).

The routine laboratory evaluation is often not helpful except to 'rule out' other causes of DPLD. Mild anemia, increases in markers of systemic inflammation (erythrocyte sedimentation rate or C-reactive protein level), hypergammaglobulinemia and nonspecific increases in rheumatoid factor and antinuclear antibodies are observed in up to 30% of patients (39–41). In the absence of other findings of a systemic illness, the presence of autoantibodies does not imply an underlying collagen vascular disease. Elevation of lactate dehydrogenase (LDH) may be noted but is a nonspecific finding common to pulmonary disorders.

The pulmonary function test

The typical findings of pulmonary function test are consistent with restrictive impairment. The lung volumes [total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV)] are reduced at some

point in the course of disease. Early on, or more commonly in patients with superimposed chronic obstructive pulmonary disease, the lung volumes may be normal (1, 45). Expiratory flow rates, FEV1, and FVC are often decreased because of the reduction in lung volume, but the FEV1-to-FVC ratio is maintained or increased in IPF. The DLCO is reduced and may actually precede the reduction of lung volume. The resting arterial blood gases may be normal initially or may reveal mild hypoxemia and respiratory alkalosis. With exercise the arterial O_2 pressure and arterial O_2 saturation fall. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities that may be seen with exercise (1, 46).

Radiology

Virtually all patients with IPF have an abnormal chest radiograph at the time of presentation (11). Indeed, basal reticular opacities are often visible on previous chest radiographs in retrospect for several years before the development of symptoms. Conversely, a normal chest radiograph cannot be used to exclude microscopic evidence of UIP on lung biopsy (47, 48). Peripheral reticular opacities, most profuse at the lung bases, are characteristic findings on the chest radiograph of patients with IPF (Fig. 2) (49). These opacities are usually bilateral, often asymmetric, and are commonly associated with decreased lung volumes. When a 'confident' diagnosis of IPF is made on the basis of the chest radiograph (compared with an 'uncertain' or 'unlikely' diagnosis of IPF), it is correct in 48% (50) to 87% (51, 52) of cases. Radiographic evidence of pleural disease or lymphadenopathy is not usually found in IPF. UIP is characterized on HRCT by the presence of patchy, predominantly peripheral, subpleural, bibasal reticular opacities, often associated with traction bronchiectasis (Fig. 3). Honeycombing is common (Fig. 4) (53). Ground glass attenuation is common, but is usually less extensive than reticular abnormality (54, 55). Architectural distortion, reflecting lung fibrosis, is often prominent. Lobar volume loss is seen with more advanced fibrosis. The extent of disease on HRCT correlates with fibrosis on biopsy and with physiologic impairment (7, 56). On serial scans in treated patients, the areas of ground glass attenuation may regress, but more commonly progress to fibrosis with honeycombing (57–60). Honeycomb cysts usually enlarge slowly over time (53). The CT pattern of UIP due to IPF can be indistinguishable from that found in UIP due to asbestosis and to collagen vascular disease. Patients with chronic hypersensitivity pneumonitis or with end-stage sarcoidosis may uncommonly develop a CT pattern similar to that of UIP (1). The CT pattern of NSIP may be indistinguishable from UIP but ground glass attenuation is the predominant finding in the majority of cases of NSIP and is the sole abnormality in about one-third of cases (60).

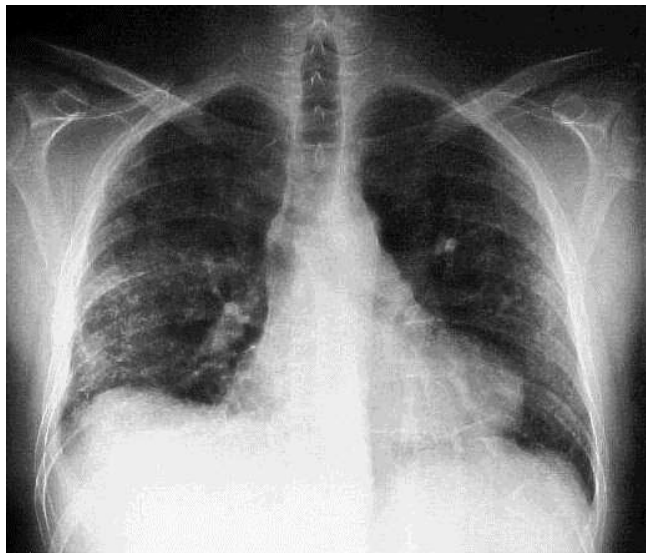


Figure 2. Chest radiograph of a patient with IPF. Chest radiograph reveals peripheral, subpleural reticular opacities, most profuse at the lung bases.

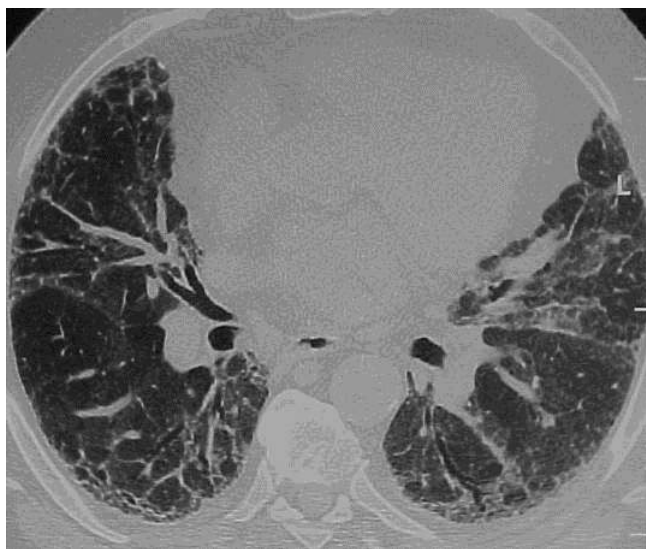


Figure 3. Chest HRCT in a patient with IPF. HRCT shows patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities, traction bronchiectasis and bronchiolectasis and irregular septal thickening. There is also ground glass.

Reticular abnormality on CT correlates with fibrosis on histopathologic examination (54, 55). Honeycombing on CT correlates with honeycombing on biopsy. When ground glass attenuation is associated with reticular lines, traction bronchiectasis, or bronchiolectasis, it usually indicates histologic fibrosis. Isolated ground glass attenuation may correlate with evidence of interstitial inflammation, airspace filling by macrophages, patchy fibrosis, or a combination of these (54, 61, 62).



Figure 4. Chest HRCT in a patient with IPF. HRCT shows predominantly peripheral and subpleural fibrosis with honeycombing.

A study examined the ability of physicians expert in the diagnosis of interstitial lung diseases to identify correctly HRCT scans from patients with biopsy-proved IPF (63). When the expert group made a confident diagnosis of IPF from the CT scan and basic clinical data, they were correct in over 80% of the cases. However, over half the patients with proved IPF had an uncertain diagnosis on the basis of HRCT and clinical evaluation. Thus, experienced clinicians can make a confident diagnosis of IPF in many patients without the need for biopsy (63–65). When the diagnostic studies do not support a confident diagnosis of IPF or the clinician is less experienced, a lung biopsy is needed for diagnosis (65).

Bronchoalveolar lavage

BAL has been helpful in elucidating the key immune effector cells driving the inflammatory response in IPF (66, 67). Increases in polymorphonuclear leukocytes (PMNs), neutrophil products, eosinophils, eosinophil products, activated alveolar macrophages, alveolar macrophage products, cytokines, growth factors for fibroblasts, and immune complexes have been noted in BAL of patients with IPF (1). Despite its value as a research tool, the diagnostic usefulness of BAL in IPF is limited. Although it is important in excluding alternative causes (e.g. malignancy, infections, eosinophilic pneumonia, pulmonary histiocytosis X), there is little evidence that it provides practical information to support a diagnosis of IPF, to monitor disease activity, or to predict the response to therapy. The pattern of inflammatory cells identified may be helpful in narrowing the differential diagnosis of fibrosing interstitial pneumonias but is not diagnostic of IPF. An increase in neutrophils (levels > 5%) is noted in 70–90% of patients, an associated

increase in eosinophils (levels > 5%) is apparent in 40–60% of patients, and an additional increase in lymphocytes is noted in 10–20% of patients (68). However, these findings are seen in a wide variety of fibrosing lung conditions other than IPF. A lone increase in lymphocytes is uncommon in IPF (< 10% of patients), so when present, another disorder should be excluded (e.g. granulomatous infectious disease, sarcoidosis, hypersensitivity pneumonitis, COP, NSIP, LIP). Increases in the percentage of neutrophils or eosinophils (or both) in BAL fluid have been associated with a worse prognosis in some but not all studies (1, 69). BAL lymphocytosis, found in fewer than 20% of patients with IPF, has been associated with a more cellular lung biopsy, less honeycombing, and a greater responsiveness to corticosteroid therapy (70). However, these relationships are too inconsistent in individual patients for BAL to be used as a reliable prognostic guide (66, 70–76).

Histology

Usual interstitial pneumonia is the histopathologic pattern that identifies patients with IPF. Surgical lung biopsy, either open thoracotomy or preferentially by video-assisted thoracoscopy, provides the best tissue samples to distinguish UIP from other forms of IIP and to exclude other processes that mimic IPF when identified in the setting of interstitial lung disease of unknown etiology (1). Biopsy specimens should be obtained from areas that reflect the entire gamut of gross disease patterns as guided by intraoperative inspection of the lung surface or correlation with HRCT abnormality (55, 77–79). Areas of gross honeycombing should be avoided, as they show end-stage disease, and areas that show intermediate or relatively preserved lung should specifically be selected for biopsy, as the lung specimen must have fibrotic lung adjacent to normal lung for the pathologist to identify the UIP pattern (60). It is also valuable to biopsy more than one lobe as fibrotic and inflammatory interstitial diseases often show heterogeneity in the histologic patterns and the additional specimen provides essential diagnostic information (80). Avoiding the tips of the lobes, including the lingula, has been recommended (81–83), as these sites may show nonspecific fibrotic or inflammatory lesions. Because the diagnosis relies on grading lesions that vary in both age and location, a large piece of lung parenchyma is required. Therefore, TBBs are used only to rule out other disorders that mimic IPF but are not helpful in making the diagnosis of UIP (1, 53, 84). Although TBBs are abnormal in many cases, they do not confirm UIP. In addition, because of the small sample size (2–5 mm), TBBs should not be used to assess the degree of fibrosis or inflammation. TBB may exclude UIP by identifying an alternative specific diagnosis in the right clinical setting or with the use of special histopathologic methods or stains (1). Surgical lung biopsy is recommended in patients with

suspected IPF and without contraindications to surgery. This recommendation is important in any patients with clinical or radiologic features that are not typical for IPF. In the instances when atypical clinical, radiographical, or physiologic features of IPF are encountered, it has been shown that histopathologic patterns other than UIP are more likely to be found, thereby often defining a process with a differential prognosis or resulting in alternative approaches to management. However, despite recommendations that histologic examination be routinely performed in these patients, two studies from United Kingdom have shown that lung biopsies are obtained in only 28–33% and 8–12% of patients, respectively (11, 85), and in 11% of patients in one study from the United States (9), likely reflecting the pessimism that findings on lung biopsy will alter the proposed treatment plan (86). In the period 1998–2000, 1382 cases were submitted to the Italian Register on diffuse infiltrative lung disorders (RIPID); the most frequent disease registered was IPF (37.6%). HRCT was considered as the most important tool for final diagnosis in the majority of cases (74.4%); 39.4% of patients underwent TBB and 39.2% of patients underwent BAL; a surgical biopsy was performed in 20.5% of patients (87).

Actually, a major purpose of morphologic assessment is to distinguish UIP from other histologic subsets of IIP that differ in a number of clinical features, particularly in the response to treatment and prognosis.

The gross morphologic findings in IPF range from a normal appearance in early cases to diffuse honeycombing in the later stages of the disease process (Fig. 5). The pleural surface of the lungs has a cobble-stoned appearance due to the retraction of scars along the interlobular septa. The overall lung size tends to be small. Disease involvement is usually heterogeneous and worse in the lower lobes. A subpleural, peripheral, and paraseptal distribution of fibrosis is often seen. The histologic hallmark and chief diagnostic criterion is a heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycomb change (Fig. 6). This marked variation from field to field, both in the degree of lung involvement and in the nature and appearance of the interstitial infiltrate, reflects the *temporal heterogeneity* of the interstitial process and constitutes the essence of the diagnostic criteria for UIP (1, 88–90). The fibrosis, often in a subpleural and/or paraseptal distribution, is temporally heterogeneous, with two major types: 1) dense scarring and honeycombing and 2) fibroblastic foci scattered at the edges of the dense scars (Fig. 7). The fibroblast foci represent sites of acute lung injury, and they are likely the earliest lesion of UIP recognizable by light microscopy. The dense fibrosis causes remodeling of the lung architecture resulting in collapse of alveolar walls and formation of cystic spaces or honeycombing (Fig. 8). The fibrotic thickened alveolar septa tend to be lined by hyperplastic cuboidal epithelial cells or a

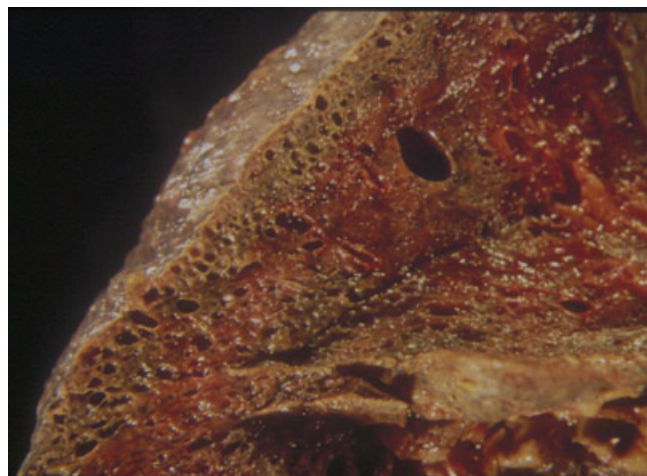


Figure 5. Gross morphologic findings in IPF. The pleural surface of the lung has a cobble-stoned appearance due to the retraction of scars along the interlobular septa. There is fibrotic areas and honeycomb cystic changes with predominantly subpleural distribution.

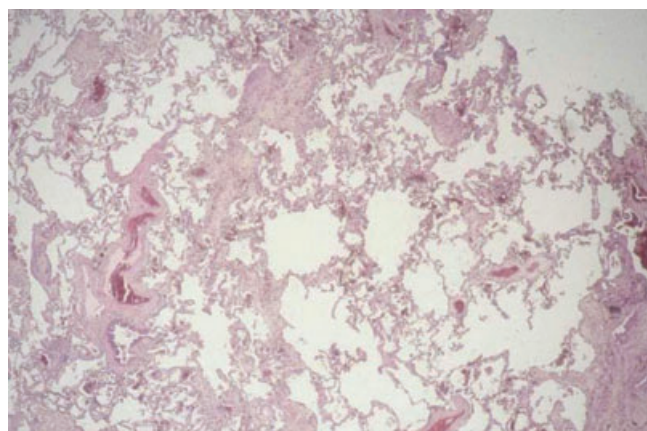


Figure 6. Histopathologic features of IPF. The figure shows a preparation of an open-lung biopsy specimen from a patient with UIP. At low magnification the interstitium is altered by a strikingly heterogeneous and nonuniform inflammatory and fibrosing process with alternating zones of inflammation, fibrosis, honeycomb change, and intervening patches of normal lung (hematoxylin and eosin, ×100, histologic section kindly provided by Prof. A. Pesci).

bronchiolar type of epithelium. Occasionally, the pneumocytes lining the alveolar walls are hyperplastic, with abundant cytoplasm, large hyperchromatic nuclei, and prominent nucleoli. Bronchiolar or cuboidal epithelium usually lines areas of cystic remodeling or honeycomb fibrosis. Interstitial inflammation is usually mild to moderate, consisting mostly of lymphocytes and a few plasma cells (91). Patients who are biopsied during an accelerated phase of their illness may show a combination of UIP and diffuse alveolar damage (92–94). It is

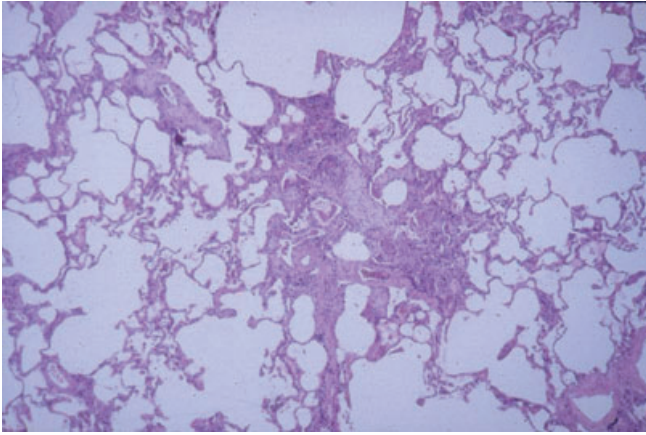


Figure 7. Histopathologic features of IPF. The figure shows a fibroblastic focus. The fibroblastic focus is visible as a nodule of spindle cells arranged in linear fashion against a pale-staining extracellular matrix. The dense collagenous scar is juxtaposed with fibroblastic focus; the adjacent alveolar septa show little histologic abnormality (hematoxylin and eosin, $\times 200$, histologic section kindly provided by Prof. A. Pesci).

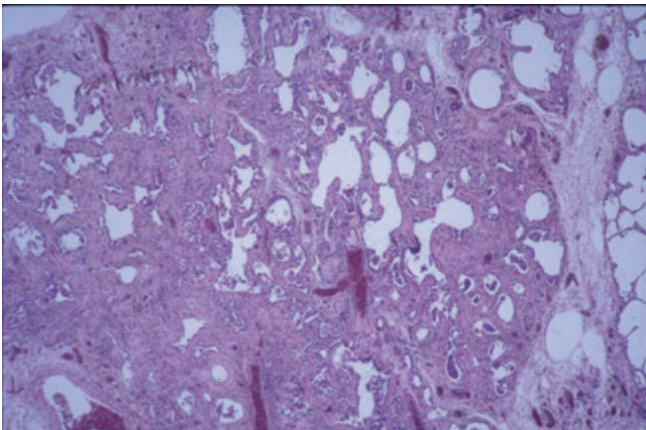


Figure 8. Histopathologic features of IPF. The figure shows a preparation of an open-lung biopsy specimen with dense scarring and honeycombing: the dense fibrosis causes remodeling of the lung architecture resulting in collapse of alveolar walls and formation of cystic spaces or honeycombing. Areas of end-stage honeycomb lung are found in almost all biopsies of UIP and may be extensive (hematoxylin and eosin, $\times 200$, histologic section kindly provided by Prof. A. Pesci).

important to acknowledge histologic features that distinguish other IIP from IPF, as the clinical course and management is different. DIP/RB-ILD is characterized by a relatively uniform thickening or thickening centered on the bronchioles of the alveolar septa, accompanied by a striking accumulation of pigment-laden intra-alveolar macrophages (95). AIP involves a diffuse fibroproliferative response to synchronous alveolar injuries; histologic features are identical to those of the exudative, proliferative and/or fibrotic phases of DAD (96). NSIP is

manifested as varying degrees of inflammation and fibrosis that are uniformly distributed within the interstitium of the lung (97). In COP, inflammation is centered on the peribronchial interstitium and alveolar ducts; characteristic plugs of granulation tissue occlude the distal air spaces (1, 7, 98).

Radiographic findings in patients with IIP demonstrated lobar heterogeneity. Flaherty et al. (99) hypothesized that heterogeneity of histologic diagnosis might exist from lobe to lobe in patients with suspected IIP. This study showed that interlobar and intralobar histologic variability is present in IIP and the presence of a UIP pattern in any sample confers a poor prognosis. Given the poor prognosis associated with a UIP pattern on any biopsy, the most important goal of the biopsy is finding UIP. Patients with a UIP pattern in all lobes were categorized as having concordant UIP; those with a pattern of UIP in at least one lobe but an NSIP pattern in another lobe were categorized as having discordant UIP. Interlobar histologic variability is common in IIP. This complicates the histologic classification of the disease. The histologic classification in 26% of the patients in the study could have differed between UIP and NSIP if only one biopsy had been obtained. Histologic heterogeneity has received little attention in the literature (80, 100, 101). No previous studies have analyzed the frequency of coexistence of histologic patterns suggestive of NSIP and UIP in the same patient. Heterogeneity of histologic patterns among lobes documents that sampling errors may result from protocols that obtain only one biopsy specimen for IIP. The study of Flaherty et al. emphasizes the value of obtaining a biopsy specimen from multiple lobes during a diagnostic evaluation for IIP (99). A histologic pattern of UIP in any lobe, even if a pattern of NSIP is seen in other lobes, is associated with a poor prognosis; Flaherty et al. propose that these patients be classified as having UIP. This proposal is based largely on finding that UIP-concordant and UIP-discordant patients had similar relative risks of mortality, and that the mortality of these groups was poor as compared with that for patients with NSIP (99).

Therapy

At present, there are no proven therapies for IPF. Conventional management of IPF is primarily based on the concept that suppressing inflammation prevents progression to fibrosis (102). However, the use of aggressive immunosuppressive and cytotoxic treatment regimens has largely failed to reduce the death rate in patients with IPF (1, 103, 104). Given the newer insights into the pathogenesis of IPF (8, 13), novel approaches must be aimed at minimizing the sequelae of repeated acute lung injury and at preventing or inhibiting the fibroproliferative response, and enhancing normal alveolar reepithelialization (105). At present, only lung

transplantation appears beneficial in selected patients (106). To date, very few multicenter trials have been conducted in IPF compared with diseases with a similar mortality (6). Current therapy has evolved without the support of large, well-controlled clinical trials. Multicenter trials require uniform diagnostic criteria and outcome variables. Although there have been concerns about diagnostic criteria, substantial progress has been made recently in our understanding of the pathogenesis, diagnostic criteria, and outcome variables that are necessary to support clinical trials in IPF and IPF-related interstitial lung diseases. A number of studies have evaluated potential therapies for patients with IPF (5, 40). Most of these studies have evaluated the effects of corticosteroids, cytotoxic agents, or colchicine, although in a few studies other drugs were tested (103, 107). In most studies, the number of patients was too small to determine efficacy, and the design of the studies did not always include a parallel placebo-controlled group.

Corticosteroids are the mainstay of therapy in IPF. Despite their ubiquitous use, no prospective, randomized, double-blind, placebo-controlled trial has evaluated the efficacy of corticosteroids in the treatment of IPF (103). A recent Cochrane review had evaluated trials that determine the efficacy of corticosteroids in the treatment of adults with IPF but no randomized controlled trials were found (108). Many studies, especially early studies, reported that 10–30% of patients with IPF have an initial, objective improvement with this form of therapy (40, 109). Correlative studies have suggested that corticosteroids reduce the so-called ground-glass opacities seen on HRCT in some patients with IPF, and that this reduction corresponds to an improvement in pulmonary function (110). A similar study found that although ground-glass attenuation on HRCT decreased in response to corticosteroids, the progression to irreversible honeycomb fibrosis was not altered (53). Reevaluation of these studies has questioned whether most of the patients who responded to therapy truly had IPF (2, 6). There are a number of reasons for this reevaluation. First, some of the patients in these studies had a collagen vascular disease and, therefore, did not have IPF. Secondly, there were few biopsies performed to establish a diagnosis of IPF. Thus, it is unlikely that all of the patients in these studies would be classified as IPF by current criteria. Two additional observations suggest that the responsive patients had a disorder other than IPF. In general, the patients who responded to therapy were younger than 50 years of age and were female. Most patients with these demographic characteristics do not have UIP on lung biopsy by current criteria (6). Recent studies of well-defined patients with IPF suggest that few, if any, patients with IPF respond to corticosteroid therapy. No studies have determined that corticosteroids alter survival when compared with untreated patients (6). If responses are to occur with corticosteroids, improvement is usually noted within 3 months. After 3 months of corticosteroid therapy,

objective clinical parameters (e.g. dyspnea scores, physiologic studies, chest radiographs, HRCT) are required to gauge response. Subjective improvement is not adequate to gauge response. Common practice has been for maintenance corticosteroid therapy to be reserved for patients exhibiting *stabilization* or *objective* improvement. Corticosteroid-responsive patients are maintained on prednisone chronically (sometimes indefinitely), but in a gradually tapering dose. The dose of corticosteroid and rate of taper should be guided by clinical and physiologic parameters. Prolonged treatment for a minimum of 1–2 years is reasonable for patients exhibiting unequivocal responses to therapy. In this context, chronic low-dose prednisone (15–20 mg every other day) may be adequate as maintenance therapy (1).

Immunosuppressive or cytotoxic agents are used among steroid nonresponders, patients experiencing serious adverse effects from corticosteroids, and patients at high risk for corticosteroid complications (e.g. poorly controlled diabetes mellitus or hypertension, severe osteoporosis, or peptic ulcer disease) (1). Several studies have evaluated the effects of cytotoxic agents and noted beneficial effects in the treatment of patients with IPF (111–115). An early study from the Brompton Hospital suggested that therapy with cyclophosphamide and prednisone improves survival compared with therapy with prednisone alone (112). However, the same reservations regarding patient selection that were noted previously for clinical trials of corticosteroids apply to this study. Others have suggested that cyclophosphamide slows the decline in pulmonary function in patients with IPF but does not alter survival (114, 115). Similar observations and reservations exist regarding the clinical trials on the efficacy of azathioprine (113). No studies address the effect of azathioprine or cyclophosphamide alone in the treatment of IPF. It is on the basis of these studies that a recent consensus statement recommends the combination of corticosteroids (prednisone 0.5 mg/kg/day tapered to 0.125 mg/kg/day over 3 months) and azathioprine (2–3 mg/kg/day, maximum 150 mg/day) or cyclophosphamide (2 mg/kg/day, maximum 150 mg/day) as first-line therapy for IPF (1). Regardless, the data supporting conventional anti-inflammatory therapy for IPF is limited at best, and the benefits relative to the adverse effects are small. Cytotoxic agents also have limiting side effects, including myelosuppression, secondary cancers, and drug-induced interstitial pneumonia, which further complicate clinical decision making. In the absence of objective improvement, therapy with these agents, in most instances, should be discontinued (7). Therapies designed to inhibit fibrogenesis have also been used in patients with IPF. Useful agents might interfere with matrix synthesis, fibroblast proliferation, or profibrotic cell–cell signaling. Two studies evaluated colchicine for the treatment of IPF (116, 117). One compared prednisone alone to prednisone plus colchicine and there was no additional benefit of colchicine (117). In another

study, the effects of colchicine alone were similar to that of prednisone alone (116). None of the patients had an initial response to therapy, and pulmonary function continued to decline in all patients. The median survival was unchanged, suggesting little effect of the drugs. The only benefit of colchicine therapy was fewer side effects when compared with prednisone. Pirfenidone, an antifibrotic agent, showed promise in IPF patients in an open label study (118). There was limited toxicity and improvement in some patients, but a larger prospective double-blind study is required to establish efficacy. In this study most patients had failed immunosuppressive and cytotoxic therapy and had advanced disease; pirfenidone was able to stabilize both respiratory function and symptomatology. D-penicillamine appears to inhibit collagen deposition by interfering with the intramolecular cross-linking of mature collagen (119). However, in the only prospective trial examining penicillamine in combination with prednisone for IPF, there was no benefit to the addition of penicillamine (117). Given the toxic side-effect profile of penicillamine, including loss of taste, stomatitis, and nephrotoxicity, penicillamine has no current role in the treatment of IPF. A promising new therapy is interferon- γ -1b, a multifunctional cytokine that inhibits fibroblast proliferation and collagen synthesis and antagonizes the effects of TGF- β (120, 121). In an exciting, albeit very preliminary study, Ziesche et al. (38) suggested that this drug could be useful in this disease. In a randomized trial of 18 highly selected patients with IPF, they showed that patients receiving interferon- γ -1b plus low doses of prednisolone for 1 year exhibited a significant improvement in lung physiology with a concomitant decrease in the tissue expression of several profibrotic molecules. Preliminary data from this group also suggest that the therapy improves survival (38). A large multicenter, randomized, double-blind, placebo-controlled, phase III study of the safety and efficacy of interferon- γ -1b has been recently completed (122). Analysis of the data suggests that although interferon- γ produces no differences in the observed rate of progression-free survival, pulmonary function or the quality of life, it did appear to decrease mortality primarily in a subset of patients with mild to moderate disease. The authors conclude that owing to the size and duration of the trial, a clinically significant survival benefit could not be ruled out. Adverse effects are common with interferon- γ but are generally mild and usually reversible at current dosages. These side effects include headache, fatigue, rigors, influenza-like symptoms, depression, myalgia, and granulocytopenia (123). However, Honoré et al. (124) described four patients who developed acute respiratory distress syndrome in an explosive manner and who eventually died from irreversible respiratory failure. Importantly, these acute events were temporally related to interferon- γ -1b therapy. Moreover, the complication occurred shortly after the initiation of the drug in three patients. The clinical behavior was similar in all four

patients, with increasing dyspnea, fever, the emergence of large new radiologic areas of ground-glass opacities and rapidly progressive hypoxemia requiring mechanical ventilation and high oxygen concentrations. In two patients, lung histology after the acute event was available, and it demonstrated extensive diffuse alveolar damage with preexisting UIP. Finally, although not conclusive, this case series raises concerns that need to be addressed by further studies examining the potential role of interferon- γ -1b in the management of IPF. It is possible that a subset of patients may be at risk of an acute, and rapidly lethal, lung exacerbation, and we need to identify them before instituting therapy. The preliminary findings from this report and the experience of others suggest that patients with advanced disease (FVC of less than 50% of predicted; DLCO of less than 40% of predicted), as well as those with some associated diseases or familial IPF, may have an increased risk of adverse outcome when treated with interferon- γ -1b (124).

In the last 20 years, lung transplantation has emerged as a feasible option for selected patients with IPF, and is now a recognized therapeutic option. This procedure can prolong life and may improve the quality of life of patients with end-stage lung disease and severe respiratory insufficiency (125, 126). After the failure of medical treatment, single-lung transplantation results in an actuarial survival of 73% at 1 year and 57% at 3 years (127). Unfortunately, most patients are not eligible, because of older age or complicating medical conditions and many limiting factors, such as a scanty supply of donor lungs and chronic graft dysfunction limit transplantation to become a long-term solution (128). Primarily, chronic lung rejection that is characterized by bronchiolitis obliterans, a rapidly progressive inflammation disorder of the small airways that provokes severe airflow limitation, has become a major obstacle for the long-term survival of lung allograft recipients (129). On the other hand, as most IPF patients die within few years after diagnosis, one critical issue for lung transplant success is the determination of the optimal referral time. Of patients awaiting lung transplantation, the death rates are highest in those with IPF, suggesting that many IPF patients are referred late for transplantation (106, 127). A limited window of opportunity exists to refer IPF patients for lung transplantation. The short transplant window is reflected in the high mortality rate in IPF patients awaiting lung transplantation (106, 130). However, it is not easy to predict survival in IPF patients who are potentially suitable for lung transplantation, and studies evaluating the role of cardiopulmonary function have been inconsistent. Thus, for example, some reports have suggested that hemodynamics and respiratory function do not predict survival, while others have shown that survival is significantly related to a number of different clinical and functional data, including evidence of pulmonary hypertension on the chest radiograph, reduced lung volume, and the presence of gas exchange

abnormalities with exercise (131, 132). Moreover, in contradiction to previous reports (133), King et al. (132) found that DLCO was not an independent predictor of survival in multivariate analysis. By contrast, others have suggested that in IPF patients < 65 years of age, the best prediction of survival is derived from a combination of the percent predicted for the DLCO and the HRCT scan fibrosis score (130). The results of the study of Timmer et al. (134) showed, for the first time, that the severity of hypoxemia at rest was the only significant difference between patients who survived and underwent transplantation, and those who died while waiting for transplantation. Thus, the question about which parameters have the best potential for optimizing the timing of referral for transplantation remains open (135).

Natural history and prognostic factors

IPF remains a difficult therapeutic dilemma with a limited response to immunosuppressive therapy. The development of a therapeutic plan for IPF is difficult. Five-year survival is estimated at 30–50% (5, 103). Few studies have identified features of IPF that are associated with an increased risk of disease progression and death (20, 72, 133, 136–138). Reported indicators, at presentation, of longer survival include: younger age (< 50 years), female, a shorter symptomatic period prior to diagnosis, less dyspnea, preserved lung function, extent of ground-glass and reticular opacities on HRCT scan, lymphocytosis (20–25%) in BAL, and a beneficial response or stable disease 3–6 months after initial corticosteroid therapy (40, 68, 69, 109, 139, 140). Features associated with shortened survival include: increased neutrophils (> 5%) (69) and/or eosinophils (> 5%) (20, 133, 141) in the BAL, a failure to respond to immunosuppression therapy, and the extent of ‘fibrosis’ on HRCT scan (142). Pretherapy pulmonary function has been studied extensively. A worse survival has been associated with a lower pretreatment diffusing capacity (139, 143), TLC (68), and FVC (68, 143–145). A lower survival has been reported in patients who experience greater reduction in pulmonary function during the initial course of therapy (133, 145, 146). Change in pulmonary function greater than 10% in TLC and FVC and 15% in DLCO, has been used to define long-term response to therapy (1). The desaturation during a 6-min walk test (6MWT) is found strongly predictive of mortality in a recent study (147). However, pulmonary function has been shown to correlate poorly with histologic severity in confirmed IPF (148, 149). Clinical (dyspnea scale), radiographic features (chest radiograph), and weighted pulmonary function parameters including exercise testing have been combined to generate a clinical/radiographic/physiologic score (CRP) (142, 150). The correlation of CRP score and histologic severity is improved, although clinical validation and use of this staging technique during prolonged therapy is limited

(150). Accordingly, diverse groups of clinical variables have been evaluated for their ability to predict outcome in IPF with varying results. Recently, HRCT has been shown to more clearly delineate the anatomy of the lungs when compared with conventional CT (62, 110). Retrospective studies have demonstrated a higher likelihood of response to therapy in those individuals with areas of ‘ground glass’ attenuation on HRCT (58, 59). When individual pathologic variables were assessed and quantified, only the granulation/connective tissue factor score was a significant predictor of survival time in patients with IPF (151). Moreover, the specific features that predicted survival were the degree of alveolar space granulation tissue deposition and extent of young connective tissue present within the fibroblastic foci. These findings support the hypothesis that the critical pathway to end-stage fibrosis is not ‘alveolitis’ but rather the apparently ongoing epithelial damage and repair process associated with persistent fibroblastic proliferation. A strong correlation between increasing extent of fibroblastic foci and both mortality and decrease in both DLCO and FVC at both 6 and 12 months after biopsy was observed in another study (152). The progression of pulmonary fibrosis or disease-associated conditions may cause death in patients with IPF (44). As patients inevitably experience worsening during the course of their illness, it may be difficult to distinguish between IPF progression and disease-related complications. However, the most frequent reason for clinical deterioration appears to be progression of the disease, with death occurring by respiratory failure. Other causes of death include heart failure, bronchogenic carcinoma, ischemic heart disease, infection, and pulmonary embolism (44). Some IPF patients have an accelerated decline or acute exacerbation of their underlying disease, with a rapid downhill clinical course (92, 94). Typically, the patients develop acute, fulminant respiratory failure, often accompanied by fever, elevation of the erythrocyte sedimentation rate, marked increase in dyspnea, and new opacities that often have an ‘alveolar’ pattern radiologically. A small percentage of patients may respond to pulse systemic corticosteroid therapy. This condition has a very poor prognosis, and death within 1 week is not unusual. The occurrence of an acute life-threatening respiratory failure during the course of IPF may require admission to a respiratory ICU and the use of mechanical ventilation. However, studies regarding behavior and outcome under these conditions are scanty. Nava and Rubini (153) assessed the mechanics of the respiratory system during mechanical ventilation in seven IPF patients with end-stage disease. The authors suggested that the hypercapnia observed in the very end stages of the disease might be related to the severe compliance decrement and increase of resistances to such a point that the respiratory muscles can no longer sustain the workload. Both hospital and long-term mortality rates of patients with IPF admitted to the ICU are very high (154).

It is now clear that with the available treatment, IPF remains a progressive, irreversible, and lethal disease. We are dealing with an aggressive lung disorder having a mortality rate higher than many neoplastic diseases.

Thus, true IPF is a grave diagnosis that should prompt early evaluation for lung transplantation, if appropriate, and timely end-of-life discussion with all patients.

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