INTERSTITIAL AND FIBROTIC LUNG DISEASES

Lake D. Morrison, MD, and Paul W. Noble, MD

Interstitial lung disease refers to any of a number of conditions in which infiltration of the alveolar walls with an inflammatory and/or fibrotic process occurs, often leading to restriction of lung function and impairment of gas exchange. In normal lungs, the alveolar septa are thin structures. Macrophages, fibroblasts, and other cells are present in small numbers. Collagen and related extracellular proteins are not prominent. In interstitial lung diseases, proliferation of the fibroblasts and excessive collage deposition occur, presumably in response to some type of injury. Depending on a number of factors yet to be fully understood, including the cause and timing of injury, as well as factors unique to certain individuals, the inflammatory component of this response may be prominent or minor, and anti-inflammatory medications may or may not be effective. Because airway disease and other lung diseases also may affect the interstitium of the lung, and interstitial lung diseases can affect the airways, the term diffuse parenchymal lung disease (DPLD) is often preferred. In this chapter, we adopt that general term.

In approaching a patient with DPLD, the clinician seeks to establish a potential cause. As described elsewhere in this text, interstitial and fibrotic lung diseases can be seen in association with a number of conditions and exposures. When no convincing association can be made, the term idiopathic interstitial pneumonia (IIP) should be used. As described below, IIPs may share many features with the DPLDs seen in conjunction with known clinical entities. In spite of this, the clinical course can vary significantly, and it is incumbent upon the practicing clinician to make an exhaustive search for the causes or known associations of a DPLD as the prognosis and potential therapies can vary widely.

This chapter outlines an approach to the patient with DPLD and describes the salient features of the individual IIPs. DPLDs associated with other conditions or exposures, including sarcoidosis, are described elsewhere [search for these topics in this book]. The categorization suggested by the American Thoracic Society/European Respiratory Society (ATS/ERS) International Multidisciplinary Consensus Committee listed in Figure 1 provides a structured way of approaching patients with DPLD.1

Approach to the Patient with DPLD

The main objective in performing a detailed evaluation of the patient with DPLD is to guide treatment. Given the nature and prevalence of these diseases, this most often distills to determining whether the patient has (a) idiopathic pulmonary fibrosis (IPF), a disease with limited treatment options, or (b) an interstitial pneumonia that might respond to therapy. Drawing this conclusion requires a comprehensive analysis of all data available as no one feature trumps all others. A detailed history, comprehensive physical examination, appropriate laboratory studies, pulmonary function testing, and imaging studies are all required in the workup of a patient with DPLD. In many cases, careful interpretation of these data may obviate the need for a tissue diagnosis, as discussed below.

History and physical examination

The two most prominent complaints in patients with DPLD are typically cough and dyspnea on exertion. Often these symptoms develop quite insidiously, with a patient, or those close to the patient, noting on careful reflection that his or her cough or dyspnea has been present for many months to even years. Likewise, patients will admit that they had ignored their dyspnea, often believing that they were either “just getting older” or “getting out of shape.” Some DPLDs, such as acute interstitial pneumonia (AIP), acute hypersensitivity pneumonitis, eosinophilic pneumonia, or cryptogenic organizing pneumonia (COP), may develop over weeks, and the clinician needs to recognize this feature.

Chest pain, especially substernal chest pain reminiscent of angina, is unusual for most of the IIPs. Pleuritic chest pain may arise in collagen vascular diseases, such as rheumatoid arthritis when an inflammatory pleural effusion is present, or may reflect a pneumothorax, sometimes seen in cystic lung diseases such as lymphangioleiomyomatosis (LAM) or Langerhans cell histiocytosis (LCH). Wheezing in DPLD suggests airways disease. When no history of asthma or chronic obstructive pulmonary disease (COPD) is present, the clinician should consider certain diseases that might affect the smaller airways, such as hypersensitivity pneumonitis or respiratory bronchiolitis. Lymphangitic spread of tumor can lead to obstruction of airways, as can endobronchial sarcoidosis. Hemothysis is uncommon in many of the DPLDs and should prompt the clinician to consider vasculitis such as Wegener or Goodpasture syndrome, or another alveolar hemorrhage syndrome. These conditions are discussed elsewhere [search for these topics in this book].

The patient’s past medical history, as well as a detailed review of symptoms in all major organ systems, requires special attention. DPLD seen in conjunction with conditions such as connective tissue diseases is most likely to be a manifestation of that disease. Asking about rashes, swallowing difficulties, muscle weakness, and joint aches can often point the careful interviewer to a more focused workup. In some cases, symptoms may be very minor when compared to the patient’s pulmonary complaints. It is also well known that pulmonary manifestations of a connective tissue disease may precede other symptoms.2–4 A careful appraisal of the interval medical history is therefore required each and every time a patient is interviewed during his or her workup.

Reviewing the social history of a patient with DPLD takes on special importance since a number of conditions are associated with exposures at home or at work. Tobacco usually plays an essential role in conditions such as LCH,
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desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis–interstitial lung disease (RB-ILD) and an important role in IPF and asbestosis and might be protective in other disorders, such as hypersensitivity pneumonitis. Drugs such as amiodarone, methotrexate, gold, bleomycin, and cyclophosphamide can lead to an interstitial pneumonitis, and the clinician needs to review not only the patient’s current medications but also those taken in the past. Occupational exposure to ores and metals, dusts, fumes, gases, and chemicals can all lead to different forms of DPLD, many of which may not manifest in terms of either symptoms or physical findings for years. Likewise, questions about pets such as birds or mold underneath the bathroom sink can lead to a diagnosis of chronic hypersensitivity pneumonitis in patients who might otherwise appear to have IPF. A number of medications have been associated with DPLD, many of which may not manifest in terms of either symptoms or physical findings for years. Likewise, questions about pets such as birds or mold underneath the bathroom sink can lead to a diagnosis of chronic hypersensitivity pneumonitis in patients who might otherwise appear to have IPF. A number of medications have been associated with DPLD, as discussed elsewhere [search for these topics in this book]. Online resources can be useful in identifying possible causative agents (see http://www.pneumotox.com, for example).

Just as the review of systems might point to a new diagnosis of a connective tissue disorder, the physical examination must be equally thorough. A rash in a shawl pattern or a “mechanic’s hand” rash in an office worker might lead to questions about muscle weakness and, ultimately, a diagnosis of dermatomyositis-related interstitial lung disease. Lymph node enlargement or erythema nodosum might point toward sarcoidosis. Bibasilar inspiratory crackles are an important feature of many of the IIPs, especially IPF. Their absence in IPF, on the other hand, should prompt considering a diagnosis other than IPF. Similarly, digital clubbing is a common feature in IPF or other advanced fibrotic diseases. On the other hand, digital clubbing in a patient with patchy alveolar infiltrates could suggest bronchoalveolar cell carcinoma. Physical findings consistent with pulmonary hypertension (PH) might lead to different treatment options, but signs of cor pulmonale might suggest end-stage disease with imminent mortality.

**Figure 1** Classification scheme of diffuse parenchymal lung disease from the 2001 American Thoracic Society consensus statement on idiopathic interstitial pneumonias. DPLD = diffuse parenchymal lung disease; IIP = idiopathic interstitial pneumonia; LAM = lymphangioleiomyomatosis; LCH = Langerhans cell histiocytosis.

**Pulmonary function testing**

Pulmonary function testing in DPLDs typically reflects a restrictive defect, in which the forced vital capacity (FVC) and volume expired in the first second (FEV$_1$) are both reduced. Total lung capacity (TLC) and residual volume (RV) are also typically reduced. In some cases, the FEV$_1$-to-FVC ratio is elevated. A gas exchange impairment is often present, as indicated by a reduction in the diffusing capacity of the lung for carbon monoxide (DLCO), even after adjustment for anemia (if present).

In cases of early DPLD, lung volumes may be normal. An isolated reduction in DLCO may be an early sign of DPLD.
but might also suggest other entities, such as PH. In patients with concomitant chronic obstructive lung disease, such as in smokers who also develop DPLD, the FVC, FEV₁, and TLC may all be normal.⁶,⁷ Evidence of frank airways obstruction (low FEV₁-to-FVC ratio, high TLC, high RV) might suggest other forms of DPLD, including LCH, chronic hypersensitivity pneumonitis, or sarcoidosis.⁸

**Laboratory Studies**

In cases supported by clinical history, but also when a diagnosis is not certain, testing a battery of antibodies associated with connective tissue disease can be especially helpful. As discussed below, brain natriuretic peptide may be helpful when PH is suspected. At our institution, we typically check any patient presenting with DPLD of uncertain origin for the symptoms outlined in Table 1.

If a diagnosis of a myositis syndrome is clinically suspected and the anti-Jo1 is negative, we also evaluate other antisynthetase antibodies, including anti-Mi2, anti-PL-12, anti-PL-7, anti-EJ, anti-OJ, anti-Ku, and anti-U2snRNP.

**Imaging**

Chest imaging is a key aspect to diagnosing DPLDs. Several different types of abnormalities can be seen, as described below. In a small subset of patients with IPF, plain chest films—and sometimes even computed tomography (CT)—can be normal.⁹,¹⁰ More often than not, however, abnormalities on the CT will be present, even when the roentgenogram is normal.¹¹

The advent of high-resolution computed tomography (HRCT) of the thorax has revolutionized the diagnostic approach to the IIPs. HRCT allows for detailed evaluation of the lung parenchyma in slices 1 to 2 mm thick [see Figure 2].¹² Not only does it provide considerably clearer images of lung anatomy than plain chest roentgenograms, it also has obviated the need for surgical lung biopsy in a number of conditions, including IPF in its classic form.⁶ It also has helped narrow the differential diagnosis significantly in other conditions. For example, pulmonologists will change their diagnosis more than half the time when HRCT is added to all other clinical information (other than biopsy).¹³ HRCT is especially helpful in diagnosing IPF, lymphangitic carcinoma, sarcoidosis, silicosis,
hypotheses, and pulmonary alveolar proteinosis. For the most part, HRCT is indicated in every patient presenting with DPLD. Several patterns have been identified in DPLDs, and recognition of these can help the clinician narrow the differential diagnosis. A peripheral reticular interstitial pattern is a common finding in many forms of DPLD, including IPF and nonspecific interstitial pneumonia (NSIP), as well as many connective tissue diseases and asbestos. On plain roentgenograms viewed in a posterior-anterior plane, an “L reverse L” pattern is typically seen, in which most disease is seen just medial to the lateral edges of the ribs, extending along the diaphragms medially [see Figure 3].

On CT images, these abnormalities are more easily identified as reticular lines, traction bronchiectasis, and honeycombing. Traction bronchiectasis refers to dilated airways in areas of otherwise fibrotic lung [see Figure 4]. Honeycombing refers to destruction of the lung parenchyma resulting in cysts between thickened intralobular septae [see Figure 5]. Honeycombing is a key feature to diagnosing IPF and should be considered present only in unequivocal cases evaluated by expert radiologists or pulmonologists. In general, radiographic abnormalities are most prominent in the periphery of the bases on the lungs, becoming less so near the apices. When predominantly upper lobe disease is seen, other diagnoses, such as hypersensitivity pneumonitis, sarcoidosis, silicosis, and drug-related diseases, should be considered [search for these topics in this book].

Volume loss is another typical feature of fibrotic lung diseases. When lung volumes are increased on radiographs, the clinician should consider other entities, such as lymphangioloieomyomatosis, LCH, sarcoidosis, or concomitant emphysema and pulmonary fibrosis, for example.

Ground-glass opacities are areas of increased lucencies that do not obscure the underlying vasculature [see Figure 6]. Ground-glass opacity is a nonspecific finding that can represent alveolar or interstitial abnormalities, reflecting any number of processes, such as infection, edema, inflammation, or early fibrosis. As discussed in the sections on specific DPLDs below, ground-glass opacities are a common finding in many conditions but typically less so in IPF.

Consolidation is a common finding in two of the IIPs, namely AIP and COP. Nodules, especially along bronchovascular structures, are not typical for IPF and would point toward other diagnoses, such as sarcoidosis, chronic hypersensitivity pneumonitis, LCH, DIP, or RB-ILD. Pleural disease is uncommon in all of the IIPs and would point toward other processes, such as lung disease associated with connective tissue diseases. Mediastinal lymphadenopathy (>1 cm in diameter) is often seen to some extent in IPF and other IIPs.

One important caveat is that breadth of experience in interpreting HRCT may be very important. A number of nonspecific findings are often present on images of patients with DPLD, and a confident diagnosis cannot be made on radiographic data alone in 25 to 50% of patients with histologically confirmed usual interstitial pneumonia (UIP). Radiologists from academic centers, presumably with more experience in DPLDs, are more likely to agree on a radiographic diagnosis than are community radiologists. Accordingly, a radiographic “final” diagnosis should be made with caution.

A summary of radiologic features in DPLDs is shown in Table 2. Integrating clinical history, physical examination, pulmonary function testing, laboratory studies, and radiography often provides substantial clues to diagnosing specific diseases appearing as DPLD. In general, however, pathology usually provides the most information.

**Bronchoscopy with Bronchoalveolar Lavage**

The role of bronchoscopy with bronchoalveolar lavage (BAL) in DPLDs has been debated. Bronchoscopy is generally a safe procedure to perform and can be diagnostic in some cases of DPLD, such as eosinophilic pneumonias, infection, malignancy, and alveolar proteinosis, among other etiologies. In IIPs, differential cell counts can provide some information on underlying disease and prognosis but are rarely definitive. An absence or paucity of lymphocytes favors a diagnosis of UIP over chronic hypersensitivity pneumonitis or sarcoidosis. Unfortunately, BAL analysis does not appear to be useful in distinguishing UIP from fibrosing NSIP.

**Tissue Studies**

**Pathology: Historical Perspective and Current Classification**

Fibrotic, interstitial pneumonias have been recognized in clinical medicine for over a century. In 1892, Osler described cirrhosis of the lung as “a fibrinoid change, which may have its starting point in the tissue about the bronchi and blood-vessels, the interlobular septa, the alveolar walls or in the pleura. So diverse are the different forms and so varied the conditions under which this change occurs that a proper classification is extremely difficult.” Subsequently, in 1944, Hamman and Rich described four cases of acute-onset,
rapidly progressive fibrotic lung disease characterized by “widespread connective tissue hyperplasia throughout the interstitial structures. The alveolar walls were tremendously thickened; in the early stages of the process crowded with fibroblasts.” For some time thereafter, the term Hamman-Rich syndrome was used for any diffuse, fibrotic lung disease, even though we have subsequently learned that these cases represent a rather small portion of interstitial pneumonias (namely, AIP, described below).

In subsequent decades, the causes and associations of many interstitial pneumonias were identified, including collagen vascular diseases, occupational exposures, medications, and familial forms. Still, a number of conditions remained unexplained. After years of using various terms, a combined clinical and pathologic classification scheme was proposed by Liebow and Carrington, in which five distinct subtypes of IIP were described. This format was further developed and refined to the one described by Katzenstein and Myers in 1998. This classification scheme has been adopted by the ATS/ERS in their consensus statement, identifying the major histopathologic patterns and their clinical correlates.

The major patterns described by Katzenstein and Myers, broadened somewhat by the ATS/ERS, include UIP, NSIP, DIP and the related respiratory bronchiolitis (RB), diffuse alveolar damage (DAD), lymphoid interstitial pneumonia (LIP), and bronchiolitis obliterans with organizing pneumonia (BOOP). In many cases, the name of the pathologic pattern is the same as the name of the disease when that pathology is seen in an idiopathic entity. As such, the ATS/ERS recommends adding the term pattern to the pathology. For example, an NSIP pattern may be seen in NSIP, an idiopathic entity, or it may be seen in interstitial lung disease associated with collagen vascular diseases, such as rheumatoid arthritis. When the names of pathology and disease differ, each is used as appropriate. When a pattern of DAD is seen in conjunction with other processes, the diagnosis is adult respiratory distress syndrome (ARDS).

Figure 4 Traction bronchiectasis. Fibrosis peripherally causes the airways to lose their normally tapering. (a) and (b) Coronal and sagittal images from the same patient. (c) A patient with more extensive fibrosis. In all cases, the peripheral fibrosis leads to airways dilatation.
Lacking a known clinical association, the clinical diagnosis is AIP.

The major features of histopathologic patterns of interstitial lung diseases are discussed separately under each of the detailed discussions of the individual IIPs below. It is important to recognize that several of these patterns of pathology will be seen in interstitial pneumonias associated with other conditions, such as various connective tissue diseases. Although many surrogate markers offer important information in the analysis of DPLD, histology, especially when UIP is found, remains the most important predictor of prognosis.

The Role of Lung Biopsy

In many of the DPLDs, a surgical lung biopsy is needed to establish a diagnosis. Specimens obtained via transbronchial technique are typically small, roughly the size of bread crumbs. Surgical biopsies are typically a few cubic centimeters in size. Table 3 shows diagnoses that can be made on transbronchial biopsies.

The role of biopsy needs to be carefully considered in patients with functionally severe disease on presentation as the clinical course might not differ depending on the diagnosis of UIP or fibrosing NSIP. The clinician should also note that patients with more severe disease are at increased risk for surgical lung biopsy. Mortality increases significantly as the DLCO approaches 30% or lower. Patients with UIP are more likely to experience a decline in FVC or an increase in radiographic ground-glass opacity in the 6 months following surgical lung biopsy than are patients with NSIP. A decrease in FVC adds to predictive value as well.

Lettieri and colleagues reported low mortality rates in a retrospectively evaluated cohort of 83 patients undergoing surgical lung biopsy for DPLD. The overall mortality rate was 6.1% at 90 days, with a slightly higher rate of 9.5% in the patients ultimately diagnosed with IPF. In their cohort, the need for mechanical ventilation and being immunosuppressed were risk factors for death. When these patients were excluded, the overall mortality rate was 1.5%. Seven (8.4%) of these patients experienced postoperative complications, with only two in patients ultimately diagnosed with IPF (4.8%). In a separate cohort of 68 consecutive patients, a similar mortality rate of 4.4% was observed, but the complication rate was much higher, at 19.1%, including frequent need for hospital readmission (10.7%) and the need for postoperative mechanical ventilation (5.9%). Finally, a series of 196 consecutive patients over 7 years in Taiwan indicated no mortality and a morbidity rate of 6.6%. This series included 43 patients with IIP, 34 with DAD, and 60 with infection disease (primarily in the setting of underlying immunosuppression).

There have been case reports of acute exacerbations of IPF following surgical pulmonary resection for malignancy. The impact of this on diagnostic biopsies for DPLD is not clear, although 2 of 11 acute exacerbations occurring in a cohort of 147 patients occurred immediately following surgical lung biopsy.

Making a Final Diagnosis

Reaching a final diagnosis in any patient with DPLD can be challenging. All aspects of the history, examination, imaging, laboratory data, and pulmonary function testing must be considered. An approach recommended by the ATS is presented in Figure 7. Often provisional diagnoses...
are made at multiple steps in the process. In some cases, a diagnosis may change months or even years after the onset of symptoms because new data have emerged, such as the clear development of a connective tissue disease.

In an important study performed by Flaherty and colleagues, a stepwise approach in which the clinician has HRCT alone initially, progressing to full clinical details and pathology, along with the input from radiologists and pathologists, is used. This approach helps in making a more accurate diagnosis. For example, in the case of interstitial lung diseases, a stepwise approach can lead to a more precise diagnosis. It is important to note that the diagnosis of interstitial lung diseases is often made at multiple steps in the process, and in some cases, it may change months or even years after the onset of symptoms because new data have emerged, such as the clear development of a connective tissue disease.

### Table 2: Radiographic Features of Various Diffuse Parenchymal Lung Diseases

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Histologic Pattern</th>
<th>Usual Radiographic Features</th>
<th>Typical Distribution on CT</th>
<th>Typical CT Findings</th>
<th>CT Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF/CFA</td>
<td>UIP</td>
<td>Basal-predominant reticular abnormality with volume loss</td>
<td>Peripheral, subpleural, basal</td>
<td>Reticular, honeycombing Traction bronchiectasis/bronchiolectasis; architectural distortion Focal ground glass</td>
<td>Asbestosis Collagen vascular disease Hypersensitivity pneumonitis Sarcoidosis</td>
</tr>
<tr>
<td>NSIP, provisional</td>
<td>NSIP</td>
<td>Ground-glass and reticular opacity</td>
<td>Peripheral, subpleural, basal, symmetric</td>
<td>Ground-glass attenuation Irregular lines Consolidation</td>
<td>UIP, DIP, COP Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>COP</td>
<td>OP</td>
<td>Patchy bilateral consolidation</td>
<td>Subpleural/ peribronchial</td>
<td>Patchy consolidation and/or nodules</td>
<td>Infection, vasculitis, sarcoidosis, alveolar carcinoma, lymphoma, eosinophilic pneumonia, NSIP</td>
</tr>
<tr>
<td>AIP</td>
<td>DAD</td>
<td>Progressive diffuse ground-glass density/consolidation</td>
<td>Diffuse</td>
<td>Consolidation and ground-glass opacity, often with lobular sparing Traction bronchiectasis later</td>
<td>Hydrostatic edema Pneumonia Acute eosinophilic pneumonia</td>
</tr>
<tr>
<td>DIP</td>
<td>DIP</td>
<td>Ground-glass opacity</td>
<td>Lower zone, peripheral predominance in most</td>
<td>Ground-glass attenuation Reticular lines</td>
<td>RB-ILD Hypersensitivity pneumonitis Sarcoidosis PCP</td>
</tr>
<tr>
<td>RB-ILD</td>
<td>RB</td>
<td>Bronchial wall thickening; ground-glass opacity</td>
<td>Diffuse</td>
<td>Bronchial wall thickening Centrilobular nodules Patchy ground-glass opacity</td>
<td>DIP NSIP Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>LIP</td>
<td>LIP</td>
<td>Reticular opacities, nodules</td>
<td>Diffuse</td>
<td>Centrilobular nodules, ground-glass attenuation, septal and bronchovascular thickening, thin-walled cysts</td>
<td>Sarcoidosis, lymphangitic carcinoma, Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>

AIP = acute interstitial pneumonia; CFA = cryptogenic fibrosing alveolitis; COP = cryptogenic organizing pneumonia; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PCP = Pneumocystis carinii pneumonia; RB-ILD = respiratory bronchiolitis–associated interstitial lung disease; UIP = usual interstitial pneumonia.

### Table 3: Diseases that Can Be Diagnosed on Transbronchial Biopsy (Rather than Surgical Lung Biopsy)

<table>
<thead>
<tr>
<th>Often</th>
<th>Occasionally</th>
<th>Rarely/Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>AIP (DAD pathology)</td>
<td>IPF (UIP pathology)</td>
</tr>
<tr>
<td>Lymphangitic spread of tumor</td>
<td>Vasculitis</td>
<td>RB-ILD or DIP</td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td>Amyloidosis</td>
<td>NSIP</td>
</tr>
<tr>
<td>Infections</td>
<td>Langerhans cell histiocytosis</td>
<td>LIP</td>
</tr>
<tr>
<td>Alveolar proteinosis</td>
<td>Lymphangioleiomyomatosis</td>
<td>COP (BOOP pathology)</td>
</tr>
</tbody>
</table>

AIP = acute interstitial pneumonia; BOOP = bronchiolitis obliterans with organizing pneumonia; COP = cryptogenic organizing pneumonia; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis–interstitial lung disease.
Using the histologic pattern of UIP on biopsy, the kappa value of the clinician reading the HRCT alone was 0.41 but increased to 0.86 when all pertinent data and consultation were allowed. These findings argue for a multidisciplinary, consensus-reaching approach to diagnosing all challenging cases of IIP.

Idiopathic Interstitial Pneumonias

Each of the IIPs is discussed separately below. For discussion of DPLDs associated with other conditions elsewhere, see 14:VII Disorders of the Chest Wall.

idiopathic pulmonary fibrosis

Epidemiology

Surprisingly, limited data are available on the epidemiology of IPF, in part because of changes in the case definition over the past several decades. In addition, lack of familiarity in the medical community with IPF and high mortality render this relatively uncommon disease difficult to characterize from a population standpoint. Estimates of annual incidence appear to be on the order of 10 per 100,000, with ranges reported from 6.8 to 16.4.3,37,38 Overall prevalence appears to be on the order of 20 per 100,000, with ranges reported from 14.0 to 42.7.3,37,38 Typically, IPF does not present until the sixth decade of life,1 and the annual incidence and prevalence increase significantly in older individuals. For example, estimates of prevalence among individuals aged 75 and older may be as high as 276.9 per 100,000 men and 192.1 per 100,000 women.38 This pattern of male predominance holds true in patients older than 65 years but may not be as pronounced in younger patients.38 Overall, males with IPF outnumber females by approximately 1.5 to 1.8:1.3,38 There has been a predominance of Caucasians reported in IPF, but there is no known racial predilection for the disease.3 There is no distinct geographic distribution for IPF.4

Figure 7  Diagnostic approach to diffuse parenchymal lung disease recommended by the American Thoracic Society. BAL = bronchoalveolar lavage; CT = computed tomography; DAD = diffuse alveolar damage; DIP = desquamative interstitial pneumonia; DPLD = diffuse parenchymal lung disease; HRCT = high-resolution computed tomography; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LCH = Langerhans cell histiocytosis; RB = respiratory bronchiolitis; TBBx = transbronchial biopsy; UIP = usual interstitial pneumonia.
Survival in IPF is poor. Symptoms are often present for months or even years before a diagnosis is made. Median survival following diagnosis is approximately 3 years. In one major center’s cohort, median survival following the onset of symptoms was greater than 6 years, suggesting that some patients may wait over 3 years before a diagnosis of IPF is made. Recent estimates suggest that mortality from IPF has increased. In this study, which analyzed data from the National Center for Health Statistics, the age-adjusted mortality rate increased 28.4% for men and 41.3% for women from 1992 to 2003 (i.e., from 40.2 to 61.0 deaths per 1,000,000 in men and from 39.0 to 55.1 deaths per 1,000,000 in women).

Risk factors for developing IPF include cigarette smoking, environmental antigens, infections, chronic aspiration, and drugs. Cigarette smoking has a fascinating impact on IPF as it paradoxically seems to both predispose individuals to IPF and “protect” them from disease progression. A majority of patients with IPF have a smoking history. At a major referral center in the United States, current smokers with IPF had an extended survival when compared with former smokers or never-smokers. In general, their disease seemed to be less severe than that of never-smokers. Interestingly, when a similar cohort at a British referral center was analyzed and disease severity was considered, severity-adjusted survival was better in never-smokers than in either current or former smokers, or in those two groups combined. Taken together, these data suggest the possibility of a “healthy smoker” effect, in which patients quit smoking as their disease worsens. Whether smoking might both predispose to fibrosis, perhaps through oxidative stress but, in turn, attenuate the fibrotic response to some degree remains to be seen.

Obesity has been associated with better survival in patients with IPF. In addition, nutritional depletion has been associated with poor survival in end-stage lung disease of many etiologies, including DPLD. Although the latter finding is intuitive, the former defies easy reasoning. The study in question was retrospective and needs to be validated.

**Histopathology**

The usual interstitial pneumonia pattern is the most commonly seen pathology in ILD. A UIP pattern is seen in IPF (also known as cryptogenic fibrosing alveolitis in Europe) and is characterized by patchy, nonuniform, and variable distribution of interstitial changes. The variability in the amount of fibrosis within a biopsy is often apparent at scanning magnification of the microscope: areas of dense fibrosis, interstitial inflammation, honeycombing, and normal lung may all be present in the same section [see Figure 8]. Even within fibrotic areas, lesions of apparently different age are present, with some zones of acellular collagen deposition and areas of presumed active fibrosis (“fibroblastic foci”) [see Figure 9]. This finding is termed temporal heterogeneity. When present, interstitial inflammation is usually mild, with lymphocytes, plasma cells, and histiocytes associated with hyperplastic type II pneumocytes. Biopsy specimens should show areas of relatively normal lung to make a pathologic diagnosis of UIP. Otherwise, the pathologist may only be able to diagnose “severe fibrosis with honeycomb change (of uncertain etiology).”

In addition to IPF, a UIP pattern can be seen in a number of other clinical settings, including collagen vascular disease, drug toxicity, chronic hypersensitivity pneumonitis, asbestosis, and rare disorders such as Hermansky-Pudlak syndrome. In some cases, further distinguishing characteristics on biopsy specimens may point to one of these diagnoses.

**Pathogenesis**

Because of the relentless progression of IPF in most individuals, our failure to understand the underlying pathogenesis has been particularly frustrating. Once thought to be an inflammatory process, IPF is now considered to be a complex interaction of epithelial cells, mesenchymal cells, and various cytokines. The relative paucity of inflammatory cells seen on histopathology at most time points has led many to believe that inflammation plays only a minor role, if any at all. This concept is supported by the fact that decades of typical anti-inflammatory therapy have not been effective in treating IPF. An inflammatory milieu, however, seems to be present in IPF, especially since proinflammatory cytokines, chemokines, antioxidants, and immunoglobulins are upregulated in patients with IPF. The common finding of mild mediastinal lymphadenopathy on CT images of patients with IPF also supports the notion that some inflammation is present.

At a fundamental level, most investigators agree on two aspects of IPF: (1) an initiating injury(ies) occurs, and (2) the host response is abnormal and persistent. Whether the injurious agent persists, whether the insult is too great to overcome, or whether the host is predisposed to abnormal recovery is uncertain. Any number of precipitating factors have been considered, including tobacco, gastroesophageal reflux and aspiration, infections, and environmental exposures, among others. Although association with these factors has been seen in many studies, no clear causative roles have been established.

In IPF, epithelial cells, especially type I pneumocytes, are damaged and undergo apoptosis. Exposure of the basement membrane in the alveolus occurs, and this damage fails to be fully repaired. Type II epithelial cells become hyperplastic, presumably in an attempt to repair the basement membrane, but they do not reestablish normal alveolar function. Some have suggested that this phenomenon results from polarization of the immune response toward T helper type 2 immunity, which, in turn, stimulates the release of profibrotic cytokines, fibroblast migration, proliferation, and differentiation into myofibroblasts.

In the setting of epithelial cell injury and basement membrane exposure, a number of growth factors accumulate, including transforming growth factor-β (TGF-β), platelet-derived growth factors (PDGFs), and fibroblast growth factor-2, among others, the consequence of which may be recruitment of fibroblasts and myofibroblasts, often through tyrosine-kinase signaling pathways. Myofibroblasts are involved in fibrosis of virtually all tissues and have a phenotype between muscle and nonmuscle
cells, with contractile and collagen-secreting properties.\textsuperscript{49} They express smooth muscle actin, a feature that distinguishes them from other fibroblasts.\textsuperscript{50} Their contractility is stimulated by a number of cytokines, including endothelin-1 and TGF-\textbeta.\textsuperscript{49} They appear to be a key player in the fibrosis of IPF. The origin of these cells is not certain, and there is debate as to whether they are resident cells in the lung, whether they result from epithelial cells transitioning to mesenchymal cells in response to injury, or whether they are circulating cells derived from the bone marrow.\textsuperscript{47} Regardless of their origin, stimulated myofibroblasts appear to organize into clusters of cells known as fibroblastic foci. These clusters are typically adjacent to damaged epithelial cells and may often be at the “leading edge” of fibrosis, near normal-appearing lung.\textsuperscript{25} Fibroblastic foci are a characteristic feature of UIP pathology, distinguishing it from the other pathologies seen in DPLD.\textsuperscript{6}

In conjunction with epithelial cell derangement and persistent fibrosis, a number of other potentially pathogenic aspects of IPF have been uncovered. Vascular remodeling in IPF includes very aberrant connections that may account for right-to-left shunting seen in IPF.\textsuperscript{7} Factors promoting angiogenesis, such as basic fibroblast growth factor and vascular endothelial growth factor (VEGF), as well as certain CXC chemokines and interferon gamma, which inhibit angiogenesis, have been implicated in IPF.\textsuperscript{31} In addition, an imbalance of extracellular matrix production and degradation may stem from increased production of tissue inhibitor of metalloproteinases (TIMPs), which inhibit breakdown of the matrix.

Given familial clustering of IPF (discussed below), several attempts have been made to identify gene polymorphisms that might be associated with sporadic IPF. At least 12 publications to date have failed to identify polymorphisms in genes associated with IPF, including genes associated with inflammation, surfactant proteins, the coagulation cascade, and fibroblast pathways.\textsuperscript{52} Ongoing studies of familial cohorts are focusing on identifying new genetic loci that might be associated with familial pulmonary fibrosis (FPF). If these studies are fruitful, genetic associations in sporadic IPF might also be unveiled.

In short, the pathogenesis of IPF is complex and poorly understood. Epithelial injury, damage to the basement membrane, and ineffective repair with features of exuberant...
fibrosis leading to the development of fibroblastic foci characterize progression of the disease. As summarized in Figure 10, important signaling molecules, including TGF-β, PDGF, VEGF, interferon gamma, endothelin-1, TIMPs, and CXC chemokines, among many others, come together in full orchestration to play out the relentless and unremitting loss of lung function seen in this devastating disease.

Clinical Features

History and physical examination The insidious onset of nonproductive cough and dyspnea characterizes IPF. Usually, these symptoms are present for more than 6 months.6 Dry, end-inspiratory, “Velcro-like” crackles are present in 80% of patients, typically originating in the bases bilaterally.1 Digital clubbing is noted in up to half of patients.1 Signs of PH and cor pulmonale may develop as disease progresses. Cyanosis also suggests more advanced disease.6

Imaging A confident diagnosis of IPF in the appropriate clinical setting can be made radiographically based on the presence of bilateral, predominantly subpleural, and basilar reticulations, with radiographic honeycombing present and absence of small nodules or extensive ground-glass opacities [see Figures 5 and 6].6,8,53 Of these findings, lower lung honeycombing [see Figure 5] and upper lung irregular lines may be the most important features; using these two factors alone gives positive predictive value for UIP pathology of 85%.16 When trained radiologists are confident of the diagnosis of IPF, they are accurate 95% of the time.53 The differential diagnosis of a radiographic UIP pattern includes collagen vascular disease, chronic hypersensitivity pneumonitis, and asbestosis.54

In terms of differentiating IPF from the other IIPs, the extent of honeycombing is perhaps the most important feature to distinguish UIP from fibrotic NSIP.55 Not surprisingly, the extent of radiographic fibrosis (reticulation and honeycombing) is an important predictor of mortality and has been shown to correlate well with impairments in gas exchange.12 Subpleural sparing is a feature more commonly associated with NSIP than UIP [see Figure 11]. UIP pathology can be distinguished from RB-ILD or DIP by less ground glass, lack of bronchovascular thickening, and greater extent of traction bronchiectasis.55 Parenchymal bands, mosaic perfusion, and subpleural branching opacities and curvilinear lines appear to help distinguish asbestosis from UIP [see Figure 12].56

As discussed below, rapid deterioration during an accelerated phase of IPF is common. Radiographic findings during these acute exacerbations include multifocal and diffuse

Figure 9 Fibroblastic focus adjacent to an airway within an area of active fibrosis in a patient with idiopathic pulmonary fibrosis (hematoxylin-eosin stain; X100 original magnification).
opacifications, often with a ground-glass appearance.\textsuperscript{35,57} It is important to recognize these, as well as to recognize other potentially treatable or significant findings on HRCT, including malignancy and atypical infections such as atypical mycobacteria, \textit{Pneumocystis}, and mycetomas attributable to \textit{Aspergillus} and other organisms [see Figure 13].\textsuperscript{58}

Diagnosis

Diagnosing IPF with certainty requires the finding of UIP on pathology in the appropriate clinical setting, namely the exclusion of other causes of UIP, such as drug toxicities, exposures, and collagen vascular diseases. Except in very early disease, restriction on pulmonary function testing with gas exchange impairments, as well as typical imaging abnormalities mentioned above, are usually seen.\textsuperscript{6} In the absence of a surgical biopsy, the ATS/ERS, in its consensus statement of 2000, outlined major and minor criteria in diagnosing IPF. In this schema, all major criteria and at least three of the four minor criteria should be present to make a confident diagnosis of IPF in an immunocompetent host:\textsuperscript{1}

\textbf{Figure 10} Pathogenesis of idiopathic pulmonary fibrosis.
Major criteria (all):
• exclusion of other known causes of DPLD
• abnormal pulmonary function with evidence of restriction and impaired gas exchange
• bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT
• transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor criteria (at least three):
• age > 50 years
• insidious onset of otherwise unexplained dyspnea on exertion
• duration of illness > 3 months

Although most of these criteria are typically employed, we believe that many practitioners do not perform bronchoscopies unless they are otherwise indicated (such as to assess for infection if clinically suspected). One group has reported the potential role of transbronchial biopsies in diagnosing UIP pathology. Although these data have not been validated yet, and traditional recommendations of surgical lung biopsy should apply for the time being.

Comorbid Clinical Conditions

Pulmonary hypertension
PH has long been known to be a complicating feature of ILD associated with certain collagen vascular diseases, such as systemic sclerosis. The role of PH in IPF is starting to be better understood. The prevalence of PH in IPF is not precisely known and has been reported to range from 32 to 85% in different populations. The reasons for this wide discrepancy in rates are probably multifold, including the notion that the prevalence of PH progresses with disease. In a retrospective analysis of patients awaiting lung transplantation, the prevalence of PH increased from 33 to 85% in a retrospective analysis of one center’s patients awaiting lung transplantation.

Right-heart catheterization remains the gold standard for diagnosing PH, and, unfortunately, no one surrogate test seems to replace it reliably. Echocardiography is relatively sensitive but overestimated PH in half of the patients undergoing lung transplantation evaluation in a retrospective cohort study. Measuring brain natriuretic peptide might be useful in identifying patients with PH. Radiographic evidence of PH on plain films (i.e., pulmonary artery enlargement) has been associated with increased mortality and should prompt further evaluation when present. In contrast, however, an enlarged pulmonary artery on HRCT did not correlate with PH in another study.

Although mean pulmonary pressures seem to correlate with mortality, changes in mean pressures do not correlate with FVC, suggesting that the mechanisms for PH in IPF extend beyond merely fibrosis and subsequent obliteration of the vasculature. A better marker for PH might be exercise...
capacity as both exercise capacity and PH affected survival on transplant waiting lists (although the two measures were not directly compared). The survival impairment attributable to PH may be more significant than just reflecting advanced disease as patients with PH who receive lung transplants fare worse following surgery than patients with no PH pretransplantation.

**Emphysema** Smoking is associated with both IPF and emphysema. Not surprisingly, some patients develop both conditions [see Figure 15], and some experts feel that this should be considered a separate entity. A retrospective study identifying patients’ radiographic evidence of both emphysema and pulmonary fibrosis suggests that this cohort is characterized by preserved lung volumes, significant impairments in gas exchange, hypoxemia with exertion, and concomitant PH in about half of the patients. The vast majority of patients in this study were males with a current or former history of smoking. The significance of the male predominance needs to be assessed in further studies. All dyspneic patients presenting with normal lung volumes and an isolated reduction in gas exchange should be assessed for PH and combined emphysema and pulmonary fibrosis.

*Figure 13 Example of concomitant development of Aspergillus mycetoma and atypical mycobacterial infection in a patient with idiopathic pulmonary fibrosis. (a) Patient baseline 14 months earlier. (b) Cavity harboring a mycetoma that had formed. (c) Adjacent consolidation that was fluorodeoxyglucose avid on positron emission tomography. Cultures from bronchoalveolar lavage grew both Aspergillus fumigatus and Mycobacterium avium complex.*
Gastroesophageal reflux disease  Aspiration of gastric contents can lead to pulmonary fibrosis. In animal models, aspiration-induced lung injury occurs, and fibrosis has been reported in a pig model. Several small series indicate that aspiration is common in patients with IPF. One small retrospective case series suggests that treating aspiration was associated with stabilization of lung function in patients with IPF. Whether these results reflect a promising avenue of therapy for IPF needs to be evaluated on a larger scale.

Other conditions  Data from a limited number of small studies suggest that some other conditions may coexist with IPF at a higher rate than in the general population, as summarized below:

- In a cohort of patients awaiting lung transplantation at a single university center, a group with fibrotic lung disease had a higher prevalence of coronary artery disease than a group with nonfibrotic lung disease (COPD,

![Figure 14](image1.png) Enlargement of pulmonary artery on plain films (a) and chest computed tomographic scan (b) in patient with idiopathic pulmonary fibrosis, emphysema, and pulmonary hypertension. In the setting of significant fibrotic lung disease, it can be difficult to identify the pulmonary artery on plain chest roentgenograms.

![Figure 15](image2.png) Concomitant centrilobular emphysema and pulmonary fibrosis. Peripheral honeycombing, (a) (thick arrow) can be difficult to distinguish from paraseptal emphysema (b) (thin arrow).
PH primarily), after adjusting for coronary artery disease risk factors.78
- Patients with DPLD may have high rates of osteoporosis and osteopenia when compared with the general population, even after adjustment for current or previous use of corticosteroids and/or bisphosphonates.79
- Patients with IPF who receive lung transplants may be at increased risk for pulmonary embolism.90 Whether this reflects a risk inherent to IPF remains to be determined.

The data from these studies need to be confirmed in follow-up analyses. Clinicians should be aware of these potential associations in managing all patients with IPF.

Course of Disease and Predicting Outcomes

A number of investigators have attempted to identify which clinical variables are most important in predicting the course of disease in IPF. Virtually all reasonable clinical parameters have been explored, including the use of composite tools. At times, the results have been conflicting. Nonetheless, it is important to understand and identify useful studies, especially considering that lung transplantation offers the most successful potential therapy. Given that lung transplantation requires a minimum threshold level of fitness and functional capacity, IPF patients who decline too rapidly may miss the window in which transplantation will be considered.

The importance of baseline characteristics has been difficult to determine. One simple reason for this relates to the combined effect of restrictive lung disease with concomitant obstructive lung disease and its impact on pulmonary function testing and imaging. Another confounding factor relates to the changes in diagnostic criteria for IPF and the other IIPs, rendering interpretation of older studies more challenging. In spite of these difficulties, some simple functional assessments, such as desaturation on a 6-minute walk test to less than 88%, correspond to an increased risk of death.81 The amount of fibrosis seen on biopsy might also predict mortality.82–84 For patients awaiting lung transplantation, the distance walked in 6 minutes may be more useful than other functional assessments.85 The 6-minute walk, a relatively straightforward study, seems to have superior predictive abilities and reproducibility than more elaborate exercise testing.86 Unfortunately, the utility of the 6-minute walk distance has not been borne out in all studies.87 Still, of all data from a single point in time, exercise capacity is probably the most useful.82,83,84,86

In a large, multicenter trial of patients with mild to moderate IPF, the extent of fibrosis seen on HRCT was associated with increased mortality.85 Interestingly, the extent of radiographic fibrosis in patients with NSIP also predicts mortality, perhaps even more accurately than the underlying pathologic diagnosis when compared with IPF.86

King and colleagues and Watters and colleagues proposed two models incorporating clinical, radiographic, and pathologic (“CRP”) data at presentation to predict survival in patients with IPF.39,90 Their revised model from 2001—which incorporates age, smoking history, clubbing, extent of interstitial opacities, presence of PH on plain film, TLC, and arterial oxygen tension (PaO2) at maximal exercise—offers a prospectively validated survival model. Unfortunately, their data have not been confirmed in follow-up studies, and the model might be cumbersome for the practicing clinician to use routinely. One interesting phenomenon that was once again shown to be present in this study related to the “protective” effect of active tobacco use, in which current smokers fare better than never-smokers, who, in turn, fare better than former smokers.91 Although smoking may retard the progression of disease, a more likely explanation is that the current smokers had less advanced disease.

Recognizing that many patients with IPF also have concomitant emphysema, a scoring system that accounts for this was devised by UK physicians. This Composite Physiologic Index (CPI) makes an adjustment for the extent of emphysema. Using radiographic criteria, the authors developed a formula based on the extent of fibrosis and emphysema on CT scans. They then developed the CPI formula based on spirometry and gas exchange measurements to reflect or predict the extent of fibrosis on imaging. This formula was then assessed in longitudinal follow-up and found to be predictive of mortality more closely than any of the isolated clinical parameters alone.92 This test may be most useful in making predictions about patients with both IPF and concomitant emphysema.93 Some investigators actually contend that IPF with emphysema should be considered a separate disease entity, often with a very poor prognosis.72

Although these indices may some day prove valuable, they are not widely used in clinical practice today. Furthermore, changes in clinical parameters over time may be more useful in predicting clinical deterioration. A number of studies have now pointed to change in FVC, often set at 10%, as being clinically predictive of further disease progression.

As mentioned before, IPF, like the other IIPs, is a heterogeneous disease. Ostensibly, similar patients may behave quite differently over time, and our ability to distinguish this on initial assessment is relatively poor. Several authors have investigated the predictive power of trends in clinical progression to predict mortality. Of the many variables investigated, a few stand out as predictive in a variety of settings, including a decline in FVC of 10% or more as early as 6 months.92–94 Other measures of disease progression, such as measures of oxygenation (A-a gradient, DLCO, amount of desaturation on a 6-minute walk test), and a decrease in six-minute walk distance may have prognostic significance.29 Of all of these, a change in FVC of 10% may be the most reliable end point.95 Unfortunately, however, a number of patients appear to decline rapidly in an acute time frame without any previously documented 10% decrement. In a large, multinational study evaluating the use of interferon gamma (see below), 43% of those who died during the observation period did not have FVC decrements of 10%.96 In general, acute exacerbations of IPF, as well as admission to an intensive care unit (ICU) for any cause, portend a very poor prognosis.93,96

Acute Exacerbations

A poorly understood and often ominous feature of IPF is what is typically referred to as an acute exacerbation. A recent consensus statement has been proposed by the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet) in
conjunction with several other internationally known investigators. In this statement, proposed diagnostic criteria included the following:

• Previous or concurrent diagnosis of IPF
• Unexplained worsening or development of dyspnea within 30 days
• HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with a UIP pattern
• No evidence of pulmonary infection by endotracheal aspirate or BAL
• Exclusion of alternative causes, including the following:
  • Left heart failure
  • Pulmonary embolism
  • Identifiable causes of acute lung injury

The incidence of acute exacerbations has been difficult to determine. Several retrospective studies have shown a wide range of incidence, ranging from 5% in 9 months to 57% in 3 years. Death is common during an acute exacerbation, with several studies reporting rates approaching 80 to 100%. Even in patients with early disease, rapid progression of IPF occurs frequently. In a retrospective analysis of the control arm of a placebo-controlled clinical trial of patients with mild to moderate IPF, 21% died during the 76-week observation period, over half of whom experienced acute or subacute progression of disease, consistent with acute exacerbations [see Figure 16].

No recognizable risk factors have been identified, other than, potentially, surgical lung biopsy, as mentioned above. The risk does not seem to be related to the level of lung impairment. Typical clinical features include worsening of dyspnea and cough over the previous month. Fever and flu-like symptoms have also been reported, complicating the notion of excluding infection in defining this entity. Lung biopsy specimens typically reveal DAD, with or without hyaline membranes, on a background of UIP. Other pathologic features, such as organizing pneumonia, may sometimes be seen. Treatment is generally supportive. If ventilated, patients should be treated with the same lung-protective strategies used to treat patients with ARDS [search for these topics in this book].

In a trial evaluating the use of anticoagulation in IPF, 32 of 56 patients were hospitalized for acute exacerbation (53% of whom died). Interestingly, mortality was lower in the treated group than in those who did not receive anticoagulation (18% versus 71%), although significant concerns about these data exist. Limited data suggest that pirfenidone, a novel antifibrotic agent, might protect against acute exacerbations.

The etiology of acute exacerbations is unknown. Whether they reflect a process intrinsic to the underlying pathology or an undiagnosed acute insult, such as a viral infection or gastroesophageal reflux with aspiration, for example, remains to be determined.

Treatment Considerations

Unfortunately, there is no proven therapy for the treatment of IPF. Clinical research has been marred by changing case definitions, a lack of placebo-controlled study arms, small numbers of patients, and a relatively short period between diagnosis and death. In spite of these limitations, pulmonologists and internists continue to prescribe medications without proven benefit in the hope that an individual patient might respond. Fortunately, more placebo-controlled trials are in progress or planned for the near future.

Anti-inflammatory medications

Based on the erroneous belief that IPF was driven primarily by inflammation, corticosteroids have been used in treating IPF for decades, although there have never been any placebo-controlled clinical trials evaluating its use as monotherapy in treating IPF. Earlier studies have suggested that 10 to 30% of patients with IPF may respond to corticosteroids, but these were performed prior to the current classification scheme and case definition of IPF and may therefore reflect misdiagnosis. Based on several careful reviews, there is no evidence of sufficient quality to justify routine use of corticosteroids alone in the treatment of IPF. As discussed below, there is marginal evidence to justify its use in conjunction with other agents. Steroids used in the treatment of IPF are associated with significant morbidity.

Cytotoxic and immunosuppressive agents

Azathioprine blocks DNA synthesis and thereby impairs proliferation of many cell lines, including neutrophils and lymphocytes. Like corticosteroids, azathioprine has been used to modulate the immune response thought to play a role in IPF. The best clinical trial conducted to date

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Figure 16  Change in view of progression of idiopathic pulmonary fibrosis. Patients were once thought to decline steadily over time. Emerging evidence suggests that the decline occurs in more of a stepwise fashion, with sudden, unpredictable deteriorations occurring during the course of disease.
compared 13 patients receiving high-dose prednisone plus placebo with 14 patients treated with high-dose prednisone and azathioprine. In this study, a small survival benefit was seen in the azathioprine arm after adjusting for age differences. In spite of the small size of this trial, therapy with azathioprine and prednisone has become commonplace, especially in Europe, where a trial of N-acetylcysteine (NAC) was designed such that prednisone and azathioprine were given to the control group (discussed below). 109

Cyclophosphamide is an alkylation agent that suppresses lymphocyte function. It is used in a number of autoimmune conditions, including many associated with DPLD [search for these topics in this book]. To date, no trial has shown a statistically significant improvement associated with IPF. 106,110 Given significant side effects, including increased risk of myelosuppression, hepatotoxicity, bladder toxicity, and several forms of malignancy, as well as the risk of DPLD attributable to cyclophosphamide, its use cannot be recommended in the treatment of IPF.

Cyclosporine, mycophenolate mofetil, and methotrexate have not been shown to be effective in treating IPF. 114 Although not directly comparable, progression of native lung fibrosis in IPF patients receiving a single lung transplant suggests that calcineurin inhibitor–based immunosuppression regimens are unlikely to be useful in treating IPF. 115,116

**Immunomodulatory and antifibrotic agents**

Interferon gamma-1b is a cytokine shown to have a number of inhibitory effects on fibroblasts. Based on a small preliminary study showing promising results, 117 a large, randomized, placebo-controlled trial was conducted worldwide evaluating its use versus placebo in 330 IPF patients who had not responded to a trial of corticosteroids. 118 Although no difference was seen between these two groups, a trend was seen toward better survival, and subgroup analyses indicated that patients with mild to moderate disease did have lower mortality. A follow-up trial focusing on these patients was recently terminated by the sponsor for increased mortality in the treatment group (http://www.clinicaltrials.gov; #NCT00075998; Press release; InterMune, March 6, 2007). As of the date of this publication, there appears to be no role for the use of interferon gamma-1b in the treatment of IPF.

Endothelin-1, a potent vasoconstrictor implicated in the pathogenesis of PH, has also been shown to have profibrotic properties. Bosentan, an endothelin-1 receptor antagonist, was evaluated in a randomized, placebo-controlled trial in the treatment of IPF (BUILD-1). 119 This trial did not show a difference in the primary end point of increase in exercise capacity but did show trends toward delayed time to death or disease progression, especially in patients with early, radiographically mild, biopsy-proven disease. 119 Based on subgroup analyses, the BUILD 3 trial is currently enrolling to determine if IPF patients with mild to moderate disease respond to treatment with bosentan (http://www.clinicaltrials.gov; #NCT00391443).

Pirfenidone is a novel agent with anti-inflammatory, antioxidant, and antifibrotic properties. A randomized, double-blind, placebo-controlled trial conducted in Japan to evaluate the effects of this medication on oxygenation in patients with IPF was terminated by the data safety monitoring board because the control group was experiencing acute exacerbations at a significantly higher rate than the treatment group. 110 Based on these findings, as well as trends toward a benefit in pulmonary function, a randomized, double-blinded, placebo-controlled trial has completed enrolment of 400 patients worldwide, evaluating patients with both low-dose and high-dose pirfenidone (http://www.clinicaltrials.gov, #NCT00287716). This trial is expected to be completed by 2009.

Colchicine inhibits collagen synthesis and a number of other elements important in fibroblast proliferation. It has been evaluated in retrospective studies and one randomized controlled trial. To date, there is no compelling evidence arguing for its use in IPF. 106,114 d-Penicillamine, another agent that interrupts collagen formation, has been used extensively in the past, but no controlled trials have been performed, and its side effects may very well outweigh any potential benefit it might have in treating IPF. 114

**Antioxidants**

NAC is an antioxidant compound used in the treatment of acetaminophen overdose. It is a precursor to glutathione and was shown to restore depleted glutathione levels in the lungs of patients with pulmonary fibrosis. 120 A large, multinational trial tested use of high-dose NAC in conjunction with prednisone and azathioprine versus prednisone and azathioprine in the treatment of IPF. 109 In this trial (the IFIGENIA study), patients in both groups experienced a decline in pulmonary function (FVC and DLCO) after a year of therapy, but the group that received NAC had less severe declines in these parameters. There was no mortality difference between the groups.

The results of the IFIGENIA trial are somewhat hard to interpret. Given that there was no placebo arm, it is impossible to tell whether prednisone/azathioprine/NAC offered a better outcome than no therapy at all. Some have postulated that NAC may have mitigated some of the possible harmful effects of azathioprine, including hepatotoxicity and myelotoxicity. 116 A clinical trial conducted by the IPFnet evaluating prednisone/azathioprine/NAC versus NAC alone versus placebo is slated to begin enrollment in the near future (“PANTHER”; http://www.ipfnet.org). It is hoped that the results of the PANTHER trial will help clarify the role of NAC alone, as well as NAC used in conjunction with prednisone and azathioprine.

**Anticoagulation**

Vascular injury and a tendency toward thrombosis may play a role in the pathogenesis of IPF. A study was performed in Japan evaluating the use of prednisolone or prednisolone plus anticoagulation in hospitalized IPF patients. 105 In this study, a survival benefit—especially in patients experiencing acute exacerbations—was seen. Unfortunately, a number of methodologic flaws in study design have rendered this small study difficult to interpret. 104 Whether a benefit to anticoagulation is shown in larger trials remains to be seen, but these results are encouraging. Given a lack of effective therapy for acute exacerbations of IPF, one might want to weigh the benefits of empiric anticoagulation in these often terminal events.

**Agents to treat PH**

As mentioned elsewhere, PH is being increasingly recognized as a comorbid condition in
patients with IPF. One particular concern with treating PH in IPF patients is that many agents affect the entire pulmonary vascular bed indiscriminately, potentially mitigating the protective effects of hypoxic vasoconstriction within particularly fibrotic areas of the lung. In some cases, however, the magnitude of PH appears to be out of proportion to the severity of lung parenchymal disease, and several investigators have postulated that treating PH might be beneficial.

Intravenous epoprostenol, well established in the treatment of idiopathic pulmonary arterial hypertension, does not appear to be effective in treating PH associated with IPF. It has been shown to decrease pulmonary vascular resistance and increase cardiac output, but at the expense of worsening shunting.\(^{21,121}\) Inhaled iloprost looked promising in pilot data\(^ {121}\) and has been studied in a multicenter phase II trial, the results of which have not yet been published (http://clinicaltrials.gov, #NCT00109681).

Open-label use of sildenafil for 3 months was associated with improvements in distance walked in 6 minutes.\(^ {122}\) Two studies are currently under way evaluating the effect of sildenafil on exercise capacity in patients with IPF. One is a multicenter trial being conducted by the IPFnet (http://www.ipfnet.org; http://clinicaltrials.gov, #NCT00517933); the other is a single-center study sponsored by the Veterans Administration (http://clinicaltrials.gov, #NCT00359737).

Calcium channel blockers are effective in a subgroup of patients with idiopathic pulmonary arterial hypertension but have not been shown to have a role in other forms of PH.\(^ {123}\) Whether the potential role for anticoagulation in IPF discussed above actually reflects treatment of the in situ thrombosis seen in PH is not clear.\(^ {101}\)

**Lung transplantation** Lung transplantation remains the only therapy for IPF with proven survival benefit.\(^ {124}\) Under the previous organ allocation system used in the United States for lung transplantation, time on the waiting list was paramount in being offered a transplant. Under this system, the median time on the waiting list was roughly 2 years. As of May 2006, the allocation system was revised such that a complex, iterative formula comparing anticipated clinical benefit from transplantation with anticipated clinical course in the absence of transplantation now determines the priority of organ allocation. As a result, the waiting time for patients with IPF has decreased considerably. As mentioned above, it is difficult to predict the course of disease in patients with IPF. Once any meaningful predictor of poor outcome has been reached, appropriate patients should be referred for transplantation. The need to refer patients at the time of initial diagnosis appears to have been obviated by the new allocation system.

**Agents under investigation** At the time of this publication, results from a number of completed trials were pending. Agents under evaluation include etanercept, imatinib, zileuton, and rapamycin, among other agents. Thus far, studies on angiotensin-converting enzyme inhibitors and statins have not been promising.

**nonspecific interstitial pneumonia**

The concept of NSIP has evolved over time from describing a “waste basket” of pathology not otherwise classifiable, to a group of interstitial lung diseases with a favorable prognosis when compared with IPF, to, more recently, a more specific clinical entity. NSIP has been described in conjunction with a number of conditions, including collagen vascular disease, chronic hypersensitivity pneumonitis, various other exposures, and, since the 1980s, HIV disease.\(^ {1}\) The concept of NSIP as an idiopathic entity is more challenging for the clinician, especially given the notion that diseases associated with NSIP may not manifest until well after pulmonary disease occurs. In fact, some have contended that “idiopathic” NSIP is merely NSIP associated with undifferentiated connective tissue disease, presenting primarily in the lung.\(^ {4}\)

**Histopathology**

In contrast to UIP, NSIP is a temporally homogeneous process [see Figure 17].\(^ {125}\) Although areas of spared lung and areas of dense inflammation or fibrosis may be present, all of the lesions appear to be roughly the same age.\(^ {125}\) This temporal uniformity distinguishes NSIP from UIP. Fibroblastic foci may be present in NSIP, but they are not prominent, nor is honeycombing, both of which would argue for a diagnosis of UIP [see Figure 9].

Today, there is a focus on classifying NSIP based on specific features rather than a lack of specific features (as might be suggested by its name). Katzenstein and Fiorelli originally described three patterns of NSIP histopathology: one with primarily cellular inflammation, one with primarily fibrosis and a relative paucity of inflammation, and a third with a mixed pattern.\(^ {121}\) In the cellular NSIP pattern, mild to moderate interstitial inflammation is seen in conjunction with type II pneumocyte hyperplasia.\(^ {126}\) Interstitial fibrosis is absent, and there is a lack of alveolar septal thickening.\(^ {126}\) In the fibrotic NSIP pattern, dense or loose fibrosis is seen, but not in the temporally heterogeneous pattern of UIP.\(^ {126}\) The lung architecture is generally not lost (special staining may be required), and chronic inflammation may be present [see Figure 18].\(^ {126}\)

**Clinical Features**

Because so many conditions can lead to NSIP, it is difficult to describe specific features of idiopathic NSIP as there are likely to be several subsets of patients captured under this classification, many of whom may be manifesting aspects of an undiagnosed or undifferentiated connective tissue disease. In general, patients seem to present at a younger age than do patients with IPF, often in their late 40s or 50s, with a very wide range in age.\(^ {127}\) No gender predominance is seen. The role of tobacco is not clear and does not seem to play the pivotal role in the development of disease that it does in other diseases, such as DIP or RB-ILD (see below). As in UIP, familial cohorts of NSIP have been identified, some with association to specific genetic mutations, such as surfactant protein C.\(^ {128,129}\)

As with other forms of DPLD, patients with NSIP present with cough and dyspnea, typically present for more than a year.\(^ {127}\) Bronchorrhea, fevers, chest paint, weight loss, and malaise have all been observed in NSIP.\(^ {127,128}\) Crackles are common on examination, often in a basilar or sometimes widespread distribution.\(^ {127,128}\) Inspiratory squeaks may be heard, and digital clubbing is seen as much as half the
time. Given the strong association with connective tissue diseases, the physical examination of any patient with suspected or biopsy-proven NSIP needs to be particularly thorough.

Pulmonary function testing resembles that seen with IPF, with restriction and impairment in DLCO. Two-thirds of patients with NSIP will develop hypoxemia with exertion. Bronchoscopy differs from UIP with the finding of increased numbers on BAL of lymphocytes and neutrophils and eosinophils to a lesser degree.

Imaging

Chest radiographs are typically abnormal in NSIP, with patchy alveolar opacities as well as interstitial changes [see Figure 19]. They are typically not helpful in the diagnosis, unlike HRCT scans. Several investigators have attempted to identify salient features of NSIP radiographically. The most common findings in NSIP on HRCT are areas of ground-glass opacity and fine reticular opacities [see Figure 20]. Reticulation can lead to traction bronchiectasis and bronchiolectasis but not to the extent of frank honeycombing. In fact, it is common to observe an absence of reticulation or any other significant radiographic abnormalities at the periphery of lungs in patients with NSIP (so-called “peripheral sparing”) [see Figure 11]. When honeycombing is seen, it seems to occur in cases of fibrotic NSIP exclusively. Examples of cellular and fibrotic NSIP are shown in Figure 20.

In many ways, the HRCT scan in NSIP is not as helpful in suggesting the pathologic diagnosis as it is in reflecting the progress or resolution of disease. Ground-glass opacifications are often present on early CT in this disease. Over time, decreased ground-glass opacity without the development or progression of reticulation has been associated with functional improvement, as is seen with successful treatment of cellular NSIP. Conversely, decreased ground-glass opacity in conjunction with increased reticulation on imaging corresponds to increased amounts of fibrosis and less inflammation.

Diagnosis

Making a confident diagnosis of idiopathic NSIP requires a surgical lung biopsy. Although NSIP is often presumed as the underlying pathology in DPLDs associated with con-
Figure 18  Cellular (a) and fibrosing (b) variants of nonspecific interstitial pneumonia (hematoxylin-eosin stain; X100 original magnification).
nfective tissue diseases, there are no radiographic or other features that would allow the clinician to make a confident diagnosis in lieu of tissue samples. A predominance of ground glass suggests a diagnosis of NSIP, but the ability of radiologists to make an accurate diagnosis ranges from 41 to 73%.89,130,135,137

Results from bronchoscopy are of some utility in NSIP but cannot be used to make a confident diagnosis. Given that BAL shows more lymphocytes in NSIP, it can be helpful to distinguish NSIP from UIP.1 Unfortunately, many of the other conditions considered in the differential diagnosis may have a lymphocytic predominance on BAL as well. Transbronchial biopsies may be consistent with NSIP, but the amount of tissue obtained is generally inadequate.1

Even with surgical lung biopsies, the diagnosis may remain difficult. All surgical lung biopsy specimens need to be thoroughly reviewed as different pathology patterns may be present in the same patient. In general, the predominant pattern is thought be the most important, except in cases in which features of UIP are present with other patterns, such as NSIP. In these cases, the disease course generally mirrors that of patients with UIP alone.138,139

Another problem associated with interpreting surgical lung biopsy specimens relates to significant interobserver disagreement in the diagnosis of specific DPLDs among expert pathologists,36,138,140 most of which centers around diagnosing NSIP. Given these uncertainties, it is essential to have an experienced surgeon biopsy three areas of the lung, ideally at the interface between normal and affected tissue, to optimize the chance of making the correct diagnosis.1

Once the pathology of NSIP is identified, it is essential to redouble efforts to search for features suggestive of the many conditions associated with NSIP as treatment and prognosis vary widely among these different entities.

**Treatment and Clinical Course**

Treating idiopathic NSIP has generally included glucocorticoid and immunosuppression (azathioprine and cyclophosphamide most commonly), although no prospective, randomized, controlled trials have been performed.127 Retrospective data indicate that cellular NSIP responds

![Figure 19](image1.png)

**Figure 19** Plain roentgenogram of a patient with nonspecific interstitial pneumonia.

![Figure 20](image2.png)

**Figure 20** Cellular (a) and fibrosing (b) variants of nonspecific interstitial pneumonia (NSIP) radiographically. Note the similarities in the extent of ground-glass opacifications and lack of radiographic honeycombing (which would suggest usual interstitial pneumonia pathology). Cellular and fibrosing NSIP cannot be distinguished radiographically.
better to therapy than does fibrotic NSIP; in either case, however, relapses are common.127

The overall prognosis in NSIP is better than that in IPF or UIP from other causes. The clinical course is more variable, with some patients improving, many stabilizing, and some progressing to death.1 In some cases, the clinical course of NSIP is relentlessly progressive, such as that seen in IPF.133

Uncommonly, acute exacerbations of NSIP—with features similar to those seen in IPF—have been reported.141

The notion that NSIP in some cases actually becomes UIP has been debated for years. When both UIP and NSIP are seen in different biopsy sites done at the same time, the clinical course more closely follows that of IPF than of idiopathic NSIP.138 In gene expression analyses, sporadic NSIP and UIP appear to be quite similar, whereas sporadic and familial IIPs differ considerably.142 Nonetheless, gene expression profiles have been successfully used to distinguish UIP from NSIP,143 suggesting that some important differences do exist. For the time being, it is probably prudent to advise patients that IPF and NSIP are truly different entities, but NSIP may, on occasion, progress in a fashion very similar to that of IPF.

Acute Interstitial Pneumonia

AIP is a rare form of fulminant DPLD that rapidly progresses to respiratory failure and often death. In retrospect, we now know that it was the lung disease originally described by Hamman and Rich and for years was referred to as Hamman-Rich syndrome.22 AIP is perhaps best thought of as idiopathic ARDS. This histopathology of AIP—namely, DAD—is also seen in a number of other conditions, including ARDS of known cause, collagen vascular diseases, hematopoietic stem cell or solid-organ transplantation, drug reactions, radiation pneumonitis, hypersensitivity pneumonitis, and acute eosinophilic pneumonia, and acute exacerbations of IPF (discussed above).1,144 When one of these is present, a diagnosis of AIP is not appropriate.

Histopathology

DAD is an injury pattern that characteristically progresses from an acute pattern to one of organization and sometimes to one of end-stage fibrosis [see Figure 21]. At any stage, the lesions appear to be of the same age, suggesting a single insult, typically occurring weeks prior to biopsy (“temporal homogeneity”).25 Initially, epithelial cell injury leads to denuding of the alveolar wall, capillary leak, edema, and formation of hyaline membranes. Interstitial inflammation may be prominent.1 In the subsequent organizing phase, active proliferation of fibroblasts and myofibroblasts occurs, with ensuing collagen deposition.145 Thrombi in small to medium-sized pulmonary arterioles may also be seen.145 If this process continues for a sufficient period, a honeycomb-like appearance may result, with progressive and severe fibrosis.20 On other occasions, complete recovery may occur.1

Clinical Features

There is no gender predilection in AIP, and no relationship to smoking has been discerned.1 The age at onset varies widely, with a mean near 49 years (range 7–83 years).146 The onset of AIP is typically abrupt, with several days of a flulike illness with headaches, myalgias, malaise, sore throat, and productive cough.146,147 Exertional dyspnea ensues, often becoming severe.1 Patients typically present within 3 weeks of the onset of their symptoms appearing quite ill. Fever is present in half of patients at presentation, but all investigations for infectious etiologies are, by definition, negative.146 Examination may show evidence of widespread consolidation or diffuse cracks. Digital clubbing is typically absent in AIP, and its presence might suggest a diagnosis of acute exacerbation of (undiagnosed) IPF.144

Pulmonary function testing, when done, shows a restrictive pattern with gas exchange impairments, which are often severe.148 Hypoxemia is present, and patients commonly require mechanical ventilation.1 By clinical criteria, patients meet the definition of ARDS, namely, an acute onset, a ratio of PaO2 to fraction of inspired oxygen of less than 200, diffuse bilateral opacities on chest imaging, and a pulmonary arterial occlusion pressure of less than 18 cm H2O.1,148

Imaging

Chest radiographs often show bilateral, patchy opacifications, with sparing of the costophrenic angles [see Figure 22].1,148 As disease progresses, diffuse consolidation occurs. In the organizing phase, less consolidation is present, and irregular linear opacities are seen.1 CT shows areas of ground-glass attenuation, bronchial dilation, and architectural distortion, in different patterns at different points of disease progression [see Figure 23].149,150 Consolidation and ground-glass opacifications may be present at various times in the course of the disease. Traction bronchiectasis, along with interlobular septal thickening, typically signifies the proliferative and fibrotic stages of DAD and has been associated with higher mortality.151,152

Treatment and Clinical Course

Unfortunately, proven therapies for AIP are lacking, and the standard of care takes clues from the treatment of ARDS. Supplemental oxygen therapy is almost always required. If disease progresses to necessitate mechanical ventilation, lung-protective strategies, as suggested by the ARDSnet trial,153 are appropriate.154 Use of positive end-expiratory pressure to limit potential oxygen toxicity, sedation to synchronize breathing with the ventilator, supplement nutrition, and all other typical aspects of respiratory care for the ICU patient are indicated.

Regarding medications, high-dose parenteral corticosteroids are often recommended, in part based on beliefs that this therapy is beneficial in improving survival in fibroproliferative ARDS.155 A recent follow-up trial suggests that moderate-dose corticosteroid therapy may be beneficial in improving pulmonary function in early, severe ARDS.156 Whether these results can be translated to AIP remains to be seen. A recent retrospective case series reports lower mortality rates in association with steroid therapy lung-protective ventilation techniques.157 Another study suggests that patients with AIP fare better than those with ARDS associated with other conditions.158 Whether the results of these small case series will impact the care of patients afflicted by AIP remains to be seen.
Mortality rates for AIP were historically high, with an overall case-fatality ratio of approximately 70%, but the range in these studies varied from 12.5 to over 90%. Unfortunately, reporting biases and other flaws in case series analyses significantly obscure any conclusions that can be drawn from these data. For those who survive, however, four general patterns of recovery have occurred: (1) complete recovery of lung function; (2) stable but persistent abnormalities in lung function; (3) progressive pulmonary fibrosis; and (4) recurrent AIP.

RB-ILD and DIP

Although often classified separately, the entities of RB-ILD and DIP are primarily smoking-related DPLDs perhaps best thought of as representing ends of a spectrum. Some confusion surrounding these diseases undoubtedly relates to the terminology used. Respiratory bronchiolitis is a pathologic lesion found in cigarette smokers in which pigmented intraluminal macrophages are found within first- and second-order respiratory bronchioles [see Figure 24]. Usually, these lesions are asymptomatic, but in rare cases, they are associated with significant symptoms, impairments in

Figure 21 Diffuse alveolar damage seen in acute interstitial pneumonia. Hyaline membranes (arrows) are present in alveolar spaces. The interstitium contains a mixed cellular and fibrotic infiltrate (hematoxylin-eosin stain; X100 original magnification).

Figure 22 Chest roentgenogram in patient with acute interstitial pneumonia. Patchy alveolar opacities are radiographically indistinguishable from those seen in adult respiratory distress syndrome.
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In these instances, the term RB-ILD is used.

On the other end of this spectrum of smoking-related IIPs, pigmented macrophages fill alveolar spaces more diffusely and in more widespread areas of the lung in DIP. In addition, inflammation is often seen in the alveolar septae, and mild to moderate fibrosis may be present [see Figure 25]. The term desquamative was originally used because it was thought that epithelial cells lining the alveolar spaces were sloughing off into the lumen. Although it was soon recognized that these cells were indeed macrophages, the terminology has persisted in spite of a recent international group considered changing the name to alveolar macrophage pneumonia. Further complicating this nomenclature is the fact that “DIP-like” lesions can be seen many other DPLDs, especially in current and former smokers.

Clinical Features

Case series describing features of RB-ILD and DIP indicate that roughly 90% of afflicted patients are current or former smokers. Other associations include drug exposures, connective tissue diseases, exposures, genetic mutations associated with DPLDs, and other conditions, such as hepatitis C infection. Although studies describing these diseases are limited to cohorts of relatively few

Figure 23  Computed tomographic image of early acute interstitial pneumonia. Ground-glass opacification is the predominant feature radiographically.

Figure 24  Respiratory bronchiolitis–interstitial lung disease histopathology. Pigmented intraluminal macrophages are found within inflamed first- and second-order bronchioles (hematoxylin-eosin stain; X40 original magnification).
patients, RB-ILD and DIP both appear to occur in men about twice as often as in women, typically arising in the fourth to fifth decades of life. As with other IIPs, patients with RB-ILD or DIP often describe the insidious onset of gradual dyspnea and a dry cough. Inspiratory crackles may be found on examination, and digital clubbing has been reported in as many as half of patients with DIP and up to a quarter of patients with RB-ILD. Pulmonary function testing shows restriction, obstruction, a reduction in gas exchange, or a combination of all three.

Imaging

Radiographs in RB-ILD/DIP emphasize the importance of using CT over roentgenograms in the evaluation of DPLDs as chest x-rays may show thickening of the bronchial walls or faint interstitial opacifications but in many cases may be normal. Common CT abnormalities seen include centrilobular nodules, ground-glass attenuation, and sometimes fibrosis [see Figure 26]. In keeping with the notion that these diseases occupy different ends of a spectrum of disease, more ground-glass opacities and more fibrosis have been observed in DIP than in RB-ILD.

Treatment and Clinical Course

Unfortunately, since RB-ILD and DIP are relatively rare diseases, the number of patients described in case series thus far does not allow for a reliable understanding of the natural history of these diseases. Nonetheless, certain observations can be made:

1. Many patients, especially after smoking cessation, seem to have a relatively stable course.
2. In spite of the above, radiographic and pulmonary function abnormalities may persist for years.
3. Mortality rates for DIP appear to be much better than for IPF, with reports of around 30% in 9 years of follow-up.
4. RB-ILD may respond to smoking cessation alone, although a recent report suggests that disease progression occurs in spite of avoiding tobacco.
5. The role of and response to corticosteroid therapy are much harder to determine because of a lack of controlled trials. Many patients with DIP have reported symptomatic improvement after the initiation of corticosteroid therapy,°6,162 and resolution of ground-glass infiltrates following corticosteroid therapy has been reported.°71

cryptogenic organizing pneumonia

As an idiopathic entity, COP was first described by Davison and colleagues in 1983°72 and then by Epler and colleagues in 1985.°73 Epler used the term bronchiolitis obliterans organizing pneumonia (BOOP) to describe the clinical disease and the pathology. The joint ATS/ERS commission has recommended using COP for the disease that would be considered “idiopathic BOOP”°1 primarily because it conveys the essential features of the entity and avoids confusion with other clinical entities, such as constrictive bronchiolitis obliterans.°1

Organizing pneumonia is a pathologic pattern seen in a number of inflammatory conditions. In many cases, simultaneous involvement of the alveoli and terminal bronchioles leads to a pattern described as BOOP. Features of BOOP have been described in association with a large number of other conditions, including postinfection, use of prescription and recreational drugs, rheumatologic conditions, immunodeficiencies, environmental exposures, and miscellaneous other diseases, such as inflammatory bowel disease, thyroiditis, and primary biliary cirrhosis [see Table 4].°74

Histopathology

The hallmarks of organizing pneumonia include excessive proliferation of granulation tissue in small airways and alveolar ducts with chronic inflammation in the surrounding tissue [see Figure 27].°75,°76 These buds of granulation tissue may extend from one alveolar duct to another, leading to a “butterfly” pattern of fibrinous pneumonia. These lesions occupy airspaces predominantly, often in a patchy distribution along bronchovascular bundles. The appearance of the lesions suggests that they are of approximately the same age (“temporal homogeneity”). Foamy macrophages are often seen in the alveolar spaces. Giant cells, granulomas, and vasculitic lesions are not present. Advanced fibrosis and microscopic honeycombing are not present at the time of diagnosis.

Clinical Features

On average, COP typically arises in the sixth decade of life, but the range has been reported as 21 to 80 years.°77 Men and women seem to be affected equally, and nonsmokers and ex-smokers are affected approximately twice as often as current smokers.°78 Unlike those afflicted with IPF, patients with COP can often describe with certainty when they first developed symptoms, which often include a flulike illness with fevers, cough, malaise, anorexia with weight loss, and progressive dyspnea.°77,°78

On physical examination, patients with COP will often have dry, inspiratory crackles, although up to a quarter of patients may have a normal respiratory examination.°79 Digital clubbing is rare.°77–°79

Laboratory studies are nonspecific and can mimic infection. Elevated white blood cell counts, as well as markedly elevated C-reactive protein and erythrocyte sedimentation rates (often exceeding >100 mm/hour), have been reported.°78,°79 Neutrophils in the peripheral blood count may be elevated; increases in eosinophils are not typical°78.

Figure 26  Computed tomographic features of respiratory bronchiolitis-interstitial lung disease may include subtle foci of ground-glass opacification (a). In desquamative interstitial pneumonia (b), more extensive ground-glass opacification may be present.
and would point toward other diagnoses, such as chronic eosinophilic pneumonia.

**Imaging**

Three main chest radiographic patterns have been described in COP: “typical COP” with multiple alveolar infiltrates, “focal COP” with a solitary opacity, and “infiltrative COP” with infiltrative opacities.178,180,181 Infiltrates may be migratory.180 On CT, there is often a bronchocentric pattern in which areas of consolidation, ground glass, nodules, and nonseptal linear or reticular opacities may follow the bronchovascular bundles [see Figure 28].178,181,183,184 Honeycombing is typically present only in late-stage, progressive disease.184 Pleural thickening, pleural effusions, hyperinflation, and cavitory lesions have been reported.177,185

**Pulmonary Function**

Lung function testing typically shows a restrictive ventilatory defect with evidence of a gas exchange impairment.178 Obstruction is seen in those with a history of smoking and underlying COPD.177,178 Hypoxemia is common, especially with exertion.177 Severe cases of hypoxemia with evidence of intra-alveolar shunting have also been reported.178

BAL samples in patients with COP are similar to those seen with hypersensitivity pneumonitis, namely, an increase in neutrophils and lymphocytes and a low CD4-to-CD8 T cell ratio.177,186 Detection of eosinophils is uncommon and would suggest an eosinophilic pneumonia as an alternative diagnosis.177

**Diagnosis**

Diagnosing COP requires a high degree of clinical suspicion. Many patients are initially misdiagnosed as having a bacterial pneumonia, often receiving one or two courses of antibiotics before COP is considered, leading to delays in diagnosis of 1 to 3 months.178 The differential diagnosis is broad and includes, in addition to bacterial pneumonia, hypersensitivity pneumonitis, ARDS/AIP, chronic eosinophilic pneumonia, and aspiration pneumonia, among several other entities.

Radiographically, bronchial dilatation and nonseptal linear or reticular opacities appear to be more common in COP than in chronic eosinophilic pneumonia, but this distinction is difficult to make with confidence.181 Generally, radiographs alone are not useful in distinguishing COP from its many mimics.

When tissue is obtained, surgical lung biopsy via thoracotomy or through video-assisted thoracoscopy is recommended. An algorithm for using the combination of BAL and transbronchial biopsies186 has been suggested, but the inadequate amount of tissue obtained via a flexible bronchoscope limits this approach.3 A pathologist experienced in examining lung tissue should be advised of the clinical and radiographic findings as the finding of organizing pneumonia should prompt a search for related conditions mentioned above [see Table 5]. Only when all other conditions associated with organizing pneumonia are ruled out clinically and by histopathology should a diagnosis of COP be made.

**Treatment and Clinical Course**

Unlike many of the IIPs, COP can often be treated effectively, at least initially. Corticosteroids are the mainstay of initial therapy, typically at moderate to high doses over several months to a year. No standardized consensus has been reached: a typical regimen includes once-daily doses of 1 mg/kg (60 mg/day) for 1 to 3 months followed by 40 mg/day for 3 months, then tapering for a total duration of 1 year,174,177,179 whereas others have suggested shorter courses initially.3 Although shorter courses may be effective in certain individuals, relapses are common, often within 1 to 3 months of discontinuing or even tapering corticosteroids.177,178,179 Parenteral methylprednisolone at doses of 500 to 1,000 mg/day (“pulse dosing”) has been
Figure 27 Bronchiolitis obliterans with organizing pneumonia histopathology seen in cryptogenic organizing pneumonia. Granulation tissue is present in small airways, whereas chronic inflammation is present in surrounding lung tissue (hematoxylin-eosin stain; X40 original magnification).

Figure 28 Chest computed tomography in cryptogenic organizing pneumonia mimics the appearance of multifocal pneumonia. Bronchocentric consolidation with scattered nodules and ground-glass opacifications is present in this image.

recommended for particularly rapidly progressing forms of COP,\textsuperscript{3} and cytotoxic therapy with cyclophosphamide and azathioprine has been used.

In some series, relapses occur in over half the cases.\textsuperscript{187} In spite of this, most patients respond to retreatment with corticosteroids, although some may require long-term therapy. In spite of this, data do not suggest long-term morbidity and mortality as a consequence of recurrence.\textsuperscript{187} Because of their anti-inflammatory effects, macrolides have been associated with effective maintenance therapy in treating a few patients with COP as well as BOOP relating to radiation injury.\textsuperscript{188,189}

**Lymphoid interstitial pneumonia**

Like other terms used to describe DPLDs, LIP has undergone some changes in its definition since first introduced by Liebow and Carrington in 1969.\textsuperscript{24} Once thought to be a
Epidemiology and Clinical Features

Idiopathic LIP is uncommon. For example, searching the clinical database of patients seen in the Interstitial Lung Disease Clinic at the National Jewish Medical and Research Center in Denver, Colorado, from 1985 to 1999 revealed only 15 cases of histopathologically confirmed LIP out of 1,167 patients biopsied. Only three of these were believed to have idiopathic LIP. LIP occurs more frequently in women, often diagnosed in the fifth decade of life. As in other IIPs, symptoms progress gradually, with cough and breathlessness being most prominent, in addition to fever, weight loss, chest pain, and arthralgias in some cases.

Table 5  Summary of Key Features of the Idiopathic Interstitial Pneumonias*

<table>
<thead>
<tr>
<th>Clinical-Radiographic-Pathologic Diagnosis</th>
<th>IPF</th>
<th>NSIP</th>
<th>COP</th>
<th>AIP</th>
<th>DIP, RB-ILD</th>
<th>LIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of illness</td>
<td>Chronic (&gt; 12 mo)</td>
<td>Subacute to chronic (months to years)</td>
<td>Subacute (&lt; 3 mo)</td>
<td>Abrupt (1–2 wk)</td>
<td>Subacute (weeks to months), smoker</td>
<td>Chronic (&gt; 12 mo), women</td>
</tr>
<tr>
<td>Frequency of diagnosis</td>
<td>47–64%</td>
<td>14–36%</td>
<td>4–12%</td>
<td>Rare (&lt; 2%)</td>
<td>10–17%</td>
<td>Rare</td>
</tr>
<tr>
<td>HRCT</td>
<td>Peripheral, subpleural, basal predominance</td>
<td>Peripheral, subpleural, basal, symmetric</td>
<td>Subpleural or peribronchial</td>
<td>Diffuse, bilateral</td>
<td>DIP: diffuse ground-glass opacity in the middle and lower lung zones</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Reticular opacities</td>
<td>Ground-glass attenuation</td>
<td>Patchy consolidation</td>
<td>Ground-glass opacities, often with lobular sparing</td>
<td>RB-ILD: bronchial wall thickening, centrilobular nodules, patchy ground-glass opacity</td>
<td>Centrilobular nodules</td>
<td></td>
</tr>
<tr>
<td>Honeycombing</td>
<td>Consolidation (uncommon)</td>
<td>Nodules</td>
<td></td>
<td></td>
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<tr>
<td>Traction bronchiectasis</td>
<td>Lower lobe volume loss</td>
<td></td>
<td></td>
<td></td>
<td>Septal and bronchovascular thickening</td>
<td></td>
</tr>
<tr>
<td>Architectural distortion</td>
<td>Subpleural sparing may be seen</td>
<td>Thin-walled cysts</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Focal ground glass (rare)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic patterns</td>
<td>Usual interstitial pneumonia</td>
<td>NSIP</td>
<td>Organizing pneumonia</td>
<td>Diffuse alveolar damage</td>
<td>DIP, RB-ILD</td>
<td>LIP</td>
</tr>
<tr>
<td>Treatment</td>
<td>Poor response to corticosteroid or cytotoxic agents</td>
<td>Corticosteroid responsiveness</td>
<td>Corticosteroid responsiveness</td>
<td>Effectiveness of corticosteroid unknown</td>
<td>Smoking cessation</td>
<td>Corticosteroid responsiveness</td>
</tr>
<tr>
<td>Prognosis</td>
<td>50–80% mortality in 5 yr</td>
<td>Unclear, &lt; 10% mortality in 5 yr</td>
<td>Deaths rare</td>
<td>60% mortality in &lt; 6 mo</td>
<td>5% mortality in 5 yr</td>
<td>Not well defined</td>
</tr>
</tbody>
</table>


AIP = acute interstitial pneumonia; COP = cryptogenic organizing pneumonia; DIP = desquamative interstitial pneumonia; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; LIP = lymphocytic interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; RB-ILD = respiratory bronchiolitis-associated interstitial lung disease.

Pulmonary preneoplastic disorder, it has since been suggested that many putative cases of LIP were actually low-grade lymphomas from the outset and that malignant transformation of LIP is a rare event. The histopathology of LIP is seen in conjunction with a number of conditions, and finding it on surgical lung biopsy warrants a thorough investigation for these conditions, which include rheumatoid arthritis, Sjögren syndrome, Hashimoto thyroiditis, pernicious anemia, hepatitis, systemic lupus erythematosus, autoimmune hemolytic anemia, primary biliary cirrhosis, myasthenia gravis, hypogammaglobulinemia, and immunodeficiency states, including HIV.
Familial pulmonary fibrosis

DPLD was first described in families over 50 years ago. FPF is generally defined as two or more members of the same family with idiopathic DPLD. Several lines of evidence point to a genetic component of FPF, including clustering in family members in distinct environments; autosomal dominant inheritance (with variable penetrance); pulmonary fibrosis in known genetic disorders, such as Herman-Pudlak syndrome, neurofibromatosis, and dyskeratosis congenita; differential responses to known fibrogenic dusts, such as asbestos; and variable expression of pulmonary fibrosis among different mice strains exposed to bleomycin.

Understanding the genetics of FPF has been challenging. Several candidate genes have been explored, but only the genes encoding for two proteins have been implicated in larger familial cohorts of FPF. A case report of a mutation in SFTPc, the gene encoding for surfactant protein C, arising in a mother and daughter with IIPs led to finding a separate mutation of the same gene in several generations of a large kindred. Mutations in SFTPc can lead to accumulation of abnormal surfactant proteins in type II cells of the lung, leading to fibrotic changes in cellular models. Thus far, at least 12 additional mutations in surfactant protein C have been associated with DPLD. To date, these mutations have rarely been observed in sporadically occurring DPLD.

A similar series approach was taken in evaluating a cohort for mutations in telomerase, an enzyme that contributes to DNA and RNA stability and that is abnormal in dyskeratosis congenita. Dyskeratosis congenital is a rare hereditary disease with a number of clinical features, including skin hyperpigmentation, oral leukoplakia, nail dystrophy, and, in one-fifth of patients, pulmonary fibrosis. Heterozygous mutations in hTERT and hTR, two genes that encode for telomerase, have been identified in a registry of families with pulmonary fibrosis. Screening in another group of patients with FPF revealed additional mutations in hTERT as well as another in hTERC, which encodes for the RNA component of telomerase. Given that smoking causes telomere shortening that would be repaired by telomerase, and smoking is a risk factor for developing FPF, a mechanistic explanation for smoking and FPF seems plausible.

Clinically, FPF appears to have characteristics similar to those of the various forms of IIPs described above. Most pedigrees are heterogeneous, with different manifestations of IIPs occurring within the same family. Smoking is strongly associated with development of disease, and the risk of mortality increases as more family members are affected. Studying the details of FPF may provide significant insight into its causes and the causes of sporadic IIPs.

Advanced fibrotic lung disease

In some cases, radiographs and surgical lung biopsy demonstrate such severe fibrosis that no underlying diagnosis can be made. Even in these cases, attempts should be made to understand the precipitating causes and disease course to hone in on a likely diagnosis as the outcome may differ substantially. Patients with asbestos or end-stage
sarcoidosis may have a better prognosis than those with IPF.

Conclusions

DPLD can be particularly challenging to characterize and treat. Over the past several decades, this field of medicine has been encumbered by changing classification schemes, a poor understanding of disease progression, and empiric use of a number of medications in spite of a lack of supporting evidence. Fortunately, consensus panels of experts have met and decided on broadly accepted classification schemes. A better understanding of the complex pathophysiology has allowed for consideration of a number of new therapies. The medical community has a better understanding and recognition of these diseases, and the advent of HRCT has led to earlier diagnosis.

Any patient with DPLD needs a thorough investigation, including a detailed history and physical examination, laboratory analyses, pulmonary function testing, HRCT of the chest, and other ancillary studies. Based on careful review of these data, the clinician determines if a surgical lung biopsy will be necessary. Diagnostic options need to be evaluated in the context of determining whether the patient has IPF, a disease with limited treatment options, or a DPLD that might be responsive to therapy. Our ability to predict the clinical course of disease is generally quite limited. As such, appropriate patients with progressive fibrotic diseases should be referred early for lung transplantation evaluation.

In recent years, several randomized, placebo-controlled, investigational trials have been completed or are in progress. Although clear and compelling treatment has not emerged, a number of agents appear to be promising, at least in some settings. Earlier recognition of disease and enrollment of patients in clinical trials will likely play critical roles in ultimately achieving effective therapies. The advent of two important consortia, the IPFnet in the United States and the European IPF Network (EurIPFnet), will undoubtedly lead to important studies in the coming years. Clinical data, along with a better understanding of the underlying pathophysiology, will someday lead to effective therapies for these devastating diseases.
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