Nonspecific Interstitial Pneumonia

Brent Wayne Kinder, MD, MS[a,b,*]

KEYWORDS

- Nonspecific interstitial pneumonia
- Idiopathic interstitial pneumonia
- Undifferentiated connective tissue disease
- Autoimmune

The etiology and classification of interstitial lung diseases (ILDs) are a challenge for scientists and clinicians interested in respiratory diseases. ILD can occur in patients with an identifiable underlying cause of lung injury (such as an environmental exposure or a systemic disease such as rheumatoid arthritis) or in isolation where the disease is classified as idiopathic (unknown cause). Over the last few decades, pathologic classification of idiopathic interstitial pneumonias (IIP) has evolved.[1,2] In-depth histopathologic evaluation has shown the clinical diagnosis of IIP to be more heterogeneous than once believed.[3] The subclassification of IIPs, based on clinical-radiologic-pathologic criteria, has important therapeutic and prognostic implications. These prognostic and therapeutic differences have led to an increased interest and, subsequently, understanding of the IIPs.

THE CLINICAL ENTITY OF NONSPECIFIC INTERSTITIAL PNEUMONITIS

Before the turn of the century, a subset of the patients diagnosed as having idiopathic pulmonary fibrosis (IPF) had cellular infiltration on lung biopsy (prominent lymphoplasmacytic inflammation), bronchoalveolar lavage (BAL) lymphocytosis, a clinical response to steroids, and a better long-term prognosis.[4–7] On retrospective reevaluation of lung histopathology, most of these cases were classified as nonspecific interstitial pneumonia (NSIP) (ie, their surgical lung biopsy showed a pattern, termed NSIP, distinct from usual interstitial pneumonia [UIP], the pattern characteristic of IPF).[8,9] Consequently, in 2002, a joint American Thoracic Society/European Respiratory Society International Consensus Panel for classification of ILD included idiopathic NSIP as a provisional clinical diagnosis and recommended further study and characterization of this condition.[10] The NSIP histopathologic pattern can be seen in a variety of other clinical scenarios, including connective tissue diseases (CTDs),[8,11–16] chronic hypersensitivity pneumonitis,[17] drug effect on the lung, and after acute lung injury.[11] Thus, the clinical context and features are critical in evaluating a patient with an NSIP pattern on surgical lung biopsy. A thorough history taking including detailed review of occupational endeavors, domiciliary environment, medication use (both current and prior), and a systematic review of symptoms for evidence of CTD are critical for appropriate diagnosis, classification, and treatment of any patient with an NSIP pattern of lung injury.

HISTORY OF THE NOMENCLATURE OF IIPS

In 1969, Liebow and Carrington[1] introduced 5 histopathologic subgroups of chronic IIP: UIP, bronchiolitis interstitial pneumonia, desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia. Liebow

believed that the most common or usual type of diffuse lung fibrosis occurring in older individuals was UIP. The investigators suggested that lung biopsy and histopathologic subclassification might help distinguish clinically distinct conditions with regard to prognosis. These subgroups identified by Liebow and Carrington formed the basis for subsequent classification schema used for IIP as described in 1998 by Katzenstein and Myers.[2] Their classification scheme included the following histopathologic distinct subgroups: UIP, DIP and a closely related pattern termed respiratory bronchiolitis–associated ILD (RBILD), acute interstitial pneumonia (AIP), and NSIP. The term NSIP was used for those IIPs that did not meet the criteria for UIP, DIP/RBILD, or AIP and thus began as a category defined but what it was not, rather than what it was. The introduction of the NSIP pattern in this classification scheme would have important implications for the prognosis and management of patients with IIP going forward. The LIP and giant cell interstitial pneumonia subgroups identified by Liebow and Carrington were removed because they were no longer idiopathic; the former being a lymphoproliferative disorder and the latter caused by cobalt resulting from exposure to tungsten carbide fumes from hard metal processing. Bronchiolitis interstitial pneumonia, subsequently known as bronchiolitis obliterans with organizing pneumonia, was also excluded because it is a predominantly intraluminal process.

In 2002, the American Thoracic Society and the European Respiratory Society revised the classification schema of Katzenstein and Myers by introducing an integrated clinical and pathologic approach to the diagnosis of IIP.[10] The classification of the American Thoracic Society and the European Respiratory Society combined the histopathologic pattern seen on lung biopsy (using Katzenstein and Myers' scheme) with clinical information to arrive at a final clinicopathologic diagnosis. This approach preserved the existing histopathologic and clinical terms while attempting to describe the relationship between them.[3] When the terms are the same for the histopathologic pattern and the clinical diagnosis (eg, DIP), it was recommended that the pathologist use the addendum "pattern" when referring to the appearance on lung biopsy (eg, DIP pattern) and reserve the initial term for the final clinicopathologic diagnosis.

NSIP HISTOPATHOLOGIC PATTERN

The NSIP histopathologic pattern is characterized by varying degrees of inflammation and fibrosis, with some forms primarily inflammatory (cellular NSIP) and others primarily fibrotic (fibrotic NSIP).[8] In the original description by Katzenstein and Fiorelli,[8] 3 subgroups of NSIP were identified on the basis of whether the histology showed chronic interstitial inflammation only (group I), a mixture of inflammation and fibrosis (group II), or predominantly interstitial fibrosis with minimal inflammation (group III). When NSIP is predominantly cellular, chronic interstitial inflammation involves the alveolar walls.[18] Type II pneumocyte hyperplasia is often seen in areas of inflammation. The distribution of inflammatory lesions may be inconsistent, but, unlike UIP, little normal–appearing lung is usually present in biopsy specimens. The fibrotic form of NSIP may include advanced fibrosis with some focal areas of architectural distortion. However, in most cases, the fibrosis shows more diffuse involvement of the lung with relative preservation of the lung architecture. Tansey and colleagues[19] have suggested that some histologic findings in NSIP may be more suggestive of an underlying CTD including the following: follicular bronchiolitis, lymphoid follicles, or lymphoplasmacytic infiltration of the pleura.

Although NSIP may have a substantial amount of fibrosis, it is usually of temporal uniformity (ie, varying proportions of interstitial inflammation and fibrosis appear to have occurred over a single time span), and fibroblastic foci and honeycombing, if present, are rare (**Figs. 1–3**). The temporal uniformity is distinct from the temporal heterogeneity observed in UIP. Although the histopathologic
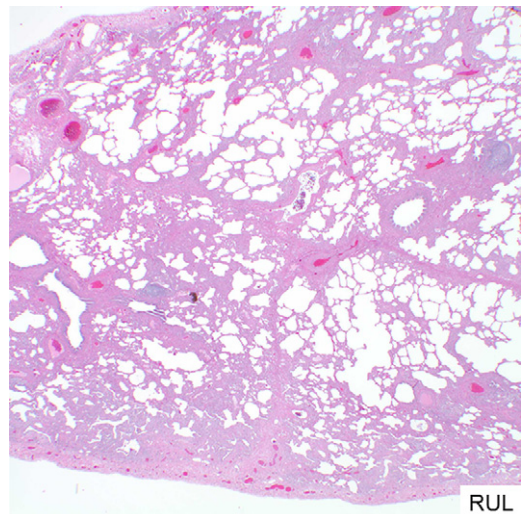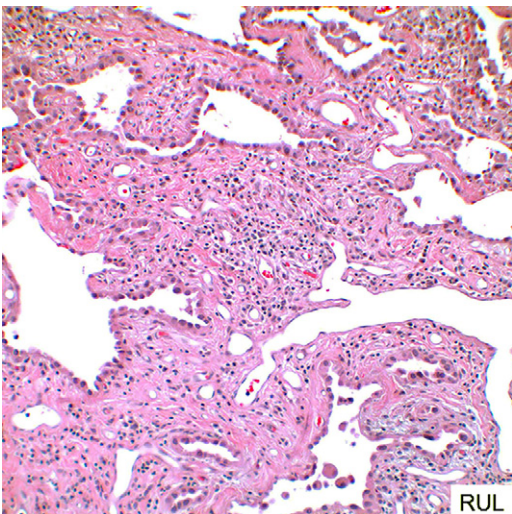

Fig. 1. A representative low-power view of a surgical lung biopsy specimen in a patient with NSIP. Temporally uniform fibrosis demonstrated is a key histopathologic feature of this disease (hematoxylin-eosin, original magnification ×30). (*Courtesy of* Dr Kathryn Wikenheiser-Brokamp, MD, PhD.)
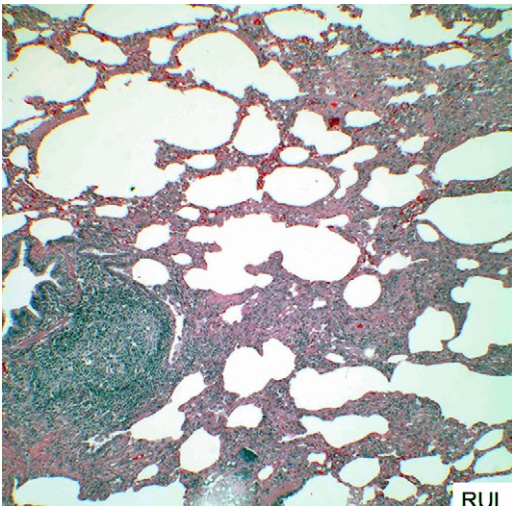
Fig. 2. Surgical lung biopsy specimen in a patient with NSIP. Interstitial expansion and a lymphoid aggregate with germinal center formation are demonstrated (hematoxylin-eosin, original magnification ×62.5). (*Courtesy of* Dr Kathryn Wikenheiser-Brokamp, MD, PhD.)

features of NSIP are now well established in the literature, the practical separation of NSIP from other IIPs, particularly UIP, is challenging.[5,20] Nicholson and colleagues[21] evaluated the level of interobserver agreement using the κ coefficient of agreement between 10 expert thoracic pathologists in the United Kingdom. The diagnosis of NSIP was present in more than half of conflicting cases, and the overall κ coefficient for a diagnosis of NSIP was only 0.32 (considered to be fair).

Fig. 3. A representative high-power view of a surgical lung biopsy specimen in a patient with NSIP. The interstitium is expanded by fibrosis and chronic inflammation (hematoxylin-eosin, original magnification ×100). (*Courtesy of* Dr Kathryn Wikenheiser-Brokamp, MD, PhD.)

THE AMERICAN THORACIC SOCIETY WORKING GROUP ON IDIOPATHIC NSIP

In early 2001, an American Thoracic Society working group was convened with the following goal: to define the clinical, radiologic, and pathologic features of idiopathic NSIP based on a pooled dataset of cases with surgical lung biopsy, high-resolution chest computed tomography (HRCT), and clinical data.[22] In addition, the group sought to determine what critical questions needed to be answered related to NSIP. The assembly identified 67 cases as definite (N = 17) or probable (N = 50) NSIP after detailed clinical-radiographic-pathologic review and completed their report in 2008. This multidisciplinary workshop showed that there is a consensus among experts that idiopathic NSIP is a distinct clinical entity with characteristic clinical, radiologic, and pathologic features that differ from other IIPs. The typical clinical presentation was breathlessness and cough of approximately 6 to 7 months' duration, predominantly in women, in never-smokers, and in the sixth decade of life. These patients with NSIP often had positive serology test results for collagen vascular disease. Most patients had a restrictive ventilatory defect on lung function testing. The key features on HRCT were bilateral, symmetric, predominantly lower lung reticular opacities with traction bronchiectasis and lower lobe volume loss that was usually diffuse or subpleural in the axial dimension but sometimes spared the subpleural lung. The key histopathologic features of the NSIP pattern were the uniformity of interstitial involvement with a spectrum from a cellular to a fibrosing process. The group revised the histopathologic features for the diagnosis of NSIP (**Box 1**). Most patients with idiopathic NSIP had a good prognosis, with a 5-year mortality rate estimated at less than 18%.

CLINICAL PRESENTATION

The clinical manifestations of NSIP are in many ways akin to that of the other IIPs. Indeed, the similarity in presentation among the IIPs is responsible for their grouping as the syndrome known as IPF until 2 decades ago. Idiopathic NSIP seems to be most common among women in their 40s to 50s who are nonsmokers.[22–25] However, these demographic trends are not universal, and NSIP can be seen in a wide range of ages and amongst men or smokers.[11] The most common respiratory symptoms are dyspnea on exertion and a cough, which is typically dry or nonproductive. The chest examination reveals bilateral inspiratory crackles in most patients, with a tendency to be heard best at the lung bases. Digital clubbing is much

---

Box 1
Proposed revised histologic features of NSIP

KEY FEATURES

Cellular pattern[a]

Mild to moderate interstitial chronic inflammation

Type II pneumocyte hyperplasia in areas of inflammation

Fibrosing pattern[a]

Dense or loose interstitial fibrosis with uniform appearance

Lung architecture is frequently preserved

Interstitial chronic inflammation: mild or moderate

PERTINENT NEGATIVE FINDINGS

Cellular pattern

Dense interstitial fibrosis: absent

Organizing pneumonia is not the prominent feature (<20% of biopsy specimen)

Lack of diffuse severe alveolar septal inflammation

Fibrosing pattern

Temporal heterogeneity pattern: fibroblastic foci with dense fibrosis are inconspicuous or absent; this is especially important in cases with patchy involvement and subpleural or paraseptal distribution

Honeycombing: inconspicuous or absent

Enlarged fibrotic airspaces may be present

Both patterns

Acute lung injury pattern, especially hyaline membranes: absent

Eosinophils: inconspicuous or absent

Granulomas: absent

Lack of viral inclusions and organisms on special stains for organisms

Dominant airway disease such as extensive peribronchiolar metaplasia

From Travis WD, Hunninghake G, King Jr TE, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008;177(12):1345; with permission.

---

less common in patients with NSIP than in those with IPF.[22,23] Systemic/inflammatory symptoms are also frequently observed, including arthralgia and esophageal abnormalities[23]; fever may be present in up to one-third of cases.[20] Pulmonary function tests usually show a restrictive ventilatory defect with impairment in gas transfer. Reports have suggested that BAL in patients with NSIP may show a higher percentage of lymphocytes,[4–7] but this is not universally the case.[26] In our practice we consider a BAL lymphocytosis of greater than 20% to be suggestive, but not diagnostic, of NSIP. Importantly, other diseases in the differential diagnosis, such as chronic hypersensitivity pneumonitis and drug-induced pneumonitis, also frequently display a lymphocytosis on BAL cellular studies.

RADIOGRAPHY

Plain film chest radiography in patients with NSIP typically reveals bilateral interstitial opacities in a lower lobe distribution.[8] However, HRCT scans provide a much more detailed evaluation of the radiographic features of NSIP. The most common features include diffuse ground-glass opacification (GGO) associated with reticular opacities and occasionally traction bronchiectasis (**Figs. 4** and **5**). These features tend to have a basilar predominance. Honeycomb cystic changes are less common and can be predictive of IPF when found in the absence of significant GGO.[27–29] The HRCT findings of idiopathic NSIP and connective tissue–associated NSIP are similar.[23,25]

The recent American Thoracic Society project provided detailed description of the HRCT features seen in 61 patients with a consensus diagnosis of NSIP.[22] Ninety-two percent of patients had lower lobe predominance. In the axial distribution, approximately half of the patients were predominantly peripherally distributed and half were diffusely distributed; a minority was predominantly centrally distributed. The most common characteristics observed included reticulation, traction bronchiectasis, lobar volume loss, and GGO. The finding of subpleural sparing of the lung opacities was seen in only 21%. Airspace consolidation was observed in 13%, whereas honeycomb change was only observed in 5%.
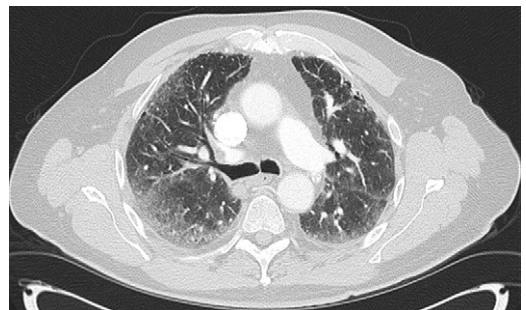
Fig. 4. A representative computed tomography of the chest from a patient with NSIP. The key features seen are ground-glass opacity, reticular changes, and traction bronchiectasis.
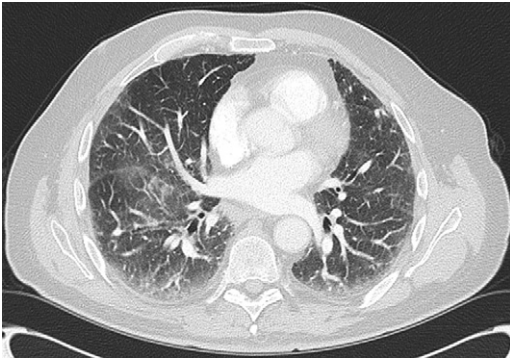
Fig. 5. A representative computed tomography of the chest from a patient with NSIP. The findings tend to be basilar predominant and bilateral.

A recent cross-sectional study evaluated the findings on HRCT that were most predictive of a surgical biopsy diagnosis of chronic hypersensitivity pneumonitis, NSIP, or IPF.[30] The features that best differentiated NSIP from the other diagnoses were relative subpleural sparing, absence of lobular areas with decreased attenuation, and lack of honeycombing. A confident diagnosis was made in 70 (53%) of 132 readings. This diagnosis was correct in 66 (94%) of 70 readings. A correct first diagnosis of NSIP was observed in 90% of NSIP cases. The accuracy for the entire cohort was reported as 80%. Interobserver agreement among readers for a confident diagnosis was in the good to excellent range ($\kappa = 0.77$–0.96).

Somewhat akin to histopathology interpretation, HRCT reading is subject to substantial interobserver disagreement.[31] In another cross-sectional study of HRCT as a diagnostic study in ILD, HRCT images of 131 patients with diffuse lung disease (from a tertiary referral hospital [N = 66] and regional teaching centers [N = 65]) were reviewed by 11 thoracic radiologists. The investigators found that the κ statistic was 0.51 for a diagnosis of NSIP, considered to be a moderate level of agreement. These data suggest that HRCT findings alone cannot definitively diagnose NSIP. However, it is unknown if the combination of characteristic clinical features (age, gender, smoking status, and so forth) and specific HRCT findings could obviate surgical lung biopsy in some patients.

DIAGNOSTIC APPROACH

A comprehensive medical, environmental, and occupational history taking is the critical first step in the evaluation of all patients with a potential diagnosis of ILD. Specific attention should be given to environmental organic antigen exposures (such as domiciliary birds or water damage in the home), and connective tissue signs and symptoms, such as hypersensitivity pneumonitis and CTDs, have many overlapping findings on radiography and histopathologic examination with NSIP. The initial testing of patients with a potential diagnosis of NSIP includes HRCT and pulmonary function testing (spirometry, lung volumes and diffusing capacity for carbon monoxide [DLCO]). These tests are used to determine the extent and severity of disease and the magnitude of impairment in lung function and to rule out other diseases with specific HRCT patterns such as IPF.[29] In addition, it is important to establish a baseline for these radiographic and functional parameters before initiating therapy.

We regularly send a comprehensive panel of serum autoantibodies and inflammatory markers when evaluating patients with incipient ILD, including antinuclear antibody, rheumatoid factor, anti-Scl-70, anti–transfer RNA synthetase antibodies (eg, Jo-1, PL-7, PL-12, EJ, OJ), anti-Ro (SS-A), anti-La (SS-B), antiribonucleoprotein, aldolase, creatine kinase, erythrocyte sedimentation rate, C-reactive protein, and anti–cyclic citrullinated peptide. These test results when positive are supportive, although not necessarily diagnostic, of a CTD diagnosis and should be interpreted in the context of the symptoms and signs of CTD.

BAL is controversial and not necessarily regularly warranted except to rule out infection. BAL is more likely to show lymphocytosis in patients with NSIP than those with IPF[32] and thus can be a clue to the diagnosis if present and surgical lung biopsy is not possible. Bronchoscopy with transbronchial lung biopsy is of limited utility in the diagnosis of NSIP because of the small tissue sample and difficulty in pathologic diagnosis.

We routinely recommend surgical lung biopsy for definitive diagnosis of NSIP. There are no data available in the literature to suggest that NSIP can be diagnosed definitively without histopathologic confirmation; however, demographic and clinical characteristics can be suggestive.[23] The underlying histopathologic features may provide some prognostic and therapeutic benefits. For instance, if multiple fibroblastic foci and microscopic honeycombing are observed, the prognosis is likely worse and response to immunosuppressive treatment may be less likely. Decrements in serial pulmonary function tests, particularly forced vital capacity (FVC) or DLCO, are likely the best indicators of progressive disease and a worse prognosis (see the section "Prognosis").[33] We use these parameters predominantly based on extrapolation from evidence in IPF.[34] We do not routinely follow serial chest computed tomographies because of the cumulative

radiation exposure risks and the potential for lengthy survival with effective treatment.

PROGNOSIS

Most data regarding clinical outcomes in patients with NSIP are from retrospective cohort studies of heterogeneous patient populations that were previously classified as having IPF or cryptogenic fibrosing alveolitis (CFA). Most of these patients had been treated with immunosuppressive agents. There are no prospective cohort studies of patients with NSIP who were not treated. Thus, the natural history of NSIP is unknown. However, these retrospective cohort studies suggest that the prognosis, and possibly response to immunosuppressive therapy, of patients with NSIP is much better than that of IPF/CFA.[4,7,28,35] In a study of 104 patients, Latsi and colleagues[36] found that patients with NSIP had an approximately 2-year increase in median survival compared with subjects with IPF.

Several studies of fibrotic ILD have demonstrated that change in pulmonary function parameters have important implications for prognosis.[34,36–38] In a retrospective cohort study of 83 Korean subjects with NSIP, a reduction in FVC at 12 months was a predictor of mortality.[39] In another retrospective cohort study, 29 patients with undifferentiated connective tissue disease–associated ILD (UCTD-ILD, see section later), the majority of which were previously classified as having idiopathic NSIP, were followed up for a median of 8 months with baseline and follow-up pulmonary function tests. During follow-up, 38% of the patients with UCTD-ILD improved (≥5% increase in percent predicted FVC), 34% stabilized, and 28% declined (≥5% decrease in percent predicted FVC) in lung function.[24] This study showed that patients with UCTD-ILD had a more favorable short-term clinical course than did patients with IPF (as measured by change in FVC), a parameter associated with increased mortality in patients with IPF.[40] It should be noted that almost all subjects with UCTD-ILDs had received immunomodulatory agents (cyclophosphamide, azathioprine, or mycophenolate mofetil) and/or corticosteroids. There are no available controlled data to determine if the natural course of NSIP is such that there are some individuals with spontaneous improvement in lung function without therapy or if immunomodulatory therapy is necessary.

UCTD

Rheumatologic studies have estimated that up to one-fourth of patients with features of a systemic autoimmune disease do not fulfill American College of Rheumatology classification criteria for CTD.[41–45] These patients are considered to have diffuse or UCTD. Most such patients (65%–94%) after years of follow-up do not develop a differentiated CTD (such as rheumatoid arthritis, lupus, systemic sclerosis, mixed CTD, and so forth).[41–46] Consequently, it has been proposed that UCTD represents a distinct clinical entity with the following criteria: signs and symptoms suggestive of a connective tissue disease, positive serologic results, and disease duration of at least 1 year.[46–48] The most common clinical manifestations of UCTD in rheumatologic populations include Raynaud phenomenon, arthritis/arthralgias, pleuritis/pericarditis, sicca symptoms, cutaneous involvement (photosensitivity, rash), esophageal involvement, fever, and myositis.[41] The specific pulmonary manifestations of UCTD in a population with respiratory disease have only recently been studied.[23] In this study it was shown that many patients presenting with idiopathic NSIP often have features suggestive of CTD and meet criteria for UCTD (**Table 1**). A more recent Italian study demonstrated that most patients initially diagnosed as having idiopathic NSIP developed evidence of autoimmune diseases within 2 years.[49] A retrospective Japanese study of idiopathic NSIP found that approximately half of the patients included met criteria for UCTD-ILD, despite the absence of prospectively collected symptom or laboratory assessment.[50] Vij and colleagues[51] performed a study of patients with idiopathic ILD and comprehensive laboratory evaluation and found that all subjects without a known cause for ILD who had an NSIP pattern on lung biopsy met criteria for UCTD similar to those we described.

The pulmonary manifestations of CTD occasionally precede the more typical systemic manifestations by months or years and are considered forme frustes of CTD (especially in rheumatoid arthritis, systemic lupus erythematosus, and polymyositis/dermatomyositis).[52] Consequently, one could expect that some of the patients initially diagnosed as having UCTD-ILD will go on to develop sufficient criteria to be classified as having another disease entity. However, if patients with ILD behave similarly to those with UCTD, in general, this is likely to be a minority of patients (eg, 25%).[41–46] Furthermore, among those patients with UCTD in whom another disorder evolve, the majority do so within the first year of follow-up.[46] Another study suggested that vitamin D deficiency in patients with UCTD may play a role in the subsequent progression into well-defined CTDs.[53] There are no prospective data published regarding the rate of evolution to another CTD among patients with UCTD-ILD. Patients with scleroderma sine scleroderma and amyopathic dermatomyositis might also meet criteria for UCTD-ILD. The study

Table 1 Diagnostic criteria for patients with UCTD	
Diagnostic Criteria	**Symptoms**
Symptoms associated with CTD	Presence of at least 1 of the following symptoms: 1. Raynaud phenomenon 2. Arthralgias/multiple joint swelling 3. Photosensitivity 4. Unintentional weight loss 5. Morning stiffness 6. Dry mouth or dry eyes (sicca features) 7. Dysphagia 8. Recurrent unexplained fever 9. Gastroesophageal reflux 10. Skin changes (rash) 11. Oral ulceration 12. Nonandrogenic alopecia 13. Proximal muscle weakness
Evidence of systemic inflammation in the absence of infection	At least 1 of the follow positive: 1. Antinuclear antigen 2. Rheumatoid factor 3. Anti-SCL-70 antibody 4. SS-A or SS-B 5. Jo-1 antibody, 6. Sedimentation rate (>2 times normal), C-reactive protein

From Kinder BW, Collard HR, Koth L, et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 2007;176(7):691–7; with permission; and *Data from* Liebow AA, Carrington DB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, editors. Frontiers of pulmonary radiology. New York: Grune & Stratteon; 1969. p. 102–41.

of UCTD-ILD is an evolving field, and, as such, there are limited published data available. However, if tertiary referral center estimates of prevalence are correct,[23,51] UCTD-associated ILD is either the first or second most common CTD-associated ILD.

Controversy Regarding Definition of UCTD-ILD

As no consensus criteria for UCTD are universally agreed on, several different schema have been used in the published literature, some by rheumatologists[42,47,54] and others primarily by pulmonologists.[23,49,50] There are no direct empirical data available in the literature to compare the performance characteristics (eg, sensitivity, specificity) of the alternative definitions. When our criteria for UCTD-ILD were applied to existing cohorts of well-characterized patients, they have been shown to be associated with specific radiologic and histopathologic patterns,[23] short-term functional outcomes,[24] and even mortality.[50]

In choosing among diagnostic criteria for a given condition, the clinician needs to consider contextual features. In screening tests, one often seeks to maximize the sensitivity of the test to avoid missing cases that may benefit from intervention. In doing so, one may be willing to compromise

some degree of specificity. This is particularly true if alternative diagnoses do not have particularly effective therapies (such as IPF). Misclassifying a patient as having IPF instead of NSIP (or UCTD-ILD) commits the patient to a pessimistic prognosis and may prevent some clinicians from offering potentially effective therapy. In contrast, a patient incorrectly diagnosed as having UCTD-ILD instead of IPF may be exposed to ineffective therapy but is unlikely to experience substantial harm if monitored carefully.

Our initial criteria did not necessarily represent the best possible diagnostic definition of UCTD-ILD. Indeed, they were chosen for a specific study based on the types of data available in the dataset and were intentionally more sensitive at the cost of some specificity. However, future iterations of diagnostic criteria for UCTD-ILD (or ILD with auto-immune features) should be rigorously compared with our prior definition with empirical data that considers important clinical outcomes.

MANAGEMENT AND TREATMENT

Most of the information available in the literature regarding treatment of NSIP is somewhat dated and from patients who were treated as having

IPF and subsequently reclassified as having NSIP.[4,7,8,11,22,28,39,50] The majority of these patients were treated with corticosteroids with or without cytotoxic agents such as cyclophosphamide or azathioprine. The treatment regimens were also varied in duration. The decision to begin treatment in a given patient is complex and must take into account several factors. The disease course of NSIP is believed to be heterogeneous, with some patients improving with treatment and others who do not have and have progressive disease. There are no high-quality data available to identify which patients are most likely to respond to therapy.

Patient Selection

A careful risk-benefit analysis for each patient is necessary when making decisions about who to treat because few ILD treatments have been rigorously studied in randomized controlled trials and the available treatments are potentially toxic. Generally, we recommend treatment of those patients who have mild to moderate symptomatic and physiologic impairment. Based on our clinical experience, we believe that this population is likely to progress and have not yet reached the end stage of fibrosis when treatment with immunomodulators is unlikely to reverse the process. In patients who are discovered incidentally (and asymptomatic) to have ILD, the decision to begin treatment is more complicated because some patients may not necessarily progress to symptomatic disease.

Treatment Regimen

There are several different regimens that have been used in patients with NSIP. We present the most common of these in our experience and in the published literature. Some ILD experts advocate corticosteroid monotherapy. However, in our experience most patients on high-dose corticosteroids will develop substantial toxic effects of the medicine if continued at even moderate doses (>15 mg/d) for the usual treatment duration of greater than 6 months. Consequently, we generally start a steroid-sparing cytotoxic agent at the initiation of therapy.

Corticosteroids and azathioprine
When used in conjunction with azathioprine, the typical starting dose of prednisone (or an equivalent dose of prednisolone) is 0.5 mg/kg/d given as a single daily oral dose (based on the patient's ideal body weight and not exceeding 40 mg/d). If the patient continues to remain stable or improves, the dose is progressively reduced over months 3 through 6 to 10 mg/d. This dose is maintained for as long as the treatment seems indicated. For azathioprine, we recommend beginning with 0.5 mg/kg/d and gradually increasing to a target dose of 2 to 3 mg/kg/d given orally as a single dose. A discernible response to therapy may not be evident until the patient has received 3 to 6 months of treatment.

Cyclophosphamide ± corticosteroids
Cyclophosphamide has been well studied in CTD-associated ILDs, which typically have an NSIP pattern on surgical lung biopsy. A National Institutes of Health–sponsored multicenter clinical trial (the Scleroderma Lung Study) assessed the efficacy and safety of oral cyclophosphamide in scleroderma-associated ILD.[55] This was a randomized placebo-controlled trial of 162 patients with early scleroderma-associated ILD (defined by the presence of ground-glass opacities on HRCT or BAL fluid with elevated neutrophils or eosinophils) to receive either oral cyclophosphamide (initial dose of 1 mg/kg/d increased to a maximum of 2 mg/kg/d as tolerated) or placebo. The concurrent use of glucocorticoids (up to 10 mg/d prednisone) was permitted. At the end of 12 months of therapy, the mean change in FVC, the primary outcome measure, showed a significantly smaller decline in patients who received cyclophosphamide compared with those on placebo (−1.4% vs −3.2%). There were more adverse events (hematuria, leukopenia, neutropenia, and pneumonia) in the cyclophosphamide-treated group. There are concerns about the long-term adverse events in the cyclophosphamide-treated group, such as bladder malignancy, that may not become clinically evident until years after treatment. Treatment with high cumulative cyclophosphamide doses has been shown to lead to a substantial risk of late-occurring serious malignancies in patients with granulomatosis with polyangiitis (GPA, formerly called Wegener). In a large population-based Danish study, patients treated with the equivalent of 100 mg of cyclophosphamide per day for longer than 1 year had a 20-times increased risk of acute myeloid leukemia and 3.5-times increased risk of bladder cancer within 7 to 19 years after therapy compared with the general population.[56] In a United States–based study of patients with GPA treated with cyclophosphamide, the estimated incidence of bladder cancer after the first exposure to cyclophosphamide was 5% at 10 years and 16% at 15 years.[57] The lack of direct clinical trial evidence, side effect profile, and potential increase in long-term risk of malignancy coupled with the modest observed clinical benefit of the intervention in CTD-ILD argue against the routine use of this regimen in patients with NSIP.

Mycophenolate mofetil ± corticosteroids

There are no controlled trials published with this regimen in patients with ILD. However, recently several major academic clinical centers have been using mycophenolate mofetil with or without corticosteroids in the treatment of CTD-associated ILD.[58] In a retrospective study of 28 patients with CTD-associated ILD, side effects occurred in 6 patients but improved with dose reduction.[59] In addition, the patients had modest improvements in lung function (average change in FVC of 2.3% predicted, total lung capacity [TLC] of 4.0% predicted, DLCO of 2.6% predicted). It should be noted that there is also a theoretical increased risk of malignancy associated with the use of mycophenolate; however, this has not been well established in the literature.

Assessing the Response to Therapy

The response to therapy should be assessed 3 to 6 months after its initiation. A favorable response to therapy is often defined by:

- A decrease in symptoms, especially dyspnea and cough
- Physiologic improvement assessed by FVC, TLC, DLCO, and both resting and exercise gas exchange
- Stabilization of lung function, radiographic abnormalities, and symptoms.

Frequently, some parameters improve, whereas others decline or are unchanged. Subjective improvement can occur in some patients who have no objective signs of improvement. In general, the subjective response should not be the only factor in determining whether to continue treatment.

The following findings are considered to represent failure of therapy and are an indication to modify the treatment regimen:

- A reduction in FVC or TLC by 10% or more
- Worsening of radiographic opacities, especially with development of honeycombing or signs of pulmonary hypertension
- Decreased gas exchange at rest or with exercise.

Clinical deterioration is most frequently caused by disease progression. However, disease-associated complications and adverse effects of therapy should also be considered.

REFERENCES

1. Liebow AA, Carrington DB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, editors. Frontiers of pulmonary radiology. New York: Grune & Stratteon; 1969. p. 102–41.
2. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis. Clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998;157:1301–15.
3. Collard HR, King TE Jr. Demystifying idiopathic interstitial pneumonias. Arch Intern Med 2003;163:17–29.
4. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 157:199–203.
5. Nicholson AG, Colby TV, Dubois RM, et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162:2213–7.
6. Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1999;160:899–905.
7. Nagai S, Kitaichi M, Itoh H, et al. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998;12:1010–9.
8. Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994;18:136–47.
9. Katzenstein AL. Idiopathic interstitial pneumonia: classification and diagnosis. In: Katzenstein AL, Askin FB, editors. Surgical pathology of non-neoplastic lung disease. Philadelphia: W.B. Saunders; 1997. p. 1–31.
10. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002;165:277–304.
11. Cottin V, Donsbeck AV, Revel D, et al. Nonspecific interstitial pneumonia. Individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med 1998;158:1286–93.
12. Fujita J, Yamadori I, Suemitsu I, et al. Clinical features of non-specific interstitial pneumonia. Respir Med 1999;93:113–8.
13. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med 2001;164: 1182–5.
14. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 2002;165:1581–6.
15. Kim DS, Yoo B, Lee JS, et al. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:121–7.

16. Ito I, Nagai S, Kitaichi M, et al. Pulmonary manifestations of primary Sjögren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 2005;171:632–8.

17. Vourlekis JS, Schwarz MI, Cool CD, et al. Nonspecific interstitial pneumonitis as the sole histologic expression of hypersensitivity pneumonitis. Am J Med 2002;112:490–3.

18. Leslie KO. Historical perspective: a pathologic approach to the classification of idiopathic interstitial pneumonias. Chest 2005;128:513S–9S.

19. Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44:585–96.

20. Flaherty KR, Martinez FJ. Nonspecific interstitial pneumonia. Semin Respir Crit Care Med 2006;27:652–8.

21. Nicholson AG, Addis BJ, Bharucha H, et al. Interobserver variation between pathologists in diffuse parenchymal lung disease. Thorax 2004;59:500–5.

22. Travis WD, Hunninghake G, King TE Jr, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008;177:1338–47.

23. Kinder BW, Collard HR, Koth L, et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 2007;176:691–7.

24. Kinder BW, Shariat C, Collard HR, et al. Undifferentiated connective tissue disease-associated interstitial lung disease: changes in lung function. Lung 2010;188:143–9.

25. Fujita J, Ohtsuki Y, Yoshinouchi T, et al. Idiopathic nonspecific interstitial pneumonia: as an "autoimmune interstitial pneumonia". Respir Med 2005;99:234–40.

26. Veeraraghavan S, Latsi PI, Wells AU, et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003;22:239–44.

27. Flaherty KR, Thwaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003;58:143–8.

28. Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J 2002;19:275–83.

29. Hunninghake GW, Lynch DA, Galvin JR, et al. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. Chest 2003;124:1215–23.

30. Silva CI, Muller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008;246:288–97.

31. Aziz ZA, Wells AU, Hansell DM, et al. HRCT diagnosis of diffuse parenchymal lung disease: interobserver variation. Thorax 2004;59:506–11.

32. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170:904–10.

33. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 2006;174:803–9.

34. Collard HR, King TE Jr, Bartelson BB, et al. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538–42.

35. Travis WD, Matsui K, Moss J, et al. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000;24:19–33.

36. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168:531–7.

37. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:543–8.

38. Jegal Y, Kim DS, Shim TS, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171:639–44.

39. Park IN, Jegal Y, Kim DS, et al. Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia. Eur Respir J 2009;33:68–76.

40. King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy end points in a controlled trial of interferon-{gamma}1b for idiopathic pulmonary fibrosis. Chest 2005;127:171–7.

41. Bodolay E, Csiki Z, Szekanecz Z, et al. Five-year follow-up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). Clin Exp Rheumatol 2003;21:313–20.

42. Williams HJ, Alarcon GS, Joks R, et al. Early undifferentiated connective tissue disease (CTD). VI. An inception cohort after 10 years: disease remissions and changes in diagnoses in well established and undifferentiated CTD. J Rheumatol 1999;26:816–25.

43. Danieli MG, Fraticelli P, Salvi A, et al. Undifferentiated connective tissue disease: natural history and evolution into definite CTD assessed in 84 patients initially diagnosed as early UCTD. Clin Rheumatol 1998;17:195–201.

44. Mosca M, Tavoni A, Neri R, et al. Undifferentiated connective tissue diseases: the clinical and serological profiles of 91 patients followed for at least 1 year. Lupus 1998;7:95–100.

45. Clegg DO, Williams HJ, Singer JZ, et al. Early undifferentiated connective tissue disease. II. The frequency of

circulating antinuclear antibodies in patients with early rheumatic diseases. J Rheumatol 1991;18:1340–3.

46. Mosca M, Tani C, Neri C, et al. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev 2006;6:1–4.

47. Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 1999;17:615–20.

48. Doria A, Mosca M, Gambari PF, et al. Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? J Rheumatol 2005; 32:213–5.

49. Romagnoli M, Nannini C, Piciucchi S, et al. Idiopathic NSIP: an interstitial lung disease associated with autoimmune disorders? Eur Respir J 2011; 38(2):384–91.

50. Suda T, Kono M, Nakamura Y, et al. Distinct prognosis of idiopathic nonspecific interstitial pneumonia (NSIP) fulfilling criteria for undifferentiated connective tissue disease (UCTD). Respir Med 2010;104:1527–34.

51. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. Chest 2011; 140(5):1292–9.

52. King TE Jr. Connective tissue disease. In: Schwarz MI, King TE Jr, editors. Interstitial lung diseases. 3rd edition. Hamilton: B.C. Decker, Inc.; 1998. p. 451–505.

53. Zold E, Szodoray P, Gaal J, et al. Vitamin D deficiency in undifferentiated connective tissue disease. Arthritis Res Ther 2008;10:R123.

54. Danieli MG, Fraticelli P, Franceschini F, et al. Five-year follow-up of 165 Italian patients with undifferentiated connective tissue diseases. Clin Exp Rheumatol 1999;17:585–91.

55. Tashkin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.

56. Faurschou M, Sorensen IJ, Mellemkjaer L, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35: 100–5.

57. Talar-Williams C, Hijazi YM, Walther MM, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996;124:477–84.

58. Zamora AC, Wolters PJ, Collard HR, et al. Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. Respir Med 2008;102: 150–5.

59. Swigris JJ, Olson AL, Fischer A, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest 2006;130:30–6.