Recent advances in the diagnosis and management of nonspecific interstitial pneumonia

Marjolein Drent, MD*, Roland M. du Bois, MD†, and Venerino Poletti, MD‡

Idiopathic interstitial pneumonia is a heterogeneous group of diseases. Recently, the importance of a detailed differentiation of nonspecific interstitial pneumonia from other idiopathic interstitial pneumonias has been demonstrated. Most critical appeared to be a proper classification based on clinical presentation, high-resolution CT findings, bronchoalveolar lavage fluid cell findings, and histopathology. This classification may guide the most appropriate therapeutic approach and has significant implications regarding prognosis. Recent advances in the diagnosis and management of nonspecific interstitial pneumonia, cellular and fibrosing variants, are discussed.

Keywords
idiopathic interstitial pneumonia, IIP, idiopathic pulmonary fibrosis, IPF, nonspecific interstitial pneumonia, NSIP

Curr Opin Pulm Med 2003, 9:411–417 © 2003 Lippincott Williams & Wilkins.

*Department of Respiratory Medicine, University Hospital Maastricht, The Netherlands; †Respiratory Directorate, Royal Brompton Hospital, Imperial College London, UK; ‡Department of Thoracic Diseases, Ospedale GB Morgagni, Forlì, Italy

Correspondence to Marjolein Drent, MD, Department of Respiratory Medicine, University Hospital Maastricht, PO Box 5800, 6202AZ Maastricht, The Netherlands; e-mail: m.drent@hetnet.nl

Current Opinion in Pulmonary Medicine 2003, 9:411–417

Abbreviations

BAL	bronchoalveolar lavage
DCs	dendritic cells
HRCT	high-resolution CT
IIP	idiopathic interstitial pneumonia
IPF	idiopathic pulmonary fibrosis
NSIP	nonspecific interstitial pneumonia
SP	surfactant protein
UIP	usual interstitial pneumonia

ISSN 1070–5287 © 2003 Lippincott Williams & Wilkins

Nagai *et al.* [1] reviewed in this journal the clinicohistopathologic spectrum and classification of idiopathic interstitial pneumonias (IIPs) and summarized the advances in prognosis and treatment. IIPs are defined in histopathologic terms as an intralobular, nongranulomatous inflammatory and fibrotic disorder of the lung basically involving alveolar walls [2••,3•,4•,5,6]. Recently, seven entities were reclassified on the basis of clinical, histopathologic, and imaging features: idiopathic pulmonary fibrosis (IPF), desquamative interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia, cryptogenic organizing pneumonia, and lymphoid interstitial pneumonia [7•].

To date, diagnostic criteria in the absence of a surgical lung biopsy are available only for IPF [7•,8,9]. IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histopathologic appearance of usual interstitial pneumonia (UIP) on surgical biopsy. Improvements of lung function and radiographic features after immunosuppressive treatment using corticosteroids and other drugs (such as azathioprine [10] and cyclophosphamide) are uncommon and the outcome is poor [7•,9,10].

Nonspecific interstitial pneumonia/fibrosis (NSIP) has been defined recently by Katzenstein and Fiorelli [11]. However, the concept of a predominant inflammatory or cellular interstitial pneumonitis was proposed by Carrington *et al.* [12] and more recently by Poletti and Kitaichi [13], who termed the histopathologic pattern "unclassified interstitial pneumonia" or "cellular interstitial pneumonia." It is therefore evident that, from the histopathologic point of view, NSIP is not a new pulmonary process. The value of the recent consensus classification was to draw attention to the clinical diseases that have this histopathologic pattern. Previous clinical reports on IPF (or cryptogenic fibrosing alveolitis) must therefore be viewed with caution, because case cohorts may contain a mixed population of IIP, and because of the difficulties (in terms of clinical approach, diagnostic uncertainty, and philosophy) in the differential diagnosis between IPF and NSIP.

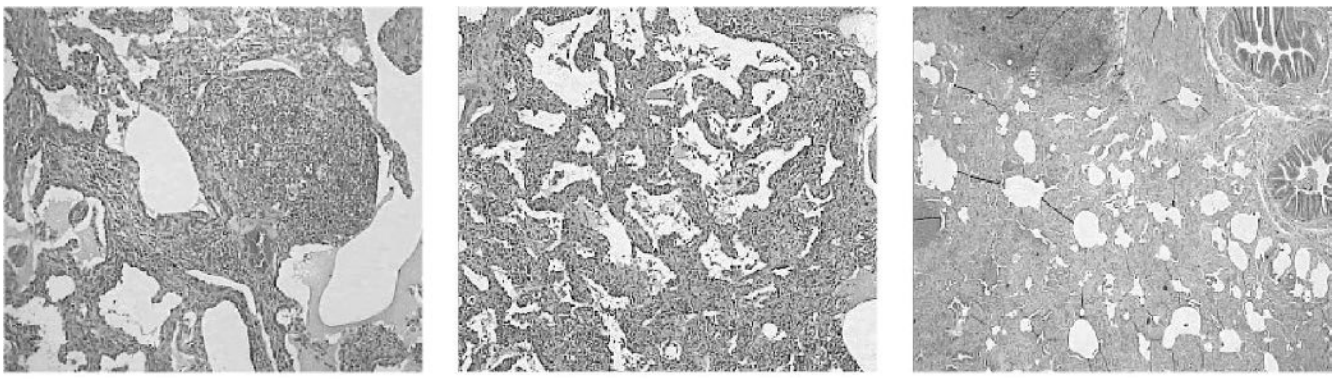
Definition and pathology

When attempts are made to stratify patients according to their histologic variant of IIPs, differences in demographic factors, prognosis, and response to therapy be-

come apparent. Because some forms of NSIP respond to a course of systemic corticosteroids and are associated with a better outcome than IPF, it is essential that a diagnosis is made with the highest level of certainty. However, the morphologic categorization of NSIP is still rough. Histopathologically, NSIP is a form of interstitial pneumonia with a uniform interstitial involvement characterized by varying amounts of fibrosis admixed with some chronic inflammatory cells, notably lymphocytes and a few plasma cells within the interstitium (Fig. 1). Cases can be subdivided as cellular NSIP with a predominance of inflammatory changes (Fig. 1A), mixed NSIP with the presence of both inflammation and fibrosis (Fig. 1B), and fibrotic NSIP with predominantly fibrosis (Fig. 1C).

The key features of NSIP are the "temporally uniform" pattern together with a "diffuse interstitial fibrosing process" and the virtual absence of fibroblastic foci and the lack of features of UIP, desquamative interstitial pneumonia, respiratory bronchiolitis associated with interstitial lung disease, organizing pneumonia, or diffuse alveolar damage [2••,4•,11,14]. The inflammatory component is evident in the cellular variant. Mononuclear cells (mostly lymphocytes) widen the interalveolar septa with a uniform or patchy distribution. The interstitium around airways, blood vessels, interlobular septa, and pleura may also be involved. Type II cell hyperplasia is always present. Focal intraalveolar organization and lymphoid aggregates are present but are not the main histopathologic component. The fibrosing variant is somewhat of a "wastebasket" and the morphologic criteria are less clear. The hallmark is the presence of dense or loose interstitial fibrosis and the lack of the temporal heterogeneity of UIP. Fibroblastic foci, if present, should be inconspicuous. A subpleural distribution, typically observed in UIP, should not be evident. Foci of honeycomb lung and smooth muscle proliferation may be seen but are not as prominent and frequent as in UIP, and the cystic changes tend to be more regular. The NSIP fibrosing pattern likely represents a group of miscellaneous fibrosing disorders of different etiology and pathogenesis with some overlap with IPF [4•,15]. The separation between the different forms is therefore important because of the better prognosis associated with the cellular variant [14]. Hematoxylin and eosin stain-based identification of different patterns in patients with a clinical profile indicating an IIP leaves hints of doubts, and in clinical practice some degree of overlap between NSIP, UIP, hypersensitivity pneumonitis or extrinsic allergic alveolitis, organizing pneumonia, desquamative interstitial pneumonia, eosinophilic pneumonia, lymphoid interstitial pneumonia, and diffuse alveolar damage may be observed [1,2,16–19,20•]. More precise categorization could take advantage of specific immunohistochemical investigations that are oriented pathogenetically [21,22]. Katzenstein *et al.* [4•] raised the question whether the presence of honeycomb change alone predicts a poor prognosis regardless of the underlying disease. Flaherty *et al.* [15,23] indicated that if a UIP pattern is present in any lobe, even if a pattern of NSIP is seen in other lobes, the clinical behavior is similar to that of IPF and is associated with a poor prognosis. Honeycomb change is present in almost all UIP cases, whereas it is found in only a minority of NSIP cases [4•]. Moreover, it was found that NSIP-like areas were common in UIP. Whether NSIP cases containing honeycombing have a worse prognosis is unknown, and should be addressed in future studies as well as the question of whether UIP cases with substantial NSIP areas have a more favorable outcome than those without. Flaherty *et al.* [15,23] found that the amount of fibrosis seen on high-resolution CT (HRCT) differed in all groups studied, being greatest in the group with concordant UIP and successively less so in the

Figure 1. Histopathologic variants of nonspecific interstitial pneumonia



Spatial and temporal homogeneity is evident in all figures. (**A**) Cellular variant: interstitial widening resulting from chronic mononuclear cell inflammation. (**B**) Mixed pattern: inflammation and fibrosis are both present. (**C**) Fibrotic variant: acellular fibrosis in the alveolar septa.

groups with discordant UIP, fibrotic NSIP, and cellular NSIP, in that order. As Katzenstein and Fiorelli [11] pointed out in their original series, the patients who they studied had markedly variable clinical features and likely represented a heterogeneous population. This has been confirmed by a number of subsequent studies. Further prospective studies are needed to define the clinical, radiologic, and histopathologic features of subsets of NSIP that might allow them to be defined more precisely. Only then might it be possible to attempt to define each entity without recourse to biopsy as in confident HRCT/bronchoalveolar lavage (BAL)-aided diagnoses of IPF.

Prevalence, etiology, and pathogenesis

Because NSIP has existed as a clinical entity for a relatively short period, even less is known about the epidemiology of the disease than the other IIPs. Moreover, historical grouping of disparate disorders under the heading of IIP makes it difficult to compare current and older studies. Studies in patients with NSIP by open lung biopsy suggested a mean age of 49 years [8] and a median survival of 13.5 years [24]. Long-term, prospective follow-up of patients with NSIP is required to determine whether their survival declines with time, as recently suggested [15,25]. A decrease in survival with time would suggest that patients with NSIP have disease that is evolving into UIP, and that their improved survival reflects lead-time bias [15].

Considerable controversy exists regarding the cause of IIP: A number of potential risk factors exist. In IIPs, inflammatory cells have the potential to damage lung epithelial cells by releasing proteases and reactive oxygen species, as well as cytokines, chemokines, and growth factors, in addition to environmental and genetic factors. Although uncertainty remains regarding the etiology, NSIP can either be idiopathic or associated with the inhalation of antigens, with previous alveolar injury, such as a manifestation of collagen–vascular disease, or may be related to drug ingestion or radiation toxicity [7•,17,18,20•,26–29].

Nonspecific interstitial pneumonia is the most common histopathologic manifestation of toxicity as a result of certain drugs, including amiodarone, nitrofurantoin, gold salts, methotrexate, vincristine, and fludarabine [19]. The prevalence of drug-induced pulmonary toxicity is increasing, and more than 100 drugs are known to cause lung injury [30]. Host factors including genetic polymorphisms may be important determinants of susceptibility to drug adverse effects. Because this lung injury can be progressive and even fatal, early recognition is important to initiate appropriate treatment.

Shimizu *et al.* [31••] speculated that the pathogenesis of NSIP is different from IPF and that the fibrosing mechanism of NSIP is associated with immunologic factors. They investigated dendritic cells (DCs) in NSIP immunohistochemically using anti-S-100 protein antibody and anti-human leukocyte antigen (HLA)-DR antibody [31••]. Many S-100 protein and HLA-DR antibody-positive but CD1a antibody-negative DCs were observed in the fibrotic areas of all NSIP cases (n = 15), but such cells were hard to find in the fibrotic areas and honeycomb areas of UIP (n = 6) [31••]. Most S-100 DCs showed a positive reaction to anti-HLA-DR antibody. S-100 DCs have a pivotal role in initiating the immune response and have been identified in the target tissues of several autoimmune diseases, including rheumatoid arteritis and polyarteritis nodosa. It seems conceivable that chronic inflammation and persisting viruses can synergistically support autoimmunity through activation of DCs with regard to the mechanisms of NSIP [31••]. However, the etiologic antigens of UIP and NSIP remain unknown. In conjunction with hereditary factors, a higher incidence of Epstein–Barr virus, influenza virus, cytomegalovirus, and hepatitis C virus infection has been reported in patients with IIP. In line with this, recently Kelly *et al.* [32] further confirmed the presumed association between active Epstein–Barr viral infection and IPF.

In the study by Shimizu *et al.* [31••], one of the most important findings was the distribution of lymphocytic subsets. Most B lymphocytes were infiltrated in the lymphoid follicles. In contrast, the distribution of CD4+ and CD8+ lymphocytes was mostly diffuse in the fibrosing areas or around the lymphoid follicles, and more CD8+ cells were located around S-100 DCs than CD4+ cells. In contrast, in polyarteritis nodosa and temporal arteritis, CD4+ cells were especially predominant in cells surrounding S-100 DCs. This differs from the distribution of the lymphocyte subsets found in NSIP. S-100 DCs may play a key role in the local CD4+ and CD8+ cytotoxic T-cell activation. Shimizu *et al.* [31••] speculated that, in NSIP, intracellular processing of endogenous antigens (including viruses) may be an important initiating process. This might cause alveolitis by damaging type II pneumocytes, which in turn may contribute to disordered repair and chronic inflammatory processes [31••]. It was concluded that DC and T-cell-mediated immune mechanisms might play a role in the development and perpetuation of NSIP.

Increasingly, a number of idiopathic diseases are being recognized as having significant genetic predisposition. In this context, a number of single nucleotide polymorphisms are being found in key candidate genes and are studied in familial or sporadic disease cohorts [33,34]. Hereditary factors may contribute to the risk of NSIP. The role of surfactant has drawn increasing attention in interstitial lung disease [34]. Surfactant protein (SP)-A plays a role in the surfactant tension-lowering abilities of surfactant [34]. McCormack *et al.* [35] hypothesized that

the alteration in the surfactant lipid composition changes its biophysical activity, diminishes lung compliance, and promotes lung fibrosis. They found reduced SP-A levels in BAL fluid [35]. Thomas *et al.* [36•] showed that mutations in the SP-C gene are linked to familial interstitial pneumonitis in a kindred that suffered from a variety of interstitial pneumonias including NSIP [36•]. The authors identified individuals heterozygous for a mutant SP-C gene mutation in exon 5 of the gene [36•]. It is suggested that expression of the mutant form results in an accumulation of propeptide SP-C within type II pneumocytes, resulting in cell injury and thus acting as the trigger in the pathogenesis of IIP. It is tempting to speculate that the variability in histopathologic pattern of IIP among affected individuals may be influenced further by the nature and biology of the SP-C mutation, amounts of the production of active SP-C peptide, and the inheritance of other genetic modifiers or exposure to environmental factors [36•].

Clinical presentation

Because the definition of NSIP was first based on the finding that the histopathologic pattern did not fit that of the classic patterns of other IIPs, histopathologic and clinical heterogeneity can be expected. To date, most clinical studies have started with pathology series in the diagnosis of NSIP. Thereafter, these data were related to clinical and imaging features. NSIP deserves to be individualized as a distinct, or possibly a series of distinct, clinicohistopathologic syndromes [37].

In general, patients with NSIP experience slowly progressive dyspnea. Other common symptoms include nonproductive cough, fatigue, malaise, anorexia, and weight loss (see also Table 1). In some cases (low-grade) fever and connective tissue disease-related symptoms have been reported [38]. Clubbing was reported in 10% of the patients with NSIP, in none of the patients with bronchiolitis obliterans organizing pneumonia, and in 65% of the IPF cases in a study by Nagai *et al.* [38]. In line with this latter study, Cottin *et al.* [37] showed a decreased diffusion capacity in all studied cases (n = 12), a restrictive ventilatory defect in 92% of the cases, and evidence of a mild obstructive defect in 42% of the cases. Seven patients (58%) were hypoxic at rest. Furthermore, at exercise the arterial oxygen tension (PaO_2) decreased significantly by 0.5 kPa or more in 67% of the cases. Physical examination revealed the presence of inspiratory crackles in almost all patients (92%) and to a lesser extent squeaks (25%) [37]. Laboratory tests are nonspecific. An increase of the erythrocyte sedimentation rate and serum lactate dehydrogenase is found more frequently.

Table 1. Summary of clinical features of nonspecific interstitial pneumonia

- Poorly defined clinically, variable onset
- Can mimic IPF
- Clubbing less usual than in IPF
- Crackles common
- Restrictive pulmonary function tests with impaired gas exchange
- Granulocytes ± lymphocytes in BAL fluid
- Better outcome than IPF
- Median survival from diagnosis, 6 to 10 y (compared with IPF, 2.5–3.5 y)

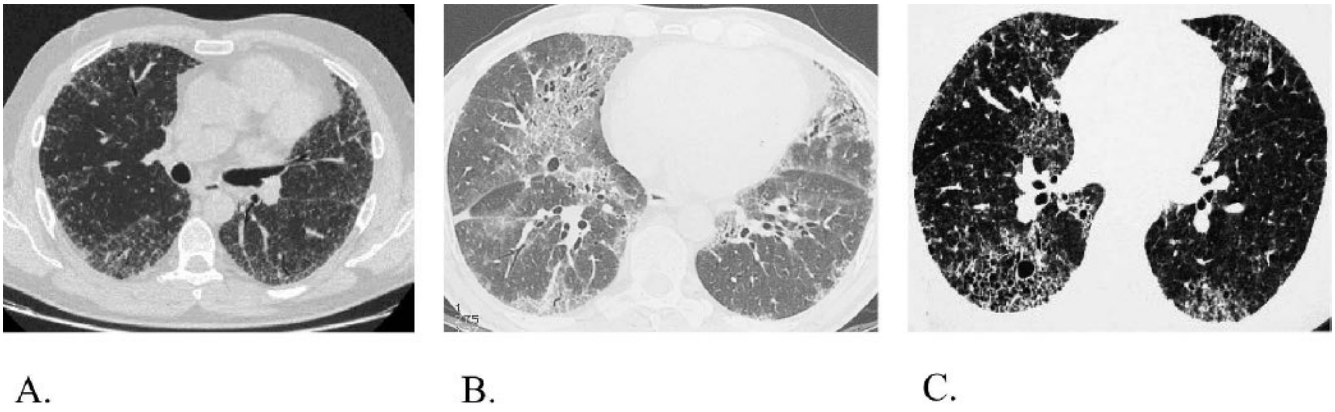
BAL, bronchoalveolar lavage; IPF, idiopathic pulmonary fibrosis.

The most important noninvasive diagnostic tool for the diagnosis and differentiation of IIPs is HRCT [2••,25]. However, there remains considerable debate about this largely because most current series appear to be reporting a very heterogeneous group of patients who happen to have a similar histopathologic pattern. In this context, surgical biopsies are more frequently required to complete the picture. The most common radiographic features of NSIP are ground glass and reticular opacities. The typical features on HRCT include a mixed pattern of ground glass opacity and consolidation in cases in which the cellular infiltrate is prominent and irregular lines with a typical peripheral, subpleural, basal, and symmetric distribution in the NSIP fibrotic variant [7,39,40,41•]. Cottin *et al.* [37] attempted to identify common features allowing NSIP to be considered as a distinct entity. The histopathologic lesions reported were temporally uniform. These latter authors concluded that temporal uniformity was the main feature differentiating NSIP from UIP. Other differences between these entities included the prominence of the interstitial inflammatory lesions in NSIP, with the absence of honeycombing [37,41•].

The HRCT features were heterogeneous, including ground glass opacities (in 9 of 12 cases) and patchy alveolar consolidation (in 6 of 12 cases). In contrast, MacDonald *et al.* [39] reported that the accuracy of thin-section CT in identifying NSIP appeared to be considerably higher than previously reported in patients with a clinical presentation of IPF. Moreover, at CT, NSIP (Fig. 2A, B) was characterized by more ground glass attenuation and a finer reticular pattern than was UIP (Fig. 2C). Nevertheless, considerable overlap in thin-section CT patterns existed between NSIP and UIP [39]. In line with Katzenstein and Meyers [8], Hartman *et al.* [42] suggested that it is important to identify instances in which there is discordance between the histologic and radiologic findings and to recognize the sampling limitations of biopsy compared with HRCT.

It is impossible to differentiate NSIP from other IIPs using transbronchial lung biopsies. However, Watanabe *et al.* [43•] suggested that patients with IIP presenting as a cellular interstitial pneumonia on transbronchial lung biopsy, in the context of radiographic features that were not typical for UIP, could expect a beneficial effect from

Figure 2. High-resolution CT (HRCT) nonspecific interstitial pneumonia (NSIP) versus idiopathic pulmonary fibrosis



(**A**) NSIP, fibrotic variant. HRCT at the lower segmental bronchi. Reticular subpleural lines with uniform distribution, bronchiolectasis, and areas of ground glass attenuation. (**B**) NSIP, cellular variant. Ground glass opacities and traction bronchiectasis. Although the subpleural posterior regions are involved, lung involvement is diffuse and patchy. (**C**) Idiopathic pulmonary fibrosis. HRCT at the level of the lower segmental bronchi. Irregular reticular subpleural and patchy opacities associated with honeycombing and traction bronchiectasis.

corticosteroids, thereby reducing the need for surgical biopsy in patients with this constellation of features.

Bronchoalveolar lavage

Provided its limitations are kept in mind, there appears to be a place for BAL in the evaluation of diffuse lung diseases. The pattern of inflammatory cells may be helpful in narrowing the differential diagnosis [44]. The lavage profile alone is nonspecific in IIP. However, the cellular BAL fluid profile in IPF appears to be quite different from the profile assessed from patients with disorders with similar clinical presentation (*eg*, sarcoidosis or hypersensitivity pneumonitis). Distinguishing IPF from NSIP using the pattern of inflammatory cells in BAL fluid is far more difficult. Patients with NSIP have a relative hypercellularity. A BAL fluid lymphocytosis with a predominance of a suppressor subset of T lymphocytes in BAL fluid is more suggestive of NSIP, cellular variant, than IPF [38]. If BAL is studied in a group of patients with the clinical features of IPF, lymphocytes are no more frequent than in IPF. The clinical value of BAL to stage or monitor interstitial lung disease is of limited value. Increases in the number of polymorphonuclear neutrophils or eosinophils have been associated with a worse prognosis, whereas a lymphocytosis in general has been noted to be associated with a better outcome and a greater responsiveness to corticosteroids.

Treatment

Only a few studies reported the effect of therapeutic interventions in NSIP [8,38]. Katzenstein and Meyers [8] underscored the importance of distinguishing IPF with its histologic correlate UIP from other causes of IIP, especially NSIP. They reported that 45% of the patients with NSIP (n = 64) recovered completely, and an additional 42% remained at least stable or improved with corticosteroid treatment. Therefore, the differentiation between non-UIP and UIP among IIPs has become more and more important. In line with this, it is mandatory to have good criteria to distinguish NSIP from clinically similar IIPs, such as IPF, to predict a favorable outcome. Furthermore, without the establishment of an accurate diagnosis, it will be impossible to test new therapies that may improve the quality of life and establish a more favorable outcome. To date no data are available regarding the quality of life in NSIP. As in IPF [26], although to a lesser extent, the severity of NSIP, the reduced life expectancy, and the sometimes disappointing response to therapy emphasize the importance of this issue. Because it is not always possible to obtain histopathologic specimens, the indications for the use of corticosteroids for patients with IIP including NSIP, unlikely to have UIP, have been determined by using clinical information, HRCT, BAL, and transbronchial lung biopsy information [43•].

Lone corticosteroid therapy

The first-line treatment for NSIP is, as for IPF, prednisolone 20 mg alternate days plus azathioprine 2.5 mg/kg to a maximum of 150 mg or cyclophosphamide 2 mg/kg to a maximum of 150 mg a day [7•]. Watanabe *et al.* [43•] reported a beneficial effect of corticosteroids in cases with NSIP presenting with cellular interstitial pneumonia in transbronchial lung biopsy. The dose of corticosteroids used varied from a daily dose of 30 to 160 mg with a mean dose of 60 mg daily in the NSIP group (n = 10) and a mean of 95 mg daily (range, 30 to 260mg) in the non-UIP group (n = 9). However, they have not compared the benefit of prednisone alone with the currently recommended first-line treatment. Moreover, the corticosteroid dosage regimen was not defined clearly. None of the included cases was treated with a comparable dose [43•]. So, the real benefit of corticosteroids should be investigated more thoroughly in a well-designed pro-

spective study including a population with an appropriate sample size and homogeneity. In that the corticosteroid response to IPF is disappointing, a response to corticosteroids after 1 month of treatment points to a non-IPF form of IIP and predicts a better outcome [38].

Combination corticosteroids and immunosuppressive therapy

In IPF some studies have been performed to evaluate the advantage of combined corticosteroids and immunosuppressive agents [5,10]. Corticosteroids combined with azathioprine were shown to be safe and seemed more effective than corticosteroids alone [10]. Nagai *et al.* [38] reported that cyclophosphamide or azathioprine was used as an immunosuppressant whenever the initial response to corticosteroids was ineffective. However, the outcome of this approach was not quite clear. So, whether this combination is useful in selected NSIP cases needs future studies.

Other therapeutic directions

Reactive oxygen species released by inflammatory cells in the lung are involved in inflammation and cell damage, and are thought to play a role in the pathogenesis of several lung diseases, including IPF [45], acute respiratory distress syndrome, and lung cancer. Furthermore, glutathione, an antioxidant, appeared to be deficient at the alveolar epithelial surface of patients with IPF [46]. More recently, Kuwano *et al.* [47••] suggested that oxidative stress and an oxidant/antioxidant imbalance might participate in epithelial cell damage in patients with IIPs including NSIP. In line with this, it is tempting to speculate that, as in IPF, a positive effect of high-dose N-acetylcysteine might be considered [45].

In IPF, attempts have been made to find therapeutic agents that interfere with or modify the progression of the fibrotic lesions. Ziesche *et al.* [48] reported preliminary data reporting the benefit of interferon-γ in patients with resistant IPF. This and other antifibrotic agents, including pirfenidone [49], are potentially ready to be studied more extensively in clinical trials. Hopefully these efforts will provide new therapeutic strategies for NSIP as well, aimed at achieving better outcomes and improvement in patients' quality of life.

Adjunctive and other treatment modalities

As in IPF, it seems reasonable to immunize against *Streptococcus pneumonia* every 5 years, and we recommend influenza vaccination every year. Oxygen therapy might be required. NSIP patients might benefit from rehabilitation programs.

Conclusion

An understanding of the alveolar microenvironment in patients with IIP is crucial to the development of new, meaningful therapeutic interventions for this disease [15]. To demonstrate efficacy and quality-of-life improvement, well-designed, multicenter, prospective, randomized clinical trials including enough patients are mandatory.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• Of special interest

•• Of outstanding interest

1 Nagai S, Kitaichi M, Izumi T: Classification and recent advances in idiopathic interstitial pneumonia. Curr Opin Pulm Med 1998, 4:256–260.

2 •• Nicholson AG: Classification of idiopathic interstitial pneumonias: making sense of the alphabet soup. Histopathology 2002, 41:381–391.
In this excellent review, the histological patterns and their clinicopathologic counterparts of IIPs are discussed.

3 • Nicholson AG, Colby TV, Wells AU: Histopathological approach to patterns of interstitial pneumonia in patient with connective tissue disorders. Sarcoidosis Vasc Diffuse Lung Dis 2002, 19:10–17.
This paper concentrates on the IIPs seen in association with most types of connective tissue disorders, particularly in the light of NSIP being recognized as a distinct histologic pattern.

4 • Katzenstein AL, Zisman DA, Litzky LA, et al.: Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol 2002, 26:1567–1577.
In this study, biopsy specimens from patients (n = 20) with UIP were reviewed to refine histologic diagnostic criteria, to identify confounders, and to assess the relationship of UIP and NSIP. NSIP-like areas were common in UIP, probably reflecting different mechanisms of fibrosis.

5 Veeraraghavan S, Nicholson AG, Wells AU: Lung fibrosis: new classifications and therapy. Curr Opin Rheumatol 2001, 13:500–504.

6 Yi X, He G, Zheng D, et al.: [A clinicopathologic study of nonspecific interstitial pneumonia.] Zhonghua Jie He He Hu Xi Za Zhi 2002, 25:81–85.

7 • 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.
This statement is an integrated clinical, radiologic, and pathologic approach to the classification of idiopathic interstitial pneumonias. It provides a framework for the future study of these entities.

8 Katzenstein AL, Myers JL: Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. Am J Respir Crit Care Med 1998, 157:1301–1315.

9 American Thoracic Society: Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000, 161:646–664.

10 Raghu G, Depaso WJ, Cain K, et al.: Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis 1991, 144:291–296.

11 Katzenstein AL, Fiorelli RF: Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994, 18:136–147.

12 Carrington CB, Gaensler EA, Coutu RE, et al.: Usual and desquamative interstitial pneumonia. Chest 1976, 69:261–263.

13 Poletti V, Kitaichi M: Facts and controversies in the classification of idiopathic interstitial pneumonias. Sarcoidosis Vasc Diffuse Lung Dis 2000, 17:229–238.

14 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.

15 Flaherty KR, Travis WD, Colby TV, et al.: Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 2001, 164:1722–1727.

16 Erasmus JJ, McAdams HP, Rossi SE: Drug-induced lung injury. Semin Roentgenol 2002, 37:72–81.

17 Jacobs RL, Andrews CP, Coalson J: Organic antigen-induced interstitial lung disease: diagnosis and management. Ann Allergy Asthma Immunol 2002, 88:30–41.

18 Jacobs RL, Andrews CP: Hypersensitivity pneumonia–nonspecific interstitial pneumonia/fibrosis histopathologic presentation: a study in diagnosis and long-term management. Ann Allergy Asthma Immunol 2003, 90:265–270.

19 Rossi SE, Erasmus JJ, McAdams HP, et al.: Pulmonary drug toxicity: radiologic and pathologic manifestations. Radiographics 2000, 20:1245–1259.

20 • Yi ES: Hypersensitivity pneumonitis. Crit Rev Clin Lab Sci 2002, 39:581–629.
A review of the epidemiology, the spectrum of clinical and pathologic manifestations of hypersensitivity pneumonitis, the overlap with NSIP in some cases, and the approach to accurate diagnosis and proper management.

21 Chilosi M, Poletti V, Murer B, et al.: Abnormal re-epithelialization and lung remodeling in idiopathic pulmonary fibrosis: the role of deltaN-p63. Lab Invest 2002, 82:1335–1345.

22 Chilosi M, Poletti V, Zamo A, et al.: Aberrant Wnt-beta-catenin activation in idiopathic pulmonary fibrosis. Am J Pathol 2003, 162:1493–1502.

23 Flaherty KR, Thwaite EL, Kazerooni EA, et al.: Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003, 58:143–148.

24 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.

25 Nicholson AG, Colby TV, du Bois 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, 162:2213–2217.

26 De Vries J, Kessels BL, Drent M: Quality of life of idiopathic pulmonary fibrosis patients. Eur Respir J 2001, 17:954–961.

27 Myers JL: NSIP, UIP, and the ABCs of idiopathic interstitial pneumonias. Eur Respir J 1998, 12:1003–1004.

28 Sattler F, Nichols L, Hirano L, et al.: Nonspecific interstitial pneumonitis mimicking *Pneumocystis carinii* pneumonia. Am J Respir Crit Care Med 1997, 156:912–917.

29 Yamadori I, Fujita J, Bandoh S, et al.: Nonspecific interstitial pneumonia as pulmonary involvement of primary Sjogren's syndrome. Rheumatol Int 2002, 22:89–92.

30 Hubbard R, Venn A, Smith C, et al.: Exposure to commonly prescribed drugs and the etiology of cryptogenic fibrosing alveolitis: a case–control study. Am J Respir Crit Care Med 1998, 157:743–747.

31 •• Shimizu S, Yoshinouchi T, Ohtsuki Y, et al.: The appearance of S-100 protein-positive dendritic cells and the distribution of lymphocyte subsets in idiopathic nonspecific interstitial pneumonia. Respir Med 2002, 96:770–776.
In this study it was speculated that the pathogenesis of NSIP is different from UIP and that DC and T-cell-mediated immune mechanisms may play a role in the development and perpetuation of NSIP.

32 Kelly BG, Lok SS, Hasleton PS, et al.: A rearranged form of Epstein–Barr virus DNA is associated with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2002, 166:510–513.

33 Whitsett JA: Genetic basis of familial interstitial lung disease: misfolding or function of surfactant protein C? Am J Respir Crit Care Med 2002, 165:1201–1202.

34 Pantelidis P, Veeraraghavan S, du Bois RM: Surfactant gene polymorphisms and interstitial lung diseases. Respir Res 2002, 3:14–21.

35 McCormack FX, King TE Jr, Bucher BL, et al.: Surfactant protein A predicts survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1995, 152:751–759.

36 • Thomas AQ, Lane K, Phillips J III, et al.: Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 2002, 165:1322–1328.
This study showed that type II cell damage may underlie the pathogenesis of pulmonary fibrosis associated with an SP-C gene mutation.

37 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, 158:1286–1293.

38 Nagai S, Kitaichi M, Itoh H, et al.: Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998, 12:1010–1019.

39 MacDonald SL, Rubens MB, Hansell DM, et al.: Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology 2001, 221:600–605.

40 Nishiyama O, Kondoh Y, Taniguchi H, et al.: Serial high resolution CT findings in nonspecific interstitial pneumonia/fibrosis. J Comput Assist Tomogr 2000, 24:41–46.

41 • Wells AU, Desai SR, Rubens MB, et al.: Idiopathic pulmonary fibrosis. A composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med 2003, 167:962–969.
This study introduces a new composite physiologic index derived from the disease extent observed by CT in IPF.

42 Hartman TE, Swensen SJ, Hansell DM, et al.: Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. Radiology 2000, 217:701–705.

43 • Watanabe K, Higuchi K, Ninomiya K, et al.: Steroid treatment based on the findings of transbronchial biopsy in idiopathic interstitial pneumonia. Eur Respir J 2002, 20:1213–1219.
This study emphasizes that transbronchial lung biopsy could be a useful additional tool in the diagnostic management of IIP in combination with clinical data.

44 Baughman RP, Drent M: Role of bronchoalveolar lavage in interstitial lung disease. Clin Chest Med 2001, 22:331–341.

45 Behr J, Maier K, Degenkolb B, et al.: Antioxidative and clinical effects of high-dose N-acetylcysteine in fibrosing alveolitis. Adjunctive therapy to maintenance immunosuppression. Am J Respir Crit Care Med 1997, 156:1897–1901.

46 Cantin AM, Hubbard RC, Crystal RG: Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. Am Rev Respir Dis 1989, 139:370–372.

47 •• Kuwano K, Nakashima N, Inoshima I, et al.: Oxidative stress in lung epithelial cells from patients with idiopathic interstitial pneumonias. Eur Respir J 2003, 21:232–240.
Oxidative stress may participate in epithelial cell damage in patients with UIP and NSIP.

48 Ziesche R, Hofbauer E, Wittmann K, et al.: A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. N Engl J Med 1999, 341:1264–1269.

49 Raghu G, Johnson WC, Lockhart D, et al.: Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study. Am J Respir Crit Care Med 1999, 159:1061–1069.