The Breathe *feature where we give you an expert and a topic, and you have the chance to ask them any questions you wish via breathe@ersj.org.uk*

See page 118 for next month's expert and subjects.

Ask the expert - diffuse interstitial lung disease

Q1. Has the high-resolution (HR) computed tomography (CT) scan completely replaced histopathological diagnosis in the case of interstitial lung diseases (ILDs)? If not, then what are the indications for bronchoscopic and/or thoracoscopic lung biopsies?
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HRCT is now a key diagnostic tool in diffuse lung disease, but has not completely replaced histopathological diagnosis. In many cases, HRCT can provide disease-specific information so biopsy can be avoided when the clinical presentation is characteristic [1]. This is relevant for some rarer interstitial lung diseases, such as lymphangioleiomyomatosis (LAM; multiple uniform thin-walled cysts; diffuse distribution), Langerhans cell histiocytosis (cavitating nodules in early stages, thin-wall cysts with bizarre outlines in late disease; sparing of extreme bases) and pulmonary alveolar proteinosis ("crazy-paving" appearance: geographical areas of ground-glass densities containing thickened interlobular septa). More common diseases with a characteristic CT pattern include idiopathic pulmonary fibrosis (IPF; predominantly subpleural and basal reticular pattern with honeycombing), sarcoidosis (bronchocentric and interlobular septal nodularity, subpleural nodules, upper zone fibrosis, hilar and mediastinal lymph node enlargement), extrinsic allergic alveolitis (in the subacute stage with variable ground-glass opacification and centrilobular nodules) and cryptogenic organising pneumonia (COP; patchy bilateral areas of consolidation). In such cases, a confident CT diagnosis by an experienced radiologist together with a consistent clinical presentation is so accurate that lung biopsy is not required. In other cases, biopsy is still needed. The first approach should always be bronchoscopy with bronchoalveolar lavage (BAL), if there are no contraindications, combined with transbronchial biopsy. When these bronchoscopic procedures are not diagnostic, video-assisted thoracic surgical biopsy should be considered. Given the potential morbidity and mortality associated with surgical biopsy, the procedure is not indicated in the invalid or elderly patient.

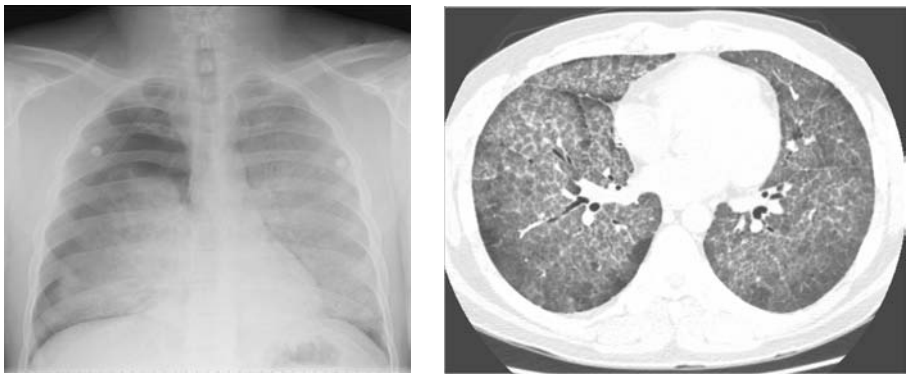

Figure 1
Alveolar proteinosis

Q2. Are there any radiological clues to differentiate various ILDs?
R. Narasimhan (Chennai, India)

Yes, there are useful chest radiographical clues [1]. These are based on the predominant location, the distribution, the radiographic pattern (reticular, nodular, *etc.*) and on ancillary radiographic signs (pleural disease, lymphadenopathy). Predominantly lower-zone abnormalities suggest IPF, connective tissue disease-related ILD, asbestosis, idiopathic fibrotic nonspecific interstitial pneumonia (NSIP) COP; in addition, cardiac failure should always be considered. Predominantly mid- to upper-zone abnormalities suggest sarcoidosis, hypersensitivity pneumonitis, post-tuberculous fibrosis, silicosis, Langerhans cell granulomatosis chronic eosinophilic pneumonia (CEP). Peripheral predominance is seen in IPF, COP and CEP. Mass-like lesions are seen in sarcoidosis, along with mediastinal and bihilar lymphade nopathy. ILD with signs of hyperinflation may indicate Langerhans cell histiocytosis or LAM. Pleural disease is frequently seen in asbestosis or connective tissue disease, or in patients with concurrent cardiac failure. Septal thickening (Kerley B lines) can be observed in malignancy, chronic congestive heart failure, LAM, and pulmonary veno-occlusive disease. Migrating or waxing and waning multifocal consolidations are seen in COP, eosinophilic pneumonia, or allergic bronchopulmonary aspergillosis.

Q3. a) Could you detail the hallmark HRCT findings in diffuse ILD? b) What is the rate of occurrence of ILD after pulmonary tuberculosis?
V. Aryan (Meerut, India)

a) Some of the hallmark HRCT findings in diffuse ILD are given in the answer to question 1. My own systematic approach to HRCT assessment is first to ask whether the CT features are those of IPF (subpleural and basal predominance, predominant honeycombing, with or without minor ground-glass component). If the classical appearance of IPF is present and American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria are met, the specificity of the correct diagnosis is >90% [2]. If CT appearances are not typical of IPF, my next question is to define the location of the changes and the pattern. A micronodular or nodular pattern is associated with sarcoidosis, early Langerhans cell histiocytosis, and silicosis/coalworkers' pneumoconiosis, as well as with lymphangitic carcinomatosis. The next pattern is ground-glass, which is seen in hypersensitivity pneumonitis (diffusely distributed and upper lobe/mid-zone predominance), desquamative interstitial pneumonia (DIP; similar distribution to IPF), respiratory bronchiolitis (RB)/ILD (important information: smoking status of the patient!) and NSIP. Consolidation is mainly seen in COP, CEP and alveolar cell carcinoma. Reticular lines are seen in IPF, asbestosis, collagen vascular disease, NSIP and subacute or chronic hypersensitive pneumonitis. The final pattern is cysts; these are associated with Langerhans cell histiocytosis, LAM and lymphoid interstitial pneumonia.
b) The rate of diffuse ILD after pulmonary tuberculosis is unknown to me. Upper-zone posttuberculous fibrosis is seen frequently, but there is no development of diffuse ILD outside areas of the infected parenchyma as sequelae of tuberculosis.

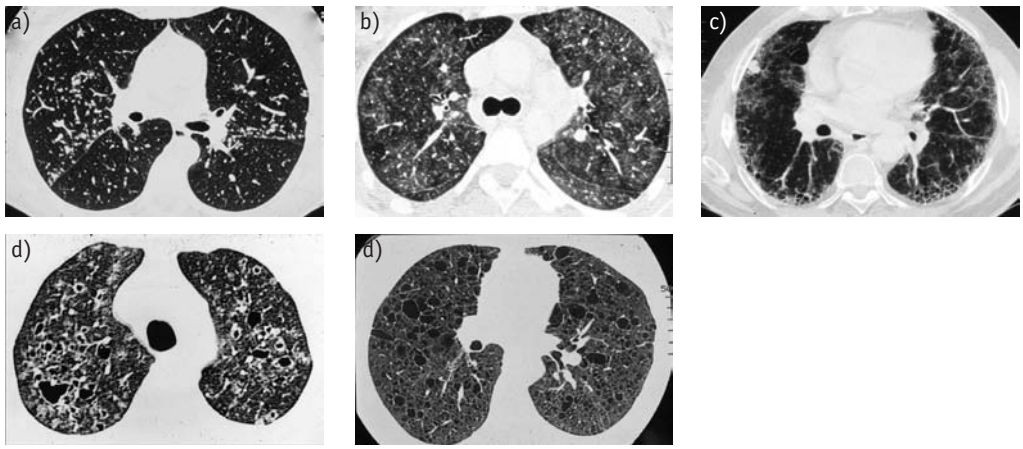

Figure 2
Characteristic HRCT findings in diffuse ILD. a) Sarcoidosis: micronodular pattern. b) Extrinsic allergic alveolitis: ground-glass pattern. c) IPF: reticular pattern and honeycombing; incidental finding peripheral lung cancer right middle lobe. d) Langerhans cell histiocytosis: irregular cysts and nodules. e) LAM: thin-walled cysts.

Q4. In ILD, is the histological spectrum of usual, nonspecific and desquamative interstitial pneumonia different stages of the same disease or do they represent different clinical entities? I find that most ILDs, irrespective of their aetiologies, have these histological appearances at different stages. Kindly give your expert comment on this.
R. Chetambath (Calicut, India)

This is a very good question which has been controversially discussed since the publication of the new ATS/ERS classification of the idiopathic interstitial pneumonia [3]. Some confusion has emerged from this new classification, since clinicians have used the name of the histological pattern for the clinical diagnosis, which is not correct. We must be aware that usual interstitial pneumonia (UIP), NSIP and DIP are histopathological patterns and not the name for the clinical disease entity. For example, the term of the final diagnosis should be IPF, and not UIP, which is just the histological pattern and is also used by some authors to describe the HRCT pattern. Neither the pathologist nor the radiologist can make the diagnosis of IPF without knowing about the history and clinical findings of the patients. It is important to recognise the necessity of the multidisciplinary clinical/radiological/pathological ap-proach in making the final diagnosis of an idiopathic interstitial pneumonia. As you correctly say, the same histological appearances can be seen in ILDs other than the idiopathic enti-ties. For example, the clinical conditions associated with the UIP pattern include IPF, collagen vascular disease (CVD), drug toxicity, chronic hypersensitivity pneumonitis, and asbestosis. Clinical conditions associated with the NSIP pattern include idiopathic NSIP, CVD, hypersensitivity pneumonitis, drug-induced pneumonitis, infection and immunodeficiency disorders. The DIP/RB-ILD pattern is actually a characteristic finding in cigarette smokers, and for this reason can be seen as a background lesion in patients with Langerhans cell histiocytosis or smokers with IPF.
For the following, let us limit the discussion to the idiopathic interstitial pneumonias. Here an important controversy existed in the belief that DIP is early UIP or a precursor of UIP, since DIP has a greater cellularity than UIP on biopsy and the DIP pattern was supposed to progress into UIP. Newer data, mainly based on the evolution of HRCT, provide little evidence to support this idea. Usually, the DIP pattern remains on CT in unchanged location and does not progress to the characteristic lesions of IPF/UIP. DIP can improve with smoking cessation, and carries a much better prognosis than UIP [3]. It is current thought, and this is also my opinion, that DIP/RB-ILD and IPF/UIP should be considered to be separate clinical entities.
The more difficult debate is whether NSIP is a distinct idiopathic entity. My opinion, and the general consensus, is that NSIP and IPF/UIP are distinct entities. The evidence is mainly based on the differences in response to therapy and survival. Even fibrotic NSIP has a better survival rate than IPF/UIP. If NSIP and UIP are found in the same patient (labelled "discor-dant UIP"), it has been demonstrated that IPF patients with this discordant UIP have the same poor survival as patients with concordant UIP (all biopsy sites showing UIP). The UIP pattern determines the prognosis in these patients [4]. In a study comparing surgical lung biopsy specimens with explanted lung specimens in 20 patients who had lung transplantation, no explant showing UIP was preceded by biopsy findings of NSIP. This strongly suggests that NSIP is not an early precursor of IPF/UIP [5].

Q5. According to your knowledge, what is the role of BAL in the diagnosis and follow-up of IPF?
H. Olivi (Santiago, Chile)

According to my experience and currently accepted knowledge, BAL is indicated as a diagnostic tool in every patient with unclear ILD or unclear pulmonary shadowing, as well as in patients with suspected IPF. The underlying disorders may be of infectious, noninfectious, immunological or malignant aetiology. BAL may also be indicated in patients with unexplained pulmonary symptoms in whom a normal BAL finding may allow the exclusion of significant, active ILD. In two international statements on ILDs, BAL was considered helpful in strengthening the diagnosis in patients with sarcoidosis in the absence of biopsy [6], and BAL and/or transbronchial biopsy were considered requirements for the exclusion of other diseases in patients with IPF who did not undergo surgical biopsy (one of the four major criteria for making a clinical diagnosis of the disease) [2]. BAL findings may sometimes be very specific and can directly confirm a particular diagnosis or condition and then replace lung biopsy, such as in alveolar proteinosis, bronchoalveolar carcinoma, alveolar haemorrhage, eosinophilic pneumonia

or pneumocystis pneumonia. A supportive BAL in combination with clinical and HRCT features is frequently sufficient for the diagnosis in IPF (neutrophils with or without eosinophils), extrinsic allergic alveolitis (lymphocytes, plasma cells, foamy macrophages), RB-ILD (smoker's macrophages) or COP (mixed cellularity, CD4/CD8 ratio low). In these disorders, the BAL findings are highly sensitive (present in almost every patient) but nonspecific, so that they are a useful adjunct to diagnosis only in the appropriate clinical setting.
There is no role in the routine follow-up of patients with ILD, including IPF, for serial BAL. In the follow-up of patients with IPF, BAL is indicated whenever new infiltrates develop suggesting infection or acute exacerbation of IPF. Serial BAL to monitor the course of disease cannot be recommended routinely at present.

Q6. What is the best therapy for IPF? What is the role of prednisone/azathioprine/*N*-acetyl cysteine (NAC)? Is there any indication for cyclophosphamide? How should we treat a severe exacerbation of IPF showing features of diffuse alveolar damage (DAD)?
R. Suchy (Donaustauf, Germany)

There is no established optimal treatment for IPF. The usual treatment strategy is anti-inflammatory, and this is unsuccessful in preventing the progression of IPF in most patients. Corticosteroids are widely used to treat IPF, but the evidence is based entirely on observational or retrospective comparative studies, none of which has involved a randomised, placebocontrolled design. In this regard, we do not know whether corticosteroids are effective, but there is also no evidence that they are completely ineffective.
My current practice is based on the ATS/ERS consensus statement recommendation and on the only placebo-controlled clinical trial that showed a positive effect on the primary end-point, *i.e.* the IFIGENIA trial using high-dose NAC added to the recommended standard treatment with prednisone and azathioprine [7]. This treatment should be offered to a patient after explaining to him/her the nature of the disease and the limited response rate. Most patients are willing to undergo this treatment. Based on literature review and my own experience, a response (improvement or stable disease) can occur transiently in 10–30% of patients, and this can be regarded as a beneficial effect of treatment. The initial corticosteroid dose is 20–40 mg per day; after 1 month the dose is slowly tapered to ~10 (5–15) mg per day. Azathioprine is given at a dose of 100–150 mg per day, and NAC at 600 mg *t.i.d.* This triple combination therapy should be continued for ≥6 months, and close monitoring every 3–6 months is recommended. Since the initial corticosteroid dose is not as high as in older reports which used 60–100 mg, the therapy is tolerated quite well even in elderly patients. If a beneficial effect is seen, the therapy should be continued using the same dose of medication indefinitely. In patients in whom the disease progresses, treatment can be modified by switching to cyclophosphamide, or lung transplantation may be considered in those patients who qualify. Another important point is that several multicentre clinical trials with promising antifibrotic agents are under way or will start soon. If a patient fulfils the enrolment criteria, I always offer the option of participation in such a drug trial.
A severe acute exacerbation of IPF showing features of DAD is treated by corticosteroid pulse therapy, such as *i.v.* methylprednisolone 500–1,000 mg daily for 3 days, this strategy being based on case studies only. Some authors add *i.v.* cyclophosphamide pulse therapy. However, only a few patients will respond and get better after a severe acute IPF exacerbation.

Q7. Some patients with IPF remain relatively stable for more than 3–4 years. Would you continue giving azathioprine? What about the risk of lymphoma?
S. Farag (Cairo, Egypt)

I would continue the above-mentioned triple therapy beyond 4 years in order to keep the patient stable. The risk of lymphoma in patients with IPF or other pulmonary disorders, such as sarcoidosis, taking azathioprine is very low, and not significantly increased. This is also true for patients with Crohn's disease and rheumatoid arthritis [8, 9]. A higher incidence of lymphoma has been noted only in patients who receive the drug following solid organ transplantation [10]. However, organ transplant patients have a significantly higher degree of immunosuppression since they receive a variety of other drugs.

Q8. Is there therapeutic progress or effective medication in the management of UIP?
J.A. Huang (China)

With regard to effective treatment of IPF, I refer to my answer to question 6 above. Therapeutic progress can be expected with the further clinical development of antifibrotic drugs. Encouraging data have recently been released from a pirfenidone multicentre study in Japan including a total of 267 patients. The utility of pirfenidone is currently further being investigated in two phase-3 clinical trials. Bosentan has also been studied as a therapy for IPF. The first clinical trial did not achieve a significant effect with regard to the primary end-point, which was the 6-minute-walk distance. Based on a *post hoc* analysis of this trial, however, a phase-3 trial with bosentan in patients with early IPF as assessed by HRCT and with a surgi-cal biopsy diagnosis is currently under way. Very recently, a phase-2 study with a tyrosine kinase inhibitor acting against fibroblast growth factors has been initiated, and several other promising agents such as antagonists against transforming growth factor-β_1 and other profibrotic mediators are in the early phase of development. A clinical trial with the tumour necrosis factor (TNF)-α antagonist etanercept showed a trend towards reduced disease progression in several parameters, but the trial was underpowered having included only 87 patients. Interferon-γ is no longer an option in the treatment of IPF, since a large randomised controlled trial involving >800 patients failed to meet primary and secondary end-points. NAC at a high dose of 600 mg *t.i.d*. significantly decreased disease progression in terms of loss of lung function after 1 year compared with placebo in a randomised controlled trial involving 155 patients all receiving the standard therapy of prednisone and azathioprine [7]. Based on the outcome of this trial, NAC can be recommended for all patients who do not wish or do not qualify to participate in a clinical trial. It is likely that a combination of antioxidant, anti-inflammatory, and antifibrotic agents will emerge as the standard treatment in the future.

Q9. How often do you perform an open-lung biopsy in patients with suspected diffuse ILD with acute presentation and on mechanical ventilation with a strategy to manage acute respiratory distress syndrome when you suspect acute eosinophilic pneumonia, acute presentation of cryptogenic or secondary organising pneumonia, acute interstitial pneumonia or exacerbation of IPF?
A. Gomez (San Luis Potosí, Mexico)

At our institution, we rarely perform an open-lung biopsy in this situation. BAL is the most important and least invasive procedure allowing the identification of infectious agents, neoplastic cells and characteristic cell profiles in the majority of cases [11]. More specifically, acute eosinophilic pneumonia can be diagnosed by an increase in BAL eosinophils above 25%. COP is characterised by a mixed cellular profile, including increase in lymphocytes, neutrophils, eosinophils and mast cells (it is important to exclude bacterial infection by negative microbiological cultures); acute interstitial pneumonia shows atypical type-II pneumocytes and a high percentage of neutrophils (>50%); the same finding is seen in acute exacerbations of IPF. I may mention that diffuse alveolar haemorrhage is another entity that would be included in the acute scenario, and here also BAL is the method of choice of demonstrating alveolar bleeding. The underlying disorder of alveolar haemorrhage has to be assessed by other diagnostic tests. In patients with acute respiratory failure and mechanical ventilation, the mortality rate of open-lung biopsy is exceedingly high, reaching 90% in one study [12], so the expected benefit of the procedure in regard to change of treatment has to be carefully evaluated against the mortality risk in each individual patient [12, 13].

Q10. When you decide to treat a patient with an ILD secondary to a CVD, what is your treatment choice? Corticosteroids alone or immunosuppressants? Both? Do you use the same approach if it is a systemic sclerosis or any other CVD?
A. Undurraga (Santiago, Chile)

There is a high prevalence of subclinical disease in all of these disorders which may show only mild changes on HRCT and/or abnormal BAL cell differentials. I do not treat such patients. The decision to treat depends on functional impairment. If the impairment is only mild, close follow-up without immediate treatment is justified. Treatment would be started in patients with moderate impairment

or when there is evidence of functional deterioration in the follow-up. My treatment of choice is prednisone, initial dose 20–40 mg daily slowly tapered within 3 months to a maintenance dose of ~10 mg daily, in combination with azathioprine, at a dose of 100–150 mg daily. For patients with systemic sclerosis and ILD, a recent controlled trial showed a significant effect with oral cyclophosphamide after 1 year [14]. This effect was not maintained after longer follow-up of 3 years in most patients. A smaller trial showed a similar small effect on forced vital capacity (FVC) with *i.v.* cyclophosphamide for 6 months followed by azathioprine, both combined with low-dose prednisone [15]. Although the best evidence is for cyclophosphamide combined with low-dose prednisone, which is also the most widespread treatment used in systemic sclerosis, azathioprine may be as effective as cyclophosphamide, based on smaller uncontrolled series and personal experience [16]. Formal comparison studies have not been done. I use the same therapeutic approach in any type of CVD. If azathioprine is not effective, I switch to cyclophosphamide. More recently, patients with rheumatoid arthritis and ILD can be switched to etanercept. This TNFα antagonist has been approved for rheumatoid arthritis, and a controlled trial in IPF showed a promising effect on lung function after 1 year, although the effect was not significant because the study was underpowered.

Q11. a) In the evolution of IPF or NSIP, which parameter (HRCT or functional) do you think is better for prognosis? b) It is said that ILD associated with CVD is not biopsied because the prognosis does not vary between the histology subtypes of ILD, principally between UIP and NSIP. In which circumstances do you advise biopsy in these situations?
M.F. Casares (Buenos Aires, Argentina)

a) The extent of fibrosis on HRCT is a good baseline predictor of mortality that correlates well with the extent of the histological fibrosis on surgical lung biopsy and the functional impairment. In the largest prospective study (on 315 patients with IPF enrolled in a clinical drug trial), the extent of reticulation and honeycombing on HRCT was the best independent predictor of mortality, better than any lung function test [17]. After HRCT, diffusing factor of the lung for carbon monoxide ($D_{L,CO}$) is another independent predictor of survival in patients with IPF [18]. Not only the extent but also the pattern of HRCT at the time of diagnosis is an important predictive factor for prognosis in patients without biopsy. If the pattern is atypical of IPF (*e.g.* high extent of ground glass) the prognosis is better and probably reflects cellular NSIP.
The most important predictors for prognosis are the serial changes during follow-up, however. During follow-up assessments of functional parameters, vital capacity (VC) and $D_{L,CO}$ are better predictors of survival than HRCT. In this regard, I think that lung function measurements including VC and $D_{L,CO}$ are more important during the follow-up than serial HRCT examinations. A longitudinal clinical study showed that a 10% decline in VC over 6 months was associated with reduced survival at 5 years (22% survival) in comparison with stable patients (46% survival) [19]. Another study reported that a decrease in $D_{L,CO}$ of >15% over 12 months was associated with a significantly reduced survival in patients with IPF and in patients with fibrotic NSIP [20]. A decrease in VC of >10% during an interferon-γ trial was associated with a 2.4-fold increase in risk of death in patients with IPF [21].
b) In patients with ILD associated with CVD, we rarely advise biopsy. This is done only in unclear clinical situations, not for differentiation of the histological subtypes, which are less useful prognostically in CVD than in idiopathic interstitial pneumonia. In systemic sclerosis, outcome differs little between UIP and NSIP, and in general UIP in CVD has a better out-come than UIP in IPF [22]. Rheumatoid arthritis may be an exception, with UIP associated with a worse outcome than NSIP in a recent series [23]. HRCT features are predictive of UIP histology in rheumatoid arthritis, however [23]. A routine surgical biopsy is therefore not justified for prognostic purposes in fibrotic lung disease in patients with CVD.

Q12. Lung transplantation seems to be a hope for end-stage diffuse ILD patients. How do you decide to recommend transplantation, and how often do you recommend a patient for transplantation?
O. Kayacan (Ankara, Turkey)

Regrettably, most patients with IPF are elderly, with many comorbidities that represent contraindications to lung transplantation. For this reason, only a minority of patients with IPF can be listed (I

assume not more than 10%). Rarely, patients are transplanted for other causes of end-stage ILD such as chronic hypersensitivity pneumonitis, LAM or Langerhans cell histiocytosis. IPF patients without contraindications should be listed early since the waiting time on the transplant list may be prolonged (up to 2–3 years) and survival in patients with advanced IPF is poor and usually shorter than this time. Patients who have a significant functional impairment, defined as a $D_{L,CO}$ <40% predicted, or who have a fall in FVC of 10% over 6 months should be listed for lung transplantation. Physicians should aim for early referral of an IPF patient to a transplant centre.

Q13. In the world of everchanging classification of diffuse ILD, the practicing pulmonologist's approach should be first to separate those mysterious entities into those that need treatment and those that do not, and then to classify the first group according to their response, between those that respond to steroids and those that do not. Would this strategy be far off the mark?
A. Papagiannis (Thessaloniki, Greece)

I strongly disagree with this strategy if you mean that is not important to make a precise diagnosis before starting treatment. Of course, there are patients who will not need treatment because they have no symptoms and no functional impairment; many patients with sarcoidosis fall into this category. However, I believe that it is crucial to make a precise diagnosis when I first see a patient. The advantage of having a firm diagnosis is that the appropriate treatment can be instituted, treatment can be changed if it has been started inappropriately, and the patient can be better informed about possible outcomes both with and without treatment. The often-used empirical approach, to give first a trial of treatment with corticosteroids and, if that fails, then to go to more invasive procedures, such as biopsy, is flawed. The major problems are: treatment will modify the disease process, making diagnosis more difficult on subsequent biopsy; the patient may have deteriorated during this waiting period, making biopsy more risky; different treatment modalities are now available for the major ILDs; and the duration of treatment in patients who respond is different – it may be lifelong in patients with idiopathic interstitial pneumonias (with the exception of bronchiolitis obliterans organising pneumonia where treatment can be limited to 6–12 months), but limited to a shorter period in patients with sarcoidosis or in extrinsic allergic alveolitis. In certain diseases smoking cessation is essential (DIP, RB-ILD, Langerhans cell histiocytosis). Some rarer diseases do no respond to corticosteriods at all, but need different treatment, such as wholelung lavage in the case of alveolar proteinosis.

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