**Contemporary Concise Review 2018: Interstitial lung disease**

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**ABSTRACT**

The term ‘interstitial lung diseases’ (ILD) refers to heterogeneous disorders with a remarkably different clinical history or prognoses. We use it to clinically define this complex and large group of diseases that share some common characteristics such as the interstitium targeting, the possibility of lung scarring or the radio- logical/histopathological pattern. In contrast with obstructive diseases or lung neoplasms, ILD are quite rare and somewhat challenging due to their unknown cause. However, there is no other field in respiratory medicine that evolved so significantly as ILD during the last 10 years, in particular the idiopathic pulmonary fibrosis (IPF). The personalized medicine is just starting to be the preferred approach for ILD management, and the scientific research is focusing on early disease bio- markers, genomic characterization, real-life treatment’s data and new potential targets in phase I/II trials. With respect to all of these challenging points, this Concise Review aims at showing the recent 2018 updates in ILD with a special focus on those disorders that can be con- sidered to be ‘hot topics’ in the miscellaneous world of ILD such as IPF, sarcoidosis, connective tissue disease associated with ILD (CTD-ILD) and hypersensitivity pneumonitis (HP).

**Interstitial Lung Disease**

ILD are a group of rare diseases, although it should be noted that the real epidemiology is unknown because only a few ILD registries are available and all of them show limitations due to the challenge of a defi- nite diagnosis.1 Using the data provided by European2,3 and American4 registries, an ILD incidence of 20–30 per 100 000 person/years is suggested to be reliable.5 Several studies were done to assess the real epidemiol- ogy of ILD but they were conducted in developed countries, and the disorder spectrum may not be differ- ent in other regions. Recently, prospective data were collected over 2 years in the north of India6 using the American Thoracic Society/European Respiratory Soci- ety (ATS/ERS) consensus statement on idiopathic inter- stitial pneumonias (IIP) as a benchmark7,8 and sarcoidosis was the most frequent diagnosis of ILD. Investigations about the role of both genetic and envi- ronmental factors have also been conducted and showed that FOXP3 polymorphisms might determine the susceptibility IIP or CTD-ILD in Chinese Han popu- lation9 and African-American race refers to a younger age at ILD diagnosis and a better survival.10 A new clus- ter analysis among adults with various chronic ILD has been conducted,11 and four distinct clinical phenotypes were identified, allowing a better prediction of clinical outcomes than the current ILD diagnostic criteria. Having been said that genetic and environments are considerable impacting ILD epidemiology and natural history, we must not forget the role of co-morbidities due to their impact on worsening of patient’s survival as seen in recent works conducted in Denmark12 and Germany13 along with the role of histopathological findings on disease progression.14

Co-morbidities have a great impact on ILD sur- vival.15,16 In particular, the role of pulmonary hyperten- sion (PH) was investigated in the last year because, despite the general improvement of PH survival in the last decade, management in the context of ILD disease remains difficult17 as well as the discordance between transthoracic echocardiography (TTE) and the right heart catheter (RHC) is nowadays progressively recog- nized.18 Recently, additional subtypes of ILD with auto- immune features were defined making the role of rheumatological assessment increasingly important to improve the diagnostic accuracy.19 The serological angle of ILD has been gradually investigated to under- stand the predictive role in clinical progression or mor- tality. The results from a retrospective two-centre study20 showed a more favourable prognosis regarding mortality from all-cause in positive serum autoantibody (AAb) ILD than the negative serum AAb group, while the production of PEP08-reactive Ro52 AAb is linked to an increase of morbidity and severity of ILD in a recent study.21 The introduction of the research entity intersti- tial pneumonia with autoimmune features22 (IPAF) made a call for ILD researchers. Retrospective studies have shown a better survival when compared to IPF and a worse outcome in non-IPF group,23 although there is no difference in survival time when the sub- group of radiological usual interstitial pneumonia (UIP) pattern of IPAF was compared to IPF.24 However, there is a strong need for prospective studies regarding IPAF entity and its role in ILD.

The diagnosis of an ILD may be challenging: the dynamic multidisciplinary discussion (MDD) is believed to be an important step when defining an ILD, although on what extent the MDD could be better than preliminary diagnosis has not been well investigated. A retrospective observational study of 983 cases25 did show that 80.5% of patients received a specific diagno- sis while 16.0% had important suggestions for further investigations before reaching a consensus, demon- strating a trend in better prognostic discrimination between IPF and non-IPF ILD when compared to pre- MDD diagnosis. According to a commentary,26 a poten- tial source for difficulties in making a diagnosis may come from some ‘vague terms’ in order to define radiological and/or histopathological findings such as ‘possible’, ‘probable’ or ‘indeterminate’ and the author’s advice is to identify a unique molecular signa- ture of ILD in order to increase the diagnostic accuracy. The surgical lung biopsy (SLB) is a valuable strategy in suspected ILD when patients lack definite HRCT fea- tures of a definite condition and are usually required in case of an ‘indeterminate’ UIP pattern, and IPF cannot be ruled out. Few data are available about the risk/benefit evaluation in elderly subjects, and a retro- spective work27 was conducted and demonstrated 30-day mortality of 10% and 90-day mortality of 15% when SLB was performed in patients aged >75 years with indeterminate UIP on HRCT. In light of the results that the subjects most likely had IPF, the execution of SLB seems to be questionable in elderly population.28 An alternative to SLB is offered by the transbronchial cryobiopsy (cTBB) and a real-life study retrospectively analysed a cohort of suspected ILD patients who underwent cTBB.29 Although cTBB has been proved to have a meaningful value, the experience is limited and the diagnostic non-inferiority compared with the SLB needs to be demonstrated, and the need for an effi- cient, less-invasive procedure must not be welcomed without more prospective investigations.30 Concerns have also been raised about the safety of the proce- dure: despite the cTBB seems to be a safe and cost- effective choice, hospitalized subjects had more incidence of pneumothorax, persistent air leak and greater 30-day mortality.31 A new strategy to detect early ILD has been tried by using lung ultrasound surface wave elastography (LUSWE), a non-invasive method of defining elastic properties of superficial lung tissue to detect early ILD,32 and a clinical/radiological correlation was assessed.

Concerning ILD management, recent studies focused on long-term effects of pulmonary rehabilitation33,34 and new treatment strategies. High-flow nasal cannula (HFNC) has been investigated as a potential option in hypoxemic respiratory failure in subjects with a do-not- intubate (DNI) order35 showing to be non-inferior in 30-day survival or in-hospital mortality when compared to non-invasive positive pressure ventilation (NPPV) but allowing patients to eat and converse until just before death. The role of palliative care (PC) should not be underestimated in ILD due to their impact on quality of life, especially in IPF.36 A collaborative MDD37 may represent an effective platform to address subject’s PC needs by integrating the PC specialist to the multidisciplinary team discussion to reduce unplanned hospital admissions. Safety of benzodiaze- pines (BDZ) and opioids in ILD has been investigated in a prospective study.38 Despite high dose of BDZ was associated with increased mortality, the use of low- dose BDZ and opioids in severely ill patients with respiratory compromise can be a valuable choice for clinicians or PC specialist. A phase I trial39 is also exploring the safety profile of morphine use in ILD refractory dyspnoea. Lastly, we would like to cite the recent design of a double-blind, randomized, placebo- controlled phase II trial40 (NCT 03099187) that will investigate the efficacy and safety of the antifibrotic pirfenidone in unclassifiable ILD, for which there are currently no treatments. ILD management will be increasingly addressed in the next future, and the role of personalized medicine is going to help clinicians to define the specific ILD and to select the correct treatment.

IDIOPATHIC PULMONARY FIBROSIS

Key Points

* Air pollution is an emerging risk factor and the link between the exposure to PM10/PM2.5 and mortality is established.
* Major updates for IPF have been released: an Official ATS/ERS/JRS/ALAT Clinical Practice Guideline and the Fleischner Society White Paper.
* Real-life data of pirfenidone or nintedanib confirmed their safe profile as antifibrotics.

IPF is the most interesting condition among the other ILD because of the increasing management evo- lution during the last years and future perspectives. The European IPF registry41 conducted an analysis that confirmed the demography, the clinical progression and the success of the antifibrotic treatment in improv- ing survival in IPF. The progression of IPF is challeng- ing and hard to foresee, but the slow gait speed in IPF42 could be a simple, reliable tool that may detect phenotypes associated with a worse clinical outcome. The efforts to better define the risk factors of IPF progression had led to the environmental analysis and a real association with air pollution and long-term exposure to PM10 and PM2.5 linked to an increase of the mortality.43,44

Notably, 2018 was a pivotal year for IPF because experts have published important updates in recom- mendations in this field. These guidance documents represent major respiratory45 and radiological46 socie- ties. This is a positive sign of the scientific community attention to ILD but bridging the recommendations is pivotal.47 The two statements show some similarities such as the role of SLB as a gold standard of tissue sampling and the withdrawal of the previous category named ‘possible’ UIP pattern in favour of the term ‘probable’. Conversely, a substantial dissimilarity may be related to the need of an SLB when a probable UIP pattern is diagnosed in an HRCT because the Fleischner Society Statement indicates that a diagnosis of IPF can be confident even when there is no histo- pathological sample and the ATS/ERS/Japanese Respi- ratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guideline recommend it. Thus, the ATS/ERS/JRS/ALAT guidelines propose the same strategy of the Fleischner Society Statement when there is a high clinical likelihood of IPF or probable UIP pat- tern and the experts supported only a ‘conditional rec- ommendation’ for SLB, providing flexibility for clinicians. More studies are needed to raise the likeli- hood of IPF, and multiple-breath washout48,49 (MBW) seems to be a new and promising lung function test for patients affected by IPF correlating small airway dis- ease with lung damage. The quantitative computed tomography (CT) analysis may also be valuable. The automated serial analysis using the quantitative CT software CALIPER (Mayo Clinic, Rochester, Minnesota, US)50,51 improved the evaluation of deterioration on CT by revealing that the increasing pulmonary vessel vol- ume is the strongest predictor of functional decline independent of baseline disease severity.

To date, few studies describe the characterization of acute exacerbations of IPF (AE-IPF), and during the last year, the scientific research has been focused on this hot topic trying to identify features and progression predictors. Potential biomarkers such as levels of IL-6 and IL-8 in the peripheral blood were found to be high and associated with a worse outcome.52 A historically controlled study was conducted in AE-IPF patients53 comparing patients who received the recombinant human soluble thrombomodulin (rhTM) to those who did not allow to consider the addition of rhTM to con- ventional treatment in future studies because of the improved overall survival. Also, the prognostic signifi- cance of Glasgow Coma Scale54 (GCS) has been proved to help predict mortality in AE-IPF probably as it is rep- resentative of the host immune response.

Pharmacological management of IPF is fundamental because of the severity and the poor outcome. The strategy must consider an early treatment55 with the two antifibrotics: pirfenidone or nintedanib. Nowadays, real-life data about safety and functional stabiliza- tion56,57 are fully available for both drugs.58,59 Particular caution should be taken when the antifibrotic therapy is started60 because the current dose adjustment guid- ance is not considering patient’s size and weight: one

retrospective study showed that pirfenidone,61 adjusted for body surface area (BSA) or body weight (BW), had significantly higher doses when an adverse effect was identified. Besides antifibrotics, there is increasing evi- dence that the use of glucocorticoid therapy could worsen the forced vital capacity (FVC) decline in suspected IPF when radiological ‘inconsistent’ UIP pat- tern is diagnosed along with a UIP pattern on biopsy.62 No significant benefit seems to be also provided by adding sildenafil to nintedanib when compared to nintedanib alone in patients with IPF and a DLCO of 35% or less of the predicted value.63 In the next future, IPF may benefit from some of the new therapeutic tar- gets that currently investigate preliminary trials around the world such as a novel integrin α1β6 inhibitor,64 a human anti-IL13 monoclonal antibody65 and recombinant human pentraxin-2.66

SARCOIDOSIS

Key Points

* Heart involvement in sarcoidosis affects the overall survival and CMR or PET imaging is the preferred diagnostic tool.
* Bosentan, an endothelin receptor antagonist, has been demonstrated relatively safe in sar- coidosis but efficacy was not significant.

Sarcoidosis is an unknown, multisystem granuloma- tous disorder that is common in young and middle- aged adults from Central Europe, United States and Japan. The course is unpredictable, and research for delineating subgroups or phenotypes is currently active and sometimes unique events such as World Trade Center-exposed firefighters have been investigated67 during the 15 years of post-exposure. To date, the phenotyping system of Wurm-Scadding should be overcome because despite a simple reproducibility across populations, it poorly correlates with disease severity or number of systems involved.68 New poten- tial biomarkers for patients affected by sarcoidosis have been proposed such as micro-RNA (miRNA) and expression analysis of extracellular miRNA provided that miR-146a and miR-150 were negatively correlated with pulmonary function,69 but the real significance of these findings on disease progression requires further investigations.70

Conversely from pulmonary sarcoidosis, the heart involvement may cause life-threatening events and car- diac granulomas usually progress to permanent scar tissue.71 Identifying the cardiac association can be chal- lenging and clinical presentations may vary from ven- tricular arrhythmias, heart block to cardiomyopathy with an unknown prognosis. In a large and multicentric series of patients with cardiac sarcoidosis,72 no treat- ment regimen was shown to reduce the rates of ven- tricular arrhythmias or better outcome. Notably, age and lack of pacemaker/defibrillator were the significant predictors of mortality for cardiac sarcoidosis.73 The use of cardiac magnetic resonance (CMR) is a valuable tool in identifying the heart involvement74 as much as the use of 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) allowing to evaluate the response to immunosuppressive treatment.75 The future of cardiac sarcoidosis should consider an inte- grated CMR/PET imaging as the preferred imaging modality standard of diagnostic strategy.76 Pulmonary sarcoidosis is an enigmatic condition and scientific research failed to develop reliable endpoints for the disease and evaluation of treatment efficacy can be dif- ficult.77 Recently, low dose defined as rapid dose taper- ing to 10 mg/day in 3.5 months of prednisone has been found to improve or preserve FVC in newly treated pul- monary sarcoidosis.78 Treatment with bosentan, an endothelin receptor antagonist, was tried in a prospec- tive 12-month, double-blind placebo-controlled trial79 but no evidence was found to support the efficacy of the drug, although patients tolerated bosentan well.

CONNECTIVE TISSUE DISEASE ASSOCIATED WITH ILD

The involvement of the interstitium in the CTD-ILD may affect the progression and the clinical outcome of the underlying rheumatological disorder.80 Recent pub- lications had addressed the burden of CTD-ILD on the average annual healthcare costs in systemic sclerosis81 and rheumatological arthritis.82 Thus, the role of rheu- matological evaluation in MDD is becoming increas- ingly important83 and may addresses an ILD towards a diagnosis or IPAF or Undifferentiated Connective Tis- sue Disease (UCTD).

Researcher efforts focused on biomarkers or predic- tive factors of disease progression. Vitamin D defi- ciency has been found to be a risk factor for CTD-ILD in a retrospective study84. Concerning systemic sclero- sis, some potential predictors were investigated such as the CX3CL1 that is linked to progression when PH is absent85 or plasma levels of ADAMTS-13, von Wil- lebrand factor and Von Willebrand propeptide (VWFpp) in systemic sclerosis with thrombosis.86 Simi- lar to IPF, rheumatoid arthritis associated with ILD (RA-ILD) can be associated with MUC5B, a minor allele, with an odds ratio of 3.8 and is linked explicitly to UIP pattern on HRCT. Idiopathic inflammatory myopathy (IMM) may also affect the lung, and CD4 + CXCR4+ T cells are a novel prognostic biomarker in IMM-ILD87 while disease progression has been studied recently.88 A retrospective work about radiographic fibrotic score showed that a high radiographic fibrosis score is a poor prognostic factor in systemic sclerosis (SScl).89

Corticosteroids and immunosuppressive agents are the backbones of CTD-ILD clinical management, but other treatments have not been thoroughly investi- gated. Recently, the combination therapy of tacrolimus plus intravenous methylprednisolone (1000 mg, 3 days/week for 2 weeks) followed by a low dose of corticosteroids (10 mg/day) demonstrated high tolera- bility and a multidimensional improvement.90 Abatacept, an immunoglobulin against CTLA4 recep- tors, has also shown treatment efficacy91 in a multi- centre trial in RA-ILD. In progressive and fibrotic CTD-ILD, sometimes, the conventional anti-inflammatory therapy may not be sufficient and the use of the new antifibrotic drugs, such as pirfenidone, has been proposed and explored in a phase II trial in non-IPF lung fibrosis.92.

HYPERSENSITIVITY PNEUMONITIS

Key Points

* Age-adjusted HP-related mortality rate increased from 1988 to 2016.
* Despite no official guidelines for HP manage- ment is available, the DELPHI consensus- based approach is recommended.
* Predicted FVC should be progressively moni- tored due to the mortality increase when a loss of more than 10% is observed.

HP, formerly ‘extrinsic allergic alveolitis’, is an immunologically mediated ILD that resulted from inha- lation exposure of a great variety of antigens. The anal- ysis of the overall survival in HP from 1988 to 2016 was the focus of a retrospective work93 that describes an age-adjusted HP-related mortality rate increase from 0.12 to 0.68 per 1.000.000 subjects in the year 2016. Thus, the burden of HP is far from being fully defined, and many questions about progression and treatment need to be addressed. Following the same path of IPF, the role of the FVC in HP was investigated and the loss >10% of predicted FVC related to a significant increase of all-cause mortality (HR: 4.13, P = 0.005) in multivari- ate analysis.94 A multicentric work95 studied the hypothesis of a genomic impact by two single- nucleotide polymorphisms (MUC5B rs35705950 and TOLLIP rs5743890) and telomere lengths in peripheral blood leucocytes, providing useful information about the effect of SNP and telomeres in HP. When lung fibrosis is defined, and honeycombing is present, the decline of FVC% is significantly impaired when com- pared to non-fibrotic HP, and poor prognosis is given by clinicians.96 HRCT is useful when the clinical pro- gression of HP is evaluated but the pivotal role is in the diagnostic process in order to detect features such as air trapping, airway centric disease, centrilobular nod- ules and ground-glass opacities. The diagnosis of HP is challenging, and the absence of any official guidelines led to the consensus-based approach developed by the DELPHI task force.97 The DELPHI group generated a guide for clinicians and a tool to systematically com- pare results between different studies and, in light of some limitations,98 may represent the first step towards official guidelines in the next future.

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Abbreviations: AAb, autoantibody; AE-IPF, acute exacerbation of IPF; ATS/ERS, American Thoracic Society/European Respiratory Society; ATS/ERS/JRS/ALAT, ATS/ERS/Japanese Respiratory Society/Latin American Thoracic Association; BDZ, benzodiazepine; CMR, cardiac magnetic resonance; CT, computed tomography; cTBB, transbronchial cryobiopsy; CTD- ILD, connective tissue disease associated with ILD; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HR, Hazard Ratio; HRCT, high-resolution CT; IIP, idiopathic interstitial pneumonia; IL, interleukin; ILD, interstitial lung disease; IMM, idiopathic inflammatory myopathy; IPAF, interstitial pneumonia with autoimmune feature; IPF, idiopathic pulmonary fibrosis; MDD, multidisciplinary discussion; miRNA, micro-RNA; PC, palliative care; PET, positron emission tomography; PH, pulmonary hypertension; PM2.5, Particulate Matter 2.5 micrometers of diameter; PM10, Particulate Matter 10 micrometers of diameter; RA-ILD, rheumatoid arthritis associated with ILD; rhTM, recombinant human soluble thrombomodulin; SLB, surgical lung biopsy; UIP, usual interstitial pneumonia.

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