Comorbidities in interstitial lung diseases

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ABSTRACT Fibrosing lung disorders include a large number of diseases with diverse behaviour. Patients can die because of the progression of their illness, remain stable or even improve after appropriate treatment has been instituted. Comorbidities, such as acute and chronic infection, gastro-oesophageal reflux, pulmonary hypertension, lung cancer, cardiovascular diseases, and obstructive sleep apnoea, can pre-exist or develop at any time during the course of the disease and, if unidentified and untreated, may impair quality of life, impact upon the respiratory status of the patients, and ultimately lead to disease progression and death. Therefore, early identification and accurate treatment of comorbidities is essential.

Infections

General considerations

In IPF, acute pulmonary infection is second only to acute exacerbation (AE) as a cause of rapid progression [3]. Viruses and bacteria have both been associated with the progression of IPF [4–6]. Moreover, MUC5B
polymorphism, which appears to have a role in normal macrophage function and effective mucociliary clearance of bacteria, confers increased risk for development of IPF [7, 8]. Plainly, immunosuppression makes ILD patients more vulnerable to infections. In PANTHER-IPF (Prednisone, Azathioprine, and N-Acetylcysteine: a Study That Evaluates Response in Idiopathic Pulmonary Fibrosis), immunosuppression had a deleterious effect leading to an excess of hospitalisations and mortality, and it is not currently recommended in IPF [9, 10]. The lessons of PANTHER-IPF are equally applicable to ILDs other than IPF, in which immunosuppression is widely used. The danger of major infection increases with age and associated immune senescence. Excessive doses of steroids or immunosuppressive agents may cause more harm than good, leading to recurrent chest infections and, paradoxically, to disease progression. In elderly patients, gentle immunosuppression with a low dose of corticosteroids, with or without an additional second-line agent at a reduced dose, may be more beneficial. In this scenario, prophylactic antibiotic therapy may have dual benefits: the prevention of infection and added immunomodulation. Azithromycin, an antibiotic with known immunomodulatory properties, first documented in the successful treatment of pan-bronchiolitis, decreases the prevalence of infective exacerbations in bronchiectasis and other chronic lung diseases, and has a beneficial effect on pulmonary fibrosis in a bleomycin lung model [11–14]. Although no controlled randomised data exists to endorse the routine use of azithromycin in ILDs, it appears logical to consider the prophylactic use of azithromycin in patients experiencing recurrent respiratory infections, with awareness of possible side-effects including reduced hearing acuity and QTc interval prolongation. In support of the long-term use of antibiotics, a recent randomised placebo-controlled trial of co-trimoxazole in fibrotic ILD showed a survival benefit in treatment-adherent patients, perhaps due to antimicrobial activity leading to a reduced rate of infections [15]. Hydroxychloroquine, a historical antibiotic used primarily to treat malaria, is widely used in pulmonary sarcoidosis for its immunomodulatory effects and may also add value in other ILDs when additional gentle immunomodulation is likely to be beneficial. Based on these considerations, it has been proposed that in IPF, a combination of an antifibrotic drug and antibiotic therapy merits formal evaluation [16].

### Acute infection

As acute respiratory infection can cause rapid deterioration of an underlying ILD, a policy of early, broad-spectrum antibiotic therapy for acute infection appears logical. This approach requires patients to have a home supply of antibiotics and to initiate treatment at the first symptomatic management of a lower respiratory tract infection. Acute infection may cause diffuse alveolar damage (DAD) in IPF with a clinical picture and outcome identical to that of AE of IPF (AEIPF), in which, by definition, overt

| TABLE 1 Comorbidities in interstitial lung diseases |
|---------------------------------------------------|
| Acute and chronic infections                       |
| Gastro-oesophageal reflux                         |
| Pulmonary hypertension                            |
| Cardiac disease                                   |
| Pulmonary embolism                                |
| Lung cancer                                       |
| Obstructive sleep apnoea                          |
| Depression                                        |

| TABLE 2 Key diagnostic and management issues with regard to comorbidities in interstitial lung diseases (ILDs) |
|-----------------------------------------------------------------------------------------------------------|
| The use of immediate antibiotic treatment for acute respiratory infections                              |
| The recognition of chronic infection as a cause of rapid deterioration of ILD                           |
| The recognition of GORD as a possible cause of the development and acute deterioration of pulmonary fibrosis |
| The recognition of disproportionate PH in patients with mild-to-moderate ILD                           |
| The stratification of patients with ILD and lung cancer according to the risk of post-operative complications |
| The recognition of PE and CAD as causes of shortness of breath that is disproportionate to the extent of the underlying ILD |
| The diagnosis of OSA and the institution of management associated with good patient compliance. The referral of patients with clinically significant depression for psychiatric advice |

GORD: gastro-oesophageal reflux disease; PH: pulmonary hypertension; PE: pulmonary embolism; CAD: coronary artery disease; OSA: obstructive sleep apnoea.
infection is not present [17], and may be a frequent occult trigger of AEIPF [18, 19]. There is a higher incidence of AEIPF during winter and spring months, coinciding with a higher prevalence of acute infection [20, 21]. In most AEIPF cases, there is a history of increasing dyspnoea over several weeks: it appears likely that infections triggering the onset of AEIPF will not be detected by the time the patient comes to medical attention. Indeed, it can be argued that DAD associated with proven infection in IPF should be included as a subtype of AEIPF [18, 19, 22]. Patients with IPF and DAD in association with infection do not differ in pulmonary function tests, high-resolution computed tomography (HRCT) findings, bronchoalveolar lavage (BAL) differential cell counts or mortality when compared to patients with AEIPF [23]. This observation is important as the use of BAL to diagnose infection in apparent AEIPF adds to risk in patients with already impaired lung function and may not add useful information in terms of treatment (as empirical antibiotic therapy is widely used in AEIPF).

By contrast, in ILDs other than IPF, and especially in connective tissue disease (CTD)-associated ILDs, in which immunosuppressive therapy is the cornerstone of management, the distinction between exacerbations of ILD and either acute or opportunistic infection has major management implications. For instance, acute-onset diffuse ILD in patients with rheumatoid arthritis on treatment with biological agents is commonly due to *Pneumocystis jirovecii* infection [24]. The dilemma for the clinician is whether to increase or decrease the level of immunosuppression and institute intensive treatment for infection, tailored to cultured microorganisms. In this scenario, BAL is a pivotal test [25]. In severely compromised patients, admission to an intensive care unit should be considered in order to perform BAL with ready access to mechanical ventilation.

**Challenges in chronic infection**

Patients with fibrotic ILDs are susceptible to chronic pulmonary infections, mainly from *Mycobacterium* and *Aspergillus* species, which often simulate traditional disease progression at both a clinical and imaging level, and pre-existing fibrotic changes may mask typical imaging appearances of infection [26, 27]. Chronic pulmonary aspergillosis occurs more frequently in sarcoidosis than in other ILDs [26]. The long-term use of steroids or other immunosuppressive drugs are predisposing factors. Initially, treatment

| Comorbidity            | Prevalence | Treatment                                                                 |
|------------------------|------------|---------------------------------------------------------------------------|
| Infections             | NA         | Broad-spectrum antibiotics, Adjust immunosuppression, Prophylactic antibiotics in case of recurrent infections, Specific therapy for chronic infections |
| Gastro-oesophageal reflux | 0–94% in IPF | Lifestyle changes, PPIs, H₂-receptor antagonists, prokinetics, Fundoplication |
| Pulmonary hypertension | 32–85% in IPF, 5–74% in sarcoidosis and 5–12% in SSc | Treatment of contributing factors, Anti-pulmonary hypertension treatment is not recommended in IPF but combination of antifibrotic agents with targeted therapy for pulmonary hypertension may be considered, Combination of immunosuppression and anti-pulmonary hypertension agents in SSc-ILD |
| Cardiac disease        | 60% in IPF, 20% in sarcoidosis | Immunosuppression when necessary, Specific pharmacological treatment for cardiac disease |
| Pulmonary embolism     | NA         | Anticoagulation [avoid vit-K antagonists in IPF] |
| Lung cancer            | 4.4–10% in IPF | Radiotherapy, chemotherapy, surgical removal, Careful pre-operative assessment |
| Obstructive sleep apnoea | 60–90% in IPF, 50% in SSc-ILD, 65% in sarcoidosis | CPAP machine, Follow-up to check compliance/adherence |
| Depression             | >20% in ILDs, 11–50% in IPF | The role of antidepressants is under debate, Pulmonary rehabilitation |

NA: not applicable; IPF: idiopathic pulmonary fibrosis; PPI: proton-pump inhibitor; SSc: systemic sclerosis; ICD: implantable cardioverter–defibrillator; vit-K: vitamin K, CPAP: continuous positive airway pressure.
includes the use of intravenous voriconazole followed by oral voriconazole or itraconazole [28, 29]. Intravenous caspofungin could be used as salvage therapy in cases refractory to standard therapy or when first-line agents are poorly tolerated and can stabilise previously progressive pulmonary fungal disease, as judged by lung function, HRCT imaging and symptoms [30].

Another challenge is to distinguish between latent or active tuberculosis and sarcoidosis, and especially to make a diagnosis of coexistent tuberculosis in sarcoidosis. The tuberculin skin test is more likely to provide false-negative results in active sarcoidosis due to cutaneous anergy to tuberculin. Therefore, the use of interferon-γ release assays (IGRAs) is more sensitive in the detection of latent tuberculosis infection in sarcoidosis and if positive, is indicative of latent tuberculosis, requiring consideration of isoniazid prophylaxis [31]. With regard to coexistent sarcoidosis and active tuberculosis, there are particular concerns about tuberculosis reactivation after treatment with steroids or tumour necrosis factor-α inhibitors, especially in countries with a high prevalence of latent infection. The diagnosis of active tuberculosis in sarcoidosis requires the presence of Mycobacterium tuberculosis in smear exam or culture. However, given the overlap in clinical features between active tuberculosis and sarcoidosis, empirical treatment for active tuberculosis may be appropriate, after multidisciplinary discussion, in culture-negative sarcoidosis patients with tuberculin skin test positivity, especially when disease is resistant to sarcoidosis specific therapy and an IGRA test is positive.

In sarcoidosis patients with recurrent upper and lower tract respiratory infections, the likelihood of an underlying immunodeficiency should be explored. In granulomatous disorders initially diagnosed as sarcoidosis, the diagnosis of common variable immune deficiency (CVID) should be considered when there is coexisting hypogammaglobulinaemia. CVID is associated with a sarcoid-like disease in the lungs and predispose to recurrent bacterial infections [32]. Granulomatous and lymphocytic interstitial lung disease (GLILD) is the most common lung complication of CVID. It differs from sarcoidosis in many aspects. The most frequent HRCT pattern in GLILD is infiltration by large nodules that are more profuse in the lower zones but are otherwise randomly distributed, whereas in sarcoidosis, micronodular HRCT abnormalities are perilymphatic and occur mostly in the upper zones. Free-standing bronchiectasis (i.e. nontraction bronchiectasis) is more commonly seen in CVID. GLILD rarely regresses spontaneously and has a worse prognosis than sarcoidosis [33].

**Gastro-oesophageal reflux**

The strong association between gastro-oesophageal reflux (GOR) and lung fibrosis has mostly been studied in IPF [34]. The reported prevalence of GOR in IPF has varied from 0% to 94% [35], with, in larger series, the prevalence of distal and proximal GOR varying from 67% to 88% and from 30% to 74%, respectively [36–40]. GOR is an important comorbidity in IPF because it has implications both for patient quality of life and, more contentiously, for IPF pathogenesis.

**Symptomatic GOR**

Potential quality of life benefits justify antacid therapy for symptomatic GOR, especially in patients with major sleep disturbance due to episodes of waking with a choking sensation. Treatment includes lifestyle changes such as small frequent meals, elevating the head of the bed on blocks, avoidance of lying supine for 3–4 h after eating, avoidance of garlic, onions, heavily spiced food, excessive tea, coffee or alcohol. Laparoscopic fundoplication may be required for severe symptomatic reflux resistant to high dosage protein pump inhibitors, H2-receptor antagonists and prokinetic agents.

**The pathogenetic significance of GOR**

The pathogenetic role of GOR in IPF (and in other ILDs) is uncertain. It is sometimes argued that GOR in ILD is entirely a secondary phenomenon associated with progressive pulmonary fibrosis because of increased negative intrathoracic pressure due to lung restriction, leading to distortion of mediastinal structures and traction on the oesophagus, weakening of the lower oesophageal sphincter and subsequent microaspiration of gastric refluxate. The current consensus, in the absence, it should be stressed, of definitive data, is that GOR is likely to be pathogenetic in some cases, providing a profibrotic stimulus due to repetitive damage of the alveolar epithelium with recurrent microaspiration. If this view is correct and GOR is a key initial fibrogenetic trigger in some patients with ILD, the development of more severe GOR in advanced disease (as a secondary phenomenon) provides a plausible pathway for accelerated disease progression and, especially, for the higher prevalence of AEIPF in patients with more severe lung restriction.

The case for a pathogenetic role for GOR in ILD arises in part from the unexpected observation that occult GOR is a major risk factor for post-transplantation acute rejection/bronchiolitis obliterans syndrome, raising the possibility that the importance of GOR as a factor inciting progression of lung disease may have been undervalued historically. Patients undergoing fundoplication prior to or shortly after lung...
transplantation have improved survival compared to those not undergoing antireflux surgery [41]. In IPF, recent clinical studies have provided indirect evidence that GOR may provoke disease progression. Initial reports showed stabilisation of IPF with antiacid therapy in a handful of IPF patients [42]. Subsequently, in a study of patients with asymmetric IPF on HRCT, the prevalence of symptomatic GOR was found to be much higher than in patients with symmetric disease. There was a very strong concordance between the distribution of IPF and the usual patient sleeping position, with the more extensive fibrosis in the dependent lung in 94% of patients. AEIPF occurred much more frequently in asymmetric IPF, with the HRCT features of acute lung injury occurring predominantly in the more involved lung [43]. Pepsin, a nonacid component of gastric juice not normally present in distal airways (and, thus, a marker of aspiration) is more often present in BAL fluid in patients with AEIPF than in those with stable IPF [44].

However, recent retrospective data from pharmaceutical cohorts is more difficult to interpret. In a meta-analysis of the placebo arms in three IPF-net trials, the rate of disease progression (as judged by serial changes in forced vital capacity (FVC)) was significantly lower in patients receiving antiacid therapy than in the remaining cases [45]. By contrast, in an analysis of the placebo arms in three pirfenidone trials, the use of antiacid treatment had no effect on the rate of FVC decline [46]. In a post hoc analysis of the two INPULSIS nintedanib studies, presented at the 2015 European Respiratory Society (ERS) International Congress, the use of concomitant antiacid therapy was actually associated with trends towards a worse outcome [47].

In large IPF clinical cohorts, survival was found to be increased in patients treated medically for GOR or undergoing Nissen fundoplication [48]. It should be emphasised that these retrospective observations have yet to be tested prospectively: at this stage, the efficacy of medical and surgical treatment of GOR in retarding disease progression in IPF remain uncertain. Based on retrospective data, antireflux treatment appears logical in patients with IPF and a hiatus hernia (a common risk factor for GOR) in the hope of reducing the rate of IPF decline in this subgroup [49].

In experimental models, chronic aspiration-related lung injury was independent of pH, implying that nonacid reflux may also be relevant [50]. Prospective studies in ILDs are needed in order to evaluate if nonacid reflux is pathogenetic, justifying the performance of 24-h pH monitoring and impedance studies.

If it is eventually established that asymptomatic GOR may contribute to IPF disease progression, a further dilemma will arise: should all IPF patients be treated with reflux therapy or only those in whom GOR is identified by means of gastroscopy, acid studies or oesophageal manometry?

**Should antiacid therapy be instituted routinely in IPF?**

The uncertainties surrounding this question are captured in the recent treatment update of the American Thoracic Society/ERS/Japanese Respiratory Society/Latin American Thoracic Society guidelines [10]. A weak positive treatment recommendation for antiacid therapy was made by the voting panel of “nonconflicted” experts (i.e. a group of experts experienced in data evaluation in various disease settings, with no perceived conflict of interest, i.e. no history of collaboration with pharmaceutical companies in the development of IPF therapies). However, as outlined in an editor’s note in the update document, the majority of “conflicted experts” (i.e. leading IPF specialists serving as a knowledge resource in the guideline formulation but not participating in voting) disagreed with the recommendation, which in effect “suggests” the routine use of antiacid agents in IPF. Given this divergence of views, it may be useful to summarise the case for and against.

In favour of routine GOR treatment is the indirect retrospective evidence that GOR might play a pathogenetic role, the inexpensiveness of antiacid therapy and the absence of major side-effects. The recommendation can perhaps be summarised as a view that as 1) IPF remains a lethal disease despite recent treatment advances, 2) symptomatic GOR may have an important pathogenetic role and 3) there is little potential downside to treatment, speculative therapy is warranted in most patients, without the need to confirm occult GOR in individual cases.

Against routine GOR treatment is the fact that it has yet to be established that asymptomatic GOR is truly pathogenetic and the exact prevalence is uncertain. There are also major reservations about the perception that routine GOR therapy poses no significant risk in IPF. Gastric acid makes a significant contribution to antimicrobial defences: the impact of regular antiacid therapy on the composition of the microbiome, recently linked to IPF disease progression [6], is entirely uncertain. In patients with more severe disease (FVC <70% of the predicted value), the rate of pulmonary infection was increased in prevalence in those receiving antiacid treatment (although antiacid usage was not associated with greater IPF progression) [46]. Pulmonary microaspirate contains pepsin and bile salts, which may cause lung injury: in asymptomatic patients, suppression of future GOR symptoms might, at least in principle, lead to failure to adopt nonpharmaceutical measures to reduce GOR (diet, change in posture, etc.), leading to increased lung epithelial injury from nonacid reflux. Furthermore, if GOR is not truly pathogenetic, the additional...
medication burden may reduce overall patient adherence, with deleterious effects on the efficacy of other therapies, including antifibrotic agents. Based on uncertain efficacy and the theoretical possibility of major disadvantages, many would share the view that formal prospective trial data are needed before routine GOR treatment can be advocated in IPF patients who may have symptomatic reflux. However, the recent weak positive recommendation reduces the likelihood that the performance of placebo-controlled trials will be achievable.

In systemic sclerosis (SSc), ILD is a major cause of death [51, 52]. There is evidence that epithelial injury makes a contribution to the pathogenesis of lung fibrosis and GOR, a common symptom in SSc, may be implicated [53, 54]. In addition, radiological and histological findings suggestive of GOR-related lung disease were observed in SSc [54]. In the case of idiopathic inflammatory myopathies (IIMs), oesophageal and pharyngeal muscle weakness can also lead to microaspiration and lung injury. Thus, GOR should be actively sought in ILDs other than IPF and treated accordingly.

Pulmonary hypertension

Classification

PH secondary to a number of individual lung diseases is grouped within a single category in the world PH classification (group 3) [55]. It is generally accepted that due to differences in PH manifestations between, for example, ILD and chronic obstructive pulmonary disease, and the existence of disease-specific PH mechanisms in individual ILDs (e.g. sarcoidosis and Langerhans cell histiocytosis), the group 3 PH disorders cannot be amalgamated in the creation of an evidence base to evaluate therapies. However, it is also clear that some form of integration is required. Because IPF is, by far, the most prevalent idiopathic interstitial pneumonia (IIP), PH-IPF tends to be reported in published manuscripts. Other forms of PH-IIP are simply too rare to allow definitive a priori evaluation of PH therapies. Amongst the IIPs, including IPF, the unifying PH association observed in clinical practice has been an association between the development of PH and progression of the underlying lung disease to an extensive fibrotic pattern with the histology of nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) (the defining histological pattern of IPF).

There are no data to suggest that PH differs in its mechanisms or clinical manifestations between IPF-PH and NSIP-PH. No differences have been reported in hypoxia-limited exercise intolerance, disproportionate reduction in measures of gas transfer, enlargement of the pulmonary artery on HRCT and echocardiographic findings typical of PH. More importantly, despite major differences in survival between IPF and idiopathic NSIP (due to differences in the progression of interstitial lung disease), in patients with diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) <35% of predicted, the two disorders have an identical high mortality and this is likely to reflect supervening PH [56].

Thus, a PH classification system in which PH is viewed as a separate disorder in very individual ILD appears counterintuitive and is bound to result in the effective disenfranchisement of rare ILDs in which definitive placebo-controlled studies are wholly impracticable. The recent acceptance of this view, with the publication of a placebo-controlled trial of bosentan for PH in fibrotic IIP [57], establishes an important precedent. It is now for expert groups to determine whether PH in chronic hypersensitivity pneumonitis and in CTD-ILD patients with severe ILD (mostly with UIP or fibrotic NSIP as underlying lung histological patterns) might be grouped in a “PH–pulmonary fibrosis” entity for trial purposes, also containing fibrotic IIP including unclassifiable disease.

Prevalence and prognostic significance

It is strongly recommend that patients with suspected PH, mainly when associated with early disease and when disproportionate to the underlying ILD, should be referred to specialist PH centres. PH is considered a predictor of poor survival and an indication for immediate listing for lung transplantation [58]. In patients with advanced IPF assessed for lung transplantation, the presence of PH at baseline is associated with higher risk for the development of AEs and consequent poor survival [59].

The prevalence of PH varies in ILDs depending on 1) patient selection (most of the studies include patients listed for lung transplantation), 2) time of investigation (the more advanced the disease the higher the prevalence) and 3) measurement technique (right heart catheterisation (RHC) or heart ultrasound). In IPF, the prevalence varies from 32% to 85% [60], in sarcoidosis from 5% to 74% [61] and in SSc from 5% to 12% [62].

Diagnosis

Physical examination may reveal signs suggestive of PH. It should be stressed that these signs (loud pulmonary component of the second heart sound, right ventricular heave, elevated jugular venous pressure and ankle oedema) are not specific and are frequently present in advanced disease. RHC remains the gold standard diagnostic procedure. Major elevation of pulmonary vascular resistance (PVR) predicts rapid
mortality and is a marker of end-stage disease [63]. However, RHC is invasive and is not free of risk; therefore, unless targeted PH therapy is under active consideration, a combination of noninvasive procedures (including lung function tests, resting hypoxia, desaturation during the 6-min walking test (6MWT), echocardiography, brain natriuretic peptide (BNP) levels and HRCT features) is sometimes sufficient to make a working diagnosis of PH.

Lung function tests may reveal a decreased DLco, transfer coefficient of the lung for carbon monoxide (Kco) (DLco adjusted for alveolar volume (VA)) and arterial oxygen tension, whereas the alveolar–arterial oxygen gradient is widened. In isolated ILDs, DLco levels are usually 20–25% lower than volumes. When DLco is disproportionately reduced and paralleled by a disproportionate reduction of Kco (also known as DLco/VA), PH should be suspected in the absence of concomitant emphysema. In patients with IIP, baseline Kco and 6-month decline in Kco are both associated with increased early and overall mortality and, in a subgroup of patients with follow-up echocardiography, are associated with the development of PH [64]. In SSc, an elevated FVC/DLco ratio (in essence, the inverse of Kco) was found to be an independent predictor for the presence of PH and is included in the DETECT as an indication for the performance of echocardiography [65]. However, in SSc patients with combined pulmonary fibrosis and emphysema (CPFE), elevation of FVC/DLco is usual, irrespective of the presence or absence of pulmonary vasculopathy [66]. Use of FVC/DLco has also been explored in IPF but this variable suffers from measurement variability as three variables must be measured (FVC, Kco and VA) whereas Kco is quantified as a single variable (integrated with VA in the computation of DLco).

Resting hypoxia is not frequent when the DLco is >30% predicted and, if present, is suggestive of PH. Pulmonary vasculopathy is likely to account for the major increase in mortality in IPF patients with DLco levels <40% predicted [67].

Desaturation <88% in the 6MWT when disproportionate to the extent of the underlying ILD should raise the possibility of PH. Thus, reduced DLco levels, a requirement for supplemental oxygen, or a poor 6-min walk performance should raise suspicion of PH in IPF [68].

Right ventricular systolic pressure (RVSP) estimated at echocardiography has a reasonably good correlation (i.e. a reasonably high r-value) with systolic pulmonary artery pressure (sPAP) at RHC, but it must be understood that echocardiography systematically overestimates pressures in chronic lung disease, except in severe PH [69–71]. This discordance has caused some clinicians to underuse echocardiography in screening for PH and may account for the fact that an echocardiographic RVSP >50 mm is associated with increased mortality in IPF, whereas echocardiographic pressures of 35–50 mm are not.

Other ancillary tests include BNP levels and HRCT. BNP levels >20 pmol·L−1 are associated with a 14-fold increase in mortality over patients with BNP <4 pmol·L−1 [72]. A combination of elevated BNP levels and sPAP at echocardiography is predictive of increased mortality over either individual test [73].

An increased pulmonary artery diameter and an increase in the ratio of pulmonary artery diameter/ascending aorta diameter (>1.0) have both been reported as predictive of findings at RHC [74]. Although neither sign appears to be sufficiently accurate in isolation, the combination of HRCT and echocardiography was found in one study to perform better in PH detection than the use of either individual test [75].

**Treatment**

Important management considerations include identification and treatment of various contributing factors (obstructive sleep apnoea (OSA), pulmonary embolism (PE) and left heart failure); reversal of hypoxia and transplantation referral are equally important. Use of supplementary oxygen in order to maintain saturation >90% at rest or during exercise, diuretics and, in the context of OSA, use of continuous positive airway pressure (CPAP) machines are advisable.

No formal role has been established for targeted PH therapy in ILD. Trial data have been conflicting although provide some evidence for a likely treatment effect. A distinction should be made between trials of targeted PH therapies in larger ILD populations (in the hope of a combined vascular and interstitial effect) and trials in ILD-PH patients.

Vasodilators have been used cautiously in IPF patients, due to the potential risk of worsened gas exchange and hypoxaemia. Sildenafil appears to cause selective pulmonary vasodilation, with maintenance of ventilation/perfusion (V′/Q′) matching and arterial oxygenation [76]. When used in patients with advanced IPF, sildenafil was associated with a placebo-controlled improvement in DLco and arterial oxygenation [77], indicating that a deleterious effect on V′/Q′ matching, if present in some patients, was, on average, relatively minor, compared to the benefits of treatment on the pulmonary vasculature. In IPF, the combination of an antifibrotic drug with sildenafil in moderate-to-severe PH is attractive in principle, as it targets both the
interstitial and vascular compartments [16]. Bosentan was found to be nonefficacious in two large placebo-controlled IPF trials [78, 79] and in another large placebo-controlled evaluation in IPF, ambrisentan was associated with increased risk of disease progression and respiratory hospitalisations [80]. A recent trial of macitentan in IPF was also unsuccessful [81]. Taken together, these data provide no support for an antifibrotic interstitial effect of these therapies, despite supportive pre-clinical data.

In PH-ILD, sildenafil appears to be safe and well tolerated, and has had a significant effect on 6-min walk distance (6MWD) and BNP levels but not on RVSP after 6 months of treatment in small cohorts [82]. In sarcoidosis, sildenafil has improved mean pulmonary arterial pressure and cardiac output in repeat RHC 4 months after treatment [83]. By contrast, bosentan was found to be entirely nonefficacious in fibrotic IIP-PH [57] but may have beneficial effects in some sarcoidosis–PH patients, especially in patients with PH and limited ILD, although the fragmentary nature of current data must be emphasised [84–87]. Ambrisentan appears to be poorly tolerated in sarcoidosis–PH [88]. In an open-label, uncontrolled ILD-PH trial, riociguat, a stimulator of the soluble guanylate cyclase, was shown to increase cardiac output, decrease PVR and improve exercise capacity as judged by the effect in the 6MWT [89]. There are no studies regarding treatment of PH in the context of SSc-ILD and our knowledge comes from larger PH studies in which patients with SSc-PH were included. Combination therapy with endothelin receptor antagonists, phosphodiesterase type-5 inhibitors and prostacyclin analogues did not affect survival but had effects on multiple outcome measures such as 6MWD, functional class and quality of life [62].

Cardiac disease
Cardiac disease can represent a comorbidity but also a consequence of deep involvement of the heart, as in the case of sarcoidosis or in IIMs. Major diagnostic uncertainties may occur in patients with ILD due to the presence of occult cardiac disease. An AE attributed initially to the underlying ILD may, in reality, be a rapid deterioration due to an exacerbation of cardiac disease. In patients with breathlessness disproportionate to the extent of the underlying ILD, proactive cardiac evaluation is warranted. HRCT findings such as profuse septal thickening, ground-glass opacities with patchy distribution and pleural effusions are suggestive of cardiac failure as a cause of rapid deterioration. In moderate-to-advanced fibrosing ILDs, a low threshold for 24-h Holter monitoring is appropriate if there is reason to suspect cardiac arrhythmias triggered by exertional hypoxia.

In historical IPF series, cardiac disease was one of the major causes of death [90]. In IPF, the prevalence of coronary artery disease (CAD) is high (60%), probably as a consequence of smoking; associated with worse survival; and, importantly, is significant but unrecognised in 20% of cases [91, 92]. In this regard, HRCT can be helpful as the presence of moderate-to-severe coronary calcification has a high sensitivity and specificity for the presence of significant CAD, whereas absence of calcification has an extremely high negative predictive value [93].

Cardiac sarcoidosis is clinically overt in 5% of patients but is present in 20–30% at autopsy, including patients with isolated cardiac disease without involvement of other major organs [94–97]. However, dyspnoea from cardiac disease may also result from left ventricular diastolic dysfunction due to age or arterial hypertension, or PH, even in the absence of pulmonary fibrosis [98]. Arrhythmias are a common manifestation: sarcoidosis may present with complete heart block or sudden death. In adults aged <55 years with unexplained atrioventricular block or ventricular tachycardia of new onset, a high suspicion of underlying sarcoidosis is warranted [99, 100]. In addition to routine investigations performed to identify systemic support for a diagnosis of sarcoidosis, advanced cardiac imaging (i.e. cardiac magnetic resonance (CMR) or fluorodeoxyglucose positron emission tomography (FDG-PET)) is now routinely advocated as a sensitive method of detecting typical patterns of cardiac involvement. Advanced imaging also offers advantages in prognostic evaluation. Apart from identifying severe left ventricular dysfunction, in itself a malignant prognostic determinant [98], CMR [101] or FDG-PET [102–104] evidence of active disease is strongly predictive of future death or ventricular tachycardia. The first-line treatment of cardiac sarcoidosis is high-dose corticosteroid therapy, which tends to be more efficacious in patients with atrioventricular conduction disease or mild-to-moderate left ventricular dysfunction than in severe left ventricular dysfunction [105]. Patients with the diagnosis of cardiac sarcoidosis and sustained second or third degree atrioventricular block and/or sustained ventricular tachycardia and/or left ventricular ejection fraction <30% should undergo implantable cardioverter defibrillator placement [99].

Amongst the CTDs, cardiac involvement is most prevalent in SSc [106] and IIM, in which cardiac disease is the third to most frequent cause of death after lung disease and malignancies [107]. Subclinical disease is more frequent than clinically relevant cardiac disease. Heart failure, valve disease, CAD, myocarditis and bundle branch block have all been identified in IIMs. ECG, echocardiography and magnetic resonance imaging should be performed if there is a suspicion of cardiac involvement. Cardiac troponin I is a
specific cardiac enzyme that allows myocardial inflammation to be identified when there is coexisting peripheral muscle involvement and elevation of creatine phosphokinase levels. In the absence of controlled data, intravenous steroid therapy with or without other immunosuppressive drugs has been used empirically, in combination with standard treatment for arrhythmias and heart failure.

Drug-induced lung disease resulting from cardiac therapies is suspected most commonly with the use of amiodarone or statins. Amiodarone, a widely used antiarhythmic drug, has been associated with various patterns of lung toxicity and generally manifests with cough, dyspnoea and new infiltrates on HRCT. Statins, widely used to reduce cardiovascular morbidity in patients with known risk factors, have been implicated in the development of pulmonary fibrosis [108]. Statin-induced lung disease is commonly suspected, due to the widespread use of these agents, but is very rare, accounting for the absence of a demonstrable association between the use of statins and the development of ILD in a large epidemiological study [109]. This observation does not refute the existence of statin-induced lung disease, for which the evidence is sometimes compelling in individual patients.

Drug-induced lung disease, primarily a diagnosis of exclusion, is increased in likelihood when there is a temporal association between drug introduction and the onset of lung disease. Further supportive evidence includes the presence of a BAL eosinophilia and stability or improvement of lung disease after drug withdrawal. Decisions to withdraw cardiac therapies in suspected drug-induced lung disease must be made on a case-by-case basis, balancing the likelihood of the diagnosis against the necessity of continuing therapy on cardiac grounds.

### Pulmonary embolism

Patients with IIPs are at increased risk of venous thromboembolic disease [110, 111]. Possible explanations include the presence of a procoagulant microenvironment in IPF [112], and immobility due to dyspnoea or to joint and muscle pains and stiffness in the particular case of CTD-ILDs. Computed tomography (CT) pulmonary angiography is the investigation of choice since it effectively excludes thromboembolism and can provide useful ancillary diagnostic information (e.g. typical CT features of cardiac failure). V′/Q′ scanning is highly nonspecific for PE in ILD as perfusion defects are almost invariably present. In a study of patients with IPF undergoing concurrent V′/Q′ scanning and HRCT, V′/Q′ mismatch, frequently seen in IPF scintigrams suggestive of PE, corresponded to honeycombing or emphysematous change seen on HRCT [113]. Honeycomb cysts are usually normally ventilated but not perfused.

In other settings, PE is routinely treated with vitamin K antagonists such as warfarin. However, the use of warfarin in a placebo-controlled trial in IPF was associated with increased mortality, raising the possibility that pro-coagulant mechanisms may be protective against disease progression in IPF [114, 115], despite the fact that pro-coagulant states have been associated with an increased prevalence of IPF in one study [116]. One possible explanation is that by depleting vitamin K stores, warfarin reduces vitamin K-dependent activation of matrix gla protein, an inhibitor of extracellular matrix calcification [117]. Based on this finding, it can be argued that low molecular weight heparin is preferable to warfarin as treatment for PE occurring in IPF patients [118]. It is uncertain whether this caveat also applies to the use of new oral anticoagulants such as factor Xa inhibitors. Venous thromboembolism heparin prophylaxis remains appropriate in hospitalised ILD patients and there are no data suggesting that vitamin K antagonists for PE are contraindicated in ILDs other than IPF.

Recurrent episodes of PE in systemic lupus erythematosus (SLE) should prompt the exclusion of secondary antiphospholipid syndrome (APS), associated with lupus anticoagulant positivity or the presence of anti-cardiolipin or anti-β2-glycoprotein 1 antibodies. The treatment of PE due to APS does not differ from standard PE therapy. Immunosuppression does not seem to halt thrombotic recurrences [119]. Interestingly, hydroxychloroquine therapy is associated with a lower likelihood of persistent lupus anticoagulant positivity in SLE and may have a useful prophylactic role [120].

### Lung cancer

The prevalence of lung cancer in IPF varies from 4.4% to 9.8% [121]. Lung cancers in IPF tend to be peripheral and located in the lower lobes, which is in accordance with the distribution of the fibrotic lesions in IPF, suggesting that the fibrotic process may play a role in the development of cancer, with smoking a common risk factor [122]. Lung cancer often manifests as a mass-like lesion in or near areas of fibrosis; distinction between malignancy and areas of confluent fibrosis may be difficult, especially when previous imaging is unavailable. Lung cancer can also develop in CTDs (mainly SSc) but is rare in sarcoidosis, probably reflecting the inverse correlation between sarcoidosis and smoking [123, 124]. Diagnosis and staging of lung cancer in ILDs should be undertaken as for any other patient. The main dilemma for the clinician arises when these diseases, each one with a very poor outcome, have been
diagnosed in the same patient. Median survival after diagnosis is worse in lung cancer–ILD than in either ILD or lung cancer alone [125–127].

Treatment options are the same as in lung cancer and the main complication is drug-induced ILD, presenting with AEILD. There are no specific guidelines and therefore management should be based on risk/benefit considerations. A single study has raised concerns about the use of stereotactic body radiotherapy in severe ILD because of a high risk of radiation pneumonitis. In subclinical disease, radiotherapy has been shown to be relatively safe with a low risk of radiation pneumonitis extending beyond the irradiated field [128]. Chemotherapy-induced acute exacerbations of lung disease have an incidence of 8.7–21% [129]. The combination of carboplatin with etoposide and of carboplatin with paclitaxel was efficacious in two small studies of patients with IIPs and small cell lung carcinoma and non-small cell lung carcinoma (NSCLC), respectively. When the authors integrated the two groups, in 35 patients, they observed 10 AEs, but in only two cases was there temporal linkage to this specific chemotherapy regimen [129, 130].

Epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely used in the treatment of NSCLC with active EGFR mutations. They have been associated with drug-induced ILD and fatal ILDs. The risk is higher in patients who receive EGFR-TKIs in association with or after chemotherapy [131]. Nintedanib, an intracellu lar inhibitor recently recommended for the treatment of IPF, targets multiple tyrosine kinases receptors, and is also used in the treatment of NSCLC and ovarian cancer. A literature search has not revealed any study suggesting that nintedanib can be related with the development of drug-induced ILD.

AEILD, the most dangerous complication after pulmonary resection for primary lung cancer, is associated with low pre-operative DLCO and KCO, FVC <80% predicted, and lactate dehydrogenase >400 IU·L⁻¹ [132–134]. However, it should be stressed that in CPFE, spirometry in isolation may be misleading because CPFE is characterised by spurious preservation of lung volumes. A composite physiologic index >40 is associated with 50% chance of post-operative acute respiratory distress syndrome [132]. The extent of resection is also important as the risk is higher with pneumectomy than with lobectomy. If pneumectomy is needed for complete resection, a detailed risk/benefit discussion with the patient is required [132]. Duration of one-lung ventilation and the manipulation of nonresected lung tissue both contribute to oxidative stress and, thus, to the development of post-operative AEILD, and should both be minimised [135].

Sleep disorders
In early series examining the association, the prevalence of OSA in IPF was reported to vary from 60% to 90% [136, 137]. In sarcoidosis and SSc–ILD, the prevalence also seems to be increased (52% and 66%, respectively) [138, 139]. However, these observations, in themselves, have produced more questions than answers, especially with regard to the indications for and efficacy of standard OSA therapy in IPF. In the general community, the prevalence of OSA is ~20% in older adults [140]. However, OSA is not screened for routinely but tends to be investigated when there is a high perceived risk, judging from daytime somnolence (quantified using validated scales). In the largest early series, the Epworth Sleepiness Scale score correlated poorly with the severity of OSA at nocturnal polysomnography (NPSG) [137]. In a recent series, <25% of IPF patients with sleep disordered breathing had an OSA clinical syndrome (with compatible Epworth Sleepiness Scale scores) [141].

The distinction is important. IPF patients have an impaired pulmonary vascular reserve, which is likely to influence the severity of desaturation during apnoeic episodes, in keeping with observed links between nocturnal oxygen desaturation and markers of pulmonary vasculopathy [142]. Thus, it is not clear whether the NPSG profile of OSA is, in itself, a malignant prognostic determinant in IPF or is merely a marker of the adverse outcome associated with pulmonary hypertension. Should OSA treatment be instituted in all IPF patients with characteristic NPSG features, in order to improve life expectancy, or only in those IPF patients with daytime somnolence, in order to improve quality of life? The latter goal appears logical but more work is needed to show that failure to treat OSA has outcome implications. Worse outcomes observed in IPF patients who do not comply with CPAP are inconclusive in this regard because difficulties with the use of CPAP machines may be more prevalent in advanced IPF [143]. An increase in mortality in IPF patients with OSA might, in theory, be linked to the promotion of GOR but this view is not supported by a study of 54 patients in which GOR promotion by OSA was definitively refuted [144]. Failure to treat OSA might, in principle, lead to worsening PH, triggered by the severity of desaturation, but if so, it is entirely uncertain whether this danger might be alleviated, at least in some patients, by nocturnal oxygen supplementation alone, without the need for routine institution of CPAP.

With regard to treatment, the most important issue is related to reduced compliance of patients with the CPAP machine for several reasons [143]. Nocturnal dry and irritating cough is a frequent symptom leading
to impairment of sleep quality. The use of heated humidification before or after CPAP titration is often helpful whereas the use of codeine-based drugs is questionable because of the effect on respiratory drive. Claustrophobia can be related to the rapid and shallow breathing pattern of these patients, and an initial trial with CPAP at low pressures may be helpful. Mood disorders and, especially, depression are common. Antidepressants have dual benefits in improving depression and reducing the severity of OSA [145, 146]. The use of steroids in ILDs other than IPF can have impact on sleep leading to insomnia and multiple nocturnal wakening [147, 148] as well as to central fat deposition in the neck region and deterioration of underlying OSA. Therefore, longer term titration of CPAP treatment is needed. Taken together, these considerations amply justify routine referral to sleep centres for the diagnosis and management of OSA in ILD.

Depression
Depression and anxiety are highly prevalent in patients with ILD. In a mixed ILD cohort [149, 150], clinically relevant depression was observed in >20% of patients. Independent predictors of depression include severity of dyspnoea, sleep quality, reduced FVC, pain and functional status [149]. Corticosteroids may also play a role in precipitating depression. In IPF, the prevalence of depression varies from 11% to 50% according to the tools used for the assessment of depression [149, 151, 152]. In ILD patients, depression has a definite impact on quality of life and on adherence to treatments [153–155]. In a recent study, the Medical Research Council score was an independent predictor of anxiety and depression in a mixed ILD cohort, in which the rates of anxiety and depression were increased without a specific predilection in any individual disease entity [156]. Importantly, prior to attending a specialised ILD centre, <2% of patients had an established diagnosis of depression. At the initial visit, following the completion of the HADS (Hospital Anxiety and Depression Scale), a tool to measure anxiety and depression in a hospital setting, depression was identified in 23% of the patients, with clinically significant depression present in 7% of patients. These findings support early referral of ILD patients to specialised ILD centres with access to expert psychiatric advice. It has been proposed that ILD patients with functional impairment should be referred for pulmonary rehabilitation, based on observed benefits on fatigue and functional capacity, and improvements in symptoms of depression and anxiety [157]. Whether all ILD patients should be screened routinely for depression and anxiety merits further investigation [149].

Conclusion
In ILD, the comorbidities discussed in this review have in common the potential to impair quality of life and to reduce life expectancy. Comorbidities can also have a major impact on case-by-case treatment decisions; for example, antifibrotic therapy is less likely to prolong life in IPF patients with advanced lung cancer or severe PH. With an increasing focus on IPF-specific antifibrotic treatments and on immunomodulation in patients with other forms of ILD, there is a danger that the importance of comorbidities may be underestimated, especially when their effect on cardiopulmonary reserve is chronic and insidiously progressive. The early detection and accurate management of the comorbidities discussed in this review have major potential benefits in reducing morbidity and mortality.

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