18.11.2 Idiopathic pulmonary fibrosis 4177 P.L. Mo

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and A.U. Wells ESSENTIALS The synonymous terms idiopathic pulmonary fibrosis and crypto- genic fibrosing alveolitis refer to a relentlessly progressive fibrotic lung disorder. Incidence is about 5 to 15 per 100 000, men are more often affected than women, and it most commonly presents in the seventh and eighth decades. Aetiology remains uncertain. Clinical features—typical presentation is with progressive exertional dyspnoea without wheeze, a nonproductive cough, digital clubbing, and very fine end-inspiratory crackles. Central cyanosis and clinical evidence of pulmonary hypertension are late features. Diagnosis—depends on careful exclusion of known causes of inter- stitial lung disease, followed by demonstration by radiological imaging or biopsy of the pathognomonic lesion of usual interstitial pneumonia. Management—two antifibrotic compounds, pirfenidone and nintedanib, have been proven to slow functional decline in idio- pathic pulmonary fibrosis. Treatments that target inflammation
(e.g. corticosteroids and immunosuppressive agents) are generally
of no benefit and may do harm, although acute exacerbations, which affect 10–15% of patients each year and are often fatal, are typically given a trial of high-dose corticosteroid. Lung transplant- ation is appropriate in selected cases. Supportive therapy is central to the management

of advanced disease. Five-year survival is 10–15%. Introduction The disorder previously known as fibrosing alveolitis, first described in 1907, was increasingly recognized following the description of a small group of patients with rapidly progressive fatal disease, grouped as the Hamman–Rich syndrome. Until late in the twentieth century, a stereotypical clinical presentation of idiopathic intersti- tial lung disease was termed idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis (CFA), with several histological pat- terns unified under this term. However, it became increasingly clear that the clinical presentation of IPF/CFA ('CFA clinical syndrome') was shared by diseases including predominantly inflammatory and predominantly fibrotic disorders, now known collectively as the idiopathic interstitial pneumonias. Their separation is essentially pragmatic, justified by large differences in treated outcome. The new classification proposed by an American Thoracic Society/European Respiratory Society nomenclature committee is now widely accepted and can be readily applied to routine prac- tice, with increasing recognition of characteristic patterns of disease on high resolution computed tomography (HRCT). Histological evaluation tends to be reserved for the few patients in whom best management cannot be based on clinical and HRCT findings. The synonymous terms IPF and CFA now refer to a relentlessly progres- sive fibrotic disorder, associated with a histological pattern of usual interstitial pneumonia (UIP) or typical HRCT and clinical features in nonbiopsied cases. Epidemiological and aetiological data are briefly reviewed and the clinical picture is summarized. Key clinical issues are then dis- cussed, including diagnosis, prognostic evaluation, routine moni- toring, and treatment. Epidemiology and aetiology IPF most commonly affects men, rarely presents before the age of 50, and exhibits considerable geographic variation. The incidence and prevalence have risen steadily in recent decades, with the incidence now likely to approximate 10–15 per 100 000, based upon evalu- ation of death certificates and registry studies in the United States, United Kingdom, and elsewhere. A recent study, using case defin- itions more reliably indicative of IPF, has suggested an incidence of 5 to 10 per 100 000. The pathogenesis of IPF remains unknown. It was historically considered that inflammation preceded fibrosis, but the paucity of evidence of inflammation in histopathological samples and the lack of efficacy of immunosuppressive therapy led to a shift in thinking. Current evidence suggests IPF develops in genetically susceptible individuals with dysfunctional alveolar epithelial repair mech- anisms following repeated episodes of alveolar injury. Repetitive injury results in myofibroblast recruitment and activation, and col- lagen deposition causing progressive accumulation of scar tissue, re- sulting in the classical radiological and histological patterns of UIP. Destruction of the lung architecture causes loss of alveolar struc- ture, impairing gas exchange and ultimately resulting in respiratory failure. The presumptive model of development therefore suggests a role in IPF for both host and environmental factors, with inter- actions between the two in all likelihood. Environmental factors Several environmental triggers have been suggested as plausible causative factors, but as yet the initial stimulus remains unidenti- fied. A history of smoking is associated with an increased risk of developing both the familial and sporadic forms of IPF, but cigarette smoke alone cannot be the only trigger as the disease also occurs in nonsmokers. Epidemiological studies have also implicated environ- mental and occupational exposures to metal dusts and wood fires, which confer an increased risk of IPF. Genetic factors Familial forms of IPF, where two or more members of a family are affected, provide strong evidence for an underlying genetic compo- nent to the disease. Familial forms of fibrosis have been linked to variants in the genes encoding two surfactant proteins (SFTPC & SFTPA2), genes that maintain telomere length (hTERT and TERC), and most recently the mucin 5B (MUC5B) gene. The strongest and most reproducible genetic association with IPF to date is that of the mucin 5B (MUC5B) gene: a polymorphism (rs35705950) in its promoter region is associated with the develop- ment of both

sporadic and familial IPF. Subjects carrying the mu- tation demonstrate an increased expression of MUC5B in the lung, which accumulates within areas of honeycombing. This association has now been robustly replicated and the association with MUC5B was also the dominant finding in two recent genome-wide associ- ation studies.

section 18 Respiratory disorders 4178 The mucin glycoproteins are a major structural component of the mucus barrier, maintaining the hydration of the airway epithe- lium and crucially entrapping particles for removal by mucociliary clearance. This has led to the hypothesis that excess production of MUC5B reduces mucociliary clearance of inhaled particles, re- sulting in prolonged and repetitive exposure, triggering an exagger- ated interstitial injury, and eventually leading to the development of fibrosis. Diagnostic criteria The publication of the ATS, ERS, JRS, and ALAT joint statement on IPF in 2011 marked a significant shift in the diagnostic paradigm for IPF. The major/minor diagnostic criteria set out in previous guidelines were eliminated, and more emphasis was placed on the multidisciplinary approach to diagnosis. The role and importance of surgical lung biopsies in the diagnostic process was also re-visited, given the emerging wealth of data regarding the specificity for the recognition of the histopathologic UIP pattern on HRCT. These 2011 diagnostic guidelines were revised and updated in 2018. The suggested diagnostic pathway (Fig. 18.11.2.1) starts with careful exclusion of known causes of interstitial lung diseases. This is achieved through a thorough history, examination, and serological testing to identify predisposing domestic and occupational envir- onmental exposures, and underlying medical conditions.
A detailed family history is also necessary as some estimates suggest that up to 10% of cases of IPF are familial. If no underlying cause can be identified the patient may have IPF, and evidence of the pathognomonic lesion of UIP is sought, initially radiologically. The 2018 guidelines clearly state the precise HRCT features that meet the criteria for ‘UIP’, ‘probable UIP pat- tern’, ‘indeterminate for UIP pattern’ and ‘alternative diagnosis’. In the appropriate clinical setting, satisfaction of HRCT criteria for a pattern of UIP obviates the need for further investigations such as cellular analysis of bronchoalveolar lavage (BAL) fluid, trans- bronchial biopsy or surgical lung biopsy. By contrast, cellular ana- lysis of bronchoalveolar lavage (BAL) fluid or surgical lung biopsy should be considered when the diagnosis is thought to be probable UIP, indeterminate for UIP or an alternative diagnosis. The weight of combined clinical, histopathological, and radiological informa- tion is then used by a multidisciplinary team to confirm or refute a diagnosis of IPF (Table 18.11.2.1). Histological features and pathogenesis In UIP, the histological pattern underlying IPF (Fig 18.11.2.2), tem- poral and spatial heterogeneity of disease is the cardinal feature. Normal lung is seen adjacent to regions of fibrosis, with enlarged cystic air-spaces (honeycomb lung) and areas of milder interstitial fibrosis. A patchy chronic inflammatory cell infiltrate is variably pre- sent. Subepithelial foci of proliferating fibroblasts (‘fibroblastic foci’) are a characteristic feature, occurring occasionally and sparsely in nonspecific interstitial pneumonia (NSIP) but not seen in other idiopathic interstitial pneumonias. Historically, it was believed that inflammation was the key patho- genetic process, preceding and leading to fibrotic disease, but this view has been largely abandoned. Corticosteroid and immunosup- pressive therapy, effective in primary inflammatory disorders, have now been shown in large studies to confer no treatment benefit. Indeed, far from demonstrating any benefit, immunosuppression has actually proven to be harmful in IPF. There is increasing evidence that IPF has an epithelial fibrotic pathogenesis, with initial epithelial damage leading to the forma- tion of fibroblastic foci and subsequently to more widespread thick- ening of the connective tissue matrix in advanced disease. Thus, IPF can be conceptualized as a disorder of abnormal wound healing. In established disease, lung injury, an immunological and inflam- matory

response, and fibrogenesis appear to occur in parallel. It is not known whether a single key mechanism is pivotal in pathogen- esis. Oxidant-antioxidant imbalance and the release of damaging enzymes from inflammatory cells appear to amplify injury, but a wide variety of biological mechanisms interact in the lungs of pa- tients with IPF, with up-regulation of tumour necrosis factor-α and chemokines (interleukin 8, and growth factors, especially trans- forming growth factor-β; and connective tissue growth factor), and activation of the coagulation cascade, known to promote fibrogenesis. However, it is not clear whether these mechanisms are primarily pathogenetic or represent physiological responses to an up-stream abnormality. The profusion of fibroblastic foci and Patient suspected to have IPF Yes Yes No No Potential cause/associated condition Further evaluation (including HRCT) probable UIP, indeterminate for UIP, alternative diagnosis UIP BAL Surgical lung biopsy* MDD Alternative diagnosis IPF per Figure 18.11.2.2 Not IPF MDD Chest HRCT pattern Specific diagnosis Fig. 18.11.2.1 Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). If a patient is suspected of having IPF but a specific diagnosis is not made or no potential cause for interstitial lung disease (ILD) is identified, further evaluation depends on the appearances of high resolution CT images (HRCT) of the chest and clinical input from multidisciplinary discussion (MDD). IPF is diagnosed if the appropriate combination of HRCT patterns and histopathological patterns are present (see Table 18.11.2.1). From Raghu G, et al. (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med, 198, e44–e68.

18.11.2 Idiopathic pulmonary fibrosis 4179 serum levels of protein markers of epithelial damage have both been linked to mortality and disease progression. Clinical features The typical presentation is progressive exertional dyspnoea without wheeze and a nonproductive cough, although sputum production is present in a minority of patients. Haemoptysis should prompt investigation for lung malignancy, which is approximately 10-fold more prevalent in IPF, after the smoking history has been taken into account. Chest discomfort, fatigue, and weight loss are occasional features. Digital clubbing is present in over 50% of pa- tients and has been an adverse prognostic determinant in some series. On auscultation, very fine end-inspiratory crackles are typical heard bilaterally at the lung bases and become widespread in advanced disease. Central cyanosis and clinical evidence of pul- monary hypertension, with or without right ventricular failure, are late features. Investigation Chest radiography The chest radiograph typically shows small lung volumes and pre- dominantly peripheral and basal reticulonodular shadowing, with obscuration of the heart borders and diaphragms in advanced dis- ease and overt honeycombing in 10% of cases. This profile is highly nonspecific, occurring in fibrotic NSIP, asbestosis, rheumatological disorders, and other fibrotic processes. Lymphadenopathy or pleural disease should suggest an alternative diagnosis or a concurrent pathological process. Cardiomegaly may occur in the absence of cardiovascular disease as a result of reduced intrathoracic volume. High resolution computed tomography HRCT appearances are virtually pathognomonic in up to 60% of pa- tients (Fig. 18.11.2.3). The disease is predominantly postero-basal and peripheral, becoming widespread in advanced disease, and consists of a reticular pattern, with or without honeycombing, and a minor component of ground-glass attenuation, usually indicative of fine fibrosis (rather than inflammation). It should be stressed that HRCT appearances are atypical in at least 40% of cases, with the most frequent variant consisting of prominent ground-glass Table 18.11.2.1 Idiopathic pulmonary fibrosis (IPF) based upon HRCT and biopsy patterns IPF suspecteda Histopathology pattern UIP Probable UIP Indeterminate for UIP Alternative diagnosis HRCT pattern UIP IPF IPF IPF Non-IPF dx Probable UIP IPF IPF IPF (Likely)b Non-IPF dx Indeterminate for UIP IPF IPF (Likely)b

Indeterminate for IPFc Non-IPF dx Alternative diagnosis IPF (Likely)b /non-IPF dx Non-IPF dx Non-IPF dx Non-IPF dx a Clinically suspected of having IPF. b IPF is the likely diagnosis when any of the following features are present: (1) moderate-to-severe traction bronchiectasis/bronchiolectasis in a man >50 years or woman >60 years; (2) >30% reticulation on HRCT at age >70 years; (3) increased neutrophils and/or absence of lymphocytosis in BAL fluid; (4) multidisciplinary discussion makes confident diagnosis of IPF. c Indeterminate for IPF—without adequate biopsy is unlikely to be IPF; with adequate biopsy may be reclassified. Source data from Raghu G, et al. (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med, 198, e44–e68. Fig. 18.11.2.2 (a) Surgical lung biopsy from a patient with IPF shows a patchy established fibrosis with a predominantly subpleural distribution. (b) At high power there is a mild degree of associated nonspecific chronic inflammation with fibroblastic foci in continuity with the established fibrosis. Note the relatively sharp demarcation between normal and abnormal parenchyma.

section 18 Respiratory disorders 4180 attenuation admixed with a fine reticular pattern and associated with traction bronchiectasis: an appearance also suggestive of NSIP (Fig. 18.11.2.4). However, IPF is also diagnosed (i.e. a histological pattern of UIP at biopsy) in occasional patients with markedly atypical HRCT appearances (Fig. 18.11.2.5 a, b). Reactive medias- tinal lymphadenopathy is usual on HRCT and is not indicative of a coexisting disease process unless also present on chest radiography. In early disease, prone HRCT sections may be required to distin- guish abnormal appearances from normal increases in density due to gravity-related increases in perfusion in dependent areas. Other imaging modalities Ventilation–perfusion scans show ventilation mismatch due to vascular ablation in areas of cystic lung, which typically continue to ventilate normally. These appearances simulate pulmonary thromboembolism and probably account for a widespread misper- ception that pulmonary embolism is a frequent complication of IPF. CT pulmonary angiography is required when pulmonary embolism is suspected, especially when DLco levels are disproportionately re- duced, but is usually negative in this context. Lung function tests Lung function tests reveal a restrictive ventilatory defect, as shown by reductions in vital capacity, total lung capacity, re- sidual volume, and pulmonary compliance. However, the wide range in normal premorbid lung volumes sometimes results in apparent normality (when lung volumes have fallen from the upper to the lower end of the normal range). Thus, meas- ures of gas transfer, especially DLco levels, may be reduced in isolation in early disease. Adjustment of DLco for reduced alveolar volume (Kco) has been advocated, as a more specific index of interstitial fibrosis, but Kco levels are disproportion- ately reduced by coexistent emphysema, which is present in over 30% of IPF patients. The combination of emphysema and IPF may result in spurious preservation of lung volumes, even Fig. 18.11.2.3 HRCT scan of a patient with biopsy-proven IPF. Appearances are typical of IPF with a subpleural distribution of microcystic and macrocystic honeycomb change. Fig. 18.11.2.4 HRCT scan of a patient with biopsy-proven IPF showing abnormalities that overlap in appearance with those seen in nonspecific interstitial pneumonia. Disease is predominantly subpleural but consists of a mixture of ground-glass attenuation and fine reticular abnormalities, without honeycombing. This appearance is seen in a significant minority of IPF patients. Fig. 18.11.2.5 (a and b) HRCT scans in patients with biopsy-proven IPF, but in both cases the HRCT appearances are markedly atypical, with no features indicative of IPF or of any other form idiopathic interstitial pneumonia. IPF should always be suspected when disease is inexorably progressive and HRCT appearances are difficult to classify.

18.11.2 Idiopathic pulmonary fibrosis 4181 in advanced disease, and disproportionate reduction in DLco levels. Overall, the severity of disease is most accurately cap- tured by DLco levels, which correlate best with the extent of IPF, as judged by HRCT findings. In early disease, arterial gases may be normal but mild arterial hypoxia with widening of the alveolar-arterial gradient and normal or low Paco2 levels are usual. Severe hypoxia is a late feature and increased Paco2 levels occur in terminal disease. Blood tests Blood tests contribute little to the management of IPF, except in rare cases in which an unsuspected underlying cause is identified. Mild increases in the erythrocyte sedimentation rate, serum immuno- globulins, rheumatoid factor, and antinuclear antibodies are fre- quent and in severe disease, secondary polycythaemia may occur. A high neutrophil count may be indicative of infection but a mod- erate increase is also seen in association with corticosteroid therapy. However, striking increases in autoantibodies may be indicative of a hitherto undiagnosed rheumatological disorder. Precipitin tests against fungal and avian antigens should be performed when there is suggestive exposure history, as chronic extrinsic allergic alveolitis occasionally presents with HRCT appearances suggestive of IPF and a pattern of UIP at surgical biopsy. Bronchoalveolar lavage Bronchoalveolar lavage is a useful ancillary diagnostic test when a surgical biopsy is not performed. Typically, there is an increase in total cell counts and an excess of neutrophils and/or eosinophils is usual. A mild lymphocytosis is not infrequent but striking rises in lymphocyte counts are not generally a feature of IPF and suggest an alternative disorder such as NSIP, hypersensitivity pneumonitis, fi- brotic sarcoidosis, cryptogenic organizing pneumonia complicated by interstitial fibrosis or drug-induced lung disease. Bronchoalveolar lavage is occasionally useful in excluding opportunistic infection in treated patients. Echocardiography Based upon recent reports of a high prevalence of pulmonary hyper- tension in IPF, routine echocardiography is warranted at presen- tation and in patients subsequently developing disproportionate hypoxia or a selective serial reduction in DLco. In some IPF pa- tients, the development of pulmonary hypertension is a feature of end-stage disease, but in other cases, early pulmonary hypertension occurs, not associated with major functional impairment due to interstitial lung disease. Surgical lung biopsy A surgical lung biopsy is the histological diagnostic procedure of choice. Video-assisted thoracoscopic biopsy is the most widely used procedure but mini-thoracotomy is occasionally required in ad- vanced disease. It is strongly recommended that at least two sites are biopsied and HRCT findings should be taken into account to ensure that the full spectrum of morphological abnormalities is sampled, and to avoid areas of end-stage disease which seldom yield diagnostic tissue. The diagnosis of IPF and other idiopathic interstitial pneu-monias cannot be based upon appearances at transbronchial biopsy, as larger biopsies are required to determine whether abnormalities are spatially heterogeneous or truly homogeneous (as in NSIP), a crucial discriminatory diagnostic feature. Diagnosis Once suspected in the symptomatic patient, IPF is usually easy to detect using lung function tests and chest radiography, but in early disease HRCT be required to confirm or exclude interstitial lung disease. However—as discussed earlier—clinical, chest radio- graphic features and physiological features are highly nonspecific in discriminating between individual idiopathic interstitial pneu- monias, and HRCT plays a crucial role in this regard. In most pa- tients with IPF, HRCT appearances are diagnostic in an appropriate clinical setting and it is seldom necessary to confirm the diagnosis with invasive techniques, especially when a typical course of re- lentless progression is already apparent. However, in a significant number of patients diagnostic imprecision leads to major prognostic and management uncertainties, and brochoalveolar lavage and/or a diagnostic surgical lung biopsy is warranted. Thus, these investiga- tions should not be performed by protocol in all cases but should be reserved for situations in which it appears realistic that clinician perceptions of best management,

including treatment and the ap- proach to monitoring, might change significantly with the addition of additional information. In less typical cases, findings at bronchoalveolar lavage may play an important ancillary role in excluding alternative disorders such as hypersensitivity pneumonitis and respiratory bronchiolitis with associ- ated interstitial lung disease (characterized by a striking lymphocytosis and a marked increase in pigmented macrophages, respectively). It should be stressed that the distinction between IPF and fibrotic NSIP (discussed in Chapter 18.11.1), based upon clinical and HRCT features, poses particular difficulty. Even when HRCT appearances are considered typical for NSIP, there is a significant likelihood that a surgical biopsy will disclose a pattern of UIP, indicative of a worse outcome. In difficult cases it is essential to review the diagnosis in a multidisciplinary meeting, with the reconciliation of clinical and radiological features, in order to confirm that a diagnostic surgical biopsy is truly required. This decision is often difficult when IPF is likely, due to patient age (typically advanced), disease severity, and the presence of comorbidity, especially cardiovascular disease. The threshold for performing a biopsy is increased in patients aged over 65 years and when DLco levels are less than 35% of predicted, as both factors are associated with a significant increase in morbidity and the latter with an increase in exacerbations following biopsy. It is also important that histological findings are no longer viewed as a diagnostic ‘gold standard’ in interstitial lung disease, although usually more diagnostically influential than clinical and HRCT fea- tures when the diagnosis is uncertain. A multidisciplinary diag- nosis, made by negotiation between clinicians, radiologists, and pathologists, is now considered optimal. A histological pattern other than UIP is considered to exclude IPF, with one important caveat: ‘sampling error’ (i.e. a biopsy taken from a nonrepresentative site) should be kept in mind when HRCT findings and the subse- quent clinical course are strongly suggestive of IPF. Conversely, when UIP is disclosed at biopsy, the final consensus diagnosis sometimes differs from the histological diagnosis. This applies

 especially to patients with clinical evidence of hypersensitivity pneumonitis or a rheumatological disorder. Prognostic evaluation Accurate diagnosis is central to prognostic evaluation. The five- year survival approximates 10–15% in IPF, as compared to over 60% in fibrotic NSIP and over 90% in patients with predominantly inflammatory idiopathic interstitial pneumonias. Until recently it was believed that all patients exhibited a gradual but relentless decline in lung function reflecting the development of progressive fibrosis. However, the clinical course of individual patients with IPF is actually variable and unpredictable, with some experiencing long periods of relative stability and some a steady decline, while others rapidly deteriorate (Fig. 18.11.2.6). There is currently no way to accurately predict the clinical course, although several adverse prognostic factors have been identified (summarized in Table 18.11.2.2). Increasing age has consistently been an adverse prognostic determinant although it is not clear whether disease is, on average more progressive in older people or, as seems more likely, comorbidity (cardiac disease and malignancy) is largely responsible for an adverse outcome. Disease extent and severity at presentation is a crucial consid- eration. Increased mortality is associated with severe functional impairment, with DLco levels providing the most accurate guid- ance to likely outcome among lung function tests performed at rest. A composite physiological index, containing DLco, FVC, and FEV1 levels, has been shown to predict survival more accurately than any single lung function test in isolation. Severe resting hyp- oxia is indicative of a very poor outcome. Maximal exercise testing is advocated as a superior prognostic de- terminant by some authorities but, in reality, there are no convincing data establishing that maximal exercise data are superior to DLco levels in this regard.

However, desaturation below 88% during a six- minute walk test has consistently identified IPF patients with a much worse outcome in several series. It is not yet clear whether desat- uration during exercise is primarily linked to incipient pulmonary hypertension. The presence of moderate to severe pulmonary hyper- tension is indicative of a very poor outcome. HRCT features have also been linked to outcome, with prom- inent honeycombing associated with a high short-term mortality, although this finding may partially reflect an association between severe honeycombing and extensive disease. Patients with biopsy- proven IPF and HRCT appearances suggestive of NSIP have a better outcome than patients with HRCT appearances typical of IPF. Smoking status may also be important, based on the observation of a better outcome in IPF in current smokers, than in ex-smokers and lifelong nonsmokers. However, it is not clear whether this pro- vocative observation represents less progressive disease in current smokers, or merely a ‘healthy smoker effect’ (with smoking cessation linked to more advanced disease). Observed disease behaviour in patients with IPF is more prog- nostically accurate than observations made at a single point in time. Serial changes in FVC have consistently predicted mortality more reliably than baseline data: serial DLco trends have been similarly predictive in some but not all reports. Worsening fibrosis on serial imaging or increased dyspnoea both also predict an increased mor- tality. The distinction between stability and significant decline at 12 months is particularly useful. Once this information is known, in mixed patient populations with UIP or fibrotic NSIP, the histo- logical diagnosis provides no additional prognostic information. Onset of disease Onset of symptoms Diagnosis A B C D Subclinical period Prediagnosis period Death 1 yr 2 yr 3 yr 4 yr 5 yr 6 yr Time Disease progression Post-diagnosis period Fig. 18.11.2.6 The potential clinical courses of idiopathic pulmonary fibrosis (IPF). The rate of decline may be rapid (a) or slow (c and d). Acute exacerbations (indicated by the black stars) can affect either course and here creates a mixed picture (curve b). From Ley B, Collard HR, and King Jr. TE (2011). Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med, 183, 431–40.

18.11.2 Idiopathic pulmonary fibrosis 4183 Routine monitoring Lung function tests have traditionally been used to identify treat- ment responsiveness (in inflammatory disorders) and deterioration (in IPF and other fibrotic disorders). However, measurement vari- ation is a limitation which requires the use of thresholds for ‘sig- nificant change’. A 10% change from baseline FVC levels, or a 15% change from baseline DLco levels, is required to identify definite regression or progression of disease: the greater measurement vari- ation in DLco may explain the fact that serial FVC trends are more predictive of longer-term outcome than serial DLco trends. It is also important to recognize that the interpretation of serial lung function must be modified in some contexts. Concurrent em- physema often has a major confounding effect on lung function tests, with spurious preservation of FVC levels, but a disproportionate re- duction in DLco (which is reduced in both disorders). In this con- text, a selective serial decline in DLco levels may be seen, with no change in FVC despite significant progression of disease. A selective reduction in DLco may also be indicative of incipient pulmonary hypertension. Thus, serial lung function trends must be integrated with clinical, HRCT and (when indicated) echocardiographic infor- mation. In advanced disease with increasing hypoxia, detailed lung function tests are often impracticable and serial tests tend to be less informative than observations of changes in oxygen saturation (in the steep component of the oxygen dissociation curve). A marginal reduction in lung function indices (a 5–10% change in FVC levels, a 10–15% change in DLco levels) commonly causes dif- ficulties for clinicians. These changes may indicate true disease pro- gression in some patients, but lie within the measurement variation of lung function tests. Symptomatic change is sometimes a useful

guide in this difficult scenario, but is sometimes misleading. Exertional dyspnoea may increase because of disease progression, loss of fitness, comorbidity, or weight gain and myopathy due to corticosteroid therapy. Serial HRCT is sometimes informative, with clear evidence of disease progression in the context of marginal lung function de- cline. However, serial HRCT should be reserved for situations in which the demonstration of disease progression is likely to influence management: it is difficult to assign significance to minor change on HRCT in the absence of lung function deterioration. In IPF, the intensity of monitoring is critically dependent upon the therapeutic goal. Regular monitoring at three to four monthly intervals is especially important in patients receiving treatment, especially novel therapies, and when referral for lung transplant- ation is contemplated. In other cases, in which no change in therapy is contemplated, less frequent monitoring may be appropriate. However, the importance of best supportive care, including the cor- rect use of oxygen in advanced disease, justifies continued moni- toring in the long term. Treatment The last decade has seen important developments in the treatment of IPF, with several well-conducted negative randomized controlled trials reshaping the therapeutic landscape. Previous therapeutic ap- proaches based around immunosuppression have been shown to be harmful, while compounds with antifibrotic actions have been found to slow decline in lung function. Immunosuppressive agents Historically, unsuccessful treatments for IPF were targeted at redu- cing inflammation, which was incorrectly felt to be the predominant underlying disease process. Large studies have shown no benefits with corticosteroids, and similar results were seen when studying the use of the immunosuppressive agents azathioprine, ciclosporin, and cyclophosphamide. Indeed, far from demonstrating any benefit of immunosuppression with the previous mainstay of treat- ment, namely a combination of prednisone, azathioprine, and N-acetylcysteine, this has actually proven to be harmful compared to placebo in IPF. Immunomodulatory drugs including IFN-γ, IFN-β, Imatinib, and Etanercept have all been trialled, and despite initial suggestions of benefits in small pilot studies, none have gone on to show any impact on disease progression or survival in larger studies. Antifibrotic agents In contrast to negative trials targeting inflammation, two antifibrotic compounds, pirfenidone and nintedanib, have now been proven to slow functional decline in IPF. Pirfenidone, a novel antifibrotic agent with antioxidant and anti-inflammatory effects, became the first drug to be licensed specifically for the treatment of IPF in Europe and the United States. Four randomized controlled trials have now demon- strated that treatment with pirfenidone reduces lung function decline, improves progression-free survival, and reduces all cause mortality at 12 months. It is generally well tolerated, with most side effects related to gastrointestinal symptoms, photosensitivity, and fatigue. These all tend to be mild and easily managed with either life style modifications or dose reduction. Indeed, effective patient education prior to com- mencement can often avoid significant side effects all together. Nintedanib is a tyrosine kinase receptor antagonist that inhibits key profibrotic growth factors, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF). Two large phase 3 randomized trials demon- strated that, compared with placebo, nintedanib consistently slowed disease progression by significantly reducing the annual rate of Table 18.11.2.2 Features associated with a worse outcome in IPF, with evidence graded as possible but uncertain (+/–), definite and moderately useful in routine practice (+), or definite and highly predictive (++). Features associated with a worse outcome Grade of evidence Increasing age ++ Male gender +/– Former smoking (versus current smoking) +/– High profusion of fibroblastic foci at biopsy + Prominent honeycombing on HRCT ++ Presence of pulmonary hypertension ++ Moderate impairment of lung function + Resting hypoxia ++ Major desaturation on maximal exercise testing + Major desaturation during a six-minute walk test ++

Increasing dyspnoea + Serial decline in FVC or DLco ++

section 18 Respiratory disorders 4184 decline in FVC. There is also a suggestion it may decrease the risk of acute exacerbations of IPF in subjects with more mild disease. It is generally well tolerated, with most side effects gastrointestinal. Up to 60% of subjects in clinical trials experienced diarrhoea, but this was easily managed, and tellingly almost all subjects involved elected to continue with the medication in the following open label phase. Both pirfenidone and nintedanib slow the decline in FVC in IPF and are now licensed in Europe and the United States for the treat- ment of mild to moderate IPF (FVC 50–80% predicted). There is no head to head data, and currently little information on the potential for combination therapy. The decision as to which agent to use as first-line treatment is therefore currently based on clinician experi- ence, patient preference, lifestyle, medical history, and concomitant medication. The availability of two agents means that patients in- tolerant of one can switch, and in the future there may be options for combination or add-on therapy. Acute exacerbations In 10–15% of patients each year there is an accelerated deterior- ation occurring over several weeks and often leading rapidly to a fatal outcome. Pneumonia, heart failure, and pulmonary thrombo- embolic disease are sometimes the trigger, but the cause for many of these episodes, termed acute exacerbations of IPF, remains poorly understood. Patients typically present with symptoms of worsening dyspnoea, cough, and fever, which are insidious in onset. Investigations focus on excluding known and treatable causes of deterioration, such as infection, heart failure, and pulmonary em- bolism. After these known causes of deterioration have been ex- cluded and a formal diagnosis of an acute exacerbation of IPF has been made, the treatment remains largely empirical and centred around treating the very same triggers already excluded, with al- most all patients initially receiving empirical broad-spectrum antibiotics. If there is no response to antibiotics then patients will subsequently receive trials of high-dose corticosteroids (e.g. 1 g/day methylprednisolone for 3 days), which are either tapered to a lower dose or discontinued based upon clinical response. While these treatments are given, careful attention is paid to optimizing fluid balance status and providing supplementary oxygen therapy. Non- invasive ventilation is sometimes useful, but mechanical ventilation should be avoided due to a uniformly poor outcome. Transplantation Single lung transplantation remains the preferred procedure. As in other end-stage lung diseases, a 3-year survival rate of over 50% can be achieved, but a worse outcome is seen in severely deconditioned patients and over the age of 65. The rapidly progressive nature of IPF, compared to other chronic lung diseases, demands the early referral of suitable cases to a transplant centre, ideally before DLco levels fall below 30% of predicted normal. Supportive therapy Supportive therapy is central to the management of advanced dis- ease. Supplemental oxygen can be provided in the home through oxygen concentrators, and ambulatory oxygen may be beneficial in improving exercise tolerance. The prompt treatment of compli- cations, including infection and heart failure (sometimes triggered by hypoxia) is also important. In terminal disease, small dosages of opiates alleviate the distressing severe dyspnoea associated with striking reductions in lung compliance. It is difficult for patients and family members to come to terms with the chronic, relentlessly progressive nature of IPF. The input of medical and nonmedical health-care professionals is indispens- able to optimal supportive management: social workers, physiother- apists, and occupational therapists all have important roles to play. Rehabilitation programmes may benefit some patients, although less likely to be useful in preterminal disease. FURTHER READING Azuma A, et al. (2005). Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med, 171, 1040–7. Carrington CB, Gaensler EA, Coutu RE (1978). Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med, 298, 801–9. Collard HR, King TE Jr,

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