Interstitial Lung Disease in 2020: A History of Progress

Sabina A. Guler, MD, MHSc[a,*], Tamera J. Corte, MD, PhD[b]

KEYWORDS

• Interstitial lung disease • Idiopathic pulmonary fibrosis • History of medicine

KEY POINTS

- The understanding of underlying mechanisms of interstitial lung diseases has changed drastically over the last centuries.
- Changing terminology over the past decades has complicated communication and collaborative research, whereas progressively detailed clinical guidelines have been provided.
- Therapeutic successes over the last decade have been substantial.

INTRODUCTION

Our understanding of interstitial lung diseases (ILDs) has evolved drastically over the last 2 centuries, and today ILD is viewed as a large, heterogenous group of distinct diseases that affect the lung parenchyma via inflammation and fibrosis.[1] Patients with ILD suffer from frequently progressive dyspnea, cough, and impaired physical function affecting their quality of life. In addition, mortality in patients with ILD can be as high as in some types of cancer. Patients with idiopathic pulmonary fibrosis (IPF), the most common of the idiopathic ILDs, have a median life expectancy of only 3 to 5 years from the time of diagnosis, although there is considerable heterogeneity with some patients living longer than 10 years after diagnosis.[2] Symptoms at presentation are typically nonspecific, which may lead to initial misdiagnosis and subsequent delay in specific ILD diagnosis. Furthermore, different ILD subtypes have overlapping pathophysiological and morphologic features, which makes ILD classification challenging.[1]

In the last decade, there have been major developments in our understanding of ILD, and consequently, our approach to its diagnosis and management. The frequently changing ILD terminology has limited communication between clinicians and researchers, and today agreement on diagnostic and management standards is still not optimal. Knowledge of underlying mechanisms of specific ILDs has grown substantially over the last few years, and particularly for IPF, effective therapies have been identified.[3–5] In this chapter, the authors aim to elucidate historical aspects of ILD and build a foundation to understand current and emerging concepts in these complex diseases. The history of ILD is intertwined with the history of anatomy, physiology, and chemistry, with changes in society, occupational developments, technical achievements, and emerging infectious diseases that have influenced the epidemiology and identification of the ILDs.

EVOLUTION OF INTERSTITIAL LUNG DISEASE CLASSIFICATION AND TERMINOLOGY

Early descriptions of "chronic interstitial pneumonia" were quite different from our current understanding of ILD, and physicians mostly referred to chronic nonresolving pneumonia, post-tuberculosis lung damage, and pneumoconiosis. Even though infectious pulmonary sequelae and occupational pulmonary fibrosis are still important causes of restrictive lung disorders, today there

[a] Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland Freiburgstrasse 18, 3010 Bern, Switzerland; [b] Respiratory Department, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW, 2050, Australia
* Corresponding author.
E-mail address: sabina.guler@insel.ch

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are many other idiopathic, autoimmune, and exposure-associated ILDs described.[1]

The terminology and classification of ILD has evolved steadily since its first descriptions (**Figs. 1** and **2**).

Idiopathic Interstitial Pneumonias

Early descriptions

In 1872, Von Buhl, a German physician, reported cases of *desquamative pneumonia* and *chronic interstitial pneumonia* where he described spindle and star cells and excessive connective tissue. His letters to a friend might have been one of the first descriptions of pulmonary fibrosis.[6] In 1892, Osler mentioned in his medical textbook the evolution of acute infectious pneumonia into a *chronic interstitial pneumonia* or *cirrhosis of the lung*, and this emphasizes that many of the chronic ILDs of that time were nonresolving pneumonias. In 1898, Rindfleisch reported a case of a 40-year-old man with progressive cough and dyspnea, who had a large right ventricle and small stiff lungs on autopsy, with multiple cystic spaces that Rindfleisch called *cirrhosis cystica pulmonum*.[7]

The clinician Louis Hamman and the pathologist Arnold Rich reported in 1933 and 1935, respectively, fulminating *diffuse interstitial fibrosis of the lungs*,[8] coining the term Hamman-Rich syndrome. Somewhat surprisingly, at that time acute and chronic cases were not distinguished, and cases were labeled Hamman-Rich syndrome as long as the typical pathologic features of diffuse alveolar damage were found (usually on autopsy). In 1957, Rubin reviewed 15 cases with Hamman-Rich syndrome[9] and found that presentations were more heterogenous than previously thought. Some patients had systemic illness, which were likely signs of connective tissue diseases. Furthermore, not all cases were rapidly progressive, and a distinction between acute and chronic forms was made. From the 1950s, *chronic Hamman-Rich syndrome* was synonymously used for chronic interstitial pulmonary fibrosis and in the 1960s this phenomenon was renamed as cryptogenic fibrosing alveolitis (CFA) (see **Fig. 2**).

In the 1960s case reports and series on conditions that were named *cystic pulmonary cirrhosis*, *bronchiolar emphysema*, *muscular cirrhosis of the lung*, and *pulmonary muscular hyperplasia* were published in the United States, Canada, Mexico, Scandinavia, France, and Britain.[10–12] Patients were reported to have suffered from dyspnea for at least a year before presentation, with little cough and sputum, a few presenting with clubbed fingers and the majority with crepitations on lung auscultation. When pulmonary function tests were performed, patients had reduced forced vital capacity and diffusion capacity of the lung for carbon monoxide. On autopsy the pulmonary tissue showed honeycombing, and replacement of alveolar tissue with smooth muscle, but little evidence of active inflammation. A few of the patients described were coal miners and others had lymph node involvement; consequently, some of these cases may have had what are now classified as pneumoconiosis and sarcoidosis.

Around that time the conceptualization of ILD (Hamman-Rich syndrome) as a chronic disease was further supported: Gross hypothesized that acute Hamman-Rich syndrome might be an acute exacerbation of the chronic Hamman-Rich syndrome,[13] and Sheridan found that patients

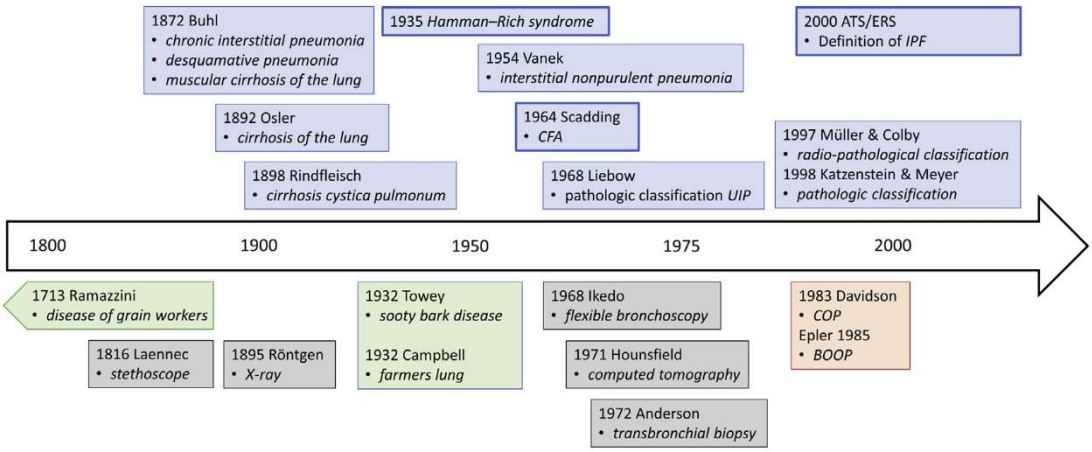

Fig. 1. Milestones for idiopathic interstitial pneumonias (*blue*), hypersensitivity pneumonitis (*green*), organizing pneumonia (*red*), and for relevant technical achievements (*gray*). BOOP, bronchiolitis obliterans organizing pneumonia; COP, cryptogenic organizing pneumonia; UIP, usual interstitial pneumonia.

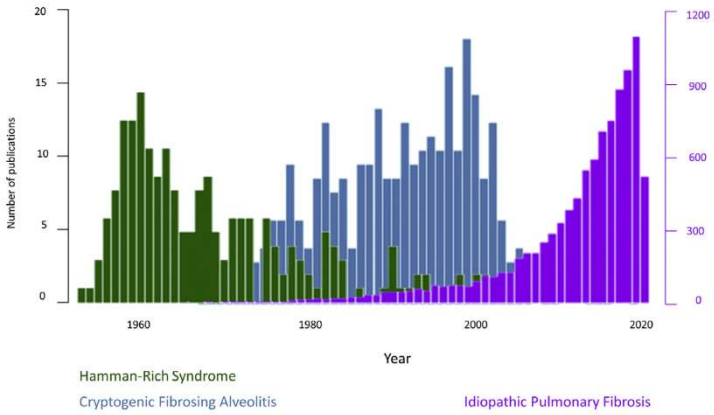

Fig. 2. Number of PubMed publications by year for Hamman-Rich syndrome, cryptogenic fibrosing alveolitis, and IPF.

survived on average for several years with this chronic lung disease.[14]

Modern descriptions

In 1968 to 69, Liebow and Carrington provided the first pathologic classification of chronic ILDs.[15] They introduced the term *usual interstitial pneumonia (UIP),* which was called *usual* because it was the most commonly observed pattern. Furthermore, they described bronchiolitis obliterans organizing pneumonia (BOOP), diffuse alveolar damage, desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia, and giant cell interstitial pneumonia. In the 1970s the clinical disease associated with UIP was called CFA (sometimes idiopathic). In 1980, Turner-Warwick discussed CFA with underlying pathologic patterns of DIP or UIP (end-stage fibrosis) depending on the stage and severity of the clinical CFA.[16]

With increasing use of chest computed tomography (CT) scans in the 1990s, the modern differentiation between IPF and other idiopathic interstitial pneumonias (IIPs) was further refined. In 1997, Müller and Colby published the first radiological-histological classification of IIPs and proposed radiological criteria for UIP, acute interstitial pneumonia (AIP), DIP, nonspecific interstitial pneumonia (NSIP), and BOOP/ cryptogenic organising pneumonia (COP).[17] The pathologists, Katzenstein and Myers, described the 1998 criteria for the pathologic classification of AIP, UIP, DIP/ respiratory bronchiolitis-ILD, and NSIP,[18] which led to the definition of IPF and its discrimination from other IIPs in the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2000 consensus statement.[19] The 2002 ATS/ERS multidisciplinary consensus classification of IIPs discriminated IIPs from diffuse parenchymal lung diseases of known cause and granulomatous ILDs. In addition, a diagnostic algorithm and sets of radiological and pathologic classification criteria were proposed.[20] The 2011 ATS/ERS/JRS/ALAT statement on IPF diagnosis allowed for a confident IPF diagnosis without surgical lung biopsy if a definite radiological UIP pattern was present.[21] Seven years later, the 2018 ATS/ERS/JRS/ALAT Clinical Practice Guideline further specified the radiological patterns as UIP, probable UIP, indeterminate for UIP, and alternate diagnosis.[2] At the same time the Fleischner Society published similar diagnostic criteria for IPF and further strengthened the role of CT by allowing a clinical-radiological IPF diagnosis in cases with a probable radiological UIP pattern (**Table 1**).[22]

Hypersensitivity Pneumonitis

In 1713, Ramazzini described grain workers in Italy who frequently developed dyspnea, cachexia, and finally edema attributed to right heart failure. Ramazzini also wrote what is thought to be the first book on occupational medicine (De Morbis Artificum Diatriba [Diseases of Workers]) wherein he described health hazard associated with different occupations.

Not until the 1930s was "farmers lung" mentioned again in more detail: Campbell reported an acute respiratory disease in North English farmers working with mouldy hay. Workers had developed severe dyspnea and cyanosis that persisted for several weeks with development of fibrosis in some cases.[23] At the same time Towey described severe dyspnea, cough, night sweats, and weight loss in railroad workers near Lake Michigan. The patients were all exposed to "black dust" on maple bark from which fungus spores were isolated (*Cryptostroma corticale*). Towey and colleagues conducted a variety of animal and human experiments with the putative antigen and concluded that the railroad workers had

Table 1
Landmark papers and guidelines for interstitial lung disease classification

Classifications and Guidelines	IIP—ILD	IPF
Historical	Liebow & Carrington 1968/69[15] Katzenstein 1998[18] Müller & Colby 1997[17]	ATS/ERS Consensus 2000 (diagnosis and treatment)[19]
Previous	*ATS/ERS 2002 (classification)*[20]	ATS/ERS/JRS/ALAT 2011[21]
Current	*Update ATS/ERS 2013*[1] *Hypersensitivity Pneumonitis ATS/JRS/ALAT 2020 (diagnosis)*[25]	*ATS/ERS/JRS/ALAT 2018 Clinical Practice Guideline*[2] *Fleischner 2018*[22]

Abbreviations: ALAT, Latin American Thoracic Association ATS; American Thoracic Society; ERS, European Respiratory Society; ILD, interstitial lung disease; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society.

developed an immunologic disease with sensitization to proteins and foreign body reaction to the fungal spores.[24]

Today, hypersensitivity pneumonitis (HP) is considered an immune-mediated inflammatory and fibrotic reaction of the lung to an inhaled antigen in sensitized individuals. Potentially inciting antigens are usually organic, including avian and microbial antigens; however, in up to half of cases at ILD referral centers, the antigen cannot be identified.[25] Traditionally, acute, subacute, and chronic forms of HP have been distinguished, depending on the duration, frequency, and intensity of the exposure.[26] Because of the challenging differentiation of these forms, it had also been suggested to classify HP as active or residual disease for clinical purposes.[27] The most recently published clinical practice guideline categorizes HP into nonfibrotic and fibrotic phenotypes, deeming this classification more objective and clinically relevant (see **Table 1**).[25]

Organizing Pneumonia

In the early twentieth century, autopsy descriptions of patients deceased from nonresolving pneumonia emerged. Intraalveolar exudates with proliferation of fibroblasts and production of connective tissue described in cases of congestion and hepatization, the classic Laennec stages of pneumonia, were not followed by resolution. Von Hansemann described "Lymphangitis reticularis" in 1915 as a morphologic pattern that destroyed the lung progressively after tuberculosis but could also develop without previous infectious disease.[28]

The perception that organizing pneumonia (OP) was always a sequela of pulmonary infection has changed to the current understanding, suggesting that OP may arise due to a variety of toxic or autoimmune triggers, or can be idiopathic. In 1986, Basset reported on intraluminal organizing and fibrotic changes occurring in a variety of ILDs, including pneumoconiosis, sarcoidosis, and hypersensitivity pneumonitis.[29] Around the same time, Davidson introduced the term "cryptogenic organising pneumonia,"[30] and Epler introduced "idiopathic bronchiolitis obliterans with organising pneumonia" (BOOP).[31]

Katzenstein and Myer did not include BOOP in their pathologic classification of *idiopathic interstitial pneumonias* (1998) because of its mainly intraluminal and not interstitial fibrosis.[18] In 2002 the ATS/ERS IIP Consensus Classification suggested using the term "cryptogenic organizing pneumonia" (COP) to avoid confusing BOOP with airways diseases, for example, bronchiolitis obliterans.[19] Currently, in the 2013 updated IIP classification guideline, COP is listed as 1 of the 6 major IIPs (see **Table 1**).[1]

Recent Developments

Combined pulmonary fibrosis and emphysema was proposed as a distinct clinical entity in 2005.[32] The combination of upper lobe emphysema and lower lobe fibrosis typically occurs in current or former smokers. Patients frequently have preserved lung volumes but severely reduced diffusion capacity for carbon monoxide and hypoxemia. The prevalence of pulmonary hypertension is estimated at 50% in this population and is an important clinical feature, as it is also prognostic.

Around 12% of patients with ILD remain unclassifiable despite the modern approach to ILD diagnosis and classification.[33] Phenotyping these patients might facilitate management decisions, and phenotyping according to specific clinical features and/or according to disease behavior is

becoming increasingly popular. Occasionally ILD is the first manifestation of a connective tissue disease (CTD). Terminology for these cases has been inconsistent including "forme fruste" CTD, lung-dominant CTD, and more recently interstitial pneumonia with autoimmune features (IPAF).[34,35] In 2015 ATS and ERS released a research statement for the IPAF concept to facilitate future research in this area. Patients with an unclassifiable ILD who did not fulfill criteria for a CTD but demonstrate clinical, serologic, and morphologic signs of autoimmunity were labeled IPAF.[34] Currently, the therapeutic implications of the IPAF phenotype are still unclear.

The approach to classifying fibrotic ILD according to disease behavior has culminated in large clinical trials investigating the safety and efficacy of antifibrotic medications in patients with progressive fibrosing ILD. A recent placebo controlled study of nintedanib included progressive ILDs of different etiologic subtypes,[36] and a study of pirfenidone recently focused on patients with unclassifiable ILD with a progressive disease behavior.[37] Lumping patients with distinct ILDs is appealing, given their frequently overlapping clinical and morphologic characteristics and the potential management implications that have been demonstrated by recent clinical trials. However, we learned from past that a detailed characterization of patients with ILD can enable the development of targeted therapies. Currently, classification according to cause and disease behavior is complementary and should not compromise a thorough, multidisciplinary ILD diagnosis.

PATHOGENESIS

In 1965, Meyer and Liebow discussed the pathogenetic mechanisms leading to honeycombing in patients with chronic interstitial pneumonia. Because of their observation that some patients had honeycombing and lung cancer, they suspected a connection between honeycombing, atypical cells, and "scar cancers." Furthermore, they stated that "Interstitial pneumonia can result from damage by a great variety of agents, of which only a few are known." Viruses; chemical exposures; collagen diseases, for example, rheumatoid arthritis; and genetic factors (familial pulmonary fibrosis) were suspected to cause honeycombing and chronic interstitial pneumonia.[38]

In the 1970s and 1980s, the accepted framework of IPF pathogenesis was of a chronic inflammatory alveolitis caused by repetitive harmful stimuli. Therapeutic efforts were aimed at stopping the inflammatory process in the hopes of preventing irreversible fibrosis.[39] Unfortunately, long-term treatment with corticosteroids did not usually prevent the hypothesized progression from inflammation to fibrosis.

Later, the hypothesis of fibrosis as a result of abnormal wound healing emerged. Fibrosis was interpreted as a result of activated macrophages that produce growth factors, which in turn stimulate fibroblasts to produce extracellular matrix.[40]

The theory of impaired restoration of alveolar epithelial cells after repetitive lung injury leading to fibrosis[41] was supported by electron microscopy studies that emphasized the role of epithelial cells in the pathogenesis of pulmonary fibrosis.[42] After 2000, UIP was recognized as a distinct pathologic entity and not only a common final pathway of inflammatory ILDs. The paradigm changed from a model of inflammation leading to fibrosis to a model of repetitive alveolar epithelial injury and abnormal wound healing with predominant fibrosis and minimal inflammation.[43]

EPIDEMIOLOGY

There has been an increase in reporting of ILD overall, as well as IPF over the second half of the twentieth century. Aside from changes in the diagnostic guidelines, and the availability of high-resolution CT scans, this also coincides with increased cigarette smoking, an established risk factor for IPF.[44] However, unlike in lung cancer and COPD it is less clear if increasing IPF prevalence developed as a direct consequence of the smoking epidemic.[45] More likely, an interaction between smoking, genetic predisposition, age, and male sex underlies the increasing prevalence of IPF.[46] In 1994 in Bernalillo County (New Mexico, half a million inhabitants), Coultas recorded all new cases of ILD over 2 years and estimated an incidence and prevalence of 31.5/100,000/y and 80.9/100,000 in men and 26.1/100,000/y and 67.2/100,000 in women, respectively.[47] Between 1991 and 2003, the incidence of IPF increased by 11% annually in the United Kingdom,[48] reflecting the increasing overall burden of IPF.

DIAGNOSIS

Clinical examination of patients with pulmonary fibrosis has always been considered important, but pathognomonic signs of the specific ILDs are lacking. In 1816 Laennec invented the stethoscope and correlated the auscultation sounds with autopsy findings. He described the fine crackles and velcro rales, which are still valuable clinical clues for advanced ILDs. In 1945 Eder described clubbing of the fingers and toes as a clinical sign of IPF.

In 1895, Röntgen discovered radiography and later received the first Nobel Prize in physics for this invention. Röntgen techniques were quickly adopted, and after World War II radiography became widely available. In 1933, Kerley described a thickening of the pulmonary septa, sometimes observed in ILD.[49] Scadding proposed a radiographic staging of sarcoidosis and demonstrated that the 4 stages were predictive of survival in patients with sarcoidosis.[50] MRI was used commercially from 1979 but did not contribute significantly to the diagnosis of ILDs. Similarly, gallium scans were used to detect "active alveolitis" and stage IPF/CFA, HP, and sarcoidosis between 1980 and 1990[51,52] but were not used widely after this period. Only the discovery of CT paved the way for modern ILD diagnosis and classification. After the discoveries of Hounsfield, the first CT scans were used on patients in the 1970s. The Fleischner Society proposed a first glossary of terms for CT of the lungs in 1984 and defined the radiological criteria for honeycombing.[53] The glossary was updated in 1996[54] and in 2008 when honeycombing was listed as a key criterion for radiological UIP.[55] In the latest expert opinion of the Fleischner Society, the role of CT imaging was further strengthened by allowing for a confident IPF diagnosis in cases with a definite or probable UIP pattern, when clinical features were compatible with IPF but surgical lung biopsy was not available.[22]

Flexible bronchoscopy was introduced in clinical practice from 1968, and bronchoalveolar lavage (BAL) fluid has been used as both a research tool and in clinical practice for various ILDs.[56] Today, BAL is a very safe procedure and BAL cellular analysis can provide valuable data for ILD diagnosis. Furthermore, BAL can be helpful to exclude infections or detect malignancy in patients with suspected ILD.[25,57] The first transbronchial lung biopsies (TBB) were performed by Anderson and colleagues in 1972.[58] Today, histologic samples from TBB are frequently performed if sarcoidosis is suspected, whereas their diagnostic value is limited for other ILDs.[1]

Transbronchial lung cryobiopsy has emerged as a new diagnostic tool for ILD over the last 10 years,[59] with higher diagnostic yield but also higher complication rate compared with conventional TBB.[60] Transbronchial lung cryobiopsy might replace surgical lung biopsy in some scenarios, and the technique continues to be used and studied in clinical practice.[61,62]

The current pathologic sampling standard for ILD diagnosis is surgical lung biopsy, which has been performed for this purpose since 1952, when Rubin performed a thoracotomy in a patient with suspected pulmonary fibrosis.[63] In 1964, Gaensler reported on 105 patients after surgical lung biopsy for suspected Hamman-Rich syndrome, concluding that the procedure can be performed safely in this population.[64] Today the 30-day mortality after elective surgical lung biopsy is estimated to be 2%, with significantly higher risk of death in nonelective procedures and high-risk patients.[65]

Multidisciplinary cancer conferences have long been an integral component of cancer care.[66] For ILD, multidisciplinary team (MDT) discussions have emerged as the diagnostic reference standard over the last few decades. The 2002 ATS/ERS consensus paper recommended a clinico–radiological–pathological case discussion for patients with unclassifiable ILD,[19] and the 2013 update proposed that MDT discussion should replace histologic diagnosis as the reference standard for ILD diagnosis.[1] Walsh and colleagues then demonstrated in 2016 an improved diagnostic accuracy with the integration of an MDT in the diagnostic process.[67] Current MDTs consist of experienced ILD physicians, thoracic radiologists, pathologists, and occasionally thoracic surgeons or rheumatologists. All available clinical, radiological, and pathologic information are synthesized in a structured manner. Ideally the patient's history (including exposures and occupation), symptoms, and clinical signs and results from pulmonary function and physical performance tests including oxygenation, echocardiography, and serologic tests for CTD should be available. Furthermore, high-quality chest CT scans with inspiratory and expiratory images, and if available results from BAL, and histologic sampling are discussed.

MANAGEMENT

Nonpharmacological Treatment

One of the earliest treatments for chronic postinfectious pulmonary fibrosis was "collapse therapy," which was used from 1930s for the treatment of tuberculosis. By artificial pneumothorax, phrenic paralysis, or thoracoplasty the lung was "set at rest to heal."[68]

In 1963 Hardy successfully completed the first human lung transplant in a patient with lung cancer.[69] However, only the introduction of potent immunosuppressive drugs along with improved surgical techniques led to long-term survival of patients after lung transplant. One of the first long-term survivors after single-lung transplant in 1986 was a man with pulmonary fibrosis.[70] Implementation of the lung allocation score in 2005, ex-vivo lung perfusion, and extracorporeal membrane

oxygenation as a bridge to transplant have further advanced the potential of lung transplantation.[71] Today, IPF is the leading indication for lung transplant in many countries; however, given the high number of comorbidities and typically advanced age of patients with IPF, lung transplant remains a treatment option that is only available to a minority of the patients.

Supplemental oxygen has been used to improve oxygenation and relieve dyspnea since 1926 when Barach demonstrated its application in a patient with pneumonia.[72] He later introduced portable oxygen systems for patients with emphysema.[72] Today, long-term oxygen therapy is well established for hypoxemic patients with chronic lung diseases, and at least some patients with fibrotic ILD experience an improvement in health-related quality of life by using ambulatory supplemental oxygen therapy.[73]

Ramazzini, the founder of occupational medicine, already warned in the seventeenth century that "sitting can lead to an early death," and "sedentary workers" were on the list of occupations with particular hazards. However, until the middle of the twentieth century patients with pulmonary diseases were advised to avoid physical activity as a mean to manage dyspnea. In 1969 a group from Denver demonstrated that patients with COPD improved their exercise tolerance and well being by participation in a comprehensive, multidisciplinary outpatient program.[74] A few years later the term "pulmonary rehabilitation" was defined by the American College of Chest Physicians and in 1981 the first ATS statement on pulmonary rehabilitation was published.[75] Patients with IPF and other ILDs benefit from pulmonary rehabilitation in terms of exercise performance and health-related quality of life,[76] and today pulmonary rehabilitation is recommended for the management of IPF.[21]

Pharmacologic Treatment

Since the 1940s corticosteroids have been used with the goal of preventing the progression of inflammation to irreversible fibrosis. Several case studies from the 1960s report improvement after initiation and worsening after stopping corticosteroids. These patients likely included cases with NSIP and CTD-associated ILD, fibrotic HP, and organizing pneumonia. In 1959 Rubin and Lubliner reported that only a minority of the patients treated with corticosteroids for Hamman Rich Syndrome improved after 1 year.[9] Similarly, in a case series from 1962 only 2 of 9 patients with "interstitial pulmonary fibrosis" had a slight subjective improvement, whereas the others did not respond to corticosteroid treatment.[77]

In the 1980s phenotypes of pulmonary fibrosis were identified that responded well or did not respond to corticosteroids. Carrington found that 50% and 14% of patients with DIP and UIP on pathology responded to corticosteroids, respectively.[78] Furthermore, patients with higher cellularity on biopsy were found to have better clinical responses to corticosteroids.[79] The notion at that time was that highly cellular DIP represented early CFA and needed to be treated with corticosteroids and immunosuppression.[80] A randomized controlled trial in 1991 concluded that azathioprine combined with prednisone was likely more efficacious than prednisone alone for the treatment of IPF.[81] It was thought, however, that the 27 patients included in that trial represented a mixture of NSIP, COP, and CTD-associated ILDs. Following these studies, the 2000 ATS/ERS consensus group suggested treating patients with IPF with corticosteroids and cytotoxic agents such as azathioprine or cyclophosphamide.[19]

In the early 2000s the exploration of therapies against antifibrotic processes improved the knowledge on the natural history of IPF substantially but did not produce therapeutic success. None of the randomized controlled trials were able to demonstrate efficacy of the investigated drugs including interferons beta/gamma, etanercept, imatinib, and endothelin receptor antagonists. Subsequently, the 2011 ATS/ERS/JRS/ALAT statement no longer recommended any specific therapy for IPF, acknowledging the lack of evidence at that time.[21] Shortly after, the National Institutes of Health–sponsored PANTHER trial completely changed the approach to IPF treatment by demonstrating detrimental effects of combined N-acetylcysteine, azathioprine, and prednisone for patients with IPF.[81]

In the meantime, the role of immunosuppression for the treatment of non-IPF ILDs was further clarified by the Scleroderma Lung Studies. The Scleroderma Lung Study I in 2006 and II in 2016 established cyclophosphamide and mycophenolate mofetil as treatment options for systemic sclerosis–associated ILD.[82,83]

Antifibrotic treatment had already been investigated in 1999, when Raghu reported stabilization of pulmonary function in 29 of 46 patients treated with the antifibrotic, pirfenidone.[84] In 2014, 3 large, randomized-controlled placebo-controlled trials demonstrated a slowed decline in forced vital capacity in patients with IPF treated with either pirfenidone or nintedanib compared with a placebo group.[3–5] Following these trials pirfenidone and nintedanib are now approved for the treatment of

IPF. In addition, Nintedanib has recently been approved by Food and Drug Administration and European Medicine Agencies for the treatment of systemic sclerosis–associated ILD and for progressive fibrosing ILD following the SENSCIS and INBUILD trials.[36,85]

SUMMARY

Historically, we have seen recurring challenges concerning the terminology, classification, and staging of the ILDs. Since the Hamman-Rich era, clinicians, radiologists, pathologists, and researchers have used emerging data to untangle the ILDs arising from different causes and with differing prognoses and treatment approaches. Although controversies and challenges persist, tremendous progress has been made over the last decade

CLINICS CARE POINTS

- The understanding of underlying mechanisms of interstitial lung diseases has changed drastically over the last centuries.
- Changing terminology over the past decades has complicated communication and collaborative research, whereas progressively detailed clinical guidelines have been provided.
- Therapeutic successes over the last decade have been substantial.

DISCLOSURE

The authors have no conflicts of interest related to this work.

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