Journal of Advanced Biomedical and Pharmaceutical Sciences

Journal Homepage: http://jabps.journals.ekb.eg

Interstitial lung disease: A review

Hanan Omar[1], Mahmoud A. El-Rehany[2], Amany A. Bekhit[1], Khaled Thabet[1]

[1] Department of Biochemistry, Faculty of Pharmacy, Minia University, Minia, Egypt
[2] Department of Biochemistry, Faculty of Pharmacy, Deraya University, Minia, Egypt

Received: September 11, 2024; revised: October 9, 2024; accepted: November 5, 2024

Abstract

Interstitial lung disease [ILD] is a term used to describe various lung conditions characterized by inflammation and, less commonly, fibrosis. Idiopathic pulmonary fibrosis is one of the most lethal ILDs, exhibiting a broad spectrum of clinical manifestations. Common symptoms of ILD are dyspnea [shortness of breath], coughing, abnormalities in gas exchange, reduced lung volumes, hypoxemia, and, in severe cases, respiratory failure. A preexisting medical condition or environmental variables may set off an ILD. Many ILDs have treatment options or even a cure, depending on the subtypes. Lung transplantation, however, is the sole curative choice in some instances. Evidence shows that common and unusual genetic variants can influence various ILDs.

Keywords

Interstitial lung diseases (ILDs), idiopathic pulmonary fibrosis (IPF), Connective tissue disorders (CTDs), Pulmonary fibrosis (PF), and Rheumatoid arthritis (RA).

1. Introduction

The term "ILD" includes a range of illnesses, with the pulmonary interstitium being the primary site of involvement in most cases but not all [1, 2].

The interstitial space, situated between the capillaries' endothelium and the alveoli's epithelium, comprises lymphatic vessels, fibroblasts, and components of the extracellular matrix. For those who are in good physical condition, it physically supports the alveolus but is just a few micrometers thick. Inflammation or fibrosis in the interstitial space, characteristic of interstitial lung illnesses, inhibits gas exchange, resulting in dyspnea, respiratory failure, or death. Over 200 disorders cause ILD, which ranges from uncommon syndromes like lymphangioleiomyomatosis to widespread multisystem diseases like rheumatoid arthritis [RA] and systemic sclerosis [SSc]; it is prevalent in the UK, constituting 1% of all deaths [3-8].

Several illnesses, such as pulmonary alveolar proteinosis, are mistakenly identified as ILD because they have similar clinical and radiological characteristics [1, 9].

Idiopathic pulmonary fibrosis [IPF], which is the most common kind of fibrotic ILD, has an inferior prognosis. The average life expectancy without treatment is typically 3-5 years following diagnosis [6].

Certain ILDs, particularly those characterized by inflammation, such as non-fibrotic hypersensitivity pneumonitis and select types of sarcoidosis, have a favorable prognosis and robust response to therapy. In the past decade, our understanding of the underlying causes of many ILDs has significantly expanded, leading to significant advancements in treatment and improved clinical results. These therapeutic advancements have changed how we diagnose and treat a particular group of ILDs that may progress to pulmonary fibrosis [PF] [10-13].

2. Classification and epidemiology of ILD

ILDs can be categorized into three main groups:
a] disorders linked to other systemic diseases, including connective tissue diseases [CTDs],
b] disorders induced by environmental exposures, such as hypersensitivity pneumonitis [HP], and c] disorders of unknown origin or etiological context, with IPF being the most prevalent type [14], as shown in Figure 1.

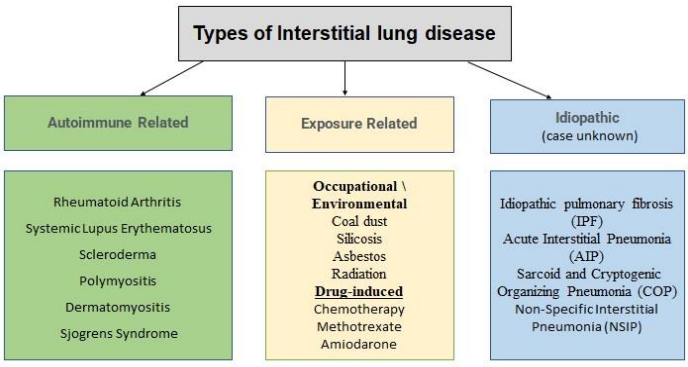

Figure 1. Schematic representation of types of interstitial lung disease.

Clinical assessments seek to determine a potential cause by looking for signs of a systemic illness [such as CTDs] or environmental causes that include pneumotoxic drug exposures, radiation therapy, occupational exposures, and allergens [15, 16]. Multiple studies indicate that the worldwide incidence of ILDs is accelerated; however, rates vary enormously across different geographical regions [17].

**** Correspondence:*** *Hanan Omar*
Tel.: *+ 01065657379*
Email Address: *hananeldawy3@gmail.com*

A. Autoimmune diseases

Connective Tissue Disease-associated Interstitial Lung Disease [CTD-ILD] is a condition affecting 30% of newly recognized cases of interstitial lung diseases. It affects multiple lung regions, making it common in rheumatologic conditions like scleroderma, systemic lupus erythematosus [SLE], and rheumatoid arthritis [RA] [18, 19].

B. Exposure Related Lung disease:

B.1. Occupational/ Environmental

Inhaled lung disease [ILD] is a prevalent respiratory condition linked to occupational exposures, including coal worker's pneumoconiosis, asbestosis, and silicosis are three common occupational diseases caused by coal dust, silicosis, and asbestos. The accumulation of harmful particles in the lungs is the root cause, with individual predisposition and immunological sensitization determining the occurrence [20].

B.2. Drug-induced ILDs

Drug-induced lung disease [DILD] is a serious lung condition characterized by symptoms ranging from benign infiltrates to potentially lethal acute respiratory distress syndrome. It develops through two main pathways: direct toxicity, influenced by drug dosage, and immune-mediated toxicity; these pathways are likely interconnected. Cytotoxic lung damage can occur due to direct trauma to pneumocytes or alveolar capillary endothelium [21]. Treatment includes antibiotics, chemotherapeutic medicines, immunosuppressive treatments, and antiarrhythmic drugs (Amiodarone)[22].

C. Idiopathic diseases

Chronic, progressive interstitial pneumonia with an enigmatic cause is known as idiopathic pulmonary disease. These most commonly include idiopathic pulmonary fibrosis [IPF], Acute Interstitial Pneumonia [AIP], and Sarcoid and Cryptogenic Organizing Pneumonia [COP]. Due to both intrinsic and extrinsic risk factors, patients with a genetic predisposition may be more likely to develop a mix of inflammation and fibrosis [23]. Histopathological characteristics allow for the differentiation of these groups, which also exhibit discrete clinical symptoms [24].

Epidemiologic studies are needed to accurately describe the frequency and geographic distribution of different subgroups of interstitial lung disease in developing nations. Additionally, there is a lack of recorded data in some areas. According to many studies, the occurrence of ILDs varied from 6.3 to 71 cases per 100,000 individuals, whereas the rate of new cases ranged from 1 to 31.5 per 100,000 person-years [25].

The frequency of ILDs varies significantly with age, gender, ethnicity, and geographical location. IPF incidence rates vary from 0-93 instances per 100,000 persons in Europe and North America to 35-130 cases per 100,000 people in Asia and South America. It is related to old age and masculine gender [26-28].

Middle-aged and older women account for more than half of all instances of idiopathic nonspecific interstitial pneumonia [IP] and CTD-associated ILD [29-31].

However, interpreting epidemiological data is difficult owing to limitations in illness coding, research techniques, and healthcare availability [32].

3. Pathogenesis

Lungs with a 75 m2 alveolar surface are susceptible to internal organ exposure, with an average adult breathing 8,000 liters daily. The air contains microscopic particles, including contaminants, pathogens, and free radicals, which can harm the alveolar epithelial structure. The lungs are essential for both inherent and adaptive immune systems, acting as physical barriers to detect pathogens. Interstitial lung disorders can be marked by inflammation, fibrosis, or a combination of these systems [33], as represented in Figure 2.

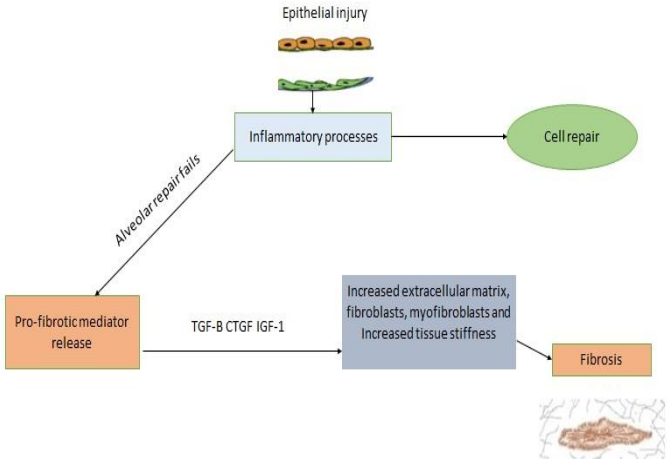

Figure 2. Pathogenesis of fibrotic-ILD.

Inflammation

Several variables may contribute to inflammation in ILD, with inflammatory disease being the most common. In individuals with genetic susceptibility, the abnormal process of citrullination, which involves replacing the amino acid arginine with citrulline, leads to various autoantibodies. RA, the best-recognized autoimmune disease, happens because the adaptive immune system is activated [34, 35].

Prostaglandins, interleukin [IL]-6, tumor necrosis factor [TNF], and other cytokines stimulate stromal cells and specialized macrophages when autoantibodies cause their production. The pathogenesis of ILD in patients with RA is still uncertain due to the lack of clear evidence about the paracrine effects of circulating cytokines and growth factors and the direct destruction of lung cells by antibodies [36].

Other autoimmune diseases, including SSc and idiopathic inflammatory myopathies, have an exact etiology with RA, even though they have different autoantibodies [37].

The presence of particular autoantibodies significantly influences the prevalence and kind of ILD in persons with systemic sclerosis and idiopathic inflammatory myopathies. This indicates that the direct harm caused by antibodies plays a substantial role in the formation of interstitial inflammation. The manifestation of ILD might exhibit many patterns, such as organizing pneumonia, nonspecific interstitial pneumonia, or typical interstitial pneumonia [38].

Granuloma development after an initial event frequently indicates inflammatory ILD[37]. Granulomata are densely packed clumps of macrophages that commonly unite to form giant multinucleated cells [39].

Sarcoidosis is a multisystem illness characterized by non-caseating granulomatous inflammation, with lung involvement in more than 90% of patients. The presence of CD4+ T-helper cells and densely populated regulatory T cells, fibroblasts, and B cells surrounding the distinctive sarcoid granulomas implies that

innate and adaptive immune responses contribute to disease development [40].
Hypersensitivity pneumonitis is distinguished by granulomatous inflammation, which arises from recurrent exposure to several potential antigens. The most common culprits are proteins from birds and fungi. The development of immune complexes mediates the disease's non-fibrotic variant. Cytokines, including IL-12 and IFN-γ, are released by dendritic and alveolar cells in the fibrotic state, which guide T lymphocytes towards a T-helper-1 phenotype and the transportation of antigens [10, 41].

Fibrosis

IPF provides the most accurate perspective on understanding the development of PF. The development of fibrosis in individuals with IPF is driven by three main factors: aging, genetic susceptibility, and a time of severe epithelium damage caused by inhaling hazardous chemicals [42].
Simultaneous occurrence of these events triggers premature senescence in alveolar epithelial stem cells, resulting in an atypical wound-healing response after further epithelial damage [43].
Epithelial senescence occurs when the alveolar epithelium fails to undergo cell division and replenish itself following injury, removing the basement membrane [44].
The activation of several pathways involved in the regular wound-healing process leads to an imbalance between growth factors that promote fibrosis and those that inhibit fibrosis. These growth factors stimulate the unimpeded production of collagen and extracellular matrix by stimulating several cells, such as macrophages, epithelium, fibroblasts, and endothelium [45, 46].
The cumulative effect of these alterations is a gradual disruption of the structural organization of the alveolar airspaces, resulting in a reduction of the surface area available for gas exchange and an atypical restructuring of the pulmonary vessels that encourages the emergence of secondary pulmonary hypertension. Modifications to the extracellular matrix and an increase in lung stiffness accelerate the course of fibrosis. This suggests that, regardless of the initial cause, PF may become self-perpetuating depending on the severity of the ailment [47, 48].
More research is needed on the pathogenic mechanisms that regulate the progression of fibrosis in various fibrotic ILD types. However, the existing data suggests that the downstream mechanisms responsible for fibrogenesis have similarities and may be the same, regardless of whether the source of fibrosis is autoimmune damage to the alveolus or exposure to the environment [2].

4. Role of genetics in interstitial lung diseases

It is recognized that several ILDs have a genetic component and may be inherited within families. Furthermore, many family pedigrees have provided evidence that distinct family members may have varied forms of fibrotic ILD [49].
According to GWAS, several genetic variants have been linked to an increased risk of IPF, which has increased our understanding of the involvement of genetics and epigenetics in the progression of IPF [50-52].
The interaction of these polymorphisms with other environmental risk factors is likely to modulate the disease's natural history, proving the unique genotype-phenotype relationship and suggesting that specific gene variants may direct the clinical outcomes. Patients with SNPs such as those of Toll-like receptor 3 [TLR3] and Toll interacting protein [TOLLIP] have a high mortality rate [53, 54].
Moreover, several novel loci related to IPF have been discovered, including Telomerase reverse transcriptase [TERT], Telomerase RNA component [TERC], and mucin 5B [MUC5B] [51], which was reported recently as a risk factor for RA-ILD [55].
A better knowledge of the genetic risk and its relationship with environmental exposure is required for a] disease treatment and prevention, b] disease diagnosis and early detection of asymptomatic cases, and c] the personalization of therapeutic options based on hereditary risk [50].

5. Clinical presentation and diagnosis

From a clinical perspective, ILDs may manifest in several presentations. The most common symptoms are dyspnea, coughing, and tiredness [56-58]. Before being diagnosed, some patients may have symptoms for an extended period, ranging from several months to even many years [59, 60].
Upon physical examination, it has been shown that 60-79% of persons with interstitial lung disorders have bibasilar Velcro-like crackles [56]. While clubbing is often associated with certain illnesses, it might also indicate the presence of other lung or heart disorders [26, 56].
Extrapulmonary symptoms indicate that interstitial lung disease may be a part of a systemic disorder. If there are early signs of graying, evidence of bone marrow failure, or liver cirrhosis, it is possible to suspect the presence of telomeropathies and familial types of ILD. Abnormalities in the skin, hands, joints, or muscles indicate a connective tissue illness [56].
When assessing individuals with CTD, it is essential to have a strong suspicion of ILD.[61] Incidental discovery of interstitial lung disorders in their first phases might occur during the examination of chest radiographs or CT scans conducted for unrelated purposes [62].
A multifaceted strategy that incorporates clinical, radiological, physiological, and occasionally histological findings is necessary [62].
Confirmation of ILD requires careful clinical history collection and a comprehensive examination, which provide valuable clues towards a diagnosis. Possible external factors that can contribute to ILD include being exposed to organic antigens [such as those from birds or molds] at home or work, taking pneumotoxic medications [such as bleomycin, amiodarone, or nitrofurantoin], or being exposed to dust known to cause pneumoconiosis [such as asbestos, silica, or coal dust] [63].
Although it is rare to see normal lung function or an obstructive pattern, pulmonary function testing frequently reveals a restrictive pattern and decreased diffusion capacity. Detecting serum autoantibodies can help identify the presence of underlying CTD [64, 65].
It is essential to highlight that specific serological autoantibodies are associated with the development and clinical advancement of ILDs in people with CTD [65].
ILD may be identified using a chest X-ray. However, small changes may not be easily observed. A high-resolution CT [HRCT] of the thorax is a diagnostic test for individuals with suspected ILD. The HRCT pattern, when paired with clinical symptoms, is insufficient to establish a diagnosis in over two-thirds of individuals with ILD [65].
When some non-idiopathic pulmonary fibrosis ILD is identified, analyzing the cells in the bronchoalveolar lavage fluid might provide helpful information. Lymphocytosis on bronchoalveolar

lavage is a notable feature of hypersensitivity pneumonitis [10, 66].
Eosinophilic pneumonia or drug-induced lung injury may be diagnosed by identifying the presence of eosinophils during bronchoalveolar lavage [66].
Additional bronchoalveolar lavage observations, such as pulmonary alveolar proteinosis or Langerhans cell histiocytosis, may assist in accurately diagnosing and excluding infections and malignancies [66].
Patients without a precise diagnosis supported by clinical, radiographic, and bronchoscopic evidence should undergo histopathological investigation following a multidisciplinary discussion [67].
Surgical lung biopsy, performed by video-assisted thoracic surgery, is considered the definitive method for assessing the histological features of ILD [68].
The therapy has a notable risk of postoperative complications, with a mortality rate of 1.5-2.4% within 30 days after the procedure [69, 70].
Consequently, surgical lung biopsy may only sometimes be required for patients; evaluating the pros and cons of obtaining tissue samples for histological investigation with the patient and in a multidisciplinary conversation is essential [71-73].
It is important to note that a biopsy alone is not considered the most reliable method for diagnosis. Instead, due to the similarities in histopathological lesions in different ILDs, it should be part of a comprehensive evaluation that includes other disciplines [74].
Evaluating the gravity of a disease is crucial for forecasting the result and establishing a suitable treatment strategy after diagnosis. People with ILD encounter several comorbidities inside or outside the lungs, which impact their clinical progress and overall quality of life. The most common coexisting medical conditions include pulmonary hypertension, lung cancer, gastroesophageal reflux disease [GERD], obstructive sleep apnea, and cardiovascular disease [75].
Echocardiography and specialized questionnaires can aid in the prompt detection of pulmonary hypertension, GERD, and obstructive sleep apnea. Although there are presently no defined protocols for screening and treating these additional health issues in persons with ILD, early detection of these disorders might influence the course and overall survival of the disease [76].

6. Screening for ILD

There are currently no guidelines for screening individuals at a higher risk for developing ILD; due to the significant occurrence of ILD in people with systemic sclerosis, HRCT screening is recommended [77].
There has yet to be a consensus about the optimal timing or specific tests for screening individuals with various CTDs. However, clinicians must be vigilant in assessing these patients for ILD [61].
To determine if ILD should be further evaluated, it is advisable to regularly inquire about symptoms such as shortness of breath, cough, and activity restriction. Additionally, completing a chest examination to detect crepitations may help guide the choice to have HRCT and pulmonary function tests. Individuals with congenital interstitial lung disease typically have their first-degree relatives referred for genetic counseling and possible screening [78-80].

Drug-induced pulmonary damage is associated with an increasing range of therapeutic drugs, such as chemotherapy, immune checkpoint inhibitors, and biological agents. The prior presence of ILD has been shown to amplify pulmonary toxicity, so it is recommended to do an imaging screening for ILD before prescribing drugs that are highly likely to induce it [81-83].

7. Management and treatment

The treatment for ILDs is based on the diagnosis due to the diverse pathogenic pathways involved. The principal therapeutic approach for a recognized etiology, such as exposure to environmental toxins or pharmaceuticals, is to remove the factors instigating the ailment; if the disease is caused by an autoimmune condition, glucocorticoids, and immunosuppressive medicines are used to control inflammation, which leads to increasing fibrosis [84].
Antifibrotic medicines have traditionally been used in patients with IPF. Moreover, recent clinical trials have suggested that antifibrotic therapy has a preferable treatment response in a diverse set of fibrotic ILDs other than IPF [16].
FDA approved two antifibrotic drugs, nintedanib and pirfenidone, in 2014 to treat IPF in the United States. In 2020, nintedanib was also approved for the treatment of all progressive fibrosing ILD [85].
However, those drugs do not provide a full cure and have some side effects. Current treatments can slow the rate of functional decline in the lungs, but they cannot halt the accumulation of scar tissue. As a result, the demand for novel medicines remains immense [86].
Lung transplantation is ultimately a potential life-extending therapy option in cases of advanced and/or progressive fibrotic ILD, especially for IPF and CTD-ILD patients. IPF has now become the most common reason for lung transplantation around the world [87].
Yet, only a small percentage of patients with end-stage ILD meet the wait list criteria and can receive a successful lung transplant, as well as a huge financial burden [88].

Conclusion

ILD is an intricate syndrome marked by the existence of PF, a condition that may result in heightened morbidity and death. Despite the diversity of ILDs, interdisciplinary discussions and treatment approaches are crucial. Antifibrotic medication and immunomodulatory medications are essential in treating this condition. Future research should focus on developing novel treatments, symptom-focused therapy, biomarker-guided care, and home-based disease monitoring.

Funding

This review has no funding.

References

[1].Travis WD, Costabel U, Hansell DM, King Jr TE, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. American journal of respiratory and critical care medicine. 2013;188[6]:733-48.
[2].Wijsenbeek M, Cottin V. Spectrum of fibrotic lung diseases. New England Journal of Medicine. 2020;383[10]:958-68.
[3].Wang Q, Luo M, Xiang B, Chen S, Ji Y. The efficacy and safety of pharmacological treatments for lymphangioleiomyomatosis. Respiratory Research. 2020;21[1]:1-12.
[4].Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, risk factors, and biomarkers in systemic sclerosis with interstitial lung disease. American journal of respiratory and critical care medicine. 2020;201[6]:650-60.

[5].McDermott GC, Doyle TJ, Sparks JA. Interstitial lung disease throughout the rheumatoid arthritis disease course. Current opinion in rheumatology. 2021;33[3]:284.
[6].Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. New England Journal of Medicine. 2018;378[19]:1811-23.
[7].Navaratnam V, Hubbard RB. The mortality burden of idiopathic pulmonary fibrosis in the United Kingdom. American journal of respiratory and critical care medicine. 2019;200[2]:256-8.
[8].Appleby J. UK deaths in 2020: how do they compare with previous years? bmj. 2021;373.
[9].Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nature Reviews Disease Primers. 2019;5[1]:16.
[10].Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. American journal of respiratory and critical care medicine. 2020;202[3]:e36-e69.
[11].Sweiss NJ, Korsten P, Syed HJ, Syed A, Baughman RP, Yee AM, et al. When the game changes: guidance to adjust sarcoidosis management during the coronavirus disease 2019 pandemic. Chest. 2020;158[3]:892-5.
[12].Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman R, Wells A. Pulmonary sarcoidosis. Lancet Respir Med. Journal Article. 2018:389-402.
[13].Costabel U, Miyazaki Y, Pardo A, Koschel D, Bonella F, Spagnolo P, et al. Hypersensitivity pneumonitis. Nature Reviews Disease Primers. 2020;6[1]:65.
[14].Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183[6]:788-824.
[15].Wytrychowski K, Hans-Wytrychowska A, Piesiak P, Majewska-Pulsakowska M, Rożek-Piechura K. Pulmonary rehabilitation in interstitial lung diseases: A review of the literature. Advances in clinical and experimental medicine : official organ Wroclaw Medical University. 2020;29[2]:257-64.
[16].Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. 2020;21[1]:32.
[17].Tinelli C, De Silvestri A, Richeldi L, Oggionni T. The Italian register for diffuse infiltrative lung disorders [RIPID]: a four-year report. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22 Suppl 1:S4-8.
[18].Mira-Avendano I, Abril A, Burger CD, Dellaripa PF, Fischer A, Gotway MB, et al. Interstitial Lung Disease and Other Pulmonary Manifestations in Connective Tissue Diseases. Mayo Clinic proceedings. 2019;94[2]:309-25.
[19].Kalchiem-Dekel O, Galvin JR, Burke AP, Atamas SP, Todd NW. Interstitial Lung Disease and Pulmonary Fibrosis: A Practical Approach for General Medicine Physicians with Focus on the Medical History. Journal of clinical medicine. 2018;7[12].
[20].Litow FK, Petsonk EL, Bohnker BK, Brodkin CA, Cowl CT, Guidotti TL, et al. Occupational Interstitial Lung Diseases. J Occup Environ Med. 2015;57[11]:1250-4.
[21].Matsuno O. Drug-induced interstitial lung disease: mechanisms and best diagnostic approaches. Respir Res. 2012;13[1]:39.
[22].Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. The open respiratory medicine journal. 2012;6:63-74.
[23].Capron F. [New classification of interstitial lung disease]. Revue de pneumologie clinique. 2005;61[3]:133-40.
[24].Antoine M, Mlika M. Interstitial Lung Disease. StatPearls. Treasure Island [FL]: StatPearls Publishing
Copyright © 2020, StatPearls Publishing LLC.; 2020.
[25].Kaul B, Cottin V, Collard HR, Valenzuela C. Variability in Global Prevalence of Interstitial Lung Disease. Frontiers in medicine. 2021;8:751181.
[26].Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. American journal of respiratory and critical care medicine. 2014;190[7]:773-9.
[27].Duchemann B, Annesi-Maesano I, de Naurois CJ, Sanyal S, Brillet P-Y, Brauner M, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. European Respiratory Journal. 2017;50[2].
[28].Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. Respiratory research. 2021;22[1]:1-10.
[29].Belloli EA, Beckford R, Hadley R, Flaherty KR. Idiopathic non-specific interstitial pneumonia. Respirology. 2016;21[2]:259-68.
[30].Raimundo K, Solomon JJ, Olson AL, Kong AM, Cole AL, Fischer A, et al. Rheumatoid arthritis–interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. The Journal of rheumatology. 2019;46[4]:360-9.
[31].Li Q, Wallace L, Patnaik P, Alves M, Gahlemann M, Kohlbrenner V, et al. Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study. Rheumatology. 2021;60[4]:1915-25.
[32].Olson AL, Patnaik P, Hartmann N, Bohn RL, Garry EM, Wallace L. Prevalence and incidence of chronic fibrosing interstitial lung diseases with a progressive phenotype in the United States estimated in a large claims database analysis. Advances in Therapy. 2021;38[7]:4100-14.
[33].Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. The Lancet. 2022;400[10354]:769-86.
[34].Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nature Reviews Rheumatology. 2021;17[1]:17-33.
[35].Zaiss MM, Joyce Wu H-J, Mauro D, Schett G, Ciccia F. The gut–joint axis in rheumatoid arthritis. Nature Reviews Rheumatology. 2021;17[4]:224-37.
[36].Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. European Respiratory Review. 2021;30[160].
[37].Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD open. 2015;1[1]:e000097.
[38].Lega J-C, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. European Respiratory Review. 2015;24[136]:216-38.
[39].Tsiakos K, Zoupas I, Chatzis L, Vamvakaris I, Poulakou G, Syrigos K, editors. Primary Sarcoidosis of the Adipose Tissue: A New Variant of Sarcoidosis. Mayo Clinic Proceedings; 2022: Elsevier.
[40].Lee S, Birnie D, Dwivedi G. Current perspectives on the immunopathogenesis of sarcoidosis. Respiratory Medicine. 2020;173:106161.
[41].Vasakova M, Selman M, Morell F, Sterclova M, Molina-Molina M, Raghu G. Hypersensitivity pneumonitis: current concepts of pathogenesis and potential targets for treatment. American Journal of Respiratory and Critical Care Medicine. 2019;200[3]:301-8.
[42].Daccord C, Maher TM. Recent advances in understanding idiopathic pulmonary fibrosis. F1000Research. 2016;5.
[43].DePianto DJ, Vander Heiden JA, Morshead KB, Sun K-H, Modrusan Z, Teng G, et al. Molecular mapping of interstitial lung disease reveals a phenotypically distinct senescent basal epithelial cell population. JCI insight. 2021;6[8].
[44].Yao C, Guan X, Carraro G, Parimon T, Liu X, Huang G, et al. Senescence of alveolar type 2 cells drives progressive pulmonary fibrosis. American journal of respiratory and critical care medicine. 2021;203[6]:707-17.
[45].Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. Science advances. 2020;6[28]:eaba1983.
[46].Habermann AC, Gutierrez AJ, Bui LT, Yahn SL, Winters NI, Calvi CL, et al. Single-cell RNA sequencing reveals profibrotic roles of distinct epithelial and mesenchymal lineages in pulmonary fibrosis. Science advances. 2020;6[28]:eaba1972.
[47].Philp CJ, Siebeke I, Clements D, Miller S, Habgood A, John AE, et al. Extracellular matrix cross-linking enhances fibroblast growth and protects against matrix proteolysis in lung fibrosis. American journal of respiratory cell and molecular biology. 2018;58[5]:594-603.
[48].Parker MW, Rossi D, Peterson M, Smith K, Sikström K, White ES, et al. Fibrotic extracellular matrix activates a profibrotic positive feedback loop. The Journal of clinical investigation. 2014;124[4].
[49].Michalski JE, Schwartz DA. Genetic risk factors for idiopathic pulmonary fibrosis: insights into immunopathogenesis. Journal of Inflammation Research. 2021:1305-18.
[50].Mathai SK, Yang IV, Schwarz MI, Schwartz DA. Incorporating genetics into the identification and treatment of Idiopathic Pulmonary Fibrosis. BMC medicine. 2015;13:191.
[51].Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nature genetics. 2013;45[6]:613-20.
[52].Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. The New England journal of medicine. 2011;364[16]:1503-12.
[53].Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. The Lancet Respiratory medicine. 2013;1[4]:309-17.
[54].O'Dwyer DN, Armstrong ME, Trujillo G, Cooke G, Keane MP, Fallon PG, et al. The Toll-like receptor 3 L412F polymorphism and disease progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2013;188[12]:1442-50.
[55].Juge P-A, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. New England Journal of Medicine. 2018;379[23]:2209-19.

[56].Behr J, Prasse A, Wirtz H, Koschel D, Pittrow D, Held M, et al. Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry. European Respiratory Journal. 2020;56[2].

[57].Guenther A, Krauss E, Tello S, Wagner J, Paul B, Kuhn S, et al. The European IPF registry [eurIPFreg]: baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respiratory research. 2018;19[1]:1-10.

[58].Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, et al. Interstitial lung disease in India. Results of a prospective registry. American journal of respiratory and critical care medicine. 2017;195[6]:801-13.

[59].Hewson T, McKeever TM, Gibson JE, Navaratnam V, Hubbard RB, Hutchinson JP. Timing of onset of symptoms in people with idiopathic pulmonary fibrosis. Thorax. 2018;73[7]:683-5.

[60].Spagnolo P, Ryerson CJ, Putman R, Oldham J, Salisbury M, Sverzellati N, et al. Early diagnosis of fibrotic interstitial lung disease: challenges and opportunities. The Lancet Respiratory Medicine. 2021;9[9]:1065-76.

[61].Distler O, Assassi S, Cottin V, Cutolo M, Danoff SK, Denton CP, et al. Predictors of progression in systemic sclerosis patients with interstitial lung disease. European Respiratory Journal. 2020;55[5].

[62].Sverzellati N, Guerci L, Randi G, Calabrò E, La Vecchia C, Marchianò A, et al. Interstitial lung diseases in a lung cancer screening trial. European Respiratory Journal. 2011;38[2]:392-400.

[63].Pérez ERF, Swigris JJ, Forssén AV, Tourin O, Solomon JJ, Huie TJ, et al. Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. Chest. 2013;144[5]:1644-51.

[64].Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, Du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. European Respiratory Journal. 2015;46[4]:976-87.

[65].Suzuki A, Kondoh Y, Fischer A. Recent advances in connective tissue disease related interstitial lung disease. Expert Review of Respiratory Medicine. 2017;11[7]:591-603.

[66].De Oliveira NC, Osaki S, Maloney J, Cornwell RD, Meyer KC. Lung transplant for interstitial lung disease: outcomes for single versus bilateral lung transplantation. Interactive cardiovascular and thoracic surgery. 2012;14[3]:263-7.

[67].Du Rand I, Barber P, Goldring J, Lewis R, Mandal S, Munavvar M, et al. British Thoracic Society guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults. Thorax. 2011;66[Suppl 3]:iii1-iii21.

[68].Sigurdsson MI, Isaksson HJ, Gudmundsson G, Gudbjartsson T. Diagnostic surgical lung biopsies for suspected interstitial lung diseases: a retrospective study. The Annals of thoracic surgery. 2009;88[1]:227-32.

[69].Durheim MT, Kim S, Gulack BC, Burfeind WR, Gaissert HA, Kosinski AS, et al. Mortality and respiratory failure after thoracoscopic lung biopsy for interstitial lung disease. The Annals of Thoracic Surgery. 2017;104[2]:465-70.

[70].Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. European Respiratory Journal. 2016;48[5]:1453-61.

[71].Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis [COLDICE]: a prospective, comparative study. The lancet Respiratory medicine. 2020;8[2]:171-81.

[72].Tomassetti S, Ravaglia C, Wells AU, Cavazza A, Colby TV, Rossi G, et al. Prognostic value of transbronchial lung cryobiopsy for the multidisciplinary diagnosis of idiopathic pulmonary fibrosis: a retrospective validation study. The Lancet Respiratory Medicine. 2020;8[8]:786-94.

[73].Maldonado F, Danoff SK, Wells AU, Colby TV, Ryu JH, Liberman M, et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung diseases: CHEST guideline and expert panel report. Chest. 2020;157[4]:1030-42.

[74].Jo HE, Glaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, et al. Clinical impact of the interstitial lung disease multidisciplinary service. Respirology. 2016;21[8]:1438-44.

[75].Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. European Respiratory Journal. 2015;46[4]:1113-30.

[76].Suzuki A, Kondoh Y. The clinical impact of major comorbidities on idiopathic pulmonary fibrosis. Respiratory Investigation. 2017;55[2]:94-103.

[77].Hoffmann-Vold A-M, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. The Lancet Rheumatology. 2020;2[2]:e71-e83.

[78].Newton CA, Oldham JM, Ley B, Anand V, Adegunsoye A, Liu G, et al. Telomere length and genetic variant associations with interstitial lung disease progression and survival. European Respiratory Journal. 2019;53[4].

[79].Hunninghake GM, Quesada-Arias LD, Carmichael NE, Martinez Manzano JM, Poli De Frías S, Baumgartner MA, et al. Interstitial lung disease in relatives of patients with pulmonary fibrosis. American journal of respiratory and critical care medicine. 2020;201[10]:1240-8.

[80].Adegunsoye A, Vij R, Noth I. Integrating genomics into management of fibrotic interstitial lung disease. Chest. 2019;155[5]:1026-40.

[81].Cadranel J, Canellas A, Matton L, Darrason M, Parrot A, Naccache J-M, et al. Pulmonary complications of immune checkpoint inhibitors in patients with nonsmall cell lung cancer. European Respiratory Review. 2019;28[153].

[82].Skeoch S, Weatherley N, Swift AJ, Oldroyd A, Johns C, Hayton C, et al. Drug-induced interstitial lung disease: a systematic review. Journal of clinical medicine. 2018;7[10]:356.

[83].Roubille C, Haraoui B, editors. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Seminars in arthritis and rheumatism; 2014: Elsevier.

[84].Meyer KC. Diagnosis and management of interstitial lung disease. Transl Respir Med. 2014;2:4.

[85].Wilfong EM, Aggarwal R. Role of antifibrotics in the management of idiopathic inflammatory myopathy associated interstitial lung disease. Therapeutic advances in musculoskeletal disease. 2021;13:1759720x211060907.

[86].Spagnolo P, Bonella F, Ryerson CJ, Tzouvelekis A, Maher TM. Shedding light on developmental drugs for idiopathic pulmonary fibrosis. Expert opinion on investigational drugs. 2020;29[8]:797-808.

[87].Kapnadak SG, Raghu G. Lung transplantation for interstitial lung disease. European respiratory review : an official journal of the European Respiratory Society. 2021;30[161].

[88].Meyer KC. Diagnosis and management of interstitial lung disease. Translational Respiratory Medicine. 2014;2[1]:4.