The interstitial pneumonias ( IPs) are a heterogeneous group of diffuse parenchymal lung diseases characterized by specific clinical, radiologic and pathologic features. While pathologically defined, significant overlap in terms of presentation as well as association with secondary diseases is known and may confound initial work-up and diagnosis. This review focuses on recent changes and additions to definitions and diagnostic criteria with implications for management.

Revised interstitial pneumonia classification

Eight pathologically defined interstitial pneumonias are included in a newly revised classification system, published in the *American Journal of Respiratory and Critical Care Medicine* in 2013 (Table, pages 2-3).

- Usual interstitial pneumonia (UIP)
- Nonspecific interstitial pneumonia (NSIP)
- Cryptogenic organizing pneumonia (COP)
- Desquamative interstitial pneumonia (DIP)
- Respiratory bronchiolitis-interstitial lung disease (RB-ILD)
- Acute interstitial pneumonia (AIP)
- Lymphoid interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

An additional category, “unclassifiable,” has also been added to include interstitial pneumonia not fitting a particular pathologic pattern. PPFE, the newest pathologic subcategory, is rare and highlighted by pleural thickening predominantly in the upper lobes. It is often associated with parenchymal or interstitial findings on CT, most commonly UIP and NSIP (Figure 1). Given the rarity of presenting cases, a confident diagnosis of PPFE is likely best achieved by biopsy as clinical and radiologic presentation alone may be equivocal.

While IPs have been studied and recognized over several decades, the new classification system provides a more intuitive organization of both the prevalence and natural course of specific histologic patterns and their related clinical findings. A first approach is to separate the eight pathologically defined patterns into six major (UIP, NSIP, COP, DIP, RB-ILD, AIP) and two rare or less commonly encountered entities (LIP and PPFE).

Of the six major patterns, a review of their courses and presentations as well as associated clinical findings further leads to three subcategorizations:

- Chronically fibrosing (UIP and NSIP)
- Smoking related (DIP and RB-ILD)
- Acutely presenting (COP and AIP)

This approach may better assist the clinician in terms of recognition and work-up of initially undifferentiated presenting disease. While any of the eight may appear independently as primary or idiopathic disease, many are involved in the progressive lung injury associated with chronic organic or inorganic exposures, drug toxicity, and...
autoimmune disease. A combined approach of not only characterizing the presenting clinical and radiologic features but also seeking a secondary cause is important to diagnosis and subsequent management.

**Interstitial pneumonia with autoimmune features (IPAF)**

Prior studies have suggested differences in survival and clinical course for interstitial lung disease (ILD) with specifically elicited clinical and serologic features of autoimmune disease. While several definitions have been previously proposed, a recent international consensus statement, published in *American Journal of Respiratory and Critical Care Medicine* in 2013, has delineated specific criteria for interstitial pneumonias with incompletely diagnosed but suggestive autoimmune disease, currently described as interstitial pneumonia with autoimmune features (IPAF). Exact criteria involve the confirmation of an interstitial process by radiologic or pathologic presentation, exclusion of other associated causes including defined connective tissue disease and at least two features from three representative clinical domains. These domains include specific autoimmune clinical signs and symptoms, positive findings on any of 12 autoimmune serologies, and morphologic findings of interstitial pneumonia. Remaining morphologic criteria also include nonparenchymal and extrapulmonary features such as evidence of serositis with pleural or pericardial disease, vasculopathy, or intrinsic airway disease.

It is important to note the inclusion of UIP pathology and radiologic patterns despite prior studies assessing the presence of autoimmune serology or clinical symptoms in these patients, noting little difference in their clinical course or survival as compared to those with idiopathic pulmonary fibrosis (Figure 2). Questions remain as to the utility of these disease criteria in clinical practice and implications for long-term management or follow-up. It is unknown

<table>
<thead>
<tr>
<th>Pathology type</th>
<th>Clinical findings</th>
<th>Radiologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual interstitial pneumonia (UIP)</td>
<td>Defining of idiopathic pulmonary fibrosis but also associated with other chronically progressive fibrotic disease — such as connective tissue disease-interstitial lung disease, chronic hypersensitivity pneumonitis and pneumoconioses; portends poorer prognosis in the idiopathic setting when compared to other histology</td>
<td>Dominated by reticular and honeycomb findings; peripheral and bibasilar in distribution</td>
</tr>
<tr>
<td>Nonspecific interstitial pneumonia (NSIP)</td>
<td>Frequently associated with autoimmune disease; portends a better prognosis when compared with UIP; generally responsive to directed anti-inflammatory therapy but may be chronically progressive and fibrotic; biopsy confirmation often needed as up to one-third of so-called radiologic NSIP may be pathologic UIP</td>
<td>Dominated by reticular and ground-glass findings; honeycombing rare, though has been reported; peripheral and central distribution, often bibasilar more than upper lobe; characteristic subpleural sparing may be seen</td>
</tr>
</tbody>
</table>
### Pathology type

**Cryptogenic organizing pneumonia (COP)**  
May present with waxing and waning infectious-type symptoms, often requiring biopsy assessment to confirm after exclusion of other known causes, such as infection; generally responsive to empiric steroids, though repeat treatment may be needed along with occasional short-term immunosuppression

**Clinical findings**  
Migratory, consolidative and ground-glass infiltrates, often bilateral and peripheral with lower lobe predominance; atoll (reverse halo) sign supportive but not frequent; minimal fibrosis or long-term sequelae

**Desquamatative interstitial pneumonia (DIP)**  
Smoking related in over 80 percent of cases; prognosis better than UIP, particularly with smoking cessation; shared spectrum of clinical and pathologic overlap with RB-ILD

**Radiologic features**  
More centrally located and diffuse ground-glass infiltrates; occasional reticular findings centrally located without peripheral predominance

**Respiratory bronchiolitis-interstitial lung disease (RB-ILD)**  
Younger age predilection in prior or active smokers; nonspecific presentation of dyspnea and cough with pigment-laden macrophages seen on pathology; smoking cessation is first order of management followed by steroid suppression

**Acute interstitial pneumonia (AIP)**  
Acute presentation of hypoxemic respiratory failure with diffuse infiltrates, often indistinguishable from idiopathic acute respiratory distress syndrome with typical diffuse alveolar damage seen on pathology; equivocal response to steroid therapy with high inpatient mortality

**Lymphoid interstitial pneumonia (LIP)**  
Rare, and now considered to be more associated with secondary disease (rheumatologic, immunodeficient or hematologic) rather than idiopathic; characterized by extensive interstitial polyclonal lymphoid cell infiltrates on pathology

**Pleuroparenchymal fibroelastosis (PPFE)**  
Pleural elastosis seen on pathology when biopsy is obtained, though clinical presentation nonspecific and often associated with underlying parenchymal disease of which UIP is most common; prognosis poor based on limited case series

**Pleural biopsy**  
Upper-lobe-predominant bilateral pleural thickening, often associated with underlying parenchymal interstitial process and varying degrees of fibrosis (possibly UIP vs. NSIP-like)

### Table. Characterizing features of interstitial pneumonias.

---

**Reframing acute exacerbation**  
Acute exacerbation (AE) represents punctuated decline in respiratory function (less than 30 days) with new and superimposed infiltrates in the setting of idiopathic pulmonary fibrosis. The exclusion of secondary causes, including performance of bronchoscopy or tracheal aspirate to assess infection, is key to diagnosis.

---

how many initial IPAF evolve to diagnosable connective tissues over time, and if connective tissue disease is not diagnosed, whether survival is simply reflective of the underlying histopathology where UIP often portends poorer outcome as compared with NSIP or other histologic patterns.
Despite well-defined criteria, a standardized approach to initial work-up remains elusive as institutional approaches vary and complete exclusion of secondary causes is often difficult in real-world practice. An example is the reluctance associated with performing bronchoscopy in patients who are not intubated and presenting with significant respiratory distress and hypoxemia. This aversion is not unfounded as further decompensation leading to intubation and mechanical ventilation is known to be associated with greater morbidity and mortality in this setting.

On the other hand, delay in performing bronchoscopy — and the selection of obtained microbiologic studies — may theoretically decrease its yield, particularly when broad-spectrum antibiotics are often empirically provided. The term “suspected acute exacerbation” was therefore recently advocated for acute worsening of respiratory symptoms unexplained by secondary causes but with incomplete work-up.

Recent updates to the international consensus definition of AE, published in the *American Journal of Respiratory and Critical Care Medicine* in 2016, have reflected on these difficulties and modified prior criteria in the hopes of better reflecting clinical practice and outcomes. New definitions no longer require complete exclusion of secondary causes, but instead include known findings as triggers of AE. An initial approach is to ensure the absence of pulmonary edema or volume overload where AE may be excluded, followed by a reasonable assessment for secondary etiologies where known and unspecified causes of respiratory failure are all categorized as forms of AE. This approach contrasts with the prior definition, where exclusion of secondary causes was important to diagnosis, in effect framing AE as an idiopathic phenomenon.

In many ways, the discussion correlates with the Berlin definition of acute respiratory distress syndrome (ARDS), a conceptual model where severity of hypoxemia along with bilateral infiltrates and clinical absence of heart failure frame the acute event. Indeed, associated triggers such as pneumonia, aspiration, septicemia or pancreatitis in acute respiratory distress syndrome are part and parcel of the work-up and management, but the focus is directed at broadly managing the acute respiratory failure syndrome, which may behave independently of the original inciting etiology. Whether this model holds similar implications for the future management of acute exacerbation in ILD is yet unknown, as historical use of low tidal volume strategies has not proved beneficial. In fact, mechanical ventilation appears to be associated with worse survival, though it is unknown whether mechanical ventilation truly causes additional harm in this setting or is simply a surrogate of more-severe and perhaps irreversible lung injury.

**For more information**


**Anti-Fibrotic Therapy in the Treatment of IPF: Ongoing Concerns and Current Practices**

While multiple trials assessing different mechanisms and approaches to treatment have proved negative over the past decade and a half, two drug therapies have recently become available for the directed treatment of idiopathic pulmonary fibrosis (IPF). Pirfenidone, a well-known anti-fibrotic drug already approved outside the U.S., and nintedanib, a tyrosine kinase inhibitor, both became available internationally in October 2014. The drugs mirrored each other in the number of phase III clinical trials leading to approval and slowing of forced vital capacity (FVC) decline, with pirfenidone touting a signal for improved mortality, and nintedanib suggesting decreased incidence of acute exacerbation in two of its three large trials.

While the availability of two agents for a progressive and fatal disease is welcomed, questions remain regarding indications and
The care of patients with progressive lung disease has been transformed by orthotopic lung transplantation. This therapy, limited by the number of donor organs and by the need to select patients who are able to tolerate the twin demands of surgery and immunosuppression, nevertheless offers the potential of years of disease-free living. As the nationwide need for organs continues to grow, the shortage of donor lungs is a major limitation. It is estimated that less than 20 percent of all donor lungs are suitable for transplant in clinical practice. In Mayo Clinic in Jacksonville, Florida, a unique academic-industry partnership with United Therapeutics Corp. is developing novel approaches to maintaining donor lungs. In a unique ex vivo lung perfusion and ventilation to resuscitate and support donor lungs that would otherwise be unavailable for transplant (Figure 1). This technology, which is currently confined to use within clinical trials, delivers low-pressure oxygenated perfusate that comprises hyperosmolar solutions to isolated organs, combined with protective (low-pressure, low-inspired oxygen) ventilation, and close monitoring for indicators of improving function. Ex vivo lung perfusion (EVLP) offers the potential of providing many more organs for transplant.

When pooling data for two of the pirfenidone trials, 21 percent of participants still had FVC decline greater than 10 percent while on therapy. Furthermore, patient variables that predict a medication response are yet to be determined. Indeed, pirfenidone has been available for a number of years outside the U.S. for IPF treatment, yet few long-term follow-up studies exist and are limited to center-specific reviews of clinical experience. Unfortunately, such studies have been more equivocal than confirmatory of clinical or survival benefit. Finally, for some patients, disease stability (defined by a relative lack of symptoms or minimally changed FVC) may be justification for deferring initiation of drug therapy, though the expectation of future progression must be acknowledged.

At this time, use of both anti-fibrotic drugs is limited to the diagnosis of IPF but will likely see expansion to non-IPF interstitial lung disease in the near future. Where patients had little opportunity to fight disease in the past, current therapies offer a chance to slow disease progression and delay severity of symptoms. Research continues to optimize selection of the target population that will most benefit and experience the fewest side effects.

### Lung Transplantation: Challenges and Opportunities

The care of patients with progressive lung disease has been transformed by orthotopic lung transplantation. This therapy, limited by the number of donor organs and by the need to select patients who are able to tolerate the twin demands of surgery and immunosuppression, nevertheless offers the potential of years of disease-free living. As the nationwide need for organs continues to grow, the shortage of donor lungs is a major limitation. It is estimated that less than 20 percent of all donor lungs are suitable for transplant. In the face of such a shortage of donor organs, Mayo Clinic in Jacksonville, Florida, is developing novel approaches to maintaining donor organs. In a unique academic-industry partnership with United Therapeutics Corp., Mayo Clinic is furthering the study of ex vivo lung perfusion and ventilation to resuscitate and support donor lungs that would otherwise be unavailable for transplant (Figure 1). This technology, which is currently confined to use within clinical trials, delivers low-pressure oxygenated perfusate that comprises hyperosmolar solutions to isolated organs, combined with protective (low-pressure, low-inspired oxygen) ventilation, and close monitoring for indicators of improving function. Ex vivo lung perfusion (EVLP) offers the potential of providing many more organs for transplant.
The combined venture is a multiyear development with plans to begin construction of a three-story lung restoration center within the heart of Mayo Clinic’s campus in Florida in 2017 (Figure 2). This facility will house the lung perfusion program as well as space for research carried out by the Center for Individualized Medicine and Center for Regenerative Medicine, to further investigation for years to come. All three Mayo Clinic sites now have active lung transplant programs; Mayo Clinic’s campus in Arizona launched a program in 2016.

Nationwide, one-year survival following lung transplant continues to improve, but longer term outcomes remain a challenge, due in large part to chronic allograft rejection from bronchiolitis obliterans, characterized by inexorable small airways obstruction. Management is aimed primarily toward prevention, but strong evidence is lacking for a specific approach. In the absence of any reliable treatments for established bronchiolitis obliterans, investigators from Mayo Clinic in Jacksonville, Florida, are conducting a clinical trial of mesenchymal stem cells in lung transplant recipients with chronic rejection.

Patients with interstitial lung disease, who have the highest death rates among patient diagnostic groups awaiting transplant, make up one of the largest groups referred for transplantation. The current allocation system favors such patients by adjusting the lung allocation score based on underlying disease, in the hopes of a more timely intervention. However, patients may still wait several years. Additional strategies include the use of donor lungs following cardiac death and the traditional donors following brain death, although the former involves a more resource-intensive commitment from the transplant procurement team. The patient with interstitial lung disease presents a few unique challenges, particularly if the lung condition is a manifestation of a systemic disease such as a rheumatologic disorder. The activity and course of extrapulmonary manifestations may impact the patient’s candidacy for transplant. Finally, because the new anti-fibrotic agent nintedanib has been associated with arterial thrombosis, this drug is typically discontinued upon the patient’s listing for transplant.

The decision concerning single- or double-lung transplantation is often of major concern to patients and is influenced by organ availability, age and functional status — single lung is generally a shorter, less complex operation — as well as past surgical history, but in general, carefully selected patients have good quality of life and often excellent lung function after single-lung transplantation.

For more information

Current Studies and Clinical Trials


Extending Preservation and Assessment Time of Donor Lungs Using the Toronto EVLP System at a Dedicated EVLP Facility
Principal investigator: Cesar A. Keller, M.D.
Primary outcome measure: Primary graft dysfunction (PGD), grade 3 and patient survival.
Time frame: PGD grade 3 at 72 hours; survival at 30 days
Contact study coordinator: Cesar A. Keller, M.D., at 904-956-3271 or keller.cesar@mayo.edu
NCT02234128

A Prospective Assessment of Patient Characteristics in Thoracic Transplantation and Their Relationship to Important Transplant Outcomes
Principal investigator: Cassie C. Kennedy, M.D.
Synopsis: A multisite prospective survey of pre-heart and pre-lung transplant patients examining factors such as resilience, attitude, self-management and quality of life.
Synopsis: A prospective qualitative research study designed to explore patients’ experiences while on the heart or lung transplant waiting list.
Contact study coordinator: Elizabeth N. Stevens at 507-266-7765 or stevens.elizabeth1@mayo.edu
1K23HL128859

A Registry for Patients by the Pulmonary Fibrosis Foundation
Principal investigator: Andrew H. Limper, M.D.
Primary outcome measure: Analysis of registry data to lead to aggregated reports summarizing the epidemiology of interstitial lung diseases, as well as disease, treatment and outcomes.
Time frame: Five years
Contact study coordinator: Pulmonary Clinical Research Unit at 800-753-1606 or PCRUE18@mayo.edu
NCT02758808

A Study Comparing the Effectiveness and Safety of High-Titer Versus Low-Titer Anti-Influenza Immune Plasma for the Treatment of Severe Influenza A
Principal investigator: Philippe R. Bauer, M.D., Ph.D.
Primary outcome measure: Subjects’ clinical status (6-point ordinal scale): death; in ICU; non-ICU hospitalization requiring supplemental oxygen; non-ICU hospitalization not requiring supplemental oxygen; not hospitalized but unable to resume normal activities; not hospitalized with full resumption of normal activities.
Time frame: Measured at Day Seven
Contact study coordinator: Sueanne (Sue) M. Weist, R.N., CCRP, at 507-255-6804 or weist. sueanne@mayo.edu
NCT02572817

Home-Based Health Management of COPD Patients
Principal investigator: Roberto P. Benzo, M.D.
Primary outcome measure: Change in number of daily steps between the intervention and control conditions as measured by the SenseWear Pro ArmBand and change in quality of life between the intervention and control conditions as measured by the Chronic Respiratory Disease Questionnaire.
Time frame: Daily steps and quality of life measured at weeks one, nine and 17
Contact study coordinator: Johanna P. Houl, CCRP, at 507-293-0190 or houl.johanna@mayo.edu
NCT02557178

Mesenchymal Stem Cell Therapy for Lung Rejection
Principal investigators: Cesar A. Keller, M.D., and Abba C. Zubair, M.D., Ph.D.
Primary outcome measure: Number of participants with serious and nonserious adverse events (patients will be assessed for their capacity to tolerate IV infusion of MSC without acute clinical or physiological deterioration) and changes in pulmonary function tests (vital signs, pulmonary function tests FEV1 and FCV), and Borg Dyspnea Index will be evaluated, and chest radiograph, CBC and serum chemistry will be performed.
Time frame: Up to two weeks
Contact study coordinator: Abba C. Zubair, M.D., Ph.D., at 904-956-3318 or zubair.abba@mayo.edu
NCT02181712

Qualitative Assessment of Pre-Transplant Patients’ Experiences
Principal investigator: Cassie C. Kennedy, M.D.
Synopsis: A prospective qualitative research study designed to explore patients’ experiences while on the heart or lung transplant waiting list.
Contact study coordinator: Elizabeth N. Stevens at 507-266-7765 or stevens.elizabeth1@mayo.edu
1K23HL128859
Mayo Clinic Pulmonary Update is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

Contact Us
Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

Phoenix/Scottsdale, Arizona
866-629-6362 (toll-free)

Jacksonville, Florida
800-634-1417 (toll-free)

Rochester, Minnesota
800-533-1564 (toll-free)

Resources
MayoClinic.org/medicalprofs
Clinical trials, CME, Grand Rounds, scientific videos, and online referrals

Education Opportunities

For more information or to register for courses, visit https://ce.mayo.edu/pulmonary-medicine/node/1664, call 800-323-2688 (toll-free) or email cme@mayo.edu.

Mayo Clinic Extracorporeal Membrane Oxygenation (ECMO) Workshop 2017
April 4-5, 2017, in Scottsdale, Ariz.
Participants explore venovenous and venoarterial physiology in initiating, monitoring and managing ECMO. Simulations and labs integrate ECMO, mechanical ventilation, ultrasound and hemodynamics monitoring techniques.

Pulmonary & Critical Care Medicine 2017
April 6-9, 2017, in Phoenix
This course features a review of current pulmonary and critical care literature, case studies, interactive case-based presentations, and Q-and-A session. Participants represent diverse medical disciplines and specialties.

Checklist for Early Recognition and Treatment of Acute Illness and Injury (CERTAIN) 2017
July 22, 2017, in Quezon City, Philippines
CERTAIN standardizes the approach for evaluation and treatment of patients with acute decompression to improve the performance of providers faced with simulated emergencies. This course features simulation-based training and adult learning theory.

20th WCBIP/WCBE World Congress Joint Meeting of the World Association for Bronchology and Interventional Pulmonology (WABIP) & The International Bronchoesophagological Society (IBES) 2018
June 13-16, 2018, in Rochester, Minn.
Participate in high-caliber scientific programs, including discussions about disease states and new techniques and technologies, and hands-on procedure workshops.