Something Old, Something New…

Acute Presentations of Interstitial Lung Disease

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***This is to acknowledge that Corey Kershaw, M.D. has disclosed that he does have prior financial interests with commercial concerns related indirectly to this program. Dr. Kershaw will be discussing off-label uses in his presentation*.**

Overview: Interstitial lung diseases represent a varied corner of pulmonary medicine. Acute presentations of ILD, whether *de novo* ILD or an exacerbation of chronic ILD, can be dramatic and similar in their symptoms, level of hypoxemia, and most have poor prognoses for complete recovery. Treatments are often off-label, based on single or small case reports. More focus in clinical trials is warranted.

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At the conclusion of this lecture, the listener should be able to:

1. **Name the broad categories of acute interstitial lung disease as well as identify various causes of acute ILD**
2. **Define an IPF exacerbation**
3. **Identify possible causes of exacerbations of IPF as well as understand whether exacerbations are preventable**
4. **Discuss basic approaches to treatment of acute ILD, acute on chronic ILD, and especially acute exacerbations of idiopathic pulmonary fibrosis**

Interstitial Lung Disease Defined

No discussion of the vast variety of interstitial lung diseases (ILD) can begin without some basic understanding of terminologies. The pulmonary interstitium refers to the space separating the alveolar epithelial barrier and the capillary endothelial barrier. In this space typically reside the supporting structures of the lung tissue such as various collagen fibers and matrix proteins.

In some sense, the term "interstitial lung disease" is misleading. The lung diseases we consider under the broad ILD umbrella share a diffuse involvement of lung parenchyma. The term "diffuse lung disease," therefore, is more appropriate to avoid a narrow vision of strict involvement of the microscopic interstitial space. But, for the purposes of this discussion, consider "interstitial lung disease," to be synonymous with "diffuse lung disease" and its anatomical implications contained therein.[1]

Classification of ILD

The term "umbrella of ILD" is apropos to demonstrate that the broad category of ILD has many possible specific diagnoses. This is illustrated in Figure 1.[2] As depicted, there are many possibilities to consider in the approach to a patient with an ILD. Only with careful acquisition of the patient history, candidate fibrogenic exposures, current and prior occupations and medications, and a careful physical examination can the journey to properly classify a patient's disease begin.

Examining the diagram more closely, the family of acute ILDs are found beneath the heading Major Idiopathic Interstitial Pneumonias (IIP). The Major IIPs can be subdivided into the smoking related ILDs (respiratory bronchiolitis interstitial lung disease and desquamative interstitial pneumonia), the ***acute ILDs (cryptogenic organizing pneumonia and acute interstitial pneumonia)***, and the fibrosing ILDs (nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis, the latter being the proper term for idiopathic usual interstitial pneumonia). Further, many of the same radiographic and histopathologic patterns of the Major IIP group can be seen in the ILD of Known Cause category, again emphasizing the importance of accurate and complete history and physical examination.

The causative histopathology of an acute ILD, whether new in a patient with no previous underlying lung disease or in an acute worsening of a chronic ILD, is most often *organizing pneumonia*, and/or *diffuse alveolar damage*. The patient may have features of one or both if a lung biopsy is obtained, especially in the acute on chronic ILD subset.

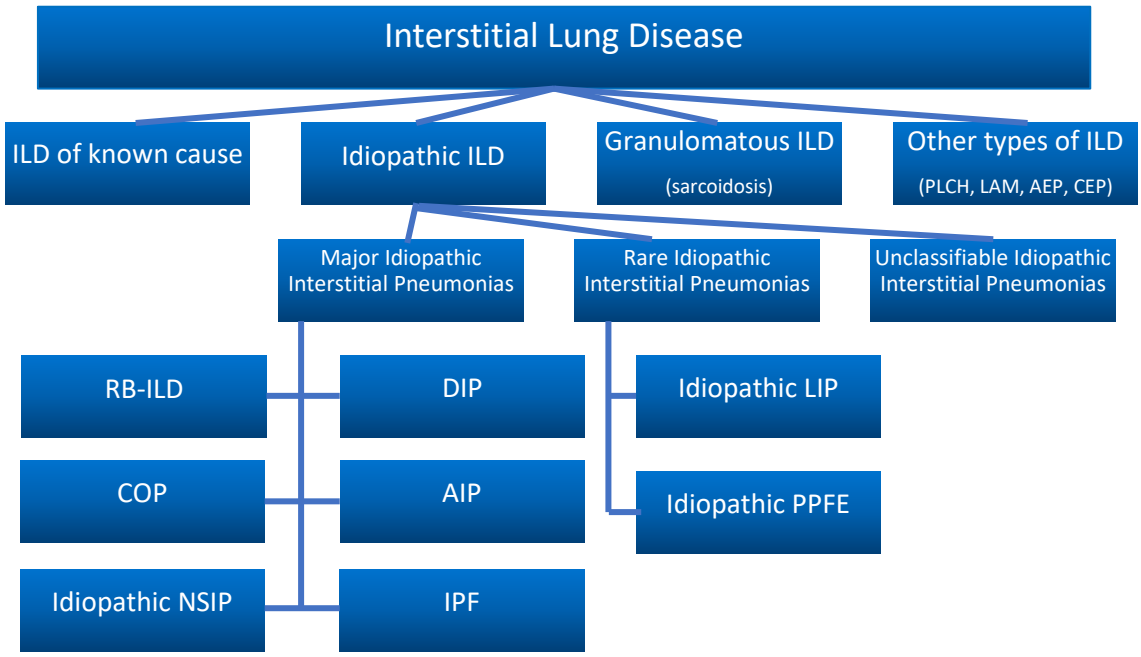

Figure 1: Schematic representation of the classifications of ILD.[2] *ILD = interstitial lung disease; PLCH = pulmonary Langerhans cell histiocytosis; LAM = lymphangioleiomyomatosis; AEP = acute eosinophilic pneumonia; CEP = chronic eosinophilic pneumonia; RB-ILD = respiratory bronchiolitis interstitial lung disease; DIP = desquamative interstitial lung disease; LIP = lymphocytic interstitial pneumonia; COP = cryptogenic organizing pneumonia; AIP = acute interstitial pneumonia; PPFE = pleuroparenchymal fibroelastosis; NSIP = nonspecific interstitial pneumonia; IPF = idiopathic pulmonary fibrosis*

Histopathology: Organizing Pneumonia

The organizing pneumonia pattern is one where loose fibroblasts are embedded in an immature collagen matrix aggregate within airspaces. The pattern may extend into or from terminal bronchioles, alveolar ducts, or the alveoli themselves (Figure 2). While this pattern may occur in numerous lung injuries, we use the term “cryptogenic organizing pneumonia” when the pattern occurs without an etiology. This entity had previously been called “bronchiolitis obliterans organizing pneumonia (BOOP),” and is sometimes still used today. This lends itself to considerable clinical confusion, especially when a pathologist may use the term “BOOP” to describe parts of the injury pattern seen on biopsy. Without proper clinical context – such as in the setting of connective tissue disease with fibrosis, for example – a clinician may misunderstand and diagnose COP inappropriately.[1]

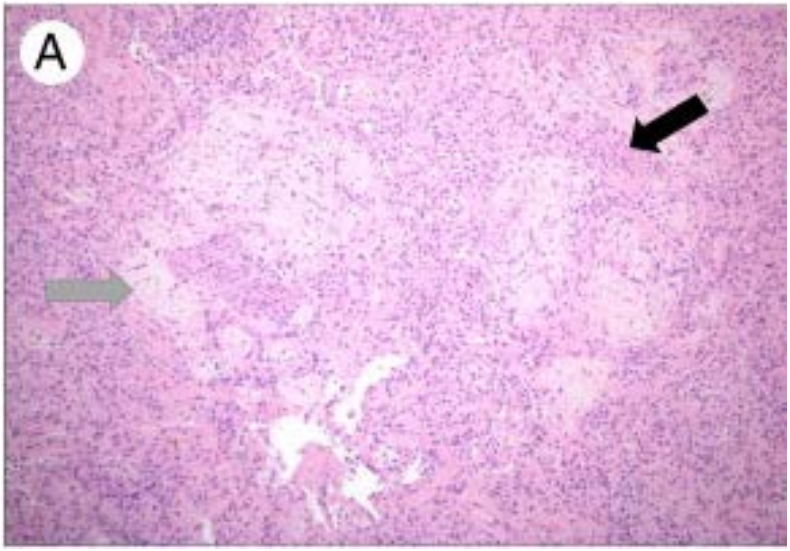

Figure 2: Histopathology of organizing pneumonia. Multifocal intra-alveolar proliferation of fibroblasts. These cellular aggregates of young fibroblasts have a myxoid matrix and are plugging the air spaces (gray arrow). Lung parenchyma away from these areas reveals a patchy, minimal mononuclear interstitial infiltrate (black arrow).[3]

Histopathology: Diffuse Alveolar Damage

Diffuse alveolar damage is extreme lung injury and can occur from multiple insults, both known and unknown.[1] The early, "acute" phase is typified by hyaline membrane formation, intra-alveolar edema, and type II pneumocyte hyperplasia. The subsequent, "organizing" phase consists of the proliferation of fibroblasts within the interstitium and the alveolar space. Collagen deposition is minimal. The path from there leads to either recovery or to a more extensive remodeling phase that results in fibrosis. Patients with fibrosing ILDs that survive an episode of DAD often are left with a significant progression of their chronic disease as a result (Figure 3).[4]

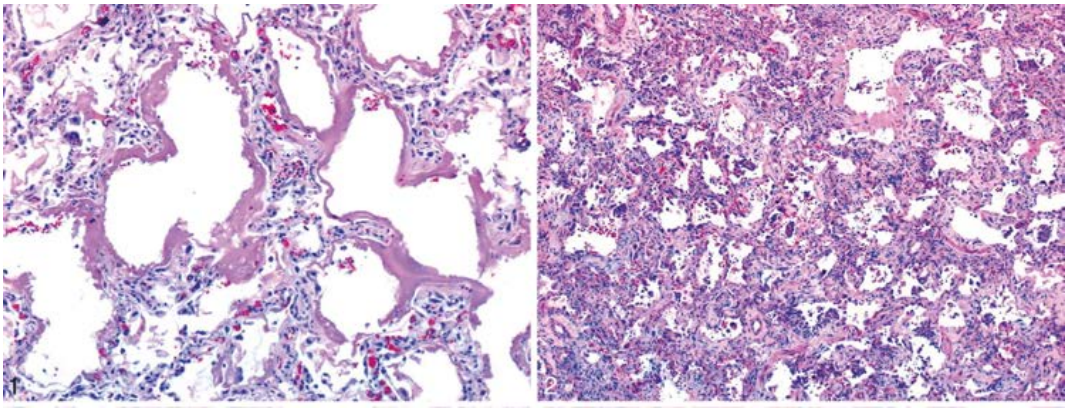

Figure 3: Histopathology of diffuse alveolar damage. Left panel depicts acute phase of DAD. Prominent hyaline membranes line alveolar spaces. The interstitium shows mild edematous widening. Right panel depicts organizing phase of DAD. A residual hyaline membrane can be seen in the upper right. The interstitium shows prominent expansion by myxoid fibroblastic tissue. Prominent type 2 pneumocyte hyperplasia is also present.[4]

How Do These Patients Present?

Symptoms typically evolve over less than 30 days, which may help in differentiating the acute presentation from the natural progression of a chronic ILD.[5] Dyspnea is the most common symptom, but a new or worsening cough may also be present. For some of the diseases of concern, unexplained fevers or flu-like complaints are possible. New or worsening hypoxemia on peripheral oxygen saturation monitor or on arterial blood gas analysis is expected and often quite severe. Admission requirement to an intermediate or intensive care unit for high flow oxygen or more advanced ventilatory support is not unusual.

Since the presentation itself may not help in determining the nature of the patient's acute ILD, high-resolution CT scan of the chest (HRCT) is an indispensable part of the workup.

Figure 4 illustrates a simple schematic to aid in the approach to a suspected acute ILD:

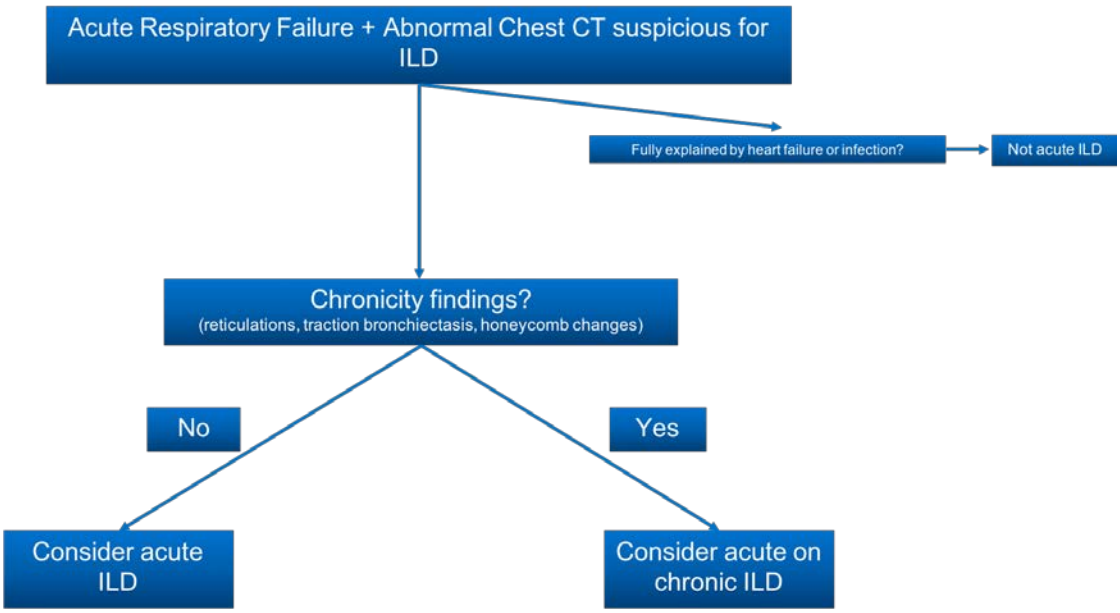

Figure 4: Simple schematic in the approach to a patient with suspected acute ILD

Some Words About Supportive Care

It may go without explicitly saying that all patients presenting with acute respiratory failure from an acute ILD or an exacerbation of chronic ILD should receive "supportive care." What applies to most critically ill patients also applies to the patient presenting with respiratory failure from acute ILD. This includes deep venous thrombosis prophylaxis, a restrictive transfusion strategy for ICU-acquired anemia, oxygen supplementation as required, optimized

nutrition, best-practices management of pain, agitation, delirium, and mobility therapy whenever possible, ventilator-associated pneumonia prevention, etc.

Acute ILD Example: Cryptogenic Organizing Pneumonia

COP presents at a mean age of 50-60 years old. Patients may present with symptoms suggestive of a pulmonary infection: fevers, dyspnea that is progressive and possibly severe, cough, malaise. Varying degrees of hypoxemia are seen depending on the severity of the patient's disease. The non-specific nature of the presentation may lead to a delay in proper diagnosis of up to 6 weeks or more, usually preceded by multiple unsuccessful courses of antibiotics.[6]

HRCT can be very helpful in the proper clinical context to making a diagnosis of COP. Common abnormalities described include diffuse, bilateral peribronchovascular and peripheral consolidations (Figure 5)[7]. Other unusual HRCT patterns such as atoll signs or a "crazy-paving" pattern of ground glass and linear infiltrates can be seen in COP.[8]

Bronchoalveolar lavage cellular patterns are usually non-specific and better used to rule out confounders such as hemorrhage or infection. Lung tissue via transbronchial biopsy will support a COP diagnosis when it is already clinically suspected based on presentation and HRCT pattern. But, care should be taken in interpreting what may be an organizing pneumonia reaction without greater context from larger tissue biopsy obtained via surgical biopsy. For example, chronic fibrosing ILDs such as NSIP can have foci of OP, and small transbronchial biopsies can miss the supporting pathological findings of NSIP.[6]

COP is quite responsive to systemic corticosteroid therapy. Though no randomized controlled trials for COP treatment exist, it is well-documented in case series and from clinical experience that most except the mildest cases will require steroids. For a typical presentation of COP, 80% patients will respond, 60% completely.[9] British Thoracic Society guidelines recommend a starting dose of 1 mg/kg/day prednisone equivalent for 3 months, tapering down thereafter. This regimen is a suggestion and should be individualized based on clinical response.

The 20% or so of patients that do not respond to steroids, and those in which the response is incomplete, should be overlapped with other systemic immunosuppression. Both cyclophosphamide and azathioprine have been used in case reports of refractory COP, as well as in scenarios of recurrent disease during the tapering phase. [10,11]

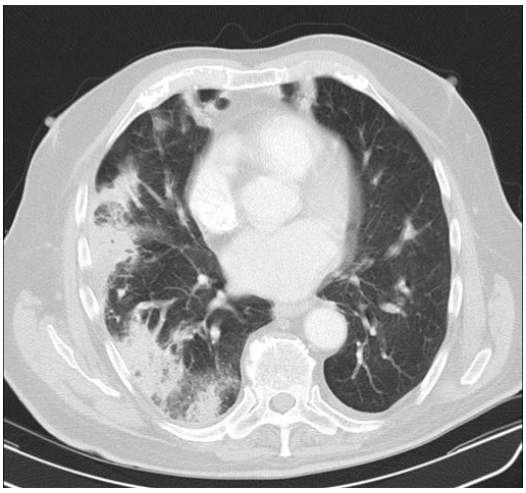

Figure 5: HRCT appearance of typical cryptogenic organizing pneumonia[7]

Acute ILD Example: Lupus Pneumonitis

Organizing pneumonia can occur in the setting of numerous connective tissue diseases (CTD) – rheumatoid arthritis and autoimmune myositis are but two examples. These would be considered acute ILDs but in the setting of CTD (and hence not referred to as Cryptogenic Organizing Pneumonia due to the presence of an etiology). However, systemic lupus erythematosis (SLE), a connective tissue disease with many pleuroparenchymal manifestations, can rarely present for the first time as an acute ILD, *lupus pneumonitis.* The overall incidence is low, around 1% of SLE patients, but it may be the first presentation of SLE in 50% of lupus pneumonitis cases.[12] Patients present with fulminant hypoxemic respiratory failure, and dyspnea, cough, and fevers are of rapid onset.[13] Figure 6 shows a typical HRCT of lupus pneumonitis, with bilateral ground glass opacities. Bilateral consolidations are also sometimes seen. It is histopathologically characterized by varying degrees of capillaritis, DAD, and interstitial edema. Bronchoscopy may be helpful in ruling out infection, but patients are frequently too tenuous for surgical lung biopsies.

Treatment requires high-dose corticosteroids plus cytotoxic agents such as cyclophosphamide or rituximab – treatment decisions are based on individual experience and comfort with the choices of medications given the absence of any controlled trials of lupus pneumonitis. Mortality is high, 50% in a frequently-cited case series.[14]

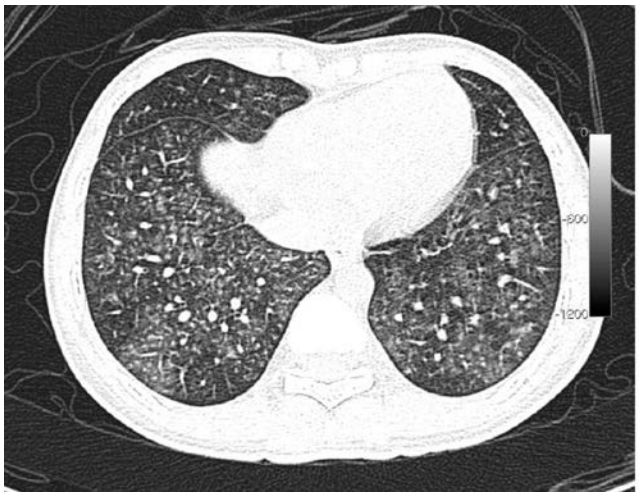

Figure 6: HRCT appearance of lupus pneumonitis[13]

A Digression: Rapidly Progressive ILD

The Anti-Melanoma Differentiation-associated Gene 5 antibody (MDA5) was first described in 2005.[15] Since, it has been associated with a rapidly progressive ILD seen in patients with dermatomyositis, especially clinically amyopathic dermatomyositis (CADM). The pathology appears to be mostly DAD, and there may be a role for the antibody itself in pathogenesis as it has been shown to correlate with disease activity. In the few reports available for review, mortality is high (close to 50% in one series).[16] Immunosuppression should be aggressive and involve high-dose corticosteroids and cytotoxic agents such as cyclophosphamide. A few single-patient case reports suggest a response to tacrolimus. Cyclosporin A has also shown benefit in case series, though the bulk of those reports are in patients of Asian descent. Generalizability to other patients is less clear.[17]

In a patient with a rapidly progressive ILD of unknown etiology, even without skin features of dermatomyositis, an extended myositis antibody panel that includes the MDA5 antibody should be part of the workup. Disease typically evolves over an average of 3 months. Hence, for this discussion, it is considered in a separate category of *rapidly progressive ILD* rather than acute ILD.

Acute ILD Example: Acute Interstitial Pneumonia (AIP)

Known for years as Hamman-Rich Syndrome, this entity is described now as acute DAD without identifiable etiology. Onset is rapid, with dyspnea evolving over 1-2 weeks.[18] The DAD seen on biopsy is typically of the organizing stage as most are taken late in the clinical course or at autopsy. The injury pattern is diffuse and suggests a single, albeit unknown, inciting event.[19]

Most patients are severely hypoxemic on admission and will require invasive mechanical ventilation. HRCT shows bilateral patches of ground glass infiltrates with or without consolidations (Figure 7).[20] The most severe abnormalities are seen in the posterior segments, similar to ARDS.[8] The role of bronchoscopy is similar to others previously discussed - to rule out other causes of respiratory failure such as infection or hemorrhage. A surgical biopsy is required to confirm the presence of DAD, but risks of the procedure should be weighed heavily.

Inpatient mortality is high, even with treatment. A large cohort study of AIP from the Mayo Clinic reported a survival of 45% in those treated with systemic corticosteroids (33% without treatment).[18] Conversely, a 9 patient cohort from Israel treated with steroids (methylprednisolone 8 mg/kg/d) – 3 patients also received cyclophosphamide – yielded zero survivors.[21] Other therapies are limited to single case reports.

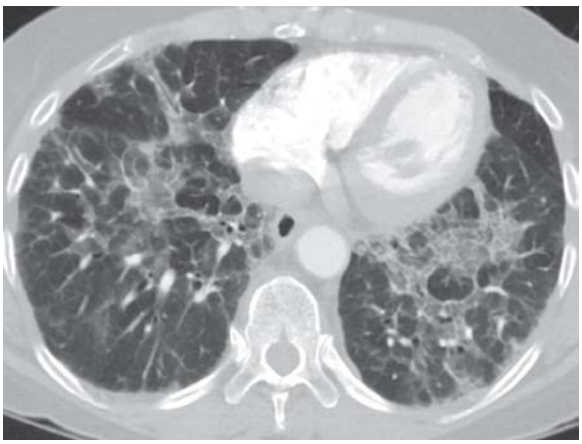

Figure 7: HRCT appearance of acute interstitial pneumonia[20]

Acute ILD Example: Acute Eosinophilic Pneumonia (AEP)

AEP was first described in a case report from 1989.[22] While there are multiple causes for eosinophilic infiltration of the lung, AEP should be considered a distinct entity that can be idiopathic or secondary. Inhalation exposures have been implicated, such as new-onset cigarette smoking or recrudescent smoking following a period of cessation.[23]

Symptoms of cough, shortness of breath, and fevers are common and typically evolve quickly, usually < 1 week. Most patients are young and otherwise healthy, and men are more commonly affected than women.[24] Hypoxemia at presentation can be severe, and many patients will require mechanical ventilation for severe hypoxemic respiratory failure.[25] Unlike patients with chronic eosinophilic pneumonia, those with AEP usually do not have peripheral eosinophilia at presentation.

CT scan shows bilateral and diffuse ground glass opacities (unlike the peripheral infiltrates seen in chronic eosinophilic pneumonia) (Figure 8).[26] Sometimes septal thickening is

found, and a “crazy paving” pattern may be seen.[8] Bronchoscopy is essential to making the diagnosis, with bronchoalveolar lavage having > 25% eosinophils on cell count differential analysis.[25]

While no controlled studies of AEP treatment are published, data from case series inform that patients respond exquisitely and rapidly to systemic corticosteroids. Resolution of hypoxemia can be realized in just hours. Mild cases have been known to remit spontaneously. Dosing and duration of therapy varies in reports. One large Korean cohort had similar resolution in patients treated with steroids for 2 weeks compared to those treated for 4 weeks. Dosing was methylprednisolone 60 mg every 6 hours for 3 days, followed by a tapering regimen.[24] Prognosis is excellent, though recurrence with the resumption of smoking is reported.[23]

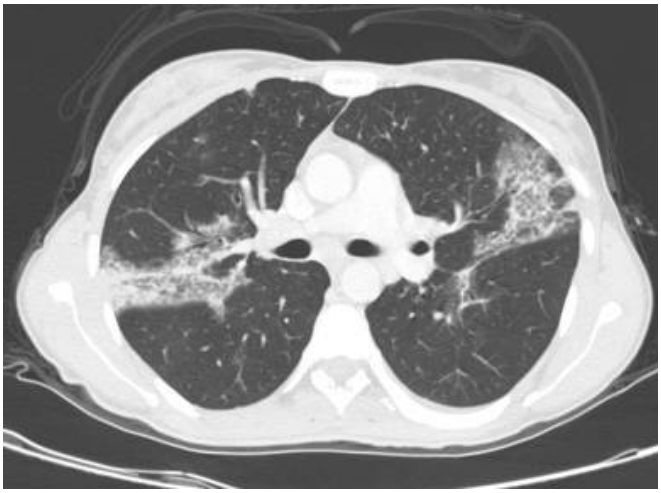

Figure 8: HRCT appearance of acute eosinophilic pneumonia[26]

Acute ILD Example: Acute Drug-induced ILD

The list of medications that can cause organizing pneumonia and/or diffuse alveolar damage is beyond the scope of this presentation. An excellent source for reports of pulmonary side effects to any and all culprit medications – including any reports of ILD, acute or chronic – can be found at www.pneumotox.com. Some of the more commonly used medications that can be associated with acute ILD include amiodarone (the entire spectrum of acute → chronic ILD has been reported), methotrexate, rituximab, sulfasalazine, and the TNF-α antibody group.

The growing use of checkpoint inhibitor therapy for malignancy deserves some mention. Toxicity has been reported with both the anti-PD1 and anti-PDL1 classes. The risk is highest in men, those with a smoking history, and those with a lung cancer diagnosis.[27-29] Incidence is 2-3% of patients with median time to toxicity being ~2 months. Like other patients with acute ILD, there is the rather rapid onset over a few weeks or less of dyspnea, cough, and hypoxemia (some manifestations may be more insidious). CT patterns are consistent with the known pathologies of organizing pneumonia and/or DAD (Figure 9), with OP being a bit more common both radiographically and on biopsy.[27]

Patients with mild, asymptomatic findings on CT may be managed with drug withdrawal only. More severe cases require the addition of corticosteroids, suggested at 1 mg/kg/day and tapering once symptoms resolve. Refractory cases may require more aggressive immunosuppression. Whether to rechallenge with the offending agent is not clear, though a patient with severe toxicity would likely not be.[30]

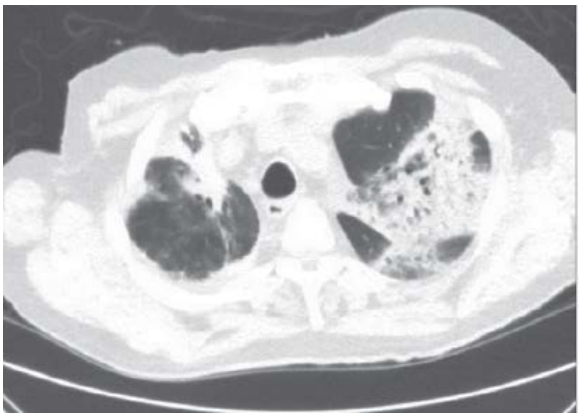

Figure 9: Organizing pneumonia following PD1 monoclonal antibody therapy[27]

Acute On Chronic ILD (non-IPF)

A patient presenting for the first time with an acute manifestation of an underlying – and sometimes previously undiagnosed – chronic fibrosing ILD represents a special challenge. Different than the patient with an acute ILD, the patient presenting with acute on chronic ILD is manifesting what can best be described as an *exacerbation*.

Some features on the patient's HRCT at admission may aid in navigating to the correct diagnosis (Figure 10). These features may include subpleural reticulations, traction bronchiectasis, honeycombing fibrosis, or airtrapping from small airways fibrosis. In Figure 10, there is also peribronchovascular consolidation that can be seen in hypersensitivity pneumonitis. Nonparenchymal CT scan findings such as pleural thickening or a patulous esophagus may support the conclusion that underlying fibrosis is due to a connective tissue disease.

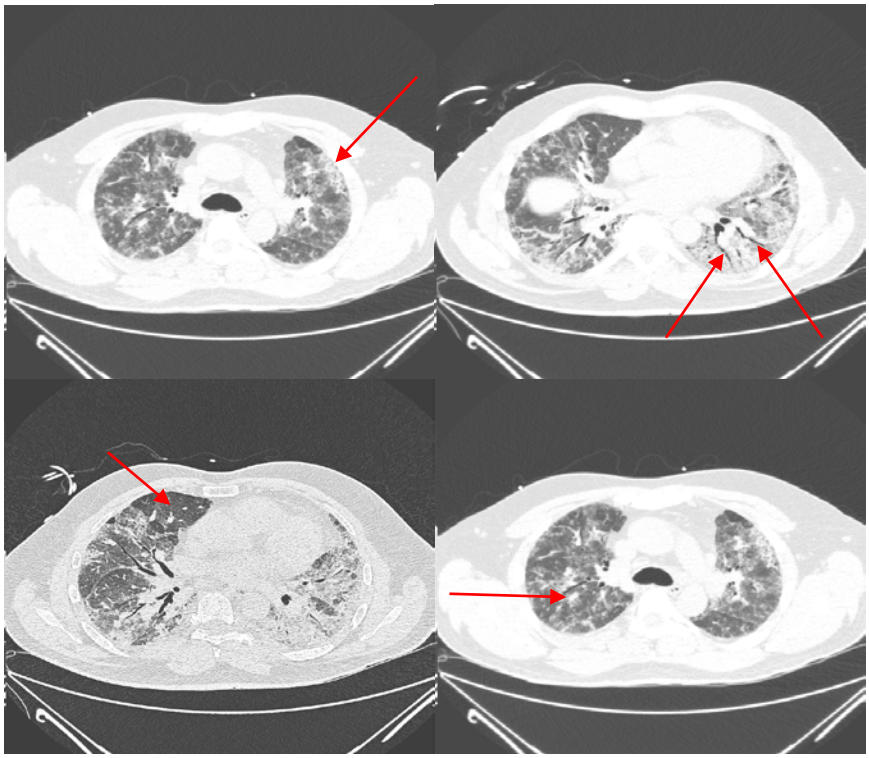

Figure 10 (previous page): Acute on chronic ILD. Features on HRCT that may support an underlying chronic ILD diagnosis in a patient presenting with acute respiratory failure include subpleural reticulations (upper left), traction bronchiectasis (upper right), air trapping (lower left), or peribronchovascular distribution of infiltrate (lower right). This scan is of a patient with underlying chronic hypersensitivity pneumonitis and ongoing exposure to antigen, presenting for the first time with acute hypoxemic respiratory failure.

The risk of exacerbation of chronic ILD is highest in patients with underlying UIP as their primary pathology, and highest in patients with rheumatoid arthritis-associated ILD.[31] The pathological correlate to an exacerbation of chronic ILD is the presence of acute and organizing DAD most commonly.[5] Features of organizing pneumonia may also be present, and to what degree likely informs how treatment responsive the patient may be. This is similar to that seen in IPF exacerbations (to follow). And, much like in the case of IPF exacerbations, causation remains elusive. Potential triggers may be infection (rather than the respiratory failure itself being due to infection) or microaspiration, but neither have been definitively proven.[5]

Diagnostic criteria for an exacerbation of chronic ILD (non-IPF) have not been established. The similarities in acute pathology, however, allow most case series to employ some modification of the IPF exacerbation criteria: underlying chronic ILD, worsening symptoms of 30-60 days duration, HRCT depicting new and unexplained ground glass opacifications on a background of fibrosis, and no complete explanation for these changes such as infection or pulmonary edema.[5] There is little diagnostic role in bronchoscopy other than to rule out infection and other potential causes of respiratory failure. While surgical biopsy can

reveal the underlying histopathology, the severity of hypoxemia often precludes going to surgery safely.

Very little data exist to aid in treatment decisions. Much like the diagnostic criteria, the general approach is similar to the treatment of IPF exacerbations: a regimen of empiric antibiotics plus some dosing of systemic corticosteroids. No dose or timing guidance is established, but provider experience dictates the aggressiveness of the regimen to be dependent on the severity of illness. Thus, an upfront pulse dosing of methylprednisolone 1000 mg daily for the first 3-5 days is not uncommon. Tapering timing is based on the balance of response versus the risk of prolonging the regimen. Non-steroid immunosuppression may have a larger role, as the patient may already be on a maintenance regimen prior to presentation for their chronic non-IPF ILD. The role of initiating immunosuppression, increasing its dosing, or the timing of changing to a different agent in this scenario is not clear, and decisions are left up to the judgement of the treating clinician.[5]

Acute Exacerbation of Idiopathic Pulmonary Fibrosis, Defined

IPF is a very unpredictable disease. The clinical definition of IPF describes a fibrosing ILD that is progressive, but the pace varies between individual patients. Whereas we used to educate patients on the slow but steady progression of disease, we now acknowledge that there are infinite combinations of slowing, stability, and rapid progression.

A 2016 workgroup refined a prior workgroup definition of an IPF exacerbation as follows: An acute, clinically significant deterioration characterized by evidence of new widespread alveolar abnormality. Specific diagnostic criteria are in Table 1.[32] Representative images are in Figure 11.[33] The HRCT on the left shows a typical usual interstitial pneumonia pattern (UIP). IPF is the clinical correlative diagnosis of idiopathic UIP. The right HRCT is an example of that same patient with an exacerbation. Note the new ground glass infiltrates on the background UIP pattern.

An exacerbation of IPF may be itself idiopathic with no identifiable cause, or it may be a triggered event, such as by an infection, an aspiration episode, or following surgery. The definition only requires that the findings cannot be *fully* explained by the triggering event alone (triggered acute exacerbation).[5]

Proposed Pathogenesis Mechanism of an IPF Exacerbation

In what is likely the accumulation of genetic, environmental, and even behavioral factors, the UIP fibrosing phenotype results in the influx of fibroblasts into the interstitial space. Fibroblasts undergo a mesenchymal transformation to myofibroblasts and subsequent deposition of extracellular matrix material. There are acute factors such as direct and indirect lung injury that are suspected to be triggers of this aberrant reparative process.

Definition	
	Acute, clinically significant deterioration characterized by evidence of new widespread alveolar abnormality
Diagnostic criteria	
	Previous or concurrent dx of IPF
	Acute worsening of dyspnea typically < 1 month duration
	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a UIP pattern
	Deterioration not fully explained by cardiac failure or fluid overload

Table 1: Definition and diagnostic criteria for an exacerbation of IPF[32]

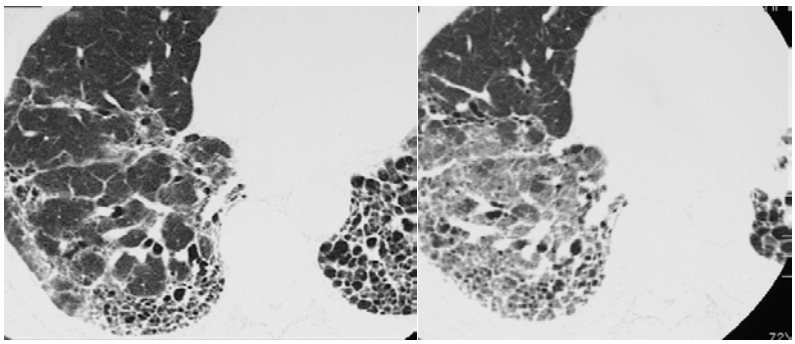

Figure 11: An example of a baseline HRCT appearance of IPF, with a subpleural and a basilar predominant reticular infiltrate along with honeycombing fibrosis (left). An example of the same patient presenting with an IPF exacerbation, now with new ground glass infiltrates on the background of the chronic fibrosis (right)[33]

In an exacerbation, an acute event occurs that leads to widespread acute lung injury. There is indirect evidence for respiratory viral infections as triggers as well as microaspiration events in patients with unchecked or unappreciated gastroesophageal reflux disease. A pattern of early hyaline membrane formation occurs, and this is further supported by the presence of acute and organizing DAD from the lung biopsy specimens of patient with an IPF exacerbation.[32]

Incidence and Risk Factors for IPF exacerbations

The placebo arms of IPF randomized controlled trials reveal a variable incidence of IPF exacerbations. Around 5-10% of patients in one-year studies experience exacerbations. The variability lies in differences between investigator-defined versus centrally-adjudicated exacerbations. In a pooled analysis of both phase 3 INPULSIS studies that led to the approval of nintedanib – one of two FDA-approved treatments for chronic IPF – the rate was 8.0 exacerbations/100 patient years.[34]

More physiologically and functionally advanced disease is the most consistent risk factor for an IPF exacerbation.[32] In a cohort of patients randomized to receive sildenafil versus placebo in advanced IPF, declines over 6 months in forced vital capacity of 10% or more or 15% or more in diffusion capacity were identified as risk factors. Worsening symptoms were also associated with increased risk of an IPF exacerbation.[35] Other risk factors include advanced age, never smoking, and higher BMI.[32,36]

Prognosis and Prevention of IPF Exacerbations

The prognosis after an IPF exacerbation is abysmal. It is estimated that almost half of all IPF deaths are preceded by an exacerbation. And, of the patients admitted to the hospital with an exacerbation in several case series, 50% do not survive to hospital discharge.[32] In the previously mentioned sildenafil versus placebo study, the median survival following IPF exacerbation was only 12 weeks.[35]

Given the dismal prognosis, prevention of exacerbations is ideal but unrealized. Beyond general health maintenance such as keeping up with required vaccinations and management of co-morbid diseases, little has been shown to be effective in preventing IPF exacerbations. In the 2015 American Thoracic Society IPF treatment guidelines, antiacid therapy in IPF was given a *conditional* recommendation for use but with very low confidence in estimates of effect.[37] Most patients – 90% or more[38] – have gastroesophageal reflux that could be clinically silent. And, as discussed previously, microaspiration has been postulated with variable supportive evidence to be an inciting source of ILD exacerbations. An analysis of three IPF Network clinical trials revealed no exacerbations in the placebo arms that were taking some antiacid therapy.[39] But a very similar pooled analysis of three pirfenidone clinical trials – the second FDA-approved treatment for chronic IPF – revealed no difference in any clinically meaningful outcome with antiacid therapy including hospitalizations and IPF-related mortality.[40] Finally, in the recently published WRAP-IPF study in which patients with IPF and endoscopically verified acid reflux were randomized to anti-reflux surgery (a 360° fundoplication) versus usual care, there was no difference in IPF exacerbations between the two groups. Given the low enrollment numbers in WRAP-IPF (58 patients over 2+ years), the authors speculate a larger trial may show benefit.[41]

The clinical trials that led to approval of nintedanib for slowing the progression of chronic IPF used time to first IPF exacerbation as a secondary outcome measure. Although the individual trials results were disparate in their conclusion for exacerbation prevention, a follow-up pooled analysis of the phase 2 and both phase 3 studies demonstrated a significant reduction in time to first exacerbation (Figure 12).[42] The phase 3 studies of pirfenidone did not measure time to or incidence of IPF exacerbations, so its effect in this sphere is not known.

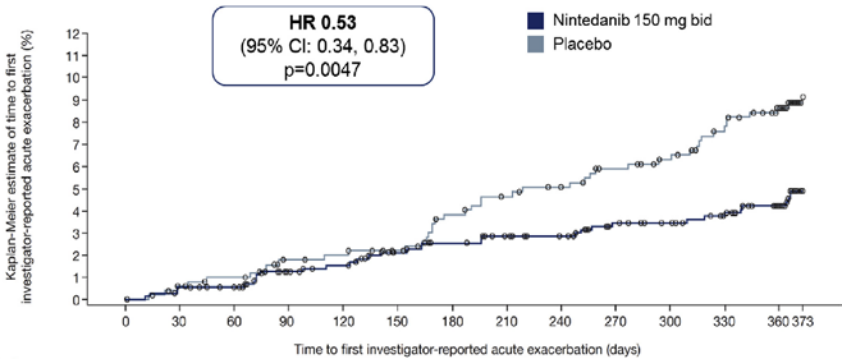

Figure 12: Pooled analysis of phase 2 and 3 nintedanib clinical trials, showing decreased time to first IPF exacerbation at one year[42]

Management of IPF Exacerbations – Non-Pharmacologic Interventions

There are no proven effective therapies for IPF exacerbations. Care must be taken when it comes to even supportive measures such as mechanical ventilation, as this may be harmful. High levels of positive end-expiratory pressure (PEEP) are sometimes employed in the mechanical ventilation of patients with severe ARDS, though the benefit of that for all ARDS patients remains in question.[43] So too in IPF, where higher levels of PEEP significantly increased mortality in one retrospective cohort study.[44] In general, the lack of recruitability of the fibrotic lung should dictate low to moderate levels of PEEP for ventilating a patient with IPF. The only published paper examining the effect of prone ventilation on pulmonary fibrosis compared to ARDS did not show an oxygenation benefit in the fibrosis group.[45] Some of the other interventions in ARDS that have reduced mortality – neuromuscular blockade and low tidal volume ventilation – have not been rigorously studied in IPF.

The outcome of IPF patients on mechanical ventilation in general is very poor, with a mortality of around 50% for all IPF patients requiring invasive ventilation in a large national cohort.[46] This same cohort study reported better mortality in patients managed with noninvasive ventilation; no cause-and-effect conclusion can be drawn from this observation.

Before the approval of nintedanib and pirfenidone in 2014, the only proven therapeutic option for IPF patients was lung transplantation. A patient presenting with an IPF exacerbation requires special attention in terms of transplant consideration given its high mortality in the short-term. Even determining transplant eligibility is an urgent barrier to overcome, as patients are often mechanically ventilated or on high-flow oxygen delivery devices. Necessary studies to

examine for comorbidities that could preclude eligibility may not be possible. Furthermore, IPF patients transplanted while on mechanical ventilation have a significantly worse outcome post-transplant compared with those transplanted without pre-transplant ventilation (Figure 13).[47] It is for this reason as much as anything else that patients diagnosed with IPF be referred early to transplant centers for evaluation well before they might be transplant-ready and certainly before an IPF exacerbation may render them ineligible due to acuity of illness.

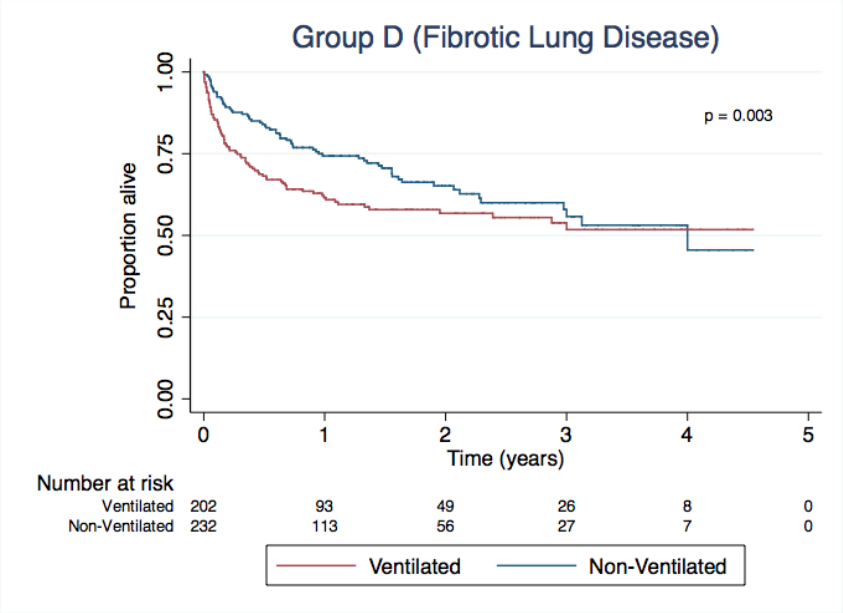

Figure 13: 6-month survival is worse in pulmonary fibrosis patients who undergo lung transplant with pre-surgical mechanical ventilation verse patients transplant without pre-surgical mechanical ventilation[47]

Interest in the use of extracorporeal cardiac life support (ECLS) continues to grow, and its use in the peri-transplant period is not uncommon. Little data exists about the outcome of these patients. Transitioning a patient to ECLS is a consideration once medical therapies are maximized and the patient is already a transplant candidate.[48] Patients placed on ECLS as a destination to recovery rather than as a bridge to transplantation have a very low likelihood of surviving to hospital discharge (Figure 14).[49]

Management of IPF Exacerbations – Pharmacologic Interventions

As with non-IPF exacerbations, there are no proven beneficial pharmacologic treatments for an exacerbation of IPF. American Thoracic Society guidelines give a weak recommendation for systemic corticosteroids without recommendation on dosing or duration.[32] Pulse dosing of methylprednisolone, 1000 mg/d x 3-5 days, makes as much sense as anything else. Tapering regimens over time are purely based on individual practice and experience. Any benefit to systemic steroids likely reflects a favorable histopathological ratio of organizing pneumonia to diffuse alveolar damage.

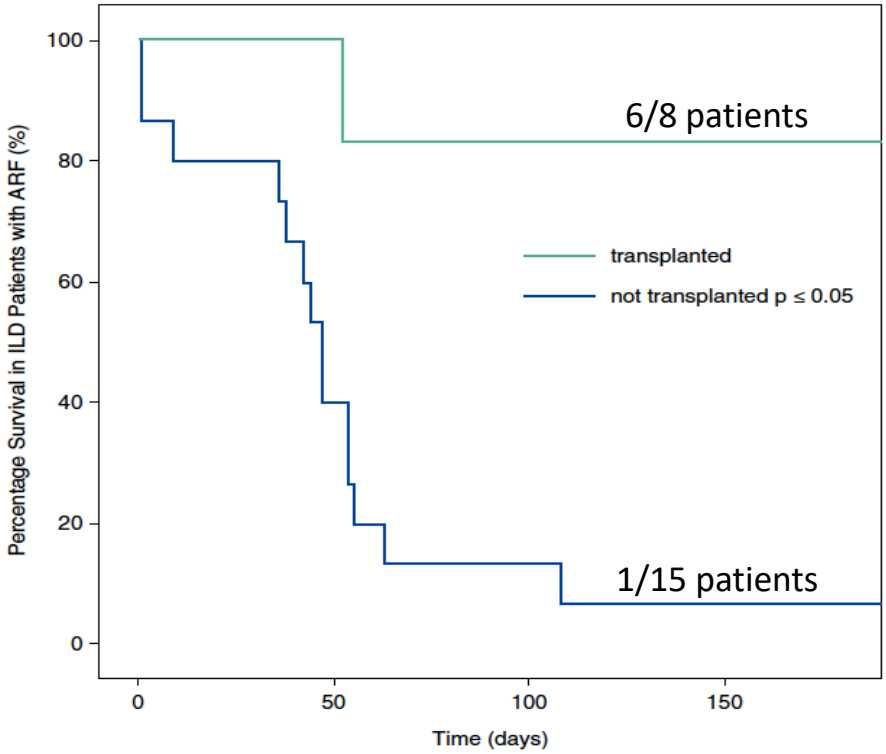

Figure 14: Survival of patients on ECLS based on transplant status. Patients transplanted from ECLS had a significantly greater survival than patients on ECLS without undergoing lung transplantation[49]

Empiric antibiotics are recommended. In the only randomized controlled trial of a treatment for IPF exacerbations, procalcitonin was used to guide the duration of antibiotic therapy. The patients treated for fewer days had the same outcomes as the comparison group not managed with procalcitonin guidance.[50] Other pharmacologic treatments having some reported benefit are based on observational cohort studies only. This includes cyclophosphamide, cyclosporine, and tacrolimus.

Polymyxin B hemoperfusion has been studied in septic shock and ARDS. The treatment employs a dialysis machine fitted with a selective endotoxin adsorption cartridge consisting of the antibiotic polymyxin B. The adsorption cartridge binds circulating endotoxin when blood is hemoperfused through the cartridge. A recent clinical trial published in 2018, however, did not show a mortality benefit in septic shock patients with circulating endotoxin.[51] ARDS studies demonstrate an improvement in oxygenation. And, as ARDS is also characterized by DAD, polymyxin B hemoperfusion has been theorized to be of benefit in IPF exacerbations.

One single-center study in patients with acute exacerbations of IPF treated 14 patients with polymyxin B hemoperfusion to compare with 17 historical controls.[52] Hemoperfusion was performed 2 to 3 times over 3 days. Oxygenation was improved within 2 days of treatment initiation, as expected, but the 12-month survival was 48.2% vs. 5.9% in the historical controls,

a significant improvement. Whether this can be a useful intervention requires more study in a true randomized, controlled clinical trial.

The use of a multimodality intervention to target autoantibody production has also been reported.[53] The study takes advantage of the B-cell aggregates and their signaling mediator C-X-C motif chemokine 13 (CXCL13) that tends to accumulate in the IPF lung. Similar increases in B-cell differentiation is observed in autoimmune disease such as SLE and rheumatoid arthritis. Given the similarities with other autoimmune diseases, the investigators used a regimen of total plasma exchange plus rituximab in 11 patients with IPF exacerbations (and compared to historical controls). They also administered IVIG to 4 of subjects (patients 8-11). Their patient population was quite sick and expected to succumb to their exacerbation in the hospital. This regimen resulted in 46% survival compared with none in the historical control group. While a provocative finding like the polymyxin B hemoperfusion data, a larger study with consistent treatment protocols would be needed before adopting widespread use of this regimen.

Conclusion

Those presenting with an acute interstitial lung disease, whether as a first presentation or as an exacerbation of a chronic fibrosing ILD, represent a distinct patient population. Though different baseline substrate, their acute symptoms may be very similar and thus require a deeper dive into the history, exam, and available radiological studies. While systemic corticosteroids form the backbone of treatment plans, response is dependent on the relative components of organizing pneumonia versus diffuse alveolar damage. Pharmaceutical therapies beyond the first-line are still experimental based on cohort data. Extracorporeal life support and transplantation are options of last resort in select patients.

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