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Review

Acute Exacerbations of Interstitial Lung Disease: Evolving Perspectives on Diagnosis and Management

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ABSTRACT: Interstitial lung diseases (ILDs) are a heterogeneous group of chronic lung diseases caused by several potential etiologies but for many, the cause of a given ILD remains unknown. Accurate epidemiologic data are hard to find because of varying definitions, overlapping characteristics once thought to be unique to specific diseases, and ongoing changes in how ILDs are diagnosed and managed. In addition, there are significant variations in prevalence among different geographic populations, likely reflecting a combination of genetic and environmental differences. Certain risk factors, including exposure to cigarette smoke or environmental toxicants (asbestos, silica, fracking, coal dust, and air pollution), genetic mutations, and single nucleotide polymorphisms, have all been associated with developing interstitial lung disease. Due to the availability of high-resolution computed tomography (CT) scans, earlier and broader recognition of subtle imaging changes, and an aging worldwide population, the incidence and prevalence of ILDs are increasing. While a given cause of particular interstitial lung disease may vary, patients often experience breathlessness and a non-productive cough due to impaired alveolar gas exchange. Patients with ILD are prone to the development of acute exacerbations, marked by acute or chronic respiratory failure because of an acute exacerbation of the underlying lung disease. In this review, we discuss the definition of an acute exacerbation and comment on what is known about the underlying pathophysiology in exacerbations of idiopathic pulmonary fibrosis and other ILDs. We also emphasize the similarities in the clinical presentation of the acute exacerbations regardless of the underlying ILD, highlight key prognostic features of the diagnosis, and underscore the importance of interdisciplinary management of acute interstitial lung disease exacerbations.

Keywords: Idiopathic Pulmonary Fibrosis (IPF); Interstitial Lung Disease (ILD); Acute exacerbation of ILD (AE ILD); Corticosteroids; Mechanical ventilation; Extracorporeal membrane oxygenation (ECMO)

1. Background

Interstitial lung diseases (ILD) are a group of over 200 disorders that are classified together because of similarities in clinical presentation, chest imaging findings, histologic characteristics, and physiological features. ILDs often arise in association with identifiable causes such as connective tissue diseases, familial, environmental exposures or medications, but also occur without an identifiable cause. When no cause can be identified, these are categorized as idiopathic interstitial lung diseases, the most prevalent being Idiopathic Pulmonary Fibrosis (IPF). Regardless of the etiology, ILDs are characterized by abnormal pulmonary parenchymal scarring and/or inflammation, leading to impairment of alveolar gas exchange, dyspnea, cough, and exercise intolerance [1]. In certain ILDs, the parenchymal abnormalities are progressive, recently classified as progressive-fibrosing phenotype, eventually leading to respiratory failure [2,3].

An acute exacerbation of the underlying interstitial disease is one of the main causes of respiratory failure and is associated with high morbidity and mortality. The etiologies of acute exacerbations of ILD (AE ILD) are poorly understood and are, therefore, difficult to predict. Even though most of the data on AE ILD is derived from acute exacerbations of IPF [4], acute events have also been increasingly recognized in other idiopathic interstitial cases of pneumonia, fibrotic hypersensitivity pneumonitis (fHP), and connective tissue disease-related ILDs (CTD ILD) [5].

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This review aims to provide a comprehensive summary of acute exacerbation of interstitial lung disease, covering aspects such as definition, epidemiology, associated risk factors, prognosis, and what is known about the pathophysiology of AE ILD. We describe characateristic features of acute exacerbations in IPF and other types of ILDs, highlighting differences based on the underlying etiology, and discuss the recommended diagnostic workup and management strategies that reflect current expert opinion guidelines. We further address the limitations of current guideline-directed therapy for exacerbations and discuss the importance of practicing patient-centered care under these dire circumstances.

2. Definition of Acute Exacerbation of ILD

Acute exacerbations of interstitial lung diseases are characterized by a rapid decline (typically less than 30 days) in respiratory function and oxygenation and the appearance of new radiological abnormalities: ground-glass opacification/consolidation superimposed on pre-existing patterns of interstitial pneumonia in patients with chronic fibrosing interstitial pneumonia. Radiographic examples of potential changes in an IPF exacerbation are provided in Figure 1. As acute exacerbations are not restricted to IPF, its definition has evolved over time. Initially reported in IPF, acute exacerbations have also been reported in other interstitial pneumonias. For this review, we will refer to AE ILD as an umbrella term for acute exacerbations of any ILD etiology. We will differentiate exacerbations of IPF and other ILDs by (i) Acute exacerbations of Idiopathic Pulmonary Fibrosis (AE IPF), and (ii) Acute Exacerbations of non-IPF Interstitial lung diseases (AE non-IPF), respectively. The similarities and differences between AE-IPF and AE non-IPF are highlighted in Table 1.

Table 1. Definitions and diagnostic criteria of acute exacerbations in IPF, and non-IPF.

	AE IPF [4]	**AE Non-IPF**
Definition	An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality	An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality in a patient with an ILD other than IPF
Characteristics		
Diagnosis	Previous diagnosis of IPF	Underlying interstitial lung disease different than IPF (i.e., CTD-ILD, fHP, unclassified ILD)
Symptoms	Acute worsening of dyspnea typically <1 month of duration	Acute worsening of dyspnea typically <1 month of duration
Alternative causes	Deterioration not explained by cardiac failure or fluid overload	Deterioration not explained by cardiac failure or fluid overload
Imaging	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP	HRCT with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern of ILD (can be UIP, NSIP, or others)
Potential Triggers	Infections, surgery, procedures, gastrointestinal reflux, and air pollution	Triggers can vary based on the underlying ILD: - CTD-ILD: opportunistic infections, new medications (DMARDs), worsening underlying CTD - fHP: environmental exposures General triggers like AE IPF: procedures, surgery, and air pollution
Prognosis	Poor prognosis	Slightly better than AE IPF, but varies depending on the severity of underlying disease, and background imaging pattern (worse in UIP, compared to NSIP or OP)

HRCT: high-resolution CT; AE, acute exacerbation; ILD, interstitial lung disease; CTD, connective tissue disease; fHP, fibrotic hypersensitivity pneumonitis; UIP, usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; DMARD, disease modifying antirheumatic drugs.

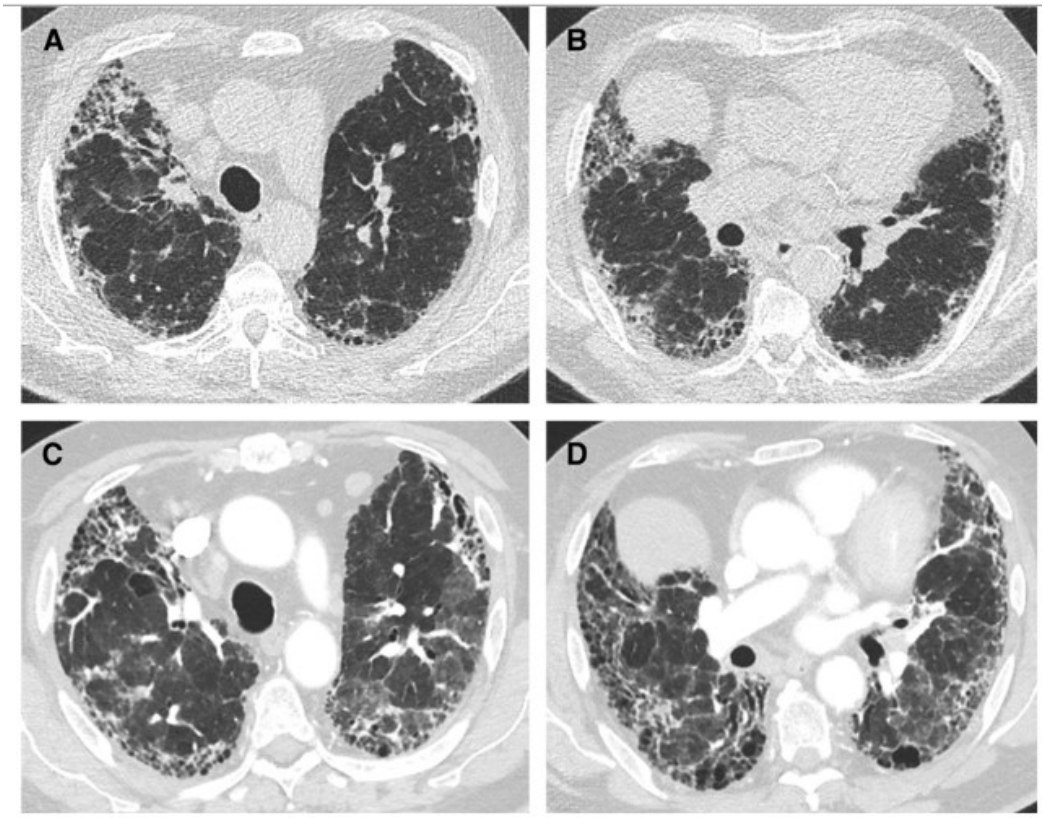

Figure 1. Acute exacerbation of IPF. (**A**,**B**). Transverse computed tomography sections obtained in the upper and mid lung zones and (**C**,**D**) during acute exacerbation showing newly developed, bilateral ground glass opacification in both lungs on a background of usual interstitial pneumonia pattern. Picture obtained from Raghu et al. [6].

2.1. Acute Exacerbation of Idiopathic Pulmonary Fibrosis (AE IPF)

Idiopathic pulmonary fibrosis is characterized by progressive, irreversible fibrotic parenchymal changes, which cause a decline in forced vital capacity (FVC) and lung diffusion for carbon monoxide (DLCO) over time. It is the most common form of idiopathic ILD, accounting for about 25% of all idiopathic interstitial pneumonias. AE-IPF is defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormalities [4]. The recommended diagnostic criteria include: (a) previous or concurrent diagnosis of IPF, (b) acute worsening, or the development of, dyspnea (typically of less than one-month duration from symptom onset), (c) new bilateral ground glass opacity and/or consolidation superimposed on a background pattern consistent with UIP, and (d) respiratory deterioration that cannot be fully explained by cardiac failure or fluid overload from other causes [4].

In addition, most of the limited clinical data regarding acute exacerbations is derived from observational studies in patients with IPF. An international working group recently revised the definition of an acute IPF exacerbation. It recommended distinguishing triggered exacerbations (infection, micro-aspiration, thromboembolic disease, acute heart failure, and post-pulmonary procedure) from idiopathic exacerbations where no precipitating event is readily identifiable [4].

2.2. Acute Exacerbations of Non-IPF ILD

As with IPF, the most common cause of respiratory failure in non-IPF interstitial lung disease is an exacerbation of the underlying interstitial process [7]. While an AE-IPF has been defined, there is no separate, specific definition of an acute exacerbation in non-IPF ILD. The diagnostic criteria applied in most studies to define AE non-IPF are based on the same criteria suggested in the most recent American Thoracic Society Working Group Statement [4]. Although there are no formal recommendations regarding the evaluation and management of AE-non-IPF, the exclusion of exacerbating factors like those outlined for AE-IPF is recommended. Connective tissue disorders are one sub-group of non-IPF ILDs that are associated with acute exacerbations. Specific definitions of AE secondary to CTD have been proposed [8], and like AE-IPF, acute respiratory failure in patients with an underlying connective tissue disorder is associated with common bacterial and opportunistic infections, diffuse alveolar hemorrhage, and exacerbation of the primary interstitial process. A distinguishing feature of the definition of AE of CTD-ILD is that the triggers of the condition include treatment with anti-

rheumatic drugs prior to hospitalization [9], which can be associated with elevation of the risk of infections, including opportunistic infections. Whether the drug is the cause of a drug-induced ILD or the trigger of an exacerbation can be difficult to determine, and both possibilities should be taken into consideration.

Another group of AE non-IPF includes exacerbations in hypersensitivity pneumonitis (HP). HP is an interstitial process associated with repeated exposure(s) to an inhaled antigen, most commonly avian, microbial (especially molds) or chemical [10]. In predisposed individuals, the inhaled antigen triggers a hypersensitivity reaction which causes a diffuse infiltration of mononuclear cells into the terminal bronchioles, alveolar wall, alveoli, and lung parenchyma, followed by the formation of granulomas and possible fibrosis [11]. Although HP can be self-limiting, repeated and prolonged exposure to the offending agent can induce interstitial fibrosis and/or acute exacerbations of the underlying lung disease, similar to that seen in IPF [12]. A case series of AE of HP showed that all patients had a clinical course similar to what is typically observed in AEs of IPF [13].

3. Epidemiology, Risk Factors and Prognosis of AE ILD

The overall epidemiology of AE-ILD is unknown, and rates vary widely depending on the analysis method and disease definition. Bearing these limitations in mind, the reported annual incidence of AE-IPF ranges from 1% to 20% in patients with IPF, and this wide range of values reflects variation in the definition used to define an exacerbation, study design and disease severity [4,14]. Exacerbation rates are typically thought to be less common in milder forms of IPF [14–16]. AE IPF is responsible for over half of IPF-related respiratory hospitalizations [15], is the second leading cause of mortality in IPF patients [17], and accounts for up to 40% of IPF-related mortality [18]. Once hospitalized, mortality can be as high as 50% in mild exacerbations and may exceed 90% for patients admitted to an intensive care unit [1]. The average survival time after an AE-IPF is on the order of 3 to 4 months [4].

While there is much less rigorous epidemiologic data on AE non-IPF, the incidence varies depending on the ILD subtype, and the majority of the studies indicate that patients with IPF are at higher risk for developing AE compared to patients with non-IPF ILD [7,19]. For example, the overall annual incidence of AE of fibrosing Non-Specific Interstitial Pneumonia (NSIP) is estimated to have an incidence of 4.2%. In contrast, an AE of CTD-ILD ranges from 1.25% to 7.2% [7,8,20]. The highest rates of AE due to CTD ILD occur in patients with rheumatoid arthritis- associated ILD (RA-ILD), systemic sclerosisassociated ILD (SSc-ILD), and idiopathic inflammatory myositis [8,21–23]. In addition to the typical rheumatic diseases, microscopic polyangiitis has also been associated with an increased risk of acute exacerbations [21,24]. Importantly, patients with rheumatologic conditions who display a radiological pattern of Usual Interstitial Pneumonia (UIP) had increased incidence of AE ILD [5,8,21].

Finally, HP prevalence varies widely, ranging from less than 2% in the United States to up to 15% in Europe and Brazil [25], and is the third most common ILD after IPF and CTD-ILD, respectively [2,26]. Evidence of AE non-IPF due to HP has a reported incident range between 11.5% and 22% [7,27,28]. In people with fHP who demonstrate a UIP pattern, the risk of an acute exacerbation was higher than those without a UIP pattern [27].

Several clinical risk factors have been associated with developing an AE ILD. Acute exacerbation of IPF is more common in patients with physiologically and functionally advanced disease; however, it is important to remain vigilant as an exacerbation can manifest at any time during the course of any ILD [5]. Several risk factors have been associated with an increased risk of AE IPF; these include a reduced forced FVC, low DLCO, decreased six-minute walk distance (6 MWD, <180 m), increased dyspnea (UCSD SOBQ and SGRQ), hypoxia (PaO2 < 62 on ambient air), and interval declinations in DLCO (>15%), and FVC (>10%) [4,29]. Similar risk factors were also noted in AE non-IPF due to HP [28]. Other important epidemiological risk factors for AE ILD include male gender, lifelong non-smokers, younger age at the time of diagnosis, a history of prior exacerbation, co-existing pulmonary hypertension, coronary artery disease, gastroesophageal reflux disease, and obesity [7]. Similarly, environmental factors such as air pollution [8] and winter season [5,30] have been linked to AE IPF, the latter possibly due to viral infections.

Mechanical stress might be another contributing factor for AE ILD. Risk factors such as surgery [7,15], prolonged mechanical ventilation, high tidal volume and high intraoperative oxygen concentration during procedures have been associated with increased risk for AE [31]. In addition, studies have shown that lung biopsy significantly increases the incidence of AE IPF, and may be as high as 23% [32] compared to approximately 4% in patients who do not undergo biopsy [4]. Due in large part to this increased risk, the most recent ATS/ERS/JRS/ALAT guideline recommends against surgical lung biopsy in patients with a high-resolution CT pattern defined as typical UIP or probable UIP [6].

Although AE ILD can occur in different histological forms of ILD, the UIP radiologic pattern was associated with a higher risk for AE-ILD in patients with fibrotic HP [27,28] and CTD ILD [5,7,8,21]. Similarly, the presence of UIP

pattern was associated with a higher risk of more severe AE ILD in patients who received chemotherapy [33] and other novel therapies [34].

The overall prognosis for AE ILD is poor and was thought to be affected by the underlying etiology, with IPF, for example, having worse outcomes compared to other fibrotic ILD associated with autoimmune disorders or hypersensitivity pneumonitis. However, recent evidence has shown that in-hospital mortality and survival after discharge were the same between IPF and patients without IPF [19,35–37]. This observation is consistent with previous studies that reported that the rate of in-hospital mortality in patients with CTD ILD and fHP is also quite high, ranging from 50–100% [5,8,13]. On the other hand, other studies found that other radiologic patterns, such as NSIP are typically associated with a relatively good discharge rate and long-term prognosis [38]. This supports the possibility that an AE ILD with a radiologic background of UIP pattern has a significant negative prognostic factor.

4. Pathophysiology–Etiology

The etiologies of AE ILD are poorly understood and are, therefore, difficult to predict. AE ILD shows histopathology consistent with acute lung injury, either diffuse alveolar damage (DAD) or organizing pneumonia [16], which is superimposed on the underlying fibrotic interstitial pneumonia regardless of the etiology of ILD [4,5,8,13,39]. DAD is a relatively generalizable finding with several forms of acute lung injury and is characterized by interstitial edema and hyaline membrane formation because of epithelial injury and hyperplasia of type II pneumocytes. As DAD evolves, the pulmonary interstitium may be thickened by myxoid fibroblastic tissue, which can further impair gas exchange and create a ventilation-perfusion mismatch [39]. DAD is found on lung biopsy in many types of acute lung injury, often being the only evident pathology. The causes of acute lung injury are extensive and include infection, aspiration, medications, sepsis, blood transfusions, surgery and/or inhalation of smoke or toxic gases. Importantly, the presence of a histological pattern of organizing pneumonia was associated with a higher survival rate than that of DAD [40]. As mentioned, most of the evidence on AE ILD is from AE IPF. It is useful to consider that acute lung injury and AE IPF share many clinical features, including the presence of diffuse alveolar damage; therefore, it can be concluded that AE in other non-IPF ILD can exhibit very similar clinical, radiological, and histological findings [4,39].

Several intrinsic and extrinsic mediators have been hypothesized to trigger an event in AE ILD. Intrinsic factors, such as epithelial homeostatic imbalance affecting fibrocyte differentiation, macrophage immune polarization, and autoimmune emergence against heat-shock proteins (HSP) and phospholipid-binding proteins have been identified in patients with AE IPF [35,41]. Similarly, activation of macrophages and neutrophils leads to the release of reactive oxygen species and proteases, causing increased lung damage, creation of damage-associated molecular patterns (DAMPs), capillary alveolar permeability, and oxygen deficiency. This is supported by evidence demonstrating that AE ILD has been associated with increased numbers of neutrophils in bronchioalveolar lavage (BAL) fluid and decreased macrophages and eosinophils similar to ARDS, which correlates with worse prognoses [42]. It is particularly relevant to mention that patients with CTD ILD can experience exacerbations due to a flare of the underlying rheumatologic disorder, which is known to occur in patients with Sjogren's syndrome, Rheumatoid Arthritis and Systemic Lupus Erythematosus.

In regards to potential extrinsic factors, pulmonary infections have been commonly associated as triggers for AE-ILD, particularly in patients with underlying CTD ILD due to immunosuppressive medications [43]. There is growing evidence that both viral and bacterial infections have been involved in developing AE ILD [44,45]. However, the causative pathogen was only found in a minority of patients [4,7]. Evidence of the role of infections is further supported by the seasonal nature of AE ILD [5,30]. Similarly, changes in the respiratory microbiome have been linked with the development of AE IPF. Specifically, alterations in *Campilobacter* and *Stenotrophomonas* species were noted in patients with exacerbations compared to stable IPF [7,8,44]. Microaspiration has also been linked to the development of AE ILD [4]. This association was noted in a *post hoc* analysis where AE IPF occurred in patients who were not taking anti-acid therapy [46]. Additional evidence demonstrated higher concentrations of pepsin (a marker of gastric-content aspiration) in BAL samples were present in patients with AE–IPF compared to individuals with stable IPF [47]. This potential trigger may be more likely in certain conditions, such as systemic sclerosis, where reflux and esophageal dysmotility are prevalent and have been associated with decreased pulmonary function.

Recent advances in treatment options for rheumatologic conditions, particularly in rheumatoid arthritis, have increased the incidence of drug-induced pneumonitis [8,34] and also may induce exacerbation of pre-existing CTD ILD [9]. However, it is also possible that the person experienced a non-triggered AE ILD. Therefore, it is often difficult to distinguish between these possibilities and clinical suspicion of drug-induced pneumonitis should remain high.

5. Diagnostic Evaluation

The diagnosis of AE-ILD relies solely on clinical and radiological findings, and a personalized diagnostic algorithm may expedite the etiology of an exacerbation and improve a given patient's overall outcome [1]. The initial diagnostic workup for acute respiratory failure in patients with chronic ILD entails a tailored approach to exclude extra parenchymal causes such as pulmonary emboli, pneumothorax, pulmonary edema, and pleural effusions. Identification of potential triggers such as infection, aspiration, thoracic or other forms of surgery and procedures, and recent changes in medications should regularly be performed. Urgent testing should include either a chest X-ray, highresolution CT (HRCT), and/or CT with contrast/angiography to exclude pulmonary embolism and provide direct evaluation of parenchymal abnormalities. Because the use of intravenous contrast can result in unpredictable attenuation of lung parenchyma, it is generally recommended that a non-contrast CT is obtained prior to one with contrast [48]. Cardiac etiologies such as decompensated heart failure and volume overload need to be ruled out, thus, other potential diagnostic tools include trans-thoracic echocardiogram and assessment of myocardial injury and atrial stretch through troponin and NT-proBNP measurement.

The utility of lavage (BAL) has been controversial in diagnosing AE ILD. In patients with chronic immunosuppression (most likely in the setting of non-IPF ILD), atypical or opportunistic infections are a consideration thus if BAL is performed, specimens should be sent for bacterial, fungal and mycobacterial cultures, including viral PCR tests [35,49]. Furthermore, cellular profile analysis of alveolar fluid may be helpful. As mentioned before, increased neutrophils in BAL have been found in AE IPF. Still, alveolar fluid cell counts (neutrophils v. lymphocytes) may help differentiate specific ILD subsets and/or predict the relative responsiveness to corticosteroids. It is important to mention that the potential benefits of bronchoscopy need to be individually tailored due to the risk of causing more severe respiratory failure and other procedure related complications (i.e., pneumothorax). For instance, a previous study demonstrated that in patients with acute respiratory failure and underlying chronic ILD who underwent bronchoscopy, 25% were transferred to the ICU after their procedure. Within that group, 71% required invasive mechanical ventilation, and only minimal changes in management and outcomes were observed [5,50]. Due to a high risk to reward ratio, other procedures, such as transbronchial biopsy and cryobiopsy should be avoided.

Laboratory workups should follow the same standard of care as for patients with acute respiratory failure. Although elevation of white blood cells and inflammatory markers have been observed in AE non-IPF compared to AE IPF, these findings are not specific [37]. Currently, there are no established biomarkers in clinical practice that can predict the onset or outcome of AE ILD, and their use remains limited in research. There are some promising biomarkers, like KL-6 and interleukin-8 (which is critical for neutrophil recruitment), which were associated with AE ILD [23,51]. Interestingly, one study reported that KL-6 was part of the initial workup for AE-IPF only in Asia (54%) but not elsewhere [52], and others have recommended that KL-6 levels should be taken with caution in non-Asian populations [53].

6. Management

There are no proven therapies for AE ILD, and international guidelines recommend supportive care, oxygen supplementation, and palliation of symptoms [5,16]. Despite evidence that failed to show a mortality improvement [54,55], current guidelines provide a weak recommendation for the use of systemic corticosteroids [4,16]. This is largely inferred from anecdotal evidence suggesting there may be a benefit when organizing pneumonia is present [5,40]. This could be the explanation for the relatively favorable outcomes of AE non-IPF compared to IPF, as patients with CTD-ILD, fibrotic HP, and other ILD with progressive fibrotic phenotype are more likely to have histopathology consistent with organizing pneumonia [5,13,56]. In patients with scleroderma-related ILD, high-dose corticosteroids should be used judiciously because a scleroderma renal crisis may be precipitated. Corticosteroids—usually methylprednisolone or prednisone—doses are variable and can include pulse dosing of methylprednisolone (500–1000 mg/day) for severe exacerbations [4,14,49,52]. However, lower initial doses of prednisone (e.g., 1 mg/kg per day) can be used in patients with milder disease, and steroid pulse dosing is typically reserved for cases of vasculitis or anti-MDA5 dermatomyositis-associated rapidly progressive ILD. It is a generally accepted practice to start corticosteroids after sampling for bacterial cultures and initiation of broad-spectrum antibiotics. Given the high mortality associated with AE-ILD and the difficulty in exclusion of infectious etiologies, empiric use of oseltamivir during influenza season is reasonable and broad-spectrum antibiotics are often administered empirically [4]. For those at risk of *Pneumocystis jirovecii* pneumonia, evaluation with PJP PCR and Beta-D-Glucan should be obtained and empiric therapy considered [14]. A study in AE

IPF using procalcitonin levels to guide antibiotic therapy reduced antibiotic exposure, but had no impact on mortality [57]. General management principles are provided in Table 2 and a diagnostic algorithm is highlighted in Figure 2.

Table 2. Comprehensive Management Strategies of Acute Exacerbation of Interstitial Lung Diseases.

Management Strategy	Description
Trigger identification and treatment	Evaluate and address potential triggers such as infections, aspiration, or drug-induced lung injury based on clinical presentation
Supportive care and respiratory therapy	Supplemental oxygen to maintain adequate oxygen saturation Delivery methods include: - High-flow nasal canula: Preferred method due to better comfort and oxygenation. - Non-invasive positive pressure ventilation (CPAP or BiPAP): for patients with respiratory distress and/or hypercapnia - Invasive mechanical ventilation - Extracorporeal membrane oxygenation: considered in selected patients only as bridge to transplant
Corticosteroids	Weak recommendation with low quality of evidence in international guidelines. Outcomes may be better in AE non-IPF No consensus on dosage, ranges from oral prednisone 1 mg/kg/day to pulse doses of intravenous methylprednisolone (500–1000 mg/day) Dosage depends on clinical practice, underlying etiology and severity (pulse doses for rapidly progressive ILD)
Immunosuppressive medications	No proven benefits in AE IPF Limited evidence also AE non-IPF, especially in CTD ILD Currently, no conclusive evidence to support their use
Antimicrobials	Empiric antibiotics are recommended by guidelines (isolation of pathogens can be difficult) Consider empiric influenza or SARS-CoV-2 treatment during virus season Evaluate for opportunistic infections and treat empirically on a case-by-case basis
Palliative and Symptoms management	Early goal of care discussions are encouraged Optimize comfort and quality of life, including pain and dyspnea control; consider palliative care involvement for advanced disease
ECMO/Lung Transplant	ECMO should be reserved for transplant-eligible patients Consider referral for lung transplantation in appropriate candidates Eligibility on a case-by-case basis

CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; ILD, interstitial lung disease; AE, acute exacerbation; IPF, idiopathic pulmonary fibrosis; CTD, connective tissue disease.

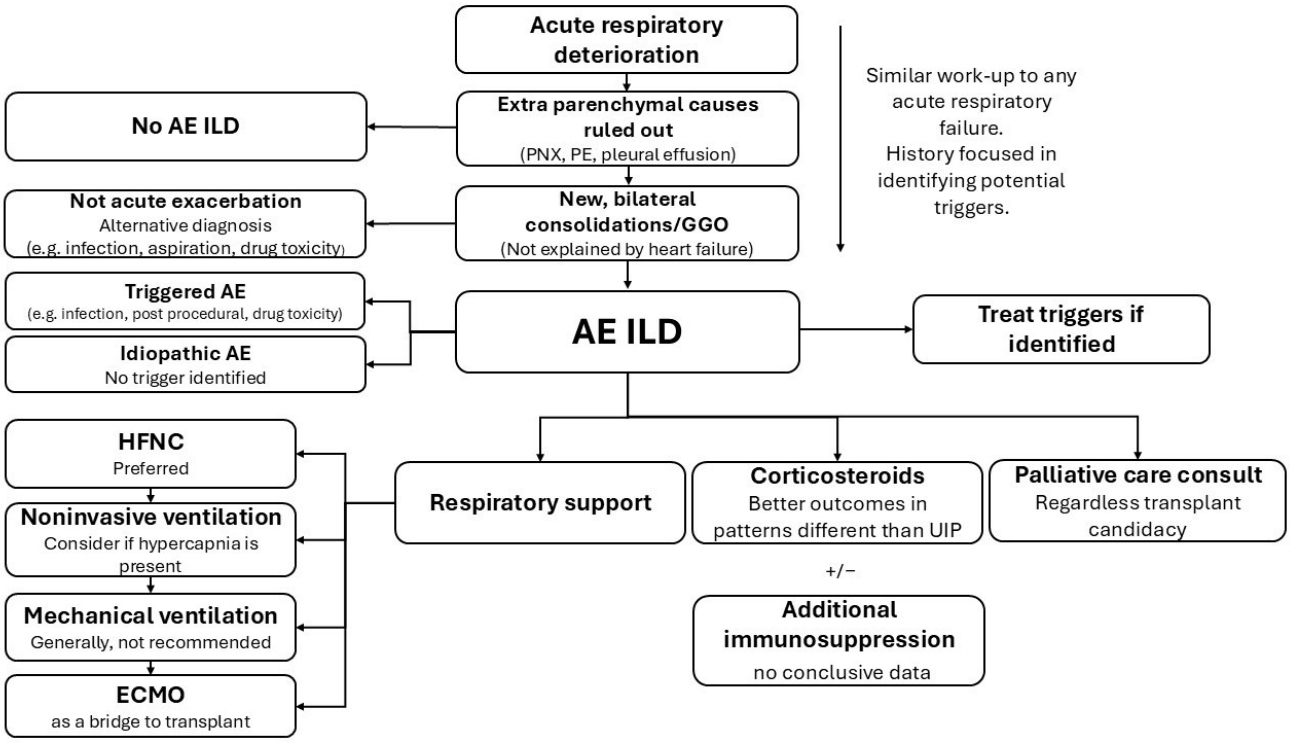

Figure 2. Proposed approach for the evaluation and management of Acute Exacerbation of ILD. AE = acute exacerbation; GGO= ground glass opacity; HFNC = high flow nasal canula; PNX = pneumothorax; PE = pulmonary embolism; UIP = usual interstitial pneumonia; ECMO = extracorporeal membrane oxygenation.

If an underlying exposure or medication is suspected, then it is imperative that the exposure be removed and/or the medication be discontinued. This is particularly relevant in AE non-IPF as withdrawal of Disease Modifying Anti-Rheumatic Drugs (DMARDs) is often the first step of the therapeutic strategy [8]. Similarly, attempts to identify and eliminate potential exposures to causative toxic agents in people with hypersensitivity pneumonitis [5].

Additional immunosuppressive agents (such as cyclosporine A, cyclophosphamide, tacrolimus, or azathioprine), usually in combination with corticosteroids, have been used for the management of AE ILD with no conclusive evidence to support their use. Recently, the EXAFIP study showed that the addition of cyclophosphamide did not improve either short-term or long-term prognosis, and an increased 3-month mortality in the treatment arm was observed [58]. Recombinant thrombomodulin, a novel agent that has anti-thrombotic and anti-inflammatory properties involved in the development of lung fibrosis, has demonstrated possible survival benefits in AE IPF [59]. However, a recent Japanese nationwide observational study failed to replicate these results [60], and most specialized ILD centers do not routinely use thrombomodulin [61]. The STRIVE-IPF trial, which is testing the efficacy and safety of the combination of plasma exchange, rituximab, intravenous immunoglobulin, and corticosteroids for the treatment of AE IPF, recently completed enrollment, and results are pending. As in AE IPF, there are no randomized controlled trials of direct therapies for exacerbations of non-IPF ILD. As the underlying causes for non-IPF ILD (e.g., CTD) are often treated with immunosuppressants, these medications may hold promise. However, the results remain inconclusive [8,49]; there may be an increased risk of side effects, and there was no survival benefit when additional immunosuppression (cyclophosphamide) was used [62].

As mentioned earlier, exacerbations may cause respiratory failure that, under normal circumstances, would require invasive mechanical ventilation. However, guidelines make a weak recommendation against its use due to high in-hospital mortality rates [4,5,16]. There are also studies demonstrating that inpatient mortality is worse in patients with AE IPF who undergo mechanical ventilation compared to non-invasive ventilation [63,64]. The decision to intubate must be assessed on a case-by-case basis as the risk may outweigh the benefits of this intervention, especially when infection and other factors have already been addressed.

Supplemental oxygen can be provided through a high-flow nasal cannula (HFNC) or non-invasive positive pressure ventilation (CPAP or BiPAP). HFNC appears to reduce mortality in acute hypoxic respiratory failure, but this has not been confirmed with prospective randomized clinical trials in patients experiencing acute ILD exacerbations [5,65]. Several potential physiologic advantages of HFNC include reducing dead space, providing some positive end-expiratory pressure (PEEP), reducing respiratory secretions, and lowering the respiratory rate and work of breathing [66]. NIPPV provides positive pressure through a nasal/oral interface. The main physiologic benefit of PEEP is increased oxygenation related to improved alveolar recruitment. Bilevel NIPPV (BiPAP) has the additional benefits of reduced breathing work and improved CO_2 levels when mixed respiratory failure is present. However, NIPPV may cause further lung injury due to increased lung volumes and airway pressure in patients with poor lung compliance [67]. In general, HFNC is better tolerated compared to NIPPV and, therefore, may be the preferred method for oxygen supplementation in patients with AE ILD [68].

If mechanical ventilation becomes necessary, it should be preceded by a discussion with the patient and their caregivers to ensure that a humane, values-based, realistic, and well-informed decision regarding goals of care can be made. Patients with fibrotic lung disease often find it difficult to ventilate due to poor lung compliance, decreased ability to achieve alveolar recruitment, and increased risk for ventilator-induced lung injury [35,67,69]. Similar to ARDS, low tidal volume protective mechanical ventilation is generally recommended, though the ideal ventilatory strategy remains unknown [69]. Additional strategies such as open lung ventilation and recruitment maneuvers or prone positioning have proven unsuccessful in AE ILD [70,71]. Importantly, a retrospective study in patients with AE ILD who received mechanical ventilation showed that radiologic extension of lung fibrosis directly correlates with worse respiratory mechanics (increases in plateau pressures and peak airway pressure) and increased mortality [72]. Similarly, a case series of seven patients with AE interstitial pneumonia with autoimmune features who received mechanical ventilation, none of them with UIP pattern, had lower mortality compared to patients with ARDS of known causes [73]. These studies might suggest that the prognosis of patients with AE ILD in mechanical ventilation is related to both the extension of the fibrotic changes and the presence of UIP pattern regardless of the underlying etiology of ILD.

Finally, extracorporeal membrane oxygenation (ECMO) has been considered an emerging modality as salvage therapy in the management of refractory hypoxic respiratory failure. In eligible patients, invasive mechanical ventilation and ECMO may serve as a bridge to lung transplant. However, ECMO experiences in the setting of AE-ILD have been limited; this modality may not be available, and many patients may not be eligible for or desire a lung transplant [5,67]. Since lung transplants are limited resource, the principle of utility requires that survival be maximized when choosing

transplant candidates. In this scenario, variable outcomes, depending on the underlying ILD, have been reported in patients who have undergone ECMO and or lung transplant. For instance, a single center study of 89 patients with IPF, of whom 37 had an AE IPF, demonstrated that only one-third of patients who were placed on ECMO survived transplantation. In addition, patients who were transplanted during AE-IPF had significantly worse short-term and long-term survival compared with patients transplanted during more stable forms of IPF. Importantly, most of the deaths in the AE-IPF transplanted group were attributed to chronic illness and other multi-organ failure in contrast to more historic causes of death after lung transplantation [74]. Another study described 110 transplant recipients with IPF, of whom 10 were done during AE IPF, showed that the AE-IPF group demonstrated a higher rate of primary graft dysfunction (30.8% vs. 14.4%); however, mortality was not reported [75].

On the other hand, ECMO and lung transplant have been described in patients with anti-MDA5 dermatomyositis. Of 15 patients with anti-MDA5 and rapidly progressive ILD who underwent ECMO, five patients, none of whom was listed for transplant prior to their hospitalization, underwent a lung transplant, and the remaining 10 patients died following a median of 30 days on ECMO [76]. Also, a case series reported that five of seven patients (71%) with an acute exacerbation of interstitial pneumonia with autoimmune features survived with prolonged mechanical ventilation and, in three cases, with ECMO [73]. However, these patients had prolonged hospitalizations and developed significant comorbidities. In general, in patients who are deemed ineligible for a lung transplant, ECMO is unlikely to improve mortality or quality of life and, therefore, should not be offered.

Patients with progressive fibrotic-ILD, including advanced IPF, suffer from a heavy symptom burden and often a poor quality of life. Incorporating palliative care and regular counselling earlier in the course of the disease will allow patients and their caregivers to obtain better and more effective pharmacological and psychosocial interventions to improve their lives throughout the disease course [77]. Unfortunately, several studies have observed poor utilization rates of palliative care before an exacerbation. For example, one study reported that only 13.7% of the patients with IPF had a formal referral to palliative care, and for the majority of those referred (71%), most occurred within 1 month of their death [78]. Another study reported that end-of-life discussions were held before the onset of AE in only 23% of the patients, and most of the discussions happened after the admission for AE-IPF [79].

In transplant ineligible individuals, HFNC seems to be the preferred oxygen support modality for patients with AE ILD at the end of their life. This modality allows patients to eat and converse with loved ones and it was associated with the highest Quality of Dying and Death questionnaire score as rated by their family members [80]. In terminally ill AE-IPF patients, opioids are an effective treatment for dyspnea and are usually administered when the recovery is deemed unlikely. Importantly, patients who had end-of-life discussions before the onset of AE were more likely to use opioids earlier [79]. This reinforces the concept that early palliative referral can have a significant benefit for patients with fibrotic lung disease.

7. Preventive Strategies

ILD specific treatments and management of comorbidities may be the best options to prevent acute ILD exacerbations. For example, in patients with IPF, nintedanib delayed the time to first exacerbation [81], and pirfenidone reduced the risk of respiratory-related hospitalizations [17,82,83]. However, since anti-fibrotic medications take weeks to months to effect changes in FVC, they should not be relied on for immediate efficacy in AE ILD. Unfortunately, severe side effects of antifibrotic therapies often lead to poor adherence or discontinuation, limiting their clinical benefits. For instance, an Italian prospective cohort study showed that patients with antifibrotic adherence above 75% of the time had a lower risk of death or acute exacerbations compared to patients with less adherence [84]. Additionally, a recent small study demonstrated that patients on a reduced dose of nintedanib experienced less annual decline in FVC compared to those who discontinued antifibrotic therapy [85]. These findings suggest that utilizing a low dose of nintedanib in patients who initially could not tolerate full doses may be a strategy worth considering to prevent exacerbations and improve survival. Because of a strong association between IPF and GERD, the use of anti-acid therapies may hold promise to prevent exacerbations [46]. Whether anti-acid medications stabilize progressive IPF and/or prevent acute exacerbations remains controversial.

8. Conclusions

AE ILD is an unpredictable serious, life-threatening event that can occur at any time during the disease course of ILD and has a poor prognosis. Although anti-fibrotic medications reduce the likelihood of an exacerbation, risk factors for AE ILD remain poorly understood, and this review attempts to provide a state-of-the-art comprehensive analysis of

these contributors. Exacerbations appear to be linked to the severity of the underlying interstitial lung disease and the presence of a UIP radiologic pattern. We emphasize certain differences between AE IPF and AE non-IPF, which can tailor diagnostic and management strategies to each subgroup. The mainstay of therapy includes supportive care and early recognition of potentially reversible causes. Corticosteroids may play a role in a subset of patients—particularly those with AE non-IPF due to CTD-ILD or those showing organizing pneumonia on imaging; however, the optimal dosage and duration have not yet been defined. Oxygen supplementation with HFNC or NIPPV is recommended, while more aggressive therapies, such as mechanical ventilation and ECMO, should be limited to patients who are potential transplant candidates. We advocate for the early involvement of palliative care to assist in managing complex discussions and minimizing suffering for patients with AE ILD. Considering the overall poor prognosis of the AE, and lack of evidence-based therapy options, more studies in this field are urgently needed to determine effective treatments.

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