Acute Exacerbation of Interstitial Lung Disease: Definitions, Epidemiology, Prognosis and Management

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INTRODUCTION

DEFINITIONS - Interstitial lung diseases (ILDs) are a wide, heterogeneous group of diseases. ILDs have a vast range of clinical presentations, disease course progression, and prognosis but they seem to share a common feature that ILDs result in fibrosis and destruction of the lung parenchyma [1–4]. Initially, the term acute exacerbation of interstitial lung disease (AE-ILD) was first used to describe exacerbations of idiopathic pulmonary fibrosis (IPF), and a criteria for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) was defined by the IPF clinical trials network (IPFnet) back in 2007, which used clinical, radiological and histopathological parameters to describe such events based of previous literature [5]. This criterion was revised in 2016 by an international working group which defined AE-IPF as a clinically significant decline of a patient's respiratory status occurring over a timeframe of less than 1 month that is accompanied by new onset radiological abnormalities on high-resolution computer tomography (HRCT) such as diffuse, bilateral ground-glass opacities in the absence of any other obvious clinical causes like left side heart failure, pulmonary embolism, pneumothorax or fluid overload [6]. In discordance with the previous IPFnet definition, the international working group in 2016 promoted the differentiation between a triggered AE-IPF (e.g., infection, post-procedural, or aspiration) and an idiopathic AE-IPF where no identifiable trigger was found [6]. The goal of the revised definition was to broaden the AE-IPF criteria to allow more inclusions. Table (1) compares the definitions of IPFnet and international working groups.

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Unfortunately, no specific criteria were made for the diagnosis of AE-ILD in non-IPF ILD; thus, a growing body of literature has been using the AE-IPF criteria to diagnose AE-ILD in non-IPF ILDs [7,8]. This action was taken due to the similarities in the histopathological findings, mainly of diffuse alveolar damage (DAD) [9], as it was not only found in IPF but also connective tissue-related ILD (CTD-ILD), especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD), idiopathic fibrotic non-specific interstitial pneumonia (NSIP) and chronic hypersensitivity pneumonitis (HP). Other findings have also been found to overlap between AE-IPF and AE-ILD, such as radiological findings on HRCT (e.g., ground-glass opacification and consolidations) [7,10–13]. However, it should still be pointed out that the international working group definition of AE-IPF refers exclusively to IPF. The authors were against a definition that included other ILDs. [6–8,10,11,14,15].

AE-ILD in the clinical setting includes a rapidly worsening respiratory profile, including shortness of breath within less than 1 month. This can also be associated with cough, fever, increased sputum production, and a flu-like prodrome. Moreover, since patients can present with severe hypoxemia and a picture of acute respiratory failure, these patients often require admission to the intensive care unit and require various methods of assisted ventilation [1,5–8,10,13,15].

EPIDEMIOLOGY - Acute exacerbations are not an event that occurs within a specific time after the diagnosis of the disease; they can sometimes even be the presenting manifestation of ILDs [1,3,5]. There has been a great variance within the literature regarding the rates for AE-ILD, which may be influenced by the change in definition, the exact ILD entity, and the severity of the disease upon presentation or even missing diagnostic studies (e.g., HRCT due to patient instability) [6,16]. Yet, the incidence of AE-IPF has been estimated to be 41 cases per 1000 person-years, with 10% of IPF patients developing an acute exacerbation in the first two years after their diagnosis [1,3,6,17,18]. However, there is much less data regarding the rate and frequency of AE-ILD in non-IPF ILD. Yet, studies have shown that IPF ILD patients are more likely to experience acute exacerbations than non-IPF ILD patients [19–22]. The estimated yearly incidence of AE-NSIP and AE-CTD was reported to be 4.2% and from 1.25% to 3.3%, respectively, and within CTD-ILD, acute exacerbations were found to be more common in RA-ILD [7,10]. Moreover, the reported 2-year incidence of AE-HP with usual interstitial pneumonia lesions on lung biopsies was 11.5% [11].

PATHOPHYSIOLOGY AND ETIOLOGY OF AE-ILD - AE-ILDs are unpredictable in nature and can occur at any point in time. Many factors have been speculated in playing a role in triggering the onset of the AE-ILD; it could be an intrinsic factor leading to the progression of the underlying disease, an external factor could also be the underlying culprit, or it could be a combination of the two [6,23]. Environmental factors and genetic factors most likely interact on the individual level, thus leading to AE-ILD in only a subset of patients with ILD [5].

Among the intrinsic factors that play a role in AE-ILD pathophysiology, epithelial injury and autoimmunity were among the most probable contributing factors [5,24,25]. In an AE-ILD, loss of cellular integrity and alveolar injury may cause an increase in fibrin production and kick-start the remodeling process. This leads to neutrophilia in bronchoalveolar lavage (BAL) and a histological pattern of DAD [5,24]. Fibroblasts have also been found to play a role in AE-ILD, as they are already elevated in stable ILD and are even more elevated during an AE-ILD, as patients with a fibrocyte count of > 5% of total leucocyte count were found to have a worse prognosis than patients who did not [26]. Heat shock protein (HSP) 47 is one of the molecular chaperons that are human collagen-specific and is involved in the early stages of secretion and biosynthesis of collagen molecules [25]. An interesting study found that 25% of patients with IPF had anti-HSP 47 IgG autoantibodies; these patients were found to be at a higher risk of AE-ILD and had a higher mortality rate compared to patients with negative autoantibodies [27].

As for extrinsic factors, air pollution [28], microaspiration [6], infection, drug toxicities [29,30], and post-procedural AE-ILD have all been reported [19,20]. Regarding microsapiration, according to a retrospective analysis of 3 IPF placebo-controlled clinical trials, none of the patients who had an AE-ILD were on antiacid treatment [31]. The theory that infection is a trigger for AE-ILD is supported by the fact that most episodes occur during between December and May [18,32]. Moreover, a group of studies showed that being on immunosuppressive medications increased the risk of developing AE-ILD [18,28,33]. As for procedure-induced AE-ILD, the etiology is thought to be due to ventilatory-induced injury, preoperative mechanical stretch, and fluid balance shifts [6,34].

RISK FACTORS - Many clinical risk factors have a role in developing an AE-ILD. First, functionally and clinically advanced ILD are both important risk factors. Thus, a low forced vital capacity

(FVC) seems to be an important risk factor [3,18,35]. Moreover, a low diffusing lung capacity for carbon monoxide (DLCO) [11,18,35], a low total lung capacity (TLC) [11], a low 6 min walking distance [18], an impaired baseline oxygenation [18,36], increased dyspnea [18,37], and a previous episode of AE-ILD [28,38] all seem to be significant clinical risk factors that increase the possibility of exacerbations.

Other risk factors include coexisting pulmonary hypertension [39], diagnosis with coronary artery disease [18], increased exposure to ozone and nitrogen dioxide compounds [28], and a higher body-mass-index [37] have also been found to increase the incidence of AE-ILD.

Cancer requiring chemotherapy has also been linked to causing AE-ILD. In a retrospective study on patients with ILD who had coexisting cancer and were treated with chemotherapy, 21.9% of these patients developed an AE-ILD during the treatment period [40].

DIAGNOSTIC EVALUATION UPON PRESENTATION

When a patient with a known ILD presents to the hospital for an AE-ILD, it is imperative to know whether the AE-ILD is idiopathic or triggered by another process like an infection. Idiopathic AE-ILD has been found to have a worse prognosis than triggered AE-ILD, mainly due to the lack of a specific target for treating the acute episode [29]. As we stated earlier, AE-ILD may be the presenting feature of the disease, but a variety of radiological findings like traction bronchiectasis and reticulation in a patient with no known ILD often suggest an undiagnosed ILD. Moreover, surgical biopsies to confirm the diagnosis of IPF are not recommended as they are linked to worse episodes of AE-ILD and have possible morbidity and mortality risks [29,41,42].

Infection can be identified by vital signs, cultures, and a range of laboratory evaluations like white blood cell count and, interestingly, procalcitonin [43]. Bronchoscopy has been found to have a relatively low yield, as only 13% of patients experiencing AE-ILD who underwent bronchoscopy have had findings that required a change in management [44]. Moreover, cultures and bronchoscopy samples should be considered for herpesvirus and pneumocystis jirovecii as patients having AE-ILD attacks are often immunocompromised [44].

HRCT remains a cornerstone of assessing patients with AE-ILD as it can distinguish between new and superimposed consolidative and ground glass abnormalities. Moreover, the extent and severity of those new findings have been found to be a strong predictor of the outcome and patient's survival of the AE-ILD episode [45,46].

MANAGEMENT OF AE-ILD

Despite the well-described poor outcomes in these patients, there is a lack of prospective randomized studies evaluating the optimal management of AE-ILD. High morbidity and mortality associated with acute exacerbations may hinder the feasibility of conducting research, as it may be difficult to obtain consent from distressed patients and their families, so the optimal treatment regimen is still undefined [47].

International guidelines for the management of AE-IPF recommend supportive care to alleviate symptoms and long-term oxygen therapy for patients with resting hypoxemia [23]. Corticosteroids have always been a part of AE-IPF treatment. However, it is weakly recommended, suggesting their use in most cases of AE-ILD, especially in acute exacerbation of NSIP and CTD-ILD and ILD associated with various vasculitis syndromes [48], but acknowledging that their omission may be reasonable in certain situations [23]. However, this recommendation is based on expert opinion and retrospective studies [4,45,48] and there is an ongoing debate regarding the need for a steroid-free approach in AE-IPF [49,50]. The dosage of corticosteroids varies and can range from 1mg/kg of prednisone to pulse steroids of 500–1000 mg of methylprednisolone, depending on institutional preferences and the severity of the presentation [47]. Prospective clinical trials are needed to address the uncertainty surrounding the use of corticosteroids in AE-ILD [47].

In cases of suspected AE, identifying and eliminating exposure to potential causative toxic agents on a case-by-case basis is recommended, especially in HP cases [47]. Antibiotics are routinely administered in AE-ILD, and appropriate workup is conducted to evaluate underlying infections [47]. A routine course of antibiotics lasting 7 to 10 days is a reasonable approach. The course should consider broad-spectrum antibiotics and coverage for atypical pathogens, as most patients are already immunocompromised. Azithromycin, known for its beneficial effects in acute lung injury [48] due to its anti-inflammatory and immune-modulating properties, has shown promise in AE-ILD [51]. In a randomized trial, the use of procalcitonin to guide antibiotic therapy in AE-IPF patients resulted in reduced antibiotic exposure without adversely affecting patient outcomes [43].

Although treatments such as antacid therapy [31] and nintedanib [52] have shown partial preventive effects in AE-IPF or AE-ILD in the outpatient setting, their efficacy during acute exacerbations has not been evaluated [47]. Nevertheless, it is reasonable to continue using antacids and antifibrotics in hospitalized patients who were previously receiving these treatments [47]. While there is limited peer-reviewed evidence supporting the initiation of antifibrotics in the acute setting, apart from rare case reports [53], antacid therapy should already be initiated in AE-ILD patients receiving corticosteroids and/or mechanical ventilation [47]. Antiviral therapy may be considered during periods of heightened risk, such as the use of oseltamivir during the influenza season [6]. Immunosuppressive agents, including cyclosporine A, cyclophosphamide, tacrolimus, or azathioprine, may be used in combination with corticosteroids, but their efficacy lacks conclusive evidence, although some positive indications have been observed in small uncontrolled studies of IPF [9,10,54–56].

Mechanical ventilation should be carefully evaluated in patients with AE of IPF who develop hypoxic respiratory failure. In-hospital mortality varies depending on the type of ventilation, with higher rates observed in patients requiring invasive mechanical ventilation (IMV) compared to those requiring non-invasive ventilation (NIV) or no ventilation support, as evidenced by a large multicenter ICU database study [57]. Studies have shown poorer outcomes in mechanically ventilated patients, both before [4,58,59] and after [29,60] The implementation of lung-protective ventilation strategies followed the ARDSnet trial in 2000. In-hospital mortality rates can be high, reaching 50%, with a one-year mortality rate of 70% [47]. In the pre-lung protective ventilation era, studies indicated that 85% of mechanically ventilated patients with AE-IPF died while on ventilation, leading to the suggestion that ICU admission and intubation might be futile [4]. NIV represents a reasonable therapeutic option that may allow certain patients to avoid the morbidity associated with IMV [57,61]. While IMV should not be systematically denied [62], the decision should be made on an individual basis, considering clinical judgment, CT characteristics, and the eligibility and pre-existing enrollment of patients for lung transplantation [47]considering the high associated mortality rate [47].

In severe cases, lung transplantation may be the last resort, although only a small number of IPF patients are likely to meet the eligibility criteria [23]. Extracorporeal membrane oxygenation (ECMO) has emerged as an effective management approach for AE-ILD. It provides extracorporeal lung support, minimizing the risk of exacerbating underlying chronic processes that could lead to fatal deterioration of the lungs [47]. ECMO can serve as a bridge to lung transplantation for selected patients [63–65]. For non-transplant candidates at high risk for poor outcomes, early discussions about hospice care should involve the family and prioritize patient comfort and end-of-life wishes [47].

While the focus of the discussion has been on AE in IPF, the management approaches discussed are likely applicable to other ILDs with a progressive-fibrosing phenotype [47]. However, further controlled studies are necessary due to the limited available data. It is important to acknowledge that there may be differences among ILDs, and specific management approaches may be required for each subtype [47].

PROGNOSIS

Several potential prognostic indicators have been identified for AE-IPF [7,8]. Lower baseline pulmonary function parameters, impaired oxygenation, and a higher fibrosis score or more extensive disease on HRCT are associated with worse outcomes [8]. In the case of acute exacerbation of idiopathic interstitial pneumonia (AE-IIP), a lymphocytosis >15% in BAL may indicate a favorable prognosis [66]. Additionally, several blood markers, such as lactate dehydrogenase, C-reactive protein, KL-6, circulating fibrocytes, and anti-heat shock protein 70 autoantibodies, show promise as prognostic markers [27]. A staging system for AE-IPF has recently been developed, incorporating some of these prognostic factors [67].

CONCLUSION

AE-ILD remains a serious complication with a high mortality rate. Timely recognition of acute exacerbations and prompt interventions have the potential to improve outcomes [8]. However, further research is necessary to establish standardized diagnostic criteria and identify reliable prognostic factors for AE-ILD in non-IPF ILDs [1]. There is also an imperative need to bridge the gap regarding the optimal treatment of AE-ILD, especially in non-IPF ILDs. Thus, randomized clinical trials of medications and ventilation strategies are important to advance our knowledge in this field.

SUPPLEMENTAL MATERIALS

Table 1. Revised and previous criteria for AE-IPF

	Revised Criterion	**Previous Criterion**
Definition	An acute, clinically significant, respiratory deterioration characterized by evidence of new-onset alveolar damage	An acute, clinically significant, respiratory deterioration with no know cause
Criterion		
Past Medical Conditions	Previous or concurrent IPF diagnosis	Previous or concurrent IPF diagnosis
Clinical Picture	Acute decline in respiratory status or new onset dyspnea in a period of less than 1 month	Worsening with no known cause or development of dyspnea within 40 days
Computed Tomography findings	New bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia (UIP) pattern	New bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia (UIP) pattern
Differential diagnosis	Deterioration not fully explained by cardiac failure or fluid overload	Exclusion of alternative causes, including left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury
Infection		No evidence of pulmonary infection by either aspirate or lavage

AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis

AUTHORS' CONTRIBUTION

M Alshneikat: Study conception and design, drafting manuscript.Z Alnajjar: Study conception and design, drafting manuscript.O Obeidat: Study conception and design, drafting manuscript.
A AL-Tanjy: Study conception and design, drafting manuscript.A Alsokhni: Critical review of the manuscript.A Innabi: Study conception and design and critical review of the manuscript.

DISCLAIMER

DISCLOSURE

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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