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Acute exacerbation of interstitial lung disease in the intensive care unit

Antonios Charokopos, Teng Moua, Jay H Ryu, Nathan J Smischney

Abstract

Acute exacerbations of interstitial lung disease (AE-ILD) represent an acute, frequent and often highly morbid event in the disease course of ILD patients. Admission in the intensive care unit (ICU) is very common and the need for mechanical ventilation arises early. While non-invasive ventilation has shown promise in staving off intubation in selected patients, it is unclear whether mechanical ventilation can alter the exacerbation course unless it is a bridge to lung transplantation. Risk stratification using clinical and radiographic findings, and early palliative care involvement, are important in ICU care. In this review, we discuss many of the pathophysiological aspects of AE-ILD and raise the hypothesis that ventilation strategies used in acute respiratory distress syndrome might be implemented in AE-ILD. We present possible decision-making and management algorithms that can be used by the intensivist when caring for these patients.

Key Words: Interstitial lung diseases; Disease exacerbation; Mechanical ventilation; Intensive care unit; Pathophysiological aspect

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Core Tip: During the acute and morbid event of acute exacerbation of interstitial lung disease, an intensivist needs to understand the pathophysiology and reversible causes of acute exacerbations, the diagnostics and treatments that are usually recommended, and the experimental therapies on the horizon. More importantly, the intensivist needs to be able to risk stratify the patients, selectively pursue mechanical ventilation, minimize ventilator induced lung injury, and involve palliative care early in non-lung transplant candidates.

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INTRODUCTION

Definitions and epidemiology
Acute exacerbations in interstitial lung diseases (AE-ILD) represent an acute, and frequently morbid, deterioration of the patients’ respiratory function, often leading to hospital admission. Intensivists are at the forefront of care for these patients, and often need to make critical decisions about treatment and whether mechanical ventilation will be beneficial. While originally and most thoroughly described in idiopathic pulmonary fibrosis (IPF), acute exacerbations are increasingly recognized in other types of fibrotic interstitial lung disease (ILD) such as fibrotic (chronic) hypersensitivity pneumonitis[1,2] and connective-tissue disease related ILD[3-5]. To distinguish between the two entities, we will refer to i) acute exacerbations of IPF (AE-IPF) and ii) acute exacerbations of non-IPF interstitial lung disease (AE-nonIPF), grouped together as AE-ILD.

The definition of AE-IPF has shifted between 2007 (Idiopathic Pulmonary Fibrosis network, IPFnet)6] and 2016 (revised criteria by international working group)[7]. The definition currently includes: (1) Known diagnosis of IPF; (2) Worsening dyspnea within the last 30 d; and (3) New bilateral ground glass opacities and/or consolidation upon a background of usual interstitial pneumonia (UIP); the previous requirement for exclusion of concurrent pulmonary embolism (PE) and identifiable infection has been eliminated[7].

The incidence rate of AE-IPF has been estimated to be 41 cases per 1000 person-years[8] with approximately 10% of IPF patients experiencing an acute exacerbation in the two years following their diagnosis[9]. AE-IPF tends to be more prevalent in those with more advanced disease, as measured by worse pulmonary function (especially forced vital capacity, and diffusing capacity for carbon monoxide), shorter 6 min walking distance, and lower baseline oxygenation[10-14].

Pathophysiology and triggers of acute exacerbations of ILD
An acute exacerbation occurring in patients with IPF and other fibrotic ILDs is often unpredictable, but specific intrinsic and extrinsic factors have been hypothesized to trigger the event. Intrinsic factors, such as epithelial homeostatic imbalance affecting fibrocyte differentiation, macrophage immune polarization, and possibly autoimmunity emergence against heat-shock proteins and phospholipid-binding proteins[15-18], have been identified in patients with AE-IPF. Several other factors, such as air pollution[19] and micro-aspiration[20,21], have also been identified. Interestingly, in a retrospective analysis of three well-known IPF placebo controlled clinical trials, none of the patients who developed AE-IPF were on anti-acid treatment[22,23]. A higher eosinophil percentage in bronchoalveolar lavage (BAL) has been associated with the onset of AE-IPF[24].

When an identifiable extrinsic trigger for AE-ILD is lacking, then the AE-ILD is considered idiopathic. On the contrary, infection, aspiration and drug toxicity are common extrinsic triggers of AE-ILD. Infection has been identified in 10% to 30% of patients with AE-ILD[25-27]. Furthermore, post-procedural AE-ILD has also been reported, including video-assisted thoracoscopic procedures and bronchoscopy with lavage[28-30]. The underlying mechanism is thought to be due to possible ventilator-induced injury (including hyperoxia or barotrauma), perioperative mechanical stretch, or fluid balance[7,31]. In a large study of acute exacerbations in all types of ILD, 52% of admissions for acute respiratory worsening were considered idiopathic, 20% due to infection, 15% due to subacute progression or end-stage disease, 6% due to heart failure or severe pulmonary hypertension, 4% due to venous thromboembolic disease, and 2% from diffuse alveolar hemorrhage or peri-procedural exacerbation[25].

Both AE-ILD and acute respiratory distress syndrome (ARDS) have bilateral ground glass opacities and/or consolidations on imaging and often refractory hypoxemia. Similar to ARDS, the most frequent histopathologic finding on lung biopsy seen in AE-ILD is diffuse alveolar damage[3,32], which involves an acute exudative phase followed by an organizing-proliferative phase[33]. It is likely that both
patients with AE-ILD and ARDS have an aberrant and defective healing response to lung injury, that involves a pro-fibrotic positive-feedback loop.[34-36]

**Diagnostic evaluation indicated on hospital or intensive care unit admission**

When a patient with ILD, or specifically IPF, is admitted for acute respiratory worsening, it is up to the inpatient physician, or more often the intensivist, to distinguish between idiopathic acute exacerbation vs acute exacerbation secondary to a specific “treatable” trigger such as infection. In-hospital survival is worse in those with idiopathic AE-ILD compared to those stemming from a known-trigger[25], possibly due to lack of targeted treatment.

Interestingly, acute exacerbation may be the first presentation of previously undiagnosed ILD, with such patients comprising 29% of one large academic cohort[25]. Radiologic findings of fibrotic disease including reticulation and traction bronchiectasis, in a patient without known pulmonary disease suggests undiagnosed ILD. Surgical lung biopsy is often avoided during AE-IPF as its results often do not alter the course of acute exacerbation[32], and have increased peri/post-operative morbidity[37].

If the patient has previously undiagnosed ILD as noted above, then autoimmune serologies, including evaluation for pulmonary vasculitis with antineutrophil cytoplasmic antibodies, would be indicated to further clarify any potential autoimmunity that would suggest a related connective-tissue disease or interstitial pneumonia with autoimmune features (IPAF). This may potentially affect management, as patients with autoimmune disease-related ILDs are more likely to be treated with immunosuppression, unlike in IPF patients[38].

Infection can be evaluated by various sources, including laboratory findings (white cell count, urine *Legionella* or *Streptococcus pneumoniae* antigens, procalcitonin[39], nasal or sputum viral polymerase chain reaction [PCR] tests), vital signs, and of course blood or respiratory cultures[40]. The yield of bronchoscopy has been found to be relatively low; only 13% of bronchoscopies in AE-ILD yielded abnormal results according to a major study[27], with 25% of patients having bronchoscopy on the general floor necessitating post-procedural ICU transfer. When bronchoscopy is performed, BAL specimens should be sent for bacterial, fungal and mycobacterial cultures, including viral PCR tests. Since AE-non-IPF patients are often immunocompromised, an intensivist should consider pneumocystis jirovecii and herpesvirus infections, which represented 25% and 18% of positive bronchoscopies in one study, respectively[27].

High-resolution computed tomography (CT) is critical in clarifying the extent of underlying fibrotic interstitial disease and suspected new or superimposed ground glass or consolidative abnormalities. The extent and pattern of superimposed infiltrates on high-resolution CT have been found to be predictive of survival in AE-IPF[41,42]. The separation of the Kaplan-Meier survival curves depending on 3 different types of CT findings (peripheral, multifocal, or diffuse pattern) was found to be quite striking[41]. A protocol assessing for pulmonary embolism - or a ventilation-perfusion and lower extremity doppler scan in patients with renal impairment - may be reasonable to exclude thromboembolic disease. However, a PE protocol study was performed in only 43% of admissions for acute respiratory worsening in ILD patients[25]. Interestingly, a link between a profibrotic and a prothrombotic state has been found[43], with studies reporting higher risk of venous thromboembolism (VTE) in IPF patients[44,45]. Physical examination, serum brain natriuretic peptide concentrations, and echocardiography are used to evaluate for any component of heart failure and pulmonary hypertension[7].

**TO INTUBATE OR NOT TO INTUBATE?**

When an intensivist encounters a deteriorating patient with AE-ILD, the decision for invasive mechanical ventilation (IMV) must be balanced with the prognosis and reversibility of the patient’s condition. Multiple studies have shown poor outcomes in this population, including studies that analyzed admissions before[46-48] and after[25,49] changes in lung protective ventilation following the publication of the ARDSnet trial in 2000. In-hospital mortality may reach 50% with 1-year mortality at 70%. In the years before lung protective ventilation strategies, studies identified that 85% mechanically ventilated patients with AE-IPF died while ventilated, and proposed that ICU admission and intubation may be futile[46]. Nevertheless, both due to: (1) the acceptance of lower tidal volumes in ICUs; and (2) Changes in the definition of AE-IPF to include potentially reversible causes, the outcomes of ventilated patients with AE-IPF have improved, but still remain poor. In a nationwide cohort from 2006-2012, in-hospital mortality of AE-IPF patients who received mechanical ventilation was 51.6% (although improved from 58.4% in 2006 to 49.3% in 2012) and of patients who received non-invasive ventilation (NIV) was 30.9%[49]. In another study of patients in French ICUs from 2002 to 2009, only 30% of those mechanically ventilated were successfully weaned[50]. As expected, in-hospital mortality varies according to ventilation type, being higher in patients requiring IMV compared to patients requiring NIV or no ventilation support in a large multicenter ICU database study[51]. NIV is a reasonable therapeutic option which may allow certain patients to avoid the morbidity of IMV[51,52].
In general, mortality is affected by disease type, with IPF for example having worse outcomes compared to other fibrotic ILD associated with autoimmune disorders or hypersensitivity pneumonitis. In a landmark study that explored admissions for acute respiratory worsening in patients with chronic fibrotic lung disease, in-hospital mortality was the same between IPF and patients without IPF (55% vs 45%, $P > 0.05$)[25], although other studies found nonspecific interstitial pneumonia to be associated with a relatively good discharge rate and long-term prognosis[4]. In a different study, 90-day mortality was found to be significantly higher in AE-IPF than AE-non-IPF (69% vs 34%)[53]. One-year mortality after hospitalization for acute exacerbation was worse in IPF than non-IPF (87% vs 71%), yet still very high in both groups[25]. Furthermore, while infection accounted for a third of AE-ILD cases in another United States cohort, outcomes did not differ between those with infection and those without[26]. However, post-operative exacerbation and respiratory failure in ILD patients is associated with a better prognosis[54]. Specific findings on high-resolution CT at admission in AE-IPF patients have been correlated with prognosis[41,42]. Artificial intelligence software is increasingly showing application and promise in the analysis of CT scans in ILD patients, and may potentially be used for prognostication[33].

In the authors’ opinion, risk stratification and goals of care discussion need to take place early on when a patient with AE-ILD is admitted to the ICU. Studies have shown that a subset of patients can be weaned from mechanical ventilation and discharged, suggesting that IMV should not be systematically denied to these patients but considered individually[50]. Risk stratification certainly depends on clinical judgement, but can also be assisted by other published insights, including the aforementioned CT characteristics[41,42]. On admission to the hospital for respiratory worsening, only 20% of patients with fibrotic lung disease have a “do not resuscitate, do not intubate” code status[25]. Palliative care should be consulted early in the patients’ admission, and eligibility (or pre-existing enrollment with previous work-up completion) of patients for lung transplant should play important roles in the management decision tree (Figure 1). While the poor outcomes of mechanical ventilation place it in the role of “bridge therapy”, lung transplant is a potential “destination therapy” even for patients with severe acute exacerbations and deteriorating oxygenation. In non-transplant candidates who are deemed high risk for poor outcome, hospice should be brought up early in family discussions and goals of patient comfort and wishes for end-of-life strongly taken into consideration.

**USUAL TREATMENTS IN ACUTE EXCERBATIONS**

While the outcomes of AE-ILD patients have been well described, well-designed prospective clinical research in the management of these patients is lacking. It is unclear if the high morbidity and mortality of acute exacerbations creates a fertile environment for research as accepted by distressed patients and their families. International guidelines for AE-IPF make a weak recommendation for the use of corticosteroids, namely that corticosteroids should be used in the majority of patients with acute exacerbation of IPF, but not using may be reasonable in a minority[56]. This weak recommendation is based on expert opinion and retrospective reports[41,46,53]. No particular corticosteroid formulation has been found preferable over another in AE-ILD, despite good outcomes with dexamethasone in ARDS and Coronavirus disease 2019 (Covid-19) associated lung injury[57,58]. Doses ranging from 1mg/kg of prednisone to pulse steroids (methylprednisolone 1 g daily for 3 d) have been used, depending on institutional preference and severity of presentation. In studies comparing corticosteroid treatment in acute exacerbations in idiopathic interstitial pneumonias vs connective tissue disease-associated ILD, both groups were observed to be treated with corticosteroids[53]. While others have argued for a steroid-free approach in AE-IPF[59,60], the frequent misdiagnosis of fibrotic hypersensitivity pneumonitis as IPF may be confounding[61]. The uncertainty but routine use of corticosteroids in AE-ILD supports a need for a prospective clinical trial.

Antibiotics are routinely used in AE-ILD, accompanied by appropriate work up to evaluate underlying infection. Both broad spectrum and coverage for atypical pathogens should be considered. Azithromycin, which has been reported to improve outcomes in acute lung injury[62], has also shown particular promise in AE-ILD[63]. This is thought to a result of azithromycin’s anti-inflammatory and immune-modulating effects rather than antimicrobial activity, as it has been compared to fluoroquinolones which also cover atypical bacteria[63]. If no underlying infection is found, a routine 7 to 10 day course is reasonable. In a randomized trial, use of procalcitonin to guide antibiotic therapy in patients with AE-ILD resulted in reduced exposure to antibiotics without adversely affecting patient outcomes[59]. Since AE-non-IPF patients are often immunocompromised prior to admission, search for opportunistic pathogens and targeted treatment is prudent (Figure 2).

Key treatments that have been shown to partially prevent AE-IPF or AE-ILD in the outpatient setting - such as antacid therapy[22] and nintendib[64] - have not been evaluated clinically during acute exacerbation. From the authors’ point of view, it is reasonable to continue inpatient use of both antacids and antifibrotics in patients previously treated with them. While there is no peer-reviewed evidence for benefit in initiating antifibrotics in the acute setting except rare case reports[65], antacid therapy should be easily and already instituted in AE-ILD patients treated with corticosteroids and/or mechanical ventilation.
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Figure 1 Suggested decision-making tree and management approach of patients admitted to the intensive care unit with acute exacerbation of interstitial lung disease. AE-ILD: Acute exacerbation of interstitial lung disease; ICU: Intensive care unit; HFNC: High flow nasal cannula; AE: Acute exacerbation; NIV: Non-invasive ventilation; IMV: Invasive mechanical ventilation; ECMO: Extracorporeal membrane oxygenation.

Figure 2 Treatment approaches for acute exacerbation interstitial lung disease. AE-ILD: Acute exacerbation interstitial lung disease; ICU: Intensive care unit; PEEP: Positive end-expiratory pressure; P-V curve: Pressure-volume curve; PCP: Pneumocystis jirovecii pneumonia; CMV: Cytomegalovirus; DAH: Diffuse alveolar hemorrhage; GERD: Gastro-esophageal reflux disease; PMX: Polymyxin-B immobilized fiber column hemoperfusion; IV rhTM: Intravenous recombinant human thrombomodulin.

OPTIMIZATION OF MECHANICAL VENTILATION

AE-ILD has some parallels with ARDS both from a clinical (ground glass infiltrates and severe hypoxemia) and histological (diffuse alveolar damage on pathology) perspective. Similar to ARDS, patients with AE-ILD are prone to ventilator induced injury. Thus, mechanical ventilation strategies used in ARDS should be reasonably utilized in patients with AE-ILD\cite{66}. Avoidance of ventilator-patient dyssynchrony (causing stacked inspired tidal volumes) and prevention of ventilator induced
lungs injury are of particular importance. Notably 42% of AE-ILD patients required paralytics in a large cohort, although paralytic use was associated with higher mortality in unadjusted analysis and possibly reflective of underlying disease severity[67]. Optimization of positive end-expiratory pressure (PEEP) and lung recruitment using pressure-volume hysteresis curves, stress index, or calculation of transpulmonary pressure with esophageal balloons present an opportunity to at least prevent iatrogenic contribution to a patient’s already difficult prognosis. While prone positioning of ventilated patients is strongly supported in ARDS[68], patients with pulmonary fibrosis may be less responsive to prone[69] in the presence of end-stage fibrosis and absence of significant non-hydrostatic pulmonary edema.

Only two studies have examined the effect of ventilator parameters on mortality in patients with AE-ILD[54,67]. The largest study examined 114 admissions for AE-ILD, of which 34% were AE-IPF and 66% were AE-nonIPF[67]. Only 50% of patients in this study achieved a low tidal volume strategy (plateau pressure ≤ 30 cm H₂O) within 3 h of intubation. A variety of modifiable and nonmodifiable parameters - including increased time to intubation, higher initial fraction of inspired oxygen or PEEP, higher mean airway pressures, vasopressor use and right ventricular systolic pressure - were associated with inhospital mortality. In the second retrospective study, step changes in positive end-expiratory pressure > 10 cm of water were found to have been attempted in 20 patients and resulted in increased airway pressures and decrease in respiratory system compliance suggestive of overdistension[54].

The importance of fluid management - with a goal of net-neutral or net-negative fluid balance - has been increasingly recognized[70], similarly to the management of ARDS. A retrospective study of postoperative AE-IPF patients surgically treated for lung cancer, a common finding in the IPF population[71], showed that more intraoperative fluid administration was associated with higher probability of AE-IPF[31]. Total net fluid status was also an important adjusted risk predictor for mortality in a large study of mechanical ventilation in AE-ILD[67].

EXPERIMENTAL TREATMENTS

In light of currently limited therapeutic options and the high mortality of patients with AE-ILD, experimental therapies have been tested in only a few small studies. Based on the premise of immune dysregulation being a primary driver of AE-IPF and/or AE-nonIPF[72], studies have focused on alternative immunosuppressants or cytokine filtration removal, often in conjunction with corticosteroids (Figure 2). Cyclophosphamide has not been studied using matched controls, but in one single-institution study administration of 1 g daily of methylprednisolone for 3 d followed by monthly cyclophosphamide administration for up to 6 doses showed a favorable overall survival at 3 mo (73%), 6 mo (63%) and 12 mo (55%) compared to the general literature[73]. Calcineurin inhibitors, such as tacrolimus and cyclosporine, have shown some benefit but have only been evaluated in small retrospective studies of 15-45 patients[74-76]. Due to possible autoantibodies in AE-IPF[18], rituximab and plasma exchange were studied in 11 patients with AE-IPF and compared to 20 controls, showing 82% of treated patients improved in terms of oxygenation with some sustaining a relapse-free response[77]. Polymyxin-B immobilized fiber (PMX) hemoperfusion is an alternative approach mostly studied in removing bacterial toxins, but has also been postulated for removing proinflammatory cytokines[78,79] and promoting antifibrotic cytokines[80]. Retrospective studies have shown notable survival benefit from PMX treatment in AE-IPF (12-month survival 41.7% in the PMX group vs 9.8% in the non-PMX group) [81,82], although this has not been confirmed in randomized trials. Disordered hypercoagulation has also been implicated in AE-IPF pathophysiology. Recombinant human thrombomodulin (rhTM), a cofactor for thrombin and anti-coagulant molecule, was recently evaluated as add-on therapy to routine corticosteroid-treated AE-IPF patients decreasing 3 mo mortality to 30%-40 from control levels of 65%-70%[83-85].

CONCLUSION

Despite the relatively common occurrence of AE-IPF and AE-ILD in general[8,9], randomized clinical trials of interventions in acute exacerbations are lacking. As noted in a recent International Working Group report, the optimal management of AE-IPF represents an area of major unmet medical need[7]. Robust prospective clinical studies and randomized trials of therapeutics and maybe ventilation strategies are critical to advance the field and improve the grim prognosis of these patients.

FOOTNOTES

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