



Oxygen Therapy in Exacerbation of Interstitial Lung Disease

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Abstract

Interstitial lung diseases (ILD) are a group of diseases that involve damage in the interstitial tissue, causing diffusion disorders which ultimately lead to hypoxemia. One of the conditions that aggravate hypoxemia in ILD patients is acute exacerbation. Acute exacerbation is a condition of deterioration of ILD that can occur in less than 1 month. During an acute exacerbation, there will be a worsening of the HRCT pattern with increased ground glass opacities and a worsening of the clinical picture including hypoxemia. Acute exacerbations are closely related to increased mortality rates. Oxygen administration is one of the supportive therapies that can be given to acute exacerbations. The provision of oxygen therapy is adjusted to the patient's needs using a high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation.

Keywords: acute exacerbation, interstitial lung disease, oxygen therapy

INTRODUCTION

Interstitial lung disease (ILD) comprises a diverse spectrum of conditions by the presence of extensive fibrous abnormalities with varying degrees of hypoxemia. The most frequent symptoms are cough and dyspnea.¹ Lung parenchymal tissue damage is indicated by inflammation, fibrosis, typical clinical presentation, and radiological manifestation. Oxygen therapy is commonly given to ILD patients to reduce shortness of breath and increase physical

capacity through better gas exchange. Although frequently used, there is only little evidence supporting its effectiveness in treating ILD.^{1,2}

The American Thoracic Society (ATS) defines acute exacerbations of interstitial lung disease (AE-ILD) as clinically acute respiratory deterioration that evolves in less than one month without any other etiology. Initially, the term AE-ILD in IPF commonly appears as acute lung injury (ALI) pathologically and diffuse alveolar damage (DAD) histopathologically in most cases.³ This review will discuss the role of

oxygen therapy in treating patients with ILD.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease refers to an extensive range of conditions characterized by lung fibrosis, classified according to physiological, pathological, radiographical, and clinical factors. Measuring the incidence of ILD in the United States poses a significant challenge because it is part of the exclusion diagnosis requiring extensive investigation. However, current guidelines and classification further ease the diagnostic process of ILD. Approximately 30 cases per 100,000 are reported each year, resulting in an overall prevalence of 80.9 and 67.2 per 100,000 population per year in men and women. The ILD classification system categorizes the diseases using clinical, histopathological, and radiological parameters.²

Classification of ILD groups according to etiologies could help differentiate endogenous and exogenous factors.² Others are classified according to the clinical, histopathological, and radiological parameters. Some known causes include occupational and environmental exposure, autoimmune disease, and idiopathic diseases. Idiopathic lung fibrosis had the worst prognosis, with an overall survival of only two to three years since the diagnosis.^{2,4}

Meanwhile, connective tissue disease-associated interstitial lung disease (CTD-ILD) had a better prognosis, with an overall survival of 6.5 years. Among other

ILDs, sarcoidosis has the best prognosis with a 5-year overall survival rate of 91.6%, compared to that of CTD-ILD and IPF, which are 69.7% and 35%, respectively.²

EXACERBATION OF INTERSTITIAL LUNG DISEASE

Definition

The ATS defines acute exacerbations of interstitial lung disease (AE-ILD) as clinically acute respiratory deterioration that evolves in less than one month without any other etiology. On the other hand, the clinical trials network defines interstitial pulmonary fibrosis (IPF) exacerbation as a worsening in pulmonary function that occurs in less than one month, followed by radiographical abnormalities on HRCT examinations such as an increase of ground-glass opacification features without other definitive causes such as fluid overload, heart failure or pulmonary embolism.³ AE-ILD often leads to poor prognosis and high mortality.⁵

Symptoms like productive or dry cough, an increase of sputum production and fever were related to the rapid worsening of the respiratory symptoms in less than one month. Many patients often require admission to the intensive care unit where ventilatory support is urgently needed due to severe hypoxemia in arterial blood gas and respiratory failure.^{3,6-8}

Abnormal gas exchange criteria are the condition of PaO₂/FiO₂ ratio <225 or a decrease in PaO₂ ≥10 mmHg. Until now, AE-ILD diagnosis has relied on clinical and

radiological findings. Bronchoscopy with bronchoalveolar lavage (BAL) in IPF patients is considered to rule out the cause of infection. However, a study showed a similar outcome irrespective of whether the cause of the exacerbation could be identified or not, as seen in idiopathic cases.⁵

Epidemiology

Understanding the epidemiology of AE-ILD precisely is challenging due to the lack of clear understanding regarding its diagnostic criteria, patient population, the severity of the underlying disease, follow-up period, and statistical methodology. Retrospective cohort studies typically

report a higher incidence and prevalence of AE-ILD. However, they may be biased towards reporting acute deterioration from known causes, such as pulmonary embolism and heart failure, as acute exacerbation of pulmonary interstitial fibrosis. A meta-analysis of seven prospective multicenter trials described an overall incidence rate of 26.3 per 1,000 patient-year (ranging from 8.9 to 206.3 per 1,000 patients). Prospective clinical trials often exclude patients with advanced disease and comorbidities. Additionally, as the risk of acute exacerbation (AE) increases with ILD severity, the incidence of AE may be higher than that estimated by the prospective studies.⁹

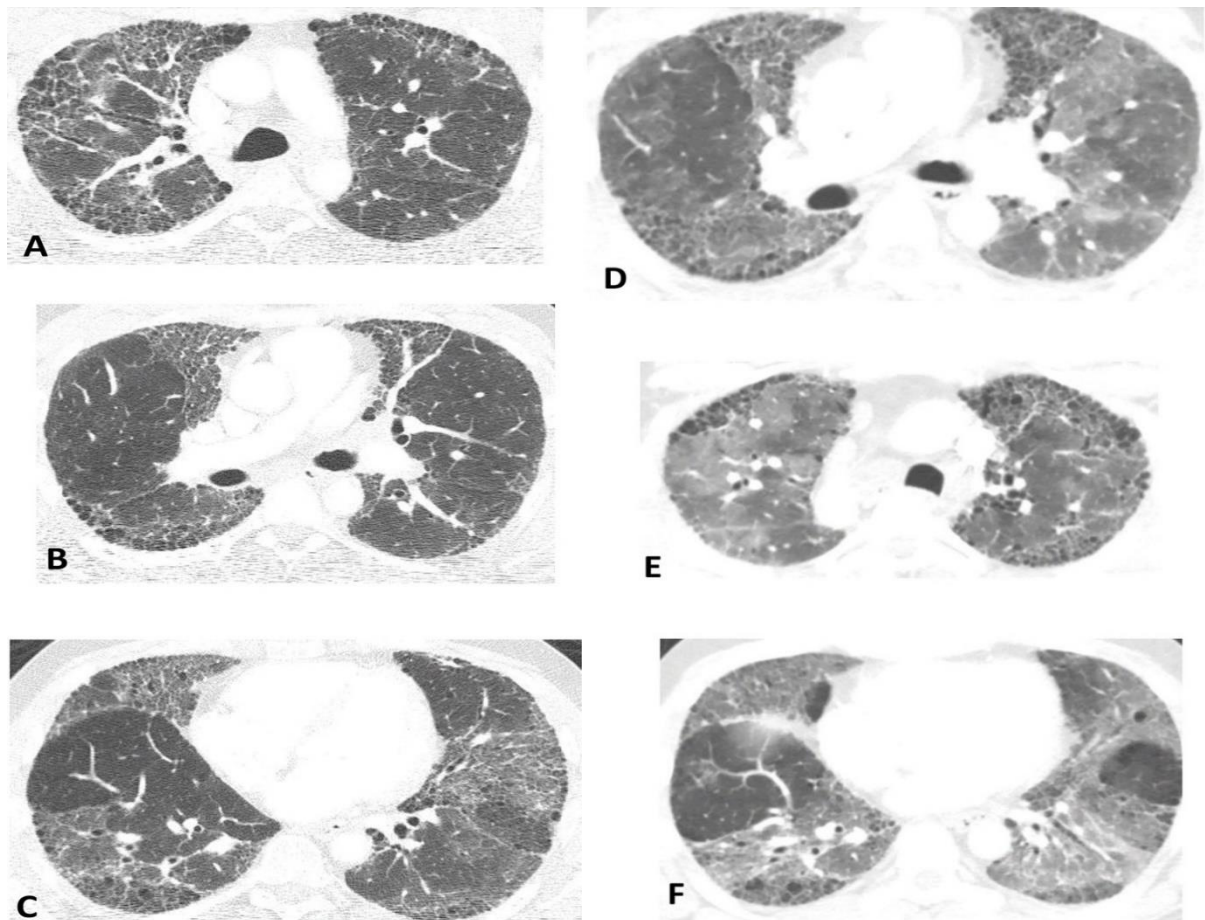


Figure 1. HRCT of a 50-year-old patient's upper, middle, and lower lung lobes (A, B, C) and HRCT images of the same patient taken 2 months later (D, E, F) showing a worsening of shortness of breath⁸

Etiology

The etiology of AE-ILD, encompassing its onset and progression remains unpredictable. Currently, it remains unclear whether AE-ILD is initiated by intrinsic factors driving the disease's progression, manifesting as a response to external factors (such as infection, microaspiration, pulmonary embolism, mechanical stress), or both.^{6,9} AE-ILD had a poor prognosis and high mortality within 6 to 12 months.³ Nevertheless, further research is needed to pinpoint the main causes of AE-ILD and any potential biomarkers.

DIAGNOSTIC CRITERIA OF ILD EXACERBATION

Four diagnostic criteria for IPF exacerbation include a previous or concurrent diagnosis of IPF at the time of exacerbation, acute worsening of dyspnea in less than 1 month, opacity or ground-glass consolidation in both lungs, with a background pattern consistent with usual interstitial pneumonia (UIP) on a computed tomography (CT) scan, and lung damage that cannot be explained as heart failure or fluid overload. Certain conditions need to be ruled out as a preliminary when considering the diagnosis of AE-IPF, such as pneumothorax, cardiogenic lung edema, lung embolism, ALI, or ARDS with an identifiable cause, lower respiratory tract infection, and pulmonary hypertension.¹⁰

Faverio et al elaborate that Acute Respiratory Failure (ARF) in known chronic ILD should be followed with laboratory

examination, CT scan (CT angiography if pulmonary embolism is suspected), and bronchoscopy to determine a work-up diagnosis. If contributing factors are not identified, AE-ILD could likely be the cause of ARF and other differential diagnoses (e.g. pulmonary embolism, congestive heart failure, infection, pneumothorax, drug-induced lung toxicity, diffuse alveolar hemorrhage) can be excluded. The worsening of AE-ILD can be triggered by occult infection, micro-aspiration, post-procedural or happens idiopathically.¹¹

EXACERBATION MANAGEMENT

The AE-ILD management approach includes oxygenation, corticosteroids, antifibrotic, pulmonary hypertension treatment, and intensive and palliative care.¹² Until now, no study has conclusively determined the most optimal management for AE-ILD.^{5,8} However, it is imperative that ILD patients utilize oxygen therapy as it has been proven to relieve shortness of breath.¹³

The international guideline for IPF management recommends supportive treatment to relieve symptoms and long-term oxygen therapy. In addition, patients are also prescribed corticosteroids as few studies have shown their benefit in patients with idiopathic AE-ILD, CTD-ILD, sarcoidosis, and certain hypersensitive pneumonitis.⁵

Methylprednisolone administered at a daily dose of 500-1000 mg for three days, followed by a daily dose of 1 mg/kg of body weight, is a frequently reported treatment

despite its unclear effect.⁸ Monitoring for steroid-related kidney side effects is crucial, particularly in patients with systemic sclerosis-associated ILD (SSc-ILD). Identifying and eliminating toxic exposure should be done among AE-ILD patients receiving broad-spectrum antibiotics.⁵

Empiric antibiotic treatment is recommended until infection can be ruled out. Research has indicated that procalcitonin levels can guide the duration of antibiotic treatments, thus preventing prolonged and unnecessary use. However, no significant difference in outcome was reported compared to the control group.⁸

Mechanical ventilatory support can be provided to ILD patients with hypoxic respiratory failure. However, a case-by-case assessment is highly encouraged because its use is associated with a higher mortality rate. A few small studies suggest using only nasal cannula oxygen as a supportive measure thereby avoiding the need for intubation or mechanical ventilation. Nonetheless, some conditions warrant invasive ventilatory support, such as with deteriorating IPF patients where lung transplantation is considered.⁵

Extracorporeal membrane oxygenation (ECMO) can be employed in patients experiencing an acute exacerbation of IPF, potentially reducing the risk of developing chronic conditions. Additionally, this management method can be applied to patients with fatal lung conditions such as ARDS and cardiogenic shock, or those awaiting lung transplants.⁵ The extracorporeal system provides

pulmonary support through venovenous (VV) settings or both circulatory and breathing support through the veno-arterial (VA) configuration.^{5,14}

OXYGEN THERAPY

The prevalence of hypoxemia among ILD patients remains unclear due to the lack of standardization in its definition and the required diagnostic modality to specify the type of hypoxemia: resting, activity-related, or nocturnal. Resting hypoxemia is characterized by advanced-stage chronic lung disease and defined by resting oxygen pressure (P_aO_2) of ≤ 55 mmHg or 56-59 mmHg with evidence of organ damage (cor pulmonale, polycythemia, and/or pulmonary hypertension). Meanwhile, exertional or activity-related hypoxemia is defined by the lowest peripheral oxygen saturation of $\leq 88\%$ and a decrease of $\geq 4\%$ with or without the lowest SpO_2 of $< 90\%$.^{6,15}

Exertional hypoxemia occurs more commonly in interstitial lung disease. Another type of hypoxemia is nocturnal hypoxemia, which affects 36-57% of ILD patients. It is defined as a breathing disorder during sleeping that is not necessarily correlated with lung function impairment's degree. A study discovered a potential relationship between nocturnal hypoxemia and pulmonary hypertension among patients with chronic obstructive pulmonary disease (COPD) and ILD.⁶

A systematic review also identified that ILD patients were at risk for nocturnal hypoxemia due to ventilation restriction

and dysregulated gas exchange, which worsens when they sleep in a supine position and experience a decrease in ventilatory drive during sleeping.¹⁶

The primary mechanism of pulmonary artery hypoxemia in ILD patients is an imbalance in the ventilation-perfusion ratio (V/Q), progressive destruction of the alveolar unit, and limited oxygen diffusion from the alveoli into the capillaries. Patients with ILD also exhibit a significant increase in respiratory rate during physical activity, with reduced tidal volume (Vt) and an increase in dead space and tidal volume ratio (RV/Vt). These factors clarify the mechanism behind the physical activities leading to the decrease in PaO₂, which is one of the main factors correlated with a worse prognosis.⁷

High-Flow Nasal Cannula

Acute exacerbation stands as the primary fatality contributor among ILD patients with lung fibrosis, frequently accompanied by severe hypoxemia. Patients with invasive mechanical ventilatory support have a poor prognosis. Limited studies with small participants showed that non-invasive positive pressure ventilation (NPPV), utilized to mitigate the complication of endotracheal intubation, can improve the prognosis of patients with lung fibrotic disease. Nonetheless, there is a lack of comprehensive knowledge regarding its efficacy and tolerability in the management of AE-ILD.¹⁷

The high-flow nasal cannula (HFNC) recently was considered a new oxygen-delivering device that has the advantage of

delivering heated and moisturized inspired gas with a high flow (up to 60 liters/minute), allowing an increase in inspired oxygen fraction (FiO₂) to 1.0 (100%).^{17,18}

A randomized controlled trial showed HFNC was found equally effective as NPPV in managing acute respiratory failure arising from diseases such as pneumonia and pulmonary edema. The high-flow nasal cannula is reported to be more suitable in treating acute respiratory failure caused by an acute exacerbation of interstitial pneumonia (AE-IP) compared to lung edema or acute exacerbation of COPD, which may need higher positive end-expiratory pressure and/or ventilatory support.^{17,18}

There are three case reports from Japan in 2016 on the use of HFNC in AE-IP patients. These case reports found two clinically significant discoveries; HFNC could rapidly increase oxygenation in AE-IP patients with respiratory failure that cannot be adequately managed with standard oxygenation therapies. High-flow nasal cannula can immediately correct severe hypoxemia caused by AE-IP with a PaO₂/FiO₂ ratio of <0.2. Those case reports did not provide guidelines for the initial protocol when using HFNC in AE-IP patients.^{19,20}

However, a FiO₂ between 0.7-1.0 and a flow rate of 40 liters/minute was shown to be successful in increasing PaO₂. Additionally, HFNC can promptly decrease patients' respiratory rate and relieve dyspnea, even in those with chronic respiratory failure or widespread lung

opacities. HFNC was also reported to have a similar effect in acute respiratory failure caused by other etiologies, such as pneumonia.^{19,20}

High-flow nasal cannula offers several benefits compared to other standard oxygen therapies by regularly flushing out the upper airway space to reduce lung dead space. Furthermore, positive air pressure as low as 3-7 cmH₂O can be adjusted automatically, resulting in high compatibility between ventilation and perfusion and thus reducing the overall work of breathing.^{17,18} The use of HFNC both in acute respiratory failure patients or stable IPF, has been proven to enhance ventilation efficiency, decrease work of breathing, and lower respiratory rate and minute volume, all without causing an elevation in capillary PCO₂ levels.^{19,20}

Another significant finding is that AE-IP patients tolerated HFNC well over three weeks. In a case report from Japan, the patient was safely transitioned between days 21 and 26 from HFNC. In line with this finding, Boyer et al reported a case of AE-IPF patients treated with HFNC in combination with a high-dose corticosteroid and cyclophosphamide for five weeks.²¹

Conversely, other studies showed that the mean of NPPV duration use for AE-IP patients was 11.7 days.^{22,23} Several studies have shown that the use of HFNC provides greater comfort compared to the use of NPPV. Due to its efficacy and the minimal discomfort, the transition from HFNC to a standard oxygenation system could be postponed until the FiO₂ reaches a

value of 0.35-0.4 at a flow of 35-40 liters/minute.²⁴

Non-invasive ventilation

Non-invasive ventilation is initiated in every patient showing CO₂ retention (PaCO₂ ≥45 mmHg) and signs of respiratory muscle fatigue (dyspnea, tachypnea, or abdominal paradox) after experiencing hypoxemia with conventional oxygen therapy of HFNC. Non-invasive ventilation is delivered through a portable ventilator set on pressure support (PS) ventilation mode. Initially, pressure support is adjusted to achieve a moderate tidal volume (6-8 ml/kg of body weight), and the ventilator settings are then adjusted based on blood gas analysis (BGA) data to ensure adequate gas exchange. Though not always optimal, this approach aims to protect the lungs from the risk of ventilator-induced lung injury (VILI).²⁵

The PS level should not exceed 25 cmH₂O. The end expiration positive pressure is typically set at 5 cmH₂O and is incrementally increased by approximately 1-2 cmH₂O, not exceeding 6-8 cmH₂O due to the higher risk of pneumothorax. Additional oxygen is introduced into the ventilator circuit, with the oxygen flow rate adjusted to achieve an arterial SaO₂ of >92% or PaO₂ >65 mmHg. The NIV device used allows for the utilization of a full-face mask.²⁴

A study observing the use of NIV in ILD patients found that 28 patients (47%) and 26 patients (44%) presented with UIP and NSIP radiological patterns, while 6 patients (9%) manifested varied

radiological patterns such as consolidation and ground-glass appearance.²⁶

Invasive mechanical ventilation

Patients who are not on the list for transplant candidates usually have a poor prognosis after ICU admission. Many patients experiencing acute respiratory failure due to ILD will receive little to no benefit from prolonged intensive care. As explained above, HFNC and NIV are potential alternatives to endotracheal intubations in ARF cases. The management algorithm does not consider elective intubation and intermittent mandatory ventilation (IMV) after NIV failure. Emergent intubation is performed under the following conditions: respiratory arrest, loss of consciousness with a respiratory pause, gasping, heart rate of <50 times/minute with loss of awareness, and hemodynamic instability with a systolic blood pressure of <70 mmHg.^{24,25}

Extracorporeal Membrane Oxygenation

The management of ILD and acute respiratory failure patients presents its own set of challenges. Currently, lung transplantation is the definitive therapy for refractory ILD, and it applies only to stable patients who are already on the transplantation list. Extracorporeal membrane oxygenation (ECMO) is considered for ILD patients with severe respiratory failure or ongoing refractory hypoxemia, uncompensated hypercapnia, or acidemia despite maximal medical therapy and using HFNC or ventilatory support.²³ The use of ECMO will be

determined when at least two intensivists agree on the potentially reversible cause of the deterioration (for example, infection or lung embolism) and if the patients provide consent, whether they are previously candidates or non-candidates for transplantation. ECMO is denied in patients with underlying advanced disease or poor prognosis, where comorbid conditions may impede the treatment.^{14,27,28}

ECMO usage on ILD with severe respiratory failure can be more beneficial than IMV. Complications such as ventilator-associated pneumonia (VAP) and ventilator-induced lung injury (VILI) can be prevented. Oral feeding, spontaneous coughing, and social interaction can be preserved. Moreover, early rehabilitation can be initiated.¹¹

Fuehner et al compare the outcome of awake-ECMO patients with terminal respiratory candidates to lung transplant to a historical cohort of patients with IMV as a bridge to transplant. The result shows an 80% 6-month survival rate after transplantation in an awake-ECMO group, whereas a 50% survival rate in the IMV group. ECMO minimizes the risk of fatal deterioration of underlying chronic processes that are most likely triggered by IMV invasiveness. However, ECMO does not change the poor outcome of severe ARF in ILD. The usage should be limited to patients with good short-term prognosis.²⁹

PROGNOSIS

AE-ILD is a life-threatening event with a high mortality rate. Among 35-46%

of IPF deaths are caused by AE-IPF. The median survival after AE-IPF ranging 1 to 4 months. Some potential prognostic factors include lower FVC and DLCO, higher fibrosis score, extensive findings in HRCT, and several markers such as lactate dehydrogenase (LDH), C-reactive protein (CRP), KL-6, circulating fibrocytes, and anti-HSP70 autoantibodies.³

Oxygen therapy can be associated with epithelial damage that may lead to lung injury. Reports in acute clinical settings show increased mortality with high targets of oxygen saturation or high-flow oxygen supplementation. It is postulated due to the accumulation of reactive oxygen species (ROS). Studies assessing this theory are still on further research. Oral administration of N-acetyl-cysteine, an antioxidant, shown to suppress systematic oxidative stress levels induced by oxygen therapy in COPD patients. Pirfenidone, an antifibrotic agent for ILD treatment, has shown antioxidant effects in experimental models. However, the therapeutic effects of antioxidative properties in ILD patients with oxygen therapy are yet to be evaluated.³⁰

CONCLUSION

AE-ILD diagnosis should be based on clinical presentation, physical examination, and additional tests. The approach to AE-ILD management includes oxygenation, corticosteroids, antifibrotic, pulmonary hypertension treatment, also intensive and palliative care. Administering supportive oxygen therapy could potentially improve

patients' clinical outcomes. Randomized control studies have shown that HFNC has the same efficacy as NPPV in managing acute respiratory failure attributed to alveolar lung diseases such as pneumonia and lung edema.

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