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Critical care management of Interstitial Lung Disease with a focus on Idiopathic Pulmonary Fibrosis: Optimizing diagnosis and treatment

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Abstract

Introduction
Exacerbations of interstitial lung disease (ILD), diffuse parenchymal lung diseases, or idiopathic pulmonary fibrosis can often lead to acute hypoxia, resulting in intensive care unit (ICU) admission. For those patients who require invasive mechanical ventilation, mortality rates can exceed 80%.
Methods
This review discusses the fundamental aspects of ILD exacerbations in the ICU setting, comprising diagnostic modalities, criteria, and management options. These include high-resolution computerized tomography, sputum analysis, treatment with immunomodulating agents, and both non-invasive and invasive ventilatory support strategies.
Conclusion
Exacerbations of ILD requiring mechanical ventilation are associated with poor prognostic outcomes. Understanding diagnostic criteria and treatment options is crucial to studying the high morbidity & mortality rates, leading to future directions focused on delivery of optimal care for this vulnerable patient population.

Keywords: Interstitial lung disease, idiopathic pulmonary fibrosis, ILD exacerbation, critical care medicine, invasive mechanical ventilation.

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Introduction

Interstitial lung disease (ILD) comprises a heterogenous group of chronic respiratory diseases, characterized by varying degrees of inflammation and/or fibrosis within the alveolar interstitium. [1] Among these, the most common pathologies include: idiopathic pulmonary fibrosis (IPF) (>30%), hypersensitivity pneumonitis (~15%), and connective tissue disease-associated ILD (~25%), which carry significant morbidity. [2]

Acute hypoxemic respiratory failure (AHRF) is the primary reason for intensive care unit (ICU) admission among ILD patients, often occurring during an acute exacerbation. However, a thorough clinical evaluation must also exclude extra-parenchymal causes such as acute coronary syndromes, pleural effusion, pulmonary embolism, and pneumothorax. [3] ILD is known to increase the risk of pneumothorax, which is attributed to architectural distortion in areas compromised by severe fibrosis. [4,5]

IPF is the most common ILD encountered in the ICU setting, with exacerbation incidence ranging from 4% to 20%. [6,7] ICU admission for AHRF in IPF patients is associated with a 43.8% mortality rate, which can rise to 81.3% when mechanical ventilation is required. [8] In contrast, the ILD subtypes associated with connective-tissue disease generally have a better prognosis, attributed to their relative responsiveness to immunosuppressive therapies. [9]

Regardless of subtype, ILD patients in the ICU require a high index of suspicion, early therapeutic intervention, and a comprehensive supportive care plan. Despite the significant morbidity and mortality associated with ILD exacerbations, few comprehensive reviews have been published since the original work by Fernandez-Perez et al, [10] and the accompanying editorial by Baydur. [11] This underscores the need to update current understanding and recommendations for critical care physicians managing ILD.

Diagnosis

Establishing the initial diagnosis ideally takes place in the outpatient setting over the course of weeks to months, following careful multidisciplinary review. Historically surgical lung biopsy (SLB) was considered the gold standard for diagnosing ILD, with usual interstitial pneumonia compromising the histopathologic pattern of interstitial changes that include microscopic honeycombing and remodeled arteries with fibroblastic foci arranged with spatial and temporal heterogeneity in the predominately lower lobe subpleural regions of the lungs. [2,12] However, given technological advances, high-resolution CT imaging (HRCT) has largely replaced SLB in the algorithm as capable of establishing a diagnosis, demonstrating approximately 91% sensitivity and 71% specificity for identifying different ILD subtypes. [13] Typical HRCT findings for IPF include bilateral, lower-lobe predominant subpleural reticular opacities with associated traction bronchiectasis/bronchiolectasis and honeycomb cyst formation. [13]

The diagnostic criteria for acute exacerbation of IPF include:

1) A previous or concurrent diagnosis of IPF
2) Acute worsening or development of dyspnea within 30 days
3) Chest imaging evidence on HRCT showing new bilateral ground-glass opacity or consolidation (Figure 1)
4) The deterioration is not fully explained by cardiac failure or fluid overload. [7]

Acute exacerbations of IPF can be triggered by infections, lung biopsy, severe gastro-esophageal reflux, or exposure to certain medications and chemicals. [7] These risk factors for acute lung injury and respiratory decompensation are shared by most, if not all, types of ILD.

Upon presentation for severe hypoxemia, it is critical to determine the primary cause of the acute respiratory failure, as those with both infectious and inflammatory pneumonia may have similar presentations including cough, progressive dyspnea, low grade fevers, leukocytosis, and elevated inflammatory biomarkers. Sputum collection is crucial as infections are the most frequent cause, and if difficult, bronchoalveolar lavage (BAL) may be considered for alveolar fluid sampling. [14] It is advised to defer empiric systemic corticosteroids until after BAL, since initiating immunosuppressive therapy may change the interstitial pathologic process and affect cell count yield. [15] A BAL cell count demonstrating lymphocytosis > 20% is consistent with a potentially steroid-responsive phenotype of ILD. [16]

Prior meta-analysis of case series exploring the diagnoses, complications, and changes in treatment after SLB in critically ill patients requiring mechanical ventilation have shown that the most common histopathological diagnoses were fibrosis and viral infections, which often resulted in therapeutic change. [17] However, obtaining additional data via SLB did come at the high cost of complications for nearly ⅓ patients, including persistent air leak and bronchopleural fistula. [17,18] Importantly, hospital mortality after the procedure was 54%, with little variation based on tissue diagnosis. [17] Perhaps this best explains why SLB is only rarely performed in the critically ill patient, as the procedural risk may outweigh the benefit of histopathologic diagnosis in most cases.

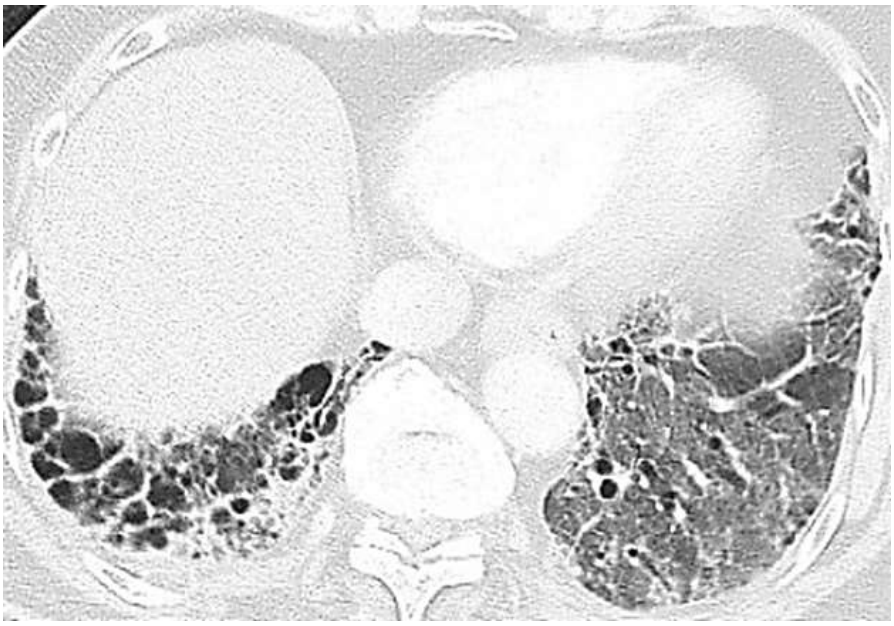

Figure 1: HRCT from a patient with IPF presenting with acute exacerbation. The scan shows new bilateral ground-glass opacities and consolidation superimposed on a background of usual interstitial pneumonia pattern with basal and subpleural predominance, reticulation, and honeycombing.

Diagnostic biomarkers for ILD

KL-6 and surfactant protein D (SP-D) are epithelial-derived proteins that tend to be high in ILD and can be used to monitor disease progression, including severity and extent of fibrosis on imaging. [19,20] KL-6 in particular holds high diagnostic accuracy for distinguishing ILD from controls, correlating with HRCT fibrosis scores and pulmonary function indices. [21] MMP-7, associated with extracellular matrix remodeling, is particularly elevated in IPF and linked to disease progression. While serum MMP-7 and SP-D may help differentiate IPF from other ILDs, evidence remains limited. [22] The ATS/ERS notes that high KL-6, SP-D, and MMP-7 levels correlate with more rapid lung function decline and reduced survival, though routine clinical use is not yet validated. [23]

Management in the ICU

Management starts with identifying and removing inciting factors such as infection, culprit medications, aspiration, and environmental exposures. [22] Below is treatment strategies regularly employed in the ICU:

High-Flow Nasal Cannula (HFNC)

HFNC can alleviate dyspnea by improving oxygenation, ventilation, and work of breathing observed in ILD-related respiratory failure. Compared to non-invasive ventilation (NIV) HFNC eases respiratory distress with better comfort and tolerability. [24] A retrospective study showed that fewer side effects and improved tolerance with HFNC compared to NIV, particularly in patients with do-not-intubate orders. [25]

Non-Invasive Ventilation (NIV)

Though established in the treatment of decompensated heart failure and acute COPD exacerbation, evidence for NIV use is limited in the treatment of ILD exacerbations. Prior meta-analysis suggests NIV improves the PaO_2/FiO_2 (P/F) ratio over standard oxygen therapy and HFNC. However, it does not significantly reduce mortality or intubation rates compared to HFNC. [25] Nevertheless, a study assessing NIV as the primary modality for ILD exacerbations reported significantly improved 60-day survival rates (65% vs. 27%, P = 0.02), shorter high-care unit length of stay (6 vs. 17 days, P = 0.03), and preserved verbal communication (0 vs. 89%), when compared with traditional mechanical ventilation. [26]

Immunosuppressive Drugs

Corticosteroids remain the cornerstone of immunosuppressive therapy for acute exacerbations of ILD despite mixed evidence. Current guidelines recommend corticosteroid doses of 0.5–1.0 mg/kg per day for acute IPF exacerbations. [13] In regards to escalating steroid treatment, pulse-dose corticosteroids equivalent to ≥250 mg/day of methylprednisolone has not shown survival benefit. [32] However, observational studies suggest that higher corticosteroid doses (1–2 mg/kg per day) may help non-IPF ILD patients where inflammation predominates. [33]

Other agents:

- Cyclophosphamide: improves dyspnea, lung function, and quality of life in systemic sclerosis patients with active alveolitis. 34
- Rituximab: increases forced vital capacity in systemic sclerosis patients and delays disease progression in other subtypes of inflammatory ILD. [35,36]
- Rituximab + Mycophenolate: helps preserve lung function in some patients. [35,36]

Nonetheless, data on these therapies in severely hypoxemic ICU patients remain limited, requiring individualized decisions based on phenotype and response.

Lung Transplantation

Lung transplant volume has risen, with over 3000 cases performed in 2023 in the United States alone. Patients with restrictive lung disease now comprise 60.7% of the waiting list. Median post-transplant survival rate is 5.2 years for idiopathic interstitial pneumonias, including IPF, and 6.7 years for other types of ILDs. [37, 38]

Barriers include candidacy criteria, institutional expertise, and organ availability. [38,39,41] Given the complexity associated with this coordination, The International Society of Heart and Lung Transplantation (ISHLT) recommends early referral before patients meet candidacy for active listing, [40] For regions using urgency-based systems, extracorporeal life support devices such as ECMO may serve as a bridge to transplantation. However, use of these resource-intensive modalities must be carefully weighted against patient prognosis and organ availability. [40] ISHLT recommends lung transplantation for patients with >80% estimated chance of 5-year survival, assuming adequate graft function. [40]

Conclusion

Managing ILD in the ICU remains a significant challenge due to the high mortality rates, especially for IPF patients requiring mechanical ventilation. A comprehensive multidisciplinary involving early HRCT-based diagnosis, supportive oxygenation strategies (HFNC, NIV), thoughtful use of IMV, tailored immunosuppression is essential. Enhanced recognition, timely intervention, and individualized care are key to improving outcomes in this high-risk population.

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