The use of mechanical ventilation in interstitial lung disease

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Mechanical ventilation in ILD is challenging due to poor lung compliance and recruitability. Management requires individualised strategies, balancing ventilation support with early palliative care and consideration for lung transplantation. https://bit.ly/4anpkIW

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Abstract

This review explores the challenges and strategies for managing mechanical ventilation in interstitial lung disease (ILD), particularly during acute exacerbations. It highlights the unique physiological barriers posed by fibrotic, non-compliant lungs, discusses evidence-based approaches to noninvasive and invasive ventilation, and emphasises the importance of balancing life-sustaining treatments with palliative care. This review aims to provide practical insights into optimising respiratory support for ILD patients while aligning treatment goals with patient prognosis and preferences.

Educational aims

- To understand the unique challenges and physiological considerations in ventilating patients with ILD, particularly during acute exacerbations.
- To explore the evidence and rationale for different respiratory support strategies, including high-flow nasal cannula, noninvasive ventilation and invasive mechanical ventilation, in ILD patients.
- To highlight the importance of integrated palliative care when managing ILD patients being considered for mechanical ventilation, particularly in patients with poor prognosis or limited therapeutic options.

Background

Interstitial lung disease (ILD) refers to a heterogenous group of conditions characterised by varying degrees of inflammation and fibrosis affecting the lung interstitium [1]. The consequence of this mixed inflammatory and fibrotic process is a distortion of lung architecture and impairment in gas exchange at the alveolar unit. Damage to the alveolar epithelium and abnormal wound repair are theorised to be key factors in the development of this disease [2]. The cause of ILD may be unknown, as in the case of idiopathic pulmonary fibrosis (IPF), although IPF is thought to result from a combination of genetic and environmental factors. The underlying pathophysiology of IPF appears to be predominantly fibrosis-mediated in the absence of overt inflammation characterised by abnormal epithelial–fibroblast communication, culminating in recruitment and activation of myofibroblasts that produce a collagen-rich extracellular matrix [3].

The diagnostic approach in ILD relies on identification of the aetiology or the trigger for development of the ILD. IPF accounts for approximately one-third of all cases of ILD [4]. Hypersensitivity pneumonitis (HP) accounts for 15% of ILD cases and connective tissue disease (CTD) accounts for 25% of ILD cases [4]. Specific causes of ILD include systemic autoimmune conditions and the subtypes of a particular connective tissue disease (CTD-ILD) [5], for example rheumatoid arthritis (RA-ILD) [6], as well as rare idiopathic interstitial pneumonias. Other causes include environmental antigens (as in chronic HP) [7] and drugs [8]. The most common symptoms are dry cough, fatigue and progressive exertional dyspnoea, all of which can cause significant distress [4].

The radiological features of the usual interstitial pneumonia (UIP) pattern, the hallmark of IPF, were described in detail in the 2018 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines for the diagnosis of IPF [9]. Lung fibrosis can be confidently diagnosed using high-resolution computed tomography (HRCT) imaging when traction bronchiectasis/bronchiolectasis and/or honeycombing are identified, although honeycombing must be distinguished from para-septal emphysema and airspace enlargement with fibrosis [10]. Honeycombing refers to clusters of abnormal, cystically dilated airspaces with walls composed of fibrotic tissue, lined by an epithelium that shares histological characteristics with the airway epithelium [9, 11]. Thoracic HRCT is approximately 91% sensitive and 71% specific for diagnosing subtypes of ILDs such as IPF [4]. There is an evolving role for the use of artificial intelligence in the detection of ILD patterns on imaging [12].

Incidence, mortality and critical care outcomes in ILD

Challenges in estimating incidence and mortality trends

Estimating the incidence of ILD has been historically challenging due to the difficulty in diagnosis and geographical differences in diagnostic criteria and thresholds. An observational study across the UK and 27 European countries between 2001 and 2017 showed an overall increasing incidence of ILD across most countries for both men and women, with men having a consistently higher mortality across the study period [13]. This study observed significant decreasing trends in ILD mortality and in mortality-to-incidence ratios (MIR) in multiple countries during the most recent 5 years of the observation period. While the advent of recent antifibrotic drugs may have contributed to the reduced mortality, the observational nature of the data precludes causal conclusions, and other unmeasured factors, such as increased use of high-flow nasal cannula (HFNC) and lung-protective ventilation strategies during mechanical ventilation may also play a role [13].

Outcomes in critical care settings

Community-acquired pneumonia necessitating critical care admission has a poor prognosis in the general critical care population, with mortality ranging between 20% and 50% [14, 15]. The greater the degree of organ dysfunction, as well as the number of organ systems involved, correlates to a higher illness severity scoring index and higher mortality [16]. Increasing age, a greater burden of comorbidities and frailty, amongst other factors, contribute to increasing mortality from community-acquired pneumonia [17, 18].

The outcomes of patients with ILD and acute respiratory failure who require critical care referral with consideration for critical care admission are generally poor, even compared with other causes of acute respiratory failure, such as community-acquired pneumonia described above. A multicentre retrospective cohort study from 2009 examined outcomes for patients with IPF admitted to critical care, revealing that only 8% survived to hospital discharge [19]. A 2008 review by Fernández-Pérez *et al.* [20] of patients with ILD admitted to critical care found that 47% of the 94 patients survived to hospital discharge, with 41% remaining alive 1 year later. High positive end-expiratory pressure (PEEP), low arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) and older age were found to be independent predictors of mortality. A study from Finland found that patients with ILD readmitted as an emergency due to respiratory failure within 6 months following critical care discharge had an average survival time of 7.2 months [21].

These data highlight the need for clinicians to carefully weigh the risks and benefits of intensive care and mechanical ventilation for ILD patients, particularly in the absence of potentially curative options like lung transplantation. Indeed, a multicentre study reported that, in the absence of lung transplantation, the mortality rates following invasive mechanical ventilation for acute exacerbations of ILD (AE-ILD) were 78% at 30 days and 96% at 6 months [22]. Early and informed discussions about prognosis and care preferences with patients and their families are therefore clearly important.

Exacerbations of ILD

The underlying aetiology of ILD dictates the choice of therapy. Antifibrotic medications, such as pirfenidone and nintedanib, are used to slow disease progression in IPF, while corticosteroids in conjunction with other immunosuppressives are considered for patients with HP and CTD-ILD [23–25]. There are subsets of patients with, for example, RA-ILD and chronic HP who will experience a disease course similar to patients with IPF. While the standard of care for patients with RA-ILD and chronic HP is immunosuppression, the optimal treatment for patients with progressive disease and also who also display a UIP pattern remains unknown [26]. As such steroids play a variable role in management of disease progression outside of acute exacerbations. Corticosteroids are associated with a higher mortality in IPF, particularly in combination with azathioprine and *N*-acetylcysteine [27]. Nintedanib is a triple kinase

inhibitor of platelet-derived growth factor receptor (PDGFR) and has been demonstrated to slow progression of IPF in phase II and phase III trials [25, 28]. Nintedanib reduced the decline in forced vital capacity (FVC), consistent with a slowing of underlying disease progression, as well as a mortality-benefit and reducing the risk of acute exacerbations [29].

AE-ILD, which are often defined using criteria for IPF, involve sudden respiratory failure marked by worsening dyspnoea and new ground-glass opacities or consolidation, without an alternative cause such as cardiac-related pulmonary congestion [30]. Acute exacerbations may be idiopathic and related to the natural course of the underlying pathology or the AE-ILD may be triggered by infection (bacterial, viral or fungal), environmental triggers, aspiration or chemical pneumonitis, blood transfusion reactions, or drug reactions. Patients with ILD may be referred to critical care for organ support, either with a confirmed diagnosis or with ILD considered as part of the differential diagnosis after admission, often when already on invasive mechanical ventilation.

While lung function tests are not usually feasible during acute exacerbations, review of trends in prior lung function testing may be informative in prognostication during exacerbations. A 5% decline in FVC over 12 months is linked with an approximately twofold increase in mortality compared with stable FVC [4]. Low FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) are significant predictors of reduced survival [30, 31].

Bronchoalveolar lavage (BAL) is often performed during acute exacerbations, but a review of ILD patients undergoing BAL in critical care found a low diagnostic yield (~13%) with minimal impact on clinical management, suggesting limited utility in this setting [32]. Therefore, because BAL can cause gas exchange to deteriorate, it may be performed on a case-by-case basis rather than routinely. A sputum sample can be sent routinely.

Treatment

The primary role of invasive ventilation in AE-ILD is to provide supportive care, allowing time for resolution through treatment or spontaneous recovery, or in specialised centres, to serve as a bridge to lung transplantation. There is no standardised treatment regimen for ILDs whose underlying mechanism may be as diverse as IPF to fibrotic HP to anti-MDA5 dermatomyositis.

During acute exacerbations, high-dose corticosteroids (*e.g. i.v.* methylprednisolone) are frequently used to reduce inflammation, although evidence for their efficacy is limited. Additional immunosuppressive agents (*e.g.* mycophenolate or cyclophosphamide) may be considered, particularly in cases with suspected autoimmune triggers. A 2023 European expert consensus statement on management of progressive pulmonary fibrosis (PPF) stated that, depending on the subtype of PPF, immunosuppression added to the background treatment of steroids may be of varying benefit [33]. However, the benefits of additional immunosuppression may take months to manifest [34]. This limits their impact during acute exacerbations when rapid clinical deterioration occurs.

Broad-spectrum antibiotics are often initiated empirically to cover bacterial infections, as infection is a common trigger for AE-ILD. If viral or fungal infections are suspected, targeted antiviral or antifungal therapies may be included. For patients already on antifibrotic therapies (*e.g.* nintedanib or pirfenidone), these treatments are typically continued, though their role in acute exacerbations remains unclear.

Proton-pump inhibitors (PPIs) are theorised to limit ILD progression by reducing micro-aspiration from gastro-oesophageal reflux, which is common in these patients. However a 2021 population-based study found no association between PPI use and reduced mortality or hospitalisation rates in patients with IPF [35]. There are studies that demonstrate an increased risk of community-acquired pneumonia associated with the use of PPIs [36–38], theorised to be related to changes in gastric acid acidity. However, a cohort study in the UK of 160 000 PPI users concluded that the association between PPI use and pneumonia is likely to be entirely due to confounding factors [39]. Given the lack of robust evidence it is difficult to draw firm conclusions and so prescription of a PPI should be made on an individual basis.

Managing respiratory failure during AE-ILD

Physiological barriers to oxygenation

Fibrotic ILD, including IPF, involves complex pathological changes through the lower airways, including replacement of the normal elastin-rich extracellular matrix with a stiff, collagen-rich matrix [40]. Lung compliance, defined as the change in lung volume per unit pressure, is profoundly reduced in ILD and IPF

due to interstitial matrix alterations and changes in surfactant composition, including decreased levels of phosphatidyl glycerol, increased phosphatidylinositol and increased sphingomyelin levels [41].

Research suggests that the reduced lung compliance in ILD correlates closely with the degree of fibrosis and progresses with the disease, but it is not linked to changes in D_{LCO} [42]. A restrictive ventilation pattern is common in ILD with a downward and rightward shift of the static expiratory pressure–volume curve [43]. In IPF, D_{LCO} is almost always reduced due to changes in the alveolar–capillary membrane and the microvasculature, along with increased dead space ventilation, and pulmonary hypertension in up to 85% of end-stage fibrotic ILD patients [4, 44].

High-flow nasal cannula therapy

HFNC oxygen delivery is a method of delivering high, titratable flow rates of humidified oxygen at an F_{IO_2} of up to approximately 100%. HFNC enhances flow-dependent carbon dioxide clearance, reduces anatomic dead space, improves work of breathing and provides benefits such as flow-related PEEP and reduced respiratory secretions [45].

There is a lack of high-quality data on use of HFNC in patients with AE-ILD. A single-centre study found that HFNC reduced respiratory rates in ILD patients compared with noninvasive ventilation (NIV) with fewer adverse events noted related to HFNC compared with NIV, such as skin damage from tight-fitting face masks. HFNC allowed patients to eat, drink and communicate with greater ease, indicating a better quality of life. HFNC use was also associated with lower device interruption, fewer discontinuations, and reduced use of sedatives, highlighting its tolerability and practicality in end-of-life care [46]. In patients with hypoxaemic respiratory failure not associated with hypercarbia, the use of HFNC might be associated with a reduced 90-day mortality [47].

Noninvasive ventilation

The role of NIV in AE-ILD is limited and remains controversial. While NIV provides ventilatory support without requiring an invasive airway and is effective for rapidly reversible conditions like flash pulmonary oedema or COPD exacerbations, such rapid reversibility is rare in AE-ILD. NIV is delivered *via* a tight-fitting mask, which can cause discomfort, pressure sores, and challenges with secretion clearance, eating and drinking, often necessitating breaks or a switch to HFNC for relief [48, 49]. NIV allows for the adjustment of airway pressure and PEEP, potentially improving carbon dioxide clearance, alveolar recruitment, work of breathing and cardiac afterload [50, 51].

However, in advanced fibrotic ILD, the structural stiffness and limited recruitability of the lungs reduce the effectiveness of NIV. NIV also carries risks such as barotrauma (pressure-induced lung injury), which may outweigh its potential benefits in this population. Despite these challenges, NIV is not a contraindication for lung transplantation unlike prolonged invasive mechanical ventilation which may limit transplant eligibility [52].

A 2014 multicentre, observational, retrospective study examined the physiological effects of NIV in ILD patients with acute respiratory failure in a critical care setting [51]. In patients with pneumonia, NIV significantly improved oxygenation (P_{aO_2}/F_{IO_2} ratio) but no such improvement was seen in patients with fibrotic lung disease. Therefore, for primarily fibrosis-driven ILD, the risks of NIV, such as pneumothorax or pneumomediastinum, might outweigh its potential benefits, while for those with coexistent diseases such as pulmonary oedema or pneumonia it could be considered on a case-by-case basis.

There is a role for the use of NIV as a means of pre-oxygenation prior to induction of anaesthesia before airway manipulation for the placement of an endotracheal tube. The recent PREOXI (Pragmatic Trial Examining Oxygenation Prior to Intubation) trial in the USA demonstrated pre-oxygenation with an oxygen face mask to be inferior to pre-oxygenation with NIV [53]. A randomised multicentre trial in Sweden in 2021 compared pre-oxygenation using HFNC with a tight-fitting face mask for the purpose of rapid sequence induction in emergency surgery [54]. No difference in desaturation was found between the groups and no difference was seen in end-tidal carbon dioxide levels in the first ventilated breath after tracheal intubation. The choice of method of preoxygenation will differ between institutions and depend on local institutional practice.

Invasive ventilation

Outcomes following mechanical ventilation in ILD are generally poor, as evidenced by survival rates between 10% and 50% in cohort studies [55]. There are no randomised controlled trials that compare different invasive ventilation strategies and practice is guided by pathophysiological reasoning and the

results of observational studies. Ventilating patients with ILD, particularly IPF, is challenging due to reduced lung compliance and volumes, impaired gas exchange, increased dead space ventilation, chronic hypoxaemia, and heightened airway sensitivity [44]. Unlike in acute respiratory distress syndrome (ARDS), where alveolar recruitability allows for the effective use of higher PEEP to improve oxygenation, the fibrotic and stiff lungs in ILD have minimal recruitability. Therefore, there are similarities but also important differences in invasive ventilation strategies when comparing ARDS and AE-ILD. Similar to ARDS, suggested tidal volume targets are approximately 4–6 $mL \cdot kg^{-1}$ of ideal body weight [56]. This reduces the risk of volutrauma and barotrauma. However, unlike ARDS, where high PEEP is often used to improve the homogeneity of ventilation and where recruitment manoeuvres can also be considered, in ILD low PEEP is generally preferred and recruitment manoeuvres avoided [57].

This paradigm is supported by observational data. A matched-control study suggested that a low PEEP strategy may improve respiratory mechanics in patients with AE-ILD [58]. Higher PEEP is a risk factor for mortality in invasively ventilated patients [20]. While tools such as electrical impedance tomography have been used to optimise PEEP in ARDS, there is little data in ILD, as titration usually requires the application of recruitment manoeuvres [59]. Some authors have advocated the concept of a "lung-resting" strategy where the minimal amount of PEEP is used to achieve the minimal acceptable oxygenation level [57]. Targets of peripheral oxygen saturations between 88% and 92% and partial pressure of oxygen values between 6.6 kPa and 8 kPa were used.

Sedation and neuromuscular blockade are frequently employed to achieve tight control of ventilation and oxygenation titration, particularly in the early phase of the critical care admission. The use of sedation, neuromuscular blockade and corticosteroid therapy, combined with the development of intensive care unit (ICU)-acquired weakness, are themselves barriers to subsequent liberation from invasive mechanical ventilation, if and when this is being considered, particularly if invasive ventilation is ongoing for days [60]. Diaphragm atrophy occurs rapidly in patients on invasive mechanical ventilation and this can be a particularly limiting step in patients with ILD who may have difficulty weaning from a protracted course of invasive ventilation [61].

Other treatments in ILD

Palliative care

Given the high mortality of ILD patients in the critical care unit, and in the weeks and months following a critical care admission in survivors, early referral to palliative care is important for symptom management in ILD patients, whose symptoms such as cough, breathlessness and fatigue, worsen as the disease progresses. This referral should be made early, and palliative care should proceed in tandem with the management plan of the respiratory team, with the focus on symptom management as the disease progresses. The 2011 ATS/ERS/JRS/ALAT statement on "idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management" recommend integrating palliative care alongside disease-focused treatments. There should be early discussions about prognosis and care goals, particularly in the absence of lung transplantation, to avoid last-minute decision making during critical care admissions [62].

Once the diagnosis of ILD is made, the primary physician should set realistic goals and expectations with the patient, particularly in terms of symptom management and expectations around end-of-life care. The discussion regarding whether invasive mechanical ventilation is appropriate should happen between the primary team and the patient and the realistic outcomes of critical care admission, particularly if invasive mechanical ventilation is offered. Patients may decide that NIV or HFNC is the maximum oxygenation therapy they would deem acceptable. If invasive mechanical ventilation is offered, then the real possibility of death either in critical care or in the weeks and months after can be discussed. The role of lung transplantation in the future can also be outlined at that time if applicable to that particular patient.

There is evidence to suggest that physicians are not good at having such early conversations regarding end-of-life care and setting ceilings of care in conjunction with patients. In a cohort of ILD patients, 34% required ICU admission within 4 months of referral, 77% died during their critical care stay, and despite palliative care being considered by 65% of physicians, only 3.8% received a palliative care referral before critical care admission [63]. The time between diagnosis of ILD and time of referral to critical care is an important window where ceilings of care, limits on resuscitation (if any), symptom management and a realistic vision of what to expect as the disease progresses should be outlined as best as possible.

Lung transplantation

Lung transplantation is a potential option for select patients meeting guideline criteria. The 2021 International Society for Heart and Lung Transplantation consensus document outlines risk factors that

may predispose to poor outcomes following lung transplantation [64]. Risk factors that may increase this risk include severe coronary artery disease, reduced left ventricular ejection fraction, significant cerebrovascular disease, severe oesophageal dysmotility, untreatable haematological disorders, severe bone marrow dysfunction, body mass index (BMI) $\geqslant 35\ kg \cdot m^{-2}$ and a BMI $<16\ kg \cdot m^{-2}$ amongst others. Examples of absolute contraindications presented include lack of patient willingness or acceptance of transplant, a malignancy with high risk of recurrence or death related to cancer, severe renal disease (unless being considered for a multi-organ transplant), acute coronary syndrome or myocardial infarction within 30 days, stroke within 30 days, liver cirrhosis with portal hypertension or acute liver failure, septic shock, limited functional status with poor potential for post-transplant rehabilitation, progressive cognitive impairment, and active substance use or dependence including current tobacco use, vaping or intravenous drug use.

Prediction of survival and disease course can be challenging in patients with ILD and guidelines therefore recommend early listing for lung transplantation [64]. Lung transplantation is typically reserved for patients with slowly progressive ILD but data also exists for its use in AE-ILD. A 2018 study found that while short-term survival after lung transplantation during an acute exacerbation of IPF was comparable to stable IPF, long-term outcomes were significantly worse [65]. In patients with acute exacerbation of IPF there was a 50% mortality at a mean of 1.6 years compared with 12% mortality at 2.6 years in those transplanted during stable IPF [65]. Poorer 1- and 2-year survival rates in patients transplanted during or shortly after an acute exacerbation of IPF are an important consideration in this context.

Ultimately the decision to refer for transplant consideration will be made by the primary physician managing the patient's ILD after weighing the individual risks and potential benefits for the long term.

Conclusion

ILD represents a complex and heterogenous group of conditions with significant challenges in diagnosis, management and prognosis – particularly during acute exacerbations. Mechanical ventilation, both noninvasive and invasive, plays an important but limited role. Ventilation strategies are guided by principles of lung protection, such as low tidal volumes and minimal PEEP, to avoid further lung injury in stiff, fibrotic lungs with poor recruitability. While invasive ventilation can provide time for recovery or act as a bridge to lung transplantation in specialised centres, outcomes remain poor. This highlights the importance of careful patient selection and early integration of palliative care. Lung transplantation offers hope for select patients, though it carries significant risks, especially during acute exacerbations. Ultimately, aligning care with the patient's goals through early and informed discussions is vital to optimising outcomes and quality of life.

Key points

- ILD presents unique challenges for mechanical ventilation due to reduced lung compliance, poor recruitability and a high risk of ventilator-induced lung injury.
- HFNC and NIV often have limited roles in managing AE-ILD, but equally invasive ventilation is associated with poor outcomes, particularly in patients who would not be candidates for lung transplantation.
- Effective management requires balancing life-sustaining interventions with early palliative care discussions to align treatment with patient goals and quality of life.
- Evidence for ventilation strategies in ILD is primarily based on observational studies, emphasising the need for individualised, pathophysiology-driven approaches.

Self-evaluation questions

1. Which of the following is the primary goal of mechanical ventilation in ILD patients with acute exacerbations?
    a) Achieve complete normalisation of blood gases.
    b) Maximise alveolar recruitment through high PEEP.
    c) Provide supportive care to allow time for treatment or resolution.
    d) Ensure tidal volumes exceed $8\ mL \cdot kg^{-1}$ to prevent hypoventilation.
2. Which ventilation strategy is most appropriate for ILD patients with acute exacerbations?
    a) High tidal volumes ($8–10\ mL \cdot kg^{-1}$) to improve ventilation.
    b) Recruitment manoeuvres and high PEEP to enhance oxygenation.
    c) Low tidal volumes ($4–6\ mL \cdot kg^{-1}$) and minimal PEEP to avoid overdistension.
    d) Avoid mechanical ventilation entirely in all cases.

3. What is a common risk of mechanical ventilation in ILD patients?
   a) Hypoventilation due to increased airway resistance.
   b) Overdistension of non-fibrotic lung areas, leading to barotrauma.
   c) Difficulty weaning due to pre-existing neuromuscular conditions.
   d) Rapid alveolar recruitment causing haemodynamic instability.
4. Which of the following therapies is most appropriate for respiratory failure in ILD patients where mechanical ventilation is not feasible?
   a) HFNC.
   b) Immediate lung transplantation.
   c) Bronchoscopy with BAL.
   d) Long-term NIV.
5. Why is palliative care essential in managing ILD patients with acute respiratory failure?
   a) To reduce the need for invasive procedures.
   b) To ensure that ventilation strategies are appropriately aggressive.
   c) To align treatment goals with patient preferences and quality of life.
   d) To manage reversible triggers of exacerbations.

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Suggested answers

1. c. The main goal of mechanical ventilation in ILD is to provide supportive care while minimising further lung injury, rather than aggressively correcting all abnormalities.
2. c. Low tidal volumes and minimal PEEP are preferred to reduce the risk of ventilator-induced lung injury in stiff, fibrotic lungs.
3. b. Overdistension of more compliant, non-fibrotic areas is a significant risk due to the stiff and poorly recruitable fibrotic lung tissue.
4. a. HFNC can provide oxygenation and symptom relief with greater tolerability, especially in patients with advanced disease or do-not-intubate orders.
5. c. Palliative care ensures that interventions are consistent with patient goals, particularly given the high mortality