

Acute exacerbation of systemic autoimmune rheumatic disease-associated interstitial lung disease: integrated pathophysiology and respiratory care

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Abstract

Acute exacerbation of systemic autoimmune rheumatic disease-associated interstitial lung disease (AE-SARD-ILD) is an uncommon but severe cause of acute respiratory failure, frequently requiring intensive care. Although commonly managed according to paradigms derived from acute exacerbation of idiopathic pulmonary fibrosis or acute respiratory distress syndrome, AE-SARD-ILD encompasses heterogeneous pathological processes with distinct respiratory mechanics, pulmonary vascular involvement, reversibility, and treatment response. Management based solely on the underlying rheumatic disease or radiological pattern may therefore be inadequate. This Perspective reviews current evidence on the diagnosis and critical care management of AE-SARD-ILD and proposes an integrated clinical–radiological–mechanical framework for physiology-guided decision-making. Moving beyond conventional disease- and imaging-based fibrotic classifications, the framework identifies four dominant, potentially overlapping physiological phenotypes arising from the interaction between the chronic pulmonary substrate and the superimposed acute insult: fibrotic/UIP-like, inflammatory/ARDS-like, pulmonary hypertension-dominant, and diffuse alveolar haemorrhage-dominant. These phenotypes provide a physiological rationale for selecting, titrating, and escalating non-invasive and invasive respiratory support, controlling excessive respiratory drive, and integrating immunomodulatory, pulmonary vascular, and extracorporeal strategies. Although prospective validation is required, physiological phenotype-based assessment may support individualized respiratory management, dynamic prognostication, and time-limited intensive care trials in AE-SARD-ILD.

Keywords Systemic autoimmune rheumatic diseases · Interstitial lung disease · Acute exacerbation · Respiratory mechanics · Non-invasive respiratory support · Mechanical ventilation

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Roberto Tonelli and Martina Orlandi share first authorship.



Abbreviations

AAV	Anca-associated vasculitisy
ACR	American College of Rheumatology
AE	Acute exacerbation
AE-fILD	Acute exacerbation of fibrotic interstitial lung disease
AE-ILD	Acute exacerbation of interstitial lung disease
AE-IPF	Acute exacerbation of idiopathic pulmonary fibrosis
AE-SARD-ILD	Acute exacerbation of systemic autoimmune rheumatic disease-associated interstitial lung disease
AHRF	Acute hypoxaemic respiratory failure
AI	Artificial intelligence
ANCA	Antineutrophil cytoplasmic antibody
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ARW	Acute respiratory worsening
AUC	Area under the curve
BAL	Bronchoalveolar lavage
CHEST	American College of Chest Physicians
CI	Cardiac index
CT	Computed tomography
CTD	Connective tissue disease
CTD-ILD	Connective tissue disease-associated interstitial lung disease
CVP	Central venous pressure
DAD	Diffuse alveolar damage
DAH	Diffuse alveolar haemorrhage
ECMO	Extracorporeal membrane oxygenation
Ers	Respiratory system elastance
FiO ₂	Fraction of inspired oxygen
FVC	Forced vital capacity
GGO	Ground-glass opacity
HACOR	Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate
HFNC	High-flow nasal cannula
HP	Hypersensitivity pneumonitis
HRCT	High-resolution computed tomography
ICU	Intensive care unit
IIM	Idiopathic inflammatory myopathy
ILD	Interstitial lung disease
IMV	Invasive mechanical ventilation
IPF	Idiopathic pulmonary fibrosis
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
KDIGO	Kidney Disease: Improving Global Outcomes
KL-6	Krebs von den Lungen-6
LDH	Lactate dehydrogenase
LV	Left ventricle
MCTD	Mixed connective tissue disease
MDA5	Melanoma differentiation-associated protein 5

MTX	Methotrexate
NIV	Non-invasive ventilation
NSIP	Nonspecific interstitial pneumonia
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OP	Organizing pneumonia
P0.1	Airway occlusion pressure at 100 ms
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PaO ₂	Arterial partial pressure of oxygen
PCR	Predicted body weight
PE	Polymerase chain reaction
PEEP	Positive end-expiratory pressure
PH	Pulmonary hypertension
PH-ILD	Pulmonary hypertension associated with interstitial lung disease
Pplat	Plateau pressure
PS	Pressure support
P-SILI	Patient self-inflicted lung injury
PVR	Pulmonary vascular resistance
PVOD	Pulmonary veno-occlusive disease
RA	Rheumatoid arthritis
ROX	Ratio of oxygen saturation/FiO ₂ to respiratory rate
RP-ILD	Rapidly progressive interstitial lung disease
RR	Respiratory rate
RV	Right ventricle
RV-PA	Right ventricular-pulmonary arterial
SARD	Systemic autoimmune rheumatic disease
SARD-ILD	Systemic autoimmune rheumatic disease-associated interstitial lung disease
SLE	Systemic lupus erythematosus
SpO ₂	Peripheral oxygen saturation
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
UIP	Usual interstitial pneumonia
VA-ECMO	Venoarterial extracorporeal membrane oxygenation
VD/VT	Physiological dead-space fraction
VILI	Ventilator-induced lung injury
V/Q	Ventilation-perfusion ratio
VT	Tidal volume
VV-ECMO	Venovenous extracorporeal membrane oxygenation
ΔP	Driving pressure
ΔPes	Oesophageal pressure swing

Introduction

Interstitial lung disease (ILD) is a major pulmonary complication of systemic autoimmune rheumatic diseases (SARDs), particularly connective tissue diseases (CTDs) and less commonly systemic vasculitis [1]. SARD-ILD encompasses heterogeneous inflammatory and fibrotic phenotypes shaped by the underlying disease, radiological

pattern, fibrotic burden, and extrapulmonary involvement [2, 3]. Usual interstitial pneumonia (UIP) predominates in rheumatoid arthritis (RA) [4], while nonspecific interstitial pneumonia (NSIP) is more common in systemic sclerosis and Sjögren disease and organizing pneumonia (OP) in inflammatory myopathies [5, 6]. Mixed patterns are frequent [5]. Pulmonary hypertension (PH), oesophageal dysfunction with aspiration, and extrapulmonary involvement may complicate the clinical picture, particularly in mixed CTD [3], while systemic vasculitis and systemic lupus erythematosus may present with acute pneumonitis or diffuse alveolar haemorrhage (DAH) [6, 7].

Acute exacerbation (AE) is among the most severe forms of respiratory deterioration in SARD-ILD, often requiring intensive care unit (ICU) management [1]. Although less frequent than in idiopathic pulmonary fibrosis (IPF), AE-SARD-ILD carries poor prognosis, with hospital mortality approaching 50–100% in severe cases particularly when invasive mechanical ventilation (IMV) is required [8, 9]. The recent International Working Group Report refined the definition of AE in fibrotic ILD (AE-fILD) and introduced the broader concept of acute respiratory worsening (ARW) [10]. However, acute respiratory failure (ARF) in SARD-ILD may reflect coexisting inflammatory, fibrotic, vascular, haemorrhagic, infectious, and autoimmune mechanisms rather than a single dominant process [1, 10, 11]. Pathologically, AE represents acute lung injury superimposed on chronic inflammatory and/or fibrotic ILD: although diffuse alveolar damage (DAD) is considered the hallmark of AE-fILD, OP, DAH, pulmonary capillaritis, and other patterns may coexist or predominate in SARD-ILD [12]. This is where AE-SARD-ILD may differ from AE-IPF and, to a lesser extent, acute deterioration in idiopathic NSIP and fibrotic hypersensitivity pneumonitis (HP), making extrapolation from the AE-IPF paradigm potentially misleading. In IPF, acute injury occurs on an irreversibly progressive fibrotic UIP substrate, with no established role for immunosuppression, which may be harmful [13]. In SARD-ILD, by contrast, the chronic substrate may range from predominantly fibrotic to inflammatory or organizing patterns, while the superimposed acute process may include potentially immunoresponsive inflammatory injury [9, 14]. Pulmonary vascular and alveolar-haemorrhagic involvement further distinguish SARD-ILD, while idiopathic NSIP and fibrotic HP occupy an intermediate, variably immunoresponsive position [15]. Respiratory infection, micro-aspiration, drug toxicity, procedures, and autoimmune reactivation may also precipitate deterioration [2, 16]. Thus, similar presentations may conceal different respiratory mechanics, recruitability, pulmonary vascular involvement, inspiratory drive, and reversibility [17].

In this Perspective, we propose a physiology-guided clinical–radiological–mechanical framework complementing current diagnostic classifications and guiding respiratory support according to the interaction between chronic pulmonary substrate, acute insult, and dominant physiological constraint.

Search strategy and legend

This Perspective was informed by a PubMed/MEDLINE search addressing pathophysiology, diagnosis, respiratory support, pharmacological treatment, and prognosis in AE-SARD-ILD, supplemented by screening of reference lists from relevant reviews, guidelines, consensus documents, and primary studies. Randomised trials, observational and physiological studies, systematic reviews, and major society statements were considered. Given the limited disease-specific evidence, clinically relevant data from AE-IPF, fibrotic ILD, ARDS, PH, and DAH were also included. To improve transparency, each management recommendations proposed was qualified using a simplified evidence framework adapted from Detterbeck et al. [18]. Study design was classified as T (trial), O (observational), or E (expert opinion, consensus, or guideline), whereas evidence directness was classified as d (direct evidence from AE-SARD-ILD or closely related populations) or i (indirect evidence extrapolated from related conditions). The resulting notation (Td, Ti, Od, Oi, Ed, Ei) is applied to each recommendation throughout the text. The literature search, evidence-selection process, and framework used to classify the directness and design of the supporting evidence are summarised in Supplementary eFigure 1.

Diagnostic assessment

The diagnostic evaluation of ARW in SARD-ILD should identify the cause of acute respiratory deterioration, distinguish AE from alternative diagnoses, and characterize the underlying chronic ILD substrate. Because no single clinical, radiological, or laboratory finding is specific for AE, patients should undergo a parallel assessment aimed at confirming acute lung injury while identifying potentially reversible competing or triggering conditions (Ei) [10]. HRCT is the cornerstone of evaluation. New bilateral ground-glass opacities with or without consolidation superimposed on fibrotic lung disease support the diagnosis of AE [11, 19, 20], but similar abnormalities may occur in infection, OP, DAH, aspiration, cardiogenic oedema, or drug-induced pneumonitis [19, 21, 22]. Imaging should therefore be interpreted together with the distribution and extent of fibrosis, honeycombing, traction bronchiectasis, and signs of pulmonary vascular or right-heart involvement (Oi/Ei) [23, 24]. CT pulmonary angiography is appropriate when pulmonary embolism is clinically suspected (Od/Ei) [25, 26].

Infection must be actively investigated because it may mimic, coexist with, or trigger AE (Ed/Ei) [19, 27]. Focal consolidation, tree-in-bud opacities, centrilobular nodules, or cavitation favour infection, although viral and opportunistic pathogens may produce diffuse ground-glass changes indistinguishable from non-infectious injury [28–31]. Microbiological testing should include respiratory and blood cultures, viral PCR, and targeted assays for opportunistic pathogens according to exposure, severity, and immunosuppressive status (Ed/Od) [19, 22].

Bronchoalveolar lavage may be useful when infection or DAH remains uncertain, but its diagnostic yield must be balanced against the risk of respiratory deterioration (Od/Oi) [32, 33]. When performed, it should include broad microbiological testing (Od/Ed) [33, 34]; progressively haemorrhagic aliquots support DAH, while haemosiderin-laden macrophages are supportive but not entirely specific [35].

Cardiopulmonary assessment should also identify left-sided cardiac disease, pericardial involvement, PH, and right ventricular dysfunction (Ed/Ei) [11, 36, 37]. Electrocardiography, cardiac biomarkers, and bedside echocardiography should be integrated with HRCT and clinical findings; right-heart catheterization should be reserved for selected stabilized patients in whom haemodynamic confirmation would change management (Ei) [37].

Physiological phenotypes

After defining the acute process and the underlying pulmonary substrate, we propose interpreting AE-SARD-ILD as a clinical–radiological–mechanical syndrome rather than a uniform form of respiratory failure. Within this framework, the dominant phenotype emerges from the interaction between the chronic lung substrate and the superimposed acute injury, providing the physiological basis for individualized respiratory support. Below we propose four dominant physiological phenotypes that reflect distinct physiological constraints with potentially different responses to respiratory support.

Fibrotic/UIP-like phenotype

The fibrotic/UIP-like physiological phenotype is characterized by dominant fibrosis, high elastance, limited recruitability, marked regional heterogeneity, and reduced functional lung volume [38]. Acute alveolar injury is superimposed on a structurally distorted and unevenly distributed ventilatable compartment with limited capacity to recruit or accommodate additional volume [39]. Respiratory system elastance may be substantially greater than in primary ARDS despite a similar degree of hypoxaemia [59]. In patients with fibrotic ILD, positive end expiratory pressure (PEEP) titration aimed at achieving a positive end-expiratory transpulmonary pressure increased elastance and driving pressure without meaningful improvement in oxygenation [59]. The fibrotic lung also displays an abnormal stress–strain relationship. Specific elastance has been reported to be approximately 2.5-fold higher than in ARDS, with a steeper stress–strain curve and crossing of a proposed VILI-risk threshold at strain values above 0.55 [39]. As strain increases, mechanical behaviour becomes progressively collagen dominated

[41, 42]. This supports the “squishy ball lung” model, in which pressure and deformation are unevenly transmitted through the fibrotic structure, producing regional overdistension despite apparently acceptable global ventilatory variables [38]. This profile is therefore highly vulnerable to both ventilator-induced and patient self-inflicted lung injury [43]. Vigorous spontaneous effort may expose residual aerated regions to large transpulmonary pressure swings, pendelluft, and regional stress amplification, affecting the same mechanically fragile interfaces exposed to positive-pressure ventilation [44]

Inflammatory/ARDS-like phenotype

The inflammatory/ARDS-like *phenotype* is more commonly associated with NSIP, OP or mixed patterns. In this setting, ground-glass opacities and consolidations are more likely to reflect inflammation, oedema, and intra-alveolar organization than fixed architectural distortion, although fibrosis of variable extent may coexist [15]. However, the mechanical behaviour of these patterns is not uniform. Cellular NSIP, diffuse alveolitis, and DAD may retain a recruitable component analogous to primary ARDS, whereas extensive OP predominantly reflects alveolar filling by intraluminal fibroblastic plugs (Masson bodies) rather than alveolar collapse [45]. Consequently, biological reversibility should not be equated with mechanical recruitability. Compared with the fibrotic/UIP-like phenotype, this profile generally preserves a larger ventilatable compartment, greater ventilation homogeneity, and a wider mechanical margin for positive-pressure support, although pre-existing fibrosis may still limit recruitment and promote regional overdistension [12, 46]. Oxygenation changes should therefore be interpreted together with compliance, driving pressure, plateau pressure, dead space, and haemodynamic response, since improved gas exchange does not necessarily indicate effective recruitment [47]. The contrasting mechanical responses of fibrotic/UIP-like and inflammatory/ARDS-like lungs to positive pressure are illustrated in Fig. 1.

Pulmonary hypertension-dominant phenotype

The PH-dominant phenotype is characterized by impaired gas exchange, increased pulmonary vascular load, and limited right ventricular reserve [48]. PH is common in fibrotic ILD and is associated with greater oxygen requirements, reduced functional capacity, and poorer survival [58, 65]. During acute deterioration, hypoxaemia, hypercapnia, acidosis, pulmonary vascular obstruction, and increased intrathoracic pressure may further increase right ventricular afterload and impair ventricular–pulmonary arterial coupling [51, 52]. Respiratory failure therefore reflects not only parenchymal dysfunction but also the limited ability of the right ventricle to tolerate further increases in pulmonary vascular resistance. Bedside echocardiography may identify right ventricular dilatation, septal flattening, systolic dysfunction, and preload dependence, helping to establish whether pulmonary vascular and haemodynamic constraints dominate the clinical picture [37, 52, 53].

Diffuse alveolar haemorrhage-dominant phenotype

DAH is a distinct acute phenotype occurring mainly in SLE and ANCA-associated vasculitis and, less frequently, in inflammatory myopathies [54–56]. Pulmonary capillaritis is the most common underlying lesion, although bland haemorrhage and DAD may also occur [56]. Alveolar flooding with blood produces severe shunt, loss of aerated lung volume, surfactant dysfunction, and secondary inflammatory injury. Lung mechanics may resemble an alveolar-filling ARDS phenotype, but the concomitant reduction in oxygen-carrying capacity, coagulopathy, haemodynamic instability, and the potential for rapid physiological improvement after control of capillary inflammation define a distinct physiological profile. Bedside physiology is therefore determined primarily by alveolar haemorrhage rather than by the underlying chronic parenchymal pattern.

The fibrotic/UIP-like and inflammatory/ARDS-like physiological phenotypes are defined primarily by their dominant respiratory mechanical behaviour, whereas the PH-dominant and DAH-dominant phenotypes are defined by the pathophysiological process that governs gas-exchange failure and response to respiratory support;

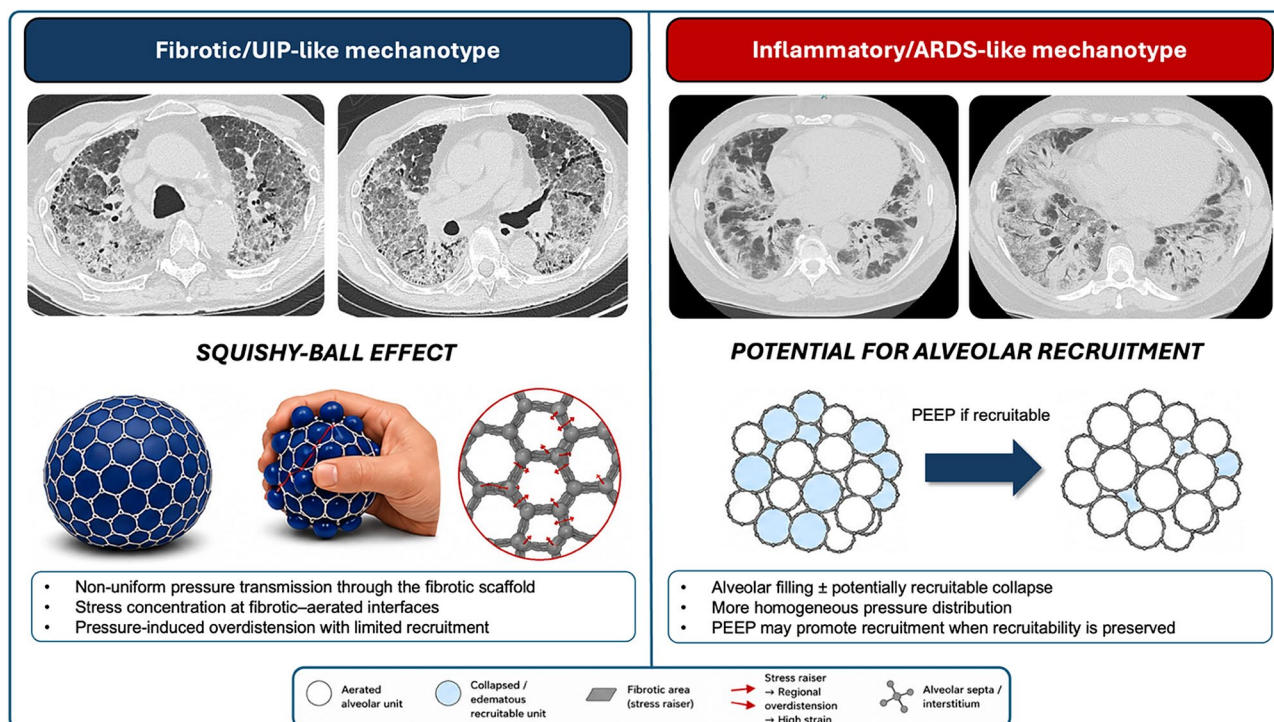


Fig. 1 Biomechanical behaviour of fibrotic/UIP-like and inflammatory/ARDS phenotypes in AE-SARD-ILD. Representative HRCT images illustrate AE occurring on a predominantly fibrotic/UIP-like substrate (left) and on a predominantly inflammatory/ARDS-like substrate (right). In fibrotic lungs, the *squishy-ball effect* depicts non-uniform pressure transmission through a heterogeneous fibrotic scaffold, resulting in stress concentration at fibrotic-aerated interfaces and preferential regional overdistension with limited recruitment. In contrast, inflammatory/ARDS-like lungs may retain greater potential for alveolar recruitment, particularly when DAD or alveolar collapse predominates, allowing positive pressure to reopen unstable units and promote a more homogeneous distribution of mechanical stress when recruitability is preserved. Abbreviations AE, acute exacerbation; ARDS, acute respiratory distress syndrome; HRCT, high-resolution computed tomography; PEEP, positive end-expiratory pressure; SARD-ILD, systemic autoimmune rheumatic disease-associated interstitial lung disease; UIP, usual interstitial pneumonia

in practice, these dimensions frequently intersect, and more than one phenotype may coexist and evolve in the same patient. When phenotypes overlap, management should address the most immediately life-threatening physiological constraint first — typically haemodynamic compromise in PH-dominant or active haemorrhage in DAH-dominant disease — while adapting ventilatory strategy to the coexisting mechanical profile and reassessing the dominant phenotype as the clinical course evolves. Although not prospectively validated in AE-SARD-ILD, this framework is intended to support bedside physiological reasoning (Tables 1 and 2).

Respiratory support and drive control

The previously described physiological phenotype carry direct implications for the selection, titration, and escalation of respiratory support, and may guide the choice between high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), IMV, together with the assessment of respiratory drive, haemodynamic reserve, and therapeutic trajectory, or ultimately the extracorporeal support (ECMO),

High-flow nasal cannula

HFNC is generally the preferred initial support in AE-SARD-ILD with mild-to-moderate hypoxaemic respiratory failure (Ei/Od) [78, 79]. Its main effects include dead-space washout, stable FiO_2 delivery, low-level positive

Table 1 Bedside identification of dominant physiological phenotypes in AE-SARD-ILD

Domain	Fibrotic/UIP-like	Inflammatory/ARDS-like	PH-dominant	DAH-dominant
<i>Typical HRCT features</i>	Honeycombing, traction bronchiectasis, reticulation; new GGO/consolidation superimposed on established fibrosis [11, 19, 24]	Diffuse GGO ± consolidation on NSIP, OP, or mixed pattern; limited or absent honeycombing [15, 19, 45]	Enlarged PA, RV/LV ratio > 1, mosaic attenuation; parenchymal changes may be modest relative to hypoxaemia severity [48, 65]	Diffuse bilateral GGO/consolidation, often gravity-dependent; rapid evolution over hours [35, 55, 56]
<i>Respiratory system mechanics</i>	High elastance (Ers often > 40 cmH ₂ O/L); low compliance; high specific elastance; steep stress–strain curve [39, 42, 59]	Variable elastance; compliance higher than fibrotic phenotype for comparable hypoxaemia; more homogeneous ventilation distribution [46, 57, 59]	Elastance may be near-normal or mildly elevated; mechanics–oxygenation dissociation (severe hypoxaemia with relatively preserved compliance) [48, 58]	Low compliance due to alveolar flooding; rapid changes in mechanics paralleling haemorrhage activity [35, 55, 56]
<i>Key bedside signs</i>	High ΔP at low VT; limited or no oxygenation response to PEEP; plateau pressure reached rapidly; persistent tachypnoea despite support [39, 42, 59, 60]	Oxygenation and compliance may improve with PEEP and prone positioning; VT may need active limitation [47, 61]	Disproportionate hypoxaemia; RV distension and septal flattening on echo; elevated NT-proBNP/troponin; hepatic congestion; peripheral oedema [65]	Falling haemoglobin without overt bleeding; haemorrhagic secretions (may be absent); progressively bloody BAL aliquots [35, 55, 56]
<i>Expected PEEP response</i>	Minimal or no recruitment; PEEP increases ΔP and elastance; risk of overdistension of residual aerated lung [59]	Variable recruitment potential; oxygenation may improve with moderate PEEP when a recruitable component is present and ΔP does not increase [12, 61, 62]	PEEP may worsen RV afterload and reduce cardiac output; oxygenation may not improve or may deteriorate [63]	Moderate PEEP may recruit flooded alveoli and provide tamponade effect; excessive PEEP may compromise venous return [55, 63]
<i>Gas exchange pattern</i>	High dead space (VD/VT); refractory hypoxaemia with limited shunt reversibility; hypercapnia common [59, 64]	Shunt-dominant hypoxaemia; potentially recruitable; dead space variable [12, 62]	Severe hypoxaemia disproportionate to parenchymal involvement; low mixed venous O ₂ ; high A-a gradient with relatively preserved VD/VT [48, 65]	Severe shunt; rapid PaO ₂ /FiO ₂ fluctuations paralleling haemorrhage; possible anaemia-related O ₂ delivery impairment [35, 55, 56]
<i>Haemodynamic profile</i>	Usually stable unless PH coexists; may deteriorate with excessive PEEP [63]	May resemble sepsis-like vasodilation if infection-triggered; usually tolerates moderate PEEP [62, 66]	Elevated CVP, low CI, RV–PA uncoupling; preload-dependent; sensitive to intrathoracic pressure changes [52, 53, 63]	Haemodynamic instability from blood loss and capillary leak; may require transfusion and vasopressors [55, 67]
<i>Expected recruitability</i>	Very limited; “baby lung” is small and fixed; recruitment manoeuvres generally ineffective or harmful [38, 43, 59]	Variable; potentially greater when DAD or alveolar collapse predominates and limited when OP or extensive coexisting fibrosis predominates [45, 62]	Recruitability limited by vascular rather than parenchymal mechanism; PEEP may worsen V/Q mismatch ^{48,62}	Potentially recruitable once haemorrhage controlled; rapid improvement possible with effective immunosuppression [55, 56, 67]

Table 1 (continued)

Domain	Fibrotic/UIP-like	Inflammatory/ARDS-like	PH-dominant	DAH-dominant
<i>Expected reversibility</i>	Low; structural injury largely irreversible; trajectory often toward transplant evaluation or palliation [1, 68, 69]	Moderate to high if inflammatory/OP component predominates and immunomodulation is timely; lower if DAD on fibrotic substrate [45, 70]	Variable; depends on whether PH is pre-existing (group 1/3) vs. acute and reversible (hypoxic vasoconstriction, PE); RV reserve is the key determinant [52, 65]	Potentially high if capillaritis is controlled rapidly; poor if DAD or multiorgan failure supervenes [56, 67, 71]
<i>Diagnostic pitfalls and overlap</i>	Infection may mimic or trigger AE on fibrotic substrate; coexisting PH is common and may be underrecognized; drug toxicity (MTX, leflunomide) may present identically [19, 22, 27, 65]	May be indistinguishable from infection-driven ARDS; OP component may be missed if not considered; may evolve toward fibrotic phenotype if treatment is delayed [1, 45]	May coexist with any parenchymal phenotype; isolated PH-dominant profile may be misattributed to parenchymal disease alone; PVOD-like involvement in SSc may contraindicate PAH-targeted therapy [48, 65]	Haemoptysis absent in up to 50%; may mimic infectious or inflammatory ARDS; coagulopathy and thrombocytopenia may be multifactorial; BAL may be non-diagnostic if performed early [55, 56]

The table summarizes the main bedside features supporting identification of fibrotic/UIP-like, inflammatory/ARDS-like, PH-dominant, and DAH-dominant phenotypes. These profiles are not mutually exclusive and may coexist or evolve during the same acute episode

Abbreviations

AE, acute exacerbation; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AE-SARD-ILD, acute exacerbation of systemic autoimmune rheumatic disease-associated interstitial lung disease; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CI, cardiac index; CVP, central venous pressure; DAD, diffuse alveolar damage; DAH, diffuse alveolar haemorrhage; ΔP , driving pressure; Ers, respiratory system elastance; FiO_2 , fraction of inspired oxygen; GGO, ground-glass opacity; HRCT, high-resolution computed tomography; ICU, intensive care unit; LV, left ventricle; MTX, methotrexate; NSIP, nonspecific interstitial pneumonia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OP, organizing pneumonia; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PaO_2 , arterial oxygen partial pressure; PE, pulmonary embolism; PEEP, positive end-expiratory pressure; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RV, right ventricle; RV-PA, right ventricular–pulmonary arterial; SARD, systemic autoimmune rheumatic disease; SSc, systemic sclerosis; UIP, usual interstitial pneumonia; VD/VT, physiological dead-space fraction; V/Q, ventilation–perfusion; VT, tidal volume

airway pressure, humidification, and reduction in respiratory rate and ventilatory demand [80]. In fibrotic ILD, HFNC may reduce minute ventilation by approximately 20%, although physiological unloading does not necessarily translate into improved dyspnoea [80, 81]. Its expected benefit varies by phenotype: In fibrotic/UIP-like disease, HFNC primarily improves oxygen delivery while partially unloading inspiratory effort; in inflammatory/ARDS-like disease, oxygenation may improve more substantially when recruitable alveolar units are present; in PH-dominant disease, HFNC may be better haemodynamically tolerated than higher-pressure NIV; whereas in DAH it may provide temporary stabilisation without delaying escalation when shunt, inspiratory effort, or haemodynamic instability worsen [63, 67, 82]. HFNC should be used as a closely monitored physiological trial. Early reassessment should integrate respiratory rate, accessory muscle use, inspiratory effort, gas-exchange trajectory, and haemodynamic status [79, 83] (Od/Ei). The ROX index may complement bedside assessment [84]. In AE-ILD, a 12-hour ROX index > 5.82 was associated with lower 30-day mortality (AUC 0.76) (Od) [85], although its performance appears less robust than in pneumonia-related acute respiratory failure and should not replace serial physiological assessment (Oi) [86].

Non-invasive ventilation

NIV in AE-SARD-ILD occupies a narrow therapeutic window between avoidance of IMV and risk of P-SILI. This risk is greatest in the fibrotic/UIP-like phenotype, where persistent respiratory drive may generate excessive tidal volume (VT) and transpulmonary pressure swings [60]. $VT > 9.5$ mL/kg PBW during NIV is associated with failure and mortality in AHRF [87], and even lower VT may produce injurious regional strain when the ventilatable compartment is markedly reduced [38]. In AE-IPF, NIV reduces oesophageal pressure swing (ΔP_{es}), respiratory rate, and minute ventilation without improving VT, compliance, transpulmonary pressure, or mechanical power, while increasing PEEP worsens oxygenation and compliance rather than promoting recruitment [60]. Consequently, NIV in fibrotic/UIP-like disease should primarily target measurable unloading rather than oxygenation alone (Od) [60]. Failure to reduce respiratory rate, ΔP_{es} , or other markers of inspiratory effort, particularly when VT remains excessive, should prompt escalation rather than further pressure titration (Oi) [88].

Table 2 Disease-modifying and immunomodulatory therapies potentially relevant to AE-SARD-ILD

Treatment	Evidence and clinical context
<i>Glucocorticoids</i>	Main empiric therapy when an immune-mediated mechanism is suspected (Ed) [1]; evidence in AE-ILD is predominantly retrospective, with no adequately powered prospective trial showing a survival benefit in unselected AE-SARD-ILD (Od) [70, 72], and ACR/CHEST conditionally recommends pulse IV glucocorticoids for SARD-associated RP-ILD (Ed) [73]. First-line when inflammatory/immune-mediated injury is likely, typically IV pulse in severe disease followed by oral therapy; optimal dose and duration uncertain (Od/Ed) [73, 74]
<i>Cyclophosphamide</i>	Evidence derives mainly from SARD-ILD/RP-ILD studies and AAV trials; can stabilize/improve FVC but with substantial toxicity (Ed) [1, 73], and is established AAV induction with glucocorticoids (Td/Ed) [73, 75]. Reserved for selected severe inflammatory/RP-ILD or disease-specific indications (AAV-associated disease, severe DAH), not routine rescue for unselected AE-SARD-ILD (Ei) [1, 73].
<i>Rituximab</i>	Trials and observational studies in SSc-, RA- and IIM-ILD suggest FVC stabilization/improvement (Ed) [73]; ACR/CHEST conditionally recommends it as an option in RP-ILD (Ed) [73], and it is established induction therapy in AAV. Disease-specific immunosuppression, particularly for AAV (Td/Ed) [73, 75] and selected inflammatory/RP-ILD, with only indirect evidence in established AE-SARD-ILD (Ei) [1].
<i>Mycophenolate mofetil</i>	Observational/low-certainty evidence supports use in SARD-ILD, and ACR/CHEST considers it a preferred first-line option and conditionally recommends it in RP-ILD (Ed) [1]. Primarily disease-modifying; may be considered in RP-ILD but not established as acute rescue therapy for AE-SARD-ILD (Ei) [1, 73].
<i>IVIg / calcineurin inhibitors / JAK inhibitors</i>	Evidence is largely disease-specific, particularly for inflammatory myopathy-associated and anti-MDA5/RP-ILD (Oi) [20], and ACR/CHEST conditionally recommends these as options for SARD-associated RP-ILD on very-low-certainty evidence (Ed) [73]. Consider in selected rapidly progressive myopathy-associated ILD (especially anti-MDA5), not as routine therapy for unselected AE-SARD-ILD (Oi/Ed) [20, 73].
<i>Plasma exchange</i>	PEXIVAS did not establish a clear mortality benefit in AAV-associated DAH (Td) [71, 76], whereas KDIGO suggests considering it in hypoxaemic DAH, particularly in severe AAV (Ed) [75]. Highly selected therapy for severe AAV-associated DAH, not routine treatment for AE-SARD-ILD (Ed) [75].
<i>Tocilizumab</i>	Slows lung-function decline in SSc-ILD (Ti) [77] and is conditionally recommended in selected SSc/MCTD-ILD (Ed) [73, 77], but has not been evaluated as rescue therapy during acute exacerbation (Ei) [1].

For each treatment, the available evidence, clinical context, and proposed role during acute exacerbation are summarized. Because no therapy has been validated in adequately powered prospective trials specifically in AE-SARD-ILD, most recommendations are extrapolated from chronic SARD-ILD, rapidly progressive ILD (RP-ILD), or ANCA-associated vasculitis (AAV) populations and should be applied according to the dominant mechanism of acute lung injury rather than the underlying rheumatic diagnosis alone

Abbreviations

AAV, ANCA-associated vasculitis; ACR, American College of Rheumatology; AE, acute exacerbation; AE-SARD-ILD, acute exacerbation of systemic autoimmune rheumatic disease-associated interstitial lung disease; CHEST, American College of Chest Physicians; DAH, diffuse alveolar haemorrhage; FVC, forced vital capacity; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; JAK, Janus kinase; KDIGO, Kidney Disease: Improving Global Outcomes; MCTD, mixed connective tissue disease; MDA5, melanoma differentiation-associated gene 5; RA, rheumatoid arthritis; RP-ILD, rapidly progressive interstitial lung disease; SARD, systemic autoimmune rheumatic disease; SSc, systemic sclerosis

Response to NIV varies according to the dominant phenotype. Infection-triggered deterioration is more likely to improve than acute fibrotic exacerbation, whereas radiological classification alone (UIP versus NSIP) does not predict response [89]. Reported NIV failure rates in IPF range from 44 to 56%, and elevated NT-proBNP may identify patients with concomitant right ventricular dysfunction and a particularly low likelihood of success [90]. Accordingly, ventilator settings should be individualised according to physiological response. In fibrotic/UIP-like disease, low pressure support and limited PEEP should minimise inspiratory effort while avoiding excessive VT (Oi) [60]. In inflammatory/ARDS-like disease, a recruitable component may permit more conventional titration, guided by oxygenation, mechanics, and haemodynamic tolerance (Ei) [91]. In PH-dominant disease, the lowest effective mean airway pressure should be used with close right ventricular monitoring (Ei) [37, 63]. In DAH, NIV may provide short-term stabilisation in selected patients but should not delay IMV when shunt, haemorrhage, or haemodynamic instability progresses (Ed/Od) [55, 67]. Interface selection should balance unloading with physiological monitoring. Helmet NIV may improve tolerance and reduce inspiratory effort but limits accurate VT measurement compared with face-mask NIV [92], an important consideration when P-SILI is a concern. Awake prone positioning has proven benefit mainly in COVID-19-related AHRF and may be considered preferentially in the inflammatory/ARDS-like phenotype, with early reassessment of oxygenation and inspiratory effort (Ti/Oi) [93, 94]. Physiological reassessment should occur within 1–2 h and include RR, VT, gas exchange,

haemodynamics, level of consciousness, and inspiratory effort (Ed/Oi) [83, 88]. The HACOR score may complement clinical assessment (Oi) [95], while P0.1, ΔP_{es} , or validated non-invasive surrogates may help determine whether NIV is providing effective unloading (Ed/Oi) [83, 96]. Persistent high respiratory drive or worsening physiology should prompt timely IMV [88] or reassessment of goals of care (Ei) [97].

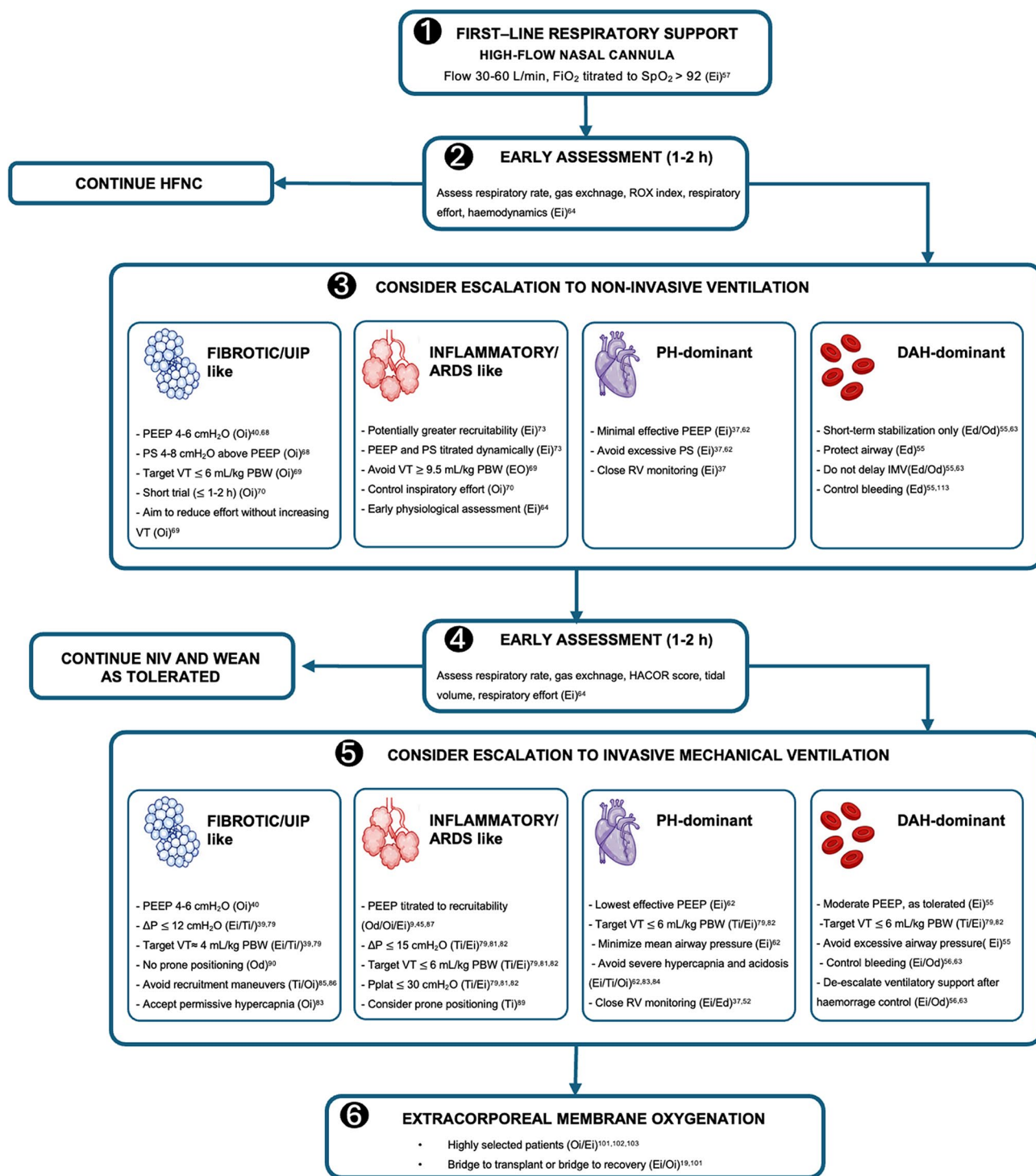
Invasive mechanical ventilation

When non-invasive strategies fail, IMV should follow lung-protective principles without assuming uniform ARDS physiology. In AE-SARD-ILD, the central challenge of IMV is that the amount of recruitable lung, the tolerance of airway pressure, and the risk of patient- and ventilator-generated injury vary markedly across physiological phenotypes. The numerical ventilatory targets proposed below should be regarded as physiology-informed suggestions rather than thresholds validated specifically in AE-SARD-ILD. Accordingly, VT may initially be set near 6 mL/kg PBW and reduced toward 4–6 mL/kg PBW when required to limit plateau pressure and ΔP ; plateau pressure should generally remain ≤ 30 cmH₂O, while ΔP should be kept as low as feasible (ideally ≤ 12 – 15 cmH₂O) recognizing that the functional “baby lung” may be substantially smaller than in classical ARDS (Ti/Ei) [61, 62, 66, 98]. Permissive hypercapnia is generally preferable to escalating transpulmonary stress, except when respiratory acidosis is likely to aggravate pulmonary vascular dysfunction (Ti/Oi) [99, 100].

PEEP remains particularly dependent on the dominant physiological phenotype, and its titration should therefore be individualized according to respiratory mechanics, gas exchange, and haemodynamic response [38] (Ei). In the fibrotic/UIP-like phenotype, available physiological and observational data support an ultra-protective “lung-resting” strategy with relatively low PEEP (e.g. 4–8 cmH₂O), VT 4–6 mL/kg PBW, avoidance of routine recruitment manoeuvres, and acceptance of moderate hypoxaemia (SpO₂ 88–92%) when necessary to limit VILI (Oi) [59]. Higher PEEP may preferentially distend residual aerated regions, worsen elastance and ΔP , and increase mortality-associated airway pressures rather than recruit collapsed lung [101, 102]. In the inflammatory/ARDS-like phenotype, the response to PEEP depends on the predominant acute process. When DAD predominates, alveolar oedema and collapse may be partially recruitable, and a more conventional ARDS approach may be justified, as supported by the better outcomes observed in CTD-ILD compared with IPF during mechanical ventilation (Od) [9]. When OP is the dominant process, intra-alveolar organization is not mechanically recruitable by PEEP; reversibility depends on the immunosuppressive response rather than on ventilatory strategy, and PEEP should be titrated conservatively (Oi/Ei) [45, 103, 104]. In both settings, oxygenation improvement should be confirmed together with stable or improved compliance, ΔP , and haemodynamics (Ti) [61]. In the PH-dominant phenotype, lower PEEP (e.g. <12 cmH₂O with preserved RV function and 3–5 cmH₂O with impaired RV function) and minimization of mean airway pressure are generally preferred to preserve RV function, while severe hypercapnia and acidosis should be avoided because they increase PVR (Ei) [63]. In DAH, moderate PEEP may facilitate recruitment of blood-filled alveoli and contribute to alveolar tamponade, while excessive airway pressure may compromise venous return and RV function (Ei) [55].

Prone positioning is physiologically most justified in the inflammatory/ARDS-like phenotype with severe hypoxaemia (PaO₂/FiO₂ ≤ 150 mmHg), where recruitable lung could be more likely (Ti/Od) [105, 106]. Its role is less predictable in fibrotic/UIP-like disease: in the only available physiological study with a very limited sample ($n=8$), no patient with pulmonary fibrosis responded to prone positioning [106]. In the PH-dominant phenotype, prone positioning should not be excluded a priori. In ARDS, prone positioning reduces RV afterload and improves RV–pulmonary artery coupling [100]; however, in fibrotic lungs with fixed vascular remodelling these benefits may be attenuated, and haemodynamic response should be carefully reassessed (Ei) [107].

Liberation from IMV in AE-SARD-ILD is constrained by the same physiological features that complicate ventilatory support. Reduced respiratory system compliance increases the work of breathing during spontaneous breathing trials and is an independent predictor of extubation failure [108]. Coexisting RV dysfunction may further compromise weaning by precipitating haemodynamic deterioration during the transition to spontaneous breathing [52, 109].



Sedation and respiratory drive control

In AE-SARD-ILD, sedation should be considered a physiological intervention to control excessive respiratory drive rather than solely to improve comfort (Ei/Ti) [110, 111]. The aim should be to reduce injurious inspiratory effort while preserving spontaneous breathing and diaphragm activity whenever compatible with lung protection (Ti/Ei) [112, 113]. This balance is most difficult in the fibrotic/UIP-like phenotype, where vigorous effort against a stiff, heterogeneous lung may generate large transpulmonary pressure swings and regional stress despite

Fig. 2 Physiological Phenotype-guided respiratory support in AE-SARD-ILD. Proposed physiological algorithm for respiratory support according to the dominant phenotype. HFNC is recommended as first-line therapy in most patients with mild-to-moderate hypoxemic respiratory failure, followed by structured early reassessment. Escalation to NIV, IMV, or extracorporeal support is guided by respiratory mechanics, gas exchange, inspiratory effort, haemodynamic status, and the dominant physiological phenotype rather than by oxygenation alone. Suggested ventilatory strategies and numerical targets represent physiology-informed guidance derived from the available direct or indirect evidence, as indicated by the corresponding evidence tags, and should not be interpreted as prospectively validated treatment thresholds for AE-SARD-ILD. Abbreviations DAH, diffuse alveolar haemorrhage; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate score; HFNC, high-flow nasal cannula; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; PH, pulmonary hypertension; Pplat, plateau pressure; PS, pressure support; ROX, ratio of oxygen saturation/FiO₂ to respiratory rate; RV, right ventricle; SpO₂, peripheral oxygen saturation; VT, tidal volume

acceptable ventilator pressures (Oi) [57]. Deeper sedation and, when necessary, neuromuscular blockade may be required when excessive VT, dyssynchrony, or effort cannot otherwise be controlled (Ei) [62]. Spontaneous breathing may be maintained in inflammatory/ARDS-like disease when protective (Ei) [113, 114], whereas sedative strategy in PH-dominant disease should account for RV function and haemodynamic tolerance (Ei) [37]; in severe DAH, excessive spontaneous effort may further amplify injury across a disrupted alveolar-capillary barrier, supporting deeper sedation during instability or uncontrolled effort (Ei) [115]. Persistent tachypnoea, dyssynchrony, excessive VT, elevated P0.1, and large ΔP_{es} suggest ongoing P-SILI risk. Deep sedation and neuromuscular blockade should be continued only while required to achieve protective ventilation and reassessed frequently (Ei) [62].

Extracorporeal membrane oxygenation

ECMO should be restricted to highly selected patients in expert centres and embedded within a predefined therapeutic trajectory (Oi/Ei) [116–118]. Selection depends primarily on reversibility and transplant candidacy. In a meta-analysis of 1,356 patients with ILD, in-hospital mortality was 45.8% and was substantially lower when ECMO was used as a bridge to transplant rather than recovery (37.8% vs. 71.3%) [116]. Similarly, 14 of 15 non-transplanted patients died in a single-centre series, whereas 5 of 6 transplanted patients survived [117]. Accordingly, in advanced fibrotic/UIP-like disease ECMO should generally be limited to bridge-to-transplant or short bridge-to-decision strategies; in inflammatory/ARDS-like disease, bridge to recovery may be justified when reversibility is plausible (Ei) [19]. In PH-dominant disease, VV-ECMO is appropriate for isolated respiratory failure and VA-ECMO when severe RV or circulatory failure coexists (Ei) [119]. In DAH, short-term ECMO may bridge to haemorrhage control and effective immunosuppression, with favourable short-term survival reported in autoimmune DAH (Oi) [120]. Across physiological phenotypes, ECMO should be viewed as a goal-directed bridge with a credible exit strategy, not as default rescue for irreversible disease (Ei) [118]. A proposed phenotype-guided pathway for respiratory support is summarized in Fig. 2.

Non-respiratory therapies

Pharmacological treatment of AE-SARD-ILD remains largely empirical, as no strategy has been validated in adequately powered prospective trials. Because no therapy has been tested specifically in AE-SARD-ILD, most recommendations are extrapolated from chronic SARD-ILD, rapidly progressive ILD (RP-ILD), or ANCA-associated vasculitis (AAV) populations. Management should therefore be guided by the dominant mechanism of acute lung injury rather than by the underlying rheumatic disease alone. Infection, inflammatory alveolar injury, RP-ILD, DAH, pulmonary vascular decompensation, drug toxicity, and acute injury superimposed on advanced fibrosis may coexist but should not be treated as interchangeable entities.

Empirical broad-spectrum antimicrobial therapy is appropriate in severe ARF after microbiological sampling, with subsequent de-escalation according to microbiological results and clinical evolution [66]. Opportunistic

pathogens, particularly *Pneumocystis jirovecii* and *Aspergillus* spp., should be considered according to the patient's immunosuppressive exposure and epidemiological context, and appropriate prophylaxis ensured in high-risk patients (Ei/Od) [121, 122].

Glucocorticoids remain the cornerstone of treatment when immune-mediated injury is plausible, despite the absence of proven survival benefit in unselected AE-SARD-ILD. High-dose regimens are supported mainly by retrospective evidence and expert opinion (Ed/Od/Oi) [1, 70, 72], and reported doses range from methylprednisolone 500 to 1000 mg/day for 3 days followed by prednisone-equivalent 0.5–1 mg/kg/day (Ed/Oi) [74, 123]; optimal dose and duration remain undefined [74, 123]. In SSc-ILD, high-dose glucocorticoids carry a recognized risk of scleroderma renal crisis and should be used at the lowest effective dose (Ed) [73]. Additional immunosuppressive therapy should be reserved for selected disease-specific indications, including ANCA-associated vasculitis (Ed/Td) [71, 75], rapidly progressive inflammatory myopathy-associated ILD (particularly anti-MDA5 disease) (Ed) [20, 73], and severe DAH, following current rheumatological recommendations (Ed) [75]. Tocilizumab, approved for slowing pulmonary function decline in SSc-ILD, represents a disease-modifying option but has not been evaluated during acute exacerbation (Ed) [77].

Antifibrotic agents target chronic fibrotic progression and should not be considered rescue therapy for established AE (Ei) [68]. During critical illness, continuation or interruption should be individualized, while initiation generally belongs after stabilization (Ei) [51]. In patients with predominant pulmonary vascular involvement, management should prioritize optimization of oxygenation, right ventricular loading conditions, and pulmonary haemodynamics. Although inhaled treprostinil improves outcomes in chronic PH-ILD, evidence supporting pulmonary vasodilator therapy during AE-SARD-ILD is limited, and these agents should be considered only in carefully selected patients with severe right ventricular dysfunction (Ti/Ei) [37, 124, 125]. In severe DAH associated with ANCA vasculitis, the role of plasma exchange remains uncertain [71, 76].

Outcome and palliation

Prognosis in AE-SARD-ILD is driven more by the dominant physiological phenotype than by the rheumatic diagnosis alone. Fibrotic/UIP-like disease generally carries the poorest prognosis, whereas inflammatory phenotypes retain greater potential for reversibility; coexisting PH and RV dysfunction identify a particularly high-risk subgroup [65, 126, 127]. Among patients requiring IMV, in-hospital mortality approaches two-thirds and one-year mortality 80%, although CTD-ILD fares better than IPF or unclassifiable ILD [9]. Prognosis should remain dynamic. The first 48–72 h may be more informative than baseline severity: improvement in oxygenation, ventilatory efficiency, haemodynamics, and response to disease-directed therapy supports reversibility, whereas persistent deterioration suggests poor outcome [128]. Lower PaO₂/FiO₂, greater fibrosis, IMV, shock, and rising KL-6 or LDH are associated with mortality or non-response [64, 129]. This supports a time-limited ICU trial: an explicitly agreed period of life-sustaining treatment with predefined objectives and scheduled reassessment (Ei) [97]. A 48–72-hour trial may align treatment intensity with physiological trajectory (Ei) [97], using oxygenation, ventilatory efficiency, response to immunomodulation, haemodynamic stability, and extrapulmonary organ function as reassessment criteria. Continuation, escalation, or transition to comfort-focused care should be discussed prospectively with the patient or surrogate (Ei) [97]. Absence of meaningful improvement, particularly with advanced fibrosis, progressive RV failure, multiorgan dysfunction, or no transplant pathway, should trigger multidisciplinary goals-of-care review (Ed) [97]. Palliative care should be integrated early to support symptom control, communication, and decision-making (Ei) [69].

Knowledge gaps and future directions

The recent International Working Group Report has provided a standardized diagnostic framework for ARW and AE in f-ILD [10]. However, its application to SARD-ILD requires prospective validation, and whether integrating physiological variables—including respiratory mechanics, inspiratory effort, gas exchange, right ventricular

function, and imaging—improves bedside decision-making beyond diagnosis alone remains unknown. Likewise, none of the biomarkers currently associated with AE predict disease onset, reversibility, or therapeutic response [19] while multi-omic endotyping remains exploratory [130]. AI-based CT analysis may further improve phenotyping and prognostication but remains unexplored in AE-SARD-ILD [131]. Evidence supporting respiratory support derives mainly from physiological studies, retrospective cohorts, and small observational series. No randomized trial has directly compared HFNC, NIV, and IMV in AE-SARD-ILD, optimal physiological targets across different physiological phenotypes remain undefined, and predictors of non-invasive respiratory support failure require disease-specific validation [51]. Similarly, pharmacological management remains largely empirical. No randomized trial has evaluated pharmacological therapy specifically in AE-SARD-ILD [1] nor have emerging antifibrotic and disease-modifying agents (i.e. nerandomilast, admilparant, bexotegrast) been prospectively evaluated across different physiological or fibrotic phenotypes [132].

Future progress will require prospective international registries integrating standardized clinical, radiological, physiological, and biomarker characterization together with adaptive platform trials capable of evaluating both pharmacological and respiratory support strategies across distinct physiological phenotypes. Such an approach may allow physiology-informed phenotyping to evolve from a conceptual framework into a validated strategy for precision critical care in AE-SARD-ILD.

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Declarations

Ethics approval and consent to participate Not applicable.

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