Acute exacerbations of ILD (AE-ILD)

Acute exacerbations of ILD (AE-ILD) represent an acute deterioration of the patients' respiratory function, often leading to hospital admission.

- While originally and most thoroughly described in IPF (AE-IPF), acute exacerbations are increasingly recognized in other types of fibrotic ILD (AE non-IPF)

DEFINITION of AE-ILD

- Known diagnosis of ILD
- Worsening dyspnea within the last 30 days
- New bilateral ground glass opacities and/or consolidation upon a background of ILD
- Heart failure or fluid overload does not fully explain the worsening

The previous requirement for exclusion of concurrent PE and identifiable infection has been eliminated

When a patient with ILD is admitted for acute respiratory worsening is important to distinguish between idiopathic acute exacerbation *vs* acute exacerbation secondary to a specific "treatable" trigger.

ETIOLOGY of AE-ILD

- Infection
- Heart failure
- PE
- Aspiration
- Drug toxicity
- Peri-procedural exacerbation such as video-assisted thoracoscopy and bronchoscopy with BAL
- Less frequent
    - Severe pulmonary hypertension - usually subacute exacerbation
    - Diffuse alveolar hemorrhage (DAH)
        - In the setting of identified triggering condition, there is an overlap between being a triggering factor for AE-ILD *vs* worsening clinical status only attributed to the new event with stable ILD
- Idiopathic
    - When an identifiable extrinsic trigger for AE-ILD is lacking, then the AE-ILD is considered idiopathic and represents 50% of the cases
        - Lack of rapid clinical response to the treatable condition supports the diagnosis of idiopathic exacerbation
        - Air pollution and micro-aspiration have been identified as probable triggering *extrinsic* factors
        - Specific *intrinsic* factors have not been conclusively identified
            - Mechanisms such as epithelial homeostatic imbalance affecting fibrocyte differentiation, macrophage immune polarization, and possibly autoimmunity emergence against heat-shock proteins and phospholipid-binding proteins have been implicated.

EVALUATION of AE-ILD

- HRCT
- CTA-PE
- BNP and echocardiogram
- PCT and cultures
- MBS for patients with risk factors for aspiration
- CBC and CMP

- If the patient has previously undiagnosed ILD: autoimmune serologies (cytoplasmic ANCA, PR3 and MPO), RF, cyclic citrullinated peptide antibodies (anti-CCP), and ANA for evaluation of pulmonary vasculitis, rheumatoid arthritis, and basic screening for other connective-tissue disease and interstitial pneumonia with autoimmune features (IPAF).
    - If ANA is positive, further autoimmune serologies would be indicated to clarify any potential autoimmunity condition.
        - Sjogren's syndrome – anti-Ro (SS-A) and anti-La (SS-B) antibodies
        - Lupus – anti-double stranded (ds) DNA antibodies
        - Dermatomyositis/Polymyiositis – Creatine kinase, aldolase, anti-tRNA synthetases
            - Dermatomyositis – anti-MDA antibody (MDA5)
            - Myositis/Antisynthetase syndrome – anti Jo-1, EJ, PL-7, PL-12
        - Anti-U1RNP - Mixed connective tissue disease
        - Anti-topoisomerase (Scl-70) antibody, anti-PM-1 (PM-Scl) antibody - Systemic sclerosis
- For patients presenting with diffuse alveolar hemorrhage add:
    - Anti glomerular basement membrane antibodies, antiphospholipid antibodies, and antistreptococcal antibodies.
- Lung biopsy
    - Similar to ARDS, the most frequent histopathologic finding on lung biopsy seen in AE-ILD is diffuse alveolar damage.
    - Surgical lung biopsy is often avoided during AE-ILD as its results often do not alter the course of acute exacerbation and have increased peri/post-operative morbidity. Furthermore, the ongoing acute inflammation mask the underlying chronic pathology.
- Bronchoscopy
    - Usually indicated with BAL and cell count for evaluation of triggering conditions.

TREATMENT (see figure 1 taken from *World J Crit Care Med* 2022; 11: 22-32)

Steroids

Are recommended in the range of prednisone 1 mg/kg/d to methylprednisolone 1 gr/d IV for three days followed by a taper, based on severity of disease and response to therapy.

- For those who are idiopathic and appear to a have a clinical response, steroids are typically tapered slowly over the course of weeks to months ensuring there is no recurrence with close follow up.
- For those with a known trigger steroids are added to the treatment regimen usually for one or two weeks.

Immunomodulators

- Corticosteroids plus other agents (e.g., IV cyclophosphamide, tacrolimus, rituximab) and immunoglobulins have shown better 6-month survival when started early.
- Plasma exchange has also been used with some success in patients with anti-MDA-5 antibody.

Antibiotics

Broad spectrum antibiotics and coverage for atypical pathogens should be considered in AE-ILD accompanied by appropriate work up to evaluate underlying infection.

- A few small studies with Azithromycin (anti-inflammatory and immune modulating effects) have shown outcome improvement in ALI and AE-ILD. A 7-day course of Azithromycin is reasonable to use.
- In a randomized trial, use of procalcitonin to guide antibiotic therapy in patients with AE-IPF resulted in reduced exposure to antibiotics without adversely affecting patient outcomes.

- Since AE non-IPF patients are often immunocompromised prior to admission, search for opportunistic pathogens and targeted treatment is prudent.

Antifibrotics (Nintedanib or Pirfenidone)
If patients have taken Nintedanib or Pirfenidone they should be continued.

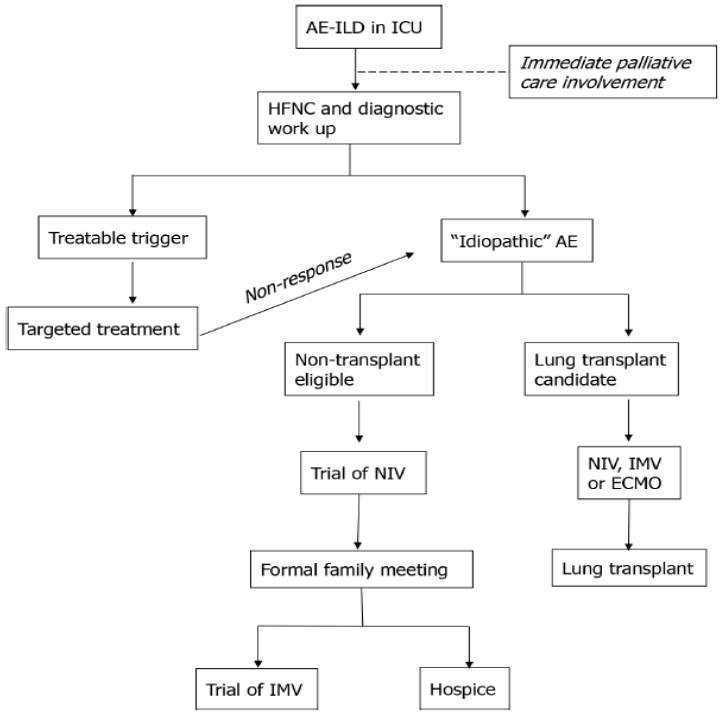
INVASIVE MECHANICAL VENTILATION (IMV)

- In-hospital mortality of AE-ILD patients who receive IMV is >50% with studies showing up to 85% mortality particularly in patients with AE-IPF suggesting that IMV may be futile.
- However, other studies have shown that a subset of patients can be weaned from MVS and discharged suggesting that IMV should not be systematically denied to these patients but considered individually.

Therefore, risk stratification and palliative care service to establish goals of care need to take place early when patients with AE-ILD are admitted. Eligibility (or pre-existing enrollment with previous work-up completion) of patients for lung transplant should play important roles in the management decision tree.

In non-transplant candidates who are deemed high risk for poor outcome, hospice should be brought up early in family discussions and goals of patient comfort and wishes for end-of-life strongly taken into consideration.

Figure 1
Decision-making tree and management approach of patients admitted to the ICU with AE-ILD*



* Taken from: Charokopos A, Moua T, Ryu J, Smischney NG. Acute exacerbation of interstitial lung disease in the intensive care unit. *World J Crit Care Med* 2022; 11: 22-32

Figure 2
ILD classification taken from X is a great summary, will add post infection as one of the main causes and antisynthetase syndrome to the DM and PM box.