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INTERSTITIAL LUNG DISEASE (A HAJARI CASE, SECTION EDITOR)

Acute Exacerbation of Idiopathic Pulmonary Fibrosis: Who to Treat, How to Treat

Tejaswini Kulkarni[1] · Steven R. Duncan[1]

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Abstract

Purpose of Review Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) are the most frequent cause of death among patients with IPF. Here, we review the revised definition and diagnostic criteria for AE-IPF and discuss management strategies including mechanistically targeted investigational therapies for this complex syndrome.

Recent Findings Novel therapies targeting various pathways including inflammation, autoimmunity, and coagulation cascade involved in AE-IPF have recently been reported. Although most of these reports are small and uncontrolled, they have provided evidence to design larger randomized, controlled, multicenter studies to improve outcomes among patients with AE-IPF.

Summary AE-IPF has a dismal prognosis and current treatment consists mainly of supportive care and symptom palliation. There is a lack of consensus on current therapies for AE-IPF, including corticosteroids, but current randomized control studies for newer therapeutic strategies may hold promise.

Keywords Acute exacerbation · Idiopathic pulmonary fibrosis · Management

Introduction

Idiopathic pulmonary fibrosis (IPF) is a lethal disease of the lung characterized by progressive fibrosis, loss of lung function and early mortality [1••]. The natural history of IPF is highly variable with a median survival of 3–5 years [2] but an estimated 10% of these patients develop acute declines in lung function and respiratory failure each year [3]. The pathogenesis of these acute exacerbations of IPF (AE-IPF) is perplexing and the current state of management of these patients is not efficacious. In this review, we discuss the presentation of AE-IPF and summarize the current and investigational medical therapies for management of these patients.

This article is part of the Topical Collection on *Interstitial Lung Disease*

✉ Tejaswini Kulkarni
tkulkarni@uabmc.edu

[1] Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Alabama at Birmingham, THT 541 D, 1900 University Blvd, Birmingham, AL 35294, USA

Definition of Acute Exacerbations of IPF

AE-IPF is defined as an acute, clinically significant respiratory deterioration typically < 1 month in duration, characterized by evidence of new widespread alveolar abnormality [4••]. In 2016, Collard and colleagues proposed revised diagnostic criteria for AE-IPF (Table 1). Criteria include a previous or concurrent diagnosis of IPF with acute worsening or development of dyspnea typically < 1 month in duration and presence of new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with the usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) scans (Fig. 1) not fully explained by cardiac failure or fluid overload.

Within the previous definition, exclusion of pulmonary infections, left heart failure, pulmonary embolism and other identifiable causes of acute lung injury were necessary to diagnose an "AE-IPF" [5]. While exclusion of respiratory deterioration due to cardiac failure or fluid overload remains important, removal of the term "idiopathic" within this broader definition is more practical in the clinical scenario. The current definition does not require the exclusion of all alternative causes of respiratory deterioration, including infections, reducing the need for invasive diagnostic testing, particularly

Table 1 Acute exacerbation of idiopathic pulmonary fibrosis: definition and criteria [3]

Definition of acute exacerbation of idiopathic pulmonary fibrosis	Acute, clinically significant respiratory deterioration typically < 1 month in duration, characterized by evidence of new widespread alveolar abnormality
Diagnostic criteria	• Previous or concurrent diagnosis of IPF • Acute worsening or development of dyspnea typically < 1 month in duration • Presence of new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern on high-resolution computed tomography scans • Clinical deterioration not fully explained by cardiac failure or fluid overload

bronchoscopy. The clinical course and management of AE-IPF remains the same irrespective of the event being "idiopathic" or related to a cause like pulmonary infection, exposures, or reflux [6]. Further, as described by Ryerson and colleagues [3], the physiological and radiological features characteristic of AE-IPF correlate with the presence of diffuse alveolar damage and should be considered in the development of potential treatments for this challenging entity.

Incidence and Prognosis

AE-IPF has been recognized as the single most common cause of death in patients with IPF [7]. Variable annual incidence rates have been reported over years based on the 2007 guidelines for AE-IPF [5]

, but the majority of data has been extrapolated from clinical trials. While the incidence reported in cohort studies has been historically higher, there is significant variation in the investigator reported versus centrally adjudicated incidence of AE-IPF [8•, 9].

The prognosis of patients experiencing an AE-IPF is dismal. Despite reports of biomarkers that predict probability of AE-IPF and survival [10–14], the onset is rather unpredictable and it can progress rapidly. Several studies have reported the in-hospital mortality rate of these patients with AE-IPF to be nearly 50% [2, 3, 6, 7, 15, 16]. Recovery of lung function and exercise capacity among the survivors is poor and the median survival among these patients is barely 3–4 months [6, 15–17].

Risk Factors and Risk Reduction

Severely impaired physiological parameters including low forced vital capacity (FVC), low diffusion capacity for carbon monoxide (D_LCO), high supplemental oxygen requirement, and previous acute exacerbation [18•] are the most validated risk factors for development of AE-IPF [4••, 6, 15, 16, 19]. Given limited treatment approaches for AE-IPF, reducing the risk of an acute exacerbation is vital. Antifibrotic agents, nintedanib and pirfenidone, were approved by the U.S. Food and Drug Administration for treatment of IPF based on their ability to slow down disease progression [20••, 21••]. While neither agent has been consistently proven to reduce the risk of an acute exacerbation, some data favor their role in reducing the time to AE-IPF and warrants further investigation. Nintedanib reduced the incidence of an AE-IPF in one phase

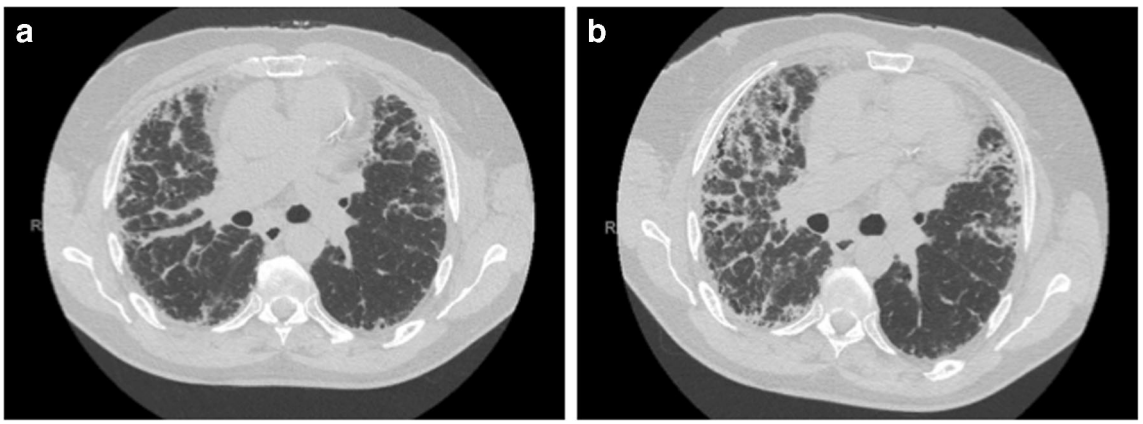

Fig. 1 High-resolution computed tomography scans of a patient with stable idiopathic pulmonary fibrosis (IPF) (**a**) and during acute exacerbation of IPF (**b**). Increased areas of ground glass opacities and consolidation are noted within a background of fibrosis during an acute exacerbation

II placebo-controlled trial [22] but this was confirmed in only one of the phase III studies [20••]. Similarly, the role of pirfenidone in reducing the rate of AE-IPF was shown in a phase II study [23] but subsequent studies did not confirm similar benefit.

An exacerbation presents acutely, over a few days in majority of the patients but some patients may present more insidiously. Most do not have any obvious triggering events.

Occult gastric acid reflux has been investigated as a potential trigger for AE-IPF [5, 24]. In a pooled post hoc analysis of the placebo arm of IPFnet randomized clinical trials, antiacid therapy including both, proton-pump inhibitors and/or histamine-2 blockers, reduced the time to AE-IPF [25]. Implementation of both pharmacological and non-pharmacological measures to reduce acid reflux may be beneficial. Infections are known risk factors of AE-IPF [26] and measures such as vaccination against influenza and pneumococcus as well as hand washing may be recommended.

Surgical lung biopsies [27, 28] and cryobiopsies [29] performed for diagnoses of IPF are a risk factor for acute exacerbation and their value should be evaluated in multidisciplinary discussion. Additionally, general anesthesia performed for any surgery could result in an acute exacerbation, likely secondary to barotrauma during mechanical ventilation [30•, 31, 32]. When possible, minimally invasive procedures with regional anesthesia should be considered [30•].

Management of AE-IPF

Therapeutic options to treat AE-IPF remain unproven. Several of the current practices do not have evidence-based guidelines supporting these approaches and are based on anecdotal experiences [5, 8•]. Additionally, the severities of these acute exacerbations may be variable and impact treatment decisions [33]. Overall, management for AE-IPF remains focused on supportive care and symptom palliation.

Who to Treat?

Patients with AE-IPF may have higher mortality and morbidity and early identification of such an episode is prudent [34]. Patients with AE-IPF often have prolonged hospital stays requiring high-intensity supportive care and the costs associated with these hospitalizations are considerable [34–36]. Mechanical ventilation is further associated with significant increased length of hospital stay and healthcare costs [36] with survival benefits from MV being very poor. Hence, it is essential to identify the risk factors for poor prognosis in IPF, including low FVC and DLCO and high supplemental oxygen requirement [2, 37], previous acute exacerbation [18•], and poor quality of life prior to hospitalization to enable decision-making regarding early initiation of palliative care discussions and decrease patient suffering. Overall, therapies such as antimicrobials and corticosteroids, as well as supportive care including supplemental oxygen to correct hypoxemia and symptom palliation should be offered to all patients with AE-IPF. Aggressive measures such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation should be carefully considered for patients who have a higher preintervention probability of clinical success.

How to Treat

Pharmacological Therapy

Corticosteroids in varying doses are widely utilized for the management of AE-IPF. This practice is primarily based on extrapolation of effect of corticosteroids on pulmonary inflammation in acute lung injury models; unfortunately, similar benefits are not well established for AE-IPF. Corticosteroids are recommended by the international guidelines for IPF management based on anecdotal reports of benefit during such episodes but no recommendations regarding dose or length of therapy was made [1••]. Given the high mortality associated with AE-IPF, conducting a randomized, placebo-controlled trial for monotherapy with corticosteroids is not practical. While some groups treat with pulse dose of corticosteroids (methylprednisolone 0.5–1 g intravenously for 3–5 days) followed by lower doses, lower doses (example 1 mg per kg body weight three times per day) are more routinely prescribed at initial presentation. Varying doses of corticosteroids have been employed in smaller studies evaluating other potential immunosuppressive agents and need further evaluation. Consideration must be given to side effects associated with high doses of corticosteroids, particularly, poor glycemic control [38] and increased risk for infections [39].

Infections are generally the first consideration in any presentation with acute respiratory failure and in fact, several patients are initially diagnosed with pneumonia. Given limited data in AE-IPF, these patients are universally treated with antimicrobial agents. A single-center randomized study reported reduced antibiotic use with procalcitonin-guided antibiotic therapy without detrimental effects on the overall clinical outcomes in patients with AE-IPF [40], but these data are yet to be confirmed with larger studies. There is insufficient evidence supporting the routine use of bronchoalveolar lavage in these patients; sensitivity to most microbiological tests is poor, does not alter management in the majority of patients, and can be associated with increased post-procedural clinical deterioration [41].

There are a few case series describing the potential benefit of antifibrotic therapy during AE-IPF [42, 43]. Although

results favored the role of nintedanib in reducing time to acute exacerbation, there was no effect of nintedanib treatment on the risk of mortality post-acute exacerbation [8•]. Based on limited data, there are no recommendations on continuation versus discontinuation of antifibrotic therapy during an acute exacerbation.

Non-pharmacological Therapy

Supplemental oxygenation is a key to the management of patients with AE-IPF. However, careful consideration to several clinical parameters, futility of care, and patient's goals should be undertaken while determining the mode and length of support. There is increasing evidence supporting the role of non-invasive techniques including high-flow oxygen [44, 45] and positive pressure ventilation [46] to improve gas exchange abnormalities in patients who fail conventional oxygen therapy. These modalities may allow clinicians to avoid or reduce the need for intubation and mechanical ventilation in select patients.

Evidence-based guidelines make a weak recommendation against the utilization of mechanical ventilation in majority of the patients with AE-IPF [1••]. There are no randomized control trials to assess the impact of various ventilator strategies for this patient population. Given the similarity of pathological features and lung mechanics of ARDS and AE-IPF [47], ventilatory strategy with low tidal volume should be considered among the select patients with AE-IPF on mechanical ventilation, to reduce the risk of barotrauma. However, application of a similar high positive end expiratory pressure strategy may be detrimental due to overexpansion of seemingly normal alveoli and should be carefully titrated [48].

The indications and utilization of ECMO for management of acute respiratory failure has evolved over time [49]. While its use as a bridge to recovery may be overzealous, there might be some promise for early use of ECMO among patients who are currently listed or may be considered for lung transplantation. Lung transplantation may be a viable option for a few patients with AE-IPF in select institutions [1••]. Limited data, however, suggests that patients receiving emergent lung transplantations during an AE-IPF have worse complications and poorer survival compared with their counterparts receiving lung transplantation during a stable state [50].

Investigational Therapeutic Strategies

One of the major hurdles to investigating effective therapeutic agents for AE-IPF is the concurrent presence of several interactive pathogenetic pathways involved in this syndrome (Fig. 2). Notwithstanding the challenges presented by AE-IPF, randomized control trials evaluating new therapeutic agents is imperative.

Several studies have evaluated the role of autoimmunity in progression of IPF and as a potential trigger for AE-IPF. Although combination therapy of azathioprine and prednisone was detrimental to patients with stable IPF [51], it is possible that targeting other areas of the immune system may be the key to treatment of AE-IPF. Based on this hypothesis, a novel mechanistically focused therapeutic strategy similar to treatment of other autoimmune conditions was reported for management of AE-IPF [52]. This protocol includes treatment with therapeutic plasma exchange to rapidly reduce circulating autoantibodies, rituximab, a chimeric monoclonal antibody to CD20 to deplete reactive B-cells and intravenous immunoglobulin to mitigate autoantibody rebound for a sustained clinical response. A majority of AE-IPF patients treated with this strategy showed substantial improvements in supplemental oxygen requirement and a sustained benefit reflected by higher one-year survival compared with historical controls treated conservatively [52]. Based on this and other

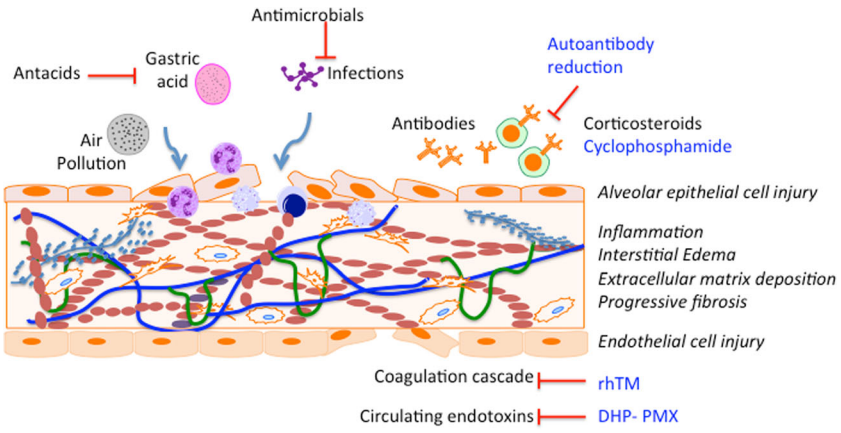

Fig. 2 Pathogenesis of acute exacerbation of idiopathic pulmonary fibrosis and therapeutic targets. Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) can be triggered by infection, microaspiration, or autoantibody-mediated injury with resultant acute lung injury. There is increased inflammation, interstitial edema, extracellular matrix deposition, and progressive fibrosis. Imbalances in the coagulation system and/or circulating endotoxins may precipitate this cascade further

unpublished data, this novel therapeutic strategy is currently under investigation as a randomized, controlled unblinded multicenter trial (NCT03286556, clinicaltrials.gov).

Treatment with another immunomodulatory alkylating agent, cyclophosphamide, in conjunction with corticosteroids, has shown some efficacy with improvement of survival rates following AE-IPF [53–55] but a more recent study did not show any survival benefit with this strategy [56]. Nevertheless, a randomized double-blind, placebo-controlled trial may provide more insight into the utilization of this agent for treatment of AE-IPF [57] (NCT02460588, clinicaltrials.gov). Survival benefits of other immunosuppressive therapies, including cyclosporine A [58, 59] and tacrolimus [60], have been reported but these agents require further investigation.

Endothelial damage and abnormalities of the coagulation system can play an important role in progression of AE-IPF [61, 62]. Human recombinant thrombomodulin (rhTM) inhibits the coagulation cascade through the activation of protein C by thrombin and its potential efficacy in improving outcomes among patients with AE-IPF has been reported [63–66]. A recent historically controlled study reported significantly higher 3-month survival rate among patients with AE-IPF treated with rhTM compared with those in the control group; both groups were treated with background pulse corticosteroid therapy for 3 days followed by tapering doses [63]. Based on these data, a phase III double-blind, randomized, placebo-controlled study is completing recruitment (NCT02739165, clinicaltrials.gov) and will provide more definitive data on the effect of rhTM on outcomes among these patients with AE-IPF.

Hemoperfusion with polymyxin B-immobilized fiber column (PMX-B HP) has been approved for septic shock and associated acute respiratory distress syndrome in Japan and Western Europe. Mechanistically, this technique decreases circulating endotoxin levels and may improve pulmonary oxygenation. Several uncontrolled studies have reported improvement in pulmonary gas exchange and survival among patients with AE-IPF treated with PMX-B HP [67–69], with higher efficacy among those patients with more severe underlying disease [70]. Unfortunately, these small studies do not confer sufficient evidence for utilization of this technique for treatment of AE-IPF until further larger, randomized control studies establish the clinical benefit.

Conclusions

Acute exacerbations of IPF are life-threatening events during the clinical course of patients with IPF. Beyond supportive care, therapeutic options that improve outcomes among patients with AE-IPF are limited. Current treatments with corticosteroids and broad-spectrum antimicrobials are based on anecdotal data; there is no consensus regarding the dosage, route of administration, or duration of such therapy. The pathobiology of AE-IPF is complex and incompletely understood. However, current randomized control studies targeting inflammation, autoimmunity, and coagulation cascade are promising and might improve survival among patients with AE-IPF.

Compliance with Ethical Standards

Conflict of Interest Tejaswini Kulkarni is a non-branded speaker for Boehringer Ingelheim Inc.

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Human and Animal Rights and Informed Consent All reported studies/experiments with human and animal subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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- •• Of major importance

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