

# Chapter 17

## Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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**Abstract** Acute exacerbation of idiopathic pulmonary fibrosis (IPF) is a clinically important complication of IPF that carries a high morbidity and mortality. In the last decade, we have learned much about this event, but there are many remaining questions: What is it? Why does it happen? How can we prevent it? How can we treat it? This chapter attempts to summarize our current understanding of the epidemiology, etiology, and management of acute exacerbation of IPF and point out areas where additional data are sorely needed.

**Keywords** Acute exacerbation • Risk factors • Pathobiology • Diagnosis • Prognosis • Management

### A Case

A 78-year-old man was referred for surgical lung biopsy in the evaluation of his interstitial lung disease (ILD). At baseline, he reported mild dyspnea on exertion and a chronic, dry cough. His past medical history was significant for hypertension and gastroesophageal reflux (GER) disease. His medications included an antihypertensive medication and a proton pump inhibitor. He was a lifelong nonsmoker and worked as a dentist. He had no family history of ILD. His physical exam was significant for dry inspiratory crackles at both bases and normal resting oxygen saturation. His pulmonary function was abnormal with a forced vital capacity of 57 %

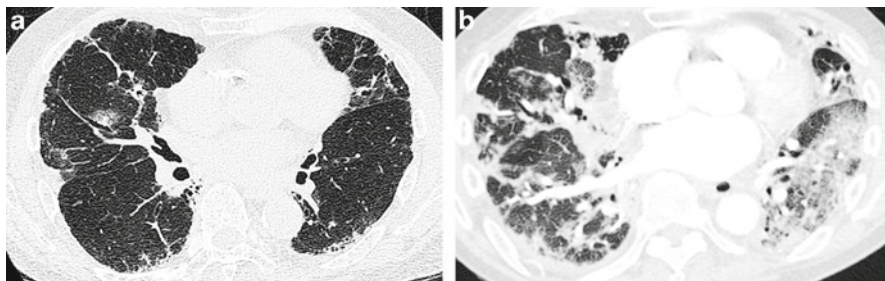
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**Fig. 17.1** *Bottom left image is presurgery demonstrating peripheral reticulation and traction bronchiectasis without honeycombing. Upper right image is 5 days postoperatively, demonstrating diffuse ground-glass opacities, most prominent in the left lung*

predicted and a diffusing capacity for carbon monoxide of 67 % predicted. His high-resolution computed tomography (HRCT) scan demonstrated peripheral, subpleural predominant reticulation and traction bronchiectasis without honeycombing.

He was referred for surgical lung biopsy and had a video-assisted thoracic surgery procedure with biopsies obtained from the right lung. His perioperative course was uncomplicated. His pathology was reviewed and was consistent with a usual interstitial pneumonia (UIP) pattern, confirming the diagnosis of IPF. His initial postoperative course was uncomplicated, but approximately 5 days postoperatively, he developed increased dyspnea and cough with occasional production of clear sputum. He had new-onset hypoxemia (88 % on room air) with diffuse crackles to auscultation that were more prominent in the left chest. A repeat HRCT demonstrated new ground-glass opacities in the left lung (Fig. 17.1). All microbiologic data were negative, and there was no evidence of cardiac dysfunction or ischemia.

This case was thought to be due to an acute exacerbation (AEx) of IPF triggered by surgical lung biopsy possibly due to single lung ventilation of the left lung. Unfortunately, the patient progressively worsened despite supportive care and subsequently died from his AEx of IPF.

## **Epidemiology, Clinical Features, and Risk Factors**

Our view of the natural history of IPF has changed over the last decade with the recognition that there are several distinct clinical courses that patients may follow [1]. Although most patients with IPF experience a steady decline in lung function over time, some will decline quickly, while others seem stable for many years. Increasingly, we recognize that some patients may also have a more unpredictable course [2]. These patients experience periods of relative stability followed by acute episodes of worsening in their respiratory status [3]. Episodes of acute respiratory decline in IPF can be secondary to complications such as infection, pulmonary

embolism, pneumothorax, or heart failure [3, 4]. Such episodes of acute respiratory deterioration have been termed AEx of IPF when the cause for the acute worsening cannot be identified. Acute exacerbations likely comprise almost 50 % of these acute respiratory events, and the clinical characteristics and prognosis are indistinguishable from acute exacerbations of known cause. This chapter will discuss only AEx of IPF.

The phenomenon of AEx has been recognized since the late 1980s, when it was initially reported in the Japanese literature [5–8]. A survey of providers in the USA suggests that most clinicians believe AEx to be somewhat or very common [9]. The true incidence of AEx remains unknown, and the incidence may vary by country due to different genetic and environmental factors. Largely due to differences in case definition, patient population, sample size, and duration of follow-up, the range of AEx incidence in clinical studies ranges anywhere from 1 % to 24 % [3, 4]. The largest and probably most robust study of 461 patients with IPF that were followed longitudinally over 3 years found a 1- and 3-year incidence of 14.2 % and 20.7 %, respectively [4].

The clinical presentation of AEx is generally quite dramatic and characterized by acute to subacute worsening of dyspnea over days to weeks [3]. Some patients experience symptoms of worsening cough, sputum production, and fever mimicking a respiratory tract infection [10, 11]. Most reported cases of AEx have required unscheduled medical attention (emergency room or hospital care), but there may well be less severe cases that do not get noted by patients and providers and, therefore, are not documented.

The occurrence of AEx is unpredictable and can sometimes be the presenting manifestation of IPF [11–13]. A few risk factors have been identified, including lower baseline forced vital capacity (FVC) % predicted and having been a non-smoker [4]. It seems likely that patients with more severe IPF are more likely to develop clinically significant AEx of disease, and this perception is supported by the increased incidence of AEx that was observed in the only study of advanced disease reported in the literature to date, namely, STEP-IPF [14]. Precipitating factors such as surgical lung biopsy and bronchoalveolar lavage (BAL) have also been reported [11, 15–20]. The occurrence of AEx after videoscopic-assisted surgical lung biopsy is particularly intriguing, as the exacerbation appears to be more pronounced in the lung that was ventilated (i.e., the nonsurgical side receiving single lung ventilation) [19]. However, the precise relationship between these precipitating factors and AEx remains unclear.

Acute exacerbations have also been described in non-IPF ILD, including nonspecific interstitial pneumonia (NSIP) [21], connective tissue disease-associated ILD [21–23], and hypersensitivity pneumonitis [24, 25]. Compared to IPF AEx, patients with an underlying NSIP pattern appeared to have a better prognosis following their AEx [21]. A UIP pattern may be a risk factor for AEx in the context of connective tissue disease-associated ILD and hypersensitivity pneumonitis, as the presence of a UIP pattern appeared to be a risk factor in some case series [21, 25]. Whether AEx of non-IPF forms of ILD shares a similar pathobiology as AEx of IPF is unknown.

## **Etiology and Pathobiology**

The etiology of AEx of IPF remains unknown. Several hypotheses have been proposed, including the following: (1) AEx of IPF represents an abrupt acceleration of the patients underlying disease; (2) AEx is a collection of occult, pathobiologically distinct conditions (e.g., infection, heart failure); or (3) AEx is a combination of both processes that can serve as an occult trigger that leads to acceleration of the underlying fibroproliferative process.

Occult aspiration of gastric contents has been suggested as a possible trigger or cause of AEx of IPF. GER is nearly universal in patients with IPF [26, 27] and is thought to be a risk factor for aspiration [28, 29]. BAL pepsin levels, a biomarker for aspiration of gastric secretions, were shown to be elevated in a subset of patients with AEx of IPF [30]. In addition, patients with asymmetric IPF on HRCT scan had a higher rate of GER and AEx compared to patients with non-asymmetric disease, suggesting a role for GER and occult aspiration in a subset of patients with IPF [31].

Infection has also been suggested as a cause of AEx of IPF. Data in support of this hypothesis include animal studies [32] as well as some human studies [33, 34]. In one case series, 75.7 % of 37 AEx cases occurred between December and May [10], lending further support to occult infection as a cause of AEx. However, in a prospective study of AEx of IPF ( $n=47$ ), acute viral infection, as determined by the most current genomics-based methodologies, was found in only 9 % of this cohort [35]. While some cases may well have been missed (i.e., the virus had come and gone by the time testing was obtained), these data suggest that there are many cases of AEx that are not primarily due to occult infection.

An alternative explanation is that AEx of IPF is caused by an inherent acceleration of the pathobiology of IPF [3]. There is indirect evidence for this in several studies that evaluated serum biomarkers and gene expression in AEx. Serum biomarkers of alveolar epithelial cell injury/proliferation have been shown to be increased in AEx, in a pattern that is qualitatively distinct from what is seen in acute lung injury (Table 17.1).

Gene expression studies performed in patients with AEx of IPF [37] have shown that patients have increased expression of genes encoding proteins involved in epithelial injury and proliferation including CCNA2 and alpha-defensins. Interestingly, there was no evidence from the same study for upregulation of genes commonly expressed in viral infection.

## **Work-Up and Diagnostic Criteria**

### ***Laboratory Evaluation***

There are no specific laboratory tests that aid in the evaluation and diagnosis of AEx of IPF. Often, patients are found to have impaired gas exchange with a decrease in

**Table 17.1** Potential biomarkers in acute exacerbation of IPF

Biomarker	Mechanism of action	Association with AEx of IPF	References
Alpha defensin	Cationic proteins with antimicrobial activity found in neutrophils	Plasma levels higher in AEx compared to stable and seemed to correlate with disease course	[36, 37]
Annexin 1	Anti-inflammatory, antiproliferative, and pro-apoptotic calcium and phospholipid-binding protein that regulates differentiation; found in alveolar type II cells and alveolar macrophages	Associated with antibody production and CD4+ T-cell response in AEx	[38]
Circulating fibrocytes	Circulating mesenchymal cell progenitors involved in tissue repair and fibrosis	Increased levels of circulating fibrocytes in AEx compared to stable IPF	[39]
High-mobility group protein B1 (HMGB1)	Nuclear nonhistone protein and involved in endogenous danger signaling and a mediator of systemic inflammation; can bind to RAGE to promote chemotaxis and production of cytokines via NF- $\kappa$ B activation	Serum HMGB1 levels are higher in AEx requiring mechanical ventilation compared to stable IPF; BAL HMGB1 gradually increases during AEx, which correlated with monocyte chemotactic protein-1 (MCP-1)	[40, 41]
IL-6	Cytokine involved in a broad range of cellular responses including inflammation	Higher levels in AEx vs. stable	[42]
KL-6	Marker of alveolar type II cell injury and/or proliferation	Plasma levels higher in AEx of IPF compared to stable; serial serum KL-6 levels increased in patients who died of their AEx	[42, 43]
PAI-1	Principal inhibitor of tissue plasminogen activator and urokinase	Higher plasma levels in AEx compared to stable	[42]
Protein C	The activated form regulates blood clotting, inflammation, and cell death	Higher plasma % in AEx compared to stable	[42]
RAGE	Marker of alveolar type I cell injury and/or proliferation	No difference in plasma levels between stable and AEx of IPF	[42]
ST2	Predominantly expressed in Th2 cells and induced by proinflammatory cytokines	Higher serum levels in AEx compared to stable with a sensitivity of 71 % and specificity of 92 %	[44]
SP-D	Marker of alveolar type II cell injury and/or proliferation	Plasma levels higher in AEx compared to stable	[42]
Thrombomodulin	Membrane protein expressed on the surface of endothelial cells which serves as a receptor for thrombin	Plasma levels higher in AEx compared to stable and log change in thrombomodulin was predictive of survival	[42]
von Willebrand factor	Marker of endothelial cell injury and is involved in hemostasis	Higher plasma % in AEx compared to stable	[42]
AEx acute exacerbation, IPF idiopathic pulmonary fibrosis, KL-6 Krebs von den Lungen-6, PAI-1 plasminogen activator inhibitor-1, RAGE receptor for advanced glycation end products, NF- $\kappa$ B nuclear factor- $\kappa$ B, ST2, SP-D surfactant protein D			

their arterial oxygen tension [10]. In patients that can tolerate bronchoscopy with lavage, an increase in BAL neutrophils has been reported [11, 45]. Nonspecific elevations in serum lactate dehydrogenase (LDH) and C-reactive protein (CRP) have also been observed [10]. Serial levels of serum KL-6 and baseline thrombomodulin may help identify patients at increased risk for death from AEx [42, 43]. Although many experimental biomarkers have been investigated, as shown in Table 17.1, none are routinely used in clinical practice.

### ***Radiologic Evaluation***

High-resolution CT scans are often obtained during AEx of IPF. The findings include new, generally bilateral, ground-glass opacities and/or consolidation superimposed on the underlying UIP pattern [46]. The pattern of ground-glass changes during an AEx may have prognostic significance, with more diffuse abnormality correlating with worse outcomes [46].

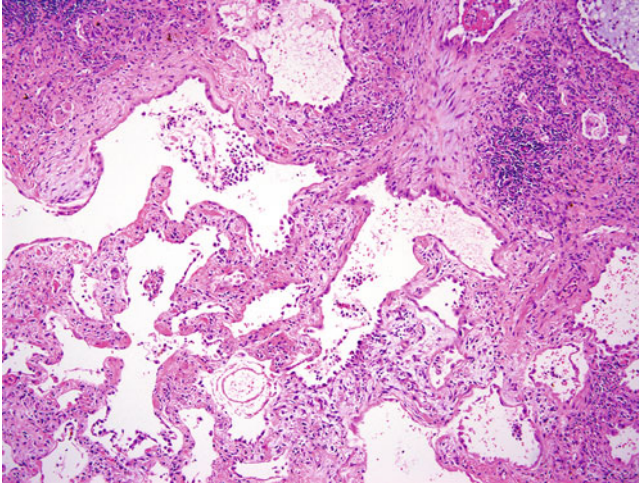
### ***Histopathologic Evaluation***

Surgical lung biopsy is not frequently obtained during AEx of IPF. A small case series of seven patients who had a surgical lung biopsy during their AEx demonstrated primarily diffuse alveolar damage (DAD) associated with underlying changes typical for UIP (Fig. 17.2) [47]. One case had organizing pneumonia and UIP and another case had DAD without underlying UIP. Autopsy series and other case series have demonstrated similar findings [6, 11, 45, 48–50].

### ***Diagnostic Criteria***

Several definitions have been used over the last decade to define AEx of IPF [3, 6, 50]. In order to standardize these criteria, a consensus definition was proposed by the National Institutes of Health-funded US IPF Network (IPFNet) in 2007 (Table 17.2) [3]. Other definitions that have been described are generally similar; however, they often include a reduction in PaO<sub>2</sub> as one of their criteria as well as bilateral chest x-ray abnormalities (instead of a HRCT scan) [6, 50].

The IPFNet criteria have helped to standardize the definition of AEx of IPF, but satisfaction of all criteria is quite difficult to achieve in many clinical settings. Specifically, it is not infrequent that in patients who appear to have AEx of IPF, microbiologic data and occasionally radiologic data are not collected due to the severity of illness or because the clinician does not feel the tests will change clinical management. By maximizing specificity at the cost of sensitivity, these criteria



**Fig. 17.2** Section from lung explant shows subpleural fibrosis with honeycombing typical of usual interstitial pneumonia. The central lung tissue shows diffuse alveolar septal thickening by edema and type II pneumocyte hyperplasia, and airspace consolidation by edema and fibrin (H&E,  $\times 100$ ). Figure courtesy of Kirk Jones, MD

**Table 17.2** IPFNet consensus criteria for acute exacerbation of idiopathic pulmonary fibrosis<sup>a</sup>

Previous or concurrent diagnosis of idiopathic pulmonary fibrosis
Unexplained development or worsening of dyspnea within 30 days
High-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia
No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage
Exclusion of alternative causes, including left heart failure, pulmonary embolism, and other identifiable causes of acute lung injury

<sup>a</sup>Patients who do not meet all five criteria should be termed “suspected acute exacerbation”

(along with the selection of only mild to moderate patients for enrollment) have likely contributed to the low prevalence of AEx observed in recent clinical trials [51–53]. The choice of definition has significant implications for outcome analyses in clinical trials and should be a focus for further discussion among clinical trialists.

## Management and Prognosis

There is no known effective treatment for preventing or improving outcomes in AEx of IPF.



## *Prevention*

While there are no data to support efficacy, vaccination and treatment of comorbidities like heart disease and GER seem prudent as measures that could prevent episodes of acute decline in respiratory function due to known causes such as infection, heart failure, and aspiration. Some novel therapies have suggested a reduction in AEx in clinical trials; these include warfarin [54], pirfenidone [55], and, most recently, BIBF 1120 [56]. Unfortunately, both warfarin and pirfenidone have subsequently been shown to have no impact on the rate of AEx, suggesting that the initial observations were inaccurate [51, 57].

## *Medical Therapy During AEx*

Although commonly prescribed for the treatment of AEx of IPF, there have been no controlled trials assessing the efficacy of high-dose corticosteroids. Recent international guidelines on IPF management suggested that the majority of IPF patients with AEx could be treated with corticosteroids [58]; however, approaches to dosing, route, and duration of therapy were not provided.

Although most clinicians would treat patients who develop an AEx of IPF with high-dose corticosteroids, the efficacy of this treatment is unclear. Perhaps we should be more critical of the use of corticosteroids to treat AEx of IPF. There are two distinct viewpoints regarding the role of corticosteroids in AEx of IPF. The first viewpoint is that AEx of IPF is histopathologically similar to acute respiratory distress syndrome (ARDS) characterized by DAD and acute lung injury [59] and should, therefore, be treated similarly to ARDS. In the ARDS literature, the mortality benefit of corticosteroids is unclear [60–65]. In one study, increased mortality was observed in ARDS patients treated with delayed corticosteroids (after 14 days) [65]. If we were to follow the ARDS paradigm, most clinicians would not use corticosteroids in the treatment of AEx of IPF. A second viewpoint for the role of corticosteroids in IPF is that some patients with AEx of IPF have organizing pneumonia on biopsy [49]. Organizing pneumonia is generally thought to be steroid responsive, and it may be that the pathobiology is different enough between ARDS and AEx of IPF to warrant continued use of corticosteroids. There remains equipoise on the efficacy of corticosteroids in AEx of IPF, and this treatment intervention should be studied more carefully [42].

The use of another immunosuppressant, cyclosporine A, to treat AEx of IPF has been reported. These studies suggest some benefit to the use of cyclosporine A plus corticosteroids [66–68]. However, conclusions that can be made from these data are limited by problems with study design and small sample size, and benefit has not yet been validated in a randomized controlled trial.

Other experimental therapies that have reported possible efficacy to treat AEx of IPF include tacrolimus [69], hemoperfusion with polymyxin B-immobilized fiber



column [70–72], and sivelestat [73]. These investigations were all limited by small numbers and suboptimal study design.

### ***Supportive Therapy During AEx***

Supportive therapy is the standard of care in AEx of IPF. Supportive care for respiratory failure almost always requires higher oxygen supplementation and consideration of additional means of ventilatory support, including mechanical ventilation (see discussion below) and noninvasive positive-pressure ventilation (NIPPV). Yokoyama et al. described the outcomes of patients with AEx of IPF treated with NIPPV to avoid intubation in acute respiratory failure [74]. In this retrospective case series of 11 patients, 6 patients failed a NIPPV trial and went subsequently succumbed to respiratory failure. The other five patients survived more than 3 months after the onset of their AEx. However, the use of ventilatory support in AEx (both mechanical ventilation and NIPPV) has never been studied in a randomized controlled trial.

### ***Lung Transplantation***

A few select centers have experience with emergent transplantation for AEx of IPF [75–78]. These critically ill IPF patients have generally been bridged to lung transplant with extracorporeal membrane oxygenation (ECMO) and/or mechanical ventilation [76]. Outcomes of patients who have undergone emergent transplantation have been mixed [77, 78]. Emergent lung transplantation requires careful patient selection and is not done at all transplant centers.

### ***Prognosis***

The prognosis of AEx of IPF is poor, with most case series reporting very high short-term mortality rates [11, 79–83]. This is particularly true for those patients requiring mechanical ventilation. A systematic review of mechanical ventilation in IPF and respiratory failure ( $n=135$ ), including AEx, reported a hospital mortality of 87 % [81]. Short-term mortality (within 3 months of hospital discharge) was 94 %. The routine use of mechanical ventilation in patients with AEx of IPF is not recommended in the international consensus guidelines because of its low likelihood of benefit and high risk of complications and further suffering [58]. Careful consideration regarding intubation and goals of care must be made, given the poor prognosis associated with this condition. Ideally, a discussion concerning end-of-life issues should be held between the patient and their provider in the outpatient setting with the inclusion of the patient's family, if applicable.

## Summary

Acute exacerbation of IPF is responsible for substantial morbidity and mortality in patients with IPF. We suggest that AEx of IPF represents an acute acceleration of the fibroproliferative process (i.e., the underlying pathobiology of IPF) that is triggered by some generally occult stress or insult to the lung (e.g., infection, aspiration, mechanical stretch from ventilation or lavage, high inspired oxygen concentration during surgery). As many patients with AEx of IPF will not meet the current consensus criteria due to missing data, it may be more useful clinically to define AEx by less stringent criteria. It seems likely that the prevention and treatment of AEx of IPF must focus on both disease-specific (e.g., anti-fibrotic therapies) and non-disease-specific (e.g., vaccination, prevention of stress) areas. The next decade will hopefully answer many of the unresolved questions concerning AEx of IPF.

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