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Review article

# Acute exacerbation of idiopathic pulmonary fibrosis: A systematic review

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**Abstract**

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a clinical entity defined by rapid deterioration of IPF during the course of the disease that is not due to infections, pulmonary embolism, or heart failure. The condition needs to be differentiated from acute interstitial pneumonia (or Hamman–Rich syndrome), which occurs in patients with no underlying lung disease. The exact etiology and pathogenesis remain unknown, but the condition is characterized by diffuse alveolar damage (on a background of IPF) that probably occurs as a result of a massive lung injury due to some unknown etiologic agent. High-resolution computed tomography can help in prognostication and management of this condition. Once infections and other causes of worsening have been excluded, treatment involves enhanced immunosuppression with pulse doses of methylprednisolone and cytotoxic agents. Our systematic review shows that the outcome, however, is poor, with 1-month and 3-month mortality around 60% and 67%, respectively. Few studies have shown beneficial effects of cyclosporine, pirfenidone, and anticoagulants in the management and prevention of AE-IPF. The etiology, risk factors, pathogenesis, therapy, prognosis, and predictors need to be studied and the potential role of newer agents in the management and prevention of AE-IPF needs to be further clarified.


*Keywords:* Idiopathic pulmonary fibrosis; Acute exacerbation; IPF; Idiopathic interstitial pneumonias; Hamman–Rich syndrome; Usual interstitial pneumonia

## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease (ILD) of unknown etiology that is characterized clinically by relentless dyspnea, reduced lung volumes, impaired gas exchange, and a histological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy [1,2]. This needs to be differentiated from other known causes of UIP, such as asbestosis, rheumatoid arthritis, and other connective tissue disease-related ILD, and from other causes that also have UIP on histopathology but are not categorized as IPF. IPF is the most common entity of the idiopathic interstitial pneumonias and accounts for approximately one-quarter of all interstitial lung diseases [3]. The survival time varies considerably from individual to individual, but the mean survival time is around 2–4 years [1]. Although studies have provided inconsistent results, generally the factors that predict survival include the age at presentation, gender, duration of dyspnea, pulmonary function, and radiological and histopathological findings [3].

IPF is a progressive and irreversible illness. However, its course is punctuated by acute exacerbations (AE) that are characterized by a rapid deterioration in lung function during the course of the disease that is not due to infections or heart failure. Several reviews of IPF are available [1,2]; however, there has been no systematic review on AE-IPF.

The aim of this review was to summarize the current knowledge of acute exacerbations of IPF. For the purpose of this review, we searched the National Library of Medicine's MEDLINE database from 1980 to 2006, with no language restrictions, for fully published articles. We limited the search to human adults (19+ years) using the key words: "acute exacerbation of idiopathic pulmonary fibrosis", "acute

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exacerbation of IPF", "IPF", "idiopathic pulmonary fibrosis", and "idiopathic interstitial pneumonias". We reviewed the reference lists of all identified studies and reviews and hand-searched our personal files. A total of 185 articles were reviewed for the purpose of this review. The focus was on clinical publications on epidemiology, diagnosis, and treatment, specifically on acute exacerbations of IPF, but we also studied other related reviews and publications on IPF.

## 2. Definitions

IPF is a fatal fibrotic lung disease of unknown etiology that is characterized by a histological pattern of usual interstitial pneumonia. In contrast, AE-IPF is characterized by rapid deterioration during the course of the disease that is not due to infection, pulmonary embolism, or heart failure.

## 3. Confusing terminologies

Numerous other terms are confused or used interchangeably with AE-IPF. They include: "acute interstitial pneumonia", "Hamman–Rich syndrome", "accelerated variant of interstitial pneumonitis", "fulminant idiopathic pulmonary fibrosis", "acute diffuse interstitial fibrosis of the lungs", and "accelerated variant of IPF".

## 4. Clearing the confusion

In 1935, Louis Hamman and Arnold Rich described four previously healthy patients with fatal fulminant respiratory failure that, on autopsy, was characterized by extensive pulmonary fibrosis [4,5]. They termed this condition "acute diffuse interstitial fibrosis of the lungs", a pattern of ILD that is not easily categorized in the subsequent classification of interstitial pneumonias. However, the eponym "Hamman–Rich syndrome" became synonymous with IPF despite clear differences in clinical presentation, radiography, pathology, and survival [6]. In 1986, Katzenstein et al. described eight patients with acute respiratory failure of unknown etiology which, on biopsy, revealed organizing diffuse alveolar damage [7]. Due to the idiopathic nature of the condition, Katzenstein et al. coined the phrase "acute interstitial pneumonitis" to distinguish it from the fibroproliferative stage of the acute respiratory distress syndrome, which also has an identical pathology [8]. Olson et al. reviewed the histological material from three of the four original cases described by Hamman and Rich and reported that the features present were those of organizing or organized DAD, and it is now inferred that AIP represents the same process that was described in the report by Hamman and Rich [9]. Finally, "accelerated variant of IPF" is probably a subset of IPF characterized by persistent and accelerated decline in lung function; it is described in more detail later. Apart from these three terminologies (acute interstitial pneumonia, Hamman–Rich syndrome, acute exacerbations of IPF and the related accelerated variant of IPF), all other terms should probably be abandoned.

## 5. Epidemiology

The exact incidence is not known and varies in different studies. However, AE-IPF is now increasingly being recognized as a common clinical event. In one retrospective series (exploratory analyses conducted on the placebo group of 168 patients enrolled in the interferon gamma-1b trial [10]), Martinez et al. reported that, over a median period of 76 weeks, 21% of these patients died, and 47% of these deaths followed an acute deterioration in the patient's clinical status [11]. In another study of 147 patients, the 1-year frequency was 8.5% and 2-year frequency was 9.6% after the diagnosis [12]. In contrast, in a series of 112 patients, Okamoto et al. reported an incidence as high as 25% during a period of ten years [13]. Kubo and colleagues also reported a high incidence of AE in their study on the role of anticoagulants in IPF (32/56, 57%). Azuma and colleagues prospectively reported 35 patients with untreated IPF and found a 14% incidence (five cases) of acute exacerbation [14].

Although no specific triggers are known, some cases have occurred following bronchoalveolar lavage (BAL) [15], surgical lung biopsy [16], and institution of interferon-gamma 1b [17]. However, it is yet not clear whether they are specific triggers or whether this was mere coincidence. Regarding the role of interferon-gamma 1b in causation of AE-IPF, a recent report that had analyzed 362 patients from two randomized, double-blind, placebo-controlled trials reported that the number of patients with serious respiratory adverse events throughout the study was similar in the interferon-gamma 1b and placebo groups in both of the randomized trials [10,18]. Moreover, this data was supported by the findings of the open-label extension study, which failed to show any increased risk for serious respiratory adverse events after recent initiation of treatment [19]. An additional placebo-controlled study that is currently ongoing should be able to better define the natural history and characteristics of mortality in patients with IPF and the effect of interferon-gamma1b in causation of acute exacerbations [20].

## 6. Pathogenesis

The exact pathogenesis of IPF and AE-IPF is not clear [21]. According to the traditional view, IPF is considered to be a progressive disease with a slow and steady decline in lung function that ultimately leads to respiratory failure and death. However, recent evidence suggests that IPF involves multiple microscopic injuries or ''hits'' to the lungs that are temporally distributed over many years [6]. According to this hypothesis, inflammation is subsequent to injury and IPF occurs as a result of a polarization of the immune response of the body to repeated injury (i.e., "multiple hits") to the lung. Recurrent exposure to the noxious agents and/or antigens somehow leads to an imbalance that favors T-helper type II immunity.