

Acute Exacerbations of Idiopathic Pulmonary Fibrosis

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Key Words

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and ultimately fatal disease, with a highly variable course in individual patients. Episodes of rapid deterioration are not uncommon, often following a period of stability. In cases of uncertain etiology, with typical clinical and high-resolution computed tomography (HRCT) features, the term 'acute exacerbation of IPF' (AE-IPF) has been coined to describe a combination of diffuse alveolar damage and preexisting usual interstitial pneumonia. In 2007, a consensus definition and diagnostic criteria were proposed. Although the presence of overt infection is currently an exclusion criterion, it appears likely that occult infection, reflux and thoracic surgical procedures are all trigger factors for AE-IPF. The development of new, usually bilateral infiltrates (ground-glass attenuation with variable admixed consolidation) is a defining HRCT feature. The outcome is poor with a short-term mortality in excess of 50% despite therapy. A number of pathophysiologic pathways are activated, with immunologic dysregulation, epithelial damage and circulating fibrocytes all be-

lieved to play a pathogenetic role. Acute exacerbations are less prevalent in other fibrotic lung diseases than in IPF and may have a better outcome, with the exception of acute exacerbations of rheumatoid lung. In AE-IPF, the exclusion of alternative causes of rapid deterioration, including heart failure and infection, is the main goal of investigation. Empirical high-dose corticosteroid therapy is generally used in AE-IPF, without proven benefit.

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Definitions

Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) represent rapid, clinically significant deteriorations of unidentifiable cause, transforming chron-

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ic insidious disease progression to acute lung injury/acute respiratory distress syndrome (ALI/ARDS) and often ending in death [1, 2]. Occasionally, ALI/ARDS presenting in a previously apparently healthy individual represents acute progression of hitherto undiagnosed IPF [1, 2].

AE-IPF are the most prevalent subgroup amongst patients with chronic interstitial fibrosis (either established or occult) who develop superimposed ALI (which may also involve fibrosis), thus developing a mixed acute-chronic fibrosing picture [1]. Although the resultant acute idiopathic illness is similar to acute interstitial pneumonia (AIP), the key difference is in the presence of underlying chronic fibrosis. The coexistence of acute and chronic disease explains the fact that AE-IPF went under-recognized in the past [1–3].

ALI/ARDS is initially characterized (days 1–3) by non-cardiogenic, interstitial edema, type I alveolar epithelial cell necrosis, endothelial cell injury and hyaline membrane formation and later (days 4–7) by type II alveolar epithelial cell hyperplasia [1]. By contrast, IPF exacerbations, characterized by an admixture of diffuse alveolar damage (DAD) and usual interstitial pneumonia (UIP), represent acute progression in underlying scarred and irreparably damaged lung. It is difficult to rationalize the fact that DAD, which is the common denominator of all ALI/ARDS, AIP and IPF exacerbations and which develops in different histological contexts (UIP in IPF exacerbations, normal lungs in AIP and normal or diseased lungs in ARDS), presents at different time intervals (7 days for ARDS, 4 weeks for IPF exacerbations and 2 months for AIP) [4].

In 1993, Kondoh et al. [2] described acute clinical deterioration in 3 IPF patients in whom acute influenza-like symptoms, cough, fever, leukocytosis and progressive hypoxia developed in the absence of an identified infection. Histologic findings from open-lung biopsy specimens showed both UIP and an organizing ALI pattern. The Kondoh criteria used to identify AE-IPF in some later series consisted of: (1) progressive dyspnea over 1 month or less; (2) new pulmonary infiltrates seen on a chest radiograph; (3) worsening hypoxemia (i.e. a fall in PaO₂ of >10 mm Hg), and (4) the absence of an underlying cause such as infection [2].

Subsequently, a simplified consensus definition of AE-IPF was developed by Collard et al. [3], consisting of (1) progressive dyspnea over 1 month or less; (2) new pulmonary infiltrates on chest radiography or computed tomography, and (3) the absence of an overt underlying cause of rapid deterioration.

Incidence – Etiology – Risk Factors

The 1- and 3-year incidences of AE-IPF were estimated at 14 and 21%, respectively, in a recent retrospective review of 461 patients [5]. An acute deterioration in IPF compatible with AE-IPF preceded death in 47% of deaths in a retrospective cohort of 168 patients [6]. Similarly, an autopsy evaluation demonstrated that AE was the most common immediate cause of death in patients with IPF [7]. In a recent study, it was established that the incidence of acute exacerbations was lower in interstitial lung disease (ILD) in connective tissue disease than in IPF [8, 9].

In the large retrospective study of Song et al. [5], AE-IPF was the most frequent cause of rapid deterioration in IPF (55%), followed by infection (31%). Opportunistic infections comprised nearly 60% of documented organisms and usually developed in patients treated with corticosteroids, regardless of whether cytotoxic agents were used [5]. Interestingly, the study of Simon-Blancal et al. [10] demonstrated that AE-IPF were more frequent in winter and spring than during summer and fall, suggesting that unidentified infections might be an important trigger.

In the study of Song et al. [5], a multivariate analysis revealed that low FVC levels and the absence of a history of smoking were risk factors for AE-IPF. However, data are conflicting regarding the role of smoking in AE-IPF [9, 11]. AE-IPF were reported in 12 patients with combined pulmonary fibrosis and emphysema [11], and more recently, it was observed that 67% of patients with AE-IPF were former or current smokers [8, 9]. The fact that smokers with IPF have a worse outcome than nonsmokers [12] is difficult to reconcile with the idea that AE-IPF are more frequent in nonsmokers. In addition, there is a high prevalence of smoking in patients with rheumatoid arthritis, who may present with a combination of pulmonary fibrosis and emphysema [13] and have a worse outcome with AE of ILD than is seen in other connective tissue diseases [14–16].

Finally, the purpose of a recent study was to evaluate the incidence, risk factors and outcomes of AE in patients with advanced IPF awaiting lung transplantation, and to examine the relationship between pulmonary hypertension at baseline and subsequent AE [17]. Interestingly, pulmonary hypertension at baseline was associated with a significant risk of AE ($p = 0.041$) [17]. Twelve of 17 patients with pulmonary hypertension developed an AE during the follow-up period, with no other associations with baseline variables being observed [17]. Moreover, the increase in mean pulmonary arterial pressure was statistically significant in the AE group but not in the non-AE group [17]. It has also been shown that neovascular-

ization is significantly increased in areas of cellular fibrosis and significantly decreased in honeycomb areas, and that there is a significant inverse relationship between mean pulmonary arterial pressure and neovascularization in areas of honeycombing [17].

Clinical Features and High-Resolution Computed Tomography

An early, accurate and secure diagnosis is critical in IPF patients presenting with a rapid deterioration, with the identification of reversible precipitating factor(s) [18]. Investigation into medical history should focus on smoking habits, toxic exposures and prescribed medications (including corticosteroid and immunosuppressive therapy, underlying cardiac disease, a history suggestive of a recent or current respiratory infection and signs and symptoms of hitherto undiagnosed autoimmune rheumatic disease) [18]. Frequent physical findings include tachypnea, cyanosis, digital clubbing, bilateral inspiratory crackles and edema of the lower extremities.

In AE-IPF, high-resolution computed tomography (HRCT) reveals new bilateral ground-glass abnormalities or consolidation superimposed on the reticular or honeycomb abnormalities typical of UIP [19]. A ground-glass pattern, especially if extensive, is not an expected finding in IPF, and its rapid development away from areas of fibrosis is highly suggestive of DAD. Akira et al. [20] propose an HRCT classification of AE-IPF based on three patterns of the distribution of ground-glass and consolidation that appear to have prognostic implications: (1) peripheral; (2) multifocal, and (3) diffuse. However, the reported prognostic significance of this classification has been questioned with uncertainty as to whether small areas of peripheral ground-glass attenuation should be regarded as indicative of AE-IPF. More recent data suggest that the extent of disease on HRCT is a more important determinant of outcome than the distribution of disease [21, 22]. In a retrospective review of 64 patients with AE-IPF, multivariate analysis revealed that the HRCT extent score was an independently significant predictor of survival, based on the receiver operating characteristics curve [22].

Outcome

AE-IPF have a poor outcome with an overall short-term mortality of >50% and a mortality of 90–100% in patients requiring ventilatory assistance [3]. In-hospital

mortality has been estimated at 50–63% and 1-year mortality at 44–85% [5, 9]. AE represent the most frequent cause of rapid deterioration requiring hospitalization of IPF patients [5].

Does Etiology Matter?

There are competing hypotheses regarding the pathogenesis of AE-IPF. One view is that AE represent a distinct but intrinsic manifestation of the underlying disease process representing accelerated IPF. However, it has also been argued that AE-IPF represents the consequence of trigger factors such as viral infection, silent aspiration or sequel of direct infective insults to the lungs [23].

The main difficulty in the current definition [3] is that AE-IPF cannot be diagnosed if potentially clinically significant infection is identified. This exclusion criterion was arguably justifiable when the consensus definition of AE-IPF was formulated, in order to standardize diagnostic criteria in a notoriously nonstandardized area. However, there is a significant subgroup of IPF patients in whom evidence of infection is associated with clinical, HRCT, bronchoalveolar lavage (BAL) and outcome features that are indistinguishable from AE-IPF [24]. Furthermore, as discussed later, it has become increasingly apparent that AE-IPF, as currently defined, may be triggered by thoracic surgical procedures or microaspiration [25]. It appears increasingly illogical to accept a definition of AE-IPF in which some triggers are accepted but others are not [23]. It can be argued that exclusion criteria should instead be focused on heart failure, pulmonary embolism and other causes of rapid decline (including infection) in which typical clinical and HRCT features of diffuse alveolar damage are not present.

In the next section, the emerging role of pathophysiology of AE in combination with recent advances in molecular medicine is discussed.

Pathophysiology

Little is known about the pathophysiology of AE-IPF, a condition that shares clinical and histopathologic features with ALI. Moreover, the molecular mechanisms underlying this lethal event of the disease are also poorly understood. The histological similarity between AE-IPF and fibroproliferative ARDS should be stressed [4, 8]. The vast majority of biopsies from patients with AE-IPF dem-

onstrate acute and organizing diffuse alveolar damage superimposed upon a pattern of UIP. This appearance suggests similar mechanisms may be involved in the pathogenesis of AE-IPF and fibroproliferative ARDS [4].

Immunologic Dysregulation

The emerging role of immunologic regulation in the pathogenesis of AE-IPF has been emphasized by recent studies in this field [26–28]. It has been elegantly shown that annexin 1 is an autoantigen that raises both antibody production and T cell response in patients with AE-IPF, and that the N-terminal portion of annexin plays some role in the pathogenesis of this disorder [28].

Heat shock protein 47 (HSP47), a collagen-specific molecular chaperone, is essential for the biosynthesis and secretion of collagen molecules. Previous studies in experimental animal fibrosis models have shown that downregulation of HSP47 expression reduces collagen production and diminishes fibrosis progression [26]. In a recent study, serum HSP47 levels were evaluated to elucidate pathogenic differences involving HSP47 between AE-IPF and stable IPF. Serum levels of HSP47, Krebs von den Lungen-6 (KL-6), surfactant protein (SP)-A, SP-D, and lactate dehydrogenase were measured in 20 AE-IPF and 33 stable IPF patients [26]. Serum HSP47 levels were significantly higher in AE-IPF than in stable IPF, suggesting that underlying fibrogenic mechanisms involving HSP47 may play a role in AE-IPF. By contrast, levels of KL-6, SP-A and SP-D did not differ significantly between AE-IPF and stable IPF. Moreover, immunohistochemical analysis revealed that pulmonary HSP47 expression was greater in DAD than in UIP tissue.

In keeping with these findings is the recent observation that IPF patients with anti-HSP70 autoantibodies have more near-term lung function deterioration and mortality. Anti-HSP70 IgG autoantibodies were detected by Immunoblot in 3% of 60 control subjects, in 25% of a cross-sectional IPF cohort ($n = 122$) ($p = 0.0004$), in 50% of IPF patients who died in the short term ($p = 0.008$) and in 70% of those with AE ($p = 0.0005$) [27]. The 6-month mortality of AE-IPF was 100% among those with HSP70 autoantibodies, as opposed to 33% among anti-HSP70-negative patients [27, 29].

Epithelial Damage

Fibrocytes are circulating mesenchymal cell progenitors that are involved in tissue repair and fibrosis and are defined as cells positive for CD45 and collagen-1 by flow cytometry [30]. Circulating fibrocytes are present in both stable IPF and AE-IPF and have prognostic significance

[8, 31]. Fibrocyte levels are increased in stable IPF ($n = 51$), and are further increased in AE-IPF ($n = 7$; $p < 0.001$ vs. control subjects). The mean survival of patients with fibrocytes $>5\%$ of total blood leukocytes was 7.5 months compared with 27 months for patients with $<5\%$ ($p < 0.0001$) [31]. One surprise in this study was that levels of circulating fibrocytes were not increased in patients with ARDS. This observation may reflect the fact that none of the 10 patients with ARDS went on to develop fibroproliferative lung disease [30, 31].

Five hundred and seventy-nine genes were found to be differentially expressed (false discovery rate $<5\%$) between stable IPF and AE-IPF [32]. CCNA2 and alpha-defensins, a group of innate antimicrobial peptides, were among the most upregulated genes in the mRNA levels and in the plasma protein level of AE-IPF patients, and were also higher and localized to the epithelium of AE-IPF patients, with widespread apoptosis detected.

The aim of another elegant study was to determine the plasma biomarker profile of AE-IPF and to compare it to profiles of stable IPF and ALI [33]. Biomarkers of type II alveolar epithelial proliferation and/or injury (KL-6, SP-D), type I alveolar epithelial cell injury (receptor for advanced glycation end-products, RAGE), endothelial injury (von Willebrand factor), inflammation (IL-6) and coagulation (protein C, thrombomodulin, PAI-1) were analyzed in the plasma of these study groups. KL-6 and SP-D levels were significantly elevated ($p < 0.0003$ and 0.01 , respectively) in AE-IPF, compared to stable IPF [33]. Levels of von Willebrand factor and IL-6 were also elevated in AE-IPF compared to stable IPF ($p < 0.003$ and 0.004 , respectively). Total protein C, thrombomodulin and PAI-1 levels were significantly higher in AE-IPF than in stable IPF. In comparison to early ALI, AE-IPF demonstrated higher levels of KL-6 and SP-D and lower levels of RAGE, von Willebrand factor and IL-6. Total protein C was significantly higher in AE-IPF than in both early and late ALI while thrombomodulin levels were significantly lower. To summarize, the AE-IPF group had higher levels of KL-6 and SP-D than the stable IPF cohort or the early or late ALI/ARDS groups, suggesting very high rates of type II alveolar epithelial cell proliferation and/or injury. On the other hand, the AE-IPF group had lower levels of RAGE than either the early or late ALI cohorts, arguing against a precipitating alveolar injury, unless it was so remote as to not be detectable by RAGE levels [33].

In keeping with these data, and suggesting prominent epithelial damage in AE-IPF, is the fact that these events are associated with increases in serum KL-6. The primary cellular source of KL-6 is thought to be type II pneumo-

cytes and respiratory bronchiolar epithelial cells, as KL-6 is expressed on these cells in normal lungs and is strongly expressed on regenerating type II pneumocytes and alveolar macrophages in ILDs [34].

Viral Infection

Previous recent studies have implicated chronic viral infection as a cause of ongoing epithelial injury in IPF; it is therefore an important cofactor, either initiating or exacerbating the disease [35, 36]. Occult viral infection has also been proposed as a possible cause of AE-IPF [35]. Pan-viral microarrays have shown additional evidence of viral infection [herpes simplex virus (n = 1), Epstein-Barr virus (n = 2) and *Torque teno* virus (n = 12)] in the BAL fluid of AE-IPF patients. *Torque teno* virus infection was significantly more frequent in AE-IPF patients than in stable IPF patients (p = 0.0003), but was present in a similar percentage of ALI controls [36]. However, the clinical significance of this finding has to be further investigated, with ongoing uncertainty as to whether occult infection alters the lung environment and induces fibrogenesis.

Cytokines and Matrix Remodelling

It is well recognized that extracellular matrix turnover is highly activated in patients with rapidly progressive IPF and, in particular, increased levels of MMP-9 have been measured in BAL fluid in this context [37]. Direct hemoperfusion with a PMX-DHP (polymyxin B-immobilized fiber column) has been used to improve oxygenation in ARDS [38]. In an interesting study, factors predictive of outcome in AE-IPF treated with PMX-DHP were evaluated [38]. Stored serum taken before and after PMX-DHP therapy was analyzed for 27 cytokines and chemokines. Serum levels of IL-7, an anti-fibrotic cytokine, increased significantly with treatment. Multivariate analysis disclosed that the greater increases in IL-7 levels were associated with improved survival [38].

Others

Coagulation. Disordered coagulation and fibrinolysis may be important components of AE-IPF [38–40]. Anti-coagulation has been investigated as a therapeutic approach in IPF as discussed later [39–41].

Reflux. Another possible mechanism leading to AE is the occult aspiration of gastric contents [42]. In a study of patients with asymmetric IPF (as judged by the distribution of disease on HRCT), the prevalence of both reflux symptoms and AE-IPF was strikingly increased, compared to IPF patients with symmetrical disease [43]. In order to further investigate this hypothesis, a recent study

aimed to determine whether pepsin, a marker of gastric aspiration, is elevated in BAL fluid obtained from IPF patients during AE [44]. There were no significant differences in baseline demographics between stable disease and AE, while pepsin level was an indicator of AE status (p = 0.04) but was not an independent predictor of survival time [42, 44].

Seasonal Variation. There is seasonal variation in the prevalence of both definite and suspected AE-IPF [45], in keeping with the idea that respiratory viral infections or increased air pollution might contribute to pathogenesis.

Drug-Related Exacerbation. Caution should be exercised when using certain drugs (13 drugs associated with AE are currently listed in 'pneumotox.com') in patients with IPF or connective-tissue-associated ILD [46–48]. Implicated drugs include biologic (anakinra, etanercept and infliximab) and nonbiologic (ambrisentan) agents, immunomodulatory agents (interferon alpha/beta, everolimus and leflunomide) and antineoplastic therapies [46–48]. In a recent review of the literature, 122 reported cases of new onset or exacerbation of ILD secondary to administration of biologic therapies (infliximab and etanercept) have been registered [48]. Drug-induced ILD had a poor prognosis, with an overall mortality rate of around one third, rising to two thirds in patients with preexisting ILD [48].

AE in Disorders Other than IPF

AE have been reported in ILDs other than IPF [9], including nonspecific interstitial pneumonia [49], chronic hypersensitivity pneumonitis [50] and ILD associated with connective tissue disease (CTD), particularly rheumatoid arthritis and idiopathic inflammatory myopathy [8, 51, 52].

However, their clinical features and outcome have not been studied in large numbers of patients. Parambil et al. [25] identified a small number of patients with a DAD pattern on surgical lung biopsy of the patients with CTD. A retrospective evaluation of 167 patients with idiopathic nonspecific interstitial pneumonia (n = 74) or idiopathic interstitial pneumonia associated with CTD (n = 93) showed that AE in nonspecific interstitial pneumonia were associated with a better prognosis than those in IPF [49]. In patients with CTD-ILD, AE occurs mostly in patients with rheumatoid arthritis, with a poor outcome. In keeping with these findings, an evaluation of 83 biopsy-proven interstitial pneumonia patients with collagen vascular disease revealed that AE of ILD in CTD had simi-

larities to AE-IPF with a similarly poor prognosis, were most prevalent in rheumatoid arthritis and were associated with more advanced patient ages [50, 51]. Tachikawa et al. [9] studied AE of ILD in CTD in consecutive patients presenting to the emergency department of a tertiary referral center. Fifteen cases of AE in CTD were compared to 47 cases of AE in IPF or other idiopathic interstitial pneumonias [9]. Patients with CTD were younger and had a better PaO₂/FiO₂ ratio than those with idiopathic disease; however, the other clinical, biological and lung imaging features were similar between groups. Three-month mortality in AE of ILD associated with CTD (33%) was similar to that of AE of idiopathic interstitial pneumonia in general (44%), but was significantly better than that of AE-IPF [8, 9].

Management Strategies

Because the clinical features of infection are similar to AE-IPF, infection, particularly opportunistic infection, is the most important and difficult differential diagnosis [8, 23]. The early identification and treatment of infection is essential, based on the culture of tracheal secretions and, in selected cases, BAL fluid. It should be stressed that the diagnosis of respiratory viruses and opportunistic infections such as *Pneumocystis jiroveci* often requires the performance of BAL and appropriate staining and molecular identification methods [53]. When there is a major deterioration in patients with IPF treated with immunosuppressive therapy, the key management distinction lies between increasing the level of immunosuppression (and treating infection) and reducing it [53, 54]. This key distinction requires the exclusion of infection upon BAL and is often the single most important determinant of the management strategy in this difficult clinical scenario [54]. Furthermore, 36% of IPF patients grow bacteria in BAL fluid in the absence of clear signs of infection, even before immunosuppression [55]. A specific role for cotrimoxazole is also suggested by a high prevalence of *P. jiroveci* colonization (23.3%) among patients with IPF associated with collagen vascular disease [56]. The importance of infection is outlined by the findings of the TIPAC study; 11/35 deaths were a result of pneumonia during the study [57]. Patients receiving immunosuppressive treatment at entry into the study were more likely to die if they were in the control group (immunosuppression: 12/35 and no immunosuppression: 2/30, $p = 0.015$) [57].

It is also important to identify and treat other reversible causes of rapid deterioration in IPF, including heart

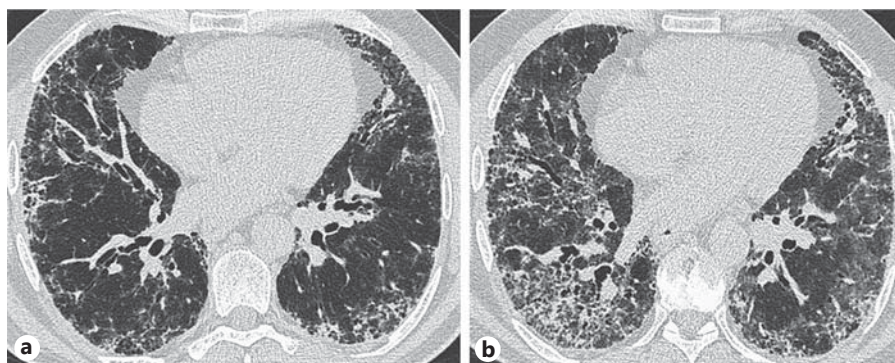
failure, pulmonary embolism and drug-induced lung disease. In particular, echocardiography should be performed routinely, as the clinical and HRCT features of supervening heart failure can mimic those of AE-IPF [3, 4, 8].

Active efforts should be made to minimize the prevalence of AE-IPF. Based on emerging data regarding the pathogenetic significance of microaspiration as a trigger for AE-IPF (discussed earlier), reflux symptoms should be treated vigorously [23, 42, 58]. Diagnostic surgical biopsies should not be performed on patients with typical IPF on HRCT, and in those undergoing biopsy or other surgical procedures, excessive oxygen therapy should be avoided [59, 60].

In the recent guidelines for the diagnosis and management of IPF, there is a weak positive recommendation for the treatment of AE-IPF with pulses of methylprednisolone [18]. This recommendation is based on case series with no randomized control trials existing in the current literature. Uncontrolled data are conflicting. Song et al. [5], in the largest current report, have shown that high-dose steroids were usually used in AE-IPF, without a demonstrable effect on outcome. By contrast, in a small case series in which 9/12 patients had IPF, better outcomes were seen with corticosteroid therapy in AE when organizing pneumonia was the predominant pattern at diagnostic surgical biopsy [61], a histologic picture present in approximately 10–15% of patients with AE-IPF and not reliably identified by clinical and HRCT findings. Similarly, in a recent report, 17 patients were treated for 11 episodes of AE-IPF over a 42-month period with steroid pulses plus cyclophosphamide [62, 63]. Patients were treated with a methylprednisolone pulse (1,000 mg) at days 1–3 and on day 4, they were placed on an escalating regimen of cyclophosphamide with an initial dose of 500 mg intravenously [63]. The dose of cyclophosphamide was increased by 200 mg every 2 weeks, with the maximum single administered dose of 1,500 mg [63]. The overall survival was 56% at 6 months and 1-year survival was 33% [63]. These uncontrolled outcome figures are better than previously reported, but do not, in isolation, establish the existence of a genuine treatment benefit. Alternative explanations include genetic differences in studied populations [8, 23, 37] and variations in disease severity and/or diagnostic criteria. Overall, it appears that high-dose corticosteroid therapy will continue to be used empirically for AE-IPF in the absence of more attractive therapeutic options.

The role of anticoagulation in AE-IPF is uncertain. This question arose from the results of a prospective study of 56 patients with IPF, in which improved survival was

Fig. 1. a An IPF patient aged 62 years, presented 1 year previously with insidious dyspnea. The FVC was 62% predicted and the diffusion capacity of 52%, while no evidence of pulmonary hypertension was present. **b** He presented with 4 weeks of more rapidly progressive dyspnea, preceded by symptoms of a lower respiratory tract infection such as fevers and green sputum. He also developed hypoxia at rest.



noted in patients treated with warfarin in combination with corticosteroids (with heparin given during AE-IPF) compared to patients treated with corticosteroids alone [39]. Most of the survival benefit could be ascribed to reductions in mortality from AE-IPF in the anticoagulant arm of the study [39]. In a recent placebo-controlled evaluation of warfarin in IPF, active treatment was associated with a worse outcome, but it should be acknowledged that in this study, AE-IPF were rare and were not prospectively identified [40, 41].

BIBF 1120 is a triple inhibitor of tyrosine kinases receptors such as platelet-derived growth factor, vascular endothelial growth factor and fibroblast growth factor receptors which are implicated in the process of fibrogenesis [64]. In a recent placebo-controlled phase II trial of the efficacy and safety of BIBF 1120 (TOMORROW Study) [64], 432 patients with IPF were assigned to receive four different doses of the drug or placebo for 12 months. Interestingly, there was a striking dose-related reduction in ‘acute exacerbations’, although it should be stressed that rigorous criteria were not used to define AE-IPF. The robustness of this observation should become apparent in the near future with the completion of 2 large current phase III trials in 2014.

Finally, the recent finding that anti-HSP70 antibodies are much more prevalent in AE-IPF than in the remaining IPF patients raises the possibility that targeting immunologic dysregulation with mechanistically focused therapies (such as rituximab) might have efficacy in AE-IPF [29]. Promising pilot data have been presented in abstract form but have not been subjected to formal peer review, at the time of writing. However, in any case, given the fact that multiple pathophysiologic pathways are involved in AE-IPF, it is questionable whether treatments targeting a single pathway are likely to be effective in the majority of patients with AE-IPF [29, 40, 58].

Empirical Management Investigation

It is important to identify and treat reversible causes of rapid deterioration in IPF, including heart failure, pulmonary embolism and drug-induced lung disease. In particular, echocardiography should be performed routinely, as the clinical and HRCT features of supervening heart failure can mimic those of AE-IPF (fig. 1).

There are no specific guidelines or overall consensus regarding the performance of BAL. In the consensus statement of Collard et al. [45], BAL was not regarded as obligatory – culture of tracheal secretions was regarded to be an acceptable substitute. We share this view as some patients are severely compromised and cannot undergo BAL without an unacceptable risk of triggering the need for mechanical ventilation.

Management

In the recent guidelines for the diagnosis and management of IPF, there is a weak positive recommendation for the treatment of AE-IPF with corticosteroid therapy. Empirical high-dose corticosteroid therapy is generally used in AE-IPF, without proven benefit. We treat our patients with pulsed methylprednisolone (1,000 mg IV) on days 1–3 with a maintenance prednisolone dose equivalent to approximately 40 mg daily. We routinely cover the patient with broad-spectrum antibiotics. There is evidence that the innate immune response is impaired in patients with IPF with a reduced functional capacity of macrophages to kill bacteria. We also add co-trimoxazole to cover pneumocystis infection and because recent findings of the TIPAC study suggested a mortality benefit in apparently stable IPF, which may reflect a better outcome in AE [57].

Regarding the prevention of AE-IPF, current guidelines recommend the treatment of symptomatic reflux in

IPF but do not suggest that investigations should be performed to exclude silent reflux or that all IPF patients should be treated empirically for silent reflux. Recent data indicate that patients treated with anti-acid have a smaller decrease in FVC at 30 weeks [65]. However, the pathogenetic significance of silent reflux remains an open question (which we are unable to answer satisfactorily from current data). Interestingly, in the impressive French study of asymmetric IPF, symptomatic reflux appeared to be the key association with AE, providing support for the current guideline view that reflux treatment should be used for symptomatic patients [43].

Finally, we do not use anticoagulation due to deleterious effects in the ACE study, discussed earlier (table 1).

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Table 1. Practical questions and answers from experts

Practical questions	Answers
Do you use BAL for diagnosing AE?	We perform BAL unless there is a high chance of triggering the need for mechanical ventilation
Do you use empirical antibiotic treatment?	We use broad-spectrum antibiotic therapy
Do you treat with antivirals?	No, unless the patient is severely lymphopenic
Do you treat for pneumocystis?	Yes, we do
Do you use anticoagulation?	No, we do not
Do you use corticosteroids?	Yes, we pulse the patient with three daily doses of methylprednisolone of 1 g each
Do you use cyclophosphamide for AE-IPF?	No

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