Acute Exacerbation of Idiopathic Pulmonary Fibrosis

An International Working Group Report

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Abstract

Acute exacerbation of idiopathic pulmonary fibrosis has been defined as an acute, clinically significant, respiratory deterioration of unidentifiable cause. The objective of this international working group report on acute exacerbation of idiopathic pulmonary fibrosis was to provide a comprehensive update on the topic. A literature review was conducted to identify all relevant English text publications and abstracts. Evidence-based updates on the epidemiology, etiology, risk factors, prognosis, and management of acute exacerbations of idiopathic pulmonary fibrosis are provided. Finally, to better reflect the current state of knowledge and improve the feasibility of future research into its etiology and treatment, the working group proposes a new conceptual framework for acute respiratory deterioration in idiopathic pulmonary fibrosis and a revised definition and diagnostic criteria for acute exacerbation of idiopathic pulmonary fibrosis.

Keywords: pulmonary fibrosis; acute exacerbation; review; diagnosis; management

Acute exacerbation of idiopathic pulmonary fibrosis (IPF) has been defined as an acute, clinically significant respiratory deterioration of unidentifiable cause (1). In 2007, the National Institutes of Health–sponsored IPF Clinical Trials Network (IPFnet) published a pulmonary perspective describing the clinical, radiological, and histopathological presentation of acute exacerbation of IPF and proposing diagnostic criteria built on the previous literature in the field (2). These criteria included a clinical worsening of less than 30 days' duration, the presence of new radiologic abnormality on high-resolution computed tomography (CT)

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(i.e., bilateral ground-glass opacification/consolidation), and the exclusion of alternative etiologies (e.g., infection, heart failure, pulmonary embolism).

It was hoped that the 2007 IPFnet perspective would help standardize inclusion criteria for future research studies of acute exacerbation of IPF and that these criteria would be revised and modified as additional insight into acute exacerbation of IPF was achieved. Indeed, in the years since their publication, many clinical scientists and sponsors adopted the IPFnet criteria for the study of acute exacerbation of IPF, and there has been a substantial increase in the evidence base.

The objective of this international working group report is to provide a comprehensive update on acute exacerbation of IPF, systematically reviewing the literature, in particular literature published since the 2007 IPFnet perspective. It also presents a revised conceptual framework and definition for acute exacerbation of IPF that the authors believe more accurately reflects the current state of knowledge in the field.

Methods

An international multidisciplinary working group was assembled by the first and last author (H.R.C. and F.J.M.), which included 21 pulmonologists, 3 radiologists, and 2 pathologists. Initial meetings were held by teleconference and were focused on developing an updated conceptual framework and definition for acute exacerbation of IPF. A face-to-face meeting was held to finalize this aspect of the report.

In parallel, an evidence-based medicine subcommittee (H.R.C., C.J.R., T.J.C., G.J., Y.K., D.J.L., J.S.L., T.M.M., and A.U.W.) conducted a literature review to identify all English text publications and abstracts relevant to acute exacerbation of IPF (Figure 1). MEDLINE, EMBASE, and All EBM Reviews databases were searched from database inception until February 14, 2016, with a total of 2,735 unique citations identified. Publications were screened in duplicate, with a total of 154 citations meeting eligibility criteria. Details of the search strategy and literature review methodology are provided in the online supplement.

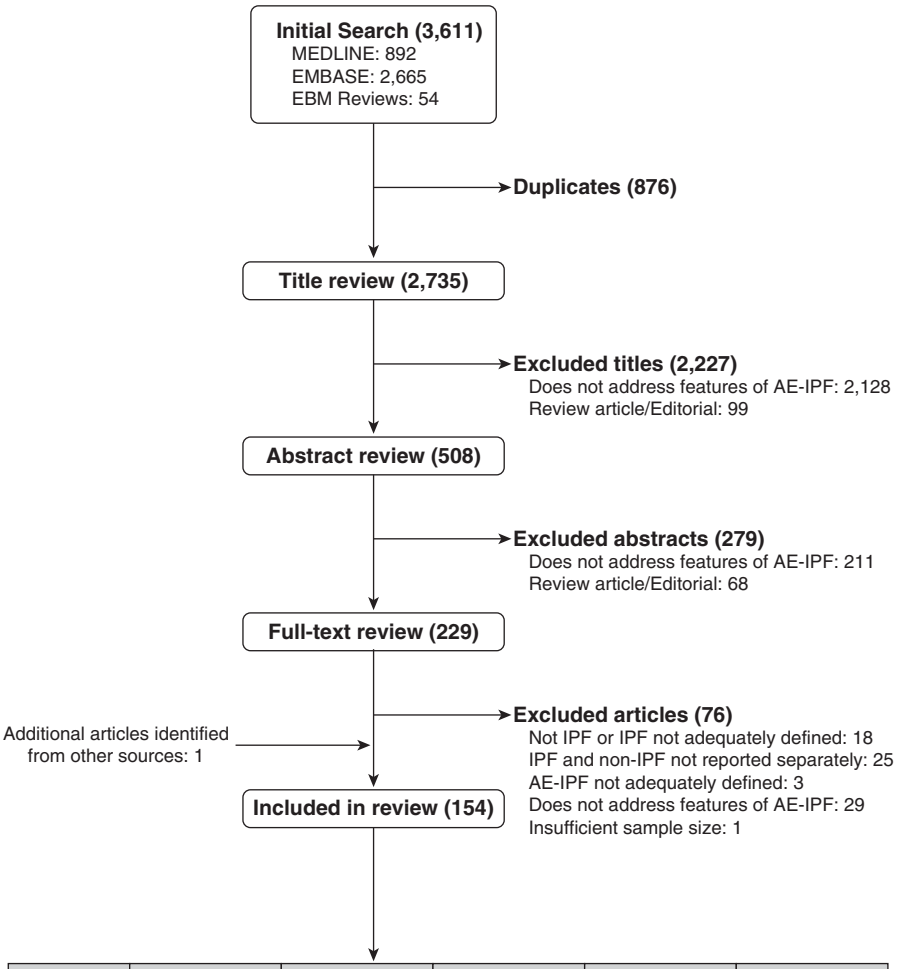

Figure 1. Systematic review search strategy and results. The initial search of Medline, EMBASE, and EBM reviews yielded 3,611 citations (articles and abstracts), of which 2,735 were unique. In sequence, these citations underwent title review, abstract review, and full-text review to exclude articles that were not related to acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) or met other exclusion criteria. This yielded 154 final citations that were included in the systematic review.

The working group was divided into writing groups on the basis of content expertise. Each group was chaired by an evidence-based medicine subcommittee member and was tasked with developing a section of the document using the evidence-based summaries and individual member knowledge of the field. Three authors (H.R.C., C.J.R., and F.J.M.) merged and edited these content drafts to produce a full draft report, which was reviewed and revised by all working group members. The final document was reviewed and approved by all members prior to submission.

Evidence Review

The following sections of the report provide evidence-based updates on the epidemiology, etiology, risk factors, prognosis, and management of acute exacerbations of IPF generated after review of the literature as described above. Summary tables of relevant articles and their abstracted findings are provided in Tables E1 and E2 in the online supplement.

Epidemiology

Clinical trials published over the last decade have reported variable incidence rates for

acute exacerbation of IPF, likely due to differences in study populations (e.g., disease severity), definition of acute exacerbation used, and statistical methodology (Table 1) (3). A recent metaanalysis of six clinical trials in patients with IPF revealed a weighted average of 4.1 acute exacerbations per 100 patient-years (4). One major limitation of clinical trial–based incidence estimates may be missed events due to missing/unavailable clinical data. For example, in the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial, a *post hoc* analysis of respiratory events demonstrated an incidence of acute exacerbation of IPF of only 4.0 per 100 patient-years when strict adherence to the 2007 criteria was required (5). The incidence increased to 20.0 per 100 patient-years when patients with definite and suspected acute exacerbations (events in which the diagnosis of acute exacerbation seemed plausible but could not be confirmed due to missing clinical information) were both included.

Cohort studies have generally reported a higher incidence of acute exacerbation of IPF than clinical trials (6–11). A registry-based U.S. study reported an annual incidence of 13.0 per 100 IPF patient-years (12); a Korean cohort study reported 1- and 3-year incidences of 14.2 and 20.7%, respectively (13); and a Japanese cohort study reported 1-, 2-, and 3-year incidences of 8.6, 12.6, and 23.9%, respectively (14). A limitation of cohort studies is potential overreporting of events due to misclassification of respiratory deteriorations of known cause as acute exacerbations. For example, in the INPULSIS program, where 7.6% of patients receiving placebo had an investigator-reported acute exacerbation of IPF over 1 year, only 10% of these events fulfilled all of the IPFnet criteria on central adjudication (15). In the three IPFnet trials, only 33% of investigator-reported acute exacerbations met criteria on central adjudication (16).

Etiology

The etiology of acute exacerbation of IPF remains uncertain (Figure 2). A central question posed by the 2007 IPFnet perspective was whether acute exacerbation of IPF represents an intrinsic acceleration of the underlying fibrotic condition or a response to occult external events (e.g., infection) leading to acute lung injury (ALI) and histopathological diffuse alveolar damage.

In addressing this question, it is useful to consider acute exacerbation of IPF in the context of what is known about the etiology of ALI. ALI and acute exacerbation of IPF share many clinical features, including increased oxygen requirements, new bilateral radiologic abnormalities (ground-glass opacification/consolidation), and the presence of diffuse alveolar damage histologically (17, 18). Indeed, occasional cases diagnosed as ALI using clinical and radiologic evaluation were found to represent acute exacerbation of IPF when the lung tissue was examined histologically

Table 1. Selected Publications Reporting Incidence of Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Study	No. of Patients	Criteria*	Incidence of Acute Exacerbation
Incidence from placebo arms of randomized clinical trials			
Collard *et al.*, 2013 (5)	180	IPFnet	4 events/100 patient-years; 16 events/100 patient-years for suspected exacerbations (placebo arms)
Richeldi *et al.*, 2011 (75)	432	Akira	15.7 events/100 patient-years (placebo arm)
Richeldi *et al.*, 2014 (15)	1,066	IPFnet	7.6% incidence over 52 wk (placebo arm)
Taniguchi *et al.*, 2010 (47)	267	Taniguchi and Kondoh	4.8% incidence over 52 wk (placebo arm)
Incidence from cohort studies			
Fernández Pérez *et al.*, 2010 (12)	37	Mixed	13 events/100 patient-years
Kim *et al.*, 2006 (7)	147	Kondoh	8.5% incidence at 1 yr; 9.6% incidence at 2 yr
Kishaba *et al.*, 2014 (43)	594	Kishaba	9.8% incidence over 10 yr of follow up
Kondoh *et al.*, 2010 (14)	74	Taniguchi and Kondoh	8.6% incidence at 1 yr; 12.6% incidence at 2 yr; 23.9% incidence at 3 yr
Johannson *et al.*, 2014 (6)	436	IPFnet	5.2 events/100 patient-years
Mura *et al.*, 2012 (8)	83	Akira	18.6% incidence at 3 yr
Ohshimo *et al.*, 2014 (9)	77	IPFnet	7% incidence at 1 yr
Schupp *et al.*, 2015 (10)	71	IPFnet	23% incidence at 2 yr
Song *et al.*, 2011 (13)	461	IPFnet	14.2% incidence at 1 yr; 20.7% incidence at 3 yr
Sugino *et al.*, 2015 (11)	64	IPFnet	28% incidence at 3 yr; 43% incidence at 5 yr
Tomassetti *et al.*, 2013 (53)	122	IPFnet	19% incidence over median follow up of 2.5 yr

Definition of abbreviations: HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; IPFnet = Idiopathic Pulmonary Fibrosis Clinical Trials Network.

*Where specified, studies used definitions for acute exacerbation on the basis of the following: IPFnet: (*1*) previous or concurrent diagnosis of IPF, (*2*) unexplained worsening or development of dyspnea within 30 d, (*3*) HRCT with new bilateral ground-glass opacification/consolidation, (*4*) no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage, (*5*) exclusion of alternative causes. Akira: (*1*) progression of dyspnea over several days to 4 weeks, (*2*) new parenchymal ground-glass abnormalities on X-ray or HRCT, (*3*) decrease in $Pa_{O_2} \geq 10$ mm Hg or increase in alveolar–arterial oxygen gradient within a 1-month period that could not be otherwise explained. Taniguchi and Kondoh: (*1*) worsening dyspnea duration < 1 month; (2) new ground-glass opacities on HRCT in addition to previous honeycomb lesions; (*3*) Pa_{O_2} is 10 mm Hg or more reduced from previous value; (*4*) obvious causes, such as infection, pneumothorax, cancer, pulmonary embolism, or congestive heart failure are absent. Kondoh: (*1*) worsening dyspnea duration < 1 month, (*2*) hypoxemia with a Pa_{O_2}/FI_{O_2} of <225, (*3*) newly developed pulmonary infiltrates on chest radiography, (*4*) absence of apparent infection or heart disease. Kishaba: (*1*) worsening dyspnea duration < 30 d, (*2*) new bilateral infiltration accompanying known IPF or evidence of honeycombing on HRCT (all patients also had negative bronchoalveolar lavage, no echocardiographic evidence of heart failure, and no pulmonary embolism).

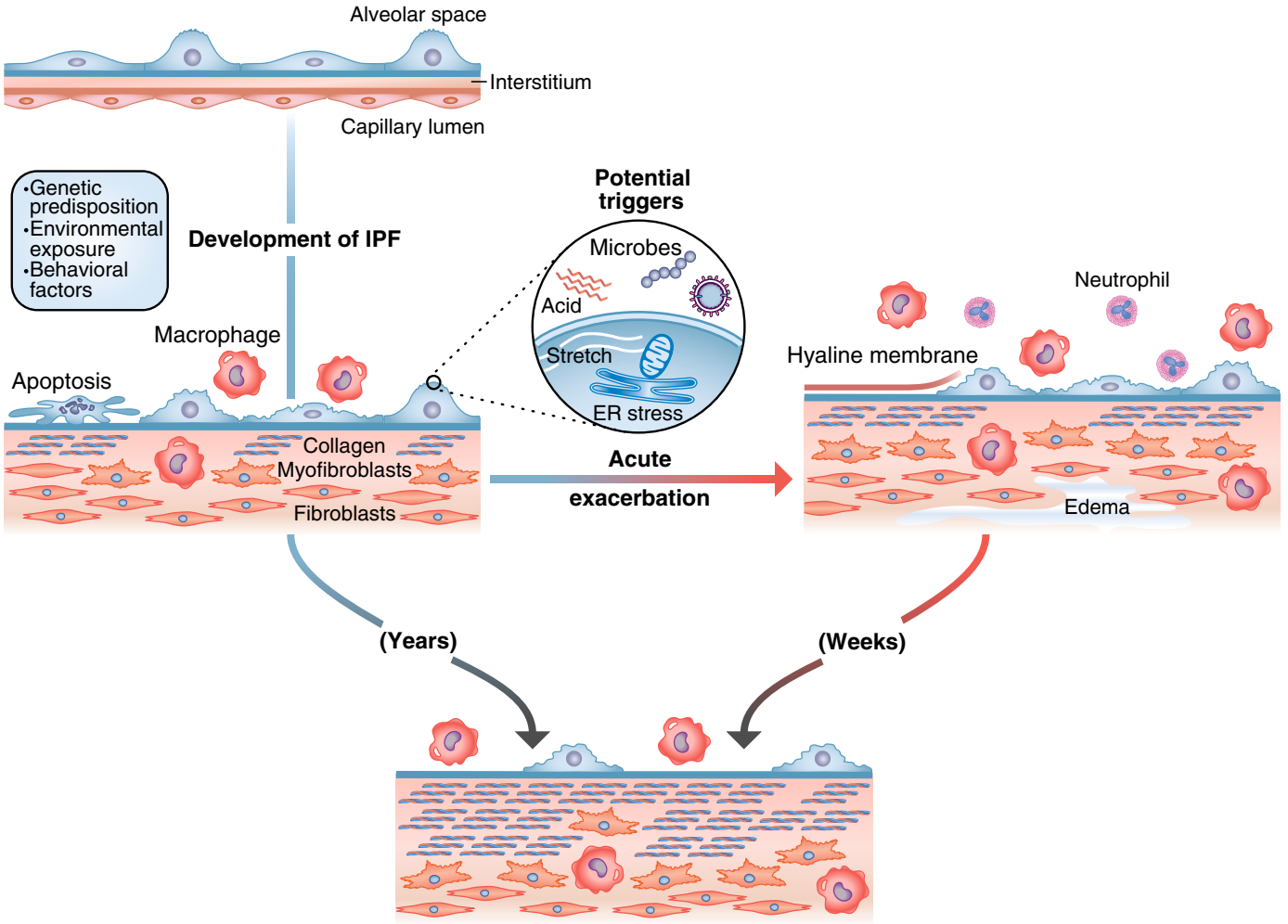

Figure 2. Pathobiological paradigm for acute exacerbation of idiopathic pulmonary fibrosis (IPF). Evidence suggests that the pathobiology of acute exacerbation of IPF involves both chronic factors (e.g., underlying epithelial cell dysfunction and fibroblast accumulation and activation) and acute factors (e.g., acute stress and acute lung injury). In IPF, a combination of genetic, environmental, and behavioral factors are believed to contribute to the development of a fibrotic phenotype characterized by extracellular matrix deposition, parenchymal scar formation, and lung remodeling. Acute exacerbation of IPF is most likely triggered by an acute event (e.g., infection, microaspiration, or mechanical stretch) that leads to widespread acute lung injury (characterized in the early stages by hyaline membrane formation and interstitial edema). Acute exacerbation of IPF may also precipitate acceleration of the underlying chronic factors contributing to the fibrotic process. ER = endoplasmic reticulum.

(19). The causes of ALI are extensive and include infection, aspiration, drugs, massive transfusion, and surgery (20). A sizable body of literature now suggests many of these same conditions may lead to events that are indistinguishable from idiopathic acute exacerbations of IPF (6, 10, 13, 21–34). Therefore, the question is not whether an external insult such as infection or aspiration can cause an acute exacerbation of IPF but whether this is the unrecognized explanation for the majority of events that occur.

Evidence of respiratory viral infection in acute exacerbation of IPF has been detected by pan-viral arrays and multiplex polymerase chain reaction, with respiratory viral RNA present in a minority of patients (32–36). Assessment of *post mortem* samples from patients who died from acute exacerbation of IPF has also identified evidence of occult respiratory infection in some (26, 28) but not all (37) cohorts. Epidemiological support for an infectious etiology comes from studies demonstrating that acute exacerbation of IPF was significantly more common in the winter and spring months (5, 29) and in patients who are taking immunosuppressive medications (5, 6, 38).

Indirect evidence relating microaspiration to acute exacerbation of IPF comes from a *post hoc* analysis of the placebo arms from three clinical trials, showing that acute exacerbation of IPF occurred only in those subjects not on anti-acid therapy (23). This was presumably due to anti-acid therapy reducing the potential for microaspiration-related lung injury. Also supporting this hypothesis are a small case-control study demonstrating elevated pepsin levels in the bronchoalveolar lavage of patients experiencing acute exacerbation of IPF (24) and a small cohort study describing an increased prevalence of gastroesophageal reflux in patients who experienced acute exacerbation of IPF (31).

As mentioned previously, the pathobiology of acute exacerbation of IPF may be related to intrinsic biological dysfunction of the lung that makes individuals with IPF more susceptible to external insults than individuals without IPF. Indirect evidence for this concept comes from comparing outcomes of thoracic surgery in patients with and without IPF. Retrospective studies have looked at the development of acute respiratory deterioration after lung cancer resection in patients with IPF, suggesting an incidence ranging from 7 to 32% (25, 30, 39, 40). Acute exacerbation has also been reported in patients with IPF after surgical lung biopsy and bronchoscopy (21, 22, 27, 41, 42). These data suggest that the IPF lung is uniquely vulnerable to the stress of thoracic surgery (either due to the surgical procedure or ventilator-induced barotrauma, volutrauma, or hyperoxia), supporting an intrinsic pathobiological contribution.

Risk Factors

Acute exacerbation of IPF is more common in patients with physiologically and functionally advanced disease. Low FVC has proven the most consistent risk factor for acute exacerbation of IPF (5, 6, 9, 10, 13, 14, 43). Other physiologic parameters have been associated with increased risk, including low diffusing capacity for carbon monoxide (D_{LCO}) (5, 8, 10, 13, 43), low 6-minute-walk distance (5), pulmonary hypertension (44), poor baseline oxygenation (5, 45), increased dyspnea (5, 14), and recent decline in FVC (14, 45, 46). Whether patients with more advanced IPF are more susceptible to acute exacerbation or are simply more likely to require unscheduled medical care as a result of an acute exacerbation (and therefore be diagnosed) is unknown.

Additional candidate risk factors for acute exacerbation of IPF include younger age (10), comorbid coronary artery disease (5), and higher body mass index (14). The data on smoking and coexisting emphysema as risk factors for acute exacerbation of IPF are discordant (8, 9, 11, 13). A prior history of acute exacerbation has also been associated with increased risk (6, 46). Finally, elevated serum level of Krebs von Lungen-6 (KL-6) at baseline has been associated with increased risk for acute exacerbation of IPF, after adjustment for clinical features including vital capacity (9). Although there has been discussion over the last decade of a possible increased risk of acute exacerbation in patients from East Asian countries, the evidence from randomized, controlled clinical trials does not support this claim (15, 47).

Prognosis

The prognostic implications of an acute exacerbation of IPF are profound. The available data suggest that up to 46% of deaths in IPF are preceded by an acute exacerbation (14, 48, 49), and the median survival of patients with IPF who experience an acute exacerbation is approximately 3 to 4 months (5, 13). Respiratory failure from acute exacerbation of IPF is associated with high in-hospital mortality—in most case series upward of 50% (7, 13, 32, 43, 50–54). Limited data suggest that patients with both acute exacerbation of IPF and suspected acute exacerbation of IPF have a similar prognosis (5, 36).

Several candidate prognostic factors have been identified in acute exacerbation of IPF. These include lower baseline FVC and D_{LCO} (13, 14, 29), more extensive CT abnormalities at the time of acute exacerbation (7, 43, 50, 55), worse oxygenation (13, 56), and bronchoalveolar lavage neutrophil and lymphocyte percentages (13). Several blood-based markers of prognosis have been suggested, including lactate dehydrogenase, C-reactive protein, KL-6, circulating fibrocytes, and anti–heat shock protein 70 autoantibodies (13, 29, 43, 50, 55, 57–60). Recently, a staging system for acute exacerbation of IPF has been proposed that includes several of these factors (43).

Management

There remain no proven, effective therapies for acute exacerbation of IPF. This leaves the patient and clinician to consider supportive care and unproven interventions. Many patients with acute exacerbation still receive systemic corticosteroids, but there is no clear evidence to support this approach. International evidence-based guidelines on the management of IPF make a weak recommendation for the use of corticosteroids in acute exacerbation of IPF, clarifying that the recommendation places a high value on anecdotal reports of benefit and the high mortality of acute exacerbation (1). The management of acute exacerbation of IPF represents an area of major unmet medical need, and it is essential that well-designed, scientifically robust clinical research be conducted over the next decade to provide a much-needed evidence base.

There is little argument that the management of acute exacerbation of IPF should include supportive care, focused on palliation of symptoms and correction of hypoxemia with supplemental oxygen. However, there is debate regarding the lengths to which supportive care should extend—in particular, the use of mechanical ventilation. The international guidelines on the management of IPF make a weak recommendation against the use of mechanical ventilation to treat respiratory failure in IPF, on the basis of an estimated in-hospital mortality of as high as 90% in this population (1). Importantly, these guidelines specify that the use of mechanical ventilation in this setting is "a value-laden decision that is best made by the patient, clinician, and family ahead of time" on the basis of a firm understanding of the patient's goals of care. It may be that more contemporary management approaches to respiratory failure and ALI (e.g., low tidal volume ventilation) are improving in-hospital survival (61); this is an area in need of careful study.

There have been many published articles over the last decade describing various potential therapies for acute exacerbation of IPF (Table 2). Unfortunately, these studies are mostly small and uncontrolled. The only randomized trial to examine an intervention for acute exacerbation of IPF compared procalcitonin (PCT)-guided antibiotic treatment to standard clinician-determined antibiotic treatment (62). In the PCT-guided group, antibiotics were given if PCT was greater than 0.25 ng/ml and were stopped when PCT was less than 0.25 ng/ml. The PCT group experienced a shorter antibiotic duration (median, 5.8 d shorter; $P < 0.001$), but the duration of mechanical ventilation and mortality were similar in both groups.

Observational cohort studies have compared each of the following treatments to a historical or parallel untreated control arm: cyclosporine (63–65), rituximab combined with plasma exchange and intravenous immunoglobulin (66), oral tacrolimus (52), and intravenous thrombomodulin (59, 60, 67). Anti-acid therapy was similarly

Table 2. Selected Potential Therapies for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Potential Therapy*	Study	Summary
Randomized controlled clinical trials		
Nintedanib (preventative therapy)	Richeldi *et al.*, 2011 (75); Richeldi *et al.*, 2014 (15)	Richeldi (2011): 432 patients. Highest dose of nintedanib resulted in lower incidence of acute exacerbation than placebo (2.4 vs. 15.7 per 100 patient-years, $P = 0.02$) Richeldi (2014): Two parallel trials, 1,066 patients. In the first, no significant difference in time to first investigator-reported acute exacerbation was found (HR, 1.15; $P = 0.67$). In the second, there was a significant benefit (HR, 0.38; $P = 0.005$)
Pirfenidone (preventative therapy)	Azuma *et al.*, 2005 (76); Taniguchi *et al.*, 2010 (47)	Azuma: 107 patients. Acute exacerbation occurred exclusively in the placebo group (5 events vs. no events, $P = 0.0031$) Taniguchi: 275 patients. No significant difference in acute exacerbation seen between treatment groups (5.6 vs. 5.5 vs. 4.8%)
Cohort studies		
Anti-acid therapy (preventative therapy)	Controlled: Lee *et al.*, 2013 (23)	Lee: 124 patients compared with 118 control subjects, all from placebo arms of clinical trials. Incidence of acute exacerbation was 0 vs. 8% favoring anti-acid therapy
	Uncontrolled: none	
Corticosteroid monotherapy	Controlled: none Uncontrolled: Akira *et al.*, 1997 (69); Al-Hameed *et al.*, 2004 (51); Suzuki *et al.*, 2011 (30); Tachikawa *et al.*, 2012 (68)	Total of 75 cases reported without control subjects
Cyclophosphamide	Controlled: none Uncontrolled: Akira *et al.*, 2008 (50); Fujimoto *et al.*, 2012 (55); Tachikawa *et al.*, 2012 (68); Yokoyama *et al.*, 2010 (70)	Approximately 128 cases reported without control subjects
Cyclosporine	Controlled: Homma *et al.*, 2005 (64); Inase *et al.*, 2003 (63); Sakamoto, *et al.* 2010 (65)	Homma: 9 patients compared with historical control subjects. Mean survival, 9.9 mo vs. 1.7 mo in control subjects Inase: 7 patients compared with 5 control subjects. Survival, 3 of 7 vs. 0 of 5 Sakamoto: 11 patients compared with 11 control subjects. Survival, 9 of 11 vs. 5 of 11
	Uncontrolled: Fujimoto *et al.*, 2012 (55); Yokoyama *et al.*, 2010 (70)	Approximately 11 cases reported without control subjects
Polymyxin-B immobilized fiber column hemoperfusion	Controlled: none Uncontrolled: Abe *et al.*, 2011 (71); Abe *et al.*, 2012 (56); Oishi *et al.*, 2013 (72); Seo *et al.*, 2006 (73); Tachibana *et al.*, 2011 (74)	Total of 127 cases reported without control subjects
Rituximab, plasma exchange and intravenous immunoglobulin	Controlled: Donahoe *et al.*, 2015 (66)	Donahoe: 11 patients compared with 20 historical control subjects; 1-year survival, 46 vs. 0% favoring rituximab and plasma exchange
	Uncontrolled: none	
Tacrolimus	Controlled: Horita *et al.*, 2011 (52)	Horita: 5 patients compared with 10 control subjects. Median survival, >92 d vs. 38 d favoring tacrolimus
	Uncontrolled: none	
Thrombomodulin	Controlled: Kataoka *et al.*, 2015 (67); Tsushima *et al.*, 2014 (60); Isshiki *et al.*, 2015 (59)	Kataoka: 20 patients compared with 20 historical control subjects. HR, 0.22 for death at 3 mo with treatment Tsushima: 20 patients compared with 6 control subjects. Survival, 13 of 20 vs. 1 of 6 Isshiki: 16 patients compared with 25 control subjects; 3-mo survival, 69 vs. 40%
	Uncontrolled: none	

Definition of abbreviation: HR = hazard ratio.
*Therapies tested in randomized clinical trials without evidence of benefit are not listed in the table. These include acetylcysteine monotherapy, ambrisentan, bosentan, imatinib, IFN-γ, sildenafil, "triple therapy" (prednisone, azathioprine, and acetylcysteine), and warfarin (80–88).

studied as preventative therapy in a large clinical trial cohort with a suggestion of benefit (23). In the above reports, in which an association between the treatment and improved survival was shown, efficacy remains uncertain due to likely confounding. For example, those with greater disease severity may be deemed "too sick" for treatment, or only those who survive long enough to be considered for experimental therapy might be treated. Furthermore, historical control populations may have received less-optimal supportive care and more frequent immunosuppressive therapy. In each of these cases, these unmeasured differences could lead to the apparent benefit of the intervention.

Uncontrolled cohorts have also been published reporting outcomes of patients with acute exacerbation of IPF treated with corticosteroids (30, 51, 68, 69), corticosteroids combined with or followed by other immunomodulatory therapies (50, 55, 66, 68, 70), and polymyxin B-immobilized fiber column perfusion (56, 71–74). Unfortunately, it is not possible to determine whether changes in the clinical status of these patients were due to the intervention, the natural history of their disease, or other unmeasured factors. Potential therapies, including the ones listed here, should be studied in randomized, controlled trials to better understand their potential benefit.

Results from clinical trials of nintedanib and pirfenidone (both currently approved for the treatment of IPF) suggest IPF therapies may help prevent the development of acute exacerbation of IPF. The data for nintedanib are more substantial, as acute exacerbation was a key secondary endpoint in all three placebo-controlled clinical trials. A 432-subject phase 2 trial of nintedanib demonstrated a delay in time to first investigator-reported acute exacerbation with nintedanib therapy (75), a finding supported but not confirmed by the 1,066-subject phase 3 program (15). Most significant in the phase 3 program was the reduction in centrally adjudicated confirmed or suspected acute exacerbation of IPF with nintedanib therapy (5.7% on placebo vs. 1.9% on nintedanib, $P = 0.01$) (15). A 107-subject phase 2 trial of pirfenidone was stopped early because of a statistically significant (but numerically small) reduction in acute exacerbation in those receiving pirfenidone, but a 275-subject subsequent trial did not replicate these results (47, 76). The definitive phase 3 clinical trials of pirfenidone did not report acute exacerbations as an endpoint (77, 78). Pirfenidone has been suggested to reduce the risk of acute exacerbation postoperatively, but these data are observational and at high risk for confounding (79). Additional data are needed to fully understand the impact of IPF therapies on the risk and outcome of acute exacerbation.

Other potential IPF therapies tested in clinical trials showed no impact on (acetylcysteine monotherapy, bosentan, IFN-γ, sildenafil) or possibly increased risk for (ambrisentan, imatinib, "triple therapy" with combination prednisone/azathioprine/acetylcysteine, and warfarin) the development of acute exacerbation of IPF (80–89).

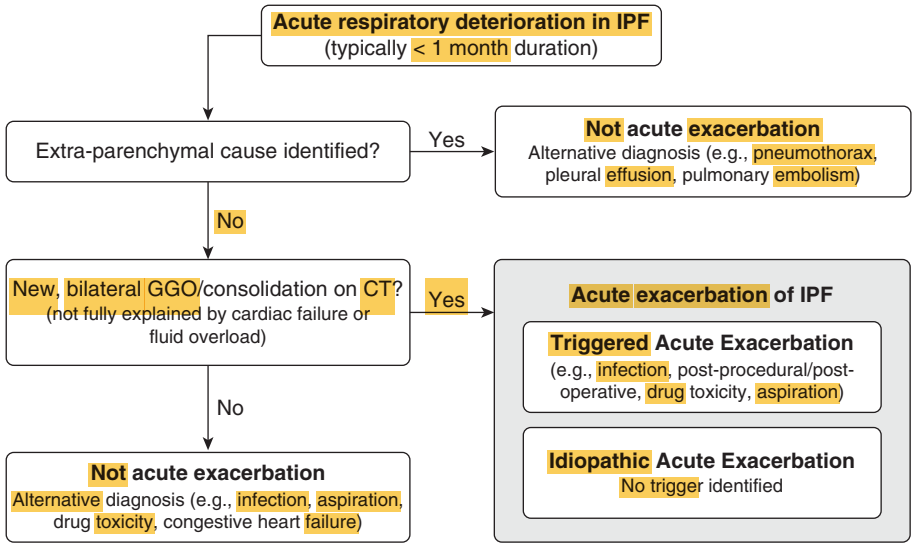

Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification (GGO)/consolidation on computed tomography (CT) that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found.

Proposed Conceptual Framework for Acute Respiratory Deterioration in IPF

To better reflect the current state of knowledge regarding acute exacerbation of IPF and improve the feasibility of future research into its etiology and treatment, the working group iteratively developed a new conceptual framework for acute respiratory deterioration in IPF (Figure 3) and revised the definition and diagnostic criteria for acute exacerbation of IPF (Table 3). The major changes are described in more detail below.

Removing "Idiopathic" from the Definition of Acute Exacerbation

There was a majority opinion that the definition and diagnostic criteria for acute exacerbation of IPF should include any acute respiratory event characterized by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload. This latter qualification parallels the Berlin criteria for acute respiratory distress syndrome and is intended to exclude isolated congestive heart failure. There was general recognition, based on the literature review conducted and summarized above, that there is little clinical or biological support for distinguishing idiopathic from nonidiopathic respiratory events. Defining acute exacerbation as

Table 3. Proposed Revised Definition and Diagnostic Criteria for Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Revised definition
An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Revised diagnostic criteria
• Previous or concurrent diagnosis of IPF*
• Acute worsening or development of dyspnea typically <1 mo duration
• Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern†
• Deterioration not fully explained by cardiac failure or fluid overload

Definition of abbreviation: IPF = idiopathic pulmonary fibrosis.
Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all four diagnostic criteria owing to missing computed tomography data should be termed "suspected acute exacerbations."
*If the diagnosis of IPF is not previously established, this criterion can be met by the presence of radiologic and/or histopathologic changes consistent with usual interstitial pneumonia pattern on the current evaluation.
†If no previous computed tomography is available, the qualifier "new" can be dropped.

idiopathic was seen as unnecessarily restrictive.

The revised definition of acute exacerbation of IPF is: an acute, clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality. This broader definition results in criteria that are more inclusive and feasible for clinicians and clinical trialists who have struggled with the historical requirement for exclusion of causes, in particular respiratory infection. The working group recognized that idiopathic events may still prove pathobiologically distinct, and the proposed subcategorization of acute exacerbations as either "triggered" or "idiopathic" allows for continued study of this hypothesis.

Changing the Diagnostic Criteria Time Interval from 30 Days to "Typically Less Than 1 Month"

There was a majority opinion that the 30-day time period was arbitrary and should be made more flexible to allow for cases that fall outside the time window by a few days to weeks. The phrase "typically less than 1 month" was believed to retain precision but allow for the inclusion of exceptions that physicians believe clinically represent acute exacerbations. The working group recognized that a more flexible time interval may lead to heterogeneity among clinical trial endpoint definitions for acute exacerbation and that this could complicate comparisons between trials.

Requiring Exclusion of Acute Respiratory Deterioration Caused by Cardiac Failure or Fluid Overload in the Diagnostic Criteria

Borrowing from the Berlin definition for acute respiratory distress syndrome (90), this qualifier was added to exclude patients with cardiogenic pulmonary edema that is believed to have a distinct pathobiology and favorable prognosis compared with other causes of acute respiratory deterioration with bilateral radiologic involvement.

Other Considered Changes

Several other possible changes were discussed, including expanding the definition of acute exacerbation to include other interstitial lung diseases, adding quantitative criteria for worsening (e.g., oxygenation or physiology), and creating a "subacute exacerbation" category for deteriorations that were more gradual. In the end, the majority opinion was that these additions were not adequately supported by the available evidence or were outside the scope of this revision.

Management Considerations

Clinicians managing a patient with IPF experiencing an acute respiratory deterioration should continue to look carefully for extraparenchymal causes (e.g., pulmonary embolism, pneumothorax, pleural effusion) and attempt to determine if there are radiologic features (i.e., new bilateral ground-glass opacification/consolidation) or histopathologic features (i.e., evidence of ALI superimposed on established fibrosis with features of usual interstitial pneumonia) to support the diagnosis of acute exacerbation. Central to this evaluation is high-resolution CT of the chest, which should be obtained in all patients in whom it can be safely performed. Transbronchial biopsy is of limited utility given the small amount of lung tissue sampled and the confounding effects of artifact on recognition of ALI, and surgical lung biopsy should generally be avoided due to its high morbidity in the nonelective setting (91). In the revised definition and diagnostic criteria for acute exacerbation of IPF proposed herein, exclusion of infection or other potential triggers is no longer required for the diagnosis of acute exacerbation; the only qualifier is that clinicians determine that the radiologic findings of new bilateral ground-glass opacification/consolidation are not fully explained by the presence of cardiac failure or fluid overload (the rationale for which is described above). This change should not discount the potential clinical relevance of identifying a triggering infection when present, as its treatment may be important to the overall management of the patient. Future studies are needed to test whether aggressive investigation (e.g., bronchoalveolar lavage, bronchoscopic cryobiopsy) of patients with acute exacerbation of IPF improves outcomes.

Future Directions

Acute exacerbations of IPF are important events in the natural history of IPF. Although many questions remain unanswered regarding the etiology, pathobiology, and clinical management of acute exacerbations, progress has been made over the previous decade that allows for reassessment of the fundamental assumptions underlying its definition and diagnostic criteria. By providing a consensus view of acute exacerbation from a diverse committee of investigators in the field, the working group authors hope that this report will lead to a shared framework for researchers and clinicians moving forward. We believe the time has come to aggressively and collaboratively test novel hypotheses regarding the mechanisms behind acute exacerbation of IPF and novel approaches to prevention, early detection, and treatment in well-designed, properly controlled clinical trials. ■

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References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, *et al*.; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement. Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
2. Collard HR, Moore BB, Flaherty KR, Brown KK, Kaner RJ, King TE Jr, Lasky JA, Loyd JE, Noth I, Olman MA, *et al*.; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007;176: 636–643.
3. Ryerson CJ, Cottin V, Brown KK, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm. *Eur Respir J* 2015;46:512–520.
4. Atkins CP, Loke YK, Wilson AM. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. *Respir Med* 2014;108:376–387.
5. Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C; IPFnet investigators. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res* 2013;14:73.
6. Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, Kim DS, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014;43:1124–1131.
7. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006;27:143–150.
8. Mura M, Porretta MA, Bargagli E, Sergiacomi G, Zompatori M, Sverzellati N, Taglieri A, Mezzasalma F, Rottoli P, Saltini C, *et al*. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. *Eur Respir J* 2012;40:101–109.
9. Ohshimo S, Ishikawa N, Horimasu Y, Hattori N, Hirohashi N, Tanigawa K, Kohno N, Bonella F, Guzman J, Costabel U. Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. *Respir Med* 2014;108:1031–1039.
10. Schupp JC, Binder H, Jäger B, Cillis G, Zissel G, Müller-Quernheim J, Prasse A. Macrophage activation in acute exacerbation of idiopathic pulmonary fibrosis. *Plos One* 2015;10:e0116775.
11. Sugino K, Nakamura Y, Ito T, Isshiki T, Sakamoto S, Homma S. Comparison of clinical characteristics and outcomes between combined pulmonary fibrosis and emphysema associated with usual interstitial pneumonia pattern and non-usual interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis* 2015;32:129–137.
12. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, Yi ES, Ryu JH. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest* 2010;137:129–137.
13. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011;37:356–363.
14. Kondoh Y, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, Sakamoto K, Johkoh T, Nishimura M, Ono K, *et al*. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2010;27:103–110.
15. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, *et al*.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
16. de Andrade J, Schwarz M, Collard HR, Gentry-Bumpass T, Colby T, Lynch D, Kaner RJ; IPFnet Investigators. The Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet): diagnostic and adjudication processes. *Chest* 2015;148:1034–1042.
17. de Hemptinne Q, Remmelink M, Brimioulle S, Salmon I, Vincent JL. ARDS: a clinicopathological confrontation. *Chest* 2009;135: 944–949.
18. Ferguson ND, Frutos-Vivar F, Esteban A, Fernández-Segoviano P, Aramburu JA, Nájera L, Stewart TE. Acute respiratory distress syndrome: underrecognition by clinicians and diagnostic accuracy of three clinical definitions. *Crit Care Med* 2005;33: 2228–2234.
19. Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. *Mayo Clin Proc* 1990;65:1538–1548.
20. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest* 2012;122:2731–2740.
21. Bando M, Ohno S, Hosono T, Yanase K, Sato Y, Sohara Y, Hironaka M, Sugiyama Y. Risk of acute exacerbation after video-assisted thoracoscopic lung biopsy for interstitial lung disease. *J Bronchology Interv Pulmonol* 2009;16:229–235.
22. Ghatol A, Ruhl AP, Danoff SK. Exacerbations in idiopathic pulmonary fibrosis triggered by pulmonary and nonpulmonary surgery: a case series and comprehensive review of the literature. *Lung* 2012;190: 373–380.
23. Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, Yow E, Raghu G; IPFnet Investigators. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. *Lancet Respir Med* 2013;1:369–376.
24. Lee JS, Song JW, Wolters PJ, Elicker BM, King TE Jr, Kim DS, Collard HR. Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. *Eur Respir J* 2012;39:352–358.
25. Mizuno Y, Iwata H, Shirahashi K, Takamochi K, Oh S, Suzuki K, Takemura H. The importance of intraoperative fluid balance for the prevention of postoperative acute exacerbation of idiopathic pulmonary fibrosis after pulmonary resection for primary lung cancer. *Eur J Cardiothorac Surg* 2012;41:e161–e165.
26. Oda K, Ishimoto H, Yamada S, Kushima H, Ishii H, Imanaga T, Harada T, Ishimatsu Y, Matsumoto N, Naito K, *et al*. Autopsy analyses in acute exacerbation of idiopathic pulmonary fibrosis. *Respir Res* 2014;15:109.
27. Sakamoto S, Homma S, Mun M, Fujii T, Kurosaki A, Yoshimura K. Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients: a retrospective study. *Intern Med* 2011;50:77–85.
28. Santos GC, Parra ER, Stegun FW, Cirqueira CS, Capelozzi VL. Immunohistochemical detection of virus through its nuclear cytopathic effect in idiopathic interstitial pneumonia other than acute exacerbation. *Braz J Med Biol Res* 2013;46:985–992.
29. Simon-Blancal V, Freynet O, Nunes H, Bouvry D, Naggara N, Brillet PY, Denis D, Cohen Y, Vincent F, Valeyre D, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: outcome and prognostic factors. *Respiration* 2012;83:28–35.
30. Suzuki H, Sekine Y, Yoshida S, Suzuki M, Shibuya K, Yonemori Y, Hiroshima K, Nakatani Y, Mizuno S, Takiguchi Y, *et al*. Risk of acute exacerbation of interstitial pneumonia after pulmonary resection for lung cancer in patients with idiopathic pulmonary fibrosis based on preoperative high-resolution computed tomography. *Surg Today* 2011;41:914–921.
31. Tcherakian C, Cottin V, Brillet PY, Freynet O, Naggara N, Carton Z, Cordier JF, Brauner M, Valeyre D, Nunes H. Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. *Thorax* 2011;66:226–231.
32. Tomioka H, Sakurai T, Hashimoto K, Iwasaki H. Acute exacerbation of idiopathic pulmonary fibrosis: role of *Chlamydophila pneumoniae* infection. *Respirology* 2007;12:700–706.
33. Ushiki A, Yamazaki Y, Hama M, Yasuo M, Hanaoka M, Kubo K. Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia. *Respir Investig* 2014;52:65–70.
34. Wootton SC, Kim DS, Kondoh Y, Chen E, Lee JS, Song JW, Huh JW, Taniguchi H, Chiu C, Boushey H, *et al*. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:1698–1702.
35. Bando M, Ohno S, Oshikawa K, Takahashi M, Okamoto H, Sugiyama Y. Infection of TT virus in patients with idiopathic pulmonary fibrosis. *Respir Med* 2001;95:935–942.
36. Huie TJ, Olson AL, Cosgrove GP, Janssen WJ, Lara AR, Lynch DA, Groshong SD, Moss M, Schwarz MI, Brown KK, *et al*. A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes. *Respirology* 2010;15:909–917.
37. Konishi K, Gibson KF, Lindell KO, Richards TJ, Zhang Y, Dhir R, Bisceglia M, Gilbert S, Yousem SA, Song JW, *et al*. Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;180:167–175.

38. Petrosyan F, Culver DA, Reddy AJ. Role of bronchoalveolar lavage in the diagnosis of acute exacerbations of idiopathic pulmonary fibrosis: a retrospective study. *BMC Pulm Med* 2015;15:70.
39. Choi SM, Lee J, Park YS, Cho YJ, Lee CH, Lee SM, Yoon HI, Yim JJ, Lee JH, Yoo CG, *et al*. Postoperative pulmonary complications after surgery in patients with interstitial lung disease. *Respiration* 2014;87: 287–293.
40. Watanabe A, Higami T, Ohori S, Koyanagi T, Nakashima S, Mawatari T. Is lung cancer resection indicated in patients with idiopathic pulmonary fibrosis? *J Thorac Cardiovasc Surg* 2008;136: 1357–1363, 1363.e1–2.
41. Sakamoto K, Taniguchi H, Kondoh Y, Wakai K, Kimura T, Kataoka K, Hashimoto N, Nishiyama O, Hasegawa Y. Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures. *Respir Med* 2012;106:436–442.
42. Samejima J, Tajiri M, Ogura T, Baba T, Omori T, Tsuboi M, Masuda M. Thoracoscopic lung biopsy in 285 patients with diffuse pulmonary disease. *Asian Cardiovasc Thorac Ann* 2015;23:191–197.
43. Kishaba T, Tamaki H, Shimaoka Y, Fukuyama H, Yamashiro S. Staging of acute exacerbation in patients with idiopathic pulmonary fibrosis. *Lung* 2014;192:141–149.
44. Judge EP, Fabre A, Adamali HI, Egan JJ. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. *Eur Respir J* 2012;40:93–100.
45. Kondoh Y, Taniguchi H, Ebina M, Azuma A, Ogura T, Taguchi Y, Suga M, Takahashi H, Nakata K, Sugiyama Y, *et al*. Risk factors for acute exacerbation of idiopathic pulmonary fibrosis: extended analysis of pirfenidone trial in Japan. *Respir Investig* 2015;53:271–278.
46. Reichmann WM, Yu YF, Macaulay D, Wu EQ, Nathan SD. Change in forced vital capacity and associated subsequent outcomes in patients with newly diagnosed idiopathic pulmonary fibrosis. *BMC Pulm Med* 2015;15:167.
47. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, *et al*.; Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:821–829.
48. Jeon K, Chung MP, Lee KS, Chung MJ, Han J, Koh WJ, Suh GY, Kim H, Kwon OJ. Prognostic factors and causes of death in Korean patients with idiopathic pulmonary fibrosis. *Respir Med* 2006;100: 451–457.
49. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, Bando M, Sugiyama Y, Takahashi H. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med* 2014;190:773–779.
50. Akira M, Kozuka T, Yamamoto S, Sakatani M. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008;178:372–378.
51. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004;11:117–122.
52. Horita N, Akahane M, Okada Y, Kobayashi Y, Arai T, Amano I, Takezawa T, To M, To Y. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2011;50: 189–195.
53. Tomassetti S, Ruy JH, Gurioli C, Ravaglia C, Buccioli M, Tantalocco P, Decker PA, Cavazza A, Dubini A, Agnoletti V, *et al*. The effect of anticoagulant therapy for idiopathic pulmonary fibrosis in real life practice. *Sarcoidosis Vasc Diffuse Lung Dis* 2013;30:121–127.
54. Usui Y, Kaga A, Sakai F, Shiono A, Komiyama K, Hagiwara K, Kanazawa M. A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia. *BMJ Open* 2013;3:3.
55. Fujimoto K, Taniguchi H, Johkoh T, Kondoh Y, Ichikado K, Sumikawa H, Ogura T, Kataoka K, Endo T, Kawaguchi A, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. *Eur Radiol* 2012;22:83–92.
56. Abe S, Azuma A, Mukae H, Ogura T, Taniguchi H, Bando M, Sugiyama Y. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. *Intern Med* 2012;51:1487–1491.
57. Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, *et al*. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:588–594.
58. Kahloon RA, Xue J, Bhargava A, Csizmadia E, Otterbein L, Kass DJ, Bon J, Soejima M, Levesque MC, Lindell KO, *et al*. Patients with idiopathic pulmonary fibrosis with antibodies to heat shock protein 70 have poor prognoses. *Am J Respir Crit Care Med* 2013;187: 768–775.
59. Isshiki T, Sakamoto S, Kinoshita A, Sugino K, Kurosaki A, Homma S. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. *Respiration* 2015;89:201–207.
60. Tsushima K, Yamaguchi K, Kono Y, Yokoyama T, Kubo K, Matsumura T, Ichimura Y, Abe M, Terada J, Tatsumi K. Thrombomodulin for acute exacerbations of idiopathic pulmonary fibrosis: a proof of concept study. *Pulm Pharmacol Ther* 2014;29: 233–240.
61. Rush B, Wiskar K, Berger L, Griesdale D. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: a nationwide retrospective cohort analysis. *Respir Med* 2016; 111:72–76.
62. Ding J, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. *Int J Med Sci* 2013; 10:903–907.
63. Inase N, Sawada M, Ohtani Y, Miyake S, Isogai S, Sakashita H, Miyazaki Y, Yoshizawa Y. Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis with corticosteroid. *Intern Med* 2003;42:565–570.
64. Homma S, Sakamoto S, Kawabata M, Kishi K, Tsuboi E, Motoi N, Yoshimura K. Cyclosporin treatment in steroid-resistant and acutely exacerbated interstitial pneumonia. *Intern Med* 2005;44: 1144–1150.
65. Sakamoto S, Homma S, Miyamoto A, Kurosaki A, Fujii T, Yoshimura K. Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010;49:109–115.
66. Donahoe M, Valentine VG, Chien N, Gibson KF, Raval JS, Saul M, Xue J, Zhang Y, Duncan SR. Autoantibody-targeted treatments for acute exacerbations of idiopathic pulmonary fibrosis. *Plos One* 2015;10: e0127771.
67. Kataoka K, Taniguchi H, Kondoh Y, Nishiyama O, Kimura T, Matsuda T, Yokoyama T, Sakamoto K, Ando M. Recombinant human thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2015;148:436–443.
68. Tachikawa R, Tomii K, Ueda H, Nagata K, Nanjo S, Sakurai A, Otsuka K, Kaji R, Hayashi M, Katakami N, *et al*. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. *Respiration* 2012;83: 20–27.
69. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. *AJR Am J Roentgenol* 1997;168: 79–83.
70. Yokoyama T, Kondoh Y, Taniguchi H, Kataoka K, Kato K, Nishiyama O, Kimura T, Hasegawa R, Kubo K. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010;49: 1509–1514.
71. Abe S, Hayashi H, Seo Y, Matsuda K, Kamio K, Saito Y, Usuki J, Azuma A, Kudo S, Gemma A. Reduction in serum high mobility group box-1 level by polymyxin B-immobilized fiber column in patients with idiopathic pulmonary fibrosis with acute exacerbation. *Blood Purif* 2011;32:310–316.
72. Oishi K, Mimura-Kimura Y, Miyasho T, Aoe K, Ogata Y, Katayama H, Murata Y, Ueoka H, Matsumoto T, Mimura Y. Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. *Cytokine* 2013;61:84–89.
73. Seo Y, Abe S, Kurahara M, Okada D, Saito Y, Usuki J, Azuma A, Koizumi K, Kudoh S. Beneficial effect of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment on acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2006;45: 1033–1038.

74. Tachibana K, Inoue Y, Nishiyama A, Sugimoto C, Matsumuro A, Hirose M, Kitaichi M, Akira M, Arai T, Hayashi S, *et al*. Polymyxin-B hemoperfusion for acute exacerbation of idiopathic pulmonary fibrosis: serum IL-7 as a prognostic marker. *Sarcoidosis Vasc Diffuse Lung Dis* 2011;28:113–122.
75. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, *et al*. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011;365:1079–1087.
76. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, *et al*. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005;171:1040–1047.
77. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, *et al*.; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370: 2083–2092.
78. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarcberg J, *et al*.; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377:1760–1769.
79. Iwata T, Yoshida S, Nagato K, Nakajima T, Suzuki H, Tagawa T, Mizobuchi T, Ota S, Nakatani Y, Yoshino I. Experience with perioperative pirfenidone for lung cancer surgery in patients with idiopathic pulmonary fibrosis. *Surg Today* 2015;45:1263–1270.
80. Martinez FJ, de Andrade JA, Anstrom KJ, King TE Jr, Raghu G; Idiopathic Pulmonary Fibrosis Clinical Research Network. Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2093–2101.
81. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012;366:1968–1977.
82. Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW; Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010;363:620–628.
83. King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, *et al*.; INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; 374:222–228.
84. King TE Jr, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, Valeyre D, Leconte I, Morganti A, Roux S, *et al*. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;184:92–99.
85. Noth I, Anstrom KJ, Calvert SB, de Andrade J, Flaherty KR, Glazer C, Kaner RJ, Olman MA; Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet). A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;186:88–95.
86. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, *et al*.; ARTEMIS-IPF Investigators. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med* 2013;158: 641–649.
87. Bando M, Hosono T, Mato N, Nakaya T, Yamasawa H, Ohno S, Sugiyama Y. Long-term efficacy of inhaled N-acetylcysteine in patients with idiopathic pulmonary fibrosis. *Intern Med* 2010;49: 2289–2296.
88. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR; Imatinib-IPF Study Investigators. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 2010;181:604–610.
89. Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, Sasaki H. Anticoagulant therapy for idiopathic pulmonary fibrosis. *Chest* 2005;128:1475–1482.
90. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307: 2526–2533.
91. Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality following surgical lung biopsy for interstitial lung disease in the USA: 2000-2011. *Am J Respir Crit Care Med* 2016;193: 1161–1167.