Acute exacerbation of idiopathic pulmonary fibrosis: shifting the paradigm

Christopher J. Ryerson[1], Vincent Cottin[2], Kevin K. Brown[3] and Harold R. Collard[4]

Number 2 in the series "Rare pulmonary diseases and orphan drugs"
Edited by S. Harari and M. Humbert

Affiliations:
[1]Dept of Medicine, University of British Columbia, Vancouver, BC, Canada.
[2]Service de Pneumologie, Centre national de référence des maladies pulmonaires rares, Hôpital Louis Pradel, Université Claude Bernard Lyon 1, Lyon, France.
[3]Dept of Medicine, National Jewish Health, Denver, CO, USA.
[4]Dept of Medicine, University of California San Francisco, San Francisco, CA, USA.

Correspondence: Harold R. Collard, MD 505 Parnassus Avenue, Box 0111, San Francisco, CA 94143, USA.
E-mail: hal.collard@ucsf.edu

ABSTRACT The goal of this review is to summarise the clinical features, management, and prognosis of acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF). AE-IPF has previously been defined based on clinical and radiological features that include the subacute onset of dyspnoea, bilateral ground glass changes on chest high-resolution computed tomography, and the absence of an identifiable aetiology. The annual incidence of AE-IPF is typically reported at 5–15%, but is less common in mild disease. Features of diffuse alveolar damage are present when a biopsy is performed. Idiopathic pulmonary fibrosis (IPF) patients with acute respiratory worsening are often initially treated with high dose corticosteroids and antimicrobials; however, there are no clear data to support these therapies, and the short-term mortality of AE-IPF is ~50%. Recent studies have shown that the features and prognosis of AE-IPF are similar to other causes of acute respiratory worsening, including infection, aspiration, air pollution and mechanical injury to the alveolar epithelium. Based on this emerging evidence, we propose a novel approach to the classification of acute respiratory worsening events in patients with IPF that focuses on clinical and radiological findings consistent with an underlying pathobiology of diffuse alveolar damage.

@ERSpublications
A review summarising the features, management, and prognosis of acute exacerbations of idiopathic pulmonary fibrosis http://ow.ly/Oer3e

Previous article in this series: No. 1: Collard HR, Bradford WZ, Cottin V, *et al.* A new era in idiopathic pulmonary fibrosis: considerations for future clinical trials. *Eur Respir J* 2015; 46: 243–249.

Received: March 14 2015 | Accepted after revision: June 07 2015

Support statement: C.J. Ryerson is supported by a Career Investigator Award from the Michael Smith Foundation for Health Research. K.K. Brown, H.R. Collard and V. Cottin report no relevant funding.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease that is characterised by worsening lung function and early mortality [1]. IPF has a median survival of ~3 years from the time of diagnosis [2, 3], and most patients die from progressive respiratory failure [4–7]. These deaths are frequently precipitated by acute respiratory worsening, including acute exacerbations of IPF (AE-IPF), which are traditionally defined as an acute worsening of dyspnoea and lung function with an unknown aetiology [8]. AE-IPF has an annual incidence of up to 20% [9–23], predominantly occurs in physiologically advanced disease [23–26], and is typically associated with a median survival of less than 3 months [22, 23, 27–30].

Consensus AE-IPF diagnostic criteria were published in 2007, with the goal of providing a framework for subsequent research that would advance our understanding of acute respiratory worsening in patients with IPF [8]. These initial AE-IPF criteria were predominantly based on expert opinion, and new data have provided further details on these events. The goal of this review is to summarise what is now known about the clinical features, management and prognosis of AE-IPF with a focus on recent findings. We highlight emerging evidence that justifies a re-evaluation of the definition of AE-IPF, and we propose a novel approach to the classification of acute respiratory worsening events in patients with IPF.

Definition

AE-IPF is currently defined as an acute worsening of dyspnoea and lung function with an unidentifiable cause [8]. The following diagnostic criteria for AE-IPF have been widely used in recent publications: 1) a previous or concurrent diagnosis of IPF; 2) unexplained worsening of dyspnoea within the past 30 days; 3) high-resolution computed tomography (HRCT) with new bilateral ground-glass opacity or consolidation; and 4) exclusion of alternative causes, including pulmonary infection by endotracheal aspirate or bronchoalveolar lavage.

There are two major limitations to this approach. First, the criteria for AE-IPF are difficult to satisfy. For example, exclusion of underlying infection by bronchoscopy is often not clinically feasible given the significant hypoxaemia typical of an AE-IPF, and the frequent inability to confidently exclude an underlying infection results in a large number of "suspected" AE-IPF cases that cannot be confirmed [24]. Second, this approach defines AE-IPF as an idiopathic event characterised by the development of pathological diffuse alveolar damage (DAD) [20, 31–34], whereas emerging evidence demonstrates that AE-IPF has similar clinical features and prognosis compared with non-idiopathic causes of acute respiratory worsening in IPF (*e.g.* infection or aspiration) [24]. Comparable data exist in patients without chronic lung disease, with multiple aetiologies of DAD having a similar presentation and poor prognosis [35]. These limitations and recent findings suggest that the need to distinguish idiopathic from non-idiopathic acute respiratory worsening is both challenging and not supported by the available evidence and that the focus should perhaps shift to the pathobiology of AE-IPF (*i.e.* acute injury to the lung resulting in DAD).

Epidemiology

The annual incidence of AE-IPF varies between 1 and 20% of IPF patients depending on the population studied (fig. 1) [9–23]. The annual incidence of adjudicated AE-IPF events is under 5% in the placebo groups from most recent clinical trials [11–19], although the incidence is generally higher for investigator-reported AE-IPF and in patients with more severe IPF. For example, the higher incidence in the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) study (4.4% over a period of 12 weeks) may be due to the advanced fibrosis of this study population, as well as the smaller sample size and shorter duration of follow-up that decrease precision in the estimation of annual AE-IPF incidence [14]. A slightly higher annual incidence of ~10% is also observed in many prospective cohort studies, predominantly in Japanese and Korean populations [20–22]. This may similarly reflect higher rates of investigator-reported AE-IPF or the use of modified AE-IPF criteria in these studies.

AE-IPF is a major cause of morbidity and mortality in patients with IPF, accounting for over half of all hospital admissions [23], and up to 40% of all deaths [5]. The prevalence of IPF has recently been estimated at nearly 500 per 100 000 person-years in an American population who were over 65 years of age [36]. Based on an annual AE-IPF incidence of at least 5%, these data suggest that confirmed AE-IPF occurs at a rate of over 25 per100 000 person-years in an elderly population, with suspected AE-IPF events occurring at a several-fold higher rate. AE-IPF and suspected AE-IPF therefore represent a significant burden given the high individual and societal costs associated with these events.

Aetiology and risk factors

The most consistently identified risk factors for AE-IPF are measurements of IPF severity, including dyspnoea, forced vital capacity and multiple radiological features [21, 23–26, 37]. Additional non-validated risk factors for AE-IPF include a high baseline Krebs von den Lungen-6 (KL-6) level [38, 39], increased body mass index [21], and the absence of a smoking history [23]. AE-IPF is idiopathic by definition;

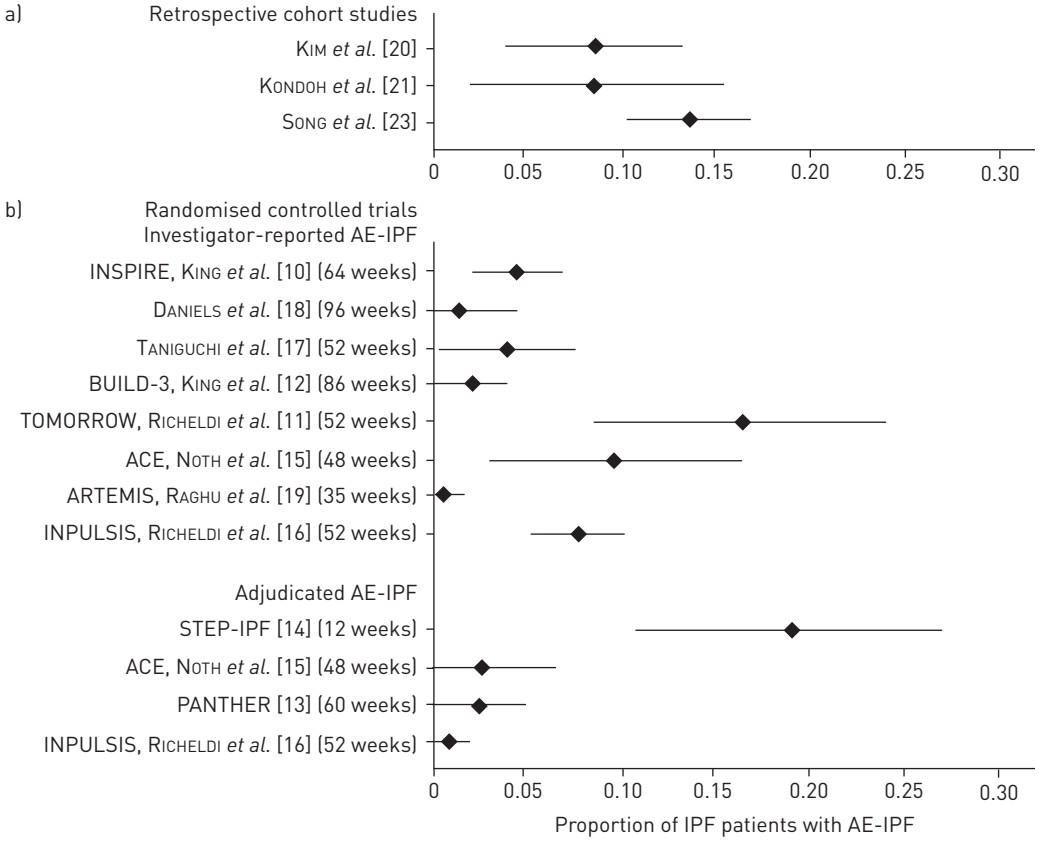

FIGURE 1 Annual incidence of acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) from a) cohort studies and b) placebo groups of randomised controlled trials. The annual incidence is proportionately extrapolated for trials that were greater than or less than 1 year in duration. The duration of each clinical trial is reported in weeks, with the median length of observation reported for studies with variable treatment duration. IPF: idiopathic pulmonary fibrosis.

however, there are increasing data that suggest similar events can occur following an identifiable trigger. For example, idiopathic AE-IPF is more common in the winter months [24, 30], and in patients that are immunosuppressed [9], indicating that some cases of idiopathic AE-IPF may be triggered by a preceding infection [40–42]. Additional potential triggers that can lead to a similar presentation in patients with IPF include aspiration [43, 44], pollution [45], thoracic surgical procedures [20, 25, 26, 37, 46–50], cryobiopsy [51] and, possibly, bronchoalveolar lavage [20, 52]. AE-IPF has also been reported following non-pulmonary surgery [47], potentially related to mechanical trauma secondary to mechanical ventilation. Acute lung injury similar to AE-IPF can also occur secondary to direct pulmonary toxicity from medications or thoracic radiation [53, 54], particularly chemotherapy and immunosuppressive biological therapies. The risk of drug-induced exacerbation appears to be higher in patients with underlying usual interstitial pneumonia compared with patients with other pre-existing patterns [55]. Some clinical trials suggest an increased incidence of acute respiratory worsening or hospitalisation in IPF patients on active treatment [9, 15, 19], supporting the possibility that some cases of AE-IPF could be secondary to the adverse effects of medication even in the absence of significant immunosuppression [15, 19].

Clinical features and diagnostic evaluation

AE-IPF is characterised by a subacute worsening of dyspnoea, generally within the preceding 30 days [8], although additional symptoms are frequently present. AE-IPF is more common in patients with advanced fibrosis [21, 23–26, 37], but it can be the initial manifestation of IPF [20, 56, 57]. Clinical features are similar in patients with other causes of acute respiratory worsening [24]. HRCT shows a background of fibrotic interstitial lung disease, with superimposed bilateral ground glass changes, with or without consolidation [58]. Transbronchial and surgical lung biopsies are generally avoided since they infrequently alter management and have a high risk of complications. When performed, surgical lung biopsy demonstrates a background of usual interstitial pneumonia and superimposed DAD with or without concurrent organising pneumonia [20, 31–34].

DOI: 10.1183/13993003.00419-2015

Management

Patients with AE-IPF generally require hospitalisation and supplemental oxygen. Mechanical ventilation should be considered only following a clear discussion of the patient's wishes and expectations, including the likelihood of recovery. Noninvasive mechanical ventilation may eliminate the need for intubation in some IPF patients with acute respiratory failure [59, 60]. Antibiotics are typically prescribed in AE-IPF since it is difficult to confidently exclude acute bacterial infection. Corticosteroids are often prescribed based on their potential to treat acute lung injury or organising pneumonia, and are recommended for the treatment of AE-IPF despite very limited evidence [1]. Some AE-IPF patients are prescribed a pulse dose of corticosteroids (*e.g.* methylprednisolone 0.5–1 g intravenously daily for 3 days). Lower initial doses of prednisone (*e.g.* 1 $mg \cdot kg^{-1}$ per day) are predominantly used in patients with milder disease. Most groups start corticosteroids after sampling for bacterial cultures and initiation of broad-spectrum antibiotics, occasionally including co-trimoxazole for treatment of possible *Pneumocystis jirovecii*. Both approaches are typically followed by a rapid taper and cessation of prednisone within several weeks, based on the rationale that chronic prednisone use is likely harmful in IPF [9]. Several other investigational agents have been studied in AE-IPF including polymyxin B-immobilised fibre cartridge [61–64], tacrolimus [65] and cyclosporine [66–68]; however, there are currently insufficient data to support the routine use of these medications.

Prevention of AE-IPF and other causes of acute respiratory worsening is important given their high mortality rate and poor response to treatment. The primary strategy for AE-IPF prevention involves targeting specific triggers that can lead to diffuse lung injury. The risk of infection can be reduced by standard infection control measures such as hand washing and vaccination against influenza and pneumococcus. Specific members of the *Streptococcus* and *Staphylococcus* genera are associated with IPF progression [69], and the role of the lung microbiome in AE-IPF requires further study. Anti-acid therapy may slow IPF progression and reduce the risk of acute respiratory worsening secondary to aspiration [70], particularly in patients that have subjective symptoms or objective evidence of acid reflux. Pollution control measures may also have a role in reducing the risk of AE-IPF in regions that have poor air quality [45].

The role of anti-fibrotic therapy in preventing AE-IPF is unclear. Anti-fibrotic therapies could theoretically reduce the frequency of AE-IPF by slowing IPF progression or directly reducing the risk of AE-IPF, and could also minimise the consequences of an AE-IPF by improving the ability of the IPF lung to undergo healing following exposure to a potential trigger. Nintedanib is a tyrosine kinase inhibitor that slows the rate of IPF progression [16]. A phase II placebo-controlled study showed that nintedanib reduced the rate of investigator-reported AE-IPF [11]; however, similar benefits were observed in only one of two phase III studies [16]. The potential benefit of nintedanib on centrally adjudicated AE-IPF is of unclear significance and requires additional study. Pirfenidone reduced the incidence of AE-IPF in one randomised controlled trial [71]; however, this potential benefit has not been tested in subsequent studies [72, 73]. Additional studies are required to determine whether anti-fibrotic therapies can reduce the incidence or improve the outcome of AE-IPF.

Prognosis

AE-IPF is the most common cause of death in some IPF cohorts [5, 57]. The short-term mortality of AE-IPF is ~50% [22, 23, 27–30], and typically exceeds 90% in patients admitted to an intensive care unit [59, 74]. Patients that survive the initial hospitalisation continue to have a high rate of mortality over the next year. All-cause respiratory hospitalisation is a major independent predictor of mortality in IPF [75], and this is probably related to the high mortality associated with AE-IPF. Prognostic variables include serum lactate dehydrogenase [22, 30], KL-6 [22], pro-calcitonin [76], circulating fibrocytes [77], severity of hypoxaemia [22], multiple radiological findings [22, 58, 76, 78], and pre-exacerbation lung physiology [30]. These variables require validation and additional studies are required to determine the prognostic value of serial changes in potential biomarkers, and whether these, or other variables, can be combined into a single prediction tool that can stratify patient's risk in a clinical setting. The prognosis of acute respiratory worsening in IPF is similar in patients with definite/suspected AE-IPF compared with other causes of respiratory worsening [24].

Discussion

Emerging evidence argues against AE-IPF necessarily being an idiopathic event. The hallmark pathological pattern of an idiopathic AE-IPF is DAD [20, 31–34], which is known to occur following identifiable triggers such as infection and aspiration, suggesting that these triggers may be responsible for many AE-IPF episodes. Further, recent data suggest that differentiating clinically "idiopathic" from "non-idiopathic" events has little prognostic relevance.

We propose that AE-IPF should be defined by pathobiology, not clinical aetiology. In this paradigm, AE-IPF would be defined as an acute respiratory worsening of any aetiology characterised by the development of DAD, and its diagnosis would hinge on clinical and radiological evidence supporting that process (table 1), acknowledging that pathology is seldom obtained in this setting. This definition of

TABLE 1 Current and proposed definitions and diagnostic criteria for acute exacerbations of idiopathic pulmonary fibrosis (IPF)

	Current	Proposed
Definition	An idiopathic acute respiratory worsening in a patient with IPF	An acute respiratory worsening characterised by diffuse alveolar damage in a patient with IPF
Diagnostic criteria	Previous or concurrent diagnosis of IPF Unexplained worsening or development of dyspnoea within the past 30 days	Previous or concurrent diagnosis of IPF Acute worsening of dyspnoea from a parenchymal cause (generally over <30 days)
	HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern	HRCT with new bilateral ground-glass abnormality with or without consolidation
	No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage	Clinical presentation consistent with diffuse alveolar damage
	Exclusion of alternative causes, including left heart failure, pulmonary embolism and an identifiable cause of acute lung injury	

HRCT: high-resolution computed tomography.

AE-IPF simplifies the approach to diagnosis by allowing diagnostic criteria to be met without performance of invasive procedures (*e.g.* bronchoscopy), and identifies a clinical phenotype with shared presentations and disease behaviour (fig. 2). Expanding the diagnostic criteria of AE-IPF to allow multiple triggers has been suggested previously [79–81], and is similar to the approach taken in acute exacerbations of asthma and chronic obstructive pulmonary disease. This would help standardise the terminology of AE-IPF with other chronic respiratory diseases and reduce the current confusion that arises from the use of similar terms that have distinct meanings in these different diseases. We believe these advantages should push stakeholders to consider revising the definition and diagnostic criteria for AE-IPF.

Figure 3 illustrates the general approach to the diagnosis of AE-IPF based on this proposed definition. IPF patients with an acute respiratory worsening should undergo clinical evaluation to look for potential

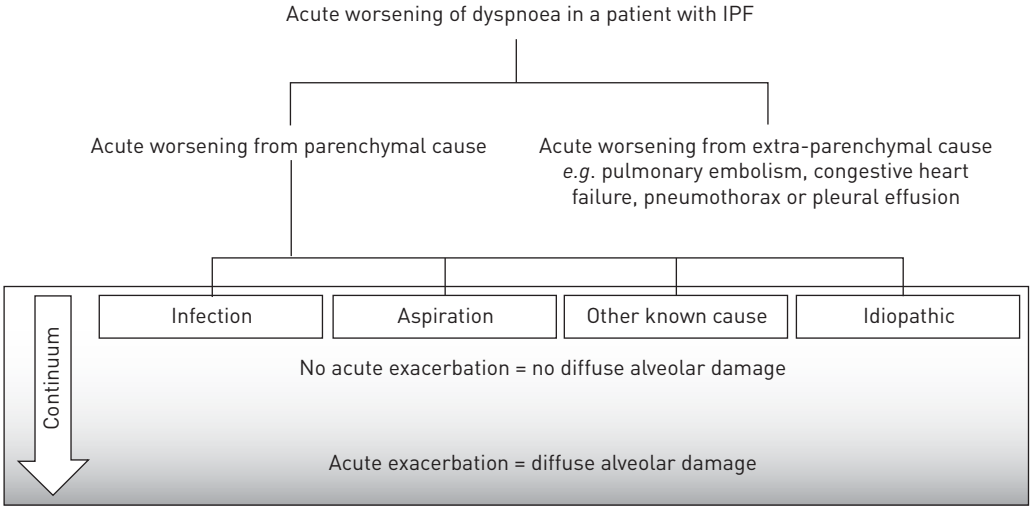

FIGURE 2 Proposed classification of acute respiratory worsening in idiopathic pulmonary fibrosis (IPF).

DOI: 10.1183/13993003.00419-2015

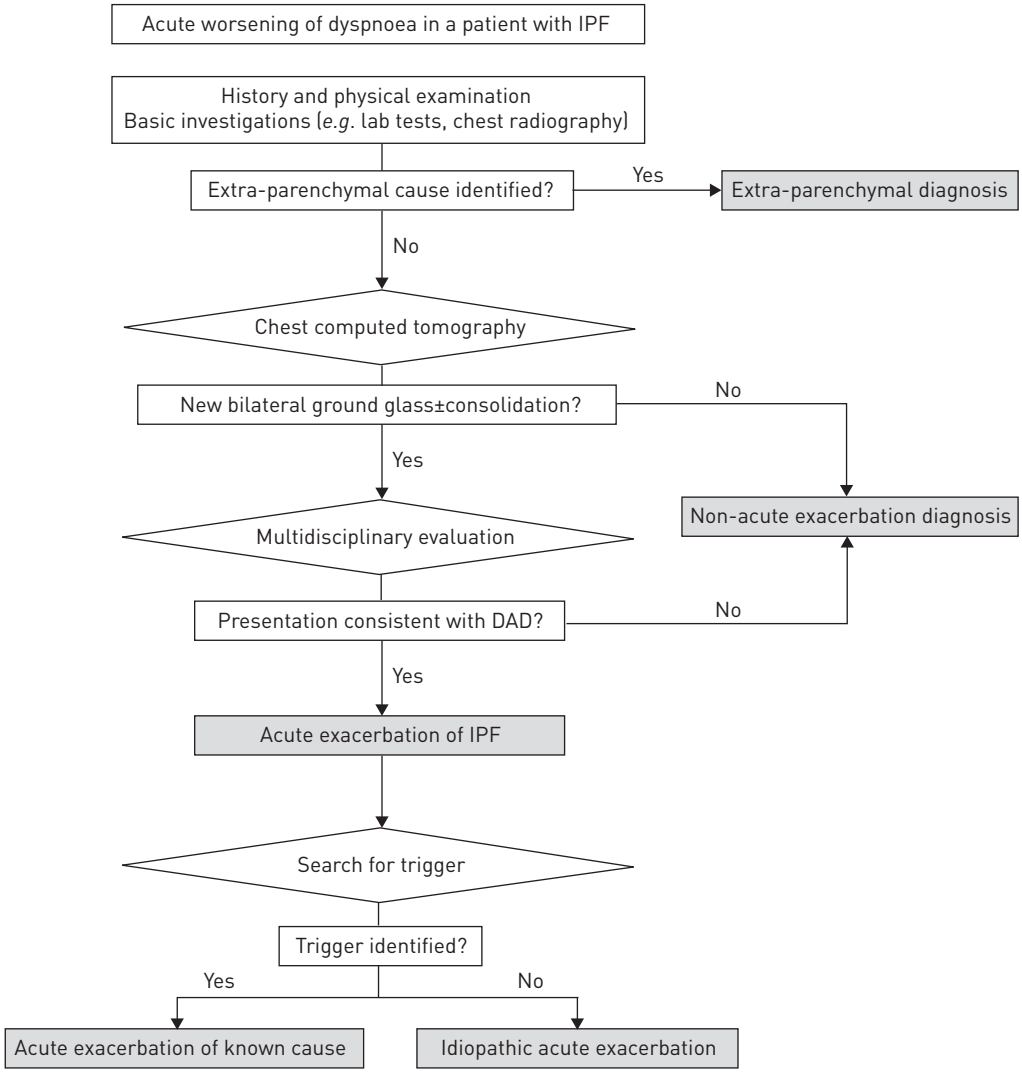

FIGURE 3 Proposed approach for the evaluation of acute respiratory worsening in idiopathic pulmonary fibrosis (IPF). DAD: diffuse alveolar damage.

parenchymal (*e.g.* infection or aspiration) and extra-parenchymal (*e.g.* pulmonary embolism, congestive heart failure, pneumothorax or pleural effusion) causes. In the absence of one of these conditions, an integrated assessment of the presentation and HRCT images would be used to determine if these suggest the presence of pathological DAD, as well as looking for evidence of potential triggers (*e.g.* infection or aspiration). This approach requires careful multidisciplinary evaluation and clinical judgment that incorporates longitudinal data, similar to the disease behaviour approach proposed in the recent update to the multidisciplinary classification of the idiopathic interstitial pneumonias [82]. Future studies would be required to validate this approach and demonstrate that clinical assessment can accurately identify patients with histopathological DAD.

The proposed definition of AE-IPF emphasises DAD as a final common pathway that can be caused by multiple aetiologies, and implies that idiopathic events are simply unrecognised episodes of triggered DAD. DAD is similarly the pathological correlate of acute respiratory distress syndrome (ARDS) that can occur following a large number of triggers in patients without chronic lung disease. There are important differences in the clinical features and prognosis of AE-IPF and ARDS despite the presence of DAD in both conditions. This may reflect the underlying biology of IPF and an impaired ability of the IPF lung to undergo normal wound healing following a trigger of DAD. High-dose corticosteroids are frequently prescribed in AE-IPF; however, these have no clear benefit in non-IPF patients with ARDS [83]. The treatment approach in AE-IPF will need to be reconsidered if future research suggests DAD in a patient with IPF is pathobiologically similar to DAD in ARDS. Additional research may also identify management strategies of AE-IPF that target pathways that are activated prior to the development of DAD.

AE-IPF has been proposed as an important end-point for clinical trials [24]; however, a key limitation is the relative rarity of idiopathic AE-IPF and the limited power to detect benefit of potential therapies. The proposed definition would substantially increase the number of events that are labelled AE-IPF, and thus improve the power of clinical trials that use AE-IPF incidence as a key end-point. This assumes, however, that these added events have the same likelihood of demonstrating a treatment effect as the more restricted "idiopathic" cases. Trials would capture all AE-IPF events and then subcategorise them as idiopathic or non-idiopathic to test this assumption. Previous studies have also categorised AE-IPF as definite or suspected [24], reflecting the extent of the diagnostic evaluation and particularly whether infection was confidently excluded using bronchoalveolar lavage. A similar approach may still be required in a clinical trial setting for patients that are felt to have an AE-IPF but do not meet all the proposed diagnostic criteria (*e.g.* due to lack of a HRCT). Additional studies are also needed to determine whether a marker of severity should be included in the criteria for AE-IPF, similar to the specific threshold of hypoxaemia that is required for the diagnosis of ARDS.

The proposed changes in AE-IPF definition and diagnostic criteria indicate the need for new data regarding the clinical features of AE-IPF. The wide variability in incidence is probably related to the use of multiple definitions for AE-IPF, as well as other population differences such as ethnicity/genetic background, IPF severity and the use of concurrent medications. Several previous randomised controlled trials have defined AE-IPF based on reporting from individual study investigators, however, up to 85% of these events are not confirmed following central adjudication [16]. In addition, multiple studies have included admission to hospital as a key criterion for defining AE-IPF [12, 19, 21, 23], excluding milder events that were managed as an outpatient and potentially omitting severe events that resulted in death prior to admission. The inconsistencies and limitations of previous studies highlight the importance of acquiring new data from well-phenotyped prospective cohorts that will allow us to determine the incidence of AE-IPF, identify its risk factors, and evaluate management strategies. The relative rarity of these events suggests that these research questions should be a key focus of large multicentre collaborations.

Conclusions and future directions

The historical definition and diagnostic criteria for AE-IPF have helped to advance research in IPF by providing a standardised classification approach to a poorly understood, life-threatening event. Recent studies have used these criteria to show that many events identified clinically as idiopathic may instead have identifiable triggers, and that AE-IPF share similar clinical features with non-idiopathic events. Based on these results, we have proposed a revised definition for AE-IPF that focuses the condition around the presence of DAD regardless of cause. A group of experts has recently been established that will create an updated consensus definition and diagnostic criteria for AE-IPF. We hope that our initial proposal will prompt further discussion by this group and that future research will test this approach and further advance our knowledge of AE-IPF.

References

1 Raghu G, Collard HR, Egan JJ, *et al.* 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 Bjoraker JA, Ryu JH, Edwin MK, *et al.* Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998; 157: 199–203.
3 Ley B, Ryerson CJ, Vittinghoff E, *et al.* A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012; 156: 684–691.
4 Martinez FJ, Safrin S, Weycker D, *et al.* The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005; 142: 963–967.
5 Natsuizaka M, Chiba H, Kuronuma K, *et al.* Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med* 2014; 190: 773–779.
6 Hutchinson JP, McKeever TM, Fogarty AW, *et al.* Increasing global mortality from idiopathic pulmonary fibrosis in the twenty-first century. *Ann Am Thorac Soc* 2014; 11: 1176–1185.
7 King TE Jr, Albera C, Bradford WZ, *et al.* All-cause mortality rate in patients with idiopathic pulmonary fibrosis. Implications for the design and execution of clinical trials. *Am J Respir Crit Care Med* 2014; 189: 825–831.
8 Collard HR, Moore BB, Flaherty KR, *et al.* Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176: 636–643.
9 Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, *et al.* Prednisone, azathioprine, and *N*-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968–1977.
10 King TE Jr, Albera C, Bradford WZ, *et al.* Effect of interferon γ-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; 374: 222–228.
11 Richeldi L, Costabel U, Selman M, *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med* 2011; 365: 1079–1087.
12 King TE Jr, Brown KK, Raghu G, *et al.* BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 92–99.
13 Idiopathic Pulmonary Fibrosis Clinical Research Network, Martinez FJ, de Andrade JA, *et al.* Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2093–2101.

 DOI: 10.1183/13993003.00419-2015

14 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010; 363: 620–628.
15 Noth I, Anstrom KJ, Calvert SB, *et al.* A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012; 186: 88–95.
16 Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
17 Taniguchi H, Ebina M, Kondoh Y, *et al.* Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010; 35: 821–829.
18 Daniels CE, Lasky JA, Limper AH, *et al.* Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 2010; 181: 604–610.
19 Raghu G, Behr J, Brown KK, *et al.* Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med* 2013; 158: 641–649.
20 Kim DS, Park JH, Park BK, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; 27: 143–150.
21 Kondoh Y, Taniguchi H, Katsuta T, *et al.* Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2010; 27: 103–110.
22 Kishaba T, Tamaki H, Shimaoka Y, *et al.* Staging of acute exacerbation in patients with idiopathic pulmonary fibrosis. *Lung* 2014; 192: 141–149.
23 Song JW, Hong SB, Lim CM, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; 37: 356–363.
24 Collard HR, Yow E, Richeldi L, *et al.* Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. *Respir Res* 2013; 14: 73.
25 Suzuki H, Sekine Y, Yoshida S, *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.
26 Shintani Y, Ohta M, Iwasaki T, *et al.* Predictive factors for postoperative acute exacerbation of interstitial pneumonia combined with lung cancer. *Gen Thorac Cardiovasc Surg* 2010; 58: 182–185.
27 Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. *Eur J Intern Med* 2008; 19: 227–235.
28 Huie TJ, Olson AL, Cosgrove GP, *et al.* A detailed evaluation of acute respiratory decline in patients with fibrotic lung disease: aetiology and outcomes. *Respirology* 2010; 15: 909–917.
29 Tachibana K, Inoue Y, Nishiyama A, *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.
30 Simon-Blancal V, Freynet O, Nunes H, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: outcome and prognostic factors. *Respiration* 2012; 83: 28–35.
31 Churg A, Müller NL, Silva CI, *et al.* Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. *Am J Surg Pathol* 2007; 31: 277–284.
32 Ambrosini V, Cancellieri A, Chilosi M, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. *Eur Respir J* 2003; 22: 821–826.
33 Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. *Chest* 2005; 128: 3310–3315.
34 Silva CI, Müller NL, Fujimoto K, *et al.* Acute exacerbation of chronic interstitial pneumonia: high-resolution computed tomography and pathologic findings. *J Thorac Imaging* 2007; 22: 221–229.
35 Parambil JG, Myers JL, Aubry MC, *et al.* Causes and prognosis of diffuse alveolar damage diagnosed on surgical lung biopsy. *Chest* 2007; 132: 50–57.
36 Raghu G, Chen SY, Yeh WS, *et al.* Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med* 2014; 2: 566–572.
37 Sugiura H, Takeda A, Hoshi T, *et al.* Acute exacerbation of usual interstitial pneumonia after resection of lung cancer. *Ann Thorac Surg* 2012; 93: 937–943.
38 Kishaba T, Shimaoka Y, Fukuyama H, *et al.* A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema. *BMJ Open* 2012; 2: e000988.
39 Ohshimo S, Ishikawa N, Horimasu Y, *et al.* Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. *Respir Med* 2014; 108: 1031–1039.
40 Wootton SC, Kim DS, Kondoh Y, *et al.* Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 1698–1702.
41 Tomioka H, Sakurai T, Hashimoto K, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: role of *Chlamydophila pneumoniae* infection. *Respirology* 2007; 12: 700–706.
42 Ushiki A, Yamazaki Y, Hama M, *et al.* Viral infections in patients with an acute exacerbation of idiopathic interstitial pneumonia. *Respir Invest* 2014; 52: 65–70.
43 Lee JS, Song JW, Wolters PJ, *et al.* Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. *Eur Respir J* 2012; 39: 352–358.
44 Tcherakian C, Cottin V, Brillet PY, *et al.* Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. *Thorax* 2011; 66: 226–231.
45 Johannson KA, Vittinghoff E, Lee K, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014; 43: 1124–1131.
46 Mizuno Y, Iwata H, Shirahashi K, *et al.* 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.
47 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.
48 Bando M, Ohno S, Hosono T, *et al.* Risk of acute exacerbation after video-assisted thoracoscopic lung biopsy for interstitial lung disease. *J Bronchology Interv Pulmonol* 2009; 16: 229–235.
49 Sakamoto S, Homma S, Mun M, *et al.* Acute exacerbation of idiopathic interstitial pneumonia following lung surgery in 3 of 68 consecutive patients: a retrospective study. *Intern Med* 2011; 50: 77–85.

50 Kondoh Y, Taniguchi H, Kitaichi M, *et al.* Acute exacerbation of interstitial pneumonia following surgical lung biopsy. *Respir Med* 2006; 100: 1753–1759.
51 Casoni GL, Tomassetti S, Cavazza A, *et al.* Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014; 9: e86716.
52 Sakamoto K, Taniguchi H, Kondoh Y, *et al.* Acute exacerbation of IPF following diagnostic bronchoalveolar lavage procedures. *Respir Med* 2012; 106: 436–442.
53 Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, *et al.* Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. *Semin Arthritis Rheum* 2011; 41: 256–264.
54 Takeda A, Enomoto T, Sanuki N, *et al.* Acute exacerbation of subclinical idiopathic pulmonary fibrosis triggered by hypofractionated stereotactic body radiotherapy in a patient with primary lung cancer and slightly focal honeycombing. *Radiat Med* 2008; 26: 504–507.
55 Kenmotsu H, Naito T, Kimura M, *et al.* The risk of cytotoxic chemotherapy-related exacerbation of interstitial lung disease with lung cancer. *J Thorac Oncol* 2011; 6: 1242–1246.
56 Sakamoto K, Taniguchi H, Kondoh Y, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis as the initial presentation of the disease. *Eur Respir Rev* 2009; 18: 129–132.
57 Daniels CE, Yi ES, Ryu JH. Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. *Eur Respir J* 2008; 32: 170–174.
58 Akira M, Kozuka T, Yamamoto S, *et al.* Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; 178: 372–378.
59 Rangappa P, Moran JL. Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis. *Crit Care Resusc* 2009; 11: 102–109.
60 Yokoyama T, Kondoh Y, Taniguchi H, *et al.* Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010; 49: 1509–1514.
61 Abe S, Azuma A, Mukae H, *et al.* Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. *Intern Med* 2012; 51: 1487–1491.
62 Takada T, Asakawa K, Sakagami T, *et al.* Effects of direct hemoperfusion with polymyxin B-immobilized fiber on rapidly progressive interstitial lung diseases. *Intern Med* 2014; 53: 1921–1926.
63 Abe S, Hayashi H, Seo Y, *et al.* 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.
64 Seo Y, Abe S, Kurahara M, *et al.* Beneficial effect of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment on acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2006; 45: 1033–1038.
65 Horita N, Akahane M, Okada Y, *et al.* Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2011; 50: 189–195.
66 Sakamoto S, Homma S, Miyamoto A, *et al.* Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med* 2010; 49: 109–115.
67 Homma S, Sakamoto S, Kawabata M, *et al.* Cyclosporin treatment in steroid-resistant and acutely exacerbated interstitial pneumonia. *Intern Med* 2005; 44: 1144–1150.
68 Inase N, Sawada M, Ohtani Y, *et al.* Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis with corticosteroid. *Intern Med* 2003; 42: 565–570.
69 Han MK, Zhou Y, Murray S, *et al.* Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. *Lancet Respir Med* 2014; 2: 548–556.
70 Lee JS, Collard HR, Anstrom KJ, *et al.* 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.
71 Azuma A, Nukiwa T, Tsuboi E, *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.
72 King TE Jr, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
73 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.
74 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.
75 du Bois RM, Weycker D, Albera C, *et al.* Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 184: 459–466.
76 Usui Y, Kaga A, Sakai F, *et al.* A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia. *BMJ Open* 2013; 3: e002971.
77 Moeller A, Gilpin SE, Ask K, *et al.* Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009; 179: 588–594.
78 Fujimoto K, Taniguchi H, Johkoh T, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: high-resolution CT scores predict mortality. *Eur Radiol* 2012; 22: 83–92.
79 Antoniou KM, Wells AU. Acute exacerbations of idiopathic pulmonary fibrosis. *Respiration* 2013; 86: 265–274.
80 Ryerson CJ, Collard HR. Acute exacerbations complicating interstitial lung disease. *Curr Opin Pulm Med* 2014; 20: 436–441.
81 Johannson K, Collard HR. Acute exacerbation of idiopathic pulmonary fibrosis: a proposal. *Curr Respir Care Rep* 2013; 2: DOI: 10.1007/s13665-013-0065-x.
82 Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.
83 Steinberg KP, Hudson LD, Goodman RB, *et al.* Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1671–1684.

 DOI: 10.1183/13993003.00419-2015