Acute exacerbations of idiopathic pulmonary fibrosis: tough to define; tougher to manage

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Idiopathic pulmonary fibrosis (IPF) is a chronic, often fatal fibrotic lung disease that typically affects adults over the age of 60 [1]. The disease is characterised by progressive fibrosis of the lung interstitium, which is associated with pronounced architectural distortion, a decline in lung volumes, and impaired gas exchange. The average survival from the time of diagnosis is between 3 and 5 years [2]. There is significant heterogeneity, however, among individual patients as the clinical course is both variable and unpredictable [3]. Some patients have a protracted course with little functional impairment. In others, periods of relative stability can be punctuated by an acute respiratory worsening, labelled as acute exacerbations of IPF that can precipitate dramatic respiratory failure [4]. Rarely, acute exacerbation of IPF is the initial manifestation of IPF leading to death within months.

Acute exacerbations of IPF often constitute the primary cause of death in patients with IPF, recently reported as high as 40% in a large Japanese cohort [3]. Exacerbations have an annual incidence of 4–20%, with those patients with physiologically advanced disease at greatest risk for acute deterioration [5]. Outcomes following an acute exacerbation are generally poor with an expected median survival of less than 3 months [6].

Acute exacerbation of IPF has been defined as an acute clinically significant deterioration of unidentifiable cause. The first proposal for diagnostic criteria was published in 2007 with the intent to enable future research into the aetiology and management of acute exacerbations of IPF. Those criteria included: 1) a previous or concurrent diagnosis of IPF; 2) unexplained worsening of dyspnoea within the past 30 days; 3) high-resolution computed tomography evidence of new bilateral ground-glass opacities or consolidation; and 4) exclusion of alternative causes, including pulmonary infection by endotracheal aspirate or bronchoalveolar lavage [4]. These criteria have been widely used in recent publications including the INPULSIS trials evaluating the efficacy of the novel anti-fibrotic agent, nintedanib, in the long-term management of IPF [7]. In the INPULSIS trials, patients who failed to meet all criteria due to missing data, but had no alternative explanation for their deterioration were designated as "suspected acute exacerbation".

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In this issue of the *European Respiratory Journal*, Collard *et al.* [8] broaden our understanding of the natural history of IPF and shed new light on the diagnosis and management of acute exacerbations using data captured from the INPULSIS trials. This represents the largest prospective dataset on acute exacerbation of IPF published to date. The authors firstly remind us of the trend towards a reduction in investigator reported exacerbations in favour of nintedanib *versus* placebo (RR 0.65, 95% CI 0.40–1.04; p=0.07). They also highlight that in these trials, an independent adjudication committee composed of three expert clinicians reviewed all available data and blindly re-evaluated all events reported by site investigators. Following this review process, only about half of all clinical events reported by the investigators were classified as either confirmed or suspected acute exacerbation of IPF. The impact of nintedanib on rate of acute exacerbation was significant when those patients with adjudicated confirmed or suspected exacerbations were evaluated (RR 0.37, 95% CI 0.19–0.73; p=0.003).

This and newer data regarding the natural history and pathogenesis of acute exacerbation of IPF have shown two major limitations to the working acute exacerbation definition: 1) the criteria proposed are difficult to satisfy, even in expert IPF centres, and 2) the importance of defining an acute deterioration as "idiopathic" is overstated. Some of the criteria used to define an acute exacerbation of IPF are difficult to apply in a clinical setting, especially the requirement for invasive microbiologic assessment that is associated with substantial risk in acutely deteriorating patients. This is particularly relevant given the >90% mortality rate in patients admitted to intensive care units and the weak recommendation against the use of mechanical ventilation to treat IPF-related respiratory failure by international guidelines [9, 10]. Thus, it is often not possible to confidently exclude infection as a cause of respiratory deterioration resulting in a large number of "suspected" acute exacerbations of IPF that cannot be "confirmed". For example, in the STEP-IPF trial, a *post hoc* analysis of respiratory events demonstrated the incidence of acute exacerbation of IPF to be 4 per 100 patient years when strict adherence to the 2007 criteria was utilised [11]. The incidence increased to 20 per 100 patient-years when patients with "definite" and "suspected" acute exacerbations of IPF were included. Furthermore, in three IPFnet trials, only 33% of investigator-reported acute exacerbations of IPF met criteria following centralised adjudication [12]. These discrepancies explain the generally higher incidence of acute exacerbation reported in cohort and registry studies, where the potential for misclassifying respiratory deteriorations of known cause as acute exacerbation of IPF is a distinct possibility [5].

When the 2007 acute exacerbation of IPF criteria were proposed it was uncertain whether the diffuse alveolar damage observed during an acute exacerbation, which is associated with the intrinsic acceleration of the underlying fibrotic process, differed from the acute lung injury observed after triggered events (*e.g.* infection, aspiration, drug exposure, lung surgery) [4]. With the emergence of advanced high-throughput microbiological techniques, preliminary evidence points to bacterial and viral infection being able to act as cofactors in the progression of IPF. Molyneaux *et al.* [13] found that increased bacterial load from bronchoalveolar lavage (BAL) fluid at the time of diagnosis identified patients with more rapidly progressive IPF and higher risk of mortality. Furthermore, culture independent techniques demonstrate that acute exacerbation of IPF is associated with an increased BAL bacterial burden compared to stable disease [14]. Evidence supporting the role of infection is further corroborated by the data presented by Collard *et al.* [8] in this issue of the *European Respiratory Journal* data that demonstrate that acute exacerbation of IPF is more common in winter months, potentially suggesting viral respiratory infection as a risk factor for acute decline. Given the poor sensitivity of standard culture methods one can hypothesise that the label of an "idiopathic acute exacerbation of IPF" may be more reflective of the limited utility of clinically available diagnostic investigations rather than a clear understanding of the underlying pathophysiology driving disease progression.

The requirement to define an acute deterioration as idiopathic in nature is further questioned by data suggesting that clinical features and outcomes in "idiopathic" acute exacerbations of IPF are similar to those encountered with respiratory worsening triggered by external events [11]. The data presented by Collard *et al.* [8] clearly support this notion as acute respiratory events identified as acute exacerbations of IPF by local site investigators, whether adjudicated as confirmed or suspected acute exacerbations of IPF, or other type of respiratory worsening, were associated with poor outcome with 180 day mortality exceeding 50% in placebo treated patients. The authors correctly point out that such similarities in outcomes do not dictate a unified management plan for acute exacerbations of IPF, as aetiological differences remain potential therapeutic targets for future investigation.

Nonetheless, these findings further strengthen the statement of an international multidisciplinary working group which provided a comprehensive update on acute exacerbations of IPF in 2016 [5]. There was a majority opinion amongst the experts that the diagnostic criteria for an acute exacerbation should include any acute respiratory event characterised by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload. This definition highlights that there is little clinical or

biological support to distinguish idiopathic from non-idiopathic respiratory events in IPF. A broadened definition should be more feasible and reproducible in clinical practice. No doubt, this change will impact the design of future clinical trials in IPF, and may reignite the interest in using acute exacerbation of IPF as the primary outcome; akin to clinical trials in other chronic respiratory conditions, such as asthma and chronic obstructive pulmonary disease.

Much of this information is confirmatory and supports the recent change in the diagnostic criteria for acute exacerbations of IPF, but the work by Collard *et al.* [8] in the *European Respiratory Journal* provides some novel and indeed rather intriguing possibilities. The data suggest that treatment with nintedanib may not only reduce the risk of developing an acute respiratory deterioration, but also reduce mortality following acute exacerbation of IPF. Although the findings were not statistically significant, the magnitude of the effect, an approximate 40% reduction in mortality following acute exacerbation of IPF, is certainly enticing. This observation requires further validation in patients managed with nintedanib, and probably also pirfenidone, or other novel anti-fibrotic agents.

Despite the general advancement of our understanding of the pathobiology of acute exacerbations, there remain numerous unanswered questions, especially as it pertains to therapeutic strategies. The prevention and successful management of acute exacerbations of IPF represent major unmet needs that will require dedicated multi-disciplinary, multi-site, international, collaborative, translational research. Progress has been made in providing a clinically useful definition of acute exacerbation, which in itself has been tough. Treating or preventing these deadly events will be even tougher. Fortunately, through collaborative efforts, the international scientific community and other stakeholders including patient advocacy groups are well positioned to meet this obstacle and impact the care of tomorrow's patients.

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