Acute exacerbation of idiopathic pulmonary fibrosis: international survey and call for harmonisation

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Lack of focussed international guidelines for management of acute exacerbation of IPF results in global variability in prevention, diagnosis and treatment strategies. Global trials are urgently needed to inform international specific guidelines for AE-IPF. http://bit.ly/3a8FB5i

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ABSTRACT Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is an often deadly complication of IPF. No focussed international guidelines for the management of AE-IPF exist. The aim of this international survey was to assess the global variability in prevention, diagnostic and treatment strategies for AE-IPF.

Pulmonologists with ILD expertise were invited to participate in a survey designed by an international expert panel.

509 pulmonologists from 66 countries responded. Significant geographical variability in approaches to manage AE-IPF was found. Common preventive measures included antifibrotic drugs and vaccination. Diagnostic differences were most pronounced regarding use of Krebs von den Lungen-6 and viral testing, while high-resolution computed tomography, brain natriuretic peptide and D-dimer are generally applied. High-dose steroids are widely administered (94%); the use of other immunosuppressant and treatment strategies is highly variable. Very few (4%) responders never use immunosuppression. Antifibrotic treatments are initiated during AE-IPF by 67%. Invasive ventilation or extracorporeal membrane oxygenation are mainly used as a bridge to transplantation. Most physicians educate patients comprehensively on the severity of AE-IPF (82%) and consider palliative care (64%).

Approaches to the prevention, diagnosis and treatment of AE-IPF vary worldwide. Global trials and guidelines to improve the prognosis of AE-IPF are needed.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrosing interstitial lung disease with a 20–40% five-year survival rate and a median survival time of 2–5 years [1]. Acute exacerbation of IPF (AE-IPF) is often the primary cause of death in patients with this disorder [2].

AE-IPF is defined as an acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality. Diagnostic criteria are previous or concurrent diagnosis of IPF, acute worsening or development of dyspnoea within 1 month duration, computed tomography with new bilateral ground-glass opacity and/or consolidation on a background pattern with usual interstitial pneumonia pattern and deterioration not fully explained by cardiac failure or fluid overload [3]. The incidence varies between 7 and 32%, and current evidence suggests that up to 46% of deaths in IPF are associated with AE-IPF [6]. In-hospital mortality after AE-IPF exceeds 50% [2, 4, 5], and the median survival after AE-IPF is approximately 3 to 4 months [6]. AE-IPF may be either triggered, *e.g.* by infection, post-procedural/post-operative, drug toxicity, aspiration or might be idiopathic [6]. Currently, no focussed international guidelines exist regarding the prevention, diagnosis or therapy of AE-IPF [3, 6]. While the clinical practice guideline for IPF provides a weak recommendation for treatment with steroids, this recommendation is based on expert opinion and there is no specific guidance on dose, route and duration or diagnostic or therapeutic approaches. Data from clinical trials especially on the treatment of AE-IPF are sparse and, currently, there are no large randomised controlled trial data on AE-IPF available.

We hypothesised that clinical approaches to the investigation and management of suspected AE-IPF might vary substantially, which may inform us about priority research questions to be addressed. Therefore, this study aimed to explore preventive, diagnostic and therapeutic strategies towards AE-IPF in an international group of respiratory physicians to guide future clinical trial design and recommendations for this condition.

Materials and methods

Questionnaire and participating physicians

To identify the items to be included in this survey, we conducted literature research on diagnostics, therapy, prevention and management of AE-IPF on www.ncbi.nlm.nih.gov/pubmed, https://scholar.google.com and

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others (supplementary file 1). Next, an expert panel was created, comprising respiratory physicians with expertise in the diagnosis and management of ILD working in specialist ILD centres and a track record of publication in this field, to participate in an email-based interview to structure the survey. The final questionnaire consisted of 20 questions regarding diagnosis, treatment and prevention of AE-IPF and suggested future perspectives in AE-IPF research (supplementary file 2). Additionally, optional questions were included on working place (including ILD-expert centres *versus* non-expert centres), country of origin, number of patients with IPF under care and estimated number of AE-IPF seen.

An internet search was performed from July 1, 2017 to November 30, 2017 to identify practising respiratory physicians worldwide with interest in ILD. This search included the European Respiratory Society assembly on Diffuse Parenchymal Lung Disease, the American Thoracic Society assembly on Clinical Problems, the Japanese Respiratory Society assembly on Diffuse Parenchymal Lung Disease and participants of the IPF Project Consortium (www.theipfproject.com) [7]. Nationality, academic status (working at a university hospital or not) or subspecialist interests within respiratory medicine did not influence inclusion eligibility. Pulmonologists were invited to participate *via* an e-mail link. The questionnaire was available on the online survey tool SurveyMonkey from December 2017 to April 2018.

Statistical analysis

For questions with categorical answers, absolute and relative frequencies were calculated and differences between continents were assessed using Chi-squared tests. For questions with answers on a continuous scale, median, first and third quartile, minimum and maximum were determined and differences between continents were assessed using Kruskal–Wallis tests. Due to the exploratory nature of this survey, all resulting p-values are solely to be interpreted descriptively and no adjustment for multiple testing was conducted. A p-value <0.05 was regarded as statistically significant. All analyses were conducted using R v.3.4.2 (http://r-project.org).

Results

Participants

Overall, 509 pulmonologists from 66 countries responded. 42.6% (n=217) were from Europe, 26.7% (n=136) from Asia, 11.2% (n=57) from North America, 9.8% (n=50) from South America, 4.9% (n=25) from Australia (including New Zealand), 1% (n=5) from Africa and 3.7% (n=19) remained anonymous (figure 1a and b). 66% of the participants worked in a specialised ILD centre/university hospital, 28% in general pulmonology departments/non-university centres and 1% on an intensive care unit (5.3% in others). The average number of IPF patients under care was 130; the estimated median number of patients with AE-IPF seen per year was 18. Overall, 1-year mortality of patients with AE-IPF was estimated to be 50–80% by 41.9%, 20–50% by 35.1%, >80% by 14.7% and <20% by 8.4%.

Diagnostic procedures for AE-IPF

High-resolution computed tomography (HRCT) (multi-slice thin-section CT, without contrast media) was performed by 76% participants with the highest rates in Asia (91%) and lowest in Europe (67%). CT with contrast media was applied less frequently (34%) but even in the absence of a clinical suspicion of pulmonary embolism. Most physicians used it in Europe (45%), fewest in Asia (20%) and Africa (20%).

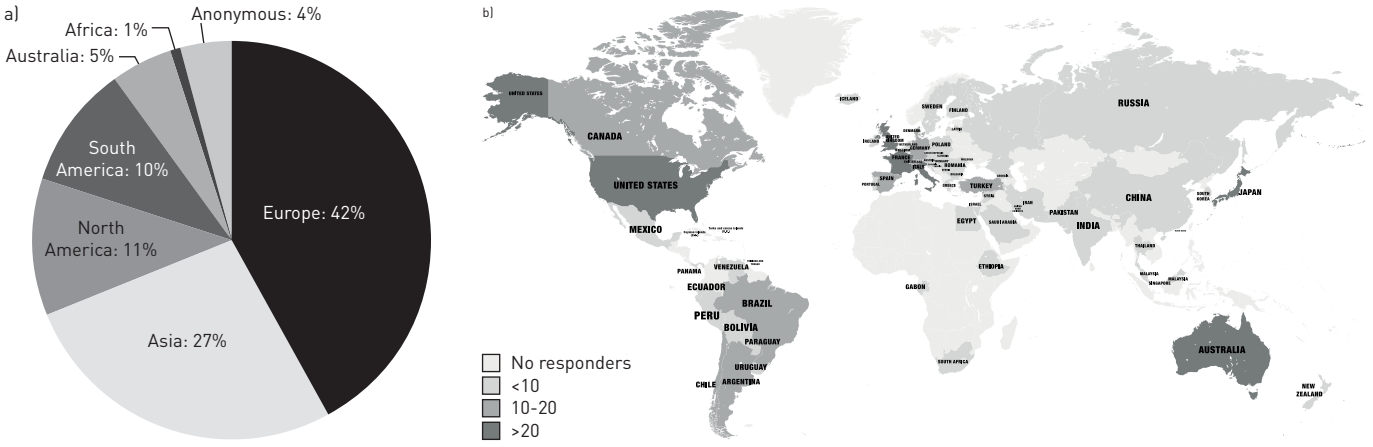

FIGURE 1 a) Participants (n=217 (42%) from Europe, n=136 (27%) from Asia, n=57 (11%) from North America, n=50 (10%) from South America, n=25 (5%) from Australia, n=5 (1%) from Africa and n=19 (4%) remained anonymous).

Echocardiography to screen for cardiac reasons for deterioration was used by 66%. N-terminal pro-hormone of BNP (NT-proBNP)/BNP (72%), D-dimer (64%) and troponins (50%) were used widely during the diagnostic workup of an AE-IPF. As a biomarker for AE-IPF, KL-6 was used in Asia (54%), but not elsewhere.

Bronchoalveolar lavage (BAL) in the context of AE-IPF was always performed by 5.8%, while the majority (70.5%) only performed BAL in case of suspected infection. For microbiology assessments, mainly sputum was collected (85%) while induced sputum was sampled by 14%. Specific pathogen screening for influenza viruses (75.7%), atypical bacterial pathogens (61.8%) and *Pneumocystis jirovecii* (58.6%) was common. Only a minority screened for other pathogens like respiratory syncytial virus (44.4%), cytomegalovirus (37.8%), *Aspergillus* spp. (37.6%), *Candida* spp. (17%) and tuberculosis (10.9%). A minority (9.2%) did not screen for any specific infections.

The main diagnostic procedures applied for AE-IPF, which vary significantly between the continents, are shown in figure 2 (further results can be seen in supplementary file 3, table S1).

Treatment approaches for AE-IPF

The majority of participating pulmonologists treated AE-IPF with methylprednisolone or equivalent with a dosage of 500–1000 mg per day for 3 days followed by a slow tapering (63%), while 11% applied pulsed high-dose steroids for 3 days only. 31% used prednisolone with a dosage of 1 $mg \cdot kg^{-1}$ per day followed by a slow tapering. On average, physicians treated AE-IPF with corticosteroids for 13 weeks.

Other immunosuppressive therapies were rarely used: 19% use cyclophosphamide (intravenous bolus), 9% cyclosporine, 5% tacrolimus and 4% rituximab. Differences between continents in the use of immunomodulators were significant (supplementary file 3, table S2). For instance, cyclophosphamide was used by 28% in Asia and never in North America. Only a minority never treated AE-IPF with any immunosuppressive therapy (4%).

Other therapies such as polymyxin B haemoperfusion, recombinant thrombomodulin and plasmapheresis/plasma exchange were used primarily in Asia (supplementary file 3, table S2).

Antimicrobial therapy was commenced regularly by 56% with broad-spectrum antibiotics combined with macrolides. 23% only used antibiotic treatment in case of a clinical and/or laboratory indication of a bacterial infection.

In AE-IPF patients without previous antifibrotic therapy, most participants would have initiated such therapy (nintedanib: 21%; pirfenidone: 14%; either nintedanib or pirfenidone: 32%), while 33% did not see an indication for an antifibrotic treatment in the acute setting. Most physicians (71%) would have waited until clinical stabilisation before initiating antifibrotic therapy. In patients already on antifibrotic therapy at the time of AE-IPF, 76% of respondents recommended its continuation, while a minority would have advised differently (4% discontinue, 3% reduce dose, 10% switch the antifibrotic drug). For gastro-oesophageal reflux disease (GORD), 19% always initiated or increased antacid therapy during AE-IPF (supplementary file 3, table S2). The main management approaches are shown in figure 3.

In case of respiratory failure, invasive ventilation was offered to all patients by 9%, and by 45% only to patients suitable for lung transplantation (LTX), as a bridge to LTX or in very selected other cases. Extracorporeal membrane oxygenation (ECMO) was offered to patients suitable for LTX as a bridge to LTX by 44%, mostly in Europe (57%) and fewest in Oceania (24%). Critically ill patients with AE-IPF were offered high-flow oxygen by 81% and non-invasive ventilation (NIV) by 74%. Palliative care was considered by 65%. Differences in these approaches were again significant between continents (supplementary file 3, table S3).

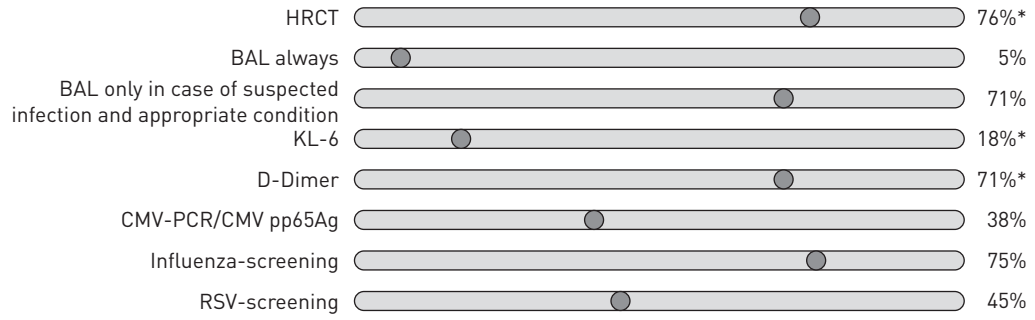

FIGURE 2 Main diagnostic procedures. *: p⩽0.0001.

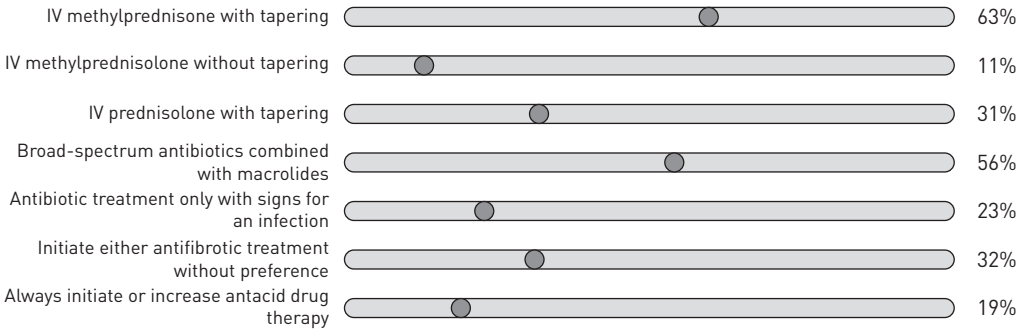

FIGURE 3 Main drug management approaches worldwide.

Preventive strategies for AE-IPF

Measures aiming to prevent AE-IPF were mainly vaccinations (*i.e.* influenza, pneumococcal) (93%), antifibrotic therapy (86%) and pulmonary rehabilitation or other forms of structured exercise therapy (58%). Antacid drugs were prescribed by 52% respondents in all IPF patients. Only a minority used long-term azithromycin (7%) or low-dose steroids (⩽10 mg) (4%). There were significant differences concerning prevention of AE-IPF between the continents (supplementary file 3, table S4). For instance, most physicians in Europe valued antifibrotic therapy as a preventive strategy (90%), opposed to significantly fewer in Asia (79%). Anticoagulation was only used by a minority (2%).

In terms of planned surgical procedures, 69% favoured preventive anaesthetic measures such as low tidal volume and avoidance of hyperoxygenation as well as regional anaesthesia over general anaesthesia when possible. 15% avoided any elective thoracic surgery. Differences between continents were again significant (figure 4 and supplementary file 3, table S4).

Unmet needs in AE-IPF

According to respondents, more research into treatment (86%) and improving our understanding of the pathophysiology of AE-IPF (83%) is needed. Furthermore, most respondents highlighted the need for consensus guideline recommendations for AE-IPF (79%) and improved education and training of physicians (66.5%) and patients and caregivers (60%). 60% see a need for improvement in the collaboration between different ILD specialists in general and 58% in multidisciplinary strategies for diagnosing and discussion.

Discussion

Despite AE-IPF being a primary driver of mortality in IPF [3], evidence on prevention, additional diagnostic approaches besides HRCT and especially on treatment of this complication is sparse and evidence-based guidance particularly is missing. Our results, which are drawn from a large international group of respiratory physicians with expertise in the management of IPF, reveal many similarities, *e.g.* the use of HRCT for the diagnosis or the use of steroids for the treatment. But there are also significant differences in the approach to AE-IPF such as in the therapy strategies beyond steroids.

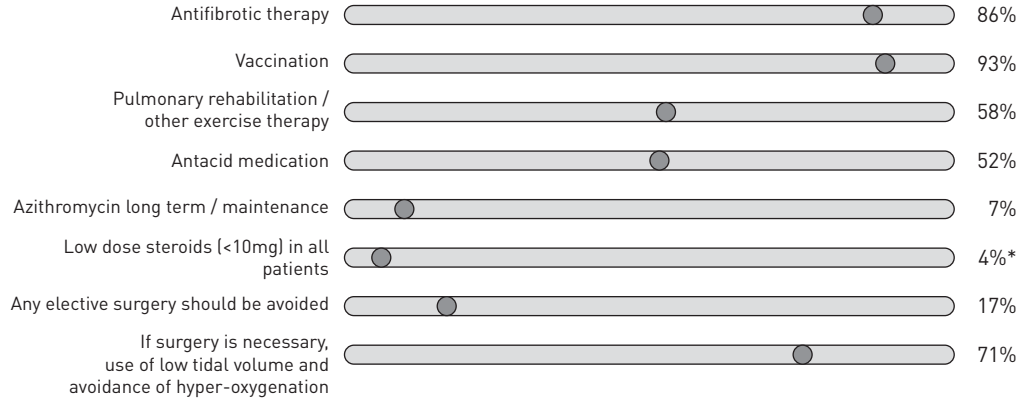

FIGURE 4 Preventive strategies. *: p⩽0.0001.

The majority of physicians use sputum analysis, HRCT, BNP and BAL in suspected infection and D-dimer for the differential diagnosis of AE-IPF, while diagnostic approaches differ regarding the use of KL-6 and viral testing.

As for treatment, high-dose steroids are widely administered, but the use of immunosuppressants and other strategies are highly variable. Very few respondents never use immunosuppression. There are also differences in the use of antifibrotic drugs in the context of AE-IPF. These results reflect an unmet need for clinical practice guidelines in this disorder.

Regarding diagnostic procedures in AE-IPF, surprisingly less than 80% of participants use HRCT despite the current definition of AE-IPF requiring evidence of new parenchymal changes on HRCT [3]. Moreover, HRCT might be critical in determining the prognosis as the extent and distribution of HRCT patterns during AE-IPF may predict outcome [8]. CT with contrast media is used by 34% of the participating physicians. Usually it is used in the process of excluding pulmonary embolism [9]. This is a very important tool because IPF patients are more likely to have a prothrombotic state compared with healthy individuals and this has an impact on survival [10].

Blood-based biomarkers in AE-IPF may also have prognostic value; KL-6 and serum decorin are reported to be predictive of AE-IPF in a Japanese population [11, 12]. Based on low level evidence there are data proving that the bacterial load and the bacterial spectrum in patients with AE-IPF differs significantly from a stable disease [13], many clinicians search for pathogens; however, significant differences in treatment practice of viral and bacterial infections exist. A recent retrospective analysis of azithromycin was associated with a reduced mortality in AE-IPF compared with fluoroquinolones [14] but it remains unclear if the reduced mortality is explained by a possible harmful effect of fluoroquinolones. Furthermore, it is unclear if azithromycin may be useful in all forms of AE-IPF or only in AE-IPF caused by infection. Ding *et al.* [15] could show that the use of Procalcitonine may prevent an unnecessary use of antibiotics in AE-IPF .

Viruses are established triggers for acute respiratory failure in chronic diseases [16]; however, data on associations of viral infections in AE-IPF are contradictory [17, 18]. This may explain the rare use of antivirals such as aciclovir (1%) and ganciclovir (2%) in the treatment of AE-IPF.

The need for a general worldwide approach to treatment is mirrored in the lack of general guidance except an expert weak recommendation for treatment with steroids in the current international guideline [6]. In particular, more evidence for the use of high-dose steroids, commonly used in AE-IPF by the participants in this study, is required. While no data exist on outcomes associated with the use of steroids in AE-IPF, high-dose long-term steroid use was associated with an increased mortality in the PANTHER (Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis) trial [19] and a history of previous immunosuppression before IPF-AE has a negative impact on mortality [20]. Notably, some physicians use an even more potent anti-inflammatory treatment approach, *e.g.* cyclosporine A, intravenous cyclophosphamide and tacrolimus (mainly in Asia, rituximab mostly in North and South America), although there is low or very low evidence for the use of these treatments [21–25].; therefore, further trials are needed.

A majority of participants report prescription of antifibrotics as a way to prevent acute exacerbations. Controlled trials suggest that nintedanib may prolong the time to the first AE-IPF [26], while *post hoc* data on pirfenidone suggest that it may reduce the risk for respiratory-related hospitalisation [5]. There are no robust data whether antifibrotics ameliorate the course of AE-IPF in patients with acute respiratory failure. Current registries have to be analysed to obtain more information on this topic and the survival during and after AE-IPF; ILD experts already aim to do so [27].

Some prospective randomised trials are currently ongoing, such as a French study assessing the role of cyclophosphamide on top of pulsed steroids (NCT02460588), two studies assessing the effect of therapeutic plasma exchange, rituximab and intravenous immunoglobulins for severe AE-IPF patients admitted to the intensive care unit (ICU) (NCT03584802) and a study from Japan assessing the effect of recombinant thrombomodulin in addition to standard of care with steroid therapy (NCT02739165). These studies and others will hopefully address some of the key unresolved issues regarding treatment of AE-IPF.

The definition of idiopathic AE-IPF relies on the exclusion of other aetiologies, including infection [3]. However, only a minority used bronchoscopy with BAL. A recent study does not support this approach as a positive bronchoscopy only affected management in 13% of patients and resulted in a change of treatment in less than 5%. In the same study, bronchoscopy resulted in a significant number of patients transferred to the ICU intubated and similarly a significant number of patients could not be extubated after the procedure [28]. In contrast, another report demonstrated the feasibility and safety of BAL aided by noninvasive ventilation (NIV) as a useful tool for differentiating or confirming triggered acute exacerbations [29]. It has to be discussed whether collection of bronchial secretion *via* bronchoscopy

might be better tolerable and at least equally effective in suspected infection in AE-IPF; yet, this has to be evaluated in future trials.

The mortality of patients with AE-IPF admitted to the ICU, particularly in ventilated patients, is high [30]. Therefore, the international guidelines recommend avoiding the ICU in patients with AE-IPF (weak recommendation) [31]. NIV and high-flow oxygen are often initiated in critical ill patients but data on this are limited [9, 32]. Other advanced therapies, such as invasive ventilation and ECMO, are usually only used as a bridge to LTX. This is in line with the current literature [33, 34] and thus included in the recommendations of the international guidelines [6].

Vaccinations theoretically play an important role in the prevention of AE-IPF but, while their use is recommended by the international guideline, there is a paucity of evidence to support this recommendation [35]. Also, it is not clear how local public health systems are dealing with these vaccinations and to what extent they are available.

Many physicians use antacid drugs as a preventive strategy for AE-IPF, although evidence on the role of antacids in IPF is controversial. Lee *et al.* [36] reported a higher pepsin level in the BAL of patients with AE-IPF compared to patients with stable diseases and also showed a positive impact of antacid drugs on the course of IPF in retrospective analyses [37, 38]. However, recent studies could not support this effect and reported potentially higher rates of respiratory infections [39] and AE-IPF [40]. Only a few physicians use low-dose steroids as a preventive strategy for AE-IPF. This is in line with the international guideline that does not recommend the use of steroids beyond AE-IPF [31]. Amongst other data, this recommendation is based on the results of the PANTHER trial that demonstrated an increased risk of hospitalisation and death for patients receiving combination therapy with *N*-acetylcyteine, azathioprine and prendnisolone compared with controls [19]. Moreover, the use of corticosteroids does not have a positive effect on the outcome of IPF patients who receive nintedanib [41]. In the end, there are no data proving a benefit for the indication for steroids in the prevention of AE-IPF.

Even though IPF patients are more likely to have a prothrombotic state (as mentioned previously) [10] and the coagulation cascade was recognised as an initiator of fibrosis, there are data showing that it seems comprehensible that nearly no one uses anticoagulation for prevention of an exacerbation. Noth *et al.* [42] showed that the use of vitamin K antagonist warfarin in IPF patients lead to a decline in survival. This was also shown in patients who received oral anticoagulation, mainly vitamin K antagonists, for other medical reasons [43].

Most of the respondents identify the unmet needs of AE-IPF in the survey. Not only are treatment trials urgently needed but also trials addressing the pathophysiology of AE-IPF have to be expanded and an improved communication and collaboration between ILD specialists has to be supported.

Our survey has several limitations. Although there was a significant contribution of pulmonologists from all parts of the world, it is based on a survey of physicians and not on objective evaluation of management and practices. Participation took place on voluntary basis and may not reflect the general practice in the respective countries/continents. While there was a significant contribution of pulmonologists from most parts of the world, there were only a few participants from Africa. Also, it has to be mentioned that certain variability in the approach of AE-IPF has to be associated with different local possibilities: between sites but also continents/countries. Especially, access to treatments, such as immunomodulation like cyclophosphamide, cyclosporine or tacrolimus, antifibrotic drugs or ECMO might be limited in some countries.

Furthermore, this study aimed to survey international habits on diagnosis and treatment of AE-IPF, it was unable to assess reliable information on incidences and outcomes of AE-IPF in the respective countries. This should be addressed in future work analysing current registries.

Not all aspects of the management of AE-IPF could be addressed in the questionnaire. Our report also has strengths as we managed to get responses from all continents and from a significant number of physicians. The questionnaire was anonymous and therefore answers are anticipated to be less biased.

In conclusion, the heterogeneity of management of AE-IPF as found in this international survey reflects the lack of evidence and focussed guidelines on important aspects of the management of AE-IPF. This strongly calls for research, education and collaborations between ILD specialists around the world to find new ways to approach this deadly complication of IPF.

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