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Early View

Original article

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

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

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"Take home" message

There are no focused international guidelines for the management of acute exacerbations of IPF (AE-IPF) resulting in global variability in prevention, diagnosis and treatment strategies. Global trials to evaluate these approaches are urgently needed resulting in international specific guidelines for AE-IPF.

Abstract

Aim

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is an often deadly complication of IPF. No focused 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.

Material and methods

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

Results

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 KL-6 and viral testing, while HRCT, BNP 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%).

Conclusion:

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.

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 to 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/postoperative, drug toxicity, aspiration or might be idiopathic.(6) Currently, no focused 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 randomized controlled trial data on AE-IPF available.

We hypothesized 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 a literature research on diagnostics, therapy, prevention and management of AE-IPF on https://www.ncbi.nlm.nih.gov/pubmed, https://scholar.google.com and others (supplementary 1). Next, an expert panel was created, comprising respiratory physicians with expertise in the diagnosis and management of ILD working in specialist ILD centers 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 2). Additionally, optional questions were included on working place (including ILD-expert centers versus non-expert centers), 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. P-values smaller than 0.05 were

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 figure 1b). 66% of the participants worked in a specialised ILD center/university hospital, 28% in general pulmonology departments/non-university centers 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 50-80% by 41.9%, 20-50% by 35.1%, >80% by 14.7% and <20% by 8.4%.

Diagnostic procedures for AE-IPF

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%).

Echocardiography to screen for cardiac reasons for deterioration was used by 66%. 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 jiroveci* (58.6%) was common. Only a minority screened for other pathogens like RSV

(44.4%), CMV (37.8%), *Aspergillus* (37.6%), *Candida* (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 1 (further results can be seen in supplementary 3, table 1).

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/kg 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 (i.v. bolus), 9% cyclosporine, 5% tacrolimus and 4% rituximab. Differences between continents in the use of immunomodulators were significant (table 2). 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 hemoperfusion, recombinant thrombomodulin and plasmapheresis/plasma exchange were used primarily in Asia (supplementary 3, table 2).
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 gastroesophageal reflux disease (GERD), 19%

always initiated or increased antacid therapy during AE-IPF (supplementary 3, table 2). 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 3, table 3).

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 (table 4). 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 3, table 4).

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%), 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.
The majority of physicians use sputum analysis, HRCT, BNP, 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 to 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 to 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. could show that the use of Procalcitonine may prevent an unnecessary use of antibiotics in AE-IPF.(15)
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 trial (19) and a history of previous immunosuppression before IPF-AE has a negative impact on mortality.(20) Notable, 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 AE. 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 is no robust data whether antifibrotics ameliorate the course of AE-IPF in patients with acute respiratory failure. Current

registries have to be analyzed 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 randomized 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 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 NIV as a useful tool for differentiating or confirming triggered AE.(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 ICU, particularly in ventilated patients, is high.(30) Therefore, the international guidelines recommend avoiding 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 is 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 this vaccinations and to what extent these are available. Many physicians use anti-acid drugs as a preventive strategy for AE-IPF,

although evidence on the role of anti-acids in IPF is controversial. Lee et al. reported a higher pepsin level in the BAL of patients with AE-IPF compared to patients with stable diseases (36) 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 do 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 to 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 is 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 above) (10) and the coagulation cascade was recognised as an initiator of fibrosis, there is data showing it seems comprehensible that nearly no one uses anticoagulation for prevention of an exacerbation. Noth et al. showed that the use of vitamin K antagonist warfarin in IPF patients lead to a decline in survival.(42) 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 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 focused guidelines on important aspects of the management of AE-IPF. This strongly calls for research, education, and collaborations between ILD-specialist around the world to find new ways to approach this deadly complication of IPF.

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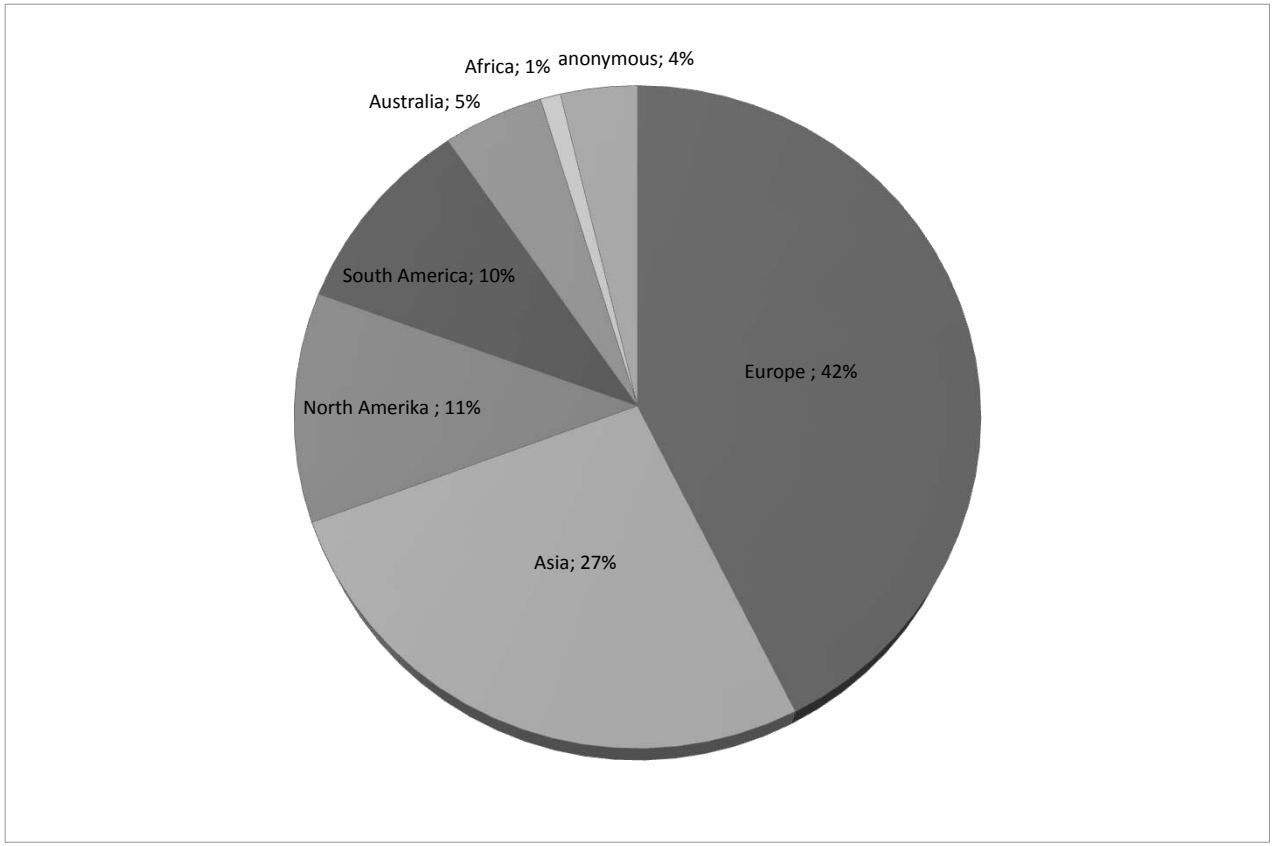
Figure 1a.: Participants (n=217 (42%) from Europe, n=136 (27%) from Asia, n=57 (11%) from North America, n=50 (10%) from South America, n=25 (5%) from Australia, n=5 (1%) from Africa and n=19 (4%) remained anonymous)




UNITED STATES
CANADA
UNITED STATES
MEXICO
Cayman islands (U.K.)
Turks and caicos islands (U.K.)
TRINIDAD AND TOBAGO
VENEZUELA
PANAMA
ECUADOR
BRAZIL
PERU
BOLIVIA
PARAGUAY
URUGUAY
CHILE
ARGENTINA
ICELAND
SWEDEN
FINLAND
RUSSIA
DENMARK
LATVIA
IRELAND
UNITED KINGDOM
NETHERLAND
POLAND
BELGIUM
GERMANY
CZECH REPUBLIC
SLOVAKIA
FRANCE
SWITZERLAND
AUSTRIA
HUNGARY
MOLDOVA
ROMANIA
ITALY
SLOVENIA
CROATIA
SERBIA
BULGARIA
GEORGIA
SPAIN
PORTUGAL
GREECE
TURKEY
SYRIA
ISRAEL
IRAN
UNITED ARAB EMIRATES
PAKISTAN
EGYPT
SAUDI ARABIA
INDIA
CHINA
SOUTH KOREA
JAPAN
HONG KONG
THAILAND
ETHIOPIA
MALAYSIA
SINGAPORE
MALAYSIA
GABON
SOUTH AFRICA
AUSTRALIA
NEW ZEALAND
No responders
<10
10-20
>20

Figure 2. Main diagnostic procedures, statistically significant differences between continents are labeled with a * (p-value = <0.0001).

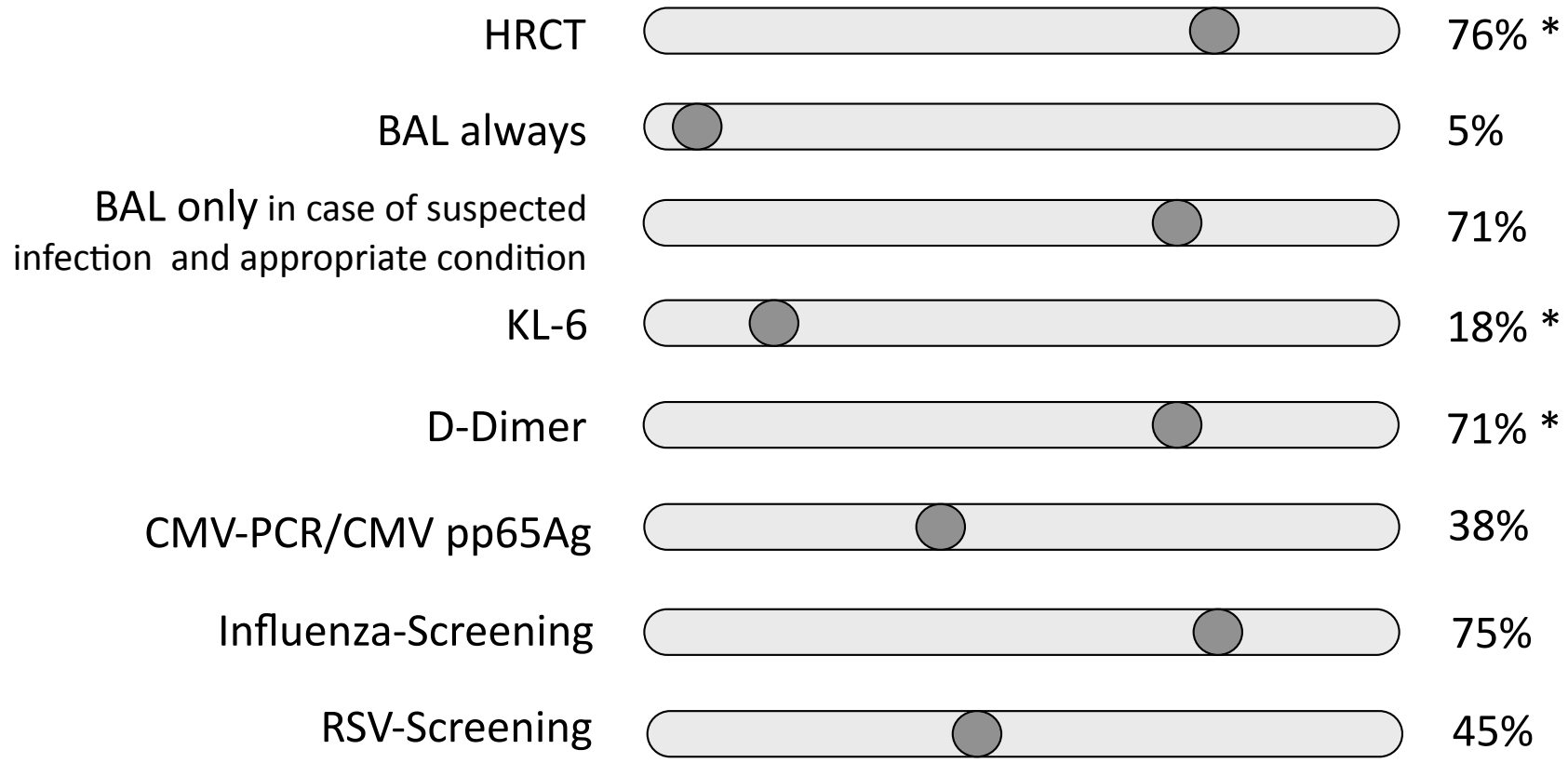


Figure 3. Main drug management approaches worldwide.

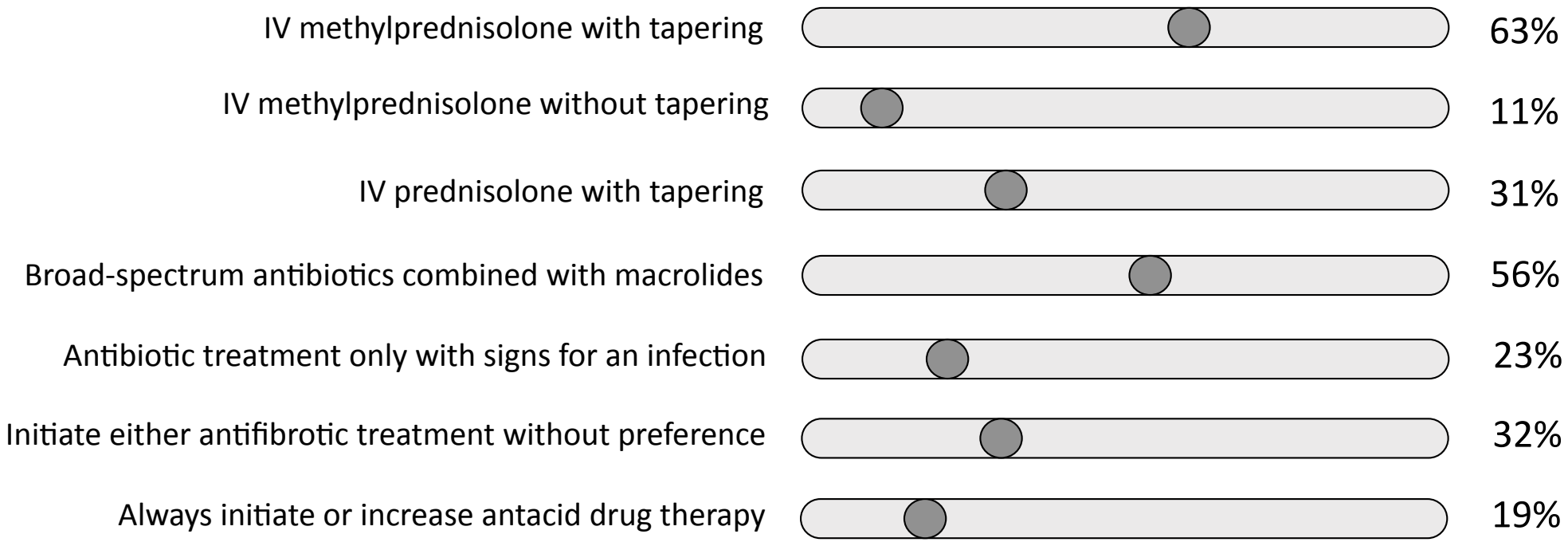
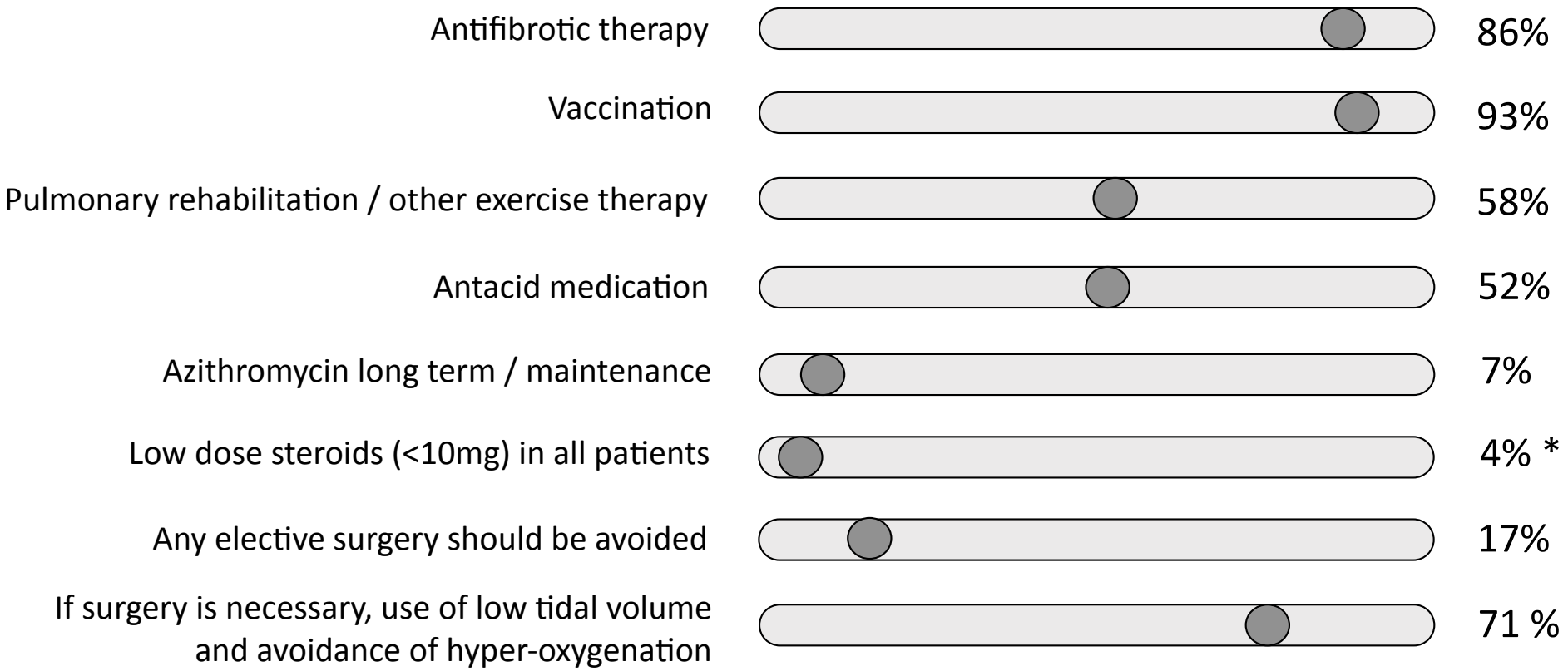


Figure 4. Preventive strategies, statistically significant differences between the continents are labeled with a * (p-value = <0.0001).



Search terminology:

Acute exacerbation of idiopathic pulmonary fibrosis,

acute exacerbation of idiopathic pulmonary fibrosis management,

acute exacerbation of idiopathic pulmonary fibrosis laboratory tests,

acute exacerbation of idiopathic pulmonary fibrosis biomarkers,

acute exacerbation of idiopathic pulmonary fibrosis bronchoalveolar lavage,

acute exacerbation of idiopathic pulmonary fibrosis respiratory deterioration,

respiratory deterioration,

acute exacerbation of idiopathic pulmonary fibrosis acute respiratory worsening,

acute respiratory worsening ,

acute exacerbation of idiopathic pulmonary fibrosis respiratory hospitalisation,

acute exacerbation of idiopathic pulmonary fibrosis therapeutic regimes,

acute exacerbation of idiopathic pulmonary fibrosis immunosuppressive therapies,

acute exacerbation of idiopathic pulmonary fibrosis antibiotic therapies,

acute exacerbation of idiopathic pulmonary fibrosis antifibrotic drugs,

antifibrotic drugs,

acute exacerbation of idiopathic pulmonary fibrosis nintedanib,

acute exacerbation of idiopathic pulmonary fibrosis pirfenidone,

nintedanib,

pirfenidone, acute exacerbation of idiopathic pulmonary fibrosis steroids,

acute exacerbation of idiopathic pulmonary fibrosis cyclosporin,

cyclosporine,

acute exacerbation of idiopathic pulmonary fibrosis cyclophosphamide i.v. bolus,

cyclophosphamide i.v. bolus,

acute exacerbation of idiopathic pulmonary fibrosis tacrolimus,

tacrolimus,

acute exacerbation of idiopathic pulmonary fibrosis rituximab,

rituximab,

acute exacerbation of idiopathic pulmonary fibrosis polymyxin B hemoperfusion,

polymyxin B hemoperfusion,

acute exacerbation of idiopathic pulmonary fibrosis recombinant thrombomodulin,

recombinant thrombomodulin,

acute exacerbation of idiopathic pulmonary fibrosis plasmapheresis,

plasmapheresis,

acute exacerbation of idiopathic pulmonary fibrosis plasma exchange,

plasma exchange,

acute exacerbation of idiopathic pulmonary fibrosis broad-spectrum antibiotic,

acute exacerbation of idiopathic pulmonary fibrosis macrolide,

acute exacerbation of idiopathic pulmonary fibrosis antacid drug,

acute exacerbation of idiopathic pulmonary fibrosis pulmonary hypertension,

acute exacerbation of idiopathic pulmonary fibrosis PH therapy,

acute exacerbation of idiopathic pulmonary fibrosis ICU,

acute exacerbation of idiopathic pulmonary fibrosis high-flow oxygen,

acute exacerbation of idiopathic pulmonary fibrosis ventilation,

acute exacerbation of idiopathic pulmonary fibrosis ECMO,

acute exacerbation of idiopathic pulmonary fibrosis palliative care,

acute exacerbation of idiopathic pulmonary fibrosis mortality,

acute exacerbation of idiopathic pulmonary fibrosis surgery,

acute exacerbation of idiopathic pulmonary fibrosis anaesthesia,

acute exacerbation of idiopathic pulmonary fibrosis preventive measures anaesthesia,

acute exacerbation of idiopathic pulmonary fibrosis prevention

Dear colleagues,

Thank you very much for accepting our invitation for this international survey on the diagnosis and treatment of acute exacerbations of IPF - a constant challenge in the treatment of patients with IPF.

We believe that your feedback will help all of us to establish future, international projects in order to improve the diagnosis and treatment of this detrimental complication.

On behalf of the AE-IPF team within “The IPFProject”

Kind regards,

Michael Kreuter

Acute Exacerbations of Idiopathic Pulmonary Fibrosis - Questionnaire

Introductory questions to the participants:

Where are you from?

If you want to remain anonymous proceed to the next question.

Where is your working place?

- ○ Specialised ILD center / university center
- ○ Pneumology department (non-university center)
- ○ Intensive care unit
- ○ Other

How many IPF patients do you have in your practice or center?

0 400 800

How many AE-IPFs do you see per year?

0 200 400

What is your name?
(and E-mail: voluntary, in case you want to be contacted for further projects of the "IPFproject")

If you want to remain anonymous proceed to the next question.

Name:

E-Mail:

What is in your experience the average time of symptoms of AE-IPF before the patient initially contacts a physician?

- ◯ 24 hours
- ◯ 3 days
- ◯ 1 week
- ◯ 2 weeks
- ◯ > 2-4 weeks
- ◯ > 4 weeks

Acute Exacerbations of Idiopathic Pulmonary Fibrosis - Questionnaire

Who do most patients with AE-IPF initially contact?

- ◯ General practitioner (GP)
- ◯ Another specialist (e.g. internal medicine, rheumatology)
- ◯ A non-ILD specialized pulmonologist
- ◯ Other options
- ◯ A community clinic without specialized ILD center (including emergency department)
- ◯ A specialized ILD center

Where should patients with an AE-IPF be hospitalized ideally if hospitalization is considered necessary?

- ○ A unit of interstitial lung diseases **with** possibility to be transferred to an intensive care unit (ICU)
- ○ A unit of interstitial lung diseases **without** access to an ICU
- ○ A general pulmonology department / section **with** possibility to be transferred to ICU
- ○ Other options

- ○ A general pulmonology department / section **without** an ICU
- ○ A department of internal medicine **with** possibility to be transferred to ICU
- ○ A department of internal medicine **without** an ICU

Which laboratory tests are in your opinion / experience mandatory to be performed during diagnostic workup of an AE-IPF? **Multiple answers possible**

- [ ] Blood gas analysis
- [ ] Standard laboratory values including CRP
- [ ] In case of elevated CRP always Procalcitonin
- [ ] D-Dimer
- [ ] Troponins
- [ ] NT-proBNP/BNP
- [ ] KL-6
- [ ] Others blood tests:

Which further diagnostic procedures are in your opinion / experience mandatory to be performed during diagnostic workup of an AE-IPF? **Multiple answers possible**

- [ ] Chest x-ray
- [ ] HRCT / multislice thin-section CT (without contrast media)
- [ ] CT with contrast media (even in the absence of clinical suspicion of pulmonary embolism)
- [ ] Bronchoalveolar lavage always
- [ ] Bronchoalveolar lavage only if infection is suspected and the patient is in an appropriate condition to undergo bronchoscopy
- [ ] Echocardiography
- [ ] Others:

What specimens do you collect regularly for microbiology assessments in suspected AE-IPF?**Multiple answers possible**

- [ ] Blood
- [ ] BAL
- [ ] Sputum
- [ ] Urine
- [ ] Induced sputum
- [ ] None of the above

Which pathogens do you regularly screen for in AE-IPF? **Multiple answers possible**

- [ ] CMV-PCR/CMV pp65Ag
- [ ] Pneumocystis jiroveci
- [ ] Aspergillus Antigen
- [ ] Candida Antigen
- [ ] Screening for atypical pathogens (Serum and or urine)
- [ ] Interferon gamma release assay (IGRA) for latent tuberculosis
- [ ] Influenza
- [ ] RSV
- [ ] None of the above
- [ ] Others (e.g. other viruses):

Do you treat AE-IPF with immunomodulation / corticosteroids? **Multiple answers possible**

- [ ] Prednisolone 1 mg / kg / day, followed by slow tapering (over weeks)
- [ ] Methylprednisolone or equivalent 500 mg-1000 mg / day for 3 days, followed by slow tapering
- [ ] Methylprednisolone or equivalent 500 mg-1000 mg / day pulsed for 3 days **WITHOUT** any tapering
- [ ] Other prednisolone dosages
- [ ] Cyclosporin
- [ ] Cyclophosphamide i.v. bolus
- [ ] Tacrolimus
- [ ] Rituximab
- [ ] I never treat AE-IPF with any immunosuppressive therapy
- [ ] Other immunosuppressive therapies:

You treat AE-IPF with other prednisolone dosages.

Please, let us know the dosage:

You treat AE-IPF with corticosteroids. How long would you treat with steroids in weeks?

0 100

How would you rank your selected therapies?

(1=the therapy which is used most of time; if you have selected only one answer, please label it as 1)

- [ ] Prednisolone 1 mg / kg / day, followed by slow tapering (over weeks)
- [ ] Methylprednisolone or equivalent 500 mg-1000 mg / day for 3 days, followed by slow tapering
- [ ] Methylprednisolone or equivalent 500 mg-1000 mg / day pulsed for 3 days **WITHOUT** any tapering
- [ ] Other prednisolone dosages
- [ ] Cyclosporin
- [ ] Cyclophosphamide i.v. bolus
- [ ] Tacrolimus
- [ ] Rituximab
- [ ] I never treat AE-IPF with any immunosuppressive therapy
- [ ] [Insert text from Other]

Do you use other therapies for AE-IPF? **Multiple answers possible**

- [ ] Polymyxin B Hemoperfusion (or similar)
- [ ] Recombinant Thrombomodulin
- [ ] Plasmapheresis / plasma exchange
- [ ] None of the above
- [ ] Other therapeutical options:

Which antimicrobial therapy do you commence regularly in AE-IPF? **Multiple answers possible**

- [ ] Broad-spectrum antibiotics
- [ ] Broad-spectrum antibiotics combined with macrolides
- [ ] Antibiotic treatment only when there is a clinical and/or laboratory indication for a bacterial infection
- [ ] Usually there is no need for an antibiotic treatment
- [ ] Other:
- [ ] Aciclovir
- [ ] Ganciclovir
- [ ] Antimycotics
- [ ] I do not agree with any of the answers

You use a broad spectrum antibiotic in AE-IPF.

Which broad spectrum antibiotic is your preferred choice?

A patient with pre-diagnosed IPF presents to you with AE-IPF **without** any previous antifibrotic treatment and eligible for such a therapy. What would be your choice as antifibrotic treatment ?

- ◯ I would preferentially initiate Nintedanib
- ◯ I would preferentially initiate Pirfenidone
- ◯ I would initiate either antifibrotic without preference
- ◯ I do not see an indication for antifibrotic therapy at all in this situation

You chose to initiate a therapy withNintedanib in the patient with AE-IPF. When would you start the treatment?

- Immediately
- Only after stabilization of the patient

You chose to initiate a therapy withPirfenidone in the patient with AE-IPF. When would you start the treatment?

- Immediately
- Only after stabilization of the patient

You chose to initiate a therapy with either antifibrotic without preference in the patient with AE-IPF. When would you start the treatment?

I would initiate ...

- ○ Immediately
- ○ Only after stabilization of the patient

A patient on treatment with Pirfenidone/Nintedanib (who tolerated the drug sufficiently) presents to you with AE-IPF. What would you do?

- ○ Pirfenidone/Nintedanib should be continued unchanged
- ○ Treatment with any antifibrotic drug should be discontinued
- ○ Pirfenidone/Nintedanib should be continued at a reduced dose
- ○ Treatment with the current antifibrotic drug should be stopped and the alternative antifibrotic should be initiated if possible
- ○ Only in case of pretreatment with pirfenidone, this drug should be discontinued and nintedanib initiated. In case of nintedanib pretreatment I would continue with nintedanib due to the reported effects on time to first acute exacerbation
- ○ Only in case of pretreatment with nintedanib, this drug should be discontinued and pirfenidone initiated. In case of pirfenidone pretreatment I would continue pirfenidone due to the reported effects on respiratory hospitalizations.

If you detect signs of pulmonary hypertension (PH) on clinical investigations (e.g. echo, BNP, clinical signs) during an AE-IPF, how would you proceed? **Multiple answers possible**

- [ ] Start diuretic therapy
- [ ] Perform a right heart catheterization
- [ ] Start PH specific treatment after established PH diagnosis
- [ ] Start PH specific treatment without a confident diagnosis
- [ ] Evaluate again after stabilization and possibly perform a right heart catheterization then
- [ ] I do not consider PH treatment during or after AE-IPF

Please name PH drug(s) here (if answer 3 or 4 was chosen)

Would you initiate or increase the dose of an antacid drug (PPI / H2 blocker) when a patient presents with an AE-IPF?

- ◯ Always initiate or increase antacid drug therapy
- ◯ Always make sure the patient receives antacid therapy but not increase the dose
- ◯ Depending on the presence / intensity of reflux symptoms
- ◯ Never prescribe antacid drug for this situation

What kind of ventilatory support would you offer critically ill patients with AE-IPF?**Multiple answers possible**

- [ ] Invasive Ventilation for all IPF patients
- [ ] Invasive ventilation only to patients suitable for lung transplantation (LTX) as a bridge to LTX
- [ ] Invasive ventilation only to patients suitable for lung transplantation (LTX) as a bridge to LTX or very selected other patients
- [ ] ECMO for all IPF patients
- [ ] ECMO only to patients suitable for LTX as a bridge to LTX
- [ ] Consultation with lung transplant center in unlisted, potentially suitable patients
- [ ] High-flow oxygen
- [ ] Non-invasive ventilation
- [ ] None of the above

Once AE-IPF is diagnosed, how would you talk to your patient and his caregivers?

- I give them all information including treatment options and average prognosis during / after AE-IPF
- I tell them an impression about treatment and prognosis but without telling hard facts
- I prefer not to tell them anything on the fatal prognosis of an AE-IPF and only some impression on treatments

Do you consider palliative care during an AE-IPF?

- ◯ Always/Usually
- ◯ Only on the initiative of the patients/caregivers
- ◯ Sometimes
- ◯ Rarely
- ◯ Never

What is your general approach after hospitalization for AE-IPF? **Multiple options possible**

- [ ] Send patients to pulmonary rehabilitation (in- or outpatient)
- [ ] Reschedule patient shortly for a follow up at my center
- [ ] If not contacted earlier during course of AE-IPF send eligible patients for lung transplant evaluation
- [ ] Refer patients not suitable for lung transplant to in- or outpatient palliative or hospice care
- [ ] Send patient home to be seen by their GP shortly for a follow up

In your experience, what is the estimated 1-year mortality in patients with AE-IPF?

- ◯ <20%
- ◯ 20-50%
- ◯ 50-80%
- ◯ >80%

What is your strategy in the case of a planned surgical procedure in patients with IPF with respect to the risk of acute exacerbations? **Multiple answers possible**

- [ ] Surgical procedures can be performed in the same way in IPF patients as in patients without IPF
- [ ] Elective thoracic surgery for any reason should not be performed
- [ ] If surgery is necessary, use of low tidal volume and avoidance of hyper-oxygenation to try to prevent injury
- [ ] Preferentially use regional anesthesia (over general) when possible
- [ ] Elective thoracic surgery should only be performed in suitable patients for the diagnosis of an ILD but not for other indications (e.g. lung cancer)
- [ ] Elective thoracic surgery should only be performed in suitable patients for the diagnosis of an ILD or for lung cancer but not for other indications
- [ ] Any elective surgical procedures should be avoided and only be performed in case of an emergency
- [ ] I do not agree with any of the statements

What measures do you use to try to prevent AE-IPF? **Multiple answers possible**

- [ ] Antifibrotic therapy
- [ ] Vaccination (influenza, pneumococcal, etc.)
- [ ] Antacids medication (PPI, H2 blockers) in all IPF patients
- [ ] Low dose steroids (<10mg) in all IPF patients
- [ ] Anticoagulants in all IPF patients
- [ ] Azithromycine long term / maintenance
- [ ] Cotrimoxazole long term / maintenance
- [ ] Early screening for PH and treatment with PAH-drugs if PH is diagnosed
- [ ] Pulmonary rehabilitation or other forms of structured exercise therapy
- [ ] I do not have a preventive strategy
- [ ] Others:

Where do you see the need for improvement in AE-IPF? **Multiple answers possible**

- [ ] Improved collaboration between different ILD specialists in general
- [ ] Improved education and training of physicians
- [ ] Improved education of patients and caregivers
- [ ] Increased research and study projects on understanding the nature of AE-IPF
- [ ] Increased research and study projects on treatment of AE-IPF
- [ ] Improved multidisciplinary strategies for diagnosing and discussions
- [ ] Consensus recommendations concerning the therapy for AE-IPF
- [ ] I do not see any need for improvements

Acute Exacerbations of Idiopathic Pulmonary Fibrosis - Questionnaire

Table 1: Diagnostic procedures of AE-IPF

	Total	Europe	Asia	North America	South America	Oceania	Africa	p-value
HRCT / multislice thin-section CT (without contrast media)	76% (N=453)	67% (N=199)	91% (N=126)	71% (N=55)	81% (N=47)	71% (N=21)	80% (N=5)	< 0.001
CT with contrast media (even in the absence of clinical suspicion of pulmonary embolism)	34% (N=453)	45% (N=199)	20% (N=126)	33% (N=55)	34% (N=47)	33% (N=21)	20% (N=5)	< 0.001
Echocardiography	66% (N=453)	66% (N=199)	64% (N=126)	65% (N=55)	81% (N=47)	57% (N=21)	40% (N=5)	0.217
D-Dimer	64% (N=457)	71% (N=201)	67% (N=127)	49% (N=55)	68% (N=47)	27% (N=22)	40% (N=5)	< 0.001
Troponins	50% (N=457)	54% (N=201)	37% (N=127)	67% (N=55)	47% (N=47)	64% (N=22)	20% (N=5)	0.0013
NT-proBNP/BNP	72% (N=457)	73% (N=201)	72% (N=127)	76% (N=55)	72% (N=47)	73% (N=22)	20% (N=5)	0.1927
KL-6	18% (N=457)	6% (N=201)	51% (N=127)	4% (N=55)	6% (N=47)	0% (N=22)	0% (N=5)	< 0.001
Bronchoalveolar lavage always	6% (N=453)	5% (N=199)	10% (N=126)	4% (N=55)	6% (N=47)	0% (N=21)	0% (N=5)	0.311
Bronchoalveolar lavage only if infection is suspected and the patient is in an appropriate condition to undergo bronchoscopy	71% (N=453)	71% (N=199)	68% (N=126)	76% (N=55)	68% (N=47)	76% (N=21)	40% (N=5)	0.551
Sputum	85% (N=453)	87% (N=199)	91% (N=126)	84% (N=55)	68% (N=47)	81% (N=21)	60% (N=5)	0.003
Induced sputum	14% (N=453)	8% (N=199)	25% (N=126)	15% (N=55)	15% (N=47)	10% (N=21)	20% (N=5)	0.003
CMV-PCR/CMV pp65Ag	38% (N=452)	40% (N=199)	51% (N=126)	27% (N=55)	13% (N=46)	29% (N=21)	40% (N=5)	< 0.001
Pneumocystis jiroveci	60% (N=452)	58% (N=199)	68% (N=126)	53% (N=55)	52% (N=46)	62% (N=21)	20% (N=5)	0.091
Influenza	75% (N=452)	71% (N=199)	70% (N=126)	93% (N=55)	78% (N=46)	95% (N=21)	40% (N=5)	< 0.001
RSV	45% (N=452)	49% (N=199)	25% (N=126)	65% (N=55)	37% (N=46)	86% (N=21)	20% (N=5)	< 0.001

Table 2: Treatments of AE-IPF

	Total	Europe	Asia	North America	South America	Oceania	Africa	p-value
Prednisolone 1 mg / kg / day, followed by slow tapering (over weeks)	31% (N=450)	26% (N=199)	28% (N=124)	45% (N=55)	35% (N=46)	43% (N=21)	80% (N=5)	0.009
Methylprednisolone or equivalent 500 mg-1000 mg / day for 3 days, followed by slow tapering	63% (N=450)	59% (N=199)	70% (N=124)	56% (N=55)	67% (N=46)	62% (N=21)	40% (N=5)	0.268
Methylprednisolone or equivalent 500 mg-1000 mg / day pulsed for 3 days WITHOUT any tapering	11% (N=450)	17% (N=199)	6% (N=124)	4% (N=55)	9% (N=46)	10% (N=21)	0% (N=5)	0.023
Cyclosporin	9% (N=450)	1% (N=199)	30% (N=124)	0% (N=55)	0% (N=46)	0% (N=21)	0% (N=5)	< 0.001
Cyclophosphamide i.v. bolus	19% (N=450)	20% (N=199)	30% (N=124)	0% (N=55)	9% (N=46)	19% (N=21)	0% (N=5)	< 0.001
Tacrolimus	5% (N=450)	1% (N=199)	17% (N=124)	2% (N=55)	0% (N=46)	0% (N=21)	0% (N=5)	< 0.001
Rituximab	4% (N=450)	3% (N=199)	2% (N=124)	9% (N=55)	11% (N=46)	0% (N=21)	0% (N=5)	0.025
I never treat AE-IPF with any immunosuppressive therapy	4% (N=450)	4% (N=199)	4% (N=124)	2% (N=55)	0% (N=46)	10% (N=21)	0% (N=5)	0.447
Polymyxin B Hemoperfusion (or similar)	8% (N=445)	3% (N=199)	25% (N=122)	0% (N=54)	0% (N=44)	0% (N=21)	0% (N=5)	< 0.001
Recombinant Thrombomodulin	10% (N=445)	1% (N=199)	34% (N=122)	0% (N=54)	0% (N=44)	0% (N=21)	0% (N=5)	< 0.001
Plasmapheresis / plasma exchange	4% (N=445)	3% (N=199)	8% (N=122)	6% (N=54)	0% (N=44)	0% (N=21)	0% (N=5)	0.121
Broad-spectrum antibiotics combined with macrolides	56% (N=443)	53% (N=197)	53% (N=122)	61% (N=54)	61% (N=44)	76% (N=21)	40% (N=5)	0.303
Antibiotic treatment only when there is a clinical and/or laboratory indication for a bacterial infection	23% (N=443)	23% (N=197)	23% (N=122)	20% (N=54)	25% (N=44)	24% (N=21)	20% (N=5)	0.996
I would initiate either antifibrotic without preference	32% (N=439)	37% (N=196)	17% (N=121)	45% (N=53)	30% (N=43)	38% (N=21)	60% (N=5)	0.001
I do not see an indication for antifibrotic therapy at all in this situation	33% (N=439)	39% (N=196)	25% (N=121)	34% (N=53)	28% (N=43)	43% (N=21)	0% (N=5)	0.061
Always initiate or increase antacid drug therapy	19% (N=434)	16% (N=192)	23% (N=121)	11% (N=53)	31% (N=42)	14% (N=21)	20% (N=5)	0.105

Table 3: intensive and palliative care during AE-IPF

	Total	Europe	Asia	North America	South America	Oceania	Africa	p-value
Invasive Ventilation for all IPF patients	9% (N=434)	3% (N=192)	17% (N=121)	13% (N=53)	14% (N=42)	5% (N=21)	20% (N=5)	0.002
Invasive ventilation only to patients suitable for lung transplantation (LTX) as a bridge to LTX or very selected other patients	45% (N=434)	49% (N=192)	33% (N=121)	57% (N=53)	43% (N=42)	62% (N=21)	20% (N=5)	0.011
ECMO only to patients suitable for LTX as a bridge to LTX	44% (N=434)	57% (N=192)	31% (N=121)	47% (N=53)	33% (N=42)	24% (N=21)	40% (N=5)	< 0.001
High-flow oxygen	81% (N=434)	86% (N=192)	79% (N=121)	89% (N=53)	55% (N=42)	90% (N=21)	60% (N=5)	< 0.001
Non-invasive ventilation	74% (N=434)	68% (N=192)	77% (N=121)	77% (N=53)	81% (N=42)	81% (N=21)	60% (N=5)	0.296
Palliative care always/usually considered	65% (N=433)	66% (N=191)	66% (N=121)	66% (N=53)	50% (N=42)	71% (N=21)	60% (N=5)	0.451

Table 4: Prevention of AE-IPF

	Total	Europe	Asia	North America	South America	Oceania	Africa	p-value
If surgery is necessary, use of low tidal volume and avoidance of hyper-oxygenation to try to prevent injury	69% (N=429)	71% (N=189)	63% (N=119)	79% (N=53)	71% (N=42)	67% (N=21)	60% (N=5)	0.384
Preferentially use regional anesthesia ...	69% (N=429)	76% (N=189)	50% (N=119)	85% (N=53)	67% (N=42)	71% (N=21)	100% (N=5)	< 0.001
Any elective surgical procedures should be avoided ...	15% (N=429)	17% (N=189)	13% (N=119)	19% (N=53)	12% (N=42)	5% (N=21)	20% (N=5)	0.528
Antifibrotic therapy	86% (N=427)	92% (N=189)	79% (N=118)	87% (N=53)	83% (N=41)	81% (N=21)	60% (N=5)	0.021
Vaccination (influenza, pneumococcal, etc.)	93% (N=427)	95% (N=189)	89% (N=118)	94% (N=53)	93% (N=41)	86% (N=21)	100% (N=5)	0.273
Antacids medication (PPI, H2 blockers) in all IPF patients	52% (N=427)	47% (N=189)	52% (N=118)	57% (N=53)	59% (N=41)	67% (N=21)	80% (N=5)	0.273
Low dose steroids (<10mg) in all IPF patients	4% (N=427)	2% (N=189)	10% (N=118)	0% (N=53)	2% (N=41)	0% (N=21)	40% (N=5)	< 0.001
Anticoagulants in all IPF patients	2% (N=427)	1% (N=189)	3% (N=118)	2% (N=53)	2% (N=41)	0% (N=21)	0% (N=5)	0.900
Azithromycin long term / maintenance	7% (N=427)	8% (N=189)	9% (N=118)	0% (N=53)	7% (N=41)	5% (N=21)	0% (N=5)	0.317
Pulmonary rehabilitation or other forms of structured exercise therapy	58% (N=427)	61% (N=189)	51% (N=118)	57% (N=53)	59% (N=41)	67% (N=21)	60% (N=5)	0.582