Recent lessons learned in the management of acute exacerbation of idiopathic pulmonary fibrosis

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ABSTRACT Recognising recent advances, the definition and diagnostic criteria for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) have been updated by an international working group. The new definition describes any acute, clinically significant respiratory deterioration (both idiopathic and triggered events) characterised by evidence of new widespread alveolar abnormality. The new criteria require a previous or concurrent diagnosis of IPF, an acute worsening or development of dyspnoea typically less than 1 month in duration, chest imaging evidence on computed tomography (CT) of new bilateral ground-glass opacity and/or consolidation superimposed on a background imaging pattern of usual interstitial pneumonia not fully explained by cardiac failure or fluid overload. Due to high in-hospital mortality rates, current treatment guidelines say that the majority of patients with AE-IPF should not receive mechanical ventilation. However, new data suggest that the prognosis may have improved. This modest improvement in overall survival seen in more recent studies may be the result of differences in the diagnostic criteria, study design, baseline clinical risk factors and/or improvements in management. Based on our updated knowledge of possible preventive and therapeutic measures, including mechanical ventilation and pharmacological therapies, the current approach to the treatment of AE-IPF requires careful decision-making.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a devastating disease with a median survival time of 3–4 years [1]. The natural history of IPF is heterogeneous; depending upon the timeframe studied, most patients follow a slowly progressive clinical course after diagnosis, while a significant minority experience episodes of acute respiratory worsening, namely acute exacerbations (AEs) [2]. AE-IPF attracts attention because of its

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prognostic impact and, to date, its inability to be predicted or prevented [3]. The international working group for AE-IPF published a comprehensive update in 2016 [4], but we focus on recent improvements in the prognosis and management of AE-IPF.

New definitions and diagnostic criteria of IPF-AE

Based on recent advances, the international working group for AE-IPF has developed a new conceptual framework for acute respiratory deterioration in IPF, and has revised the definition and diagnostic criteria for AE-IPF (table 1) [4]. The new definition and diagnostic criteria include any respiratory event characterised by new bilateral ground-glass opacification/consolidation not fully explained by cardiac failure or fluid overload, which parallels the Berlin criteria for acute respiratory distress syndrome. Because of the difficulty in distinguishing idiopathic from respiratory events triggered by known causes [5–7] (apart from cases with evident infectious pneumonia), both idiopathic and triggered events (*e.g.* infection, post-procedural/postoperative, drug toxicity, aspiration) resulting in worsening respiratory symptoms and widespread alveolar damage can be diagnosed as AE-IPF. However, the difference between infection-triggered AE and pneumonia in terms of therapeutic strategy and prognosis remains unknown [8].

Improving prognosis

The available data suggest that up to 46% of IPF-related deaths are preceded by an AE [9–13], with the majority of patients dying within the first month and most of the rest dying within a year [5].

In studies prior to 2007, mortality rates of up to 80% (178/223) were reported [3] and when mechanical ventilation was required, an in-hospital mortality of 87% and overall mortality of 94% among 135 cases was seen [14]. Hence, current IPF guidelines say that while the majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, it may be a reasonable intervention in a minority (weak recommendation, low-quality evidence) and that noninvasive ventilation (NIV) may be appropriate in some [1]. Management of AE-IPF in the intensive care unit may be justified particularly in patients in whom the possibility of lung transplantation exists and in those who have not yet undergone clinical evaluation for the cause of the respiratory worsening.

However, more recent studies that include 995 patients with AE-IPF suggest modestly better survival, including 1 month 66% (177/270; range 47–85%), 3 month 41% (142/344; range 0–54%), and survival to hospital discharge of 44% (227/517; 4–77%), respectively [6, 7, 11, 15–44]. For patients treated with invasive (IMV) or noninvasive (NIV) mechanical ventilation, in-hospital mortality has been reported as 67% among 193 patients in studies published after 2008 (table 2) [44–49]. More recently, two national cohorts were reported. Analysis of the US cohort revealed an in-hospital mortality of approximately 50% (51.6% with IMV and 30.9% in NIV) among 2481 patients with IPF who were mechanically ventilated [50]. Analysis of the Japanese cohort demonstrated that among 209 patients receiving an average of 12.8 days of IMV, short-term (within 30 days) survival was 44.6% and long-term (within 90 days) survival of 24.6%. Therefore, within the past decade, prognosis of AE-IPF has improved considerably [51]. These changes may be due to a number of issues, including differences in diagnostic criteria and their application, study design variables, the clinical characteristics of the population studied (*e.g.* severity of the

TABLE 1 Proposed revised definition and diagnostic criteria for acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF)

Revised definition

An acute, clinically significant respiratory deterioration characterised by evidence of new widespread alveolar abnormality

Revised diagnostic criteria

- Previous or concurrent diagnosis of IPF[#]
- Acute worsening or development of dyspnoea typically <1 month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern[¶]
- Deterioration not fully explained by cardiac failure or fluid overload[+]

[#]: If the diagnosis of IPF is not previously established, this criterion can be met by the presence of radiological and/or histopathological changes consistent with usual interstitial pneumonia pattern on the current evaluation. [¶]: If no previous computed tomography is available, the qualifier "new" can be dropped. [+]: Events that are clinically considered to meet the definition of acute exacerbation of IPF but fail to meet all four diagnostic criteria owing to missing computed tomography data should be termed "suspected acute exacerbations". Reprinted from [4], with permission from the publisher.

TABLE 2 Prognosis of acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) with mechanical ventilation: summary of studies published after 2008

First author [ref.], country (timeframe)	N	Patients	Methods	Hospital survival	Overall survival
Yokoyama [44], Japan (1998–2004)	11	MV for AE-IPF	NIV (IMV) CPAP 10 cmH_2O, PS/PEEP 5/10 cmH_2O	45% (5/11) 3 month	45% 3 month
Mollica [46], Italy (2000–2007)	34	MV for ARF in ICU	IMV or NIV V_T 7.5 $mL \cdot kg^{-1}$ or PS/PEEP 18/7 cmH_2O	15% (5/34)	3% 6 month
Güngör [47], Turkey (2000–2007)	96	MV for ARF in ICU	IMV or NIV V_T 6–8 $mL \cdot kg^{-1}$, PEEP 5–7 cm H_2O	36% (35/96)	–
Fernández-Pérez [45], USA (2002–2006)	30	MV for ARF in ICU	IMV V_T 7–8 $mL \cdot kg^{-1}$	40% (12/30)	–
Gaudry [48], France (2002–2009)	22	MV for ARF in ICU	IMV V_T 5.9 $mL \cdot kg^{-1}$, PEEP 7.1 cm H_2O	23% (5/22) ICU discharge	–
Vianello [49], Italy (2005–2013)	18	MV for ARF in ICU	NIV (IMV) V_T 6–8 $mL \cdot kg^{-1}$, PEEP 6.4 cm H_2O	14% 90 days	–
Total	193			33% (63/193)	13%

MV: mechanical ventilation; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; CPAP: continuous positive pressure ventilation; PS: pressure support; PEEP: positive end-expiratory pressure; ARF: acute respiratory failure; ICU: intensive care unit; V_T: tidal volume.

underlying disease and/or of the acute event), selection criteria for the institution of MV and improvements in management, especially protective ventilation.

Influence of diagnostic criteria, missing data and diagnostic accuracy

A variety of diagnostic criteria have been used both in retrospective and prospective studies (table 3). Differences in these criteria and their application may have a significant influence on both the incidence and prognosis of AE [19, 52–62].

Because of the common inability to obtain all required clinical data during the evaluation of an AE, the term, "suspected AE" has been used in many clinical studies, *i.e.* patients with an otherwise idiopathic acute respiratory decline that could not be classified as a definite AE due to missing data. However, the prognosis of these patients appears to be very similar to those with a definite AE [7, 61], suggesting that the process of accelerated disease itself rather than the underlying cause of the AE (*i.e.* idiopathic *versus* events with a recognised trigger) is driving the prognosis.

Importance of non-elective hospitalisation

Non-elective hospitalisations are associated with considerable cost [63], and respiratory-related hospitalisations in particular have prognostic significance in IPF [64–66]. Brown *et al.* [65] have reported that most hospitalisations in IPF are respiratory-related, and associated with high in-hospital mortality and limited survival beyond discharge. Even in the setting of a respiratory-related hospitalisation, the presence of AE is associated with a worse prognosis. Moua *et al.* [66] reviewed consecutive patients with a fibrosing interstitial lung disease hospitalised with acute respiratory worsening and found that those diagnosed with an AE had a worse prognosis than those without (OR 4.06, 95% CI 1.32–13.8; p=0.014). These studies emphasise the prognostic importance of both non-elective and respiratory hospitalisation as well as AE in IPF.

Influence of study design

In prospective treatment trials, study subjects are under active observation and evaluated at predetermined intervals, making this study design particularly valuable when evaluating the incidence and short-term prognosis of AE; however, these data are most informative only for the patient population described by the inclusion and exclusion criteria used in the underlying treatment trial. Retrospective cohort studies often include the full spectrum of disease severity, but the results need to be corrected for the known baseline prognostic factors present at the time of the AE [67, 68]. Recent evidence from the placebo arm subjects of prospective clinical trials [60], as well as a number of retrospective studies, suggests that the incidence and prognosis of AE-IPF are influenced by the baseline degree of physiological impairment [6, 11, 30]. In a prespecified subgroup analysis of INPULSIS trials, the one-year-incidence of AE in patients with a forced vital capacity (FVC) of <70% predicted and FVC ⩾70% predicted were 14.9% and 3.3%, respectively [69]. This factor probably explains a large part of the variability observed across studies.

TABLE 3 Definition of acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) in clinical trials

First author [ref.]	Year	Intervention	AE-IPF	Symptom	Radiology	Oxygenation	DDx
Kubo [19]	2005	Warfarin	Part of the primary outcome	Deterioration of dyspnoea within a few weeks	New GGO/ consolidation and honeycombing on HRCT or CXR	P_{aO_2}/F_{IO_2} <300	Exclusion of identifiable cause
Azuma [52]	2005	Pirfenidone	Secondary outcome	Deterioration of dyspnoea within a month	New GGO/ consolidation and honeycombing on HRCT	Deterioration of P_{aO_2} ⩾10 torr	Exclusion of identifiable cause
King [53]	2008	Bosentan 1	Part of the primary outcome	Deterioration of dyspnoea within a month		Supplemental oxygen ⩾5 L	
King [54]	2009	IFNγ1b	Tertiary outcome	Deterioration of dyspnoea	New GGO on HRCT	Deterioration of P_{aO_2} ⩾8 torr	Exclusion of identifiable cause
Taniguchi [55]	2010	Pirfenidone	Tertiary outcome	Deterioration of dyspnoea within a month	New GGO/ consolidation and honeycombing on HRCT	Deterioration of P_{aO_2} ⩾10 torr	Exclusion of identifiable cause
Zisman [56]	2010	Sildenafil	Secondary outcome	Deterioration of dyspnoea or cough within a month	New GGO/ consolidation on HRCT or new infiltrates on CXR	Deterioration of S_{pO_2} ⩾5% or P_{aO_2} ⩾8 torr	Exclusion of identifiable cause with no physical and microbiological findings suggesting infection
King [57]	2011	Bosentan	Part of the primary outcome	Deterioration of dyspnoea within 4 weeks		Needs supplemental oxygen ⩾5 L	
Richeldi [58]	2011	Nintedanib	Secondary outcome	Progression of dyspnoea within 4 weeks	New GGO on CXR or HRCT	Deterioration of P_{aO_2} ⩾10 torr	Exclusion of identifiable cause of acute lung injury
Noble [59]	2011	Pirfenidone	Secondary outcome	Deterioration of dyspnoea within 4 weeks	New GGO ⩾ one lobe on HRCT	Deterioration of P_{aO_2} ⩾8 torr	Exclusion of identifiable cause, cardiac disorder, pulmonary embolism, aspiration and infection
Noth [60]	2012	Warfarin	Secondary outcome	Deterioration of dyspnoea within 30 days	New GGO/ consolidation on HRCT or new infiltrates on CXR	Deterioration of S_{pO_2} ⩾5% or deterioration of P_{aO_2} ⩾8 torr	Exclusion of infection by sputum culture or BAL culture, and identifiable cause of acute lung injury
Martinez [62]	2014	Pirfenidone+ azathioprin+ N-acetylcystein	Secondary outcome	Deterioration of dyspnoea within 30 days	New GGO/ consolidation on HRCT or new infiltrates on CXR	Deterioration of S_{pO_2} ⩾5% or deterioration of P_{aO_2} ⩾8 torr	Exclusion of infection by sputum culture or BAL culture, and identifiable cause of acute lung injury
Richeldi [61]	2014	Nintedanib	Secondary outcome	Deterioration of dyspnoea within 30 days	New diffuse infiltrates on CXR or GGO on CT		Exclusion of infection by routine clinical practice and microbiological studies, left heart failure, pulmonary embolism, and identifiable cause of acute lung injury

DDx: differential diagnosis; GGO: ground-glass opacities; HRCT: high-resolution CT; CXR: chest X-ray; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inhaled oxygen fraction; BAL: Bronchoalveolar lavage; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

Influence of proximate trigger of respiratory decline

Despite previous criteria for the diagnosis of AE focusing on the importance of excluding recognised causes of respiratory decline, it appears that neither the presence nor absence of a known trigger has an impact on prognosis. In separate studies, both Huie [5] and Song [6] showed no differences in prognosis between patients with a definite idiopathic AE (all known causes excluded) and those with a respiratory decline triggered by infection. Separately, the results of the STEP-IPF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial suggested that patients with both definite and suspected AE-IPF had a prognosis similar to those with identifiable trigger of the acute respiratory decline [7].

Influence of baseline prognostic variables

Several clinically defined prognostic factors have been identified. Similar to IPF in general, lower baseline FVC and diffusing capacity of the lung for carbon monoxide (*D*LCO) predict mortality [30], as do a shorter duration of symptoms prior to diagnosis and poor gas-exchange at the time of hospitalisation [32, 39]. On chest imaging, the high-resolution computed tomography (HRCT) pattern at the time of diagnosis is important, with higher mortality when a diffuse ground-glass pattern is present compared to a multifocal or peripheral distribution [23]. Higher composite HRCT scores including extent of ground-glass opacification, consolidation, traction bronchiectasis and honeycombing predict mortality [23, 29]. Blood-based biomarkers of a worse outcome include elevated lactate dehydrogenase [23, 41], C-reactive protein [6], Krebs von den Lungen-6 (KL-6) [29, 41], pro-calcitonin [40], circulating fibrocytes [70], elevated interleukin-17 [28] and anti-heat shock protein 70 autoantibodies [39], but none of these have been validated prospectively, or impact clinical decision making. Recently, a staging system for AE with several variables was proposed [41]. Such prognostic information may be useful in future decision making about the level and continuation of care.

Influence of management strategies

There are no currently proven beneficial management strategies for patients with AE-IPF [1–4, 8], but there are several possible approaches that may influence prognosis [8, 71, 72].

Preventive measures

Prevention is likely more effective than any therapeutic strategy. Measures to prevent respiratory infection are important, as infection is thought to be an important trigger for AE [4] (table 4). Vaccination for influenza virus and *Pneumococcus* are felt to be useful [71]. Hand washing and avoidance of sick contacts, especially in the winter season, may also be useful [71]. Because gastro-oesophageal reflux disease (GERD) has been suggested to be a risk factor for AE [32], the use of pharmocological and non-pharmocological measures to minimise reflux is thought to be appropriate. However, a recent study reported that antacid therapy increased the risk of overall infection and pulmonary infection in patients with advanced IPF (*i.e.* FVC<70%) [72]. Therefore, the balance of benefit and risk of antacid therapy for prevention of AE-IPF may vary by clinical situation. Because exposure to air pollution has also been reported as a possible risk factor [38], the avoidance of airborne irritants or air pollution may be appropriate.

With a fibrotic, non-compliant lung, ventilator-induced lung injury is always a risk [8, 71]. Fernández-Pérez *et al.* [45] reported that the use of high positive end-expiratory pressure (PEEP) is associated with worse prognosis. In those patients with IPF and acute respiratory failure who are appropriate for mechanical ventilatory support, in order to reduce the risk of barotrauma, there is a trend towards the use of a protective ventilation (low tidal volume) strategy. Alternatively, NIV may also lower the risk of ventilator-induced lung injury and a recent study of high-flow nasal cannula oxygen in subjects with acute hypoxemic respiratory failure suggests its superiority over NIV [73]. Ventilator-induced injury during surgery, particularly thoracic surgery, is also a speculated mechanism of AE [74]. Strategies to minimise the risk of lung injury during surgery, such as reducing the partial pressure of oxygen and tidal volume and less invasive surgical techniques, may be of benefit [8, 71, 75, 76].

Therapies shown to be beneficial for the treatment of IPF itself may reduce the risk of AE-IPF. A phase 2 trial of nintedanib in the treatment of IPF (TOMORROW) demonstrated a delay in the time to first investigator-reported AE-IPF with nintedanib therapy [58]. The subsequent phase 3 trials showed mixed results; INPULSIS-1 showed no significant difference in the time to development of AE-IPF between the nintedanib and the placebo groups, but INPULSIS-2 demonstrated a benefit of nintedanib therapy [61]. The time to first adjudicated AE-IPF in the prespecified pooled analysis (INPULSIS 1 and 2) and the time to first investigator-reported AE-IPF in a separate pooled analysis of all three trials (TOMORROW and INPULSIS-1 and 2) demonstrated a delay with nintedanib therapy [77].

A Japanese phase 2 placebo-controlled randomised clinical trial of pirfenidone was stopped early because of a reduction in the rate of AE-IPF in those allocated to receive pirfenidone [52]. However, the following Japanese phase 3 clinical trial did not confirm this result [55], and the subsequent multinational phase 3 clinical trials of pirfenidone (CAPACITY and ASCEND) did not report acute exacerbations as an end-point [59, 78]. Pirfenidone has also been suggested to reduce the risk of postoperative AE by observational study [79]. Additional data are needed to fully understand the impact of IPF therapies on the risk and outcome of acute exacerbation [4].

Therapeutic measures

The evidence-based IPF guidelines in 2011 recommended that the majority of patients with AE-IPF be treated with corticosteroids, but that not treating with corticosteroids may be reasonable in a minority

TABLE 4 Possible preventive and therapeutic measures in acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF)

Prevention	**Recommendation**
• Influenza and pneumococcal vaccination	+
• Hand washing, avoidance of sick contacts	+
• Approaches to minimise gastro-oesophageal reflex	+/–
• Avoidance of airborne irritants and pollutants	+
• When mechanical ventilation is required, strategies to minimise ventilator-induced lung injury Low tidal volume ventilation Noninvasive ventilation High-flow nasal cannula oxygen therapy	+/–
• Nintedanib	+/–
• Pirfenidone	–/+
• Avoidance of the combination of prednisone and azathioprine	+

Therapeutics	**Recommendation**
Ventilation	
• Low tidal volume ventilation	+
• Noninvasive ventilation	+
• High-flow nasal cannula oxygen therapy	+/–
Pharmacology	
• Corticosteroid	+
• Empiric antibiotics	+/–
• Immunosuppressant[#]	–/+
• Thrombomodulin	–/+
Lung transplantation	+/–
Others	
• Extracorporeal membrane oxygenation	–[§]
• Polymixin B haemoperfusion	–/+
• Rituximab, plasma exchange, intravenous immunoglobulin	–
• Non-steroid approach[¶]	–

+: Would consider using in most patients as potential benefit seems to outweigh potential harm; +/–: would consider using in selected patients as the balance of benefit and risk varies by clinical situation; –/+: would not consider using in majority of patients as the balance of benefit and risk varies by clinical situation; –: would not consider using in most patients as evidence is lacking to support a clinical benefit. [#]: Cyclophosphamide, cyclosporine, tacrolimus. [¶]: Immediate cessation of immunosuppression (if any), best supportive care, broad-spectrum antimicrobials. [§]: Would consider as a bridge to lung transplantation.

(weak recommendation, very low-quality evidence) [1]. This recommendation places a high value on anecdotal reports of benefit and the high mortality of AE-IPF. The appropriate dose, route and duration of therapy are not clear [1]. Several studies have suggested that the combination of an immunosuppressant with corticosteroids is more effective than corticosteroid monotherapy [80–83]. Because these studies are mostly small and uncontrolled, the results are inconclusive.

Patients with AE-IPF occasionally present with fever and flu-like symptoms, and the majority of them are treated with high-dose corticosteroids. So, it is reasonable that most of them receive empiric antibiotic therapy [8, 71, 75]. One prospective study suggests the possible usefulness of azithromycin therapy for AE-IPF [84]. In addition, one prospective randomised trial showed that procalcitonin-guided antibiotic treatment resulted in a shorter duration of therapy, with a similar mortality to that of standard clinician-determined antibiotic treatment [85].

Several investigators studied the efficacy of recombinant human soluble thrombomodulin (rhTM), which exhibits a range of physiologically important anti-inflammatory, anticoagulant and antifibrinolytic properties for AE-IPF [68, 86–88]. They found a favourable mortality rate in the rhTM groups compared with historical control groups, but caution should be used when interpreting such uncontrolled studies. A phase 3 clinical study of rhTM for AE-IPF is now ongoing (JapicCTI-163326). It remains uncertain whether any of the vast number of pharmacological strategies has influenced survival [4, 8].

The IPF guideline also recommends that appropriate patients with IPF undergo lung transplantation (LTx) [1]. It is therefore appropriate that transplant-eligible patients with IPF be referred to a transplantation centre for evaluation early in the course of their disease, before an episode of AE-IPF. In selected patients

with AE-IPF who fulfil the criteria for LTx, mechanical ventilation alone or in combination with extracorporeal membrane oxygenation (ECMO) may be appropriate as a bridge to LTx [89, 90]. Although this is associated with a worse prognosis than LTx without a bridge [91–93], it can provide a survival chance for patients who would probably have died otherwise [93, 94]. In addition, recent strategies of ambulatory ECMO or awake and non-intubated ECMO as a bridge to LTx have shown encouraging results [95–97].

The polymyxin B-immobilized fibre column (PMX), which removes endotoxin, has been studied in patients with AE-IPF. The therapeutic benefits of direct haemoperfusion with PMX (PMX-DHP) are postulated to be based on the adsorption of proinflammatory, profibrotic and proangiogenic cytokines by PMX-DHP fibres. Several uncontrolled studies and one observational cohort with historical controls suggest some efficacy [67, 98–100].

Recent evidence that autoantibodies may be involved in IPF progression has prompted the use of therapies for AE-IPF that target autoantibodies. Donahoe *et al.* [101] performed a pilot study to evaluate the efficacy of plasma exchange, rituximab and intravenous immunoglobulin for AE-IPF, and showed better one-year survival than historical controls without serious adverse events. On the other hand, based on the results of the PANTHER trial, which demonstrated that the combination of prednisone, azathioprine and N-acetyl cysteine was harmful for IPF [102], Papiris *et al.* [103] hypothesised that previous immunosuppression and the administration of high-dose steroids adversely affect outcome of AE-IPF, and studied a protocol of immediate cessation of immunosuppression (if any), best supportive care and broad-spectrum antimicrobials. Their uncontrolled results revealed that the steroid avoidance strategy might be of benefit. Overall, significant debate remains when choosing among the varying approaches to the treatment of AE-IPF. A summary of possible preventive and therapeutic measures are shown in table 4.

In summary, IPF patients who experience an AE remain at high risk for early mortality, with in-hospital mortality rates of 55–80%. Recent results suggest that the prognosis may have improved. The modest improvement in short-term overall survival seen in more recent studies may be the result of differences in the diagnostic criteria used and their application, study design, baseline risk factors and/or improvements in management. However, patients who survive an AE-IPF event are at very high risk of further events, leading to very high longer-term mortality. Careful decision making for AE-IPF should be conducted based on recent knowledge gains regarding possible preventive and therapeutic measures.

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