Review Article

Acute exacerbation of idiopathic pulmonary fibrosis a narrative review primary focus on treatments

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Background and Objective: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia, which is the commonest type of idiopathic interstitial pneumonia in the clinic. For most patients, the course of the disease is slow and prolonged, but a percentage of them develop an acute respiratory worsening during the disease, known as an acute exacerbation of IPF (AE-IPF). The updated guidelines define AE-IPF as an acute worsening of dyspnea in an IPF patient within 1 month and exclude other conditions such as left heart failure and pulmonary embolism. However, the prevention and treatment of AE-IPF are still unclear. Based on the high mortality rate caused by AE, in this article, we will focus on the latest research advances in AE-IPF treatment strategies and provide a comprehensive review of its pathogenesis, risk factors, clinical features, and diagnosis.

Methods: This study searched for relevant literature published from 2018 to 2023 in the PubMed database. The search terms used were as follows: "Acute exacerbation", "Idiopathic pulmonary fibrosis", "Biomarker", "Pathogenesis", "Treatment", "HRCT", "Antifibrotic", "Infection", "Immunosuppressant", "Autoantibody", "Oxygen therapy", "Hemoperfusion", "Inflammation".

Key Content and Findings: The review found that corticosteroids are still the primary treatment strategy at present, although there is some controversy regarding the dosing and tapering of corticosteroids. However, corticosteroids combined with intravenous cyclophosphamide have been shown to be detrimental to the prognosis of patients with AE-IPF. Given its deadly high mortality rate, early intervention is crucial. Pirfenidone and nintedanib have been proven to reduce incidence of AE. Meanwhile, in the future, the lung microbiome may also be a break-through.

Conclusions: This study reviewed the pathogenesis and risk factors of AE-IPF and updated the current and potential treatment strategies regarding AE-IPF. The pathogenesis of AE-IPF is not exact, multiple mechanisms may be involved simultaneously. Corticosteroids remain the mainstream treatment modality in the medical treatment of AE-IFP. Many other treatment modalities have been proposed in succession, but no clear conclusions can be drawn about the effectiveness and safety of these interventions.

Keywords: Acute exacerbation (AE); idiopathic pulmonary fibrosis (IPF); treatment; pathogenesis

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, parenchymal lung disease of unknown cause that presents histologically and/or on chest high-resolution computed tomography (HRCT) as usual interstitial pneumonia (UIP), with a median survival after diagnosis usually of 3–5 years (1). The naturally occurring course of IPF is characterized by a high degree of heterogeneity at the individual level, with a minority of patients experiencing acute respiratory deterioration termed as acute exacerbation of IPF (AE-IPF), which is manifested on imaging as UIP in the setting of presence of new bilateral ground-glass shadows with or without solid shadows. AE can occur at any stage in the course of IPF and is an important cause of death. The incidence and prevalence of AE-IPF are difficult to determine, but in general, the incidence of AE in patients with IPF is about 5–10% per year (2). The occurrence of AE usually indicates a poor prognosis, with the median survival of IPF patients experiencing an AE being approximately 3–4 months (3-5), and in-hospital mortality due to AE-IPF being upwards of 50% (6-8). Compared with the 2007 diagnostic criteria (2), the 2016 updated definition of AE-IPF places more emphasis on its pathophysiological changes rather than etiology, so the new definition does not require invasive tests to diagnose AE, and, to some extent, avoids the potential risk of AE induced by mechanical manipulation (9). The pathogenesis of AE-IPF is not exact, multiple mechanisms may be involved simultaneously, and therefore there is no good treatment for it. The efficacy of corticosteroids has never been confirmed in randomized control trials, they are still the primary treatment strategy at present. Although there is some controversy regarding the dosing and tapering of corticosteroids. Corticosteroids combined with intravenous cyclophosphamide have been shown to be detrimental to the prognosis of patients with AE-IPF (10). Pirfenidone and nintedanib have been proven to reduce incidence of AE, but it remains unclear whether to continue dosing after the onset of AE. A increasing number of studies have found a higher microbial load in the lungs of patients with AE-IPF (11). However, whether AE is associated with viral infection remains to be studied (12), and anti-infection therapy is currently often used in conjunction with other therapies for the majority of those with AE-IPF. We describe a list based on the current literature about the potential management strategies (*Table 1*).

In that review, we summarize the pathogenesis and risk factors of AE-IPF and update the current and potential treatment strategies regarding AE-IPF. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1565/rc).

Methods

A comprehensive and systematical online literature search via PubMed database for the 2018 to 2023 was performed for articles published using the following search terms: “Acute exacerbation”, “Idiopathic pulmonary fibrosis”, “Biomarker”, “Pathogenesis”, “Treatment”, “HRCT”, “Antifibrotic”, “Infection”, “Immunosuppressant”, “Autoantibody”, “Oxygen therapy”, “Hemoperfusion”, “Inflammation”. The search strategy is summarized in *Table 2*.

Pathogenesis and risk factors

Interstitial lung disease (ILD) is characterized mainly by inflammation or fibrosis, or a combination of both. The main features of AE-IPF are acute lung injury and diffuse alveolar damage (DAD) (40). Its specific pathogenesis is not fully understood. Existing evidences suggest that acute inflammation may have a significant role in AE as levels of various pro-inflammatory factors such as interleukin (IL)-8 and IL-6 are elevated during AE-IPF (41) and some inflammatory factors lead to abnormal wound healing through M2 macrophage activation (42). In addition, the increase of IL-23 in bronchoalveolar lavage fluid (BALF) perhaps involved in lung fibrosis and airway inflammation in AE through the IL-23/IL-17A and IL-23/IL-22 axes (43). Accelerated progression of chronic fibrosis may be another pathogenetic mechanism of AE (44), but serum levels of those representative pro-fibrotic factors are not significantly increased in AE-IPF patients, therefore, the view is still controversial. Enhanced lung epithelial cell injury/proliferation and elevated α-defensin protein levels in AE-IPF compared to IPF may explain the involvement of infection in the development of AE (45), and viral infection and altered lung microbiome may also act as an antigenic stimulus to worsen the pulmonary fibrosis process and thus trigger AE (46). IPF are often combined with gastroesophageal reflux, and the levels of pepsin in the BAL of patients with AE-IPF are significantly higher than those of controls (47), and therefore insidious aspiration of gastric contents secondary to gastroesophageal reflux may be one of the mechanisms that can lead to AE-IPF.

Many risk factors are known to predict AE-IPF. Reductions in vital capacity (VC), forced vital capacity

Table 1 Summary of potential management strategies in the review

Management strategies	First author, year	Study type	Main findings
Pharmacological treatment			
Corticosteroids	Cuerpo S, 2019 (13)	Single-center, retrospective study	Higher doses of corticosteroids (≥55 mg/day or higher) may be associated with higher in-hospital mortality
	Sakamoto S, 2019 (14)	Single-center, cohort study	A low corticosteroid maintenance dose (0.5 mg/kg/day) improves patient survival at 3 months
	Jang HJ, 2021 (15)	Single-center, cohort study	High-dose corticosteroids (prednisolone >1.0 mg/kg/day) would not improve the prognosis of patients with AE-IPF
	Yamazaki R, 2021 (16)	Single-center, retrospective study	An increase in the total dose of corticosteroids within 30 days after AE is associated with a reduced risk of recurrence within 1 year of the first exacerbation
	Anan K, 2022 (17)	Multicenter, cohort study	High-dose corticosteroids (prednisolone >1.0 mg/kg/day) have positive effects in cases of AE-non-IPF ILD, but would not improve the prognosis of patients with AE-IPF
Corticosteroids and immunosuppressants	Aso S, 2018 (18)	Multicenter, cohort study	Cyclosporine A combined with methylprednisolone do not reduce mortality of AE-IPF patients
	Hozumi H, 2019 (19)	Multicenter, retrospective study	CS + IVCY do not significantly improve post-AE 90-day survival rates for patients with IPF with a first idiopathic AE
	Aso S, 2019 (20)	Nationwide observational study	High-dose methylprednisolone + cyclophosphamide is not associated with improved in-hospital mortality
	Naccache JM, 2022 (10)	Multicenter, randomized controlled trial	High-dose glucocorticoids + IVCY shock therapy will increase 90-day mortality in AE-IPF patients
Anti-infection therapy	Arcadu A, 2017 (21)	Single-center, retrospective study	With and without positive bronchoscopy findings does not affect in-hospital mortality, this may be related to the empirical use of broad-spectrum antibiotics prior to the procedure
	Kawamura K, 2017 (22)	Single-center, cohort study	The use of azithromycin within 24 hours of diagnosis of AE is associated with a reduction in patient mortality at 60 days
	Liu L, 2024 (23)	Single-center, case-control study	ILD is a high-risk group for PCP, with more than one third of patients with IPF are colonized with pneumocystis jirovecii
	Shulgina L, 2013 (24)	Multicenter, randomized controlled trial	Treatment with co-trimoxazole may improve survival in people with IPF
	D'Alessandro-Gabazza CN, 2022 (25)	Animal experiment	Intrathecal injection of anticorisin mAtb 21A in a corisin-induced AE-IPF model mouse improves the CT score of pulmonary fibrosis and reduces the levels of related lung injury markers
Antifibrotic drug	Ohkubo H, 2015 (26)	Case report	The addition of pirfenidone after one week of ineffective corticosteroid therapy led to remission in patients with AE-IPF after lung cancer surgery
	Ito Y, 2019 (27)	Case report	Nintedanib can improve the clinical symptoms in AE-ILD patients without corticosteroids or antibiotics, and the HRCT suggests multifocal type
	Vianello A, 2019 (28)	Single-center, retrospective study	Pirfenidone can prolong the survival time in AE-IPF patients, however patients were also treated with corticosteroids and rhTM

Table 1 *(continued)*

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Management strategies	First author, year	Study type	Main findings
	Isshiki T, 2021 (29)	Real-world retrospective study	Continued use of pirfenidone or nintedanib after the occurrence of AE did not differ in 3-month survival between the two groups, but both were better than those without use
Autoantibody-targeted treatments	Kulkarni T, 2021 (30)	Single-center, retrospective study	Plasma exchange + rituximab + IVIG can improve lung gas exchange in AE-IPF patients, and plasma HEp-2 autoantibody titers are higher among the survivors
	Higo H, 2022 (31)	Nationwide, cohort study	After receiving corticosteroid shock therapy, low-dose IVIG (5 g/d) can improve 90-day survival in IIPAE (including IPF) patients
Human recombinant thrombomodulin	Wang B, 2020 (32)	Meta-analysis	rhTM may improve the short-term mortality in patients with AE-IPF
	Kondoh Y, 2020 (33)	Multicenter, randomized controlled trial	ART-123 do not improve 90-day survival in AE-IPF patients and have a higher risk of bleeding in the safety population
	Awano N, 2022 (34)	Nationwide observational study	rhTM combined with high-dose mPSL does not improve prognosis in AE-IPF patients who developed severe respiratory failure requiring mechanical ventilation
Nonpharmacological treatment			
Hemoperfusion with polymyxin B-immobilized fibers	Oishi K, 2016 (35)	Single-center, cohort analysis	PMX-DHP improves 12-month survival in patients with AE-IPF, and the median survival time correlates with the time of initiation of treatment
	Oishi K, 2022 (36)	Single-center, retrospective study	The use of PMX-DHP within 48 h of corticosteroid shock therapy improves patient prognosis, especially for patients with a modified GAP index ≤8 points
Noninvasive respiratory support	Rush B, 2016 (37)	Nationwide retrospective cohort analysis	Inpatient mortality was lower with non-invasive mechanical ventilation for patients with IPF (including AE-IPF)
	Vianello A, 2019 (38)	Single-center, retrospective cohort analysis	HFNC can reduce the short-term mortality of patients admitted to RICU due to ARF to less than 50%
Lung transplantation	Dotan Y, 2018 (39)	Single-center, retrospective study	Both short-term and long-term survival is significantly lower after lung transplantation in AE-IPF

AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ILD, interstitial lung disease; CS, corticosteroids; IVCY, intravenous cyclophosphamide; PCP, pneumocystis jirovecii pneumonia; CT, computed tomography; HRCT, high-resolution computed tomography; rhTM, recombinant human soluble thrombomodulin; IVIG, intravenous immunoglobulin; IIPAE, AE of fibrotic idiopathic interstitial pneumonias; mPSL, methylprednisolone; PMX-DHP, polymyxin B-immobilized fiber column extracorporeal hemoperfusion; GAP, gender-age-physiology; HFNC, high-flow nasal cannula oxygen therapy; RICU, respiratory intensive care unit; ARF, acute respiratory failure.

(FVC), and total lung capacity (TLC) in pulmonary function tests, decreased partial pressure of oxygen (PaO_2), and increased alveolar-arterial oxygen difference ($AaDO_2$) are all related to increased risks of AE-IPF. Although bronchoalveolar lavage and surgical lung biopsy are powerful tools in the diagnosis of ILD, these may also be potential AE risk factors (9). Chronic exposure to high levels of air pollution and infections may also trigger AE (48,49). Growth differentiation factor-15 (GDF-15) and leptin promote pulmonary fibrosis by enhancing M2 macrophages to induce fibroblast activation and inhibiting PPAR-γ to enhance fibroblast TGF-β1 signal expression, respectively (50,51). Leptin is also a pro-inflammatory cytokine, both of which are independent predictors of survival in IPF patients. The risk of AE in IPF patients was significantly increased when the serum GDF-15 level was above

Table 2 The search strategy summary

Items	Specification
Date of search	03/02/2023 to 03/09/2023
Databases searched	PubMed
Search terms used	"Acute exacerbation", "Idiopathic pulmonary fibrosis", "Biomarker", "Pathogenesis", "Treatment", "HRCT", "Antifibrotic", "Infection", "Immunosuppressant", "Autoantibody", "Oxygen therapy", "Hemoperfusion", "Inflammation"
Timeframe	2018 to 2023
Inclusion and exclusion criteria	Inclusion criteria: articles based on acute exacerbations of idiopathic pulmonary fibrosis (study type: original article, research article, review article, meta-analysis), no limitation on language
	Exclusion criteria: editorial; literary work; only mentioned idiopathic pulmonary fibrosis, not acute exacerbations
Selection process	The selection process was conducted by X.L. and F.X. independently, then removing duplicated results. Consensus on additional papers consideration and review of the final list of references included was performed by all authors

Table 3 Summary of risk factors and prognostic factors in the review

Clinical outcomes	Source of markers		
	Serum	BALF	Clinical scoring
Risk factors	GDF-15	IL-23	Pulmonary function tests (VC, FVC, TLC)
	Leptin	Neutrophil count	PaO_2
	KL-6		$AaDO_2$
	SP-A		Mechanical operations
	SP-D		Environmental pollution and infections
	Monocyte count		
	IL-6		
	IL-8		
Prognostic factors	WBC values	–	PaO_2/FiO_2
	LDH		GAP
	HMGB1		
	Serum osteopontin		
	Serum ferritin		
	S100A8/A9		
	MIF		
	IL-1β		

BALF, bronchoalveolar lavage fluid; GDF-15, growth differentiation factor-15; IL-23, interleukin-23; VC, vital capacity; FVC, forced vital capacity; TLC, total lung capacity; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein-A; SP-D, surfactant protein-D; IL-6, interleukin-6; IL-8, interleukin-8; PaO_2, partial pressure of oxygen; $AaDO_2$, alveolar-arterial oxygen; WBC, white blood cell; LDH, lactate dehydrogenase; HMGB1, high-mobility group box 1; MIF, migration inhibitor factor; IL-1β, interleukin-1β; FiO_2, fraction of inspired oxygen; GAP, sex-age-physiology.

989.3 pg/mL or the leptin level was above 15.52 ng/mL (50,52). Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), and surfactant protein-D (SP-D) are biomarkers of IPF. Studies have shown that serum levels of KL-6, SP-A, and SP-D in AE-IPF are notably higher than those in the stable stage (53,54), which are considered additional risk factors for AE-IPF. The researchers also revealed a significant increase in neutrophils in the BALF and a positive correlation between IL-23 levels when IPF presented with AE (43). Peripheral blood monocytes, a biomarker of IPF prognosis, can migrate to the injured lung tissue and differentiate into pro-fibrotic macrophages or even fibroblasts, however, an abnormal increase in blood monocytes may result in the continuation of fibrosis or even the development of AE (55).

Clinical characteristics, diagnosis and prognosis

Most AEs-IPF are characterized by dyspnea or reduced exercise tolerance over for days to weeks (generally <30 d) and may be accompanied by a cough, mostly dry cough or with a little white sputum (56). Some patients develop fever and flu-like symptoms later in the course of the disease (57), while others begin with a cough, fever, or flu-like symptoms that are rapidly followed by progressive dyspnea (58), but rapidly progressive dyspnea is the most prominent symptom in almost all patients, and some of the clinical symptoms are very familiar to those of acute respiratory distress syndrome (ARDS) (40). The signs of AE-IPF are mainly shortness of breath, terminal cyanosis of the extremities and lips, and the typical basal sound of both lungs (Velcro rales) at the end of inspiration. The guidelines on AE-IPF are in a continuous process of improvement. The 2016 International Working Group report updated the definition and diagnosis of AE-IPF again (59). An AE-IPF is a clinically significant acute respiratory deterioration characterized by new DAD (60). The diagnostic criteria are as follows: (I) previous or current diagnosis of IPF; (II) significant worsening of dyspnea within 1 month without obvious cause; (III) HRCT showed new imaging abnormalities such as diffuse bilateral ground-glass shadows or consolidation on a background of the UIP pattern, and excluded other causes such as volume overload, left heart failure, or pulmonary embolism (59). UIP is defined by subpleural, basal-predominant honeycombing, and reticular abnormality, with or without traction bronchiectasis. This update also distinguishes AE-IPF for the first time in terms of triggering and idiopathic, the former includes episodes related to infection, drug toxicity, and those that occur after surgery and postoperatively. Compared with the 2007 criteria, the revised guidelines also have significantly expanded the diagnostic coverage of AE-IPF. Yoo *et al.* reviewed 445 patients with IPF and they found that the modified definition increased the occurrence of AE by approximately 20% and decreased in-hospital mortality by approximately 10% (61). Overall, the updated criteria were more favorable for early diagnosis and intervention of AE-IPF. Since the mortality rate of patients with AE-IPF is extremely high, it is important to correctly identify AE. Based on the updated guidelines, when faced with patients with IPF presenting with suspicious manifestations such as dyspnea, we should first exclude extrapulmonary factors (59) (pulmonary embolism, pleural effusion, etc.), and then look for characteristic imaging manifestations (ground glass shadow or consolidation), and finally combine history, physical examination, laboratory and imaging tests to confirm the diagnosis. In patients diagnosed with AE-IPF, we should actively distinguish the cause of AE: triggering or idiopathic. to follow up with more effective treatment options.

It is also clear that HRCT is the key to the diagnosis of most suspected ILDs. HRCT pattern in combination with clinical manifestations is sufficient to confirm the diagnosis, while the degree and pattern of CT involvement are of higher predictive value for patient survival than clinical and laboratory data. Three HRCT patterns of AE-IPF were classified as peripheral, multifocal, or diffuse, pulmonary parenchymal opacification in the peripheral type occurs mostly in the inner peripheral zone adjacent to the preexisting subpleural honeycomb structures, the multifocal type occurs mainly in the central and peripheral regions, whereas the diffuse type presents with heterogeneous and extensive pulmonary involvement, and the multifocal type is also considered to be an early manifestation of the diffuse type (60), all occurring on a background of UIP, and peripheral has a relatively better prognosis (62). Akira and colleagues, after reviewing 17 patients with AE-IPF, found that patients with HRCT of the peripheral type had varying degrees of symptom improvement after corticosteroid treatment (63). In a subsequent study, they identified potential CT histopathological correlations during the autopsy of 23 patients with AE-IPF: the diffuse type corresponded to DAD, whereas the peripheral type was mainly associated with organizing pneumonia (OP) or numerous fibroblastic foci (60), which may bring some reference in the choice of subsequent treatment modalities. The presentation of AE-IPF on HRCT can be asymmetrically distributed, and asymmetric AE is diagnosed

when the ratio of right to left parenchymal turbidity is ≥2.0 or ≤0.5. The clinical relevance of this phenomenon was first evaluated by Sokai *et al.* who found that asymmetric distribution of bilateral pulmonary ground glass shadow and consolidation was associated with a better prognosis (64). The patients with AE-IPF tend to have a poor prognosis, and multivariate analysis has shown that decreased partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio, increased lactate dehydrogenase (LDH) and white blood cell (WBC) values are associated with poor prognosis in AE (65). In addition, IL-6 and IL-8, as pro-inflammatory and pro-fibrotic cytokines in peripheral blood, are significantly increased in the early stage of AE-IPF development and are associated with poor prognosis (41). Several recent studies have found that elevated levels of high-mobility group box 1 (HMGB1), serum osteopontin, serum ferritin, calc-binding protein S100A8/A9, macrophage migration inhibitor factor (MIF), and IL-1β are potentially related with poor prognosis of AE-IPF (66-70). The gender-age-physiology (GAP) model has been used to predict 1-year mortality rates of 6%, 16%, and 39% for the three risk stages of IPF patients (71). Suzuki *et al.* first proposed the use of GAP model for the prognostic classification of AE-IPF (72), the post-AE 90-day cumulative survival rates of patients with GAP stages I, II, and III were 59.3%, 68.8%, and 60%, respectively. In addition, when GAP score is incorporated into statistical models of progression index score along with circulating serum biomarkers, they will more accurately predict disease progression at 1 year (73). Although this still needs to be validated by more prospective studies. Although there is still a lack of effective markers that can independently predict the occurrence and prognosis of AE-IPF, combinations of biomarkers may provide a more accurate diagnosis of the disease, and researchers are currently trying to use combinations of biomarkers to predict disease progression (73). In clinical practice, the use of peripheral blood (e.g., monocytes) and inflammatory cells in BALF to quickly determine disease severity and prognosis is certainly a simple and effective way. We provide a list summarizing the risk and prognostic factors for AE-IPF (*Table 3*).

Treatment strategies

There are many treatment options for AE-IPF, such as corticosteroids, immunosuppressants, biologics, antifibrotic agents, anti-infectives, and nonpharmacologic treatments, but to date, there is still no clear evidence on these therapeutic strategies, especially pharmacologic treatments. The 2015 UK Consensus Statement on Acute Exacerbations of Idiopathic Pulmonary Fibrosis states that in the absence of contraindications all patients should be considered for corticosteroids, but that antifibrotic therapy should not be initiated in the setting of AE (74). The 2018 Japanese IPF Treatment Guidelines recommend that patients with AE-IPF should receive corticosteroid therapy, including pulsed therapy (1 g/day for 3 days, repeated 1–4 times per week, followed by maintenance at 0.5–1 mg/kg/day and subsequent dose reductions every 2–4 weeks depending on the patient's condition), which also suggests that for most patients immunosuppressive therapy can be used (75). However, randomized controlled trials have recently confirmed that cyclophosphamide increases mortality in patients. The 2022 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/ERS/JRS/ALAT) clinical practice guideline, in contrast, considers the addition of glucocorticoids in AE of IPF but does not recommend the use of mechanical ventilation and does not recommend antacid drugs to improve the prognosis of IPF based on evidence-based recommendations (76).

Corticosteroids are used as traditional therapy, but due to the lack of evidence-based, although they are mentioned in various guidelines, they are mostly weakly recommended and there has been no specific dosage therapy. For nonpharmacological treatments, supportive treatments such as high-flow nasal cannula oxygen therapy (HFNC) and non-invasive ventilation can benefit patients to some extent, and given the similarities between AE-IPF and ARDS, perhaps we can learn from the management of patients with ARDS. Lung transplantation is used as a last resort treatment, but it may only mean a short extension of life.

Pharmacological treatment

Corticosteroids

Acute aggravation of IPF is serious and has a high fatality rate, but there is still a lack of guidelines for its effective treatment. Systemic corticosteroid is the most frequently used treatment in clinical practice, but there is no clear evidence to support it. There are inflammatory components in AE-IPF, so some patients with AE-IPF mediated by inflammation may be effective for corticosteroid therapy. The 2018 Japanese IPF Treatment Guidelines recommended that patients with AE-IPF should receive corticosteroids therapy, including pulse

therapy (75). However, Jang *et al.* who reported that high-dose corticosteroids (prednisolone >1.0 mg/kg/day) might have positive effects in most cases of AE-ILD, especially in cases of AE-non-IPF ILD, but would not improve the prognosis of patients with AE-IPF (15), and higher doses of corticosteroids (≥55 mg/day or higher) may even be associated with higher in-hospital mortality as well (OR: 1.044) (13), but these are all based on retrospective studies. Once hormone therapy is initiated, it should be reduced as soon as possible, otherwise, long-term use of hormones may aggravate the deterioration of the disease. A retrospective study from 2022 showed that a gradual reduction of corticosteroid dose in AE-IPF patients within 2 weeks of admission can reduce the risk of in-hospital mortality, independent of the initial dose (17). However, how to reduce the dose, the optimal maintenance dose, and the duration of maintenance are not yet known. A retrospective study of 88 patients found that after high-dose corticosteroid pulse therapy (methylprednisolone 1,000 mg/day for 3 days), a low corticosteroid maintenance dose (0.5 mg/kg/day) was found to improve patient survival at 3 months (HR: 0.13; P=0.002) (14). Notably, an increase in the total dose of corticosteroids within 30 days after AE was associated with a reduced risk of recurrence within 1 year of the first exacerbation (5,185±2,414 mg/month, 93.5±44.0 mg/kg/month) (16). In conclusion, corticosteroid therapy still needs to be evaluated in more randomized controlled trials in the future.

Combination corticosteroids and immunosuppressants

High-dose corticosteroids combined with immunosuppressants are commonly used in the empiric treatment of AE-IPF, especially intravenous cyclophosphamide. However, multiple retrospective studies have shown that high-dose corticosteroids combined with cyclophosphamide are not beneficial in the treatment of AE-IPF (19,20). A recently completed randomized, double-blind, placebo-controlled, Phase 3 trial in France demonstrated that the use of intravenous cyclophosphamide shock therapy increased 90-day mortality in AE-IPF patients receiving high-dose glucocorticoids [n=119; 27/60 (45%) in patients given cyclophosphamide *vs.* 18/59 (31%) in the placebo group] (10). These data suggest that intravenous cyclophosphamide should not be used to treat patients with AE-IPF. Cyclosporine A is an immunosuppressant that inhibits the activity of T helper lymphocytes. Aso and colleagues evaluated retrospectively the impact of high-dose methylprednisolone combined with cyclosporine A on in-hospital mortality in 989 patients with AE-IPF admitted from July 1, 2010, to March 31, 2014. Results showed that the addition of cyclosporine A to systemic glucocorticoids in patients with AE-IPF does no effect reducing mortality compared to methylprednisolone alone (25.3% *vs.* 24.9%, respectively) (18), and more randomized controlled trials are needed in the future to validate this conclusion. However, as of now, it seems that high-dose corticosteroids combined with immunosuppressants should not be a good clinical option for the treatment of patients with AE-IPF.

Anti-infection therapy

There is growing evidence that infection induces AE-IPF. Altered lung microbiome burden, diversity, and composition may lead to AE-IPF (11). Despite the fact that many AE-IPF patients received antibiotics before bronchoalveolar lavage, Molyneaux and colleagues still observed an increased bacterial load in BAL fluid in patients with AE-IPF compared to the stable phase and a higher relative abundance of Campylobacter sp. and Stenotrophomonas sp. Operational Taxonomic Units (OTUs) (77). Not coincidentally, an earlier retrospective study also showed that the Staphylococcus and Streptococcus genera may be associated with IPF disease progression (78). Evidence for viral infections in the development of AE-IPF remains limited. While the researchers did detect a higher percentage of virus positivity in AE-IPF, the most important viruses were human herpes virus (HHV) as well as influenza A virus (48). In addition, common respiratory viruses such as respiratory syncytial and cytomegalovirus (CMV) were also detected during AE (79). Torque teno virus (TTV) was present in the BALF of patients with AE-IPF compared to the stable phase, and it was positively associated with mortality in patients with IPF (80). However, a meta-analysis suggested that persistent or chronic viral infections increase the risk of developing IPF, but not exacerbation of IPF (12). While another case report noted that native-lung AEs-IPF are associated with acute CMV disease in patients who underwent single-lung transplantation (81). There are no clear criteria regarding the choice of antibiotics. Bronchoscopy is an important modality to clarify pathogenesis, and although studies have concluded that with and without positive bronchoscopy findings does not affect in-hospital mortality in patients, this may be related to the empirical use of broad-spectrum antibiotics prior to the procedure, and therefore broad-spectrum antibiotics, such as third-generation cephalosporins, may initially be used in patients who are unable to undergo bronchoscopy (21).

Azithromycin is one of the macrolides that have been shown to be effective in patients with acute lung injury (82). A prospective, open-label study with historical controls found that patients with chronic fibrosing interstitial pneumonia treated with intravenous azithromycin had a lower 60-day mortality rate than those treated with fluoroquinolones (20% *vs.* 69.6%; P<0.001) (83). Similarly, a single-center retrospective study from Japan also showed that patients with AE-IPF who received intravenous azithromycin (500 mg/day) for 5 days within 24 h of AE diagnosis, in the context of corticosteroid therapy, had a significantly lower 60-day mortality rate than in patients treated with fluoroquinolones (26% *vs.* 70%; P<0.001) (22). It was found that procalcitonin (PCT) can guide antibiotic therapy for AE-IPF, and that giving antibiotics when serum PCT values >0.25 ng/mL or treating patients until PCT values ≤0.25 ng/mL, if antibiotics are started can shorten the duration of antibiotic administration (84). ILD is a high-risk group for pneumocystis pneumonia, with more than one third of patients with IPF are colonized with Pneumocystis jirovecii, and a history of glucocorticoid therapy is associated with the development of pneumocystis pneumonia in ILD (23). However, corticosteroids are still the primary treatment for AE-IPF, so co-trimoxazole should be considered for the prevention of opportunistic pneumocystis infection in patients already treated with corticosteroids (24). In a recent study, a proapoptotic peptide of corisin was secreted by lung microbes to induce apoptosis of lung alveolar epithelial cells, and its levels were significantly increased in patients with AE-IPF. Intrathecal injection of anticorisin mAtb 21A in a corisin-induced AE-IPF model mouse improved the CT score of pulmonary fibrosis and significantly reduced the levels of related lung injury markers. Therefore, corisin may be a new potential therapeutic target for AE in pulmonary fibrosis (25).

Antifibrotic drug

The antifibrotic drugs pirfenidone and nintedanib have been approved for the treatment of patients with IPF. The application of antifibrotic drugs immediately after the diagnosis of IPF can effectively reduce the occurrence of adverse events. A pooled analysis of a Phase II TOMORROW trial and two Phase III trials (INPULSIS-1 and -2) showed that the incidence of AE at 52 weeks in IPF patients after nintedanib treatment was lower than in controls (85). A phase II trial and a phase III trial from Japan have reached conflicting conclusions about whether pirfenidone can prevent the occurrence of AE (86,87). However, Wu *et al.* pointed out that pirfenidone can reduce the risk of AE and deterioration of IPF (RR: 0.64) after summarizing nine randomized controlled trials (88). Recently a retrospective single-center study including 195 patients with IPF showed a reduction in the cumulative incidence of AE-IPF after treatment with either pirfenidone or nintedanib, and a significantly lower incidence of AE-IPF in patients treated with pirfenidone than in those treated with nintedanib (log-rank test).There was no significant difference in the 3-month survival rate after the onset of AE-IPF between the two groups (29). On the question of whether antifibrotic drugs have a positive effect on the treatment of AE-IPF, a small sample retrospective study showed that pirfenidone can prolong the survival time in patients with AE-IPF (P<0.001), however patients were also treated with corticosteroids and recombinant human soluble thrombomodulin (rhTM) (28). In one case of triggered AE-IPF resulting from lung cancer surgery, treatment with pirfenidone was initiated after 7 days of corticosteroid treatment while the disease was still progressing, and remission was achieved after a week, but whether this was related to the delayed effects of the hormone remains to be discussed (26). Two case reports described improvement of clinical symptoms in patients with AE-ILD (including IPF) treated with nintedanib (300 mg/day) without corticosteroids or antibiotics, and it is worth mentioning that the HRCT of these two patients was mainly peripheral and multifocal (27,89). There is no clear clinical evidence on whether to use antifibrotic drugs during AE, but it can be regarded as a treatment option.

Autoantibody-targeted treatments

B-cell abnormalities in autoimmune diseases are also common in IPF, so autoantibodies may also be involved in IPF progression, which may explain, to some extent, why some AE-IPF patients do not respond well to corticosteroids and other nonspecific drugs. During the treatment of patients with AE-IPF, Donahoe *et al.* proposed that plasma exchange + rituximab + intravenous immunoglobulin (IVIG) could improve lung gas exchange in patients with AE-IPF and that this regimen improves 60-day survival (55%±15%) compared to corticosteroids alone (90). Similarly, a trial of 24 patients with AE-IPF found that a triple-modality autoantibody reduction regimen (plasma exchange + rituximab + IVIG) reduced patients' additional oxygen demand and improved activity endurance, and this improvement was strongly correlated with anti-epithelial autoantibody levels (30). The above two studies suggest that the initial use of plasma exchange can

rapidly improve gas exchange in patients with rapid disease progression, but since circulating autoantibodies are always being generated, plasma exchange alone is very limited in improving the long-term prognosis of patients, and rituximab, as a therapeutic complement, initiates an immune response to mediate B-cell lysis and reduces autoantibody production, so that the use of rituximab alone at the time of AE is not effective. The role of IVIG in the triple-modality autoantibody reduction regimen is still debatable as to whether it is adjunctive or critical. IVIG has auxiliary anti-inflammatory and anti-infection effects. A retrospective study has shown that low-dose IVIG (5 g/d) can improve 90-day survival in patients with IIPAE (including IPF), but it is unclear whether higher doses are more effective for AE (31). Based on this, a prospective study from Japan on whether IVIG improves survival of AE-IPF is ongoing (jRCT1061220010) (31).

Human recombinant thrombomodulin

rhTM has anti-inflammatory, anticoagulant, and other physiological properties. Acute lung injury is a major feature of AE-IPF, and studies suggest that there is both strong procoagulant activity and severe inflammatory response in the lung parenchyma in acute lung injury (91). In a meta-analysis of 291 patients with AE-IPF from 6 studies, methylprednisolone shock treatment for 3 days followed by administration of 0.06 mg/kg/day (380 U/kg/day) of rhTM significantly reduced patient mortality at 28 and 90 days [odds ratio (OR): 0.25, 95% confidence interval (CI): 0.08–0.77, P=0.02; OR: 0.29, 95% CI: 0.17–0.49, P<0.001, respectively] (32). It is noteworthy that rhTM was administered for 7 days in one of the included studies, while the rest were 6-day rhTM regimens, and patients in 3 studies were treated with immunosuppressants. Although meta-analysis has shown that rhTM improves the short-term prognosis of patients and does not increase the risk of bleeding. However, rhTM does not improve prognosis in patients with AE-IPF who developed severe respiratory failure requiring mechanical ventilation (34). In addition, in a randomized placebo-controlled trial, thrombomodulin alfa (ART-123) did not improve 90-day survival in patients with AE-IPF and had a higher risk of bleeding in the safety population than in the control group (23.8% *vs.* 10.5%) (33).

Nonpharmacological treatment

Hemoperfusion with polymyxin B-immobilized fibers

Polymyxin B-immobilized fiber column extracorporeal hemoperfusion (PMX-DHP) was initially used to treat sepsis or septic shock and is now also used as a new therapy for AE-IPF. Studies have shown that PMX fibers can adsorb circulating pro-inflammatory, pro-fibrotic, and pro-angiogenic cytokines, and serum levels of various cytokines are reduced in AE-IPF patients treated with PMX-DHP (92,93). Two retrospective single-center studies from Japan showed that the use of PMX-DHP improved 12-month survival in AE-IPF patients, with a significant increase in P/F ratios at 2 days after PMX-DHP treatment, especially in stage GAP II and III patients. In conclusion, PMX-DHP treatment was an independent predictor of better prognosis (35,94). In addition, the median survival time for patients treated with PMX-DHP was 192 days, and up to 381 days for patients treated with PMX-DHP as early as possible after the onset of AE (35). Similarly, in a review of 30 patients with AE-IPF treated with PMX-DHP, Oishi *et al.* pointed out that regardless of the severity of patients in the stable phase, early PMX-DHP initiation, specifically within 48 h after the corticosteroid pulse therapy can significantly improve the prognosis of patients when AE occurred, especially for patients with a modified GAP index ≤8 points (36). However, PMX-DHP is unlikely to be effective in all patients with AE-IPF due to a variety of clinical factors, and its therapeutic role in AE-IPF patients needs to be confirmed by additional randomized controlled studies.

Noninvasive respiratory support

AEs-IPF are often accompanied by severe respiratory failure with a range of blood gas abnormalities such as refractory hypoxemia, and supportive therapy plays a large role at this point. However, for the majority of patients with AE-IPF, conventional oxygen therapy does not improve the dilemma they face, and in-hospital mortality is higher with invasive mechanical ventilation (IMV) compared to patients receiving non-IMV (NIMV) (51.6% *vs.* 30.9%, P<0.001) (37). Therefore, noninvasive respiratory support is important in the treatment of AE-IPF, and noninvasive positive pressure ventilation (NIV) and HFNC are commonly used. HFNC is an effective treatment for hypoxemic acute respiratory failure, which regulates the fraction of inspired oxygen more precisely, while the applied high flow rate of gas creates a certain pressure on the airway, generating a positive end-expiratory pressure, which increases the end-expiratory lung volume and promotes alveolar re-expansion, as well as decreases the physiologic dead space and improves the efficiency of ventilation (95). It has been

found that HFNC can improve the short-term prognosis of patients who have failed conventional oxygen therapy by correcting hypoxemia to some extent, while NIV seems to reverse CO_2 retention after hypoxemia correction (38). At the present, clinicians at various institutions generally prefer to apply HFNC or NIV (96).

Lung transplantation

Lung transplantation as a non-pharmacological treatment may potentially save the lives of patients with AE-IPF. However, studies have found that the benefits of lung transplantation during AE-IPF are not high. Dotan and colleagues reviewed 89 IPF patients listed for lung transplantation from 2012–2016, and they found that both short-term and long-term survival was significantly lower after lung transplantation in patients with AE-IPF compared to patients with stable IPF (P<0.001) (39). While lung transplantation does provide some benefit to some patients with AEs, as a whole, lung transplantation is of little therapeutic significance.

Conclusions

AE-IPF still cannot be accurately predicted and prevented so far, but based on its fatal characteristics of high in-hospital mortality, it is crucial to actively search for the pathogenesis and avoid high-risk factors while intervening early. Judging from recent research trends, finding independent predictors of the development of AE-IPF seems to be difficult, and perhaps several biomarkers, or even clinical scores or imaging in combination with biomarkers, could be more effective in predicting the early progression of AE-IPF. Similarly, in terms of treatment, a single therapeutic strategy seems to be of little benefit, whereas a combination of strategies may provide a turnaround, although of course we should determine, as much as possible, the most important reason for the patient's AE, as well as the severity and grading of the AE, before proceeding with the appropriate treatment. Corticosteroids remain the mainstream treatment modality in the medical treatment of AE-IFP although international evidence-based guidelines weakly recommend them, however, the context of corticosteroid use is present in almost all studies on treatment. Many other treatment modalities have been proposed in succession, but limitations in study design and the small number of patients in these trials. Therefore, no clear conclusions can be drawn about the effectiveness and safety of these interventions. In conclusion, further studies on the pathogenesis and risk factors of AE-IPF are urgently needed to find safer and more effective treatment methods.

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Footnote

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