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Review

Acute exacerbation of Idiopathic Pulmonary Fibrosis

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Abstract: Idiopathic Pulmonary Fibrosis (IPF) is most common idiopathic interstitial pneumonia. IPF is often seen in elderly men who smoke. Diagnosis of IPF requires integration of a detailed clinical history, specific physical examination, laboratory findings, pulmonary function tests, high-resolution computed tomography (HRCT) of the chest, and histopathology. IPF has a heterogeneous clinical course, from an asymptomatic stable state to progressive respiratory failure or acute exacerbation (AE). AE of IPF has several important differential diagnoses, such as heart failure and volume overload. The International working project proposed new criteria of AE of IPF in 2016 dividing it into triggered and idiopathic AE. On the basis of these criteria, physicians can detect AE of IPF more easily. The recent international IPF guideline emphasized the utility of chest HRCT. In addition, two anti-fibrotic agents have become available. We should attend not only to management of AE, but also to its prevention. The diagnostic process, laboratory findings, typical chest imaging, management and prognosis of AE are comprehensively reviewed.

Keywords: Acute exacerbation; consolidation: GGO; HRCT; Idiopathic; IPF; LDH; Nintedanib; Pirfenidone; Triggered

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic parenchymal lung disease of unknown etiology, and the most common fibrotic lung disease among Idiopathic Interstitial Pneumonias [1]. The majority of IPF patients are male, greater than 60 years old, and smokers [1,2]. Familial clustering is identified in approximately 3% of cases [3]. Genetic factors, such as MUC5B, are associated with development of IPF [4,5]. Natural history of IPF is quite heterogeneous, from chronic stable to progressive respiratory failure or acute exacerbation (AE)[6]. The incidence of AE of IPF is 5-10% per year [7]. However, incidence varies according to ethnicity. Japanese patients are more susceptible to AE of IPF [8]. Therefore, some genetic regulatory factor may be related to AE [9]. In this review, I will describe clinical pictures, laboratory findings, and chest imaging, especially high resolution computed tomography (HRCT) findings, as well as management and prognosis of AE of IPF.

2. Risk factors

Studies have reported that reduced pulmonary function, especially forced vital capacity (FVC), never smoking status, and baseline serum Krebs von den Lungen-6 (KL-6) are crucial risk factors that predict AE of IPF [10-13]. Reduced FVC patients often have decreased normal area due to extensive fibrosis. Patients with these characteristics are prone to develop severe lung injury consistent with gefitinib-associated interstitial lung disease (ILD)[14]. In never smoking IPF patients, baseline dyspnea grade and serial progression of dyspnea can predict the short-term development of AE [15]. Recently, Collard et al reported that baseline FVC, baseline supplemental oxygen, baseline antacid medication, and smoking are important risk factors for AE of IPF [16]. So, once we diagnose IPF, serial physiological evaluations and reducing impairment of daily activity due to AE are the main tasks for the physician.

3. Diagnosis process

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The international working group report proposed revised criteria of AE of IPF in 2016 [17]. Important background is a previous diagnosis of IPF and acute worsening or development of progressive dyspnea of less than one month duration. Another important change is that bronchoalveolar lavage is no longer necessarily required for diagnosis of AE, compared with the 2007 criteria [18](Table 1). Therefore, AE of IPF can be diagnosed in a general hospital. These criteria provide rather broad coverage compared to original 2007criteria [7,17].

Table 1 Comparison of 2007 and 2016 criteria for AE of IPF.

Table 1. Comparison between 2007 and 2016 criteria of AE of IPF

	IPF diagnosis	Course	HRCT findings	Exclusion
2007 guideline	Previous or concurrent diagnosis	Less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Exclusion of alternative etiologies, such as infection, heart failure, and pulmonary embolism; BAL is required
2016 guideline	Previous or concurrent diagnosis	Typically less than 1 month	New bilateral GGO and/or consolidation on a background pattern of UIP pattern	Deterioration not fully explained by heart failure or fluid overload

AE: acute exacerbation; IPF: idiopathic pulmonary fibrosis; HRCT: high resolution computed tomography; GGO: ground-glass opacity; UIP: usual interstitial pneumonia; BAL: broncho-alveolar lavage

(Reference 18)

New criteria divided AE of IPF into two groups, triggered and idiopathic. Triggered AE consists of episodes related to infection, drug toxicity and aspiration, as well as those that occur after procedures and post-operatively. (Figure 1) By history, disease duration is less than 1 month, and we should exclude pneumothorax and pleural effusion by chest radiography, and exclude pulmonary embolism by a combination of clinical history and contrast enhanced chest CT. Furthermore, if we see bilateral infiltrates on plain chest radiographs, chest CT will be required for evaluation of bilateral ground glass opacity (GGO), and consolidation with chronic fibrotic findings such as honeycombing, traction bronchiectasis/bronchiolectasis or reticular opacity. Before arriving at a diagnosis of AE of IPF, we should exclude heart failure or volume overload clinically.

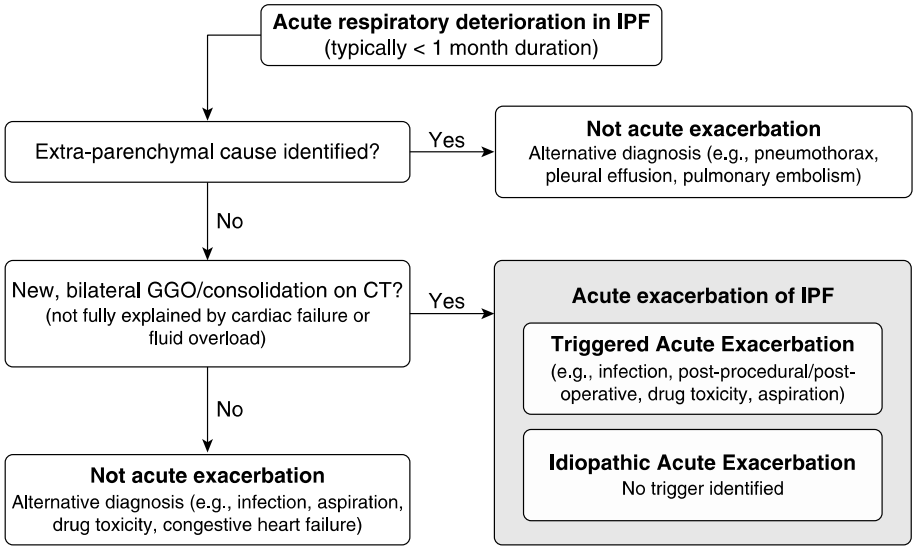

Figure 1. Proposed algorithm for AE of IPF. (Reference 17)

In terms of physical findings, patients invariably exhibit acute respiratory distress, with prominent use of auxiliary muscles for respiration, especially the scalene muscles of the neck. Lung auscultation reveals bilateral diffuse fine crackles. IPF patients sometimes have clubbed fingernails.

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4. Biomarker

In laboratory findings, classic inflammatory markers such as white blood cell counts and C-reactive protein are usually elevated [1]. In the chemistry panel, lactate dehydrogenase (LDH) is a simple and sensitive marker that predicts the short-term prognosis of AE of IPF patients. Kishaba et al reported that the serial trend of serum LDH is associated with 90-day mortality of AE [19]. In addition, Enomoto et al showed that serum Ferritin over 500 ng/ml predict a poor prognosis in AE of IPF [20]. Recently, serum periostin has received attention as a potentially attractive biomarker of IPF. Serum periostin is elevated both the acute phase and the chronic stable phase in IPF patients [21,22]. Furthermore, serum decorin is a small, leucine-rich proteoglycan that has been introduced as a novel marker for AE of IPF. Nikaido et al reported that serum decorin had a significant association with oxygenation [23]. Further multi-center studies will be required for further validation.

Both serum KL-6 and surfactant protein-D (SP-D) are useful markers of IPF [24,25]. However, KL-6 is a high-molecular weight protein. Therefore, the response of KL-6 is slower than that of LDH and elevation of serum KL-6 is commonly seen after the acute phase of AE. Elevation of serum SP-D reflects inflammatory processes, so this is often elevated in patients with severe pneumonia [26]. Distinguishing AE of IPF from severe pneumonia by serum SP-D alone is therefore quite difficult.

5. Clinical characteristics according to the new IPF criteria

On the basis of the 2016 new proposed criteria, we reported that patients with triggered AE of IPF showed more extensive new shadow compared to those with idiopathic AE. [19] (Table 2). Multivariate analysis showed that serum LDH and the serial trend of LDH predicted 90-day mortality [19] (Table 3). In Figure 2, the Kaplan-Meier survival curve showed that over 80 IU/L of serum LDH within 2 weeks was associated with poor survival (p=0.046) [19]. Yamazoe et al showed that patients with idiopathic AE were more likely to receive corticosteroids and more likely to develop AE during the winter months. On the contrary, the triggered group was more likely to have underlying lung cancer, compared to the idiopathic group (59.1% vs. 7.1%, P<0.001). In the idiopathic group, white blood cell and haemoglobin levels were independent predictors of in-hospital mortality [27]. Teramachi et al reported that AE of IPF accounted for approximately one-third of first hospitalizations for acute respiratory deterioration [28].

Table 2 Clinical characteristics of triggered and idiopathic AE of IPF patients.

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Table 2. Clinical characteristics of patients with idiopathic pulmonary fibrosis with acute exacerbation according to the ATS criteria

Parameters	Triggered (n=12) Mean±SD	Idiopathic (n=53) Mean±SD	P-value
Age (years)	77.1±8.4	74.2±11.8	0.214
Gender (male/female)	8/4	32/21	0.654
Pack-year (years)	49.3±51.3	28.5±37.3	0.056
mMRC	3.2±1.1	2.7±0.9	0.075
Dyspnea duration (days)	4.4±3.7	7.0±6.1	0.918
Clubbing (%)	42	26	0.151
WBC (mm3)	11,008±5116	11.450±5468	0.601
CRP (mg/dl)	8.2±6.5	8.2±7.5	0.504
LDH (IU/l)	410±153	389±144	0.332
KL-6 (IU/l)	2825±2354	1700±1502	0.024
Survival time (months)	1.4±0.4	11.4±3.6	0.094
Imaging findings			
Traction bronchiectasis	2.3±0.7	2.3±0.1	0.395
Honeycombing	1.4±0.5	1.7±0.7	0.858
GGO+consolidation	7.3±6.7	4.2±3.3	0.010
Total extent	11.1±10.7	8.5±5.2	0.005

mMRC: modified Medical Research Council; WBC: white blood cell; CRP: C-reactive protein; LDH: lactate dehydrogenase; KL-6: Krebs von den Lungen-6; ATS: American Thoracic Society; GGO: ground-glass opacity

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Table 3 Univariate and multivariable analysis of predictors with 90-day mortality.

Table 3. Univariate and multivariable associations of predictors with 90-day mortality

	Univariate		Multivariable	
Variable	HR (95% CI)	p	HR (95% CI)	p
New criteria	2.275 (0.874, 5.926)	0.009	0.618 (0.312, 1.227)	0.169
LDH	1.002 (1.000, 1.005)	0.002	1.003 (1.001, 1.005)	0.004
ΔLDH	1.009 (1.002, 1.016)	0.013	1.004 (1.001, 1.008)	0.017
ΔKL-6	1.001 (1.000, 1.002)	0.023	1.000 (0.999, 1.001)	0.197
P/F ratio	1.001 (0.520, 1.728)	0.080	0.994 (0.990, 0.999)	0.010

HR: hazard ratio; LDH: lactate dehydrogenase; KL-6: Krebs von den Lungen-6; P/F: ratio of partial pressure of oxygen to the fraction of inspiratory oxygen

(Reference 19)

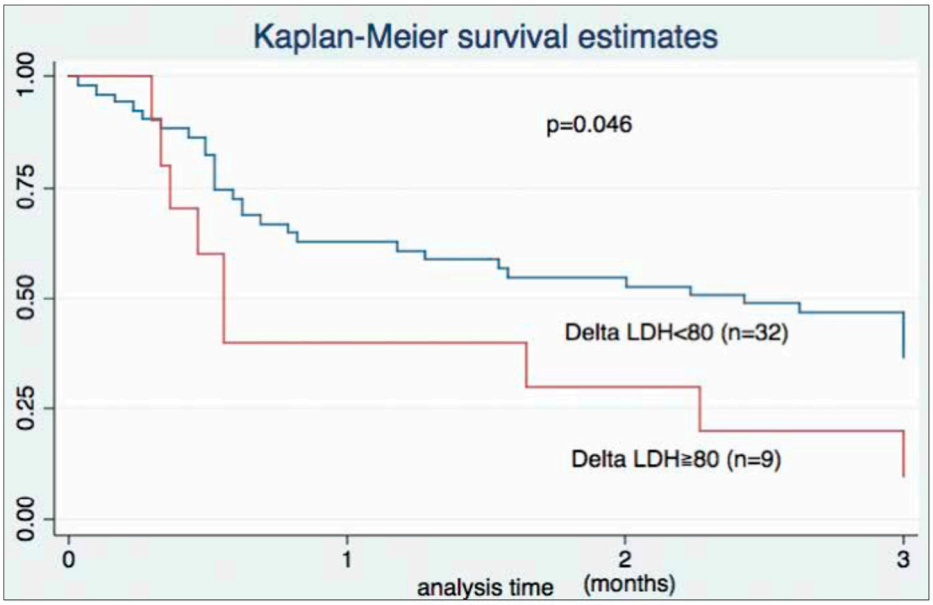

Figure 2 Survival curve based on serial trend of LDH. (Reference 19)

5. Imaging

In chest radiographs, new bilateral diffuse shadow superimposed on lower lobe reticular shadow is the typical finding in AE of IPF patients. Comparison with previous films is a necessary first step in diagnosis.

The latest international IPF guidelines (2018) strongly insist upon the importance of chest HRCT for AE of IPF [1]. We should look for co-existence of usual interstitial pneumonia (UIP) pattern such as subpleural and basal predominant opacity, with peripheral dominant and heterogeneous distribution, and architectural distortion such as traction bronchiectasis and honeycombing [29]. Akira et al proposed that the CT findings of AE of IPF should be divided into three patterns, consisting of peripheral, multifocal and diffuse infiltrates [30](Figure 3). The prevalence of new parenchymal shadow was significantly more frequent than the other two patterns. They also evaluated several follow up CT scans. In survivors with the peripheral pattern, the majority of GGO and consolidation regressed back to baseline levels of abnormality. In survivors with multifocal scan findings, GGO and consolidation disappeared with corticosteroid therapy. By contrast, survivors with the diffuse pattern demonstrated significant extension of GGO and consolidation. Kaplan-Meier survival curve showed significant difference based on CT pattern [30](Figure 3). In multivariate analysis, the diffuse CT pattern was the strongest predictor of mortality

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(Table 4). Another study, Kishaba et al showed that staging of AE of IPF is useful for prediction of prognosis. Four important parameters were identified: serum LDH, KL-6, the ratio of partial pressure of oxygen to the fraction of inspiratory oxygen concentration, and the sum of the GGO and consolidation scores. They assigned points for each parameter [31] (Table 5) and divided patients into two groups, with limited or extensive involvement [31](Table 6). In addition, patients in the extensive group had poor prognoses compared to the limited group [31](Figure 4). According to these studies, detailed assessment of the chest HRCT findings in patients with AE of IPF can inform management and prognosis for physicians.

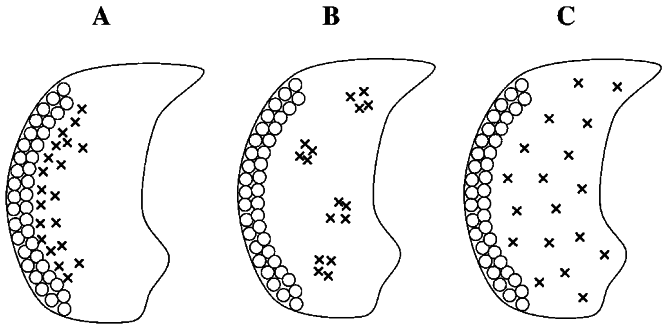

Figure 1. Scheme of computed tomography (CT) patterns. (A) Peripheral pattern; (B) multifocal pattern; (C) diffuse pattern.

Figure 3 CT patterns of AE of IPF (Reference 30).

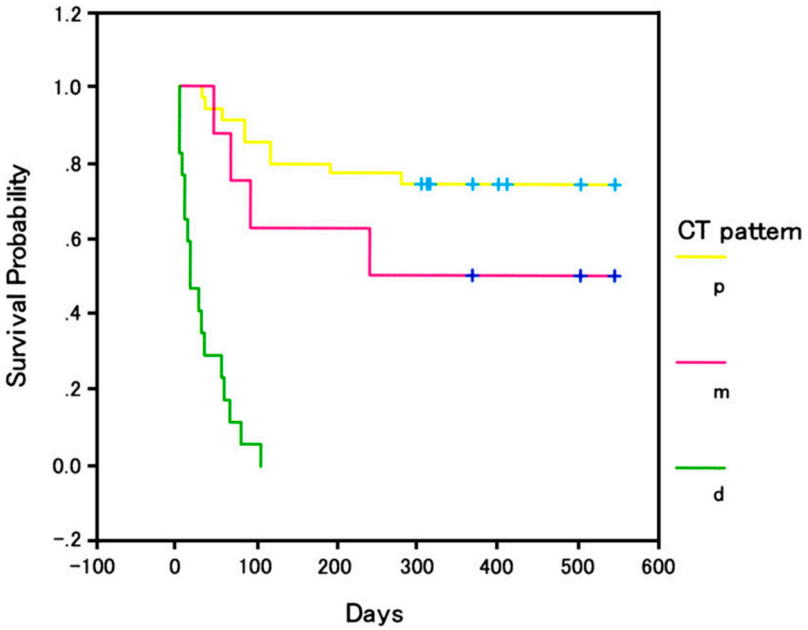

Figure 3 Survival curve based on HRCT pattern (Reference 30).

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Table 4 Multivariate analysis of AE of IPF.

TABLE 5. MULTIVARIATE ANALYSIS OF SURVIVAL IN PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA WITH ACUTE EXACERBATION

Parameter	Hazard Ratio	95% Confidence Interval	*P* Value
Age, yr	0.999	(0.955, 1.044)	0.952
Male sex	0.913	(0.343, 2.427)	0.855
Positive smoking history	2.473	(0.913, 6.701)	0.075
Baseline FVC	0.984	(0.961, 1.008)	0.185
Baseline D_{LCO}	1.016	(0.996, 1.037)	0.124
CT Patterns	4.629*	(1.900, 11,278)	0.001
CT extent	1.068	(1.022, 1.115)	0.003
Extent of alveolar opacity	0.984	(0.950, 1.019)	0.361
LDH	1.002	(1.000, 1.004)	0.011

(Reference 30)

Table 5 Point assignment of staging of AE of IPF.

Table 6 Point assignment for AE staging

Definition	Point
LDH	
\ 280	0
] 280	1
KL-6	
\ 1,000	0
] 1,000	1
P/F ratio	
] 100	0
\ 100	1
Ground-glass opacity ? consolidation score	
\ 20	0
] 20	1

(Reference 31)

Table 6 Staging of AE of IPF.

Table 8 Staging system for patients with AE of IPF patients

	Points
Limited exacerbation (n = 22)	0-2
Extensive exacerbation (n = 36)	] 3

(Reference 31)

6. Management

The 2018 Japanese IPF treatment guidelines suggested that IPF patients with AE be treated with corticosteroids, including pulse therapy [32]. Steroid pulse therapy is typically administered for consecutive three days. Weekly pulse therapy may sometimes be repeated once or twice. Prolonged pulse therapy may often be complicated by opportunistic infections such as pneumocystis pneumonia and viral infections. Therefore, meticulous titration of prednisolone dosage is required during maintenance phase. IPF itself is a fibrotic lung disease. However, there is a component of inflammation in AE of IPF [2]. Therefore, some patients respond to corticosteroids. In addition, when we see a partial response with prednisolone, we commence treatment with chronic immunosuppressants such as intravenous cyclophosphamide [33]. However, this treatment strategy is not supported by robust evidence. Recently, two novel therapies have been reported to have

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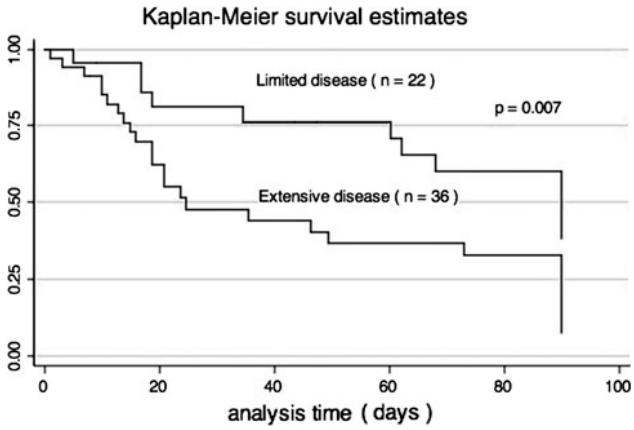
possible value in AE of IPF. A recent report showed that direct hemoperfusion with a polymyxin B-immobilized fiber column (PMX-DHP) is effective for AE and prolongs survival of AE of IPF patients [34-36]. PMX-DHP was originally introduced to manage sepsis or septic shock via neutrophil removal by the column. Early introduction of PMX-DHP within 3 days after disease onset was effective especially for dermatomyositis [37]. Based on these reports, when we see severe inflammation with AE of IPF patients, we may consider PMX-DHP as possible therapeutic option. Recombinant human soluble thrombomodulin (rhTM), which has anti-inflammatory effects and mitigates the coagulation cascade, was also developed as treatment for sepsis. In acute lung injury, there is both intense procoagulant activity and severe inflammation in the lung parenchyma [38]. Therefore, rhTM's mechanisms of action make it a plausible therapeutic agent with for AE of IPF. Several reports have shown intravenous administration of rhTM for six consecutive days improved survival of AE of IPF patients [39-43]. Medical insurance does not cover these two therapies for AE of IPF, so should discuss the use of such novel treatments with patients and their families very thoroughly. Tomioka et al reported that a case of AE of IPF improved with the use of nintedanib alone [44]. When we see mild AE of IPF patients, anti-fibrotic agents may play a role during acute and chronic phases. In addition, high-flow nasal cannula (HFNC) is sometimes used for IPF recently, with reduced tachypnea and improvements in minute ventilation [45]. In AE of IPF patients, pharmacological treatment with HFNC can provide relief of dyspnea [46]. Future multi-center studies of HFNC will be eagerly anticipated.

6. Prognosis

AE of IPF is usually associated with a poor prognosis. Natsuizaka et al reported that AE accounts for 40% of IPF death [47](Figure 5). Mean survival of AE of IPF is less than one year and 90-day mortality is approximately 50%. Therefore, prevention of AE is crucial. Recent anti-fibrotic agents, especially nintedanib, were shown to prevent AE of IPF in an international clinical trial [48]. Subgroup analysis showed a 75% reduction of AE with nintedanib, especially among Japanese patients [49]. Pirfenidone combined with prednisolone and rhTM may improve survival in patients with AE of IPF [50]. Therefore, judicious use of these anti-fibrotic agents is likely to provide good prognoses and prevention of AE of IPF patients [51](Table 7).

Figure 4. Survival curve based on staging of AE of IPF.



(Reference 31)

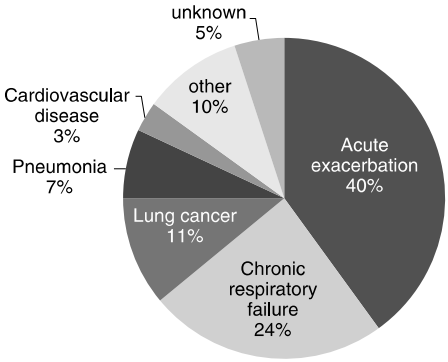


Figure 4. Causes of death in patients with idiopathic pulmonary fibrosis.

189

190 **F**igure 5 Cause of death of IPF (Reference 47).

191 **T**able 7 Characteristics of Anti-fibrotic agent.

Table 3. Pharmacologic Management of IPF.*

Variable	Nintedanib	Pirfenidone
Mechanism of action	Tyrosine kinase inhibition	Inhibition of TGF-β production and downstream signaling, collagen synthesis, and fibroblast proliferation (selected list)
Efficacy	Slows FVC decline by 50%	Slows FVC decline by 50%
FDA-approved dose	150 mg by mouth twice daily	801 mg by mouth thrice daily
Common side effects	Diarrhea	Anorexia, nausea, photosensitivity
Enzyme metabolism	Ester cleavage (major), CYP 3A4 (minor)	CYP 1A2 (major), other CYP enzymes (minor)
Cautions	Risks of both bleeding and arterial thrombosis; risk of gastrointestinal perforation (rare); anticoagulant and prothrombotic drugs should be avoided	CYP 1A2 inhibitors (e.g., fluvoxamine and ciprofloxacin) can raise pirfenidone levels; CYP 1A2 inducers (e.g., omeprazole and smoking) can lower pirfenidone levels
Need for liver-function monitoring	Yes†	Yes‡
Clinical strategies to minimize side effects	Use of antidiarrheal agents, temporary dose reduction to 100 mg twice daily	Slow dose increase over 14-day period, medication to be taken with food, use of antacids, use of antiemetic agents, sun avoidance

192

193 (Reference 51)

194 **Reference**

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