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Acute exacerbation of idiopathic pulmonary fibrosis: Application of the diagnostic criteria and the role of respiratory intermediate care unit and mechanical ventilation

Joana Daniela Rodrigues Barbosa, Sara Moreira da Silva Trindade Salgado, Maria Paula Cruz Mata Nazaré Pinheiro Esteves

[1]Chest Department, Pulmonology Unit, Unidade Local de Saúde Santa Maria, Hospital Pulido Valente, Lisbon, Portugal

Abstract. *Background and aim:* Acute exacerbations of Idiopathic Pulmonary Fibrosis (AE-IPF) have a poor prognosis, and the majority of evidence supports the lack of benefit of invasive mechanical ventilation. The objective was to evaluate patients with AE-IPF admitted to a Respiratory Intermediate Care Unit (RICU). *Methods:* A retrospective study was conducted on AE-IPF patients admitted to a Portuguese RICU from 2014 to 2018. *Results:* Thirty-one admissions (n=20) corresponded to IPF (9 were suspected AE by the diagnostic criteria of IPFnet 2007 and 15 by the International Working Group Report 2016). The mean age was 70±11 years, and 53% were male. FVC was 69.7±29% and DLCO was 38.7±14%. The initial PaO_2/FiO_2 was 145±71, as opposed to 228±91 in non-AE patients. Bronchoscopy was performed on three patients. Regarding treatment, 60% had non-invasive ventilation, and 40% had high-flow oxygen therapy. Methylprednisolone pulses were used in two patients. Eight patients died during hospitalization (53%); four died within five months, and only one survived. *Conclusions:* Recent diagnostic criteria of AE-IPF help identify these patients, contrary to old criteria. Bronchoscopy is not always possible to perform, and a small number of patients receive methylprednisolone pulses. No statistically significant differences were observed between the discharged and deceased groups, but higher levels of LDH at admission and lower DLCO could help identify risk groups. AE-IPF has a poor prognosis, and admission at RICU could be helpful in the management of these patients, reducing the need for admission to intensive care units, and consequently costs and risks of invasive mechanical ventilation.

Key words: fibrosis, idiopathic pulmonary fibrosis, acute exacerbation, respiratory care unit, mechanical ventilation

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is defined as a form of chronic, progressive and fibrotic idiopathic interstitial pneumonia associated with a pattern of usual interstitial pneumonia (UIP) in high-resolution computed tomography (HRCT) and/or histological findings (1). It is the most common form of idiopathic interstitial pneumonia, often seen in elderly men who smoke. The median survival after diagnosis is between 2 and 5 years (2). Acute exacerbations of Idiopathic Pulmonary Fibrosis (AE-IPF) have an estimated incidence of 5 to 10% per year and poor prognosis with high incidence of hospital mortality that may reach 96% (3-5). Diagnostic criteria were defined by IPFnet 2007 consisting of diagnosis of IPF, unexplained dyspnea within 30 days, new bilateral ground-glass opacities and/ or consolidation on a background of UIP in CT (2,3).

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Correspondence: Joana Rodrigues Barbosa, MD
Chest Department, Pulmonology Unit, Unidade Local de Saúde Santa Maria, Hospital Pulido Valente, Lisbon, Portugal
E-mail: dr.joana.rodrigues.barbosa@gmail.com
ORCID: 0000-0001-5161-0616

Exclusion of alternative causes is mandatory, and absence of infection demonstrated by endotracheal aspirate or BAL is necessary (3). The revised definition of AE-IPF by the International Working Group Report 2016 is an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality (6). The revised diagnostic criteria only exclude the diagnosis when deterioration can be explained by heart failure or fluid overload, not mentioning the need of endotracheal aspirate or BAL to exclude respiratory infection (6). In real practice, realization of endotracheal aspirate or BAL is not always possible in non-intubated patients with severe illness, thus many patients with possible AE-IPF were never confirmed. With the new criteria it is simpler to define these patients and to treat accordingly (Table 1).

The proposed conceptual framework for evaluation of acute respiratory deterioration in IPF mentioned in the International Working Group Report 2016 excludes patients with extra-parenchymal cause identified (e.g. pulmonary embolism, pneumothorax, pleural effusion) and defines patients with new bilateral ground-glass opacification/ consolidation on CT, differentiating in triggered acute exacerbation (e.g. infection, post-procedural/post-operative, drug toxicity, aspiration) or idiopathic with no trigger identified (6). Treatment generally involves supportive care and high-dose corticosteroid therapy, but optimal therapy has not been established (3,6-10). The recent clinical trial EXAFIP which added intravenous cyclophosphamide pulses to glucocorticoids showed an increased 3-month mortality, and other therapies are unproven (7-10). Literature supports that patients admitted to an ICU with need of intubation have a poor prognosis and no evidence of benefit with invasive mechanical ventilation (IMV) (Table 2) (4,11-20). However, a recently study related to outcomes of mechanical ventilation (MV), showed that in patients with fibrotic interstitial lung disease (f-ILD), including IPF patients, IMV may effectively treat acute exacerbation of f-ILD if good ventilation and general conditions can be maintained (19).

The aim of this study was to evaluate a population of patients with AE-IPF admitted to a Respiratory Intermediate Care Unit (RICU) in Lisbon.

Methods

Study design

This was a retrospective, descriptive, observational study based on the medical records of all individuals diagnosed with AE-IPF in a four-year period (from January 1, 2014 to December 31, 2018) admitted to a Respiratory Failure Unit that is comprised of a 13-bed medical RICU in a tertiary university hospital (Hospital Pulido Valente in Lisbon). All patients with "IPF", "pulmonary fibrosis" or "UIP" on clinical records were evaluated and the selection of IPF patients was based on diagnostic criteria (exclusion of other causes of interstitial lung disease, the presence of a HRCT pattern of UIP and/or characteristic histopathological patterns). Patients with probable UIP who had information on clinical files who permitted the exclusion of other causes of interstitial lung disease were included. The criteria of

Table 1. Diagnostic criteria applied in AE-IPF (3,6)

Diagnostic criteria by IPFnet 2007 (3)	**Diagnostic criteria by International Working Group Report 2016 (6)**
Diagnosis of IPF	
Unexplained dyspnea within 30 days	Acute worsening or dyspnea < 1 month duration
New bilateral ground-glass opacities and/or consolidation superimposed on background findings consistent with UIP in CT	
No evidence of infection by endotracheal aspirate or BAL	Deterioration not fully explained by heart failure or fluid overload
Exclusion of alternative causes	Excludes patients with extra-parenchymal cause identified (e.g., pulmonary embolism, pneumothorax, pleural effusion)
	Differentiates in triggered acute exacerbation (e.g., infection, post-procedural/ post-operative, drug toxicity, aspiration) or idiopathic (with no trigger identified)

Abbreviations: IPF – Idiopathic Pulmonary Fibrosis, UIP – Usual Interstitial Pneumonia, CT – Computed tomography, BAL – Bronchoalveolar Lavage

Table 2. Outcome studies on IPF patients admitted in an ICU and respective conclusions (4,11-20)

Study	Sample n	Mortality n (%)	Conclusions
Fumeaux T. et al. Intensive Care Med, 2001	14	14 (100%)	MV was associated with 100% mortality, despite aggressive therapeutic and diagnostic procedures (11).
Blivet S. et al. Chest, 2001	15	11 (73%)	Outcome of patients with IPF referred to the ICU for ARF was very poor and not improved by MV. Without a clearly identified reversible cause of ARF, these patients should not benefit from admission to the ICU (12).
Stern J. et al. Chest, 2001	23	22 (96%)	MV does not benefit IPF patients presenting with ARF. Initiation of MV in IPF patients is questionable and should be restricted to patients in whom lung transplantation can be performed within a few days after initiation of MV (13).
Saydain G. et al. Am J Respir Crit Care Med, 2002	38	Mortality at ICU 17 (45%) Hospital mortality 24 (61%) Two months after discharge - 92%	Patients with IPF admitted to the ICU have poor short- and long-term prognosis (14).
Molina-Molina M. et al. Med Clin (Barc.), 2003	20	20 (100%)	MV and aggressive life support measures do not seem to provide any further benefit (15).
Ambrosini V. et al. Eur Resp J, 2003	5	4 (80%)	Only one patient did invasive MV and died. One patient did NIV and survived. In the other three patients only comfort and palliative measures were carried out. The smaller extent of alveolar lesions seems to be associated with a better prognosis (16).
Al-Hameed F. et al. Can Respir J, 2004	25	24 (96%)	In the absence of a reversible cause, patients with IPF who develop acute exacerbation of IPF may not benefit from ICU admission and mechanical ventilation. It is imperative to rule out an infection or other reversible causes of respiratory failure before admission to the ICU is denied (4).
Mollica C. et al, Respiration, 2010	34	85%(100% for invasive MV, 74% for NIV).	MV does not appear to have a significant impact on the survival of patients with end-stage IPF. NIV may be useful for compassionate use (17).
Vianello A. et al, J Crit Care, 2014	18 (6 AE-IPF)	10 (56%) RICU mortality	Poor outcome for IPF patients who were administered NIV. Use of NIV was found to be associated with clinical benefits in selected IPF patients, preventing the need for intubation and reducing the rate of complications/death (18).
Matsunashi A. et al, Respiratory Investigation, 2023	28 (10 AE-IPF)	15 f-ILD (53.6%)	IMV may effectively treat acute exacerbation of f-ILD if good ventilation and general conditions can be maintained (19).
Sim J, et al, Korean J Intern Med, 2024	1227 IPF	Overall mortality 69.4% (90-day mortality 85.3%)	Prognosis of patients with IPF receiving MV has not improved significantly. Use of MV should be made with careful deliberation (20).

Abbreviations: MV – Mechanical Ventilation, NIV – Noninvasive Mechanical Ventilation, f-ILD – Fibrosing Interstitial Lung Diseases, IMV – Invasive Mechanical Ventilation, IPF – Idiopathic Pulmonary Fibrosis, ICU – Intensive Care Unit, ARF – Acute Respiratory Failure, RICU - Respiratory Intermediate Care Unit.

IPFnet 2007 and the International Working Group Report 2016 were subsequently applied to the patients with IPF diagnosis, with the selection of patients with acute exacerbations (Figure 1). A follow up until January 31, 2024, was performed and mortality was compared between IPF versus non-IPF patients. All data were processed anonymously according to the institution's privacy policy.

Data collection and analysis

Information regarding demographic characteristics, clinical, analytical, imaging, therapeutic data and outcome of patients with AE-IPF were evaluated. Diagnostic criteria of IPF net 2007 and criteria of International Working Group Report 2016 were applied. Patients without criteria of AE-IPF were excluded. The SPSS Statistics software (version 23.0 for Windows) was the main data analysis tool used in this study. Data were summarized as frequencies for categorical variables, as mean ± standard deviation for normally distributed data (using Kolmogrov-Smirnov and Shapiro-Wilk tests or Skewness and Kurtosis) and median (IQR = Q_3-Q_1) for data non normally distributed. Comparisons between the groups (AE-IPF patients discharged *versus* deceased during hospitalization) were explored using independent T-test for continuous variables normally distributed.

Results

Of the 2114 admissions at RICU, 135 patients were selected, however 104 patients were excluded after reviewing the patients' files: 28 with chronic hypersensitivity pneumonitis, 24 with pulmonary involvement associated with autoimmune disease, 8 with fibrotic idiopathic nonspecific interstitial pneumonia, 9 with drug-induced pneumonitis, 8 with other diseases and 27 without a definitive diagnosis/unclassifiable pulmonary fibrosis. Thirty-one admissions corresponded to IPF (n=20 patients), of those, 9 had criteria of AE by IPFnet 2007 and 15 by the revised diagnostic criteria of 2016. Five patients had two or more hospitalizations during the selected period. These 15 admissions corresponded to 13 patients (two patients were readmitted with AE-IPF during the selected period). Other admissions corresponded to causes unrelated to AE, such as heart failure, pulmonary embolism, respiratory infection such as pneumonia or acute tracheobronchitis, pneumothorax, etc. We reported some associated triggers: one patient did chemotherapy; one was a post-operative patient and eleven with suspected infection. No identified triggers were detected in two patients (idiopathic AE). Of these patients, 53% were male, the mean age was 70 ± 11 years, with a mean of 34 ± 29 months from diagnosis to admission. The GAP score was 6-8 in 13.3%, 4-5 in 73.4% and 0-3 in 13.3%. Mean FVC was 69.7 ± 29% and mean DLCO was 38.7 ± 14%. The most identified comorbidities were diabetes (46.7%), heart disease (46.7%) and pulmonary hypertension (40%). The mean initial PaO_2/FiO_2 was 145 ± 71, as opposed to 228 ± 91 in non-AE patients. Four patients were on antifibrotic treatment: 2 nintedanib and 2 pirfenidone

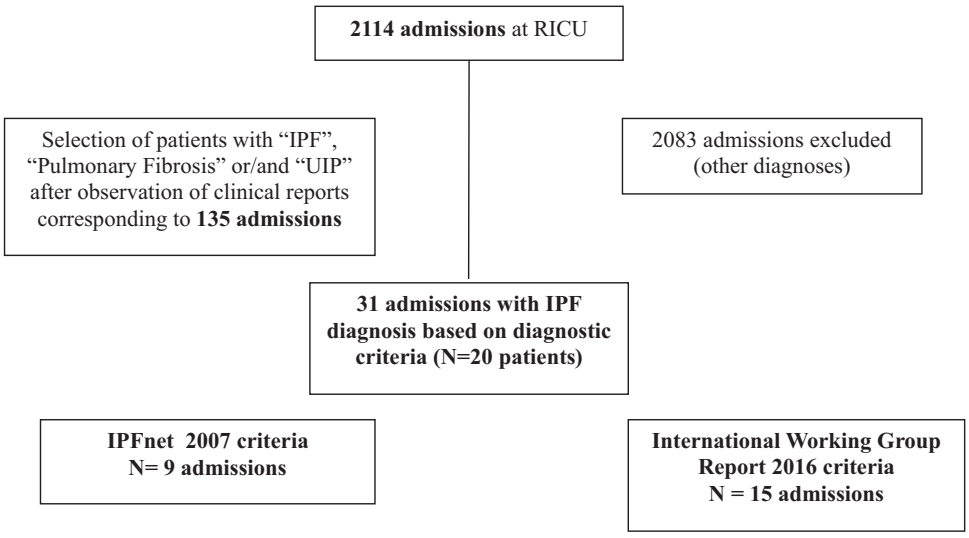

Figure 1. Flowchart with study design and patients who were admitted with AE-IPF.

and 80% were under long-term oxygen therapy (LTOT). Only three patients with AE-IPF underwent bronchoscopy and a negative microbiological exam was observed in all the patients. Ten patients (66.7%) collected sputum samples, only positive in two cases, but 80% of the patients were under antibiotic therapy. Regarding treatment, 60% had noninvasive ventilation (NIV), 40% high-flow nasal cannula therapy (HFNC) and all underwent corticotherapy, but methylprednisolone pulses were only used in two. The mean days of hospitalization was 24 ± 16. Eight patients died during hospitalization (53% versus 26.9% in non-IPF group). After discharge (7 hospitalizations corresponded to 5 patients, two were hospitalized twice), four died within five months and only one survived (97 months of survival to date). This patient was under treatment with pirfenidone. Comparing to non-IPF patients, mortality in IPF patients (with or without AE-IPF) was 90% during follow-up (93.3% in AE-IPF patients), different from 67.3% in non-IPF group. The mean LDH was 469 ± 178 U/L in patients who were discharged and 659 ± 272 U/L in patients who died. However, there is no statistically significant difference between the average LDH of the two groups (p-value = 0.131). Although some tendencies could be identified, there was no statistically significant difference between discharged group *versus* deceased group (p-value > 0.05), namely in average age, FVC, DLCO, LDH, CRP, NT-proBNP, PaO_2/FiO_2, $PaCO_2$ and use of NIV, HFNC and methylprednisolone pulses during hospitalization. General characteristics of the patients with AE-IPF can be observed on Table 3 and differences between discharged group *versus* deceased group on Table 4.

Table 3. General characteristics of the admissions with AE-IPF (n = 15 admissions related to 13 patients with 2 readmissions)

Baseline characteristics	**N = 15**
Gender male (%)	8 (53%)
Age (years)	70 ± 11
Cigarette smoking (former smokers, %)	80%
FVC (% predicted)	69.7 ± 29%
DLCO (%)	38.7 ± 14%
GAP score 1-3 (%) 4-5 (%) 6-8 (%)	 13.3% 73.4% 13.3%
Mean of diagnosis to admission (months)	34 ± 29
Histologic diagnosis of UIP (%)	4 (27%)
Comorbidities	
GERD (%) Diabetes mellitus (%) Lung cancer (%) Pulmonary hypertension (%) Sleep apnea (%) Heart disease (%) Pulmonary embolism (%) Depression (%)	26.7% 46.7% 13.3% 40% 6.7% 46.7% 6.7% 13.3%
Previous treatment	
Pirfenidone Nintedanib LTOT (%)	2 2 80%
Triggers	
Idiopathic (%) Respiratory infection (%) Chemotherapy (%) Pos-operative (%)	2 (13%) 11 (73%) 1 (7%) 1 (7%)
Laboratory data	
CRP at admission (mg/dL) Leukocytosis at admission (x 10^9/L) LDH at admission (U/L) NT-proBNP (pg/mL) PaO_2/FiO_2 at admission PaO_2/FiO_2 at discharge $PaCO_2$ at admission (mmHg)	8.2 ± 6.8 11.594 ± 4.270 570 ± 245 1307 (4987) 145 ± 71 202 ± 92 43.6 ± 11.6
Treatment during hospitalization	
Corticotherapy (%) Pulses of methylprednisolone (%) Antibiotic therapy (%) Noninvasive ventilation (%) High-flow oxygen therapy (%)	15 (100%) 2 (13%) 12 (80%) 9 (60%) 6 (40%)
Outcome	
Days of hospitalization Death during hospitalization (%) Discharge	24 ± 16 days 8 (53%) 7

Abbreviations: FVC – Forced Vital Capacity, DLCO – Diffusing capacity for carbon monoxide, UIP – Usual Interstitial Pneumonia, GERD – Gastroesophageal Reflux Disease, LTOT – Long-term Oxygen Therapy, CRP – C-reactive protein, LDH – Lactate Dehydrogenase

Discussion

The present study demonstrates that old criteria for AE-IPF are difficult to apply in the context of hospitalization and a complete exclusion of associated causes is not always achieved, making it difficult to confirm a suspicion of AE, contrary to recent criteria (5). Some procedures to confirm respiratory infection, such as bronchoscopy, could not be feasible in non-intubated patients with low PaO_2/FiO_2. Despite the small number of patients, the data obtained allowed us to infer that AE has a poor prognosis and RICU allows proper management, as intensive care units and invasive mechanical

Table 4. Differences between discharged group *versus* deceased group

	Discharged group N=7 admissions	Deceased group N=8 admissions	p value
General characteristics previous to admission			
Age (years)	76 ± 5	65 ± 13	p=0.063
FVC (%)	66.71 ± 38.0	72.36 ± 20.7	p=0.722
DLCO (%)	42.3 ± 16.9	35.5 ± 11.5	p=0.373
Data analyzed during admission			
LDH (U/L)	469 ± 178	659 ± 272	p = 0.140
CRP (mg/dL)	8.6 ± 6.9	7.8 ± 7.3	p = 0.838
NT-proBNP (pg/mL)	4212 ± 5069	2036 ± 2670	p = 0.308
PaO_2/FiO_2	137 ± 73	153 ± 74	p = 0.690
$PaCO_2$ (mmHg)	47.8 ± 11	39.9 ± 12	p = 0.200
NIV	42.9% (3/7)	75% (6/8)	p = 0.315
HFNC	14.3% (1/7)	62.5% (5/8)	p = 0.119
Methylprednisolone pulses	0% (0/7)	25% (2/8)	p = 0.467

Abbreviations: FVC – Forced Vital Capacity, DLCO – Diffusing capacity for carbon monoxide, LDH – Lactate Dehydrogenase, CRP – C-reactive protein, NIV – Noninvasive Ventilation, HFNC – High-Flow Nasal Canula

ventilation have no benefit, given the high mortality rate and the lack of effective therapy (5). The management of the AE-IPF varies slightly from country to country. Since these patients need high levels of oxygen therapy and ventilation support, our department preferentially admits them in a RICU or ICU, although in the absence of RICU or ICU beds they could be admitted in a regular pulmonary ward. ICU admissions were reserved to younger patients, on a lung transplant list and admitted with reversible causes, although most patients do not comply these criteria. In our unit a small number of patients received methylprednisolone pulses, showing some apprehension in the use of this therapy, consistent with the fear of adverse effects and complications and the mistrust of a failure in the diagnosis. We observed that the only two patients who underwent corticosteroid pulses died, so this intervention did not interfere with the outcome of these patients. The low number of patients admitted to our unit under antifibrotics can be explained by the fact that some patients weren't initially followed in our department, some didn't have functional criteria for approval in our hospital, and by the study period (since 2014), in which some patients had not yet started this therapy in our country. In our department, antifibrotics could only be prescribed since 2009, through clinical trials (nintedanib), and since 2013 through a specific authorization (AUE-Authorization for Exceptional Use). INFARMED (Portuguese national authority for drugs and health products) only approved pirfenidone in 2016 and nintedanib in 2017, so there were some difficulties during this period for our patients to begin treatment, and some patients were waiting for the approval to start the medication. Another explanation could be the reduction of the risk of acute exacerbation in patients doing antifibrotics, reducing hospital admissions, however this hypothesis must be confirmed. Although there is also no statistically significant difference between the group who was discharged *versus* deceased, some factors could help us identify risk groups for poor prognosis. The limitations to this study were the low number of patients included and the lack of a comparative group, namely with patients admitted to an ICU. However, data of our ICU in the same selected period, showed that five patients were admitted, were mainly younger males compared to RICU-patients, invasive mechanical ventilation (IMV) was used in the majority (n=4) and all patients died during hospitalization. In recent years, there has been an effort to discover drugs that can prevent or halt the formation of fibrosis and fibroblast, and several decades of research have contributed to a better understanding of its pathogenesis (21,22). To date, only two drugs (nintedanib and pirfenidone) have shown treatment efficacy by slowing

the decline of lung function, and are approved in IPF patients (22). The pathogenesis of IPF remains unclear and involves multiple complex interactions and mechanisms (22). Several clinical trials were conducted, some of them with drugs that had little or no impact on the defined outcomes. Novel agents are under investigation such as HZN-825 (Fipaxalparant), Nerandomilast (BI 1015550), Jaktinib, BBT-877, Saracatinib, Inhaled Treprostinil, Atezolizumab, Bexotegrast (PLN-74809), BMS-986278, Axatilimab, SHR-1906, Setanaxib (GKT137831), Tazarotene (GRI-0621), Anlotinib, Ifenprodil, Garadacimab, C21, RXC007, Taladegib (ENV-101), Deupirfenidone (LYT-100), Leramistat, TTI-101, DWN12088, LTP001, Vixarelimab, ARO-MMP7, Ifetroban, Cudetaxestat (BLD-0409), AK3280, INS018_055, CMR316, Sufenidone (SC1011), GSK3915393, BI 1819479, VUM02-Human umbilical cord tissue derived mesenchymal stem cells injection, REGEND001-Autologous transplantation of P63+ lung progenitor cells, etc. (22-33). In summary, recent diagnostic criteria of AE-IPF helps in identifying these patients more easily. Poor prognosis is the main scenario and admission at RICU could be the choice to manage this condition. This study supports that RICU could be helpful in the management of these patients, reducing the need of admission in an ICU, and consequently costs and risks of invasive mechanical ventilation, that do not bring any long-term benefit to these patients. Future research is needed to identify novel therapies to slow the progression of disease and reduce exacerbations.

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