Acute Exacerbation of Idiopathic Pulmonary Fibrosis: Outcome and Prognostic Factors

Virginie Simon-Blancal, Olivia Freynet, Hilario Nunes, Diane Bouvry, Nicolas Naggara, Pierre-Yves Brillet, Damien Denis, Yves Cohen, François Vincent, Dominique Valeyre, Jean-Marc Naccache

Services de Pneumologie, Radiologie et Réanimation Médico-Chirurgicale, Hôpital Universitaire Avicenne, Assistance Publique-Hôpitaux de Paris, and EA 2363 Université Paris 13, Bobigny, and UMR 6553 ECOBIO, Université de Rennes 1, Campus de Beaulieu, Rennes, France

Background: Acute exacerbation is a substantial cause of death in patients with idiopathic pulmonary fibrosis with poorly described prognostic factors. Objectives: To review the features associated with acute exacerbation of idiopathic pulmonary fibrosis and assess its prognostic factors. Methods: Thirty-seven occurrences of acute exacerbation of idiopathic pulmonary fibrosis were retrospectively reviewed in the medical records of 27 patients. Clinical presentation, radiographic studies, pulmonary function tests, laboratory data, treatment, and outcome were analyzed. Results: Acute exacerbation of idiopathic pulmonary fibrosis occurred more frequently between December and May (75.7%) than between June and November (24.3%) (p = 0.01). In-hospital mortality was 27% and median survival was 4.2 months (range 0.2–36.6). Significant differences between nonsurvivors and survivors included the time elapsed between their admission and the initiation of treatment for acute exacerbation (6 vs. 3.1 days, p = 0.04), lactate dehydrogenase levels at admission (801 vs. 544.6 IU/l, p = 0.002), impairment of the prior forced vital capacity (51.2 vs. 65%, p = 0.01) and diffusing capacity for carbon monoxide (21.7 vs. 34%, p = 0.01). Furthermore, the evolution of gas exchange in the first 10 days after the initiation of treatment was associated with in-hospital and long-term mortality. Conclusions: Acute exacerbations of idiopathic pulmonary fibrosis are more frequent during winter and spring. The time between admission and initiation of treatment is a new prognostic factor that should be investigated further. This finding highlights the need for a fast diagnostic approach that should probably be standardized. Early gas exchange modifications reflect the response to treatment and predict the prognosis.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of idiopathic interstitial lung disease. It usually presents with an insidious onset. Its symptoms slow-
ly progress over a period of months to years, with a median survival ranging from 2 to 4 years [1, 2]. However, cases of acute deterioration have been described. This disease may occur secondary to infection, pulmonary embolism, or heart failure but also without any identifiable cause; it is then termed acute exacerbation of IPF (IPF-AEx) [3].

After the first description by Kondoh et al. [4], this clinical entity is now well recognized by physicians as a highly morbid clinical event. The 1-year incidence of IPF-AEx was recently estimated at 14.2% and the 1-month mortality rate at 59.5% [5, 6]. Various treatment strategies have been used but the most effective therapy remains to be determined. Recent international guidelines in IPF stated that corticosteroids should be used in the majority of patients with IPF-AEx [7]. Radiological pattern, lactate dehydrogenase (LDH), and C-reactive protein (CRP) at the time of IPF-AEx are the only described prognostic factors [5, 8, 9]. Moreover, as lung transplantation may be the last therapeutic option for some patients, accurate estimates of individual survival can be extremely useful for making the right clinical decisions.

This retrospective study was carried out on a large cohort of patients hospitalized for IPF-AEx. The goal of this report is to review our experience with IPF-AEx and highlight potential predictors of mortality and criteria for response to treatment.

Methods

Study Subjects

A retrospective review of the medical records of all patients with IPF-AEx who had been hospitalized at Avicenne Hospital (Assistance Publique Hôpitaux de Paris) was conducted between January 2002 and October 2009.

The Institutional Review Board of the French Learned Society of Respiratory Medicine approved this observational analysis of medical records; informed consent was not required.

Diagnosis of IPF-AEx was based on the following criteria: a prior or concurrent diagnosis of IPF; unexplained worsening or development of dyspnea within 30 days; newly developing ground glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with an usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) scans, or new alveolar opacities on chest radiographs, and exclusion of alternative causes including pulmonary infection, left heart failure, pulmonary embolism, or identifiable cause of acute lung injury [3].

Thirty-seven cases of IPF-AEx were included in this study. All patients, including 14 who underwent surgical lung biopsy, met the diagnostic criteria for IPF according to ATS/ERS guidelines [1]. Eleven acute episodes were excluded because of other causes (n = 4), a longer time period (above 30 days) for clinical deterioration (n = 2), or chest imaging missing data (n = 5).

IPF History and Data at Admission

Data on demographic characteristics, tobacco use, past medical history, last results of pulmonary function tests, and current treatment of AE were collected. Significant events occurring in the 2 months preceding the AEx were systematically searched as potential precipitating factors. Data recorded at admission included the following: time elapsed between the first symptoms and hospital admission, pulmonary symptoms, body temperature, arterial blood gas analysis, blood neutrophil count (n = 36), CRP (n = 37), procalcitonin (n = 23), enzyme-linked immunosorbent assay-based D-dimer test (n = 29), N-terminal pro-B-type natriuretic peptide (Nt-proBNP, n = 24), LDH (n = 26), and estimation of systolic pulmonary arterial pressure via tricuspid regurgitant velocity on echocardiography (n = 28).

HRCT Examination

Scanning was performed using a standard chest protocol with contrast enhancement to exclude pulmonary embolism. HRCTs were available for review in consensus by two of us (N.N. and P.Y.B.) in 32 IPF-AEx episodes. Newly developing pulmonary opacities were classified into ground glass attenuation and consolidation as well as into peripheral, multifocal, and diffuse patterns according to Akira et al. [9].

Treatment Options

The therapeutic approach of AEx, in particular the decision to proceed to antibiotic, anticoagulation, cyclophosphamide, and/or ventilation treatment, was left to the referring physician’s judgment.

Treatment modalities and the time between hospital admission and treatment initiation were recorded.

Outcome Data

The primary clinical end point was in-hospital mortality. The secondary clinical end point was long-term mortality. Early evolution of IPF-AEx was determined from the gas exchange modifications occurring in the first 10 days after the initiation of treatment as shown in table 1.

Statistical Analysis

Continuous variables are reported as means ± SD or medians (range) when more appropriate and discrete variables as numbers or percentages. The Mann-Whitney U test was used to compare the frequency of IPF-AEx between the periods of December to May and June to November. Univariate analysis (Mann-Whitney U test and Fisher’s exact test) was used to identify factors associated with in-hospital mortality. To compare the prognostic impact of early modification in gas exchange under treatment, survival curves were drawn using Kaplan–Meier estimates and compared with the logrank test. Two-tailed p < 0.05 were considered statistically significant. Analyses were carried out using Statistica 6 software (Statsoft France, Maisons-Alfort, France) and Statview statistical software (SAS Institute Inc., Cary, N.C., USA).


**Patient Characteristics**

The 37 IPF-AEx episodes occurred in 27 patients (22 males and 5 females, gender ratio 4.4). The median age (range) at the time of IPF diagnosis and IPF-AEx was 66 (9–77) and 69 (31–81) years, respectively. Seven patients (26%) had more than 1 episode of AEx. Five patients had 2 episodes; 1 patient had 3 episodes, and the last had 4. Recurrences occurred 6 months (range 2–38) after the previous episode.

Infectious disease was excluded through several microbiological samples. Cultures of sputum for bacteria (n = 34), mycobacteria (n = 22), and fungi (n = 22) were negative. Analysis of bronchoalveolar lavage for detection of bacteria (n = 11), various viruses (n = 11), and *Pneumocystis jirovecii* (n = 9) was negative. Urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila* (n = 35), and serological studies for viruses (influenza A, influenza B, parainfluenza 1–3, adenovirus, rhinovirus, and respiratory syncitial virus; n = 34), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *L. pneumophila* (n = 37), were negative. Nasopharyngeal aspirates for detection of respiratory viruses (influenza A, influenza B, parainfluenza 1–3, respiratory syncitial virus, and cytomegalovirus; n = 24) were negative. Left heart failure was excluded by using the mode of presentation and/or echocardiography (n = 28), and pulmonary embolism was excluded by using computed tomographic pulmonary angiography (n = 35) or low clinical probability with a negative D-Dimer test (n = 2).

Sixty-seven percent of patients were former (n = 15) or active (n = 3) smokers. Twelve patients corresponding to 19 IPF-AEx had combined pulmonary fibrosis and emphysema. Relevant past medical history included hypertension in 10 patients, diabetes mellitus in 6 patients, and pulmonary carcinoma in 2 patients diagnosed 5 and 7 months before IPF-AEx, respectively. Eight patients were under proton pump inhibitors for gastroesophageal reflux diagnosed based on typical clinical symptoms (n = 5) or positive 24-hour ambulatory pH monitoring (n = 3).

**Clinical Course of IPF-AEx**

AEx occurred at a median of 40 months (range 5–147) after IPF diagnosis. Last pulmonary function tests [forced vital capacity (FVC), n = 33; diffusing capacity for carbon monoxide corrected for hemoglobin level (DLCO), n = 30] and arterial blood gas analysis (n = 37) were performed 4 months (range 1–44) before AEx. The mean percentages of predicted FVC and predicted DLCO were 61 ± 8 and 31 ± 11%, respectively. The mean partial pressure of arterial oxygen (PaO₂) was 72 ± 13.9 mm Hg.

Twenty-nine of the 37 AEx (78.3%) episodes occurred in patients treated for IPF. Treatment consisted mainly of corticosteroids (n = 24) in monotherapy (n = 9) or associated with immunosuppressive therapy (n = 6) and/or N-acetyl-cysteine (n = 16). Two patients were treated with immunosuppressive drugs only and 3 were included in a randomized, placebo-controlled trial (NCT00075998, NCT00287716). No patient received chemoprophylaxis for *P. jirovecii* infection.

**Clinical, Biological, and Radiological Features of IPF-AEx**

In most patients no AEx precipitating factor was identified. Two patients developed AEx after BAL and lobectomy for lung cancer, respectively, 6 days after the procedure. Six patients developed AEx 42 days (range 30–60) after an acute respiratory infection (n = 5) or sinusitis (n = 1), which had resolved at presentation. One patient developed AEx 1 month after pulmonary embolism.

The incidence of AEx was higher between December and May, with 28 (75.7%) of the episodes occurring in this
period, than between June and November, with 9 (24.3%) episodes (fig. 1; p = 0.01).

In all cases, patients presented with a rapid deterioration of respiratory symptoms, including dyspnea (n = 37; 100%), cough (n = 29; 78%), and sputum production (n = 23; 62%), for a median duration of 10 days (range 1–30) before admission. Fever (38.5 ± 0.5°C) was present in 9 cases (24%).

The laboratory data on admission are shown in table 2. The respiratory condition had worsened in all cases. Eighteen arterial blood gas analyses could be compared with previous results performed in the same conditions. The mean decrease in PaO₂ was 19 ± 8.8 mm Hg. Arterial blood gas measurements were performed with various flow rates of supplemental oxygen. PaO₂/FiO₂ could be calculated in 23 episodes and the mean PaO₂/FiO₂ was 235.8 ± 87.9 mm Hg.

At the time of AEx, pulmonary hypertension evidenced by a systolic pulmonary arterial pressure >50 mm Hg was found in 19 episodes.

On CT scans, newly developing abnormalities consisted of ground glass opacities alone in 25 cases (78%) or combined with consolidations in 6 cases (19%). One patient (3%) had only consolidations. The distribution pattern was peripheral in 7 cases of AEx, multifocal in 13, and diffuse in 12.

**Treatment Options**

All patients received oxygen therapy and 4 AEx patients required invasive mechanical ventilation. Broad-spectrum antibiotics were given in 32 episodes and low-molecular-weight heparin at a standard curative dose was administered in 19 episodes.

Thirty-five of the 37 cases of AEx were treated with a daily intravenous (IV) pulse of methylprednisolone (250–1,000 mg/day) for 3 days. Nine were treated with 1 pulse of IV cyclophosphamide immediately after methylprednisolone (day 4) in 8 cases and as the only treatment in 1 case. One patient died before any treatment could be administered. The mean time between admission and treatment of AEx was 4 ± 3.3 days.

**Outcome and Prognostic Factors**

Ten patients (27%) died from respiratory failure during hospitalization within 4–35 days. Among the 4 AEx requiring mechanical ventilation, 1 led to death. At the end of follow-up, all patients had died except for 2 who received a lung transplant 9 and 15 months after AEx, respectively. The median survival from the time of AEx was 4.2 months (range 0.2–36.6).

The univariate analysis is shown in table 3. Factors associated with in-hospital mortality included a higher impairment of FVC and DLCO before AEx, a higher LDH level at the time of AEx, and a longer time between admission and initiation of treatment for AEx.
Concerning the response to treatment, gas exchange improvement occurred 4.9 ± 2 days after the initiation of treatment in 12 cases. In 13 cases the patients were stable, and in 12 cases the patients deteriorated. Deterioration was associated with a significantly higher in-hospital mortality as compared to stabilization or improvement (p < 0.001). The Kaplan-Meier analysis showed a significant difference in overall survival between the groups (fig. 2). Patients whose gas exchange worsened had a higher risk of mortality than the others, with a median survival of 1 versus 8 months (p < 0.001).

**Discussion**

This study reports an outcome of 37 occurrences of IPF-AEx in 27 patients hospitalized in a tertiary hospital. IPF-AEx were more frequent during winter and spring. The in-hospital mortality was 27% and the median survival from the time of AEx onset was 4.16 months. The prognostic factors associated with in-hospital mortality in univariate analysis included a longer time between admission and the initiation of treatment, the impairment of pulmonary function tests before AEx, and a high LDH level at the time of AEx. The early evolution of AEx based on gas exchange modifications reflected the response to treatment and predicted the prognosis.

The diagnosis of IPF-AEx can be challenging. Its widely accepted definition is an acute respiratory deterioration of unidentifiable cause in a patient with underlying IPF. However, numerous diagnosis criteria have been proposed [2–4, 8, 10]. First of all, 30 days or less as a time course has been chosen to separate AEx from gradual progression of IPF. Collard et al. [3] proposed that the diagnosis of IPF-AEx needs an HRCT that shows new bilateral opacities. However, CT scans can be unavailable,

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**Table 3. Univariate analysis of clinical, laboratory, HRCT scan, and treatment data comparing survivors and nonsurvivors (n = 37)**

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Survivors (n = 27)</th>
<th>Nonsurvivors (n = 10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at IPF diagnosis, years (n = 30)</td>
<td>65 (51–77)</td>
<td>66 (29–72)</td>
<td>0.57</td>
</tr>
<tr>
<td>Age at AEx, years (n = 30)</td>
<td>68 (60–81)</td>
<td>69 (31–75)</td>
<td>0.46</td>
</tr>
<tr>
<td>Males/females, n (%)</td>
<td>23 (85)/4 (15)</td>
<td>8 (80)/2 (20)</td>
<td>0.59</td>
</tr>
<tr>
<td>Clinical course of IPF before AEx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between IPF diagnosis and AEx, months</td>
<td>47 ± 27.5</td>
<td>40 ± 48.0</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulmonary function test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, % pred</td>
<td>65 ± 18</td>
<td>51.2 ± 12.3</td>
<td>0.01*</td>
</tr>
<tr>
<td>DLCO, % pred</td>
<td>34 ± 9.1</td>
<td>21.7 ± 9.3</td>
<td>0.01*</td>
</tr>
<tr>
<td>Previous AEx</td>
<td>9 (31)</td>
<td>2 (20)</td>
<td>0.50</td>
</tr>
<tr>
<td>Characteristics of AEx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms, days</td>
<td>15 ± 9.4</td>
<td>10.0 ± 9.33</td>
<td>0.11</td>
</tr>
<tr>
<td>LDH, IU/l</td>
<td>544.6 ± 155.4</td>
<td>801.0 ± 163.7</td>
<td>0.002*</td>
</tr>
<tr>
<td>Neutrophil count, /mm³</td>
<td>8,591 ± 3,214</td>
<td>7,581 ± 3,794</td>
<td>0.21</td>
</tr>
<tr>
<td>D-dimers, ng/ml</td>
<td>852.15 ± 793</td>
<td>1,623.9 ± 1,727.0</td>
<td>0.46</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>69.7 ± 72.8</td>
<td>46.8 ± 61.0</td>
<td>0.79</td>
</tr>
<tr>
<td>NT-proBNP, ng/l</td>
<td>2,837 ± 2,828</td>
<td>1,997 ± 2,684</td>
<td>0.71</td>
</tr>
<tr>
<td>Pulmonary hypertension1</td>
<td>12 (44)</td>
<td>6 (60)</td>
<td>0.92</td>
</tr>
<tr>
<td>Combined IPF and emphysema, n (%)</td>
<td>13 (48)</td>
<td>6 (60)</td>
<td>0.71</td>
</tr>
<tr>
<td>CT pattern2, n (%)</td>
<td>19 (79)/5 (21)</td>
<td>8 (89)/1 (11)</td>
<td>0.62</td>
</tr>
<tr>
<td>Treatment option</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay before initiating therapy, days</td>
<td>3.1 ± 2.6</td>
<td>6.0 ± 4.1</td>
<td>0.04*</td>
</tr>
<tr>
<td>Anticoagulant therapy, n (%)</td>
<td>14 (48)</td>
<td>5 (50)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cyclophosphamide pulse, n (%)</td>
<td>9 (33)</td>
<td>0 (0)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD, n (%), or medians (range). * p < 0.05.

1 Systolic pulmonary arterial pressure >50 mm Hg.

2 Combined multifocal and diffuse pattern/peripheral pattern.
or some patients can be too critically ill to have them performed. So, new opacities on chest X-rays have been considered sufficient by the other authors [2, 4, 8, 10]. On the other hand, these authors did not consider bilateral opacities as an indispensable feature. A recently published series by Tcherakian et al. [11] shows that some patients could have acute exacerbations with unilateral opacities, especially in cases of asymmetrical IPF.

In our series most patients did not have endotracheal aspirates or BAL performed to rule out infection. However, patients with IPF-AEx frequently present with acute respiratory failure and there is a high risk associated with bronchoscopy. In view of the very poor prognosis of IPF patients under invasive but also noninvasive mechanical ventilation, it seems very important to keep them from deteriorating [12]. In the 26 cases of AEx without bronchoscopy, infection was ruled out by using less invasive procedures such as sputum culture, urinary antigen tests, nasopharyngeal aspirates, and serological studies. Moreover, procalcitonin levels, which can be used to identify patients with a bacterial respiratory tract infection for whom antimicrobial treatment is beneficial, were normal in all tested patients [13].

Several case reports have suggested that bronchoscopy or lung surgery can contribute to the onset of IPF-AEx [14–18]. The hypothesis that infection or another acute stress to the lung is a triggering factor has also been proposed [3]. On the other hand, Wootton et al. [19] did not detect viral infection in the majority of the 43 tested IPF-AEx patients. In our series, 2 patients developed AEx 6 days after BAL or lobectomy. The occurrence of AEx after pulmonary embolism in one of our patients had not been previously described and may be incidental. Six patients presented with AEx a few weeks after a respiratory infection had been resolved. Moreover, the high frequency of occurrence of AEx in winter and spring suggests a potential link between the seasonal epidemic and the responsibility of subclinical infection. Although Wootton et al. [19] did not find a virus in the majority of IPF-AEx cases, the role of a previous infection as a trigger could not be definitively excluded.

IPF-AEx has a poor prognosis. In a recent systematic review, Agarwal et al. [6] estimated a 1-month mortality rate of 59.5% (95% CI 48.5–69.6). In our series, the in-hospital mortality was 27% and death occurred in the first 35 days after admission. This low mortality could be explained by less severe disease, as suggested by the PaO₂/ FiO₂ in our patients. In the study by Akira et al. [9] the extent and pattern of HRCT and LDH levels, to a lesser degree, were predictive of survival in IPF-AEx patients. Patients with new parenchymal abnormalities, classified as multifocal or diffuse pattern, have a worse prognosis compared to patients with only peripheral involvement. Besides, Song et al. [5] found that the CRP level was also a prognostic factor of IPF-AEx. In our study, LDH values were also increased in most patients and were associated with in-hospital mortality while CRP was not. However, LDH has limited value as a prognostic biomarker since it is neither sensitive nor specific and its values can be affected by numerous pathological conditions. On the other hand, the extent of parenchymal abnormalities was not quantified and no association was found between CT patterns and prognosis. However, only 1 of our 7 patients with a peripheral pattern died, while 8 of 25 patients with a multifocal or diffuse pattern died. This difference could suggest that the statistical power of our analysis was too low to show any association between HRCT pattern and prognosis.

The correlation with impairment of pulmonary function tests found in our study contradicts the findings of Akira et al. [9]. However, these authors analyzed baseline pulmonary function tests whereas we analyzed tests performed 4 months (range 1–44) before AEx. Thus, it seems logical that patients with more severe IPF have a worse prognosis in the event of an AEx.

![Fig. 2. Comparison of survival rates after specific treatment in patients with IPF-AEx grouped according to evolution in the first 10 days (Kaplan-Meier method). Survival was significantly worse in the worsening subgroup than in the other two (p < 0.001). Survival did not differ significantly between the stabilization and improvement subgroups.](image-url)
Concerning the treatment strategies, IPF-AEx patients are administered pulse doses of methylprednisolone (0.5–1 g/day for 3 days) in almost all studies. Some studies also use additional immunosuppression with cyclophosphamide [20, 21]. To date, no randomized controlled trial supports a specific therapy except for the use of anticoagulation, which remains controversial [22]. Although our study was not a controlled trial, the efficacy of our treatment approaches was analyzed. First and most interestingly, a shorter time from admission to the initiation of AEx treatment was associated with a lower inhospital mortality in univariate analysis (3 ± 2.6 days in survivors vs. 6 ± 4.1 days in nonsurvivors, p = 0.03). Second, cyclophosphamide was used in 9 of the 27 in-hospital survivors vs. none of the in-hospital nonsurvivors (p = 0.07). It is important to note that only 1 patient who received cyclophosphamide had positive antinuclear antibodies without any other sign of autoimmune disease. Third, the use of a curative dose of anticoagulation was not associated with the prognosis.

The shorter time between admission and the initiation of IPF-AEx treatment is of major importance. However, and as was noticed above, its diagnosis needs to exclude numerous differential diagnosis. This highlights the probable need for a fast diagnostic approach that should be standardized.

The poor prognosis of patients with IPF-AEx is a challenge. It is crucial to improve the clinical status as quickly as possible. It is important to give consistent information to the patient and his/her family, and the possibility of lung transplantation needs to be considered carefully so that the patient can be listed. Indeed, a recent change in organ allocation in France means that the medical urgency and transplant benefit of a patient may be used to determine priority. For this reason, we chose to analyze the association between early changes in gas exchange and prognosis. A deterioration of gas exchange in the first 10 days following treatment is associated with a poor prognosis.

This study displays several limitations that restrict a possible extrapolation of its conclusions. It is a retrospective case study that was conducted in a single center. Unfortunately, all relevant studies on IPF-AEx are designed as retrospective with their associated limitations and biases. The choice to analyze all AEx cases, even if they occurred in the same patient, may also have introduced some bias. However, previous AEx were not found to affect the prognosis of recurrence. The results of our treatment options should be interpreted with caution and no conclusion can be made about the best therapeutic regi-

In conclusion, IPF-AEx seems to be most frequent during winter and spring. The time between admission and the initiation of treatment is a newly reported prognostic factor that should be investigated further. The need for treatment initiated without delay probably requires a fast diagnostic approach that should be standardized. In this approach, early changes in respiratory condition have to be taken into account; their evaluation helps to predict evolution and to determine subsequent medical care.

Acknowledgement

We thank Mrs. Kaufman for her careful editing and English language corrections.

Financial Disclosure and Conflicts of Interest

None.
References


