Diffuse Interstitial Lung Disease and Pulmonary Fibrosis

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Key points

Diffuse interstitial lung disease (DILD):

- Eliminate pulmonary infection (intracellular pathogens, Pneumocystis, viruses) and cardiogenic involvement by history, clinic, thoracic TDM, peripheral microbiological specimens, echocardiography and bronchoalveolar lavage (cytology and microbiology) when possible.
- Eliminate drug- or environment-associated toxicity, carcinomatous lymphangitis, connective tissue disease and granulomatosis by the analysis of

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history, extrapulmonary signs, HD-thoracic TDM, BAL cytology, and immunological investigations before concluding an idiopathic cause. Multidisciplinary discussion is necessary before lung biopsy.
- Non-invasive ventilation is rarely effective, but can help in carrying out BAL. Invasive ventilation must be protective.
- Antibiotic treatment (consider anti-intracellular pathogens, Pneumocystis) is usually prescribed before microbiological results.
- Corticotherapy has poor efficacy outside connective tissue diseases, granulomatosis, eosinophilic pneumonia, histiocytosis and cryptogenic organising pneumonia.
- The prognosis is extremely poor in patients with established pulmonary fibrosis.

Introduction

Diffuse interstitial lung disease (DILD) is a heterogeneous group of lung disorders characterised histologically by diffuse inflammation and fibrosis affecting predominantly, but not exclusively, the pulmonary interstitium. Pulmonary fibrosis is a progressive feature of many lung disorders and more than 200 diseases can present in the form of DILD [1]. Several types can be distinguished: (i) idiopathic DILD [2]; (ii) DILD of known cause; and (iii) DILD associated with connective tissue disease or granulomatosis [1]. Figure 1 summarises the main types of DILD. Faced with a clinico-radiological picture of DILD compatible with pulmonary fibrosis, the main problem is to identify the aetiologies accessible to curative treatment. The therapeutic (e.g. anti-infective agents vs. corticotherapy) and prognostic (e.g. high probability of recovery from an infectious cause vs. terminal progression of idiopathic pulmonary fibrosis (IPF)) implications require rigorous diagnostic and therapeutic approaches which are usually invasive (bronchoalveolar lavage, lung biopsy).

Diagnostic Strategy

Principal Diffuse Interstitial Lung Diseases of Interest to the Intensivist

The most frequently encountered DILDs in intensive care, except for cardiogenic oedema, are: infectious DILD (pneumocystosis, intracellular bacteria, viruses, tuberculosis), IPF, non-specific interstitial lung disease (NSILD, which should lead

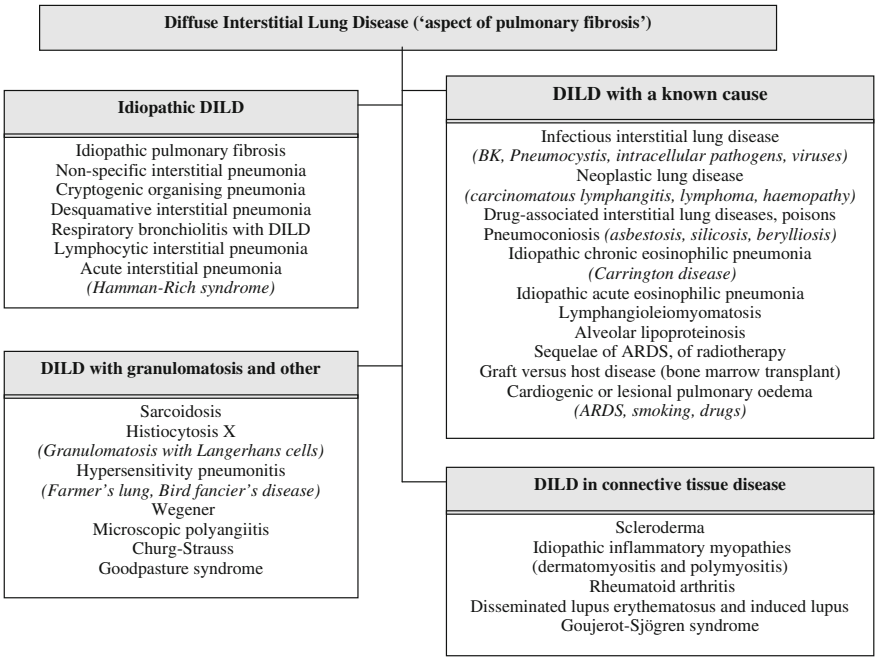

Fig. 1 Classification of diffuse interstitial lung disease (DILD) (according to the American Thoracic Society—European Respiratory Society)

to investigations for connective tissue disease), neoplastic DILD, DILD associated with connective tissue disease or granulomatosis, drug-associated and toxic DILD, and acute interstitial lung disease. Tables 1 and 2 show the main characteristics of idiopathic DILD and DILD associated with connective tissue disease. Lung disease with intra-alveolar haemorrhage is not discussed in this chapter (Goodpasture, Churg-Strauss syndrome, Wegener, microscopic polyangiitis). For the intensivist, acute respiratory failure (ARF) in relation to DILD may present as one of two clinical scenarios: (i) previously known DILD. The patient is admitted with ARF, sometimes in the context of chronic restrictive respiratory failure. An aggravating factor should be investigated (heart disease, pulmonary embolus, pneumothorax, infection, drug toxicity) before concluding that it is an exacerbation of the known lung disease. This is a diagnosis of exclusion; (ii) previously unknown DILD. The diagnostic process is focused on identifying the aetiology of DILD.

Previously Known Diffuse Interstitial Lung Disease

Figure 2 outlines the diagnostic procedure when a DILD has been identified previously. The aim of the diagnostic approach is to demonstrate a curable acute

Table 1 Characteristics of the main idiopathic diffuse interstitial lung diseases (DILD)

	Idiopathic pulmonary fibrosis	Nonspecific interstitial pneumonia	Acute interstitial pneumonia	Desquamative interstitial pneumonia	Cryptogenic organising pneumonia
Clinical	Age > 50 years (65 years) Smoking + Insidious onset >3 months Few general signs Digital clubbing Crackles/rales "velcro" Absence of other causes	Age: 45–50 years Less insidious onset General signs (AEG) Inspiratory squeaks Look for associated connective tissue disease ++	Age: 50 years Acute onset General signs Pseudo-influenza syndrome Picture of ARDS	Age: 50 years Smoking +	Age: 55 years Subacute onset General signs and pseudo-influenza syndrome
Frequency in idiopathic DILD	55 %	25 %	<1 %	15 %	3 %
Relative frequency in idiopathic DILD in intensive care	+++	+++	++ (Picture of ARDS, Hamman-Rich syndrome)	+	+
High-definition TDM	Bi-basal and sub-pleural reticular opacities Sub-pleural pseudo-cysts (honeycomb) Traction bronchiectasis	Bi-basal and sub-pleural 'frosted glass' opacities Reticular opacities Rare sub-pleural pseudo-cysts (honeycomb)	Alveolar condensations Reticular opacities Antero-superior parenchymal distortion Honeycomb (aspect of ARDS)	Bi-basal and sub-pleural 'frosted glass' opacities Basal reticular opacities Centrolobular emphysema of the apexes	Parenchymal condensations with sub-pleural, peribronchial air bronchogram 'Frosted glass' opacities Migratory opacities

(continued)

Table 1 (continued)

	Idiopathic pulmonary fibrosis	Nonspecific interstitial pneumonia	Acute interstitialpneumonia	Desquamative interstitial pneumonia	Cryptogenic organising pneumonia
BAL	Hypercellularity (neutrophils)	Hypercellularity (lymphocytes > 20 %) Alveolitis "mottled"	Hypercellularity (neutrophils ± lympho.) Siderophages Atypical pneumocytes	Moderate hypercellularity Brown pigmented macrophages	Hypercellularity (lymphocytes > 20 %) Alveolitis "mottled"
Treatment (except for transplantation)	Discuss corticosteroids ± an immunomodulator ± N-acetylcysteine, Pirfenidone	Corticoid ± azathioprine or cyclophosphamide	Corticoid	Corticoid Stop smoking	Corticoid
Mortality	90 % at 10 years (median survival = 3 years)	30 % at 10 years	>50 % at 3 months	30 % at 10 years	Rare

Table 2 Characteristics of the main diffuse interstitial lung diseases (DILD) associated with connective tissue disease

	Scleroderma	Rheumatoid arthritis	Idiopathic inflammatory myopathies (dermatomyositis or polymyositis)	Goujerot-Sjögren syndrome	Disseminated lupus erythematosus (particularly if induced lupus)
Associated extra-pulmonary attacks	Raynaud syndrome Cutaneous sclerosis Telangiectasis Renal attack Digestive attack Cardiac attack	Deforming arthritis Rheumatoid nodules	Raised CPK Purple rash on eyelids Myalgia Picture of "myopathy" Myocardiopathy Polyarthritis Problems swallowing Hyperkeratosis of hands	Dry syndrome (Xerostomia, Xerophthalmia) Arthralgia	Erythema, Raynaud, Arthritis, Nephrotic syndrome, Pericarditis, Endocarditis, Haemolytic anaemia, Leuco-thrombopenia Dry syndrome Convulsions, Psychosis Livedo
Associated pulmonary attacks	Nonspecific interstitial pneumonia (NSIP) PAH Mediastinal adenopathies	NSIP Pleurisy Bronchial dilation	NSIP (precedes extrapulmonary signs) Cryptogenic organising pneumonia Inhalation pneumonia	Chronic cough Lymphocytic ILD Pulmonary lymphoma	Pleurisy PAH (APLS) Intra-alveolar haemorrhage Lupic pneumonia Shrinking lung syndrome
Frequency of DILD in connective tissue disease	50–70 % (especially if anti-SCL70 Ab)	20 % (particularly in males)	10–20 % (especially if anti-Jo-1 Ab)	10–20 %	<10 %
Paraclinical	Anti-SCL70 Ab Anti-centromere Ab	Rheumatoid factor Anti-CCP Ab	Anti-Jo-1 Ab (anti-synthetase syndrome) Raised CPK (polymyositis)	Anti SSA(Ro) Ab	Complement consumption Anti-native DNA Ab Anti-Sm Ab Anti-histone Ab in induced lupus
BAL	Nonspecific	Hypercellularity (neutrophils)	Nonspecific	Hypercellularity (lymphocytes ++)	Frequent intra-alveolar haemorrhage (siderophages > 30 %)

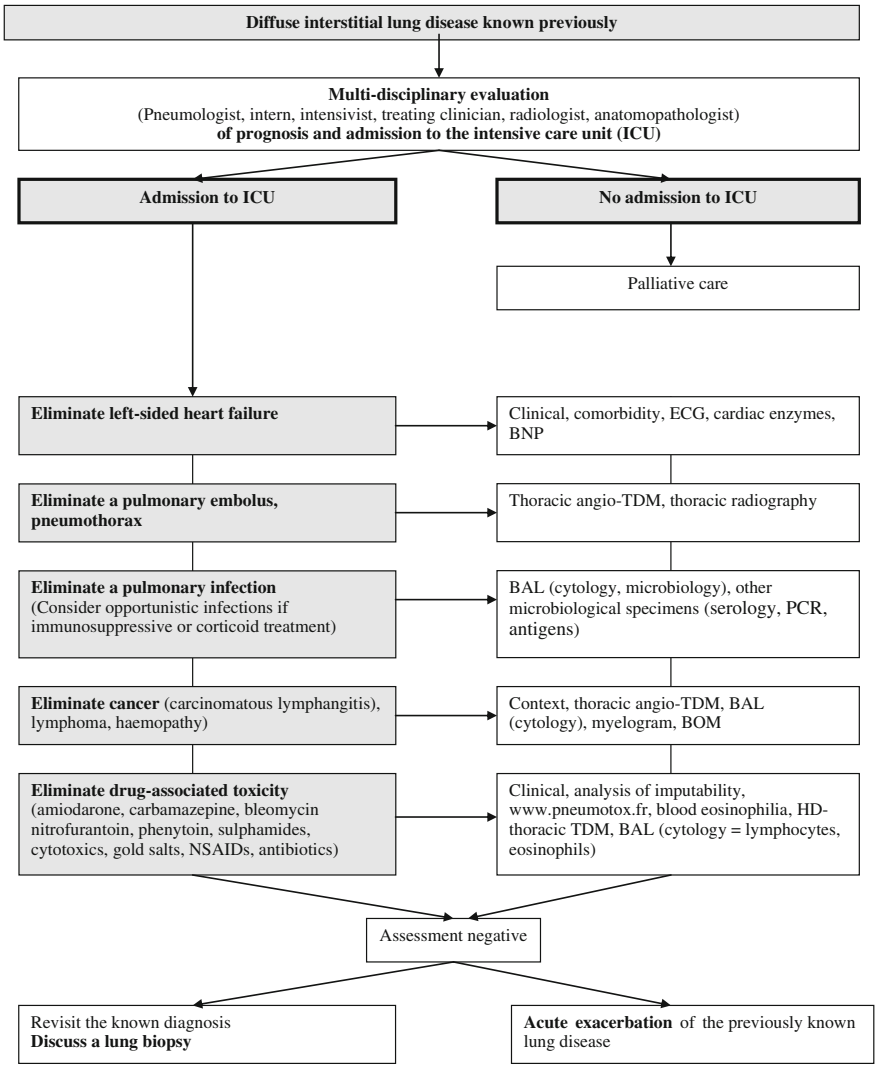

Fig. 2 Management of acute respiratory failure when diffuse interstitial lung disease (DILD) has been identified previously

disease complicating the DILD. The initial approach consists of looking for a cardiac aetiology by measuring Brain Natriuretic Peptide (BNP), troponin Ic, carrying out electrocardiography (ECG), cardiac echography, and even right-sided catheterisation to determine left and/or right haemodynamic participation. Angio-TDM may reveal a pneumothorax or pulmonary embolus (particularly if pulmonary arterial hypertension (PAH), vasculitis or anti-phospholipid antibodies (Ab) are present). Bronchopulmonary infection should also be eliminated (clinical, hyper-leukocytosis, inflammatory syndrome, raised C-reactive protein, procalcitonin),

particularly as the immunosuppressive and corticoid treatment received by these patients increases the risk of infection. Bronchial specimens, BAL and protected distal sampling should be used to look for community, nosocomial, usual and opportunistic pathogens. Special staining techniques and culture, serology, antigen detection, PCR and immunofluorescence are carried out to look for *Legionella*, atypical intracellular bacteria (*Mycoplasma*, *Rickettsia*, *Chlamydia*), viruses (adeno-, rhino-, herpes-, influenza-, cytomegalovirus), *Pneumocystis*, *Aspergillus*, *Mycobacterium tuberculosis* or atypical mycobacteria. The treatments received by the patient should also be reviewed systematically, particularly as some treatments administered during DILD may cause pulmonary toxicity (methotrexate, cyclophosphamide, antibiotics, etc.). Sometimes it is not possible to identify the cause of respiratory decompensation.

The possible causes of respiratory decompensation should be investigated thoroughly before concluding that it due to an exacerbation of DILD that could correspond to terminal progression of pulmonary fibrosis. In a patient receiving spontaneous ventilation, pulmonary specimens should be obtained by an experienced team weighing up the benefit/risk ratio. Non-invasive ventilation (NIV) may be useful to support bronchial fibroscopy with BAL. Finally, when investigations are negative, a lung biopsy should be discussed with an experienced centre and the previous pneumological diagnosis questioned. A lung biopsy will modify the therapeutic management in more than one-half of cases.

Previously Unknown Diffuse Interstitial Lung Disease

The patient is admitted with ARF without any previously identified lung disease. As explained above, investigations should be performed to look for a decompensating factor (heart failure, pulmonary embolus, pneumothorax). The diagnostic strategy is focused on looking for the aetiology of the "de novo" lung disease (Fig. 3).

Anamnesis (importance of questioning the proxies) should clarify how the disease became established, possible prodromes, medical history (in particular cardiac, renal, pulmonary, endocrine, neurological, osteo-articular, dermatological), previous lung infection, acute respiratory distress syndrome (ARDS) and more generally, invasive ventilation, cancer, recent and previous treatments (radiotherapy, methotrexate, amiodarone, cytotoxics, gold salts, carbamazepine, phenytoin, nitrofurantoin, antibiotics, NSAIDs), environmental and professional risk factors (carbon, silica, beryllium, asbestos, tobacco, cocaine, wood industry, pesticides, agricultural environment, contact with birds). Data from previous thoracic imaging are valuable. An analysis of clinical signs system by system permits the investigation of pulmonary symptoms (pleurisy, adenopathy, crepitations, squeaking) and extra-pulmonary signs (adenopathy, articular, cutaneous, renal, neurological and gastrointestinal attacks) that are evocative of connective tissue disease, vasculitis or granulomatosis.

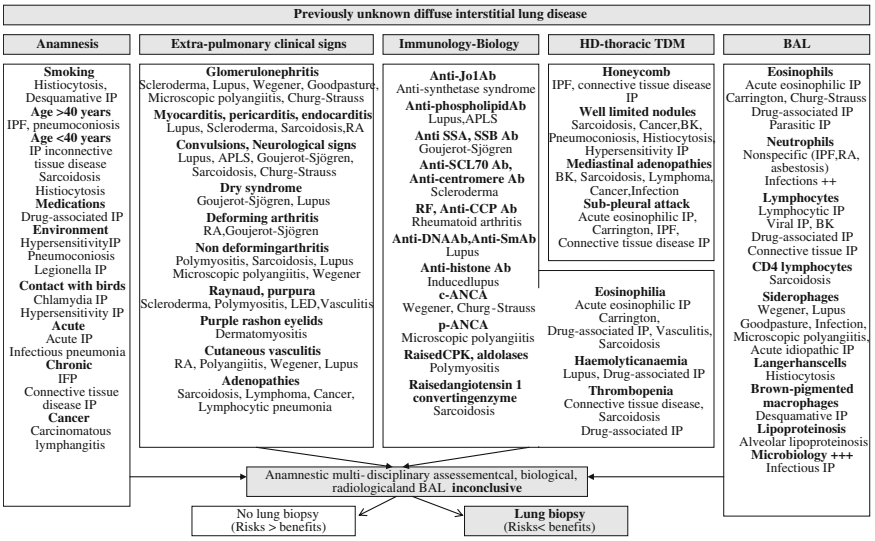

Fig. 3 Main diagnostic orientations as a function of clinical, radiological, biological and BAL results in a patient with previously unknown diffuse interstitial lung disease (DILD)

Biological investigations are orientated by these anamnestic and clinical data. It is useful to measure: creatinine clearance, proteinuria, haematuria, full blood count (eosinophils), CPK, aldolases, serum precipitins, rheumatoid factor, anti-nuclear antibodies (Ab), anti-native DNA Ab, anti-neutrophil cytoplasmic Ab, cryoglobulinaemia, thyroid assessment, angiotensin-converting enzyme. Other auto-antibodies may be requested depending on the disease suspected (cf. Table 2, Fig. 3).

Thoracic TDM is useful because may reveal features that are evocative of certain diseases (IPF, histiocytosis, lymphangioleiomyomatosis) and may sometimes be enough to make the diagnosis (Table 1). It can also be used to determine the best site for BAL (and lung biopsy if necessary).

Bronchial fibroscopy with BAL is essential when looking for an infectious cause. Special staining and culture techniques, serology, antigen detection, PCR and immunofluorescence are used to look for *Legionella*, intracellular bacteria (*Mycoplasma*, *Rickettsia*, *Chlamydia*), viruses (adeno-, rhino-, herpes-, influenza-, cytomegalovirus), *Pneumocystis*, *Aspergillus*, *Mycobacterium tuberculosis* or atypical mycobacteria. BAL cytology can contribute to the diagnosis (presence of neoplastic cells for carcinomatous lymphangitis, siderophages for associated intraalveolar haemorrhage, eosinophils for eosinophilic pneumonia, Churg-Strauss syndrome, CD4 lymphocytosis for sarcoidosis, Langerhans cells for histiocytosis, alveolar lipoproteinosis). Sometimes clinical data (adenopathy, mucocutaneous lesions, dry syndrome, muscular or gastrointestinal attack) will direct the histological diagnosis via biopsy of lymph nodes, skin, muscles, digestive tissue or salivary glands (cf. chapter "Systemic diseases"). Lung cancer or carcinomatous lymphangitis are more rarely the cause of respiratory decompensation. A positive

diagnosis is often obtained by bronchial fibroscopy, BAL cytology, high definition (HD)-angio-TDM and, sometimes, lung biopsy). If these investigations are negative, in particular BAL, a lung biopsy should be discussed with a multidisciplinary team and an experienced centre. In 15–25 % of cases, transbronchial biopsies are associated with pneumothorax and haemorrhagic complications in mechanically ventilated patients. They contribute to the diagnosis in only 50 % of cases, but remain useful for the detection of granulomatosis, sarcoidosis, eosinophilic pneumonia or neoplasia. Surgical lung biopsy (open thorax or thoracoscopy) contributes to the diagnosis in 65–100 % of cases and leads to a modification of treatment in 65–85 % of cases. Pneumothorax and pleuropulmonary fistula are the most frequent complications (10–40 % of cases). Lung biopsy may be guided by data from HD-thoracic TDM.

Therapeutic Management

Ethical Problems

Two types of case should be distinguished on admission to the ICU: (i) the DILD is inaugural without any previously identified lung disease (e.g. DILD in connective tissue disease, infectious DILD, drug-associated, idiopathic acute eosinophilic pneumonia, acute interstitial lung disease); or (ii) the DILD has been identified previously, but without severe chronic respiratory failure (CRF) and with a relatively favourable prognosis (e.g. DILD in connective tissue disease, granulomatosis, PINS, respiratory bronchiolitis with DILD), or the DILD has been identified previously with severe CRF with a poor short- or medium-term prognosis (all cases of terminal stage pulmonary fibrosis). In the case of CRF with IPF, median survival from IPF is 3 years after diagnosis and 10-year mortality is approximately 100 % [4, 5].

In the first case, admission to the ICU does not pose an ethical problem. In the second case, multidisciplinary discussions (pneumologist, treating clinician, intern, intensivist) on the possibilities of recovery should take place because there are no specific treatments that can significantly increase survival and mortality in the ICU is >85 % [5]. The precise therapeutic objectives (admission to ICU, intubation, tracheotomy, catecholamines, extrarenal dialysis) should be clearly discussed with the patient or his/her next of kin. These decisions are recorded in the medical file. If it is decided not to admit the patient to the ICU, palliative care should be proposed. In the context of an emergency admission due to vital distress, if these ethical problems cannot be approach “cold”, the prognostic factors and wishes of the patient should be discussed quickly (confident, family) so that active treatments can be limited and/or discontinued [4, 5]. However, in the case of ARF with a reversible cause during postoperative follow-up in a patient with pulmonary fibrosis, the prognosis is generally more favourable (40–95 % short-term survival) [4].

Mechanical Ventilation

NIV is associated with a high rate of failure (>80 %). It may be proposed but its efficacy should be assessed within a few hours (clinical, blood gases). More than 85 % of patients require invasive ventilation. A strategy of protective ventilation comparable to that in ARDS with acceptable tolerance of hypercapnia is recommended (plateau pressure $\leq$ 30 cm H_2O, running volume of 6 mL/kg predicted weight). The mortality of mechanically ventilated patients with IPF is around 90 % [4–7].

Haemodynamics and Pulmonary Arterial Hypertension

Evaluation of the cardiogenic component is essential during ARF in DILD. Investigations for PAH are carried out by right-sided catheterisation or by ECG. Inhaled nitric oxide and other pulmonary vasodilatory treatments can then be discussed (epoprostenol, bosentan, sildenafil). However, in the case of ARF in pulmonary fibrosis, no study has confirmed the benefit of these treatments [3, 5, 6]. Anticoagulant treatment (or its continuation) is indicated particularly in the presence of PAH, pro-coagulant connective tissue disease and, for some medical teams, in all fibroses [3, 6]. However, the value of starting anticoagulant treatment should be discussed in line with the benefit/risk to the patient.

Anti-Infective Treatments

Faced with the possibility of infectious pneumonia complicating pulmonary fibrosis or responsible for DILD, broad-spectrum antibiotics covering intracellular and opportunistic pathogens are often started after taking microbiological specimens (BAL). Investigations for *Pneumocystis* should be carried out systematically and the disease treated. Treatment should be reassessed systematically as soon as the microbiological results are available and as a function of the evolution of the patient after 48–72 h.

Corticoid and Immunosuppressive Treatment

When DILD has been diagnosed previously (e.g. IPF, fibrosis associated with connective tissue disease, granulomatosis), the patient is often already receiving treatment with corticoids. After elimination of a infectious cause, boluses of corticoids (poorly codified in the literature, 1–15 mg/kg for 1–3 days) are frequently prescribed, particularly because withdrawal of corticotherapy is sometimes

associated with exacerbation. Some teams also add cyclophosphamide. However, these treatments have not yet been validated when the patient is hospitalised in the ICU. In the case of IPF, a recent "international evidence-based guideline" was published not recommending corticotherapy, colchicine, cyclosporine A and corticoid + immunomodulator combinations: interferon-γ, bosentan and etanercept [6]. For some patients with IPF, the combination acetylcysteine + azathioprine + prednisone, acetylcysteine alone and prifenidone are recommended [6]. The prognostic impact in the ICU is often modest and a significant benefit in terms of survival has not been demonstrated when fibrosis is established [3, 4, 6]. DILD associated with pneumocystosis is treated with corticotherapy (1 mg/kg) in association with anti-*Pneumocystis* treatment. Eosinophilic pneumonia, cryptogenic organising pneumonia, DILD in connective tissue disease and systemic granulomatosis, and histiocytosis usually respond favourably to corticotherapy.

Lung Transplantation and Extracorporeal Respiratory Assistance

Lung transplantation concerns patients with previously diagnosed lung disease and placed on a waiting list. A multidisciplinary discussion (pneumologist, intern, intensivist, thoracic surgeon, anaesthetist) is necessary in order to rule out lung transplantation, which usually takes place in the context of a national priority termed "a lung super emergency" whose prognosis is poor. Sometimes, lung transplantation may be discussed after ARF when withdrawal of mechanical ventilation is impossible. Extracorporeal respiratory assistance is an exceptional therapeutic option which should only be used in patients waiting for a lung transplant ("bridge to lung transplantation") or in those with curable fibrosing DILD while waiting for the effects of specific treatment (e.g. infectious DILD with severe ARDS, idiopathic acute eosinophilic pneumonia).

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