Management of Autoimmune Systemic Diseases in the Intensive Care Unit

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Key Points

- Specific clinical (syndromic associations) or biological signs should lead the intensivist to suspect an autoimmune systemic disease.
- Several biological (i.e., ANCA autoantibodies) investigations can be rapidly performed in the ICU to help the diagnosis.
- Early detection and management of infections that may occur simultaneously with the flare-up of the systemic autoimmune disease is a priority. An exhaustive workup including, if necessary, invasive investigations

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(i.e., pulmonary biopsy) should be proposed before the introduction of immunosuppressive therapies.

- Corticosteroids and sometimes IVIG are the preferred initial options, especially when concomitant infection is suspected or uncontrolled.
- Referent centers should be asked for validation of the therapeutic options, especially when some drugs are used off-label for these severe patients.

Introduction

The term 'systemic disease' (SD) refers to a 'systemic' autoimmune disease, in contrast to autoimmune diseases targeting a specific organ such as diabetes or thyroiditis. SDs can be mainly separated into two types: connective tissue diseases and systemic vasculitis [4]. This distinction is supported by different physio-pathological mechanisms, clinical expression, prognosis and management. Patients presenting with a SD may be admitted to an intensive care unit (ICU) at different stages in the evolution of their disease. First, they may present during a severe inaugural flare-up of the SD where the intensivist should know how to evoke the diagnosis. More frequently, the patient is seen during a flare of an already diagnosed SD; in this case, the challenges are on the one hand to define when the patient should be transferred to the ICU and, on the other, to adapt specific treatments to the setting of ICU. At this stage, it is sometimes difficult to distinguish an infectious complication from a flare of the SD. Indeed, due to exposure to immunosuppressive treatments, these patients are at particularly high risk of developing opportunistic and/or severe infections. Finally, considering that even the most severe organ dysfunction can be reversed in some of these autoimmune conditions, the intensivist may need to use maximal supportive treatments. These different situations will be discussed sequentially while attempting to provide practical ideas for intensivists who may face these patients.

Diagnosis of a Systemic Disease in the Intensive Care Unit

"To learn how to diagnose a SD, it is necessary to have learnt how to evoke one". These diseases, often called "orphans", are not as rare as many people in the medical community might think (e.g. the prevalence of systemic lupus erythematosus is 30/100,000). Intensivists may take care of these patients when the SD has not yet been identified. Indeed, some patients may present with an initial acute flare-up of the SD, while others may present with an atypical form of the SD, causing a delay in diagnosis until more severe complications develop.

How do we evoke a diagnosis of a SD in a patient admitted to IC? As multi-organ failure is an everyday event in IC patients, only some clinical and biological signs are relevant to alert the intensivist (Table 1). Some syndromic associations should also lead to the suspicion of a SD.

Many SD can present with diffuse-alveolar hemorrhage, either isolated or as part of a pneumo-renal syndrome (Table 2).

Investigations for anti-polynuclear neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane antibodies (GMB) should be requested urgently and the results obtained within 24 h.

The association of muscle symptoms with a rapidly progressive infiltrative pneumopathy (in a few weeks) should lead to investigations for a polymyositis or a dermatomyositis. Autoimmune myositis may be associated with a neoplastic disease that must be diagnosed as soon as possible, since the staging of the cancer may limit the use of invasive and prolonged supportive resources needed in the most severe cases.

The association of severe asthma with extrapulmonary manifestations (poly-neuritis, cutaneous vascularity, and sinusitis) may suggest Churg-Strauss syndrome.

Finally, some less specific manifestations are frequently observed during SD: arthritis, cytopenia (autoimmune or mechanical in the context of a thrombotic microangiopathy), acute renal failure with or without signs of glomerulopathy (nephritis or nephritic syndrome), central nervous system (multiple strokes, meningo-encephalitis) or peripheral nervous system involvement.

Arterial and venous thromboses are found in vasculitis and in anti-phospholipid syndrome (APS). The intensivist should recognise the fulminant form of APS, referred to as "catastrophic" APS (or CAPS), which has been identified relatively recently. This very acute form is responsible for multiple arterial and venous thromboses occurring over a very short period of time (less than one week), associated with multiple organ failure. The prognosis of CAPS is extremely poor and the mortality rate is around 50 % [1]. The triggering factor is often infectious in nature, but can also be traumatic, neoplastic or linked to the recent withdrawal of long-term anti-coagulants. Systemic lupus is the autoimmune disease most frequently associated with APS and CAPS. CAPS is responsible for multi organ injuries involving the: kidneys (80 %), lungs (65 %), central nervous system (55 %), heart (50 %) and skin (50 %). The adrenal glands and gastrointestinal tract can also be the site of thromboses. Biologically, signs of TMA (mechanical hae-molytic anaemia with schizocytosis) and disseminated intravascular coagulation are frequently observed during CAPS. Increased levels of lactate dehydrogenase (LDH) correspond both to the extent of tissue infarction and the intensity of haemolysis. Thrombopenia, sometimes profound, should not delay the introduction of curative anticoagulation with unfractionated heparin. Other therapeutics consist of high dose corticotherapy, plasma exchanges, immunosuppressants and/or intravenous immunoglobulins (IVIG).

Finally, some elements of anamnesis (often determined by questioning the patient's relatives) may orientate or support the diagnosis: history of autoimmunity,

Table 1 Clinico-biological signs of systemic diseases in the intensive care unit and corresponding diagnostic tests

Systemic disease	Clinical signs	Biological signs	Biological diagnostic tests
Systemic lupus erythematosus	Butterfly erythema (vespertilio)	Low CRP	ANA
	Alopecia	Complement consumption	Anti-DNA antibodies
	Oral ulceration	Autoimmune cytopenias	Anti-Sm antibodies
		TMA	
Systemic sclerosis	Sclerodactylia	TMA	ANA
	Raynaud's syndrome		Anti-centromere or
	Telangiectases		Scl70
Autoimmune myositis (PM/DM)	Purple rash over the upper eyelids	Raised CPK	ANA
	Gottron sign		Anti-jo1…
	Muscular weakness		
APS/CAPS	Livedo	Prolonged APTT	Lupus Anticoagulant and/or anti-cardiolipin and anti-B₂GpI antibodies
	Multiple arterial or venous thromboses	TMA	
Adult onset Still's disease	Transient skin eruption on the trunk	Raised ferritin (glycosylated fraction <20 %)	
	Pharyngitis	hemophagocytic syndrome	
Behçet's disease	Pseudo-folliculitis, Bipolar aphtha		Pathergy test
	Uveitis		HLA B5
	Arterial or venous thromboses		
Churg-Strauss syndrome	Severe cortico-dependent asthma	Significant eosinophilia (>1,500)	p-ANCA
Wegener syndrome	Sinusitis, otitis		c-ANCA
	Nasal deformation—saddle nose		
Micropolyangitis	Pneumo-renal syndrome		p-ANCA
Cryoglobulinemia	Purpura	C4 consumption	Cryoprecipitate
	Raynaud's syndrome	High CRP + low SR	HVC serology
Periarteritis nodosa	Livedo racemosa		No ANCA
	Ulcers		HBV serology
	No pulmonary involvement		

C4 complement fraction 4; *CRP* C-reactive protein; *ANA* anti-nuclear antibodies; *PM* polymyositis; *DM* dermatomyositis; *Gottron* purple eruption on the webs of the fingers sparing the joints; *APS* anti-phospholipid syndrome; *CAPS* catastrophic *APS; TMA* thrombotic microangiopathy; *pathergy test* hypersensitivity at 48 h to puncture points revealed by an intradermal reaction with saline; *ANCA* anti-polynuclear neutrophil cytoplasmic antibodies; *HBV and HVC* hepatitis virus B and C; *SR* sedimentation rate

Table 2 Aetiologies of diffuse-alveolar hemorrhage and/or pneumo-renal syndrome

Systemic lupus erythematosus
Micropolyangitis
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangeitis)
Wegener syndrome (granulomatosis with polyangeitis)
Goodpasture syndrome
APS
Cryoglobulinemia
Rheumatoid purpura
Thrombotic microangiopathy
Sarcoidosis
SD with renal failure causing cardiogenic pulmonary oedema
Pulmonary infections complicating SD responsible for acute renal failure

recent initiation of oestroprogestative contraception or recent pregnancy (lupus), history of repeated miscarriages or thromboses (APS). Epidemiologically, these patients are usually young, with a female predominance for autoimmune connective tissue diseases. The next step is diagnostic confirmation of the SD. This depends on blood tests and histological documentation.

For connective tissue diseases, the key investigation is the demonstration of anti-nuclear antibodies (ANA) whose absence makes the diagnosis unlikely. In contrast, their presence has only low specificity (ANA are frequently positive under several medications) and requires investigations for anti-DNA antibodies (lupus) and anti-ECT (or ENA) antibodies: Sm (lupus), SSA and SSB, RNP, Scl70 and centromere (scleroderma), Jo1 and other myositis-specific autoantibodies.

The detection of anti-cardiolipin antibodies and circulating lupus anticoagulant (the latter being interpreted in the absence of heparin) are necessary biological criteria to confirm the diagnosis of APS (ideally one of the two on two occasions, 12 weeks apart).

In systemic lupus, the presence of hypocomplementaemia (CH50, C3 and C4) is additional evidence which can be obtained rapidly. In the case of renal involvement, a kidney biopsy is necessary to confirm the diagnosis of lupus nephritis and to determine its prognosis. These biopsies are often difficult to obtain because it is necessary to position the patient in strict ventral decubitus with control of respiration. In the context of ICU patients, kidney biopsies can be guided by echography or tomodensitometry or in the case haemostasis/coagulation abnormalities, transjugular biopsy is an alternative, although the quantity of renal material obtained is often smaller. Morbidity of this procedure in the ICU context seems to be acceptable with high diagnostic and therapeutic contributions.

In myositis, magnetic resonance imaging (MRI) can guide a muscle biopsy, carried out in the quadriceps or the deltoid.

For vasculitis, positivity of anti-polynuclear neutrophil cytoplasmic antibodies (ANCA) facilitates the diagnosis. Immunofluorescence (IF) reveals either perinuclear (p-ANCA) or cytoplasmic (c-ANCA) fluorescence. The antigenic target is then specified by ELISA: proteinase 3 (PR3) for c-ANCA and myeloperoxidase

(MPO) for p-ANCA. The absence of ANCA does not eliminate the diagnosis of vasculitis, especially for micropolyangitis (MPA) or Churg-Strauss (CS) syndrome where p-ANCA are present in approximately 70 and 40 % of cases, respectively. Positivity for c-ANCA is quite specific for granulomatosis with polyangeitis (formerly Wegener's disease) and may allow postponement of a risky biopsy (e.g. renal). Conversely, it is not unusual to observe false-positive ANCA (often discordant IF and ELISA) in an infectious or toxic context (endocarditis, cocaine). Biopsy of the temporal artery is a minimally invasive procedure, usually performed to confirm the diagnosis of giant cell arteritis, but which sometimes enables the diagnosis of necrosing vasculitis. An electromyogram can confirm peripheral neurological involvement and/or guide a possible neuro-muscular biopsy. These two examinations rule out the differential diagnosis of a critical illness polyneuropathy. Finally, the detection of cryoglobulinaemia is a lengthy process (>1 week) and presents many technical difficulties which lead to the repetition of this test if there is a strong suspicion (3 consecutive days). Low levels of C4 (with normal levels of C3) and positivity for rheumatoid factor are indirect clues in favour of a cryoglobulinemic vasculitis (CV) and are easier to obtain. Finally, the aetiological assessment of CV should include the search for certain viruses (HIV, HBV, HCV, parvovirus B19) because the treatment can be radically different.

Overall, the clinical picture of a SD usually includes the involvement of several organs (Fig. 1) for which the usual aetiological investigations are negative. In addition to investigations for rarer infectious agents or neoplasia, it is necessary, faced with this clinical picture, to know how to evoke and diagnose an autoimmune SD. First-line biological assessment rapidly strengthens the suspicion. The SD is then confirmed histologically.

Management of a Severe Flare of a Systemic Disease in the Intensive Care Unit

The intensivist who has to manage a patient with an already diagnosed and treated SD, irrespective of the organs involved, should ask only one question: "Is it a flare-up of the SD or a concurrent complication (infectious, iatrogenic)"? Diagnosis is complicated by the frequent presence during a SD of a fever, a biological inflammatory syndrome with a clear increase in CRP (except in the case of lupus where an elevation in serum CRP is only observed in cases of seritis or infectious complications) and unavoidable delays in obtaining the results of blood cultures and immunological investigations. Assessment of the procalcitonin level (PCT) may seem useful to differentiate some infections (particularly bacterial) from SD flares (where PCT is normally negative). However, this PCT-based approach is limited both by false-negatives ("localized" bacterial infections with negative plasma PCT) and false-positives (increase in PCT in hemophagocytic
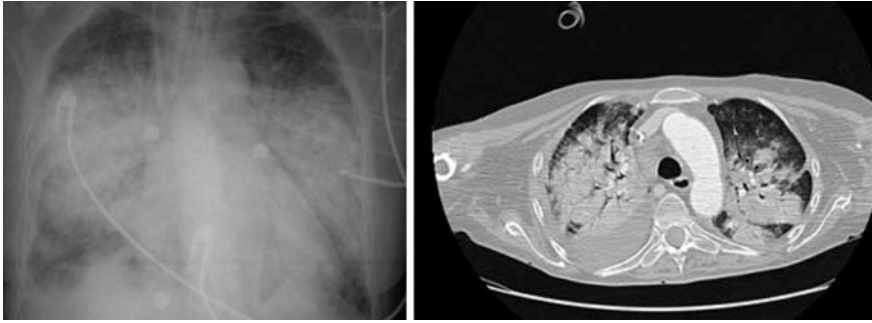
Fig. 1 Systemic disease visualised by thoracic radiography (*left*) and a thoracic scan (*right*)

lymphohistiocytosis syndrome and/or Still's disease) [2]. Furthermore, it is not uncommon to observe the simultaneous occurrence of a SD flare and a concurrent infection. Indeed, one of the possible factors triggering the flare of an autoimmune disease can be an infection. Conversely, a flare-up of the disease could transiently lead toward increased immunosuppression and favour the occurrence of an opportunistic infection. The infections encountered are extremely varied and depend on the disease, the intensity and the nature of the immunosuppressive treatments used. The risk of developing opportunistic infections is not well cor-related with the extent of lymphopenia, and pneumocystis prophylaxis is often proposed in patients who receive treatment with cyclophosphamide, irrespective of the results of their TCD4+ lymphocyte count. In the case of respiratory mani-festations, the differential diagnosis depends on obtaining broncho-alveolar lavage (BAL) with cytological analysis of alveolar fluid (investigations for intra-alveolar haemorrhage with Perls staining; polynucleosis points to an infectious process or a predominance of lymphocytes may indicate a flare-up of the disease). The microbiological analysis of BAL should be extensive (BK culture and PCR, *Pneumocystis jirovecii* PCR, CMV PCR, HSV culture and PCR, galactomannan *Aspergillus* level, panbacterial 16S PCR, etc.) and associated with serological investigations (aspergillus galactomannan, pp65 antigenaemia and quantitative CMV PCR, serology for atypical germs).

In the case of an unfavourable respiratory evolution, BAL performed for sucsipion of an opportunistic infection should be repeated ideally after stopping all anti-infective treatments for 48–72 h. When several repeated BAL remain negative, or when the respiratory parameters deteriorate (decrease in lung compliance may suggest a process of fibrotic scarring), or when no diagnosis is established, an open lung biopsy should be performed rapidly by a surgeon at the patient's bedside. The risk of complications is low (<5 %) and the benefits in terms of diagnostic and therapeutic impact are important [5]. It may give information that is not obtained from other specimens, often of a nature to radically change the therapeutic man-agement such as the addition of antiviral treatment when cells exhibiting the characteristic cytopathogen effect of herpes viruses are observed. Corticotherapy

should be started when interstitial or endo-alveolar fibrosis is observed. The recent aspect of fibrosis can also predict the response to corticotherapy. Finally, histologic studies can, in some cases, confirm the diagnosis of a SD. When lung biopsy is contra-indicated, suspicion of post-aggressive lung fibrosis may be approached in the future by high levels of procollagen 3 either in blood or in BAL samples.

The "best timing" for deciding when to transfer a patient to the ICU is difficult to codify. These patients are usually heavily immunosuppressed by the disease itself and particularly by the treatments for the SD. A rapid unfavourable evolution is often observed, leading to transfer to an ICU when organ failure is already present. In that situation, there is no place for sequential treatments and the mechanically-ventilated patient receives both broad-spectrum anti-infective treatment and salvage corticotherapy. In some cases, it may therefore appear more judicious to admit the patient to the ICU before respiratory deterioration and to carry out an early BAL without waiting for failure of first or second-line anti-infective treatments. Fiberoptic bronchoscopy under noninvasive ventilation with mild sedation can be safely performed in the ICU even in severe hypoxemic patients.

Conventional ventilation (with orotracheal intubation) is responsible for over-mortality due to infections and barotrauma, notably in Wegener's disease where spontaneous pneumothorax has been reported.

Once the diagnosis of a flare-up of SD has been established, the question of the prognosis and treatment arises. The prognosis in IC is not evaluated using specific scores (e.g. Five Factor Score for vasculitis), but relies on the scores developed by intensivists (e.g. SAPS II, SOFA scores). Nevertheless, it is important to determine the severity of the flare-up using paraclinical and histological tools. It is not unusual that, for technical reasons (mechanical ventilation, haemostasis, etc.), some biopsies are delayed or even cancelled as the benefit-risk ratio of these investigations is unfavourable. The most manageable treatment remains intravenous corticotherapy (methylprednisolone) usually administered in the form of a bolus (500–1000 mg), for 1–3 consecutive days, and followed by corticotherapy at 1–2 mg/kg in more severe cases. Corticotherapy is often well tolerated (when infusions are not shorter than 30 min). However, rapid initiation of immunosuppressive treatment is required in more severe forms of SD (notably, lupus and vasculitis). The treatment of choice is cyclophosphamide (endoxan) used at a dose of 0.5–0.7 mg/m^2 according to protocols dependant on the SD as well as age and/or renal function. Endoxan is readministered every 2–4 weeks with monitoring of blood counts and prevention of organ toxicity by hyperhydration and/or Mesna (Uromitexan®). Due to the high frequency of anaphylactic reactions reported with Mesna in autoimmune conditions and its non-superiority compared to hyperhydration alone, it appears prudent to reserve this drug for patients in whom hyperhydration is problematic due to a high risk of fluid overload. In the case of suspected or proven infection concomitant to the flare-up, there are few alternatives. The use of monthly IGIV in the case of systemic vasculitis appears to be a good transient solution before resuming, as soon as possible, classical immunosuppressive therapy [3]. Rituximab (a monoclonal anti-CD20 inducing the

selective depletion of B-lymphocytes) may be another alternative in these "high risk" infectious situations. Recent data for the induction of SD remission (especially during ANCA vasculitis) are encouraging, but the infectious risk of this biotherapy may be underestimated. It is important to discuss the initiation of such treatments with centres of expertise and/or reference for these SD. Finally, "older" therapies merit the attention of the intensivist. Enzyme-conversion inhibitors are the drugs of choice to manage sclerodermic renal crises, which affect the prognosis of patients. Of note, corticotherapy greater than 15 mg/day is not advised in sclerodermic patients because this treatment could favour the development of renal crises. Plasma exchanges used in cases of thrombotic microangiopathy (lupus and/or APS) also appear to be interesting for the treatment of Goodpasture syndrome (notably intra-alveolar hemorrhages) and improve the renal prognosis of vasculitis with severe renal failure (>500 µmol/L). It should be noted that if, for infectious reasons, the usual corticoid treatment of the patient is interrupted on admission, the intensivist should prevent the development of acute adrenal failure by administering 100–200 mg of hydrocortisone/day until the resumption of corticosteroids.

It should also be noted that the detection of pregnancy by measuring βHCG levels is essential in SD like lupus (triggering factor) and for which detection will affect the choice of treatment (only corticoids, azathioprine, cyclosporine, antimalarials and IVIG are theoretically allowed during pregnancy).

Institution of Supportive Treatments in Intensive Care

Except for scleroderma and forms of autoimmune myositis associated with aggressive pulmonary fibrosis (and/or underlying neoplasia), SD are diseases in which the damage to the organs is usually reversible. From an organ perspective, early initiation of immunosuppressive treatment is crucial to avoid long-term sequelae and loss of function following repeated flare-ups. Patients affected by SD are usually "young" and the fact that most inflammatory lesions are reversible in these patients justifies maximum investment in terms of supportive treatments initiated by the intensivist while waiting for remission. Even in scleroderma or other SD with irreversible pulmonary fibrosis, lung transplantation remains an option because the one-year survival rates are comparable to those of transplanted non-sclerodermic patients There may be a long delay after registration on a non-priority transplantation list and it may be peppered with episodes of nosocomial infection in ventilated patients (bacterial and/or viral).

Acute respiratory failure is the most frequent type of organ failure. Diffuse alveolar hemorrhage (DAH) is responsible for hypoxaemia via a shunt effect. The presence of hypercapnia is the sign of respiratory muscles exhaustion or the existence of a dead-space effect related to micro-thrombi within the pulmonary circulation. Hypoxaemia and/or hypercapnia should lead to a first trial of NIV. Apart a hemostatic effect of positive pressure by NIV, an improvement of oxygenation is expected in DAH whereas it is very inconstant in pulmonary

fibrosis or interstitial infectious disease. It is therefore the evolution of the patient after 1–2 h of NIV that determines continuation of respiratory assistance. If NIV is not well tolerated the use of high flow humidified oxygen therapy way be an alternative. If polypnoea or hypoxaemia persist, the decision to use invasive mechanical ventilation should be made without delay. This will enable BAL to be obtained under good conditions and will reduce oxygen consumption linked to respiratory muscle work. Finally, injuries of the pulmonary parenchyma often lead to worsening or *de novo* pulmonary hypertension.

Aggravation of preexisting pulmonary arterial hypertension (PAH) may lead to refractory hypoxaemia or right ventricular failure, which is particularly prejudicial in this context. The development of acute dilation of the right ventricle leads to acute renal failure and worsens the prognosis of the patient (related mortality of 50 %). Monitoring of pulmonary arterial pressure (PAP) and right ventricular (RV) function is therefore essential in this situation. The pulmonary arterial catheter (PAC) is still the reference tool. However a non invasive and prompt evaluations of PAP and RV function can be easily performed by Trans Thoracic Echocardiography or better in case of mechanical ventilation by Trans Oesophageal Echocardiography. From a therapeutic perspective, the existence of threatening PAH justifies the use of vasodilator treatments. The effect of these drugs is recommended under PAC monitoring. Inhaled nitric oxide (NO) leads to stimulation of GMPc in the smooth muscle cells of the pulmonary capillaries and ensures selective vasodilation in the ventilated areas. If a decrease is observed, the dose of NO should be reduced progressively in order to obtain the minimum dose necessary. If NO is stopped suddenly, there could be a rebound effect. Other classes of drugs are available but only in a galenic oral form. Sildenafil (Revatio®) is a selective inhibitor of phosphodiesterase V. It causes pulmonary vasodilation but also peripheral vasodilation responsible for hypotension 15–30 min after administration. It can be administered via a gastric probe in the ICU at a dose of 20 mg, three times a day. This can be considered as a treatment for the acute phase of PAH but it is not recommended for ARDS. In contrast, Bosentan (Tracleer®), whose mode of action is selective antagonism of the receptors for endothelin-1, is considered more as long-term treatment (delay in action of 4–6 weeks). Stopping this latter drug may be associated with pulmonary hypertensive rebound. It is logical therefore to continue Tracleer® via a gastric probe at the full dose (125 mg twice/day). The administration of prostacyclin (Iloprost®) intravenously or as an aerosol is expensive but offers an alternative solution. Intravenous form of some of the oral drugs mentioned above might be soon available.

Finally, in the case of right ventricular failure that is refractory to vasodilators and to inotropes (dobutamine) and/or refractory hypoxaemia, Extracorporeal Corporeal Membrane Oxygenation (ECMO) may be justified. For a predominantly pulmonary attack (hypoxaemia-hypercapnia), veno-venous ECMO with a centrifugal pump is indicated. Venous-arterial ECMO is indicated when left ventricular failure is associated. RV failure alone secondary to hypoxemia-hypercapnia is not a contra-indication for VV ECMO since after correction of hypoxemia-hypercapnia, pulmonary arterial pressure should drastically decrease. In this situation, ECMO is

only a temporary replacement technique while waiting for either remission from the flare-up after a bolus of an immunosuppressive drug or a bridge to lung or heart–lung transplant. Control of anticoagulation will be particularly difficult due to the quasi-constant thrombopenia and frequent thrombopathy. For this reason, veno-venous assistance is preferable because it does not require anticoagulation at a curative dose. In all cases, the decision to initiate ECMO should be discussed collectively taking into account a number of factors such as the patient's age, number of failing organs, level of platelets and the therapeutic perspectives. When the patient is already on a transplant waiting list, the situation may be revised and the status of the patient changed to a "super-emergency", always in consultation with a specialised multi-disciplinary team. Of course, the early transfer of these patients to a reference centre capable of carrying out an emergency lung transplant is desirable. Furthermore, ECMO can be performed before out of hospital transfer with a specialized mobile team.

Conclusion

In conclusion, dialogue should be encouraged between specialists in autoimmune SD (internists, nephrologists, etc.) and the intensivists who manage SD patients during the most dangerous periods in their disease. The intensivist should know how to evoke a diagnosis of SD. When the diagnosis is already established, the role of the intensivist is to ensure the temporary replacement of vital functions while waiting for the effects of immunomodulatory treatments. The intensivist should be particularly vigilant in the detection and management of infections that are often atypical, severe and may occur simultaneously with the flare-up of the SD. Finally, the intensivist is the central spokesperson among the different specialists in these diseases. In this context, discussions with referent centres should take place daily. An integrative diagnostic and therapeutic approach is proposed to guide the intensivist in this management (Fig. 2).

Three successive steps can be distinguished (which can be performed at the same time) with diagnostic (positive and differential) and therapeutic (specific and symptomatic) goals. The first step is principally diagnostic: investigations for auto-antibodies should be requested urgently (telephone call to the immunologist) and after 24–48 h, particularly if auto-antibodies are negative, an extrapulmonary biopsy should be discussed. At this step, procalcitonin (PCT) and bronchoalveolar lavage (BAL) cytology may help. At 48–72 h, the microbiological results of BAL (bacterial and viral culture, PCR) will allow adaptation of anti-infective treatment initiated at admission due to the severity of the illness. At the end of this first week, if the diagnosis of SD is not established, a lung biopsy should be discussed. When a diagnosis of SD has been made specific immunosuppressive treatment with cyclophosphamide should be initiated in the absence of an uncontrolled infection. While waiting for improvement, symptomatic measures (NO) may enable the patient to get over the hypoxaemic peak. In the case of an unfavourable evolution,
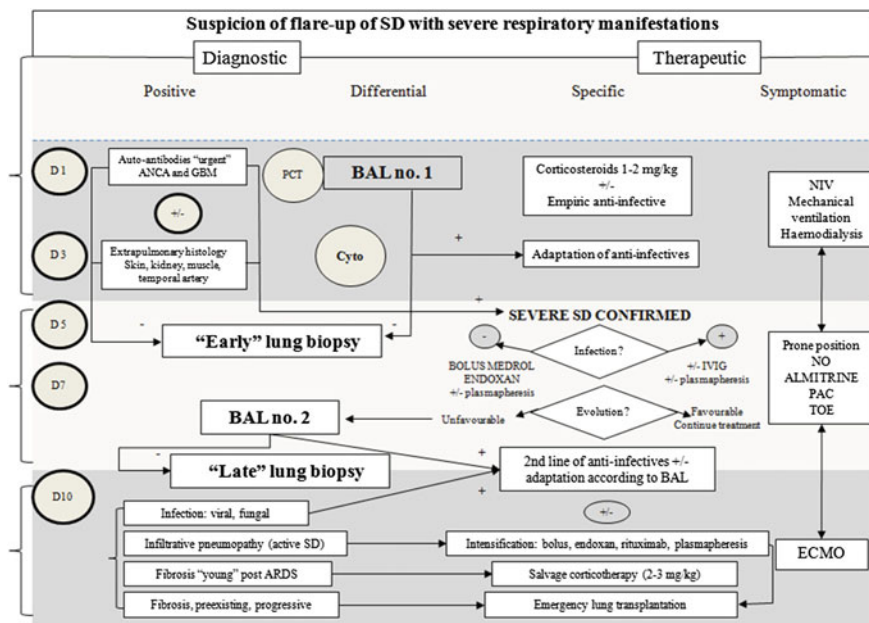
Fig. 2 Management of a probable systemic disease (SD) with severe respiratory manifestations

a final "salvage" step should be undertaken in which treatment will be at best "guided" (BAL and/or lung biospy). While waiting for the results of these investigations and/or the effect of the new therapies initiated, ECMO may be justified in the case of expected reversibility and/or a foreseeable lung transplant.

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