

# Chapter 2

## Alveolar haemorrhage syndromes



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### Summary

Alveolar haemorrhage (AH) is a rare and potentially life-threatening condition characterised by diffuse blood leakage from the pulmonary microcirculation into the alveolar spaces due to microvascular damage. It is not a single disease but a clinical syndrome that may have numerous causes. Autoimmune disorders account for fewer than half of cases, whereas the majority are due to nonimmune causes such as left heart disease, infections, drug toxicities, coagulopathies and malignancies. The clinical picture includes haemoptysis, diffuse alveolar opacities at imaging and anaemia. Bronchoalveolar lavage is the gold standard method for diagnosing AH. The lavage fluid appears macroscopically haemorrhagic and/or contains numerous haemosiderin-laden macrophages. The diagnostic work-up includes search for autoimmune disorders, review of drugs and exposures, assessment of coagulation and left heart function, and search for infectious agents. Renal biopsy is often indicated if AH is associated with renal involvement, whereas lung biopsy is only rarely useful. Therapy aims at correction of reversible factors and immunosuppressive therapy in autoimmune causes, with plasmapheresis in selected situations.

**Keywords:** Anti-glomerular basement membrane disease, anti-neutrophil cytoplasmic antibodies, granulomatosis with polyangiitis (Wegener's), leptospirosis, microscopic polyangiitis, systemic lupus erythematosus

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**A**lveolar haemorrhage (AH) is a rare but potentially life-threatening condition that can have numerous causes, including autoimmune diseases, infections, drug toxicities, coagulopathies, malignancies and cardiovascular disorders. Clinical worsening may occur within days, and lead to acute respiratory failure or damage to extrathoracic organs such as the kidney, if AH is part of a multisystemic disorder. Admission to the intensive care unit is required in up to 50% of cases. Average mortality is 20–30% [1–3], and may reach 50–60% in some conditions [4–7]. Prompt therapy may be life-saving and preserve organ function, especially in disorders of immune origin. Rapidly and accurately identifying the cause of AH is therefore a key issue.

## Definitions

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The terms AH, diffuse AH and intrapulmonary haemorrhage are considered synonymous. AH designates bleeding from the pulmonary microcirculation (pulmonary arterioles, alveolar capillaries and pulmonary venules) as a result of microvascular damage leading to blood leakage into the alveolar spaces. AH is a diffuse phenomenon simultaneously affecting multiple areas in both lungs. Bleeding is usually documented indirectly by bronchoalveolar lavage (BAL).

AH must be distinguished from localised bleeding originating from the bronchial circulation caused by airway disorders such as bronchiectasis, infection and tumours. Haemorrhage of bronchial origin almost always manifests with haemoptysis. As the volume of the tracheobronchial tree is only 150 mL, even small amounts of blood may cause asphyxia by airway obstruction, although it is usually not sufficient to produce anaemia. In contrast, AH occurs distally in the alveolar spaces and haemoptysis is not always present despite significant blood loss, which may cause severe anaemia. Localised alveolar filling by blood of bronchial origin is not considered as AH.

Two situations can occur clinically, overt acute or subacute AH and, more rarely, occult chronic AH. Overt AH is defined by the presence of macroscopically haemorrhagic, either pink or red, BAL fluid, which classically becomes increasingly red on successive aliquots. BAL cytology shows numerous red blood cells and haemosiderin-laden alveolar macrophages when AH lasts for >3 days. Haemosiderin-laden macrophages may be absent in AH of <3 days' duration. Chronic occult AH is defined by the presence of haemosiderin-laden macrophages representing >20–30% [4, 7, 8] of the macrophage BAL population, or by a Golde score >100 (see later in this chapter) [9], with or without red blood cells.

## Aetiology

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AH is not a single disease but a clinical syndrome that may have numerous causes (table 1). The cause may be limited to the lung, such as in pulmonary infection, or affect several organs, such as in systemic vasculitis. AH may be at the forefront of the clinical picture and represent a life-threatening condition. Conversely, it may be infraclinical if the disease mainly threatens another organ such as the kidney. When AH is associated with glomerulonephritis, the term pulmonary–renal syndrome is used.

Causes of AH can be broadly divided into immune and nonimmune [1, 58, 60]. The most frequent immune causes of AH are small vessel vasculitis (microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's) (GPA)), systemic lupus erythematosus (SLE) and Goodpasture's syndrome [1, 58]. Immune cases have probably been over reported in the past. Hence, in four recent series of AH, an immune origin was found in only 19–42% of cases, whereas the cause was not immune in 58–81% [1, 4, 7, 58]. Thus, more than half of cases of AH are of nonimmune origin and these causes should not be overlooked [58, 60, 63]. The most frequent nonimmune causes of AH are heart diseases, especially left ventricular failure and mitral stenosis, infections, drugs and coagulation disorders [1, 58].

## Clinical manifestations

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The clinical picture typically includes: 1) haemoptysis, 2) diffuse alveolar opacities at chest radiography, and 3) anaemia. Many cases do not exhibit this classical triad, but an AH should be suspected when at least two signs are present. Symptoms may develop acutely in hours or days, or subacutely in weeks to months. Haemoptysis is present in 40–80% of cases but is rarely abundant, even in severe AH, because of the distal location of the bleeding source. Dyspnoea is of variable severity, and results from both ventilation/perfusion mismatch secondary to alveolar filling, and anaemia. Chest pain occurs in a minority of cases. Systemic symptoms (fever, myalgias, arthralgias), ocular manifestations, ear-nose-throat symptoms or skin changes may be present in systemic

**Table 1.** Aetiology of alveolar haemorrhage (AH) syndromes

Diagnostic category	Common causes of AH	Rare causes of AH
<b>Systemic vasculitis<sup>#</sup></b>	Granulomatosis with polyangiitis (Wegener's) <sup>†</sup> [2, 10], microscopic polyangiitis <sup>†</sup> [2, 3]	Henoch–Schoenlein purpura <sup>†</sup> [11], Churg–Strauss syndrome <sup>†</sup> [2, 12–14], Behçet syndrome [15], mixed cryoglobulinemia due to hepatitis C virus [16], pauci-immune pulmonary capillaritis (with or without anti-neutrophil cytoplasmic antibodies), polyarteritis nodosa related to hepatitis B virus, Takayasu disease [17]
<b>Connective tissue diseases<sup>#</sup></b>	Systemic lupus erythematosus <sup>†</sup> [5, 6, 18]	Rheumatoid arthritis [19], systemic sclerosis, idiopathic inflammatory myopathies [20], mixed connective tissue disease [19]
<b>Other immune causes<sup>#</sup></b>	Anti-basement membrane antibody disease <sup>†</sup> [21]	Pauci-immune glomerulonephritis <sup>†</sup> , immune complex glomerulonephritis <sup>†</sup> , haemolytic uraemic syndrome <sup>†</sup> , immunoglobulin A nephropathy <sup>†</sup> , coeliac disease [22], inflammatory bowel diseases, cows' milk intolerance [23]
<b>Infections</b>	Leptospirosis <sup>#,†</sup> [24]	Invasive aspergillosis, systemic candidiasis, strongyloidiasis, staphylococci (including <i>Staphylococcus aureus</i> producing Panton–Valentine leukocidin), legionellosis, <i>Mycoplasma</i> , <i>Cytomegalovirus</i> , Herpes simplex virus, <i>Hantavirus</i> , AIDS, H1N1 influenza [25], malaria, <i>Strongyloides stercoralis</i> , <i>Stachybotrys chartarum</i> [26–28]
<b>Drugs</b>	Propylthiouracil <sup>#</sup> [29, 30]	Alemtuzumab [31], abciximab [32], transretinoic acid <sup>#</sup> [33], aminoglutethimide [34], amiodarone [35, 36], azathioprine <sup>#</sup> , carbamazepine, carbimazole, cyclosporine, clomifen, cytarabine, dextran, dihydralazine <sup>#</sup> , dimethylsulfoxide, D-penicillamine <sup>#</sup> [37], everolimus <sup>#</sup> [38], fludarabine, gemcitabine, glibenclamide <sup>#</sup> , methotrexate <sup>#</sup> , mitomycin [39], moxalactam, nitrofurantoin <sup>#</sup> [40], nitric oxide, phenytoin <sup>#</sup> [41], quinidine, rituximab <sup>#</sup> , sirolimus <sup>#</sup> [42], sunitinib [43], tirofiban [32, 44]; see also haemostasis disorders
<b>Toxic</b>	Cocaine <sup>#</sup> [45]	Trimellitic anhydride <sup>#</sup> [46, 47], pyromellitic dianhydride [48], isocyanates [49], hydrocarbon derivatives
<b>Intravascular metastasis</b>		Angiosarcoma, Kaposi sarcoma [50], choriocarcinoma, epithelioid haemangioendothelioma, multiple myeloma, renal cell carcinoma [7]
<b>Transplantation</b>	Bone marrow transplant [51, 52]	Solid organ transplantation
<b>Haemostasis disorders</b>		Disseminated intravascular coagulation [7], thrombocytopenia, anti-phospholipid syndrome <sup>#</sup> [53], thrombotic thrombocytopenic purpura <sup>#</sup> , haemophilia [54], drugs (oral anticoagulants [55], anti-aggregants [56], anti-glycoprotein IIb/IIIa [32], fibrinolytic agents [57])
<b>Pulmonary vascular disease</b>		Idiopathic and thromboembolic pulmonary hypertension, pulmonary veno-occlusive disease, pulmonary capillary haemangiomas
<b>Heart disease</b>		Mitral stenosis [58], left heart failure [58], left atrial myxoma
<b>Other</b>		Acute respiratory distress syndrome, idiopathic pulmonary haemosiderosis [23], amyloidosis [59], lymphangioleiomyomatosis, sarcoidosis, idiopathic pulmonary fibrosis, barotrauma, fat embolism

<sup>#</sup>: causes with definite or suspected immunological mechanism; <sup>†</sup>: pulmonary–renal syndromes. Adapted from [60–62].

vasculitis. Conversely, systemic manifestations may be mild or absent in some conditions such as Goodpasture's syndrome. AH can present as acute respiratory distress syndrome (ARDS) requiring admission to the intensive care unit, without being suspected until BAL is performed [4, 7]. The respiratory clinical examination may disclose fine crackles reflecting alveolar filling. A careful search for signs of vasculitis and connective tissue disease is important, including ocular, ear-nose-throat, skin, osteoarticular and neurological systems.

## Biological findings

Anaemia can occur abruptly as a haemoglobin level drop of 20–40 g·L<sup>-1</sup> within 1–2 days, or as iron deficiency anaemia in chronic forms. Progressive decrease of haemoglobin level over several consecutive days in the presence of lung opacities should raise the suspicion of AH. Elevated C-reactive protein and sedimentation rate are common in the immune causes but do not provide useful diagnostic information. Renal impairment can manifest by microscopic haematuria, proteinuria or raised creatinine level. Other specific biological findings are detailed in a later section of this chapter.

## Imaging

Chest radiography usually shows bilateral symmetrical opacities, but asymmetrical or unilateral involvement may sometimes occur. AH may appear as ground-glass alveolar opacities, consolidation with air bronchogram, or multiple nodules reflecting acinar filling. Pulmonary apices and costodiaphragmatic angles may be relatively spared (fig. 1). In massive AH, the chest radiograph shows bilateral extensive alveolar opacities. Conversely, when AH is mild, the chest radiograph may be nearly normal. Chest opacities may also result from fluid overload or superimposed infection. Pleural effusion is uncommon.

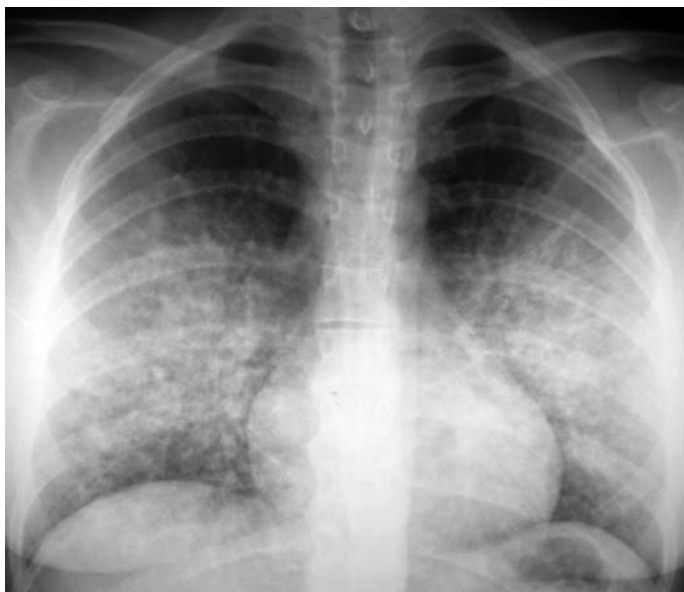
High-resolution computed tomography (HRCT) shows ground-glass opacities or consolidation, with predominantly central involvement and relative sparing of the lung periphery (fig. 2). At a later stage, alveolar opacities are replaced by more reticular opacities and micronodules, reflecting haemorrhage resorption in the pulmonary interstitium. HRCT may be more informative than chest radiography by revealing masses or nodules suggestive of GPA. However, HRCT is not essential for the diagnosis of AH and it may be delayed in an unstable patient.

## Lung function tests

The lung function manoeuvres may be difficult to perform in patients with severe shortness of breath. When performed, lung function tests show a restrictive ventilatory defect and hypoxaemia.

As they do not provide any specific diagnostic information, lung function measurements are unnecessary in acute AH.

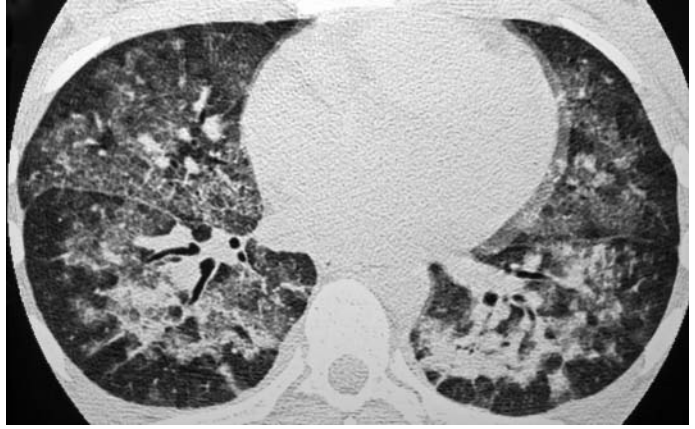
An increase in diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ) has been reported in AH and attributed to increased carbon monoxide uptake by intra-alveolar red blood cells [64–67]. As a result,  $DL_{CO}$  measurement has been classically considered as a useful diagnostic test in AH. However, a recent study of AH in Goodpasture's syndrome showed that  $DL_{CO}$  was increased in only a quarter of cases, and was reduced in half of them, probably as a result of ventilation/perfusion mismatching [21]. Therefore,  $DL_{CO}$  has no practical interest for the diagnosis of acute AH and should no longer be performed for this purpose.



**Figure 1.** Chest radiograph in a patient with alveolar haemorrhage: diffuse bilateral alveolar opacities with relative sparing of the costodiaphragmatic angles are visible.

## BAL

A macroscopically haemorrhagic BAL fluid, especially with increasing blood content on successive aliquots, is considered diagnostic of acute AH. After a bleeding episode, haemoglobin is converted to haemosiderin by alveolar macrophages in 36–72 h. Haemosiderin-laden macrophages reside in the lungs for 4–8 weeks. The presence of iron in haemosiderin-laden macrophages is revealed by Perls stain. Subacute AH can be diagnosed if haemosiderin-laden macrophages represent >20–30% of the total macrophage count [4, 7], or with a Golde score >100 [9], with or without red blood cells. The Golde score is a semiquantitative assessment of haemosiderin-laden macrophages, which evaluates both the percentage of macrophages containing haemosiderin and the intensity of staining on a scale between 0 and 4. The result of this score may vary between 0 and 400.



**Figure 2.** Chest computed tomography scan in a patient with alveolar haemorrhage: diffuse bilateral alveolar and ground-glass opacities are visible.

## Pathology

Lung biopsy is rarely performed in AH. When available, it shows numerous red blood cells and/or haemosiderin-laden macrophages filling alveolar spaces. AH may or may not be associated with pulmonary capillaritis. Capillaritis is a vasculitis affecting small vessels characterised by fibrinoid necrosis of the capillary walls, intravascular thrombi, and neutrophilic infiltrates of the alveolar interstitium with oedema and fibrin deposits. It results in damage to the alveolo-capillary basement membrane and leakage of red blood cells into the alveolar spaces. The presence of capillaritis suggests that AH is caused by an immune mechanism. However, capillaritis may be mild and go unnoticed in the case of massive alveolar filling by red blood cells. AH without capillaritis is called “bland AH”.

In Goodpasture’s syndrome, immunofluorescence staining may show linear immunoglobulin (Ig) deposits along alveolar walls, but it is an inconsistent finding on pulmonary biopsy, in contrast to renal biopsy, which is the preferred procedure in most cases. In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis with AH, pauci-immune capillaritis (*i.e.* without Ig deposits along basement membranes) is observed at lung biopsy [68]. The presence of other histopathological features, such as diffuse alveolar damage and presence of hyaline membrane lesions, may be at the forefront and may orient the diagnosis towards ARDS. In chronic AH, haemosiderin deposits may be observed in the alveolar walls together with intra-alveolar haemosiderin-laden macrophages. Appropriate stains may also reveal infectious agents.

## Main causes of AH

### Coagulation disorders

Anti-phospholipid syndrome [53] and thrombotic thrombocytopenic purpura have been associated with AH in isolated cases. All drugs acting on haemostasis have also been incriminated in the occurrence of AH, including oral anticoagulants, heparin, thrombolytic agents and anti-platelet agents including anti-glycoprotein IIb/IIIa [32, 44]. Patients with AH caused by oral anticoagulants have a high prevalence of allelic variants of genes *VKORC1* (encoding the target of oral

anticoagulants vitamin K epoxide reductase complex 1) and CYP2C9 (encoding cytochrome P450 2C9 involved in the catabolism of coumadins), which may explain over-anticoagulation and bleeding complications [55].

## Haemodynamic causes

Elevated pulmonary venous pressure due to left heart disease, especially mitral stenosis, has been known for a long time as a cause of AH. AH may be chronic and occult, manifesting as haemosiderin-laden macrophages in the alveoli (*i.e.* chronic pulmonary haemosiderosis). Less commonly, left heart disease, especially mitral stenosis, may manifest with acute haemoptysis and massive AH [69]. The presumed mechanisms include elevated hydrostatic pressure in pulmonary capillaries and/or bronchial veins at the surface of bronchial mucosa, with consecutive rupture in the alveolar spaces and/or airway lumen [69, 70]. Nonvalvular systolic or diastolic left heart failure may also manifest with AH, which could even be its first manifestation [58]. As rheumatic valvular heart disease is now uncommon, left heart dysfunction has become a more frequent cause of AH than mitral stenosis. In one large series, left heart dysfunction accounted for 22% of all cases of AH, and 34% of nonimmune cases, whereas valvular heart disease represented only 5% and 8% of cases, respectively [58]. Mitral regurgitation may also lead to AH, and its severity may be underestimated on transthoracic echocardiography compared with transoesophageal echocardiography [71]. AH of left heart origin may be worsened by anticoagulation therapy, given for instance for atrial fibrillation. Pulmonary veno-occlusive disease can also cause AH, which generally remains subclinical.

## Drugs and toxic causes

Besides drugs affecting haemostasis, several drugs can cause AH by an immune mechanism and the occurrence of capillaritis, especially D-penicillamine [37], propylthiouracil [29, 30], phenytoin [41] and transretinoic acid [33]. D-penicillamine can cause AH and glomerulonephritis with granular deposits of immune complexes in glomerular capillaries. AH may also complicate diffuse alveolar damage induced by nitrofurantoin [40], sirolimus [42] and cytotoxic drugs [39].

Massive haemoptysis and diffuse AH have been reported after inhalation of cocaine [45]. Trimellitic anhydride is a chemical compound used in the manufacture of plastics and resins. Its inhalation at high temperatures is associated with the development of AH, anaemia and specific circulating antibodies [46, 47].

## GPA and MPA

GPA is a systemic ANCA-associated vasculitis that mainly affects the upper airways, lungs and kidneys, but which may occasionally involve any other organ. Limited forms affecting only the respiratory system also occur [10]. The pathological characteristic of GPA is a necrotising granulomatous vasculitis of the paranasal sinuses, upper airways, trachea and lung parenchyma, as well as necrotising pauci-immune glomerulonephritis. ANCAs are positive in >80% of cases, usually with a cytoplasmic fluorescence (c-ANCA) and anti-proteinase 3 specificity. Lung involvement is observed in >80% of cases of GPA, generally in the form of multiple, often cavitory pulmonary nodules, and more rarely as an isolated nodule or a parenchymal consolidation. GPA may occasionally manifest as AH with associated pulmonary capillaritis [10], either as the first disease manifestation, or as a secondary complication or relapse. AH may be subclinical and recurrent.

MPA is a small-vessel ANCA-associated vasculitis that was initially considered as a variant of polyarteritis nodosa. It is actually closer to GPA and its treatment is identical. What distinguishes them is the presence of a granulomatous inflammation in GPA, whereas granulomas are absent in MPA. ANCAs in both conditions are frequently positive, c-ANCA with anti-proteinase 3 specificity in GPA, and perinuclear immunofluorescence (p-ANCA) with anti-myeloperoxidase specificity in MPA, although exceptions exist. Both vasculitis are characterised by segmental and focal necrotising

glomerulonephritis. MPA is more frequently associated with AH than GPA, and AH is often severe and life-threatening in MPA (table 2) [2, 3].

### Anti-basement membrane antibody disease (Goodpasture's syndrome)

Anti-basement membrane antibody (ABMA) disease is a rare autoimmune disorder characterised by rapidly progressive crescentic glomerulonephritis and AH. Its pathogenesis involves an autoimmune response against neoepitopes of the noncollagenous-1 domain of the  $\alpha 3$  and  $\alpha 5$  chains of collagen IV located on alveolar and glomerular basement membranes [72]. Neoepitopes appear after conformational changes of the normal collagen IV structure, thereby exposing buried amino acid residues, which become antigenic and elicit an autoimmune response [72]. Conformational changes may be triggered by events such as oxidation, nitrosylation, glycation or proteolytic cleavage, presumably triggered by smoking or other exposures [72]. Hence, 85% of patients with ABMA disease are active smokers, and exposure to another inhaled agent has been reported in up to one-third [21]. The disease mainly affects young males in their third decade, but can also occur in females, older subjects and nonsmokers. In approximately half of cases, pulmonary and renal involvement are both clinically apparent. In the other half, renal impairment predominates, whereas AH is only subclinical or even absent. In 5–10% of cases, AH occurs in isolation with no or only subclinical renal impairment. The diagnosis is established by the detection of anti-basement membrane antibodies, either in serum (in approximately 80% of cases) or as linear deposits along glomerular basement membranes revealed by immunofluorescence staining on renal or sometimes lung biopsy (in the remaining 20%). 10–20% of patients with ABMA disease also have ANCA [73]. The standard treatment includes a combination of plasmapheresis, corticosteroids and cyclophosphamide. Plasmapheresis aims at rapid removal of circulating antibodies, and immunosuppressive therapy at stopping antibody synthesis. In the first case series reporting its use, this therapeutic regimen allowed prompt termination of AH in all patients in whom it was a presenting feature, as well as improvement of renal function in non-anuric patients, whereas no benefit was observed in anuric patients [74]. A small randomised controlled trial comparing immunosuppression with plasmapheresis to immunosuppression alone showed a more rapid disappearance of circulating antibodies and a significantly better renal outcome with plasmapheresis [75], although imbalance between groups in severity of glomerulonephritis could have been a confounder. Prompt treatment is essential as renal function impairment may be rapidly progressive and renal outcome strongly depends on initial creatinine level [76]. Plasma exchanges are usually administered every 2–3 days, and fresh frozen plasma is used as major replacement fluid to avoid complement and fibrinogen depletion [75]. Anticoagulation during plasma exchanges should be avoided in the context of AH. Plasmapheresis is continued until disappearance of circulating antibodies [74, 76]. Corticosteroid and immunosuppressive treatment is continued for a median duration of 6 months [21]. Relapses

**Table 2.** Comparison of the main causes of immune pulmonary–renal syndrome

	GPA	MPA	ABMA disease	SLE
<b>ABMA</b>			80–100	
<b>c-ANCA, anti-PR3</b>	90	15		
<b>p-ANCA, anti-MPO</b>	5–10	50–75	10	
<b>Anti-nuclear antibodies</b>				Present
<b>Alveolar haemorrhage</b>	5–10	10–50	80–90	4–20
<b>Renal impairment</b>	60–80	80–90	40–70	Often
<b>Nasal involvement</b>	70–90	2–25 <sup>#</sup>		Sometimes
<b>Granulomas at biopsy</b>	Present	Absent	Absent	Absent
<b>Relapse rate</b>	50	30–40	5–10	15

Data are presented as %. GPA: granulomatosis with polyangiitis (Wegener's); MPA: microscopic polyangiitis; ABMA: anti-basement membrane antibody; SLE: systemic lupus erythematosus; c-ANCA: anti-neutrophil cytoplasmic antibodies with cytoplasmic fluorescence; anti-PR3: anti-proteinase 3 specificity; p-ANCA: anti-neutrophil cytoplasmic antibodies with perinuclear fluorescence; anti-MPO: anti-myeloperoxidase specificity. #: nasal involvement in MPA is nonspecific.

of AH occur in 5–10% of cases, *i.e.* less frequently than in ANCA-associated vasculitides [21], but may be fatal (table 2) [74].

## SLE

AH is one of the most serious complications of SLE. Its prevalence varies between 1% and 5% in patients with SLE [5, 6]. Symptoms usually develop in an abrupt and unpredictable manner within a few days. Patients present with dyspnoea, cough, fever, haemoptysis, diffuse opacities on chest radiography and acute anaemia. Granular Ig deposits and complement are found in alveolar and vascular walls, but the pathogenetic mechanisms of AH in SLE are unknown. Some studies have suggested that the presence of nephritis and a high disease activity index were risk factors for the occurrence of AH [77, 78]. In a recent retrospective study of 21 cases of AH compared with 83 controls among 1,521 patients with SLE, predictors of AH were thrombocytopenia, low C3, higher disease index activity, previous need for higher doses of prednisone and coexistence of neuropsychiatric events [5]. Autoantibody profiles, including anti-phospholipid antibodies and lupus anticoagulant, were not predictive of AH [5]. Therapy comprises high-dose corticosteroids, immunosuppressive agents, plasmapheresis and intravenous Ig [5, 78]. Mechanical ventilation is required in up to three-quarters of cases. The prognosis is severe, with mortality ranging from 36% to 62%, mostly by respiratory failure or superimposed infection [5, 6]. The systematic search for infection and the administration of broad-spectrum antibiotics is therefore recommended. Relapses have been reported [78].

## Other immune causes

AH has occasionally been reported in connective tissue diseases such as rheumatoid arthritis [19], systemic sclerosis, idiopathic inflammatory myopathies [20] and mixed connective tissue disease [19], as well as in other vasculitis such as Churg–Strauss syndrome [2, 12–14], Henoch–Schoenlein purpura [11] and IgA nephropathy. AH has rarely been described in myasthenia gravis, Grave's disease, autoimmune hepatitis and coeliac disease. Another presumably immune cause of AH is isolated pauci-immune pulmonary capillaritis, a small-vessel vasculitis limited to the lungs without any other signs of systemic impairment, pulmonary–renal syndrome or ANCA.

## Leptospirosis

Leptospirosis is a ubiquitous zoonosis caused by the spirochete *Leptospira*. It is endemic in tropical areas, and considered to be re-emerging in temperate regions. Human transmission occurs through contact with water or soil contaminated by urine of infected animals, especially rats, dogs and cattle. Penetration of bacteria occurs through minor skin lesions, intact mucous membranes or bites [79]. Risk factors include occupational or recreational exposure to domestic or wild animals, water activities (swimming, canoeing, fishing) and floods, especially in tropical regions [80]. However, in one series of 147 cases, a risk factor could be retrospectively identified in only 48% of cases [24]. The incubation period lasts 7–12 days [80]. The severity of the clinical manifestations is variable, ranging from a nonspecific flu-like illness with myalgia to a severe form with hepatitis, acute renal failure and haemorrhagic manifestations. The disease typically follows a biphasic course. The first phase of 4–9 days' duration is characterised by the sudden onset of fever, myalgia, headache, abdominal symptoms and conjunctival haemorrhage. After a symptom-free interval of 1–3 days a second phase begins, with kidney, liver, pancreatic, cardiovascular, neurological and pulmonary manifestations [79]. Lung involvement occurs in up to 85% of cases [24] and is characterised by respiratory distress of rapid onset and massive AH. More than half of patients require intensive care, and mortality is 5–13% [24, 80, 81]. Mild forms of pulmonary involvement, as well as cases with normal liver and/or renal function, have been reported [81]. The cause of AH is poorly understood but toxic and/or immune mechanisms seem to play a role. The presence of linear Ig deposits and complement along alveolar walls has been recently demonstrated [82, 83]. Diagnosis is usually serological. The earliest positive IgM titres appear 6–10 days after the first symptoms. Titres >1/320 are suggestive of



leptospirosis, whereas lower titres may reflect early infection or cross-reactivity. A convalescent serology (IgM ELISA and microscopic agglutination test) should be obtained >10 days after disease onset to confirm the diagnosis [80]. A PCR test has been recently developed and might provide earlier diagnosis [84]. Antibiotics are considered useful in the early phase, but appear less effective if administered at a later stage [24, 79]. Pre-emptive antibiotic treatment with doxycycline or penicillin is recommended whenever the disease is suspected, given the nonspecific presenting features and the delay to obtain serological confirmation [80]. Other therapeutic measures include haemodynamic and respiratory support, dialysis and platelet transfusions. Improved survival has been observed after administration of methylprednisolone bolus [85], as well as a combination of cyclophosphamide and plasma exchange [86], in agreement with the hypothesis of immunological mechanisms.

## Other infectious causes

Inhalation of a mould of the environment, *Stachybotrys chartarum* (or *Stachybotrys atra*), has been incriminated in the occurrence of AH in 41 small children in the region of Cleveland, OH, USA, between 1993 and 2000 [26–28]. 12 deaths occurred. The causal link between *S. chartarum* and AH was based on case–control epidemiological studies and toxicological experiments on animal models, although these analyses have been criticised [87]. *S. chartarum* produces various mycotoxins causing cellular apoptosis, release of pro-inflammatory cytokines, and protein and DNA degradation, which could explain damage to the alveolar capillaries. The mycotoxin sachlylsine could be especially involved in the occurrence of AH [88]. Passive smoking [28] and genetic predisposition [89] could be cofactors. Corticoid treatment seems beneficial. Removal from the presumably offending environment decreased the risk of recurrence, but occult bleeding persisted in most patients [28]. No similar observations have been reported from other countries to date.

AH has been observed in necrotising pneumonia due to *Staphylococcus aureus* producing Pantone–Valentine leukocidin (PVL) [90, 91]. This bacterial toxin, produced by <5% of *S. aureus* strains, creates pores in leukocyte cell membranes leading to release of cytokines, activation of proteases and cell death. Distinctive features of PVL-secreting *S. aureus* necrotising pneumonia include occurrence in otherwise healthy children and young adults without any risk factors for infection, frequent influenza-like illness in the preceding days, frequent haemoptysis, and high mortality (38% in the first 2 days and 75% overall) despite the use of effective antibiotics [90]. The clinical picture is characterised by diffuse alveolar infiltrates and severe gas exchange impairment, consistent with adult respiratory distress syndrome, pleural effusion, leukopenia and multi-organ failure [90, 91]. Autopsy findings include massive AH with necrosis of alveolar septa, large clusters of Gram-positive bacteria, extensive necrosis of airway mucosa, and a relative lack of inflammatory infiltrates possibly attributable to the cytotoxic properties of PVL [90, 91].

AH has occasionally been reported in H1N1 influenza [25]. Other infectious causes of AH are mentioned in table 1.

## Idiopathic pulmonary haemosiderosis

Idiopathic pulmonary haemosiderosis (IPH) is a rare disease characterised by either recurrent acute episodes of AH with cough, dyspnoea and haemoptysis, or insidious and progressive disease with weight loss or growth failure, iron-deficiency anaemia and chronic respiratory impairment [92]. Incidence has been estimated at 0.2–1.2 per million per year [93, 94]. 80% of cases occur in childhood in the first decade of life and the remaining 20% occurs in adults, usually before the age of 30 yrs. In the absence of any pathognomonic features, the diagnosis of IPH is made by exclusion of other causes of AH. At histology, airspaces contain abundant haemosiderin-laden macrophages and red blood cells without capillaritis or immune deposits [23, 95]. Long-standing disease may be associated with the development of interstitial fibrosis and restrictive ventilatory defect [23, 95, 96]. The pathogenesis of IPH is unknown. An immune mechanism is suggested by the presence of circulating immune complex in some cases and the development of autoimmune disorders in some patients [96]. A relationship with coeliac disease has been suggested [22, 97],

and a gluten-free diet has been reported to induce improvement or remission of AH. Similarly, precipitins and IgE against cows' milk have been observed in some cases, with clinical improvement under a milk-free diet [23]. Corticosteroids have been reported as beneficial to control the acute phase and to prevent recurrences [23, 97], although their use is limited by side-effects. Hydroxychloroquine and azathioprine have been used as steroid-sparing agents [23]. Long-term therapy is usually needed. The outcome appears highly variable in published studies [23, 92, 98]. Mortality rates of up to 60% have been reported [92, 98]. In contrast, a 5-yr survival of 86% has been reported in 17 children receiving prednisone and immunosuppressive therapy [23]. Deaths were due to massive AH.

## Diagnostic approach

A rapid assessment is considered essential in AH because of the risk of progression towards acute respiratory failure or organ damage, especially rapidly progressive renal failure. Hence, in a series of ABMA disease with AH, a worsening of renal parameters occurred in four out of 10 cases between hospital admission and treatment onset, over a median delay of 10 days [21]. The diagnostic strategy thus aims at promptly establishing the diagnosis of AH and identifying its cause. Diagnostic criteria to define AH are not uniform in the published literature. Haemoptysis, alveolar opacities at imaging, anaemia, hypoxaemia and/or increased  $DL_{CO}$  have been used in older studies to define AH. However, pulmonary opacities and hypoxaemia are not specific and may have other causes, such as infection or fluid overload. Haemoptysis and anaemia are indirect markers of low or indeterminate diagnostic value, and  $DL_{CO}$  has been shown to have no practical interest [21]. In one series of ABMA disease, these indirect parameters were less sensitive than BAL to detect AH [21]. For these reasons, BAL should be considered as the gold standard to diagnose AH.

When AH is suspected or diagnosed, the work-up must include a careful history in search of the cause (table 3). The presence of extra respiratory symptoms is an important clue for an immune issue, especially in the case of associated renal impairment. Importantly, aetiological enquiries must not be limited to immune disorders and must include a careful search for nonimmune causes.

Blood tests should include a complete blood picture and coagulation panel. The search for autoantibodies should include ANCA with determination of c-ANCA or p-ANCA fluorescence and anti-proteinase 3 or anti-myeloperoxidase specificity, anti-basement membrane autoantibodies, antibodies associated with connective tissue diseases including anti-nuclear antibodies, anti-double-strand DNA antibodies, rheumatoid factor, anti-cyclic citrullinated peptide, anti-nucleoproteins, and anti-phospholipids. The results should be available as soon as possible, ideally within 24 h. Echocardiography should be performed to search for left ventricular failure and valvular heart disease. N-terminal pro-brain natriuretic peptide may be useful to identify heart failure, but its diagnostic value is significantly blunted by concomitant renal failure, thus reducing its interest in patients with pulmonary–renal syndromes.

Fibreoptic bronchoscopy is indicated in virtually all patients with suspicion of AH. It aims at ruling out a bleeding of bronchial origin, establishing the diagnosis of AH, and searching for infectious agents. Transbronchial biopsy is, however, of little value and is generally not recommended [75]. AH may not be initially suspected in a patient admitted to the intensive care unit for ARDS of unknown cause, and the diagnosis of AH may appear only at BAL [4, 7]. In one study, only three out of 37 patients with proven AH admitted to intensive care were initially suspected of having AH, whereas AH was not suspected in the vast majority because haemoptysis was absent [4]. In addition, in 11% of these patients, BAL was not macroscopically haemorrhagic and the diagnosis of AH was made only by Perls staining showing >20% haemosiderin-laden macrophages [4].

Renal function must be evaluated immediately by serum creatinine, urine sediment and creatinine clearance. Abnormal findings should prompt rapid discussion of percutaneous renal biopsy with the nephrologist. The decision to perform a percutaneous renal biopsy must, however, not delay

**Table 3.** Proposed evaluation of a patient with alveolar haemorrhage

In all cases	Depending on the clinical context
<p><b>Targeted history and clinical examination:</b>            Review of exposures and inhaled agents            Review of medication and illicit drugs            Search for features of systemic vasculitis:            general symptoms (fever, asthenia, weight loss),            nasal symptoms (crusty rhinitis, septal erosions),            ocular symptoms (episcleritis, retinal vasculitis),            skin changes (palpable purpura, subcutaneous            nodules, erythema, livedo), musculoskeletal            symptoms (arthralgias, myalgias), neurological            symptoms (mono- or multinevritis)            Search for connective tissue disease            Exposure to infected animals or their urine,            immersion in contaminated water (swimming,            fishing, floods), bites; recent stay in tropical areas</p>	
<p><b>Chest radiography, HRCT, echocardiography</b></p>	Lung function tests
<p><b>Complete blood picture, coagulation studies,            urea, creatinine, urinary dipstick and            sediment, creatinine clearance, 24-h proteinuria,            NT-pro-BNP (limited value in renal failure)</b></p>	Rheumatoid factor, anti-cyclic citrullinated peptide antibodies, anti-nucleoproteins, serology for leptospirosis (IgM ELISA, microscopic agglutination test), cryoglobulin, complement, anti-cardiolipin antibodies, immunoelectrophoresis, anti-gliadin, anti-endomysial and anti-transglutaminase antibodies
<p><b>Arterial blood gases or pulse oxymetry</b></p>	Viruses (in immunosuppressed patients)
<p><b>Anti-nuclear antibodies, anti-double-strand            DNA antibodies, anti-basement            membrane antibodies, anti-neutrophil            cytoplasmic antibodies</b></p>	
<p><b>Bronchoscopy with BAL: macroscopic            appearance, cytology with differential cell            count, Perls staining with percentage of            haemosiderin-laden macrophages and            Golde score, routine bacteriology, fungi,            mycobacteria, <i>Pneumocystis jiroveci</i></b></p>	Biopsies: renal (with immunofluorescence), other (nasal), rarely lung biopsy
<p>HRCT: high-resolution computed tomography; NT-pro-BNP: N-terminal pro-brain natriuretic peptide; Ig: immunoglobulin; BAL: bronchoalveolar lavage. Adapted from [60, 99].</p>	

the treatment. The main abnormalities that should lead to consideration of renal biopsy in the context of AH are : 1) renal insufficiency of recent onset (plasma creatinine  $>120 \mu\text{mol}\cdot\text{L}^{-1}$  or clearance  $<70 \text{ mL}\cdot\text{min}^{-1}$  per  $1.73 \text{ m}^2$ ), 2) glomerular haematuria, or 3) proteinuria  $\geq 0.3 \text{ g}$  per 24 h. When a pulmonary–renal syndrome is suspected, renal biopsy is usually more informative and less invasive than lung biopsy. In ANCA-associated vasculitis, renal biopsy may show segmental and focal extracapillary necrotising pauci-immune glomerulonephritis. The diagnostic yield of renal biopsy in demonstrating glomerulonephritis in patients having GPA and active renal disease may reach 90% [100]. However, the absence of glomerulonephritis does not completely rule out pulmonary–renal syndrome, as glomerular involvement may be absent in the early stage. Vasculitic lesions are sometimes observed. Immunofluorescence is especially useful for the diagnosis of ABMA disease by showing linear Ig deposits along glomerular basement membranes. If the clinical picture of pulmonary–renal syndrome is typical, positive ANCA or ABMA may obviate the need for renal biopsy for diagnostic purposes. However, the nephrologist may still request renal biopsy to obtain prognostic information. Of note, the presence of renal and pulmonary symptoms does not always reflect an immune-mediated pulmonary–renal syndrome, and may also result from two unrelated conditions [101]. The diagnostic yield of renal biopsy in the absence of

proteinuria, haematuria, renal insufficiency and any feature suggesting immune pulmonary–renal syndrome is unclear but probably low, although there are occasional reports of diagnostic renal biopsy in such circumstances in ABMA disease [21, 102]. In this situation, analyses in search of renal involvement should be repeated and other causes of AH should be ruled out before considering this option.

Nasal examination may show erosion of the septum or mucosal inflammation, and prompt biopsies of the nasal mucosa are required, especially if GPA is suspected.

Lung biopsy is only rarely performed in AH, for several reasons. First, it is not necessary for the diagnosis of AH, which can be made less invasively by BAL. Secondly, lung biopsy does not consistently provide specific aetiological information in AH. Although the presence of neutrophilic capillaritis at histopathology suggests an immune process, it does not indicate its precise cause. Performing a lung biopsy in the search for capillaritis is therefore not justified. Only GPA could be diagnosed by lung biopsy when granulomatous lesions or polymorphonuclear cell microabscesses are found, but diagnostic findings suggestive of GPA can usually be obtained less invasively by ANCA, or nasal or kidney biopsy. In a retrospective series of 34 cases with AH who underwent lung biopsy, GPA undiagnosed by other procedures was found in only one case [103]. Another reason to avoid lung biopsy in AH is that it may be risky in unstable patients with respiratory failure. Thus, surgical lung biopsy should be considered in only a minority of cases of AH when the diagnosis remains unclear despite a thorough diagnostic work-up, and after having carefully weighted the risk–benefit ratio. Situations in which surgical lung biopsy may be useful include nondiagnostic renal biopsy, absence of specific autoantibodies, and suspicion of infection despite nondiagnostic BAL. Part of the biopsy specimens should be frozen for immunostaining. Around 14% of cases of AH remain without aetiological diagnosis despite comprehensive work-up, and are considered idiopathic [58].

A study has attempted to identify predictors of immune AH using simple clinical parameters available in the first 24 h of admission [1]. Four predictors were identified in a retrospective series of 76 immunocompetent patients: time since first symptoms  $\geq 11$  days, fatigue and/or  $>5\%$  weight loss within 1 month, arthralgia/arthritis, and proteinuria  $\geq 1 \text{ g}\cdot\text{L}^{-1}$  [1]. A scale derived from these parameters might help to identify AH of immune origin and allow earlier institution of corticosteroid therapy, but further validation is required.

## Therapeutic approach

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Respiratory failure should be handled with oxygen and, if needed, mechanical ventilation. Attention should be paid to limit barotrauma and oxygen toxicity. Fluid overload should be avoided, especially in the case of renal insufficiency, as it may worsen alveolar bleeding. Coagulation disorders should be corrected. Administration of recombinant activated coagulation factor VII has been reported to be beneficial in isolated cases [104–106], and needs further evaluation in the setting of life-threatening AH.

AH of nonimmune cause should be treated according to the involved pathophysiological mechanisms, *i.e.* pharmacological treatment of heart failure, antibiotic therapy or removal of an offending drug. Antibiotics for leptospirosis should be initiated early upon clinical suspicion. Temporarily withholding anticoagulation and/or anti-aggregant therapy in patients with AH due to left heart failure has been suggested [58].

In AH of immune cause, treatment consists of prompt administration of corticosteroids, immunosuppressive agents and, in selected disorders, plasmapheresis [107]. In ANCA-associated vasculitis, oral prednisone is usually started at  $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , maintained for 1 month and then reduced, but not below  $15 \text{ mg}\cdot\text{day}^{-1}$  for the first 3 months, and later tapered to  $10 \text{ mg}\cdot\text{day}^{-1}$  or less during maintenance therapy [107]. Intravenous high-dose steroid pulses (methylprednisolone  $7.5\text{--}15 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  for 1–3 days) are commonly administered as part of the remission induction therapy, although they have not really been evaluated *versus*  $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  in ANCA-associated

vasculitis. The most frequently used immunosuppressive agent is cyclophosphamide, given intravenously at a dose of 500–700 mg·m<sup>-2</sup> every 2 then 3 weeks for 3–6 months followed by oral immunosuppressants such as azathioprine, which have fewer adverse effects [107]. Prophylaxis of *Pneumocystis jiroveci* pneumonia with trimethoprim/sulphamethoxazole is recommended in all patients treated with cyclophosphamide [107]. The dose and duration of corticosteroid and immunosuppressive treatment varies according to diagnosis: a minimum treatment duration of 24 months is recommended for ANCA-associated vasculitis. In ABMA disease, treatment is usually shorter (median duration of 6 months) [21]. In a recent randomised trial, rituximab appeared to have similar efficacy to oral cyclophosphamide to induce remission in ANCA-associated vasculitis (GPA and MPA), including in patients with AH. However, since patients with severe AH requiring ventilator support were excluded from the study, the efficacy of rituximab in this subgroup remains uncertain [108]. Plasmapheresis is indicated in ABMA disease and has been reported to be beneficial in AH associated with lupus erythematosus. Recent data support the use of plasmapheresis in ANCA-associated vasculitis with severe renal failure [109]. However, the value of plasmapheresis for the control of AH is not clearly established in ANCA-associated vasculitis [107].

## Prognosis

During the acute phase of AH, the main determinant of survival is respiratory failure. In one series, mortality due to refractory hypoxaemia was 21%. In a large series of 97 cases of AH of both immune and nonimmune origin, the in-hospital mortality was 25% and the overall mortality was 37% [58]. Survival was similar for immune and nonimmune causes, but was significantly reduced in AH due to left heart disease compared with all other causes [58]. Nonpulmonary predictors of in-hospital mortality were shock, glomerular filtration rate <60 mL·min<sup>-1</sup> and plasma lactate dehydrogenase greater than twice the upper normal limit. Predictors of long-term mortality were previous cardiovascular disease and chronic dialysis [58]. In another series of AH of varied causes with severe respiratory failure, overall survival was 49% [4]. Patients with AH of immune or undetermined origin had better survival than those with AH due to coagulopathy or sepsis (82% versus 22%) [4]. In MPA with AH, short-term mortality is around 25%. In ABMA disease, fatal AH occurs in 7–10% of cases [76, 110]. Mortality of AH in SLE appears higher than in other autoimmune diseases, with an average value of 40%. Death is due to refractory hypoxaemia and superimposed infectious complication, or failure of other organs, including cardiac insufficiency. The relapse rate of AH is around 30% in MPA [3], 15% in SLE and 5–10% in ABMA disease.

Several months after acute AH, elevated Golde scores are still found at BAL in ABMA disease [21]. Haemosiderin-laden macrophages reflecting subclinical alveolar bleeding are also frequently found in patients with ANCA-associated vasculitis in the absence of clinically apparent AH [111]. Whether this finding reflects a low-grade but still active immune process, or irreversible damage to alveolo-capillary walls resulting in chronic leakage of red blood cells into alveolar spaces, is currently unclear. Persistent alteration of lung function tests was observed in 24% of cases after AH in MPA, mostly with a restrictive ventilatory defect [3]. In ABMA disease with AH, persistent alteration of DL<sub>CO</sub> was observed in the long term [112]. As development of interstitial fibrosis has been observed in IPH [23, 95, 96], one can hypothesise that chronic occult alveolar bleeding and haemosiderin accumulation may also lead to pulmonary fibrosis in other causes of AH. Hence, an association between pulmonary fibrosis and ANCA positivity (especially with anti-myeloperoxidase specificity) and ANCA-associated vasculitis (especially MPA) has been reported in several case series [113–117]. Lung fibrosis usually preceded the occurrence of MPA: in one series of 33 cases of MPA, lung fibrosis was present in 36% at diagnosis of vasculitis [117]. Prognosis of ANCA-associated pulmonary fibrosis was generally poor and similar to idiopathic pulmonary fibrosis. Whether and how lung fibrosis is causally related to ANCA positivity, occurrence of MPA and overt or occult AH remains unclear at the present time.

## Conclusion

AH syndromes encompass a broad spectrum of causes, severity and associated extrapulmonary manifestations. They require rapid and thorough investigation and prompt therapeutic decisions, which constitute a challenge for the clinician. Appropriate management is better achieved in large tertiary centres used to managing such disorders in a multidisciplinary setting.

## Statement of interest

None declared.

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