Management of Alveolar Hemorrhage in Lung Vasculitides

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ABSTRACT

Alveolar hemorrhage (AH) is an important pulmonary manifestation of small vessel vasculitis because severe presentations are the most common vasculitic cause of early death. Renal vasculitis is usually present with AH; the combination is known as pulmonary-renal syndrome. Early diagnosis and intensive therapy are of particular importance to reduce early mortality and improve longer-term outcomes. The commonest immune-mediated cause of AH is anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (80%), with other vasculitides, including systemic lupus erythematosus and anti-glomerular basement membrane disease accounting for 20%. One quarter of AAV patients develop AH, which when mild is associated with a good outcome, but mortality rises to 50% for cases with respiratory failure requiring ventilator support. The prognosis of AH in the other vasculitides is generally favorable, but cases are rare and experience is limited. Treatment follows similar regimens to those for other AAV presentations, although when severe there is widespread use of parenteral glucocorticoids together with plasma exchange. These interventions have developed empirically supported by a theoretical rationale but have not been validated by randomized clinical trials. Sepsis and cardiovascular and thromboembolic events are important early complications. and long-term follow-up is required to monitor for and prevent relapse and manage disease-related damage. A minority of cases develop on a background of pulmonary fibrosis, or progressive pulmonary fibrosis develops after vasculitis has gone into remission.

KEYWORDS: Alveolar, hemorrhage, vasculitis, lung, ANCA, management

DEFINITION AND ETIOLOGY OF AH

Pulmonary hemorrhage is usually defined as bilateral alveolar infiltrates on radiological imaging without alternative explanation plus at least one of the following features: hemoptysis, increased carbon monoxide diffusing capacity, bronchoscopic evidence of hemorrhage, or an unexplained drop in hemoglobin.

Alveolar hemorrhage (AH) is a heterogeneous syndrome with multiple causes. Vasculitis was reported as the third most common cause of AH requiring intensive care support (19% of patients), after thrombocytopenia (27%) and sepsis (22%).[1] A minority of cases were due to drug toxicity (11%) or stem cell transplantation (5%) or were idiopathic (16%).

The majority (80%) of these vasculitis cases with AH are due to anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (Fig. 1). AH is the most common respiratory manifestation of AAV, occurring in 24%.[2] Geographic variability has been reported, with a lower incidence in France (11.8%)[3]

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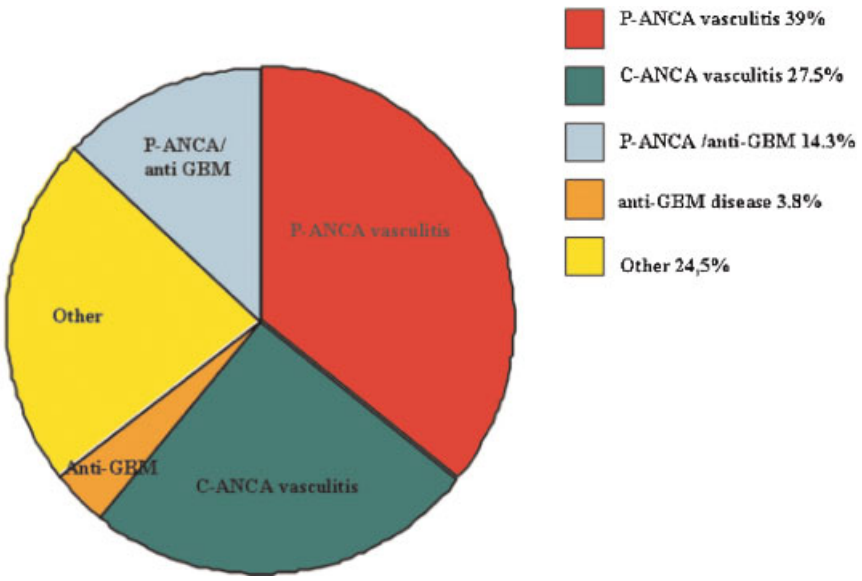

Figure 1 Relative frequencies of conditions contributing to pulmonary-renal syndrome in the intensive care unit. Adapted from Papiris et al.[12]

compared with Japan (22.2%).[4] Of the AAV subgroups AH occurs in 29% of patients with microscopic polyangiitis (MPA)[3] and between <10 and 45% of patients with Wegener granulomatosis (WG), according to different reports (reported more frequently in recent reports, possibly representing changes in diagnostic definitions).[5–7]

AH is rare in the Churg-Strauss syndrome.[8–11] The second-most-common vasculitis associated with alveolar hemorrhage is anti-glomerular basement membrane (anti-GBM) disease (discussed in the previous article by Dr. Sanders et al.) Rarely, other vasculitides, such as cryoglobulinemia, Henoch-Schönlein purpura, Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, ANCA-negative pauci-immune vasculitis, and secondary vasculitides may cause AH. Drugs known to induce vasculitis include hydralazine, propylthiouracil, and cocaine, which may be associated with anti-myeloperoxidase ANCA (MPO-ANCA) or atypical (antielastase, anti-lactoferrin, etc.) ANCA. This syndrome can also occur in systemic lupus erythematosus (SLE), antiphospholipid syndrome, systemic sclerosis, mixed connective tissue disease, and polymyositis.

Other nonimmune causes giving rise to secondary AH include sepsis, coagulopathy, stem cell transplantation, malignancy, renal failure, and cytotoxic drugs (Table 1).

PATHOGENESIS OF AH

The pathogenic process underlying AH involves inflammation of the small pulmonary blood vessels (arterioles, venules, capillaries) and fibrinoid necrosis resulting in vessel wall disruption, hence extravasation of red cells and neutrophils into the alveoli. However, alveolar hemorrhage has also been reported in the absence of these features.[13,14]

There is a close correlation between the presence of ANCAs and AH, with 95% of cases with pauci-immune histology being ANCA-positive. This is similar in frequency to that seen with pauci-immune crescentic glomerulonephritis and supports a pathogenic role for ANCAa in these presentations. ANCAs have been shown, in experimental models, to cause glomerulonephritis and microvascular hemorrhage by amplifying the interaction between neutrophils and endothelial cells.[15]

The role of MPO-ANCAs in inducing alveolar hemorrhage and glomerulonephritis is supported by case reports of transplacental ANCA transfer in humans[16] and mouse models,[17] although the latter have proved difficult to establish for proteinase 3 (PR3)-ANCA.

DIAGNOSIS OF AH

When occurring in the setting of a systemic vasculitis, the approach to diagnosis in an AH patient is similar to that for vasculitis in general. Typically there is a prodromal phase with several months of constitutional symptoms, then vasculitis develops in other organ systems, especially in the kidneys, as well as in the joints, skin, and lungs. The secondary causes of vasculitis and mimics of vasculitis should be excluded before confirmation of the diagnosis by ANCA testing with or without tissue biopsy.[18]

Important differential diagnoses of AH include pneumonia, left ventricular failure, and acute respiratory distress syndrome. Also, the absence of overt clinical

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Table 1 Relative Frequencies, Treatments, and Outcomes of Alveolar Hemorrhage in Vasculitides

Type of Vasculitis	Frequency of AH	Treatment	Evidence	Outcomes
PRIMARY				
Small Vessel Vasculitis				
- ANCA-associated vasculitis	-Increasingly recognized (up to 45%)	glucocorticoids (GC)+ cytotoxics+ ?PLEX if severe AH	uncontrolled cohorts no RCTs	No increase in mortality if mild AH
Wegener granulomatosis				High mortality if ventilation needed
Microscopic polyangiitis	-Commonest respiratory manifestation (29%)	GC+ cytotoxics+ ?PLEX if severe AH	Uncontrolled cohorts no RCTs	No increase in mortality if mild AH High mortality if ventilation needed
Churg-Strauss angiitis	-Less common than in WG and MPA	GC+/−cytotoxics	Uncontrolled cohorts no RCTs	Good Lower mortality than WG or MPA
-Henoch-Schönlein purpura	-Uncommon (case reports)	GC+/−cytotoxics	Case reports	Variable
-Cryoglobulinemia	-Uncommon (case reports)	GC + cytotoxics +/− PLEX +/− interferon if hep C+	Case reports	Poor High mortality - 60%
Medium Vessel Vasculitis				
-Polyarteritis nodosa	-Very rare (case report)	Glucocorticoids + cytotoxics + PLEX	Case reports	Good recovery
Large Vessel Vasculitis				
Takayasu arteritis	- Rare (case reports)	Glucocorticoids	Case reports	Good recovery
Giant cell arteritis	- Very rare (case report)	Glucocorticoids	Case reports	Good recovery
SECONDARY DUE TO:	Common	Address cause	Uncontrolled cohorts	
Sepsis		Supportive		Poor
Cancer				Higher mortality than AH due to primary vasculitis
		Supportive		
Drugs		? Steroids		Good Frequent reversal of vasculitis on stopping drug

AH, alveolar hemorrhage; GC, glucocorticoids; MPA, microscopic polyangiitis; PLEX, ??; RCTs, randomized controlled trials; WG, Wegener granulomatosis.

symptoms such as hemoptysis in one third of patients,[19] especially if AH is chronic, means that this presentation needs to be actively considered in all vasculitis patients. Cough and shortness of breath should raise suspicions for AH, especially in the context of a drop in hemoglobin.

Radiological imaging reveals bilateral airspace infiltrates (Fig. 2), with higher resolution on thoracic computed tomographic (CT) scans compared with plain radiographs.

Pulmonary function tests in AH are characterized by increased (>100%) diffusion capacity for carbon monoxide (DLco) but they are difficult to carry out in critically ill patients.[20]

Bronchoscopy is a valuable diagnostic tool for AH and may reveal overt hemorrhage or progressively more blood-stained returns from the bronchoalveolar lavage (BAL) fluid.

A raised content (>5%) of darker colored, hemosiderin-laden macrophages on Prussian blue staining of BAL also suggests subclinical alveolar hemorrhage, which is commonly (53%) encountered in AAV, unlike in other connective tissue disorders.[21]

Rarely, recurrent subclinical pulmonary capillaritis may give rise to interstitial pulmonary fibrosis that could predate the actual diagnosis of MPA by months or years[22–24] and is associated with high mortality.[25]

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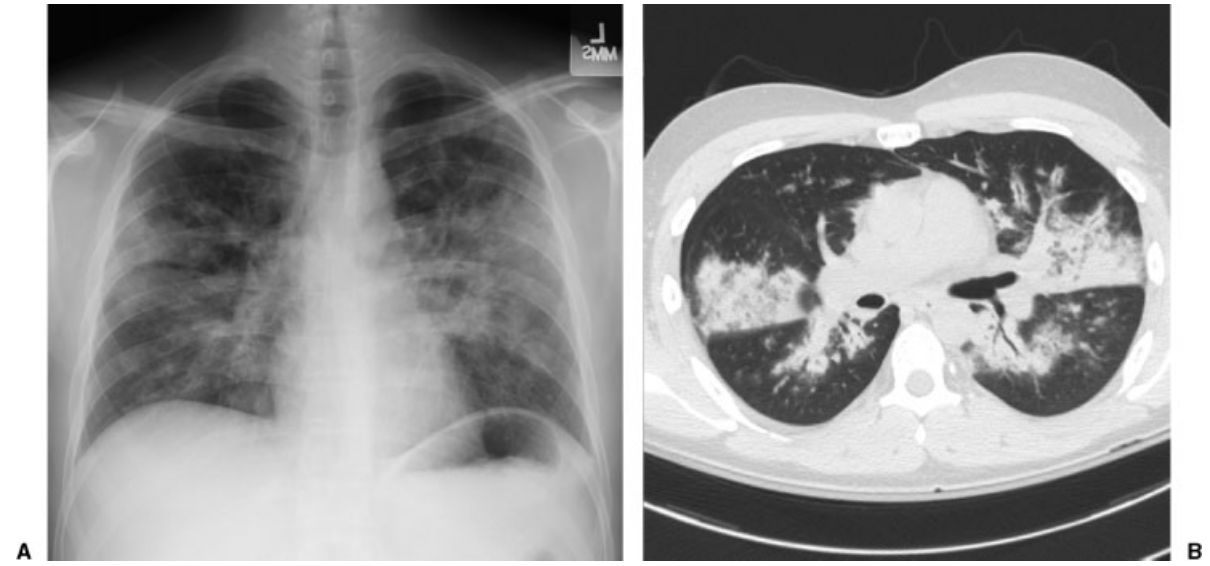

Figure 2 (A) Chest x-ray and (B) computed tomographic scan from a 24-year-old male patient with active Wegener granulomatosis and alveolar hemorrhage, showing bilateral alveolar infiltrates. In addition, there is significant peribronchial inflammation. (Reproduced with permission from Dr. Ulrich Specks.)

Twenty-three cases of pulmonary fibrosis preceding MPA have been described in the literature.

Lung biopsy is not usually required for the diagnosis of AH if abnormal serology and extrapulmonary features of disease are present. Transbronchial biopsy carries a 40% diagnostic sensitivity for the detection of vasculitis and is preferable to open or video-assisted biopsies, which carry a significant risk. In rare cases of localized bronchial artery hemorrhage, labeled red cell scan or bronchial angiogram may locate the hemorrhage with the potential for therapeutic embolization.

SMALL VESSEL VASCULITIDES AND AH

AH in AAV

AH appears similar in the PR3-ANCA and MPO-ANCA groups with regard to clinical features and severity of both respiratory and renal failure,[26,27] suggesting that the two subtypes could be considered as a continuous spectrum of ANCA-associated pauci-immune necrotizing vasculitides. Furthermore, 10% of WG cases are MPO-ANCA associated, whereas 20 to 30% of MPA cases are PR3-ANCA associated.

Diffuse AH has previously been considered a fulminant disease occurring in association with renal failure in pulmonary-renal syndrome, as resulting from the common pathogenic process of capillaritis. However, mild AH is more common (in 24 to 28% of AAV[2,28]), and it is not uncommon for AH to be indolent, with as many as 28% of patients retrospectively reporting previous symptoms suggestive of AH for >12 months before diagnosis.[26]

The majority of AAV patients with AH have coexisting extrapulmonary involvement, especially renal (>90%[29]), musculoskeletal, and ears-nose-throat (ENT).[26] Nevertheless, isolated AH has been reported,[30] albeit with unclear severity and outcomes.

AH has been found to be associated with the presence of nephritis but not with the severity of its clinical[2,26] or histopathological[30] presentation. Co-occurrence of ANCAs and anti-GBM antibodies is seen in 5% of patients with AAV and 30% of patients with anti-GBM disease. AH is more common in this subgroup, occurring in almost 50%, and renal disease is more severe than in AAV without anti-GBM antibodies. Renal histology implies both vasculitis and anti-GBM disease pathogenic processes are active. Although smoking has been associated with AH in anti-GBM disease, there is no association with the presence of AH in AAV.

Management Approach to AH in AAV

The therapeutic approach depends on the severity of alveolar hemorrhage and extent and severity of extrapulmonary disease. Patients should be treated according to recent evidence-based treatment recommendations for AAV with AH and managed in a center experienced in vasculitis therapy. Severe AH places particular demands on intensive care and respiratory support, and careful assessment and prevention of respiratory and systemic infection are essential. Both parenteral glucocorticoids and plasma exchange are widely used for severe presentations but lack an evidence base from randomized trials. Induction treatment aims to induce a remission within a few weeks or months while maintenance treatment aims to prevent relapse. Disease states

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in vasculitis have been defined by consensus statements.[31]

Disease-Modifying Immunosuppressive Therapy of AH in AAV

Since its introduction in patients with AAV in the 1970s, immunosuppression (in the form of glucocorticoids and cyclophosphamide) has transformed outcomes from a 5-month median survival in generalized WG to 90% remission at 6 months. This therapeutic regimen remains the cornerstone of treatment in AAV; however, disease control is suboptimal in 20% of patients, mortality rates are 10% at 1 year and 25% at 5 years, and 50% of survivors relapse by 5 years. Furthermore, almost all patients suffer from treatment-related toxicity, which directly impacts survival and longer-term health.

The intensity of therapy has been adjusted to the extent and severity of disease. Several systems to categorize patients and determine therapy have been developed: the Five-Factor Score, developed by the French Vasculitis Study Group,[32] is based on prognostic factors for survival and divides patients into good or poor prognostic subgroups; a second system divides patients into those with limited or severe disease, largely based on the presence or absence of renal or severe pulmonary disease.[33] The European Vasculitis Study Group has proposed five severity subgroups:

Category 1 localized disease (such as, isolated upper airway disease).

Category 2 early, systemic disease (active vasculitis with constitutional symptoms but no threatened vital organ dysfunction).

Category 3 generalized disease (threatened organ function, such as, glomerulonephritis).

Category 4 severe/life-threatening disease (presence of vital organ failure, such as, respiratory or renal failure).

Category 5 refractory disease (not responsive to conventional therapy).

AH may "fall" into category 2, 3, 4, or 5 depending on its severity.

Induction Therapy for AH in AAV

TREATMENT OF MILD AH WITHOUT IMPAIRMENT OF PULMONARY FUNCTION (CATEGORY 2)

Cyclophosphamide-based regimens have been used most commonly in early systemic AAV, but less toxic agents such as methotrexate[34] and rituximab[28] are equally efficacious in this patient subgroup. The NORAM trial[34] concluded that methotrexate is a currently accepted alternative to cyclophosphamide in AAV patients with early ENT disease, with fewer adverse events but longer time to remission and higher relapse rates. Mortality and end-stage renal disease (ESRD) rates in AAV patients with mild AH are low and not influenced by the presence of AH.[2]

TREATMENT OF MODERATE AH RESULTING IN IMPAIRED PULMONARY FUNCTION BUT NOT REQUIRING MECHANICAL VENTILATION (CATEGORY 3)

Cyclophosphamide and glucocorticoids are recommended therapy, with rituximab as an alternative to cyclophosphamide.[18,28,35] In a planned subgroup analysis of the RAVE trial, control of moderate AH, present in 28%, was equally efficient with either cyclophosphamide or rituximab.[28] The CYCLOPS[36] trial showed pulsed intravenous cyclophosphamide to be equally efficacious to oral cyclophosphamide at inducing remission of AAV while resulting in less leucopenia and lower cumulative dosage.

TREATMENT OF SEVERE AH REQUIRING RESPIRATORY SUPPORT (CATEGORY 4)

Cyclophosphamide in conjunction with parenteral glucocorticoids (intravenous methylprednisolone 500 to 3000 mg) are widely used for severe AH. They have the advantage of being reasonably cheap, available, and feasible to administer. Some presentations with AH will rapidly improve with this treatment and are recommended as initial therapy while the diagnosis is being secured and other treatments planned (Table 2).

The timing of cyclophosphamide administration in the setting of AH associated with respiratory failure and mechanical ventilation remains controversial and varies according to individual physician experience.

Plasma exchange has been shown to improve renal recovery rates in AAV presenting with serum creatinine >500 μmol/L[37] and may also benefit those with less severe renal impairment.[38] The mechanism of plasma exchange is unclear: although removal of ANCAs may contribute, removal of coagulation factors, cytokines, chemokines, or other immune reactants may also be important. The plasma exchange techniques of centrifugation and plasma filtration have not been directly compared. The use of alternative antibody removal techniques including immunoabsorption and double filtration apheresis have been reported, but they risk not removing potentially important elements and have not been compared with plasma exchange. The MEPEX trial[37] used seven, 60 mL/kg exchanges administered over 7 to 14 days and a similar protocol has been selected for the ongoing PEXIVAS trial (www.pexivas.bham.ac.uk, http://clinicaltrials.gov/ct2/show/NCT00987389), which will be the first to systematically assess the effect of adjunctive PLEX on ESRD and mortality in AAV patients with AH of any severity.

The modes of vascular access and anticoagulation and the nature of blood product replacement have not been separately studied, although it is recommended to replace coagulation factors toward the end of each

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Table 2 Factors to Consider in a Patient with Severe Alveolar Hemorrhage

- Disease control
  - Intravenous glucocorticoids, cyclophosphamide or rituximab
  - Plasma exchange
- Monitoring of disease control
  - Hemoptysis, respiratory function, radiology
  - Control of extrapulmonary disease
  - C-reactive protein and anti-neutrophil cytoplasmic antibodies
- Diagnosis and management of ''refractory'' disease
  - Infection, acute respiratory distress syndrome, fibrosis
  - Intravenous immunoglobulin, rituximab
- Detection and management of infection
  - Minimizing infective risks of glucocorticoids and immunosuppression
  - Blood and sputum cultures
  - Bronchoscopy and culture
  - Prophylaxis
- Supportive measures
  - Respiratory support with noninvasive ventilation if possible
  - Minimizing pressure support
  - Maintaining a normal fluid balance and avoiding volume overload
  - Maintaining hemoglobin >10 g/L
  - Correcting coagulation defects

plasma exchange session in patients with active AH. Dosing of cyclophosphamide or rituximab is timed to occur immediately after a plasma exchange session, but uncertainty exists with rituximab regarding the extent to which subsequent plasma exchange interferes with its therapeutic effect by removing the circulating drug.

Plasma exchange is often used with cyclophosphamide and glucocorticoids undertaken in severe AH, although there are no randomized controlled trials to support its efficacy. A case series[39] reported 95% survival and 100% resolution of the initial AH episode in 20 AAV patients treated with plasma exchange; of note, 55% of patients did not require ventilation and 30% had normal renal function, both known prognostic factors influencing mortality. In contrast, another study[40] with longer follow-up, revealed 50% mortality at 22 months despite plasma exchange, mainly due to sepsis; however, all patients required mechanical ventilation for AH, and 86% also had severe renal failure requiring dialysis. A retrospective Japanese study[41] reported that administration of PLEX in 27% of 79 AAV patients with pulmonary-renal syndrome did not impact beneficially on patient survival, but the use of PLEX was biased toward those with more severe disease.

These conflicting outcomes are at least partially explained by the differences in follow-up periods, the severity of AH, and renal impairment between the studies.

On the basis of evidence from management of anti-GBM disease, PLEX is intuitively recommended in AH patients with dual anti-GBM/ANCAs, although their renal recovery rate is poor despite intensive treatment.[42] The correlation between these two autoantibodies is uncertain: no cross-reactivity has been detected, but the glomerular membrane damage caused by ANCAs may unmask occult antigen and thus allow the generation of anti-GBM antibodies.[43]

Case reports[44] have shown granulocytapheresis combined with double filtration plasmapheresis to improve AH in patients with MPA, in conjunction with low-dose glucocorticoids, although the widespread use of these techniques is limited by cost and incomplete understanding of the therapeutic mechanism.

Several case reports found life-threatening, uncontrollable alveolar hemorrhage to benefit from intrapulmonary administration of recombinant, activated factor VII[45–47] or extracorporeal membrane oxygenation (ECMO), which improves oxygenation and "buys time" until other therapies take effect.[48]

Noninvasive ventilation with pressure support may maintain oxygenation in some patients with severe AH without the need for intubation. The co-occurrence of renal vasculitis and renal failure is often accompanied by fluid overload, which exacerbates AH, and renal support with hemofiltration or dialysis should aim to reverse overload and achieve normal pulmonary venous pressures. Increasing positive end-expiratory pressure is often required but risks the complication of pneumothorax, a negative predictor in this setting. High levels of inspired oxygen are often required to maintain systemic oxygenation but have the theoretical risk of increasing neutrophil activation and damage through reactive oxygen species. Antibiotic prophylaxis against *pneumocystis jiroveci* pneumonia and fungal infections has been recommended.

Refractory AH in AAV

The diagnosis of refractory pulmonary vasculitis has to be differentiated from AH patients with ongoing respiratory failure due to sepsis, secondary adult respiratory distress syndrome, or pulmonary fibrosis. Failure to respond to conventional therapy is associated with increased mortality.[33] It is important to perform a thorough microbiological analysis with bronchoscopy because many of these patients have lower respiratory tract microbial colonization and infection that has either become the major disease process or is serving as a drive for persisting vasculitis. Continuation of high-dose glucocorticoids will increase the risk of severe infection. It is unclear how cyclophosphamide should be dosed in this setting and whether it is justified to increase the dose in poor responders; the

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development of cyclophosphamide-induced leukopenia increases the risk of sepsis and should be avoided.

High-dose intravenous immunoglobulin is safe to use in the intensive care setting, has an antivasculitic effect, and allows dose sparing of glucocorticoids and cyclophosphamide.[49] Further plasma exchange probably also permits reduced glucocorticoid dosing.

The B cell depleting anti-CD20 monoclonal antibody, rituximab, may have a better safety profile when compared with cyclophosphamide, is effective in refractory disease,[50–53] and was more effective than cyclophosphamide in relapsing AAV patients.[28,35] To date, there are no studies comparing different therapies specifically in refractory AH due to AAV.

Other potential options for refractory AAV include anti-tumor necrosis factor (TNF) biologics (such as infliximab[54,55]), and deoxyspergualin.[56] Lymphocyte depletion with alemtuzumab[57] or antithymocyte globulin is associated with a high risk of sepsis and increased mortality and should probably be avoided in this setting.

The frequent co-occurrence of infection with refractory pulmonary disease argues for reduced glucocorticoid and cyclophosphamide dosing and less immunosuppressive therapies such as immunoglobulin and rituximab.

Maintenance of Remission

The immunosuppressive regimens employed to maintain remission are less intensive than induction therapies. A sequential design, whereby cyclophosphamide is withdrawn after 3 to 6 months and replaced with a less potent immunosuppressive, such as azathioprine or methotrexate, has been validated by the CYCAZAREM[58] and WEGENT[33] studies and is not associated with an increased relapse rate when compared with prolonged cyclophosphamide. Leflunomide was more effective than methotrexate in a small randomized trial, whereas mycophenolate mofetil has been shown to be less effective than azathioprine for relapse prevention.[59] The WGET study[60] found no benefit with addition of the soluble TNF receptor etanercept to maintenance immunosuppression and glucocorticoids in WG.

The role of glucocorticoids in the maintenance of remission is not fully elucidated and a meta-analysis of seven randomized controlled trials (RCTs) and three observational studies found that continued low-dose glucocorticoids (5 to 7.5 mg/day) was associated with lower relapse rates.[61]

Respiratory tract disease is a risk factor for future relapse, together with treatment withdrawal, persistent ANCA positivity, WG, nasal carriage of *Staphylococcus aureus*, and the absence of renal disease.[62]

The optimal duration of maintenance therapy is not known, but withdrawal of therapy is a strong predictor for flare, especially if ANCAs remain present, and such patients should be followed regularly. Relapse can occur many years after original presentation and diagnosis of AAV and may be missed if there is a low suspicion for recurrent disease.

Outcomes of AH in AAV

Alveolar hemorrhage was found to be the most common cause of admission to hospital[63] or to the intensive care unit[64] in patients with AAV and pulmonary involvement. In these studies, mortality was reported as 11% at 1 month and 29% at 1 year, lower than the previous estimates of 25% and 50%, respectively.[65]

The survival during the intensive care admission for AH was higher for underlying primary vasculitis (85%) compared with AH secondary to sepsis, chemotherapy or cancer (20 to 25% survival).[1]

Massive AH requiring ventilation has been associated with a ninefold increase in mortality in AAV.[62] However, the outcome of mild AH is much better, with some studies reporting similar mortality to patients without AH, ~18% at 1 year, 32% at 5 years.[2,26,28] Most fatalities were due to sepsis rather than to active AH.

Long-term outcomes of AH survivors, and especially for respiratory function, are not fully established. WG generally has a higher propensity for relapses at a rate of 75% at 5 years; however, MPA relapses are also seen at a rate of 30% at 5 years. The severity of relapse depends on the rapidity of its diagnosis and treatment.[66–68] Relapsing AH does occur in dialysis-dependent patients and requires long-term meticulous follow-up[3] of patients with AH due to MPA. The majority (69%) were reported to recover normal lung function after treatment.[26] The remainder developed obstructive or restrictive defects with chronic interstitial fibrosis, especially if AH was persistent or recurrent.[14,22,69–71] In contrast, the majority (67%) of patients with treated pulmonary WG were left with considerable residual damage[72].

AH in Cryoglobulinemia

Overt AH in cryoglobulinemia is rare (3.2%[73]), with no more than 10 cases reported, half in mixed cryoglobulinemia associated with hepatitis C infection.[74,75] AH is a grave prognostic indicator associated with 60% mortality[73] regardless of the intensity of treatment, sometimes including immunosuppression, interferon-α, and PLEX.

AH in Henoch-Schönlein Purpura

Henoch-Schönlein purpura (HSP) is more common but less serious in children than in adults.

Transient asymptomatic pulmonary function abnormalities (eg, reduced transfer factor for carbon monoxide) have been reported in the vast majority of HSP

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children during the active phase of disease,[76,77] possibly caused by deposition of immunoglobulin A (IgA) immune complexes along the pulmonary alveoli,[77] and are not associated with subsequent lung disease.[76] In contrast, AH is a rare (3%[78]) but serious occurrence in HSP, with mixed outcomes. Some studies report fatal outcomes in both adults and children[79–81] despite treatment with prednisolone, whereas others found resolution of AH with prednisolone alone[82,83] or combined with cyclophosphamide[84] or cyclosporin.[85] No HSP cases with AH treated with plasma exchange have been reported to our knowledge.

MEDIUM VESSEL VASCULITIS AND AH

AH in Polyarteritis Nodosa

Respiratory system involvement is very rare with only a few case reports of AH in classical polyarteritis nodosa[86] and associated with hepatitis B virus,[87] successfully treated with cyclophosphamide and prednisolone and with adjunctive plasma exchange, respectively.

LARGE VESSEL VASCULITIDES AND AH

AH in Giant Cell Arteritis

AH is rare in giant cell arteritis but is found to be steroid responsive in case reports[88].

AH in Takayasu Arteritis

Pulmonary vascular involvement is often subclinical in Takayasu arteritis and detected in a majority of this patient group, usually in a noninvasive manner on lung perfusion scans[89] or positron-emission tomography.[90]

Over half (56%) of 250 patients with Takayasu arteritis were found to have pulmonary artery involvement on angiography.[91] However, there are only a few case reports of respiratory failure secondary to severe alveolar hemorrhage in Takayasu arteritis, due to capillaritis, severe pulmonary hypertension,[92] or rupture of microaneurysms/collateral circulation formed due to pulmonary stenoses and obstructions.[93,94] Supportive care and glucocorticoids usually achieved good recovery.

Management of AH due to Secondary Lung Vasculitis

The mainstay of treatment is supportive and involves addressing the underlying cause of AH. Stopping the suspected drug frequently reverses the AAV. The optimal management remains uncertain. A subgroup of patients with drug-induced or post–stem cell transplant AH seem to benefit from immunosuppression[95]; however, the latter is contraindicated for septic or aplastic patients with AH.

CONCLUSIONS

Alveolar hemorrhage in AAV is caused by a pulmonary capillaritis with a complex underlying etiology, which may present fulminantly as a pulmonary-renal syndrome. AAV is by far the most common autoimmune cause of AH. Mild AH is not uncommon in AAV, and its outcome is generally good; however, high mortality is reported with ventilator-dependent cases. Mortality is also high in AH secondary to other small vessel vasculitides or nonimmune causes such as sepsis or malignancy. AH in medium and large vessel vasculitides seems to respond well to immunosuppression in the few cases that have been reported.

Severe AH is frequently treated aggressively with glucocorticoids, cytotoxics, and PLEX; however, literature reports are conflicting, and systematic evidence for the benefit of PLEX in the form of RCTs is so far lacking. The current ongoing PEXIVAS trial should help to guide best practice.

It is not clear why the frequency of AH differs between the various types of vasculitides. Given the prognostic importance of AH, a thorough integration of clinical, laboratory, radiological, and histopathological data is needed to assess its severity and optimal management.

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