Diffuse Alveolar Haemorrhage in ANCA-associated Vasculitis

Stephen West¹, Nishkantha Arulkumaran¹, Phillip W. Ind² and Charles D. Pusey¹

Abstract

Diffuse alveolar haemorrhage (DAH) is a serious complication of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). A literature review was performed to ascertain the diagnostic features, treatment, and outcome of this rare but serious condition. Haemoptysis and dyspnoea are common but non-specific features. Chest radiography is usually abnormal, and high-resolution computerised tomographic scanning is more sensitive. Increased uptake of inhaled carbon monoxide and reduced clearance of C¹⁵O on lung function testing is suggestive of intra-alveolar blood. Fiberoptic bronchoscopy and bronchoalveolar lavage are useful when a super-added infection is suspected. Concurrent renal disease is common and contributes to the morbidity and mortality. Treatment should be individualised, and it is based on glucocorticoid and cyclophosphamide induction with azathioprine maintenance. The role of plasmapheresis is unclear, and is currently being evaluated. Patients are at risk of disease and treatment-related long-term complications. Ongoing research into the most efficacious therapeutic regimens associated with the least side effects is especially important.

Key words: ANCA, vasculitis, alveolar haemorrhage


Introduction

Granulomatosis with polyangiitis (GPA, previously known as Wegener’s granulomatosis), microscopic polyangiitis and Churg Strauss syndrome (CSS) are small vessel vasculitides associated with anti-neutrophil cytoplasmic antibodies (ANCA), which can present with the ‘pulmonary renal syndrome’ of rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar haemorrhage (DAH) (1). They share the common histological feature of a ‘pauci-immune focal and segmental necrotising crescentic glomerulonephritis (2). ANCA-associated vasculitis (AAV) is a rare, but serious, condition with an estimated annual incidence of 20 per million per year in Europe. It commonly affects people over 65 years of age (3), and is associated with a high mortality if untreated (4).

DAH may be one of the most serious manifestations of AAV, while renal involvement is the most common severe presentation of AAV (5, 6). Autoantibodies and cell-mediated immunity underlie the pathophysiology of immune-mediated DAH in several autoimmune diseases including AAV (7).

Detailed characteristics of patients with AAV and associated DAH have been limited to case reports and a few case series, due to the rarity of the condition. Therefore, a systematic review was conducted to ascertain the epidemiology, diagnostic features, renal function, requirement for mechanical ventilation and renal replacement therapy at presentation, and short- and long-term outcomes of patients with DAH in association with AAV. Definitions of AAV are based on the paper from the Chapel Hill Consensus Conference (8). Several studies including patients with DAH as part of an AAV cohort have not been included because they lack clinical data that relate specifically to patients with DAH. Relevant clinical trials of therapeutic strategies have been discussed.

Epidemiology

A total of 9 studies between 1985 and 2012 included de-

¹Renal Sections, Department of Medicine, Imperial College London, Hammersmith Hospital, UK and ²Respiratory Sections, Department of Medicine, Imperial College London, Hammersmith Hospital, UK

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Correspondence to Dr. Nishkantha Arulkumaran, nish_arul@yahoo.com
Table 1. Demographics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>n</th>
<th>% of total AAV cohort</th>
<th>Age (Years) Mean (±SD)</th>
<th>Male : Female</th>
<th>ANCA pattern</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haworth [11]*</td>
<td>1985</td>
<td>32</td>
<td>36% (Not stated)</td>
<td>56 (Not stated)</td>
<td>(Not stated)</td>
<td>GPA: 22 MPA: 10</td>
<td>PR3-ANCA</td>
</tr>
<tr>
<td>Gallagher [10]</td>
<td>2002</td>
<td>13</td>
<td>(Not stated) (±2)</td>
<td>65 (±2)</td>
<td>6:7</td>
<td>MPO-ANCA: 5 PR3-ANCA: 5 PR3-ANCA + GBM: 2 Negative: 2</td>
<td>GPA: 2 MPA: 11 CSS: 2</td>
</tr>
<tr>
<td>Lin [14]</td>
<td>2009</td>
<td>12</td>
<td>9% (±17)</td>
<td>60</td>
<td>9:3</td>
<td>MPO-ANCA: 2 PR3-ANCA: 10</td>
<td>GPA: 2 MPA: 9 CSS: 1</td>
</tr>
<tr>
<td>ter Maaten [16]*</td>
<td>1996</td>
<td>7</td>
<td>(Not stated)</td>
<td>48 (26-73)</td>
<td>6:1</td>
<td>MPO-ANCA: 6 PR3-ANCA: 1</td>
<td>PR3: 1</td>
</tr>
<tr>
<td>Chen [9]*</td>
<td>2009</td>
<td>5</td>
<td>8% (17-78)</td>
<td>60 (13-63)</td>
<td>3:2</td>
<td>PR3-ANCA: 5 MPO-ANCA: 0 Positive: 1</td>
<td>ANCA + GBM: 2 MPA: 21 CSS: 6</td>
</tr>
<tr>
<td>Kostianovsky [17]</td>
<td>2012</td>
<td>80</td>
<td>(Not stated)</td>
<td>49 (13-86)</td>
<td>3:2</td>
<td>ANCA + GBM: 2</td>
<td>GPA: 49</td>
</tr>
</tbody>
</table>

*Only included patients with respiratory failure in ICU.
*Only includes AAV patients with ESRD.
† ANCA type not specified


tails on the clinical features and investigations of DAH (9-17). The study sizes varied from 5 to 80 patients and included a total of 207 patients. The incidence of DAH in AAV is between 8% and 36% (5, 11, 14, 18-20) (Table 1). Eight of the 9 studies listed the mean age at presentation and gender (9, 10, 12-17). The mean age at presentation was 57 years, with a similar number of male and female patients (53% and 47% respectively). Seven studies including 90 patients, reported the ANCA type, and all studies reported the clinical diagnosis (9, 10, 12-16). 57% of patients presenting with DAH in AAV are positive for PR3-ANCA, 39% are positive for MPO-ANCA, 1% are positive for both P-ANCA and MPO-ANCA, and 2% are negative for ANCA. 1% of patients had circulating anti-glomerular basement membrane antibodies in addition to PR3-ANCA (‘double positive’ disease). The most common clinical diagnosis is microscopic polyangiitis (MPO) (52%), followed by granulomatosis with polyangiitis (GPA) (41%), and CSS (6%). One patient (1%) was diagnosed with MPA coexisting with anti-glomerular basement membrane disease (10).

Diagnosis of Diffuse Alveolar Haemorrhage

The presentation of DAH is non-specific, ranging from acute respiratory failure to a more insidious course. There is no consensus on the diagnostic criteria for DAH. Most centres use a combination of criteria in the appropriate clinical context (Table 2) (10-15, 17). The common exclusion criteria to diffuse alveolar haemorrhage include the presence of clinical evidence of haemoptysis that promptly resolves with the treatment of pulmonary oedema, haemoptysis explained by severe pneumonia, and active lung malignancy. Clinical characteristics are neither sensitive nor specific. Dyspnea and haemoptysis may be absent in some cases of DAH (Table 2). Hypoxia, anaemia, haemoptysis and dyspnoea may be secondary to pulmonary (non-haemorrhagic) vasculitis or complications including infection or pulmonary oedema (14, 16).

Mechanical ventilation is required for the most severely hypoxic patients that may also have cardiovascular instability, fluid overload due to renal failure, and associated infection (Table 3). Twenty-seven per cent of patients presenting with DAH require mechanical ventilation (9, 10, 12-17).

Thoracic imaging: The initial imaging evaluation of patients suspected to have DAH should be a plain chest radiograph (CXR). The CXR is a sensitive investigation, with 94% of patients having radiological evidence of DAH on presentation (10, 11, 13-16). However, the CXR features of DAH are non-specific. The CXR images of DAH are char-
Table 2. Diagnostic Features of Diffuse Alveolar Haemorrhage

<table>
<thead>
<tr>
<th>Reference</th>
<th>Haemoptysis/ Dyspnoea</th>
<th>Oxygen saturation/ kPa</th>
<th>Hemoglobin value (g/dL)</th>
<th>Bronchoscopy and bronchoalveolar lavage (BAL)</th>
<th>CXR (Abnormal/ No. scanned)</th>
<th>CT scan (Abnormal/ No. scanned)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haworth [11] 1985</td>
<td>Haemoptysis: 32 (100%)</td>
<td>None recorded</td>
<td>8.5 (±1.1)</td>
<td>Not recorded</td>
<td>28/32 (88%)</td>
<td>None recorded</td>
</tr>
<tr>
<td>Lauque [13] 2000</td>
<td>Haemoptysis: Not recorded 69% had severe dyspnoea</td>
<td>P_{O_2} &lt;10kPa in 10/22 Mean P_{O_2} 9.0kPa</td>
<td>P_{O_2}: FiO₂ = 167±83 P_{O_2}: FiO₂&lt; 300 in 11 Reduction by 1.8±1.7g/dL in 24hrs</td>
<td>Performed in 27 (93%) Grossly haemorrhagic in 25 (93%) PB stain in 21: All with &gt;30% haemosiderin laden cells (mean 87%)</td>
<td>28/29 (97%)</td>
<td>18/18</td>
</tr>
<tr>
<td>Klemmer [12] 2003</td>
<td>None recorded</td>
<td>None recorded</td>
<td>Mean Hb: 8.2 (±0.6)</td>
<td>Haemoptysis or direct visualisation of bleeding at bronchoscopy in all</td>
<td>None recorded</td>
<td>None recorded</td>
</tr>
<tr>
<td>Gallagher [10] 2002</td>
<td>(Haemoptysis or direct visualisation of bleeding at bronchoscopy in all)</td>
<td>P_{O_2} : 6.0kPa (±0.5)</td>
<td>None recorded</td>
<td>Haemoptysis or direct visualisation of bleeding at bronchoscopy in all</td>
<td>None recorded</td>
<td>None recorded</td>
</tr>
<tr>
<td>Lin [14] 2009</td>
<td>Dyspnoea: 11/12 (97%) Frank Haemoptysis: 5/12 (42%) Blood- streaked sputum: 6/12 (50%)</td>
<td>P_{O_2}: FiO₂ = 167±83 P_{O_2}: FiO₂&lt; 300 in 11 Reduction by 1.8±1.7g/dL in 24hrs</td>
<td>None recorded</td>
<td>Performed in all 12 patients Grossly haemorrhagic in 11/12 In the other patient, haemosiderin macrophages &gt; 80%</td>
<td>None recorded</td>
<td>11/12 (92%)</td>
</tr>
<tr>
<td>Ravindran [15] 2010</td>
<td>Haemoptysis: 9/9</td>
<td>None recorded</td>
<td>Baseline 8.8 (±1.4)</td>
<td>None recorded</td>
<td>9/9 (100%)</td>
<td>None recorded</td>
</tr>
<tr>
<td>ter Maaten [16] 1996</td>
<td>Dyspnoea and Haemoptysis: 3/7 Dyspnoea alone: 1/7</td>
<td>None recorded</td>
<td>Respiratory failure: 7/7</td>
<td>Not stated</td>
<td>BAL (done in 5/7) consistent with DAH in all tested patients 3 had lung Bx: 2 with vasculitis and 1 with inflammation (2 Bx at autopsy)</td>
<td>7/7 (100%)</td>
</tr>
<tr>
<td>Chen [9] 2009</td>
<td>Not stated</td>
<td>‘Fall in P_{O_2}’: 4/5 25 (31%) had ‘alveolar haemorrhage associated hypoxia’</td>
<td>None recorded</td>
<td>None recorded</td>
<td>None recorded</td>
<td>None recorded</td>
</tr>
<tr>
<td>Kostianovsky [17] 2012</td>
<td>Haemoptysis: 77 (96.3%) Dyspnoea: not recorded</td>
<td>48 (60%) had drop &gt;1g/dl during 48 hours after DAH</td>
<td>None recorded</td>
<td>71 (88.7%) underwent bronchoscopy and BAL. DAH confirmed on bloody aspirate, Golde score &gt;20 and/or &gt;20% siderophages in 48 (68%) of these</td>
<td>68 (85%) had CT or CXR consistent with DAH</td>
<td>See CXR</td>
</tr>
</tbody>
</table>

CT: computed tomography, CXR: chest radiograph, DAH: diffuse alveolar haemorrhage, kPa: kilopascals, P_{O_2}: partial pressure of arterial oxygen

characterised by rapidly changing opacities with a perihilar distribution, either worsening (further bleeding) or clearing (blood reabsorption), usually within a 48 hour period. The presence of pleural effusion suggests pulmonary oedema, fluid overload and cardiac failure.

High-resolution computerised tomography (HRCT) should be considered if further imaging is required to aid in the diagnosis. DAH is associated with features ranging from localised ground-glass opacification to more extensive consolidation with air bronchograms on HRCT, even in the presence of a normal CXR (21, 22). Despite the improved diagnostic yield there are still no specific changes on HRCT that point towards DAH, opacities can be diffuse or more focal in nature (20, 23). Ando compared the CT findings with lung biopsy specimens in 62 ANCA positive patients with anti-MPO antibodies (51 patients with MPA and 11 patients with Churg-Strauss syndrome (CSS)) (24). Fifty-one out of 62 CT scans were abnormal, with the most common abnormality being ground glass attenuation in 94% of the patients. The extent of ground glass attenuation corresponds to alveolar haemorrhage, chronic interstitial inflammation in the alveolar septa, and vasculitis in small sized arteries. Consolidation is also common (present in 78% of patients), corresponding to either DAH or to vasculitis resulting in prominent eosinophilic infiltrates. Although this study provides valuable information on CT findings and the pathological correlation, it is unclear how many of these patients were diagnosed with DAH by clinical criteria. Two series specifically describing DAH in AAV have reported the appearances of diffuse bilateral opacities, including ground glass densities, dense nodules, and consolidation in all scanned patients (13, 14).

**Fiberoptic bronchoscopy and bronchoalveolar lavage**
Fiberoptic bronchoscopy (FOB) and bronchoalveolar lavage (25) to look for frank blood and/or hemosiderin-laden macrophages are often used in the diagnosis of DAH. In the
context of an acute bleed, one may see fresh blood on FOB or increasingly hemorrhagic return on serial bronchoalveolar lavage (BAL). Greater than 5% of hemosiderin-laden macrophages on Prussian blue staining suggests insidious onset or recurring DAH (26, 27). A murine model of alveolar hemorrhage first detected hemosiderin staining within alveolar macrophages in the BAL and lung tissue at day 3, peaked at day 7, and persisted for 2 months. An analysis of the BAL revealed an acute inflammatory reaction that resolved within 2 weeks (28). The exact percentage of hemosiderin-laden macrophages required to make the diagnosis of acute DAH that necessitates urgent treatment is unclear. Up to half of the patients with GPA and CSS may have subclinical alveolar bleeding on BAL, with 5% defined as the upper limit of normal renal function in acute DAH (19, 20). Recent DAH (within the past 48-72 hours) should be strongly considered when the ratio of uptake to clearance is increased. One study found that 13/15 patients with GPA and 7/7 patients with MPA and DAH had an elevated transfer coefficient (11). The non-invasive nature, safety, and reliability of this method, make it a useful investigation. Repeated measurements, which show vital capacity and CO transfer changing in opposite directions, are BAL has limitations, including false negative results due to sampling errors (29). An upper airway source of bleeding, e.g. granuloma in GPA, can lead to large volume aspiration of blood causing false positives (23). However, FOB and BAL can prove helpful in complex cases where there is diagnostic difficulty or the presence of a superadded infection is likely.

Transfer coefficient: The pattern of restrictive lung function testing, increased uptake of inhaled carbon monoxide (CO) and delayed clearance of the radioisotope C⁹⁸O from lung fields should alert clinicians to the possibility of intra-alveolar blood (30). Recent DAH (within the past 48-72 hours) should be strongly considered when the ratio of uptake to clearance is increased. One study found that 13/15 patients with GPA and 7/7 patients with MPA and DAH had an elevated transfer coefficient (11). The non-invasive nature, safety, and reliability of this method, make it a useful investigation. Repeated measurements, which show vital capacity and CO transfer changing in opposite directions, are

**Table 3. Management of Acute Diffuse Alveolar Haemorrhage in ANCA- Associated Vasculitis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Renal features at presentation</th>
<th>HDx</th>
<th>MV</th>
<th>Treatment at induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haworth [11] 1985</td>
<td>57% out of 89 patients had Cr &gt; 500 μmol/L</td>
<td>29/89 (33%)</td>
<td>Steroids:</td>
<td>89</td>
</tr>
<tr>
<td>Lauque [13] 2000</td>
<td>Haematuria in 97% (28)</td>
<td>8/29 (28%)</td>
<td>CyP: PEX</td>
<td>89</td>
</tr>
<tr>
<td>Klemmer [12] 2003</td>
<td>Normal Cr in 6 patients</td>
<td>7/20 (35%)</td>
<td>IV MP</td>
<td>20</td>
</tr>
<tr>
<td>Gallagher [10] 2002</td>
<td>10 had renal biopsy: FSNGN in the 8 AAV patients, 1 GBM, 1 SLE</td>
<td>11/13 (86%)</td>
<td>Steroids</td>
<td>13</td>
</tr>
<tr>
<td>Lin [14] 2009</td>
<td>10 had acute renal failure</td>
<td>3/12 (25%)</td>
<td>CyP</td>
<td>12</td>
</tr>
<tr>
<td>Ravindran [15] 2010</td>
<td>Abnormal renal function in 6</td>
<td>3/9 (33%)</td>
<td>IV Cy</td>
<td>8</td>
</tr>
<tr>
<td>ter Maaten [16] 1996</td>
<td>All had renal ‘impairment’</td>
<td>4/7 (57%)</td>
<td>Steroids</td>
<td>7</td>
</tr>
<tr>
<td>Chen [9] 2009</td>
<td>All on chronic haemodialysis</td>
<td>(NA)</td>
<td>CyP</td>
<td>7</td>
</tr>
<tr>
<td>Kostianovsky [17] 2012</td>
<td>61 (76%) had pulmonary renal syndrome</td>
<td>(Not stated)</td>
<td>Steroids</td>
<td>80 (100%)</td>
</tr>
</tbody>
</table>

desirable because of the wide normal predictive values. However, few centres have so far reported the use of this method. The main limitation with using transfer coefficients is measurements taken in the presence of co-existing respiratory pathology. The re-breathing methodology is not routinely used, and is technically demanding, so some authors consider this an impractical approach (31).

**Exhaled nitric oxide:** Measurement of exhaled nitric oxide (NO) may be a safe and effective way to aid the diagnosis of DAH (32). NO is continuously produced in the respiratory tract. Exhaled NO can be measured even in acutely ill patients by collection of exhalate in a bag. NO combines with haemoglobin more rapidly than CO. Patients with DAH may therefore have a reduced amount of exhaled NO. The resolution of DAH correlates with the sequential increments of exhaled NO. This method has been demonstrated in isolated cases and it thus requires further evaluation.

**Lung histology:** Obtaining tissue specimens for histology may be considered the ‘gold standard’ in confirming the diagnosis of small vessel vasculitis. A relatively large series found vascular lesions in 21 (78%) of the 27 patients studied (33). The most common underlying vascular lesion was capillaritis (63%), comparable between those with PR3-ANCA or MPO-ANCA. Acute alveolar haemorrhage is characterised by collections of red blood cells completely filling multiple alveoli, and chronic alveolar haemorrhage characterised by hemosiderin-laden interstitial alveolar macrophages. The frequency of acute alveolar haemorrhage, chronic alveolar haemorrhage, and a combination of acute and chronic alveolar haemorrhage is 7/13, 2/13, and 1/13 in PR3-ANCA positive patients, and 9/14, 2/14, and 6/14 in MPO-ANCA positive patients, respectively (33). There is a strong correlation between capillaritis (defined as neutrophilic infiltrates distinctly aligned along and within expanded and often focally disrupted alveolar capillaries) and acute alveolar haemorrhage.

Numerous other studies have also demonstrated pulmonary capillaritis in lung biopsy specimens of AAV patients with alveolar haemorrhage (33-37). Granulomatous inflammation with foci of necrosis may be found in GPA (38). Although these studies provide valuable information on the histopathology, it is unclear how well the histological features correlate with the clinical severity of DAH and systemic vasculitis. Furthermore, there are concerns about to the practicality and safety of transbronchial or video assisted thoracoscopic or open biopsy of the lung in acute clinical situations.

**Renal injury associated with DAH in AAV**

Renal involvement occurs in up to 70% of patients with AAV, with histological features of pauci-immune, focal and segmental necrotising crescentic glomerulonephritis (FSNGN) (39). Most patients with DAH in AAV have co-existing renal impairment (Table 3), with a mean serum creatinine on presentation ranging from 212 to 554 μmol/L (10, 12, 14, 17), and 53% needing renal replacement therapy (RRT) (10-16). Histology is reported in most studies with FSNGN found in all patients that underwent a renal biopsy (10, 13, 14, 17). Most patients have an active urinary sediment, with microscopic haematuria and proteinuria found in 97% and 79% respectively (13). Most patients who present with DAH requiring RRT are dialysis-dependent at one year (12, 13). The incidence of DAH among AAV patients on chronic renal replacement therapy (RRT) seems to be much lower (9). However, the findings of these reports must be carefully interpreted due to the small number of studies and the potential for reporting bias.

**Treatment**

DAH in association with AAV is a rare but a potentially life-threatening condition. Prompt diagnosis is required as early treatment is crucial. Therapy for DAH cannot be isolated from the overall disease management, because AAV represents a group of heterogeneous presentations with multi-organ involvement. The treatment of DAH in AAV should therefore not be oversimplified into treating everyone with the same approach, although general principles apply.

**Induction treatment:** Outcomes for those with AAV have significantly improved since glucocorticoids and cyclophosphamide were introduced (40, 41). The administration of glucocorticoids and cyclophosphamide remains the cornerstone of treatment for the induction of remission in acute AAV. All studies included in this review used a combination of cyclophosphamide and oral or intravenous steroids (9-17). Methylprednisolone has been used intravenously as part of induction treatment, although the evidence for this is less robust and it may be associated with higher rates of infection (42). Rituximab (an anti-CD20 chimeric monoclonal antibody) is as effective as cyclophosphamide, as part of induction treatment of AAV with renal involvement, including those with alveolar haemorrhage and ‘advanced’ renal failure (18, 43). Rituximab is more efficacious than cyclophosphamide for inducing remission of relapsing disease (18). However, patients with severe alveolar haemorrhage requiring mechanical ventilation were excluded from this study. Plasmapheresis should be performed if there is associated severe renal dysfunction (44) and should be considered in patients with severe DAH.

**Plasmapheresis:** One of the key questions that remain unanswered is the role of plasmapheresis in AAV-associated DAH. Anti-GBM antibodies are directly pathogenic (as evidenced by their presence in a renal biopsy in patients with anti-GBM disease) and hence their removal by plasmapheresis is theoretically sound. Furthermore plasmapheresis is beneficial in DAH associated with anti-GBM disease (45). However, definitive evidence supporting the use of plasmapheresis in DAH associated with AAV is lacking. Although ANCA are not deposited in the kidney, there is evidence for their pathogenic role in AAV (46-48); though this has been debated (49). Recent studies demonstrating that B-cell depleting agents are beneficial for the treatment of AAV (18, 50), and that the addition of adjunct therapy with
plasmapheresis for those with severe renal vasculitis improves renal recovery (44) provides an argument for the use of plasmapheresis in DAH associated with AAV.

The addition of plasmapheresis to immunosuppression is a safe and effective combination for the resolution of DAH associated with AAV (12). Randomized control trials are clearly required to evaluate the value of plasmapheresis in DAH associated with AAV. The efficacy of plasmapheresis and glucocorticoid dosing in the treatment of ANCA-associated vasculitis will be evaluated in the ongoing multicentre, randomised controlled trial, Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA)-Associated Vasculitis (PEXIVAS) (51). Novel therapies such as immunoadsorption require further evaluation (52, 53).

Refractory disease: Management of AAV refractory to induction treatment is particularly challenging. Risk factors for induction-refractory disease include DAH and serum creatinine at presentation of >200 μmol/L (54). Massive alveolar haemorrhage is associated with a poorer prognosis in induction-refractory disease. Rituximab (25), intravenous immunoglobulin (55), daclizumab (56), infliximab (57), alemtuzumab (58), and anti-thymocyte globulin have been licensed following successful induction therapy. This can be interpreted as drug-resistant disease (59). Remission needs to be maintained following successful induction therapy. This can be challenging as AAV frequently relapses (59). Induction therapy should be tapered over several months, with cyclophosphamide withdrawn over 3 to 6 months (60). The risk of relapse is highest over the first 2 years so glucocorticoids are usually not fully withdrawn until after this (61). Some authors argue that steroids can be stopped earlier in patients with MPO-AAV that are less likely to relapse. The precise duration of maintenance therapy thereafter is unclear, though stopping steroid treatment altogether in the context of a persistent positive ANCA titre may result in disease relapse (62). Cyclophosphamide should not be first choice as maintenance therapy because the side effects increase with cumulative dose (63). Sepsis, often related to leukopenia, is a major concern, particularly in older patients (64). Malignancy, haemorrhagic cystitis, and cytopenia are other complications (65, 66). Cyclophosphamide should therefore be discontinued by 3-6 months if the disease is in remission. A 3-month course of cyclophosphamide followed by azathioprine is as efficacious as a 12-month course of cyclophosphamide in AAV with moderate renal involvement (66). In addition, daily oral cyclophosphamide has no benefit over pulse intravenous therapy, with a lower cumulative dose in those on parenteral treatment (63). Mycophenolate mofetil is an alternative maintenance agent, though it may not be as efficacious as azathioprine (67). The relapse rate in GPA may be further reduced by the administration of Co-trimoxazole, at a prophylaxis dosage (68).

Outcome

DAH associated with AAV increases the relative risk of death 8.6 times, making it one of the strongest predictors of early mortality (5, 11). The reported mortality varies between different series. This is likely to represent the heterogeneity of the disease, patients, and different treatment. Law and colleagues reported survival in a series of patients with DAH associated with AAV as 82% and 68%, at 1 and 5 years respectively (13). The mortality quoted by Gallagher, however, was significantly higher (10) with 1- and 2-year survival rates of 50% and 36% respectively. Mortality among the general AAV cohort is associated with end stage renal failure, age, and peak creatinine in the first month (6, 69-71). Kostianovsky reported that DAH alone is not responsible for the increased mortality. All patients with acute DAH in their series were successfully treated, despite 13% of patients requiring mechanical ventilation. They found that renal impairment associated with DAH was a predictor of late morbidity and mortality (17). The incidence of recurrent DAH requiring is relatively low, ranging from 10% (12) to 31% (13, 17).

Data on the long-term effects of DAH on subsequent lung function or respiratory compromise is limited. It has been suggested that DAH could progress to interstitial pulmonary fibrosis in 1 series of vasculitis patients (24). However, this was not borne out in other patients; only 6 out of 14 patients with MPO-ANCA positive MPA that developed interstitial pulmonary fibrosis had a history of DAH and in none did it precede the diagnosis of pulmonary fibrosis (72).

The reported literature is sparse, because DAH in AAV is a relatively rare condition and may it not be immediately identified in non-specialist centres. It is unclear how the reported patients were selected. This review did not include patients with DAH reported as part of many general series of AAV, because of the lack of details relating to lung disease. Some studies reporting DAH in AAV have not differentiated between patients with GPA and MPA, or between patients with MPO-ANCA and PR3-ANCA. This is probably because, except for one study (11), none of the other studies had a significant number of patients in these different categories. Controlled trials of optimal investigation and treatment protocols are therefore required.

Conclusion

DAH in association with AAV is a rare but life-threatening condition. Prompt diagnosis is required as early treatment is crucial. The clinical features of haemoptysis, dyspnoea, anaemia and hypoxia in a patient with known or suspected AAV vasculitis warrant further investigation for DAH. The most appropriate investigations are based on the clinical context, the practicality, and safety of the investigation. A normal CXR does not preclude DAH, and HRCT imaging may be required. Serial measurements of lung function and transfer factor are useful non-invasive tests that aid
in the diagnosis and monitor the progress, though they may be difficult in practice. FOB and BAL can be valuable for confirming the diagnosis and thereby ruling out other causes of lung injury. DAH in AAV does not invariably require the same treatment for all patients. Rather, the severity of different organ involvement, age of the patient, and previous immunosuppression history should all be factors in determining the optimal treatment for a particular patient. Further work is required to determine if the clinical picture and outcome in DAH differs between patients with GPA and MPA. Concurrent renal involvement is common and it also contributes to the long-term morbidity and mortality. The early mortality from DAH associated with AAV is significant, and further trials are required to establish the best treatment strategies. Key questions include the value of plasmapheresis in DAH associated with ANCA, and the role of newer, less toxic treatment regimens using biological agents.

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References

33. Gaudin PB, Askin FB, Falk RJ, Jennette JC. The pathologic spec-


