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Extracorporeal membrane oxygenation for Life-threatening ANCA-positive pulmonary capillaritis. A review of UK experience

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ABSTRACT

Introduction: Anti-neutrophil cytoplasmic antibody positive pulmonary capillaritis complicated by diffuse alveolar hemorrhage is a potentially fatal condition for which extracorporeal membrane oxygenation can facilitate improved outcomes and potential cure. Diffuse alveolar hemorrhage can be the initial presentation of an autoimmune disorder. The management is centered on the use of immunosuppressive therapy, which requires time, with fatality often occurring for these patients. We showed two very young patients with no previous history of vasculitis presenting with life threatening pulmonary hemorrhage due to anti-neutrophil cytoplasmic antibody positive vasculitis, whose management was facilitated with extracorporeal membrane oxygenation.
Methods: We reviewed the clinical presentation and course of the first two patients with diffuse alveolar hemorrhage for anti-neutrophil cytoplasmic antibody positive vasculitis managed with veno-venous extracorporeal membrane oxygenation. We highlighted and analysed the unique challenges encountered in managing these patients.
Results: The two patients were referred for extracorporeal membrane oxygenation since conventional ventilation was inadequate to provide physiologic support for respiratory failure. Clinical improvement was achieved without exacerbation of the pulmonary hemorrhage despite the use of anticoagulants. This provided time for the immunosuppressants to take effect. Both patients were discharged and were cured of the underlying condition.
Conclusions: Extracorporeal membrane oxygenation has a role in the management of patients with severe respiratory failure due to anti-neutrophil cytoplasmic antibody positive capillaritis. Early recognition and referral for extracorporeal membrane oxygenation are vital to achieve a favourable outcome.

Keywords: *ANCA associated vasculitis, ECMO, respiratory failure, immunosuppression, hemoptysis.*

INTRODUCTION

The use of extracorporeal membrane oxygenation (ECMO) in the management of respiratory failure unresponsive to conventional ventilation has become a well-established practice (1, 2). However, this has created new challenges for ECMO practitioners as there has been increasing pressure to extend this therapy to more difficult and complex conditions not considered before (3, 4). Anti-neutrophil cytoplasmic antibody (ANCA) positive pulmonary capillaritis complicated by diffuse alveolar hemorrhage (DAH) is an often fatal condition that has only become amenable to ECMO after recent technological

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advances. DAH is rare with an incidence of less than 5 % (5, 6) and can be the initial presentation of an autoimmune disorder. It is associated with poor outcomes: mortality figures between 11 and 50 % have been reported (5, 7).

Before accepting a patient with suspected DAH, ECMO specialists need to carefully balance the risks and benefits since the price for improved oxygenation, and buying the patient time for immune-modulating therapy to take effect, is the eventual need for anticoagulation in the face of active bleeding. We review the current state of the debate illustrated by two cases, which were the first adult patients with DAH in the UK to be treated with ECMO.

ANCA is thought to contribute to the pathogenesis of vasculitis by activating cytokine-primed neutrophils and monocytes, which express ANCA antigens - proteinase 3 and myeloperoxidase - on their surface. Neutrophils respond by developing the capability of adhering to cytokine-activated endothelial cells, generating a respiratory burst, releasing proteolytic granule contents and secreting pro-inflammatory cytokines. ANCA also interferes with the normal processes of resolution of inflammation. Neutrophil apoptosis is dysregulated by ANCA activation of neutrophils, preventing apoptotic cell removal, which in turn allows progression to secondary necrosis of the alveolar cells and vascular endothelium (8).

METHODS

We reviewed the clinical presentation and management of two patients who presented with severe respiratory failure not amenable to conventional ventilation. They represent the first two patients with severe pulmonary hemorrhage due to ANCA positive vasculitis managed this way in the UK. Case 1 was managed at the University Hospital of South Manchester, Manchester whilst Case 2 was managed at Papworth Hospital, Cambridge. Data was extracted from their hospital notes by two authors independently (IM and PH for Case 1, KR and FF for case 2). IM and FF were actively involved in the management of the two patients. HY collated the data and prepared the manuscript with expert contributions from JP, IM and FF. The case details have been presented anonymously and consent was obtained from both patients. Ethics approval was deemed unnecessary after discussions with the local research and ethics committee of both hospitals.

RESULTS

Case 1. A 23-year-old female suffering with otitis media requiring grommets and with recurrent epistaxis for which no cause had been determined, was treated in the community with two weeks of oral antibiotics for presumed tonsillitis. When her symptoms did not improve she attended her local Emergency Department (ED) with increasing shortness of breath, pyrexia and hemoptysis. Commencing IV antibiotics for community-acquired pneumonia (CAP) proved ineffective and her condition continued to deteriorate. When she developed mouth ulcers, hearing loss, facial pain, tingling in her fingers and gritty eyes the day after admission a diagnosis of ANCA positive vasculitis was considered. While lab results were pending her condition worsened and she was intubated. At this point IV methylprednisolone was started empirically, 1 g daily for 3 days, based on the clinical suspicion of Granulomatosis with Polyangiitis (GPA). Despite being mechanically ventilated, high inspired oxygen levels and rising airway pressures, her oxygenation became increasingly precarious with low oxygen saturation (SaO_2 80 %).

She was referred to the local ECMO centre and veno-venous ECMO was initiated on day 2 via a mobile unit before being transferred to a specialist unit.

Cannulation was performed using a 27 F double lumen Avalon cannula in the right internal jugular vein (Maquet, Germany) under image intensifier and transoesophageal echocardiography monitoring The ECMO circuit used Levitronix Centrimag pump heads (Levitronix LLC; Waltham Massachusetts) with a flow of 3.5-4 L/min and the oxygenator used was a Medos Hilite 700 LT (Medos Medizintechnik AG, Stolberg Germany) which incorporates a heat exchanger. The flow was achieved with a rate of between 4500 and 4800 rpm with minimal anti-coagulation (*Figure 1*).

Whilst on VVECMO he had pressure control ventilation with peak inflation pressure of 20 cmH_2O and PEEP of 10 cmH_2O. She was found to be c-ANCA positive and Serine Proteinase 3 (PR3) levels were 11.2 U (< 0.9 U); MPO and anti-GBM negative. Pulsed IV methylprednisolone dosed at 1 g daily was continued for three days before switching to 100 mg/day IV. Along with this, treatment with cyclophosphamide was started on a modified NIH regimen (0.9 g/m^2), which required G-CSF for 3 days due to the subsequent neutropenia. She received full supportive care including antimicrobial prophylaxis and a percutaneous tracheostomy. He was screened for opportunistic viral infections (EBV, CMV, Herpes Simplex, H1N1) and they were all negative. The patient responded very well to this aggressive treatment and further bronchoscopies showed only mild inflammation and old blood clots. The patient was trialed off

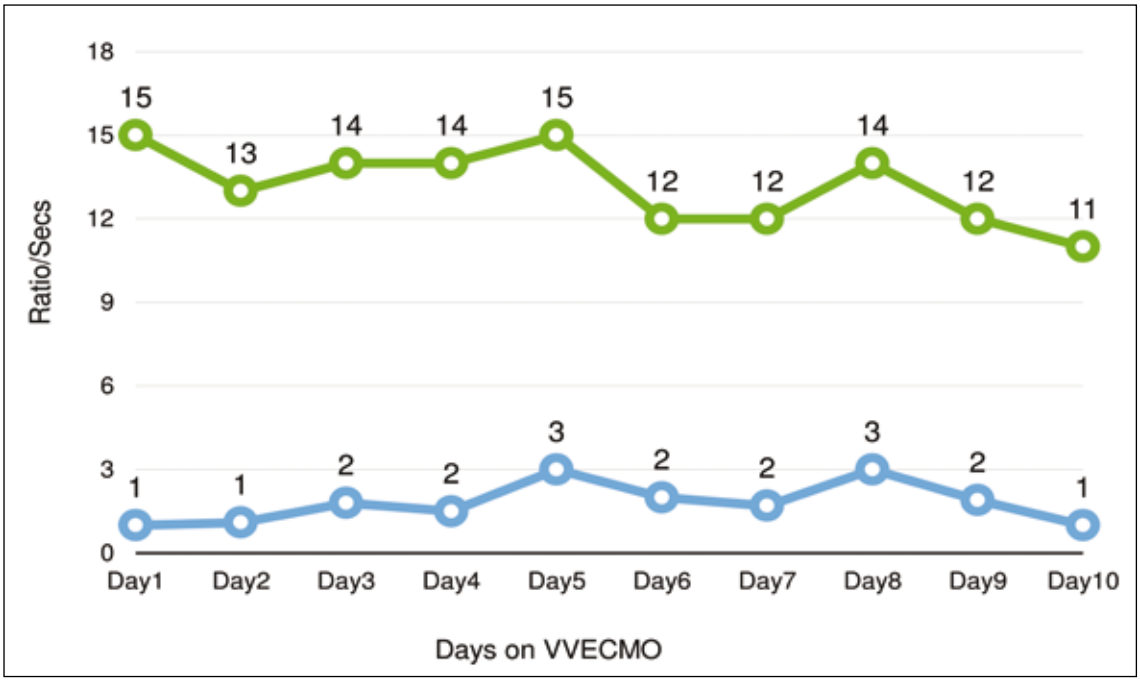

Figure 1 - *APTT ratio and prothrombin time whilst on VV ECMO (Case 2). APTT ratio target 1.8-2.8. Prothrombin time target less than 15 seconds.*
APTT = activated partial thrombin time; VV ECMO = veno-venous extracorporeal membrane oxygenation.

10 days after the commencing VV ECMO by gradually reducing the sweep gas flow whilst ventilating the patient with pressure controlled ventilation and, by day 13, the cannula was removed. The tracheostomy cannula was removed three weeks after her initial admission. She was discharged into the care of her local rheumatology and regional vasculitis service and continues to do well.

Case 2. A 27 year-old male presented to his local hospital with a one-week history of cough, hemoptysis and malaise on a background of a four-month history of weight loss and night sweats. He had had bilateral grommets fitted 2 years prior and reported worsening otalgia and deafness over the six months preceding his presentation. His functional capacity was considered above average.

On admission to his local ED he received a course of intra-venous antibiotics to cover community acquired and atypical pneumonia. He progressively developed worsening, type 1 respiratory failure and had to be intubated and ventilated. A trans-bronchial biopsy, taken on day 5, revealed widespread intra-alveolar hemorrhage. On day 12 his chest radiograph showed extensive diffuse bilateral infiltrates, and despite intubation, maximal ventilatory support, sedation and neuromuscular blockade his SaO_2 fell to 45 % and he became hemodynamically unstable. At this point the patient was referred to the local ECMO center.

Due to the patient's age, the immediate threat to his life and the lack of a clear diagnosis, it was decided to instigate VV ECMO before transfer to a specialist unit. Cannulation was performed using a 27 F double lumen Avalon cannula (Maquet, Germany) in the right internal jugular vein under image intensifier. ECMO flows were kept above 3.6 L/min with a Levitronix Centrimag pump head (Levitronix LLC; Waltham Massachusetts) without anticoagulation. The oxygenator used was a Medos Hilite 700 LT (Medos Medizintechnik AG, Stolberg Germany) which incorporates a heat exchanger. There were difficulties with oxygenation and flows greater than 4 L/min caused suck down and very negative drainage pressures (> -90 mmHg), therefore an additional drainage cannula (21 Fr, 38 cm, Avalon, Maquet, Germany) was inserted to achieve flows greater than 4.5 L/min (at least 2 L/min in each drainage cannula).

Following ECMO initiation, SaO_2 improved to 82 % which correlated with a PO_2 of 7 kPa. Despite a total ECMO flow of 4.5 L/min, the patient was hyperdynamic with a high cardiac output due to inflammation, therefore the proportion of the shunted deoxygenated blood was sufficient enough to impact on systemic PO_2. A bronchoscopy showed extensive active bronchial bleeding and due to this invasive ventilation was not possible initially. A CT scan on arrival at the specialist unit revealed an acute and widespread dense consolidation throughout both lungs in keeping with DAH. Supportive treatment with antimicrobial prophylaxis, tracheostomy and renal replacement therapy was started. The mechanisms for his acute kidney injury were thought to be primarily as a result of the vasculitis. It is possible that a pre-renal, relative hypovolemia contributed to it as well. Renal replacement therapy was instituted to treat metabolic acidosis and for intra-vascular fluid management. The vasculitis screening conducted on admission revealed that he was strongly positive for cytoplasmic ANCA (cANCA) confirming the suspected diagnosis of GPA with DAH.

The ECMO circuit was initially run without systemic anticoagulation. However as clots began to appear in the oxygenator on day 2, systemic heparin was introduced aiming to keep the activated partial thrombin time (APTT) ratio between 1.5 and 1.8.

By day 3 on ECMO there was no further evidence of active bleeding.
The underlying GPA was treated with 3 doses of pulsed IV methylprednisolone followed by daily hydrocortisone dosed at 50 mg IV four times a day as well as eight cycles of plasma exchange followed by rituximab and IV immunoglobulin, followed by maintenance immunosuppression from day 21 with mycophenolate mofetil.
On day 20 the patient VV ECMO was weaned by gradually reducing sweep gas flow guided by regular blood gas estimation. The ECMO cannulas were removed 24 hours after turning off the sweep gas and he transferred for specialist treatment of his renal failure and management of immunosuppression. He was successfully weaned from renal replacement therapy and mechanical ventilation and was discharged from hospital care 20 days later.
He is currently free of all immunomodulatory therapy and has returned to work in the armed forces.

DISCUSSION

The Evolution in ECMO technology has been driven largely by the need to reduce complications associated with this procedure but also, as illustrated here, to safely extend the use of ECMO to other life threatening conditions. The development of synthetic surfaces with covalently attached heparin (Larm et al. 1983) has significantly reduced this risk allowing ECMO circuits to be run with little or no anticoagulation (1).
Similarly, the technology for the pumps has evolved from the DeBakey roller pumps (1934) to more refined forms used for most cardio-pulmonary bypass operations today. However there is an increased incidence of acquired coagulopathy (thrombocytopenia, acquired von Willebrand diseases) with these pumps. The introduction of centrifugal pumps and axial flow pumps, which have a reduced shearing effect on cellular blood components, has further reduced bleeding complications (11). Centrifugal pumps were used in both cases described (Levitronix, Massachusetts). It consists of a magnetically levitated rotor that eliminated the need for bearings or seals. The rotor surface is completely washed by blood reducing the risk of stagnation and turbulence hence reducing hemolysis and thrombosis.
These recent improvements in ECMO technology have allowed ECMO to expand to niche area including trauma, cardio-pulmonary resuscitation and interstitial lung diseases (3, 4).
The evidence for the use of ECMO in patients with severe respiratory failure due to DAH from ANCA associated vasculitis (AAV) is restricted to a small number of case reports (5-10). This is not surprising given the rarity of this condition and the fact that these patients often are very sick and cannot wait for the effect of immunosuppression, with death being a common outcome. The cases presented here describe two young patients whose first presentation is at the severe end of the spectrum and whose prognoses would have been likely infaust without ECMO.
As demonstrated, the key role of ECMO in these cases is that it provides time for life saving treatments to be instituted. Both patients were in extremis and it is unlikely that with conventional ventilation they would have survived long enough for the immunosuppressive therapy to be effective in halting the pathologic process. This is unique as ECMO is not used as a treatment modality but serves as to facilitate the application of an established therapy in patients presenting with very severe forms of respiratory distress, thereby significantly reducing mortality. *Figure 2* aptly illustrates the

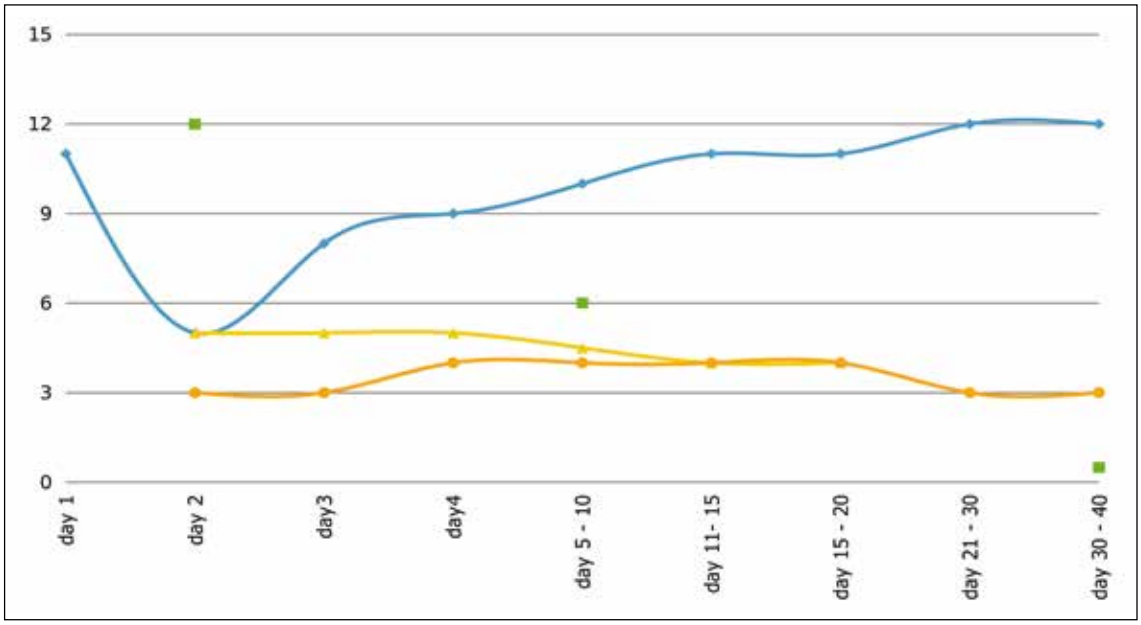

Figure 2 - *VV ECMO to allow adequate immunosuppression for severe vasculitis complicated by DAH (Case 1).*
VV ECMO = veno-venous extracorporeal membrane oxygenation; DAH = diffuse alveolar hemorrhage.

relationship between the use of ECMO, the pathology and treatment in patient 2. On the day VV ECMO was initiated, disease activity was at its highest as demonstrated by high PR3 levels and this correlated with disease severity (PO_2-5 kPa).

Disease activity gradually reduced with a demonstrable falling PR 3 levels whilst the effects of the disease (hypoxia) were corrected by VVECMO. Both presented patients were cured of their condition and are back to work. Once treated, patients with GPA have a very good prognosis and enjoy and excellent quality of life (9).

Despite the acuity of the situations there was considerable discussion about the feasibility of establishing these patients on ECMO in view of active and on-going bleeding. Conditions with a significant risk of systemic bleeding with anticoagulation could be considered a relative contraindication to ECMO (12, 13). The extracorporeal life support organisation (ELSO) specifies that contra-indication should be considered on a case-by-case basis after weighing risks and benefits. However in these cases due to lack of good evidence an objective assessment is often difficult (12). In both cases the potential for exacerbation of the pulmonary hemorrhage was a major concern.

In both cases, a single bolus of IV heparin was given at the time of cannulation (case 1 5,000 IU, case 2 2,500 IU) and the circuit was run without any anticoagulation for 48 hours.

In Case 2 the circuit was run without anticoagulation initially but systemic heparin infusion had to be commenced when clots appeared in the circuit and the oxygenator. In both cases efforts were taken to ensure that anticoagulation was kept at bare minimum as much as possible. The blood transfusion strategy was liberal with a minimum hemoglobin target of 9 g/dL and platelet target of > 100,000/μL. This strategy was employed to provide a margin of safety if a

major bleeding occurred. There is no evidence in literature to support this practice but it was felt to be the safest strategy in this clinical context.

There was no exacerbation of lung hemorrhage and all active bleeding ceased after commencing ECMO. This is most likely to be attributable to the fact that the patient had received two pulses of methylprednisolone and two cycles of plasma exchange in order to slow down the disease process sufficiently by the time he had to be anticoagulated. Adult and pediatric case reports seem to support our observation that hemorrhage can resolve despite systemic anticoagulation following the initiation of ECMO (12-19).

Case reports in literature have described the concomitant use of ECMO and aggressive immunomodulatory therapy in treating diffuse alveolar hemorrhage as described in our case reports, however it is difficult to decipher the comparative contributions of intensive immunomodulatory therapy and of ECMO on the resolution of the lung hemorrhage. In a case report by Matsumoto et al., (17) pulmonary hemorrhage persisted despite aggressive immunomodulatory therapy including plasma exchange and pulsed steroids. It only resolved 82 hours after commencement of VV ECMO. Zhang et al. (15) describe a case of microscopic polyangitis complicated by DAH. Pulmonary hemorrhage resolved after initiation of ECMO but before targeted vasculitis treatment started. Suggested mechanisms for this include removal of the well-described detrimental effects of high FiO_2 and barotrauma. It is difficult to draw any firm conclusions from these observations but they may provide some evidence that anticoagulation on VV ECMO might not worsen pulmonary hemorrhage.

The combination of high-dose corticosteroids and cyclophosphamide are the mainstay of treatment for vasculitides and disease resistance to this combination is rare. Remission of Wegener's granulomatosis (WG) or microscopic polyangitis (MPA) has been reported in up to 90 % of cases (19). Disease that is truly resistant to a corticosteroid/cyclophosphamide regimen is more common in fulminant disease. Rituximab and intravenous immunoglobulin have been shown to be of benefit in recent randomized controlled trials specifically in patients with renal complications of acute vasculitis (24-26). Most clinicians favor this approach due to the lower risk of infection and the long-term association of cyclophosphamide with cancer.

The role of plasma exchange is still far from clear. Initial trials showed benefit when plasma exchange was used in addition to a corticosteroid and cyclophosphamide regimen, but only in cases in which there was dialysis dependence at presentation or concurrent anti-glomerular basement membrane disease (a rare overlap) (23). Although the role of ANCA in DAH is not known, the patients who do well are the ones in whom the ANCA titer falls with treatment. Treatment of any infections is critical as this is often the precipitating cause. The PEXIVAS trial is currently recruiting patients to investigate the role of plasma exchange in reducing mortality and end stage renal failure (ClinicalTrials.gov, identifier: NTC00987389).

The major factor for successful treatment of ANCA-associated vasculitis is to start treatment early, before the onset of respiratory failure from alveolar hemorrhage and renal failure from rapidly progressive glomerulonephritis. The difficulty is that time is often spent treating more common explanations to the symptoms. Waiting for the results of the autoantibody screening can critically delay the initiation of immunosuppression therapy, thereby further contributing to poor outcome.

Intensivists and ED physicians should have

Figure 3 - *Key Points.*

	Key Points
1	VV ECMO has role in the management of severe life-threatening pulmonary hemorrhage due to ANCA positive vasculitis
2	Pulmonary hemorrhage does not preclude anticoagulation on VV ECMO
3	Early referral to an ECMO centre in patients not responding to conventional ventilation should be considered
4	Early diagnosis and targeted management is facilitated by early involvement of specialist physicians

VV ECMO = veno-venous extracorporeal membrane oxygenation; ANCA = anti-neutrophil cytoplasmic antibody.

a low threshold to involve specialists when there is the clinical suspicion of an autoimmune disease.

CONCLUSION

Acute vasculitis complicated by diffuse alveolar hemorrhage can present with life threatening respiratory failure which in the most severe form would lead to death.
Effective treatments are available which can potentially offer cure but take time to instigate and to take effect. ECMO can provide the opportunity to establish immunosuppression and time for it to take effect.
It is crucial that clinicians in non-specialist hospitals have a low threshold to seek advice and refer promptly these often young patients, as the use of ECMO can dramatically improve the clinical outcome (*Figure 3*).

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