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Immunoadsorption Techniques and Its Current Role in the Intensive Care Unit

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Abstract

Immunoadsorption is an extracorporeal technique used for the removal of antibodies and molecules from the blood. A large number of different adsorbents are now available allowing for the non-selective removal of all subclasses of immunoglobulins such as IgG or more selective removal of disease specific molecules such as lipoprotein(a) and CRP. This selectivity, coupled with its highly efficient removal of the molecule, along with a favourable side-effect profile, has made immunoadsorption an attractive option in a range of autoimmune diseases. Here we discuss the mechanism and technique of immunoadsorption and review the current evidence and indications for its use, particularly in relation to sepsis.

Keywords: sepsis, immunoadsorption, extracorporeal therapy, autoimmune disease

1. Introduction

Immunoadsorption (IA) was developed in the 1990s as a method of extracorporeal removal of molecules from the blood, in particular molecules of the immune system. There are now a large number of devices/columns on the market, each with a different active component to which the molecule of interest attaches, allowing for selectivity in the molecules removed. This selectivity is one of immunoadsorption's significant advantages over other apheresis techniques, in that it negates the need for replacement of factors such as albumin and plasma. With the vast majority of IA systems directed against components of the immune system, its use has traditionally been in autoimmune conditions and transplantation, although new systems are increasingly being used for other indications such as sepsis (**Figure 1**).

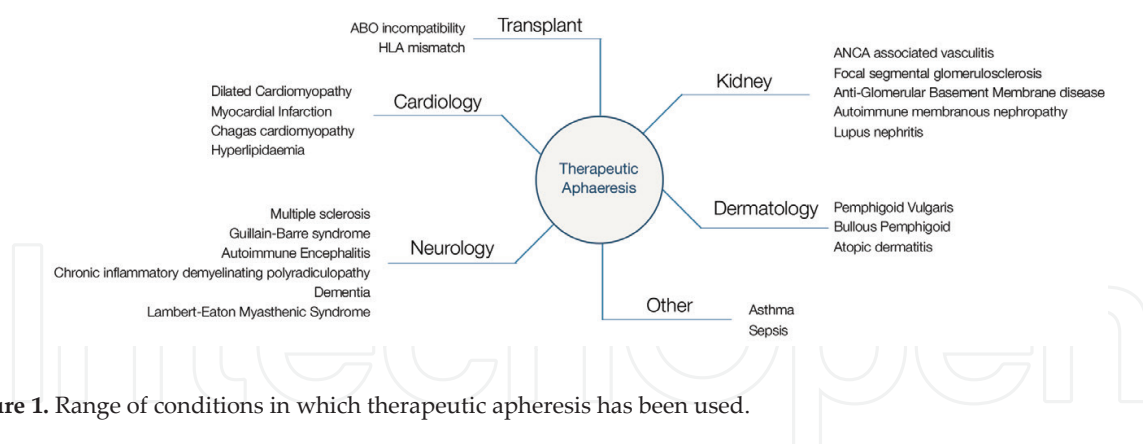


Figure 1. Range of conditions in which therapeutic apheresis has been used.

2. Procedure

Despite the large number of IA columns available the basic principle of the procedure is similar throughout. As with other extracorporeal therapies central venous access is required in order to ensure an adequate blood flow of ~100–150 ml/min through the system. The system itself is a closed system using single use tubing passing the blood from the central venous catheter to a plasma or cell separator, through the column, before combining with the blood components and back into the body via the central venous catheter (**Figure 2**).

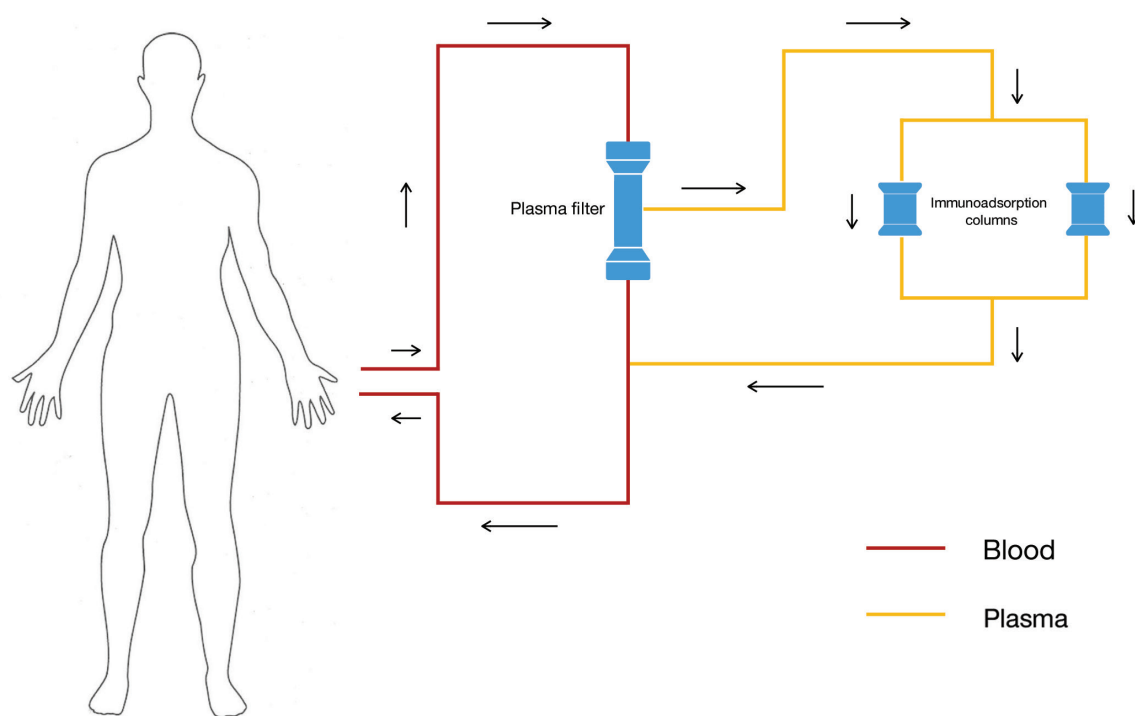


Figure 2. Immunoabsorption schematic. Blood first passes to plasma filter. Plasma then passes on to immunoabsorption column before returning to patient. Schematic shown is dual column system. As the plasma is passing through one column, the second column is being regenerated. Once the first column is saturated the flow switches to the second column whilst the first is then regenerated.

The initial step in immunoadsorption is therefore separation of plasma from the blood cells. Currently there are a number of machines available for this; the *Art Universal* plasma separator (Fresenius Medical Care), *Octo Nova* plasma separator (Diamed Medizintechnik), COBE Spectra Apheresis system (Terumo), Plasmaflo OP plasma separator (Asahi Kasei Medical Co.) and the COMTEC cell separator (Fresenius Medical Care).

The plasma then flows through to a second machine and into the immunoadsorption column. A number of machines are on the market for this stage of the procedure in order to monitor and regulate the plasma flow through the column; the Adsorption-Desorption-Automated system (ADAsorb, Medicap Clinic GmbH) being the most common dual column system in use today.

In dual column systems, the plasma passes through one column whilst the second column is being regenerated. Once the active column has been saturated, the plasma flow switches to the second column whilst the first column itself undergoes regeneration. This system allows for continuous treatment of the plasma with no theoretical upper limit on the number of plasma volumes that can be treated.

All columns share the same fundamental basics, with a matrix containing the molecule used to bind the required immunoglobulin. It is through this matrix that the plasma flows with immunoglobulin binding as it passes. The binding molecule in each adsorber come from a number of different sources both synthetic and organic and this heterogeneity adds to the versatility of the treatment. For example, protein A is found in the cell wall of *Staphylococcus aureus* and has been shown to bind immunoglobulins and in particular IgG with high affinity. It has the ability to bind all the subclasses of IgG with very little binding of other immunoglobulins [1]. The Globaffin adsorber, in contrast, uses a synthetic peptide (Peptid-GAM) to bind IgG with high affinity, and again, all subclasses [2] (**Table 1**).

Treatment prescriptions for immunoadsorption are based on plasma volumes with differing recommendations for each condition as discussed below. Depending on the condition being treated, sessions can be daily or intermittent, again discussed below for each indication. For most patients, plasma volume can be calculated using the Kaplan formula; estimated plasma volume = $(0.065 \times \text{Weight (kg)}) \times (1 - \text{Haematocrit})$ [3]. This formula however does assume a normal body mass index with decreasing accuracy for outliers. In these situations, particularly relevant in patients with nephrotic syndrome and morbid obesity, body composition monitoring may be of benefit to assess a patient's normohydration/ideal body weight (IW). This can then be used in the Kaplan formula for a more accurate plasma volume:

$$\text{Estimated plasma volume} = (0.065 \times \text{IW (kg)}) \times (1 - \text{Haematocrit}). \quad (1)$$

All patients undergoing IA need anticoagulation. This usually takes the form of citrate sodium with IV calcium replacement. In our centre we use 10 ml 10% calcium gluconate for every 2 L of plasma treated. Heparin can also be used as an anticoagulation although generally in combination with sodium citrate and not as the sole agent.

Immunoadsorption type	Binding material	Available columns
Selective	Sepsis and septic shock	Pocard Toxipak
	CRP	PentraSorb CRP
	C1q	Miro
	ABO	Gylcosorb ABO and ABO Adsopak
	PDCM075 and PDCM349	Coraffin
	IgE	IgEnio
	Cholesterol	DALI
	Lipoproteins and macromolecules	MONET
	LDL cholesterol	Pocard LDL Lipopak
	Lipoprotein(a)	Pocard Lp (a) Lipopak
Semi-selective	Staphylococcal protein A	Immunosorba
	Sheep anti-human Ig	Therasorb and Ig-Adsopak
	Peptide-GAM	Globaffin and Ligasorb
Non-selective	Phenylalanine	Immunosorba PH
	Tryptophan	Immunosorba TR-350
	Dextran sulphate	Selesorb
Extracorporeal devices	oXiris	Endotoxins and cytokines
	CytoSorb	Cytokines
	Toraymyxin	Endotoxins

Table 1. Immunoadsorption and extracorporeal columns from non-selective to selective showing the wide range of systems available.

All columns are single patient use only. However, the number of times a column can be used differs from single use, such as the Ligasorb (Fresenius Medical Care) up to 2 years for the Globaffin column (Fresenius Medical Care).

Due to the disposable single use consumables and patient specific columns along with the fact that there is no reliance on blood component replacement, the risk of blood borne disease is minimal. However, there is still a theoretical risk cross-infection and pre-therapy screening for blood borne viruses is advisable.

Of note is the contraindication for the use of concomitant angiotensin-converting enzyme inhibitors (ACEi) with the use of columns using a native peptide such as tryptophan immunoadsorption [4]. This is due to the ACEi induced reduction of bradykinin metabolism following its release during IA. In columns using a synthetic peptide such as the Globaffin, this appears to be less of a concern and the use of ACEi is not contraindicated.

3. Immunoadsorption therapy prescription: example

Patient name	
Date of birth	
Hospital number	
Primary disease for treatment	
Dates of therapy	
Frequency	Daily/weekly
Plasma volumes to treat	
Weight	kg
Plasma volume (PV)	$[\text{Body weight (kg)} \times 0.065] \times [1 - \text{Haematocrit}] = \dots\dots\dots \text{L}$
Treatment volume	Plasma volumes to treat $\times$ PV = $\dots\dots\dots \text{L}$
Flow rate	25 ml/min (1.5 L/h)
Expected time	Treatment volume/1.5 L = $\dots\dots\dots \text{h}$ and $\dots\dots\dots \text{min}$
Anticoagulation	Citrate sodium/heparin <i>Calcium infusion as per local guidelines</i>
Name of prescriber	
Signature of prescriber	
Date	

4. Immunoadsorption therapy and its use in sepsis

4.1. Definition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The previously used diagnostic criteria of the presence of two or more features of the Systemic Inflammatory Response Syndrome (SIRS) was replaced in 2016 with new consensus definitions (see Box 1) to provide a more reliable diagnostic criteria, improve consistency across clinical trials and facilitate earlier diagnosis and management [5].

Box 1. Diagnosis of Sepsis and Septic Shock according to the “Third International Consensus Definitions for Sepsis and Septic Shock” [5].

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection.

- The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction.
- ASOFAscore_2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤ 100 mmHg, or respiratory rate ≥ 22 /min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

4.2. Incidence

As a result of these changing definitions and the inherent clinical heterogeneity of sepsis syndromes, precise incidences are often difficult to estimate. A point prevalence study from the Netherlands in 2004 using the older diagnostic criteria found an incidence of 0.054% of the population, 0.61% of hospital admissions but 11% of ICU admissions [6]. A post hoc analysis of patients in Australian and New Zealand Intensive Care Units found that a significantly larger proportion of patients met the criteria for diagnosis of sepsis when using the new (SOFA) versus the old (SIRS) definitions, 87.1 versus 58.9% [7]. It is apparent that despite these difficulties in classification, the incidence of sepsis is increasing, likely secondary to an ageing population and the increase in risk factors such as cancer, chemotherapy and other chronic diseases.

4.3. Pathophysiology

The pathogenesis of sepsis remains incompletely understood. The progression of a simple localised infection through to septic shock and multiorgan dysfunction involves a complex interplay of proinflammatory and anti-inflammatory cytokines and coagulation factors which result in endothelial disruption, alterations in fluid homeostasis, tissue oedema, reduced end organ perfusion and eventually multiorgan failure. These interactions and their ultimate clinical sequelae depend on factors related to the antecedent infection, the host's response, the presence of comorbidity and the extremes of age, and are mitigated by, and often worsened by, iatrogenic interventions aimed at halting and reversing these conditions. A not infrequent clinical syndrome ensues, familiar to most Intensive Care Physicians, of a patient mechanically ventilated on the intensive care unit, requiring high dose vasopressors and renal replacement therapy. Inoculation with a virulent pathogen triggers a cascade of events resulting in the activation of the innate immune response and the release of proinflammatory cytokines. The initial host response is triggered by

recognition of the invading pathogen's molecular signatures (Pathogen Associated Molecular Patterns) or the tissue damage caused by the cellular apoptosis such as ATP and mitochondrial DNA (Damage Associated Molecular Patterns). These activate receptors (Toll-like receptors and C-type lectin receptors) and result in the systemic release of proinflammatory cytokines, predominantly interleukin-1 (Il-1), Il-6 and tumour necrosis factor alpha [8].

This release of cytokines triggers further activation of the hosts immune response, resulting in migration of macrophages and activating further cells of the innate immune systems to release more cytokines, proteases and reactive oxygen species. Coagulation pathways are also activated with widespread activation by tissue factor and by impaired intrinsic anticoagulants such as protein C. It is thought that protease-activated receptors (PAR's) that result from widespread thrombin deposition may play a role in endothelial-cell barrier function breakdown and widespread inflammation [9]. Activation of these pathways results in widespread endothelial release of inducible nitric oxide synthase and this along with other mechanisms causes vasoplegia resulting in systemic hypotension and compensatory activation of the renin angiotensin pathway. These perturbations and the responding compensatory pathways result in a high incidence of acute kidney injury in sepsis with estimates ranging from 19% in 'moderate sepsis' to 51% in 'septic shock' [10].

4.4. Treatment

The mainstay of management for sepsis continues to be early recognition and the institution of appropriate antimicrobial therapy and supportive care. A retrospective cohort study in 2006 demonstrated an increase in mortality associated with a delay in antibiotics beyond 1 h after the recognition of septic shock and an increasing mortality associated with further delay [11]. The institution of the sepsis six 1-h bundle by the Surviving Sepsis Campaign (www.survivingsepsis.org) aimed to enforce the time critical nature of these interventions with delay in administration of antibiotics associated with an increasing mortality (see Box 2). Despite early enthusiasm and uptake for the use of goal directed therapies in critical care, more recent randomised controlled trials have not demonstrated their superiority to standard care in patients admitted to the ICU with sepsis. Supportive management will often involve the use of vasopressor and inotropic support, mechanical ventilation and continuous renal replacement therapy.

Box 2. Surviving Sepsis Campaign Hour-1 bundle of care.

- Measure lactate level
- Obtain blood cultures before administering antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate level ≥ 4 mmol/L.
- Apply vasopressors if hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg.

There is ongoing debate as to the role of corticosteroid therapy in sepsis and septic shock. Recent randomised controlled trials have demonstrated that hydrocortisone improves the resolution of septic shock in patients who are refractory to vasopressors but the evidence for improvement in mortality is mixed. In the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHS) Trial there was evidence of an improvement in 90 day mortality in patients treated with hydrocortisone 200 mg daily with fludrocortisone compared to placebo (43.0 versus 49.1%) [12]. The Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial however failed to demonstrate a mortality difference in patients treated with hydrocortisone 200 mg daily versus placebo (27.9 versus 28.8%) [13]. Both trials however showed that the use of hydrocortisone was associated with a faster resolution of septic shock and the use of vasopressors as secondary outcomes. It is possible that the difference in the primary outcome of mortality between these two landmark studies may be the additional use of mineralocorticoid therapy but it may also be related to the differing patient groups and predicted mortality between the two trials, with the APROCCHS trial demonstrating an improvement in 90 day mortality in patients who were more unwell and with a higher overall mortality [14]. There remains large clinical variation in the use of hydrocortisone therapy in septic shock but it is likely that some clinicians will continue their use judiciously in patients with septic shock refractory to vasopressor support. Beyond the use of steroids there has been much interest in the use of immunomodulatory therapies in the treatment of sepsis. Perhaps the most well studied of these is the use of recombinant human activated protein C (rhAPC). Initially encouraging trials showed a mortality benefit of the use of rhAPC in patients with sepsis and multiorgan dysfunction, felt in part due to its anticoagulant effect mitigating the procoagulant and frequent disseminated intravascular coagulation seen in more severe forms of sepsis [15]. It was also favoured for its anti-inflammatory properties. Unfortunately, despite these early positive trials, subsequent randomised controlled trials failed to show a benefit of rhAPC and it was quickly removed from the market by its manufacturer [16]. Despite improvements in supportive care, sepsis remains a heavy burden on intensive care units worldwide and continues to be associated with a high mortality in critically ill patients with an ongoing need for novel, effective treatments.

4.4.1. Extracorporeal therapy

Given the active role of immune system factors in sepsis there has, over the years, an interest in the use of extracorporeal devices for the removal of these perceived pathogenic components. Toraymyxin is an extracorporeal method of removing endotoxins using the polypeptide polymyxin-B immobilised onto polystyrene fibres. Also known as PMX haemoperfusion (PMX-HP), it was developed in the early 1990s in Japan and approved for use in Europe in 2002. Since that time, it has been used in a significant number of patients with sepsis or septic shock in ICU. However, evidence for its benefit has been inconsistent and a recent meta-analysis has concluded that there is no strong evidence for its routine use [17].

Other extracorporeal systems for use in the setting of sepsis include CytoSorb and oXiris. CytoSorb is a single use column designed for the removal of excessive cytokines. Despite showing a significant reduction in circulating cytokine levels, there is a lack of evidence to show an improvement in outcomes and as such its use is not currently recommended by

regulatory bodies such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom [18, 19]. oXiris is an acrylonitrile and methallylsulfonate (AN69) membrane that has been shown to remove both endotoxins and cytokines *in vitro* and is now the subject of a number of randomly controlled trials investigating its benefit clinically [20].

4.4.2. Immunoadsorption in sepsis

In a recent study, IA was used to selectively remove LSP, IL-6 and C5a in 11 adult patients (and 22 controls) with severe sepsis admitted to ICU. The treatment was well tolerated and patients had no ongoing anticoagulation abnormalities following IA therapy. All three factors were markedly reduced following treatment in the IA group, in addition to which C-reactive protein (CRP) and fibrinogen were reduced to 27 and 36% of their initial values. There was no change to the inflammatory factors in the control group. Using a number of markers of disease severity, those patients in the treatment group showed a meaningful improvement compared to the control group. Number of days ventilated and the number of days in ICU were both significantly less in the treatment group as was the amount of norepinephrine needed. There was a tendency to a reduction in the number needing renal replacement therapy although this was not statistically significant. Acute Physiology and Chronic Health Evaluation II (APACHE II), mean Sequential Organ Failure Assessment (SOFA) and mean Multiple Organ Failure (MOF) scores all improved significantly more in the treatment group compared to the control group [21].

This pilot study shows that IA appears to be safe and tolerated well in patients with severe sepsis with significant objective improvements as measure both biochemically and clinically.

5. Other indications for the use of immunoadsorption

5.1. Nephrology

5.1.1. Transplantation

As patients reach end-stage renal disease (ESRD) and require renal replacement therapy (RRT), dialysis can be a lifeline but long-term outcomes remain poor. Renal transplantation can not only improve a patients' quality of life but also extend it beyond that of dialysis [22–24]. Traditionally renal transplantation matching has been based on a close Human Leukocyte Antigen (HLA) match and ABO compatibility. With an ever-increasing population reaching ESRD and necessitating RRT but with the continued donor kidney shortage, methods to allow for a relaxation of these matching criteria can greatly increase the uptake of renal transplantation [25].

5.1.1.1. ABO-incompatibility

Early attempts to use transplantation in the presence of ABO-incompatibility (ABOi) proved unsuccessful and its use was contraindicated for many years due to the risk of hyperacute

and acute allograft rejection [26–30]. The ABO blood group system was first described by Landsteiner in 1901 [31]. Patients can have A, B, both or neither antigens on their erythrocytes along with antibodies to the antigens they do not possess. For example, patients with blood group A will have A antigens on their erythrocytes, and antibodies to B antigen (anti-B) in their plasma. Since the 1980s there has been an increased understanding of the underlying mechanisms of ABOi rejection. This rejection is triggered by the recognition by the recipient antibodies (anti-A or anti-B) of the corresponding A and/or B blood group antigen on the graft endothelium. Earlier attempts at removing these antibodies to allow for ABOi transplantation involved intensive perioperative plasma exchange, splenectomy and judicious immunosuppression with resulting high mortality and morbidity but with little improvement in outcomes [26].

Given the anti-A/B blood group antigens are of the IgG and IgM subclass, the use of immunoadsorption offers the ability to selectively remove these antibodies and there is now strong evidence for its use with long-term follow up [26, 32].

In 2001, Tydén et al. published a protocol utilising immunoadsorption and rituximab as an adjunct to standard triple therapy immunosuppression to significantly reduce the blood group antigens prior to transplantation. This regimen has now been used extensively, particularly in Europe, with excellent long-term outcomes, comparable to ABO compatible transplantation [33–38].

5.1.1.2. HLA mismatch

In a similar manner to ABOi, recipient antibodies directed against donor HLA are a major cause of graft rejection [39, 40]. Unfortunately, a large number of patients on the transplant waiting list will have these antibodies as a result of blood transfusions, pregnancy or previous transplants [41–44]. As with ABOi, the presence of these antibodies can reduce the chance of a patient receiving a transplant and increase time on the waiting list. Methods have therefore been sought to desensitise patients in order to improve their chances of a suitable match and to improve outcomes post transplantation. Most strategies at present employ plasma exchange and IVIg with good results showing that the removal of these antibodies can confer a favourable outcome for the patient [45]. Given its more selective nature, IA offers an alternative to plasma exchange and has been used in a number of small studies with varying degrees of success.

In 1996, Higgins et al. used IA in 13 highly sensitised patients prior to transplantation. Three patients' grafts failed due to rejection and six of the remaining 10 patients had reversible episodes of rejection [46]. Since that time there have been a number of studies showing IA is a viable therapy for desensitisation prior to transplantation [47, 48].

5.1.2. Autoimmune membranous nephropathy

Despite being a rare disease, autoimmune membranous nephropathy (MN) is among the most common causes of adult nephrotic syndrome worldwide [49–54]. In the majority of patients, it

is associated with the M-Type Phospholipase 2 Receptor autoantibody (Anti-PLA₂R), discovered in 2009 [55]. Since that time there has been a tremendous increase in our understanding of the disease process although this has yet to translate into disease specific therapies for patient. At present, the current standard of care involves the use of a rotating regimen involving high dose steroids and cyclophosphamide over a 6 month period, known as the Ponticelli regimen, and has been in use in various forms for almost 20 years [56–58]. This regimen was developed before the discovery of the anti-PLA₂R but with the belief that the condition was an autoimmune disease. It takes a blunderbuss approach to suppressing the immune system with good clinical response but with a significant side-effect burden both in the short term and the long term.

The anti-PLA₂R antibody itself is an IgG antibody and current evidence appears to suggest that it is a pathogenic antibody [55, 59–62]. This makes it not only a good biomarker for disease activity and response to treatment but potentially a target of treatment in itself.

Before the discovery of anti-PLA₂R, Esnault et al. use protein A immunoadsorption on four patients with membranous nephropathy. All four patients had an improvement in their proteinuria with very little side-effects. However, the study only had a short follow up period of 4 weeks and no antibody data [63].

A clinical trial using the Fresenius Peptide GAM immunoadsorption column Globaffin has at the time of writing completed recruitment and treatment of 12 patients. The Globaffin column has a specificity for IgG antibodies of all subclasses and as such is expected to render the patients anti-PLA₂R negative. Follow up is ongoing but unpublished reports suggest that this is a promising new therapy for autoimmune membranous nephropathy with a drastically reduced side-effect burden when compared to the Ponticelli regimen [64].

5.1.3. *Anti-glomerular basement membrane disease*

Anti-glomerular basement membrane disease (anti-GBM), also known as Goodpasture's syndrome, is a rare life-threatening autoimmune disease, typically presenting as rapidly progressive crescentic glomerulonephritis and lung haemorrhage. It is invariably fatal unless treated promptly with an intensive regime of immunomodulation with high dose steroids, immunosuppression and plasma exchange. With current treatment standards mortality has improved although renal impairment remains a significant challenge [58, 65]. Patients who are dialysis dependent on presentation unfortunately rarely recover renal function [58, 66, 67].

The disease is associated with the pathogenic anti-GBM autoantibodies which are directed against the glomerular basement membrane [68] and in particular the non-collagenous domain 1 (NC1) of $\alpha 3$ chain of type IV collagen. These antibodies are predominantly IgG, occasionally IgM, and can be readily detected in the circulation as well as being demonstrated along the glomerular basement membrane on histology, a combined finding that is confirmation of the diagnosis [65].

Treatment strategies are aimed at the removal of the pathogenic antibody with oral prednisolone at the earliest clinical suspicion of the disease. Once a diagnosis has been confirmed,

cyclophosphamide is started as is plasma exchange. Plasma exchange continues for 14 sessions or until the serum antibody is negative. If a patient goes into remission, unlike many other autoimmune diseases, patients rarely have a return of the antibody or relapse of the condition [58].

Given its superiority in removing antibodies compared to plasma exchange, immunoadsorption provides a promising alternative to the rapid reduction of the offending autoantibodies. Currently there are no RCTs investigating the efficacy of IA versus standard of care and for many years evidence was conflicting based on small case series from around the world using different adsorbers.

The first published treatment of Goodpastures using IA was in 1985 by Bygren et al. using protein A immunoadsorption resulting in a dramatic clinical improvement in a patient who had failed to respond to plasma exchange [69]. In four Chinese patients using protein A IA, all saw a reduction in their antibody levels and resolution of their pulmonary haemorrhage. One patient managed to recover renal function in order to stop haemodialysis but the three others remained dialysis dependent. All three of these had 100% crescent formation on biopsy [70]. However, two patients with dialysis dependent anti-GBM disease treated with protein A immunoadsorption by Esnault et al. showed no clinical improvement at all [71].

Two patients treated in Spain showed a reduction in the circulating antibody and improvement in respiratory symptoms but no renal improvement [72]. A Swedish study treating three patients with Goodpasture's also showed no clinical improvement using IA (Excorim, Sweden) although all patients were dialysis dependent on initiation of the treatment [73]. Two patients from Vienna were successfully treated using the TheraSorb adsorber, one of whom regained renal function despite presenting with 100% crescents on histology [74].

The largest series to date though, reveals some encouraging results. Biesenbach et al. treated 10 consecutive patients using either the TheraSorb (Miltenyi Biotec, Germany) or the Immunosorba (Fresenius Medical Care, Germany), treating 2.5–3.0 PV per session. All patients had adjunctive prednisolone and cyclophosphamide. All 10 patients were rendered anti-GBM antibody negative within nine sessions and with greater efficiency than demonstrated in PE. Two patients were initially treated with plasma exchange but switched to IA when the antibody failed to reduce. Clinical improvement was seen in both pulmonary haemorrhage and in renal impairment, with three of six patients who had initially presented with dialysis dependency managing to recover renal function. One patient died of fungal infection after the antibody had become negative but otherwise the safety profile was acceptable with no major adverse events recorded [75].

5.1.4. *Lupus nephritis*

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organs with up to 60% of patients having renal involvement (Lupus Nephritis) [76]. SLE is caused by a loss of immune tolerance leading to the production of autoantibodies, such as anti-double-stranded DNA (anti-dsDNA) autoantibodies, and the development of immune complexes [77–79].

The current standard of care is the use of intravenous cyclophosphamide therapy and is aimed at the inhibition of formation, and reduction of, these pathogenic antibodies [58].

There are now multiple case series, showing a favourable response to IA with a reduction in proteinuria and anti-dsDNA levels, and disease activity as characterised by the Systemic Lupus Activity Measure (SLAM) and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [80–89]. Many of these studies have treated patients with severe disease activity resistant to immunosuppression with very few side effects. As yet there are no RCTs investigating the use of IA versus immunosuppression alone or in combination. Despite this, the use of IA has shown promise as an alternative or adjunctive treatment in lupus nephritis in both the short and long term.

5.1.5. Focal segmental glomerulosclerosis

Focal segmental glomerulosclerosis (FSGS) is a histological diagnosis of a heterogeneous group of conditions. It is the most common cause of adult nephrotic syndrome in the US and one of the most common causes worldwide and its incidence is rising [54, 90]. It is separated into either primary or idiopathic FSGS or secondary FSGS. Secondary FSGS can be further subdivided into genetic, virus-associated, drug-induced or adaptive FSGS [91].

Given this heterogeneity, a sound pathogenic basis of the disease has been elusive. The initiation of the disease process undoubtedly follows a number of different routes, all with resultant podocyte injury. In primary FSGS an immunologic cause has long been suspected with a number of circulating factors now identified as potential candidates such as the IgG anti-CD40 autoantibody although further work is needed in this area [92].

Based on this supposition, the use of immunoadsorption both for primary disease and for recurrent disease post-transplant has been used with varying degrees of success [93, 94].

Haas et al. used IA in five patients with native kidney disease and three patients with recurrent disease in their grafts. Six patients used protein-A IA (Immuno-adsorba, Excorim, Sweden) and two patients with an anti-IgG column (Ig-TheraSorb, Germany). Patients initially had five sessions within 10 days at 2.5 plasma volumes per session. If proteinuria did not improve by more than 50% in this time they underwent another cycle. In four of the eight patients, proteinuria reduced by more than 50% although the mean time to relapse was only 21 days. Following relapse, patients had a further cycle of IA which did appear to provide a benefit with one patient having stable remission for 1.5 years and a second patient being stable for 2 years. However, of the two others who had initially responded, one became resistant to treatment and the other lost his graft after 3 months [93].

LDL-apheresis has also shown some promise with reports from Japan suggesting it may have a role in not only reducing cholesterol, triglycerides and low-density lipoprotein but also proteinuria and an improvement in renal function [95–97]. This has led the ASFA to classify FSGS as a category III condition with grade 2C evidence (Optimum role of apheresis therapy is not yet established based on weak evidence and decision making should be individualized) [98].

5.1.6. ANCA associated vasculitis

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is an autoimmune disorder affecting small vessels. It can involve any organ although has a predilection for the upper airways, lungs and kidneys. It is a chronic relapsing-remitting disease following the general pattern of many autoimmune diseases with a genetic component, environmental or infective trigger and the formation of autoantibodies resulting in an immune cascade and subsequent injury [99, 100].

Prior to the introduction of steroids and immunosuppression, the disease was invariably fatal [101]. Nowadays the vast majority of patients will survive but given the judicious amounts of steroids and immunosuppression required for remission, many patients will have iatrogenic complications of the treatment itself [102–106].

The disease is associated with the formation of autoantibodies to either myeloperoxidase (MPO) or proteinase 3 (PR3) found on the granules of neutrophils and the lysosomes of monocytes in 90% of patients. As well as being a biomarker for the disease, there is evidence to suggest that it has at least some pathogenic features, particularly in animal models of the disease [99]. Along with this and the fact that it is an IgG antibody [107], a number of groups have investigated the use of immunoadsorption in the treatment of AAV. There does appear to be effective removal of the antibodies, however numbers in these studies are limited, there is concomitant use of immunosuppression and the results inconsistent [71, 73, 108, 109].

5.2. Cardiology

5.2.1. Hyperlipidaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic defect resulting in raised serum cholesterol and an increased risk of cardiovascular disease. Patients can present as either homozygous or heterozygous FH, with homozygous patients exhibiting a more severe phenotype. If left untreated patients with FH have a significantly increased risk of cardiovascular disease. The majority of patients exhibit a mutation in the LDL receptor, although mutations in the Apo B and proprotein convertase subtilisin/kexin type 9 genes have also been detected [110–112].

Initially patients should be treated with lifestyle changes and aggressive statin therapy, however, in many patients this will not suffice. In the United Kingdom, the National Institute for Health and Care Excellence (NICE) suggests considering the use of IA for adults and young patients with homozygous familial hypercholesterolaemia (FH) and in heterozygous FH progressive, symptomatic coronary heart disease despite maximal medical therapy. This is generally on a weekly or biweekly regimen and given the frequency, an arterio-vascular fistula is recommended [113].

In the United States (US), LDL-apheresis is approved for use by the Food and Drug Administration (FDA) in patients who have not responded to treatment after 6 months. In homozygous FH non-response is defined patients with an LDL cholesterol of above 300 mg/dL

or a non-HDL-cholesterol level of above 330 mg/dL. In heterozygous FH, non-response is defined as HDL-cholesterol above 300 mg/dL and 0-1 risk factors. In patients with established coronary heart disease, cardiovascular disease or diabetes, an HDL-cholesterol level of above 160 mg/dL is used [114].

Lipoprotein(a) is a plasma protein consisting of a low-density lipoprotein (LDL) covalently bonded to an apolipoprotein(a) molecule. Elevated lipoprotein(a) levels have consistently been reported as an association for increased risk of cardiovascular disease although much of this has been a causal link. However, given the weight of evidence for its involvement in cardiovascular disease, the European Atherosclerosis Society Consensus Panel on the treatment of lipoprotein(a) recommends treatment to ensure the serum level is below 50 mg/dL [115]. Therapeutic agents are limited with the standard therapy being niacin, alone or in combination with statins, with little impact from lifestyle changes. In patients unresponsive to or intolerant of pharmacological solutions immunoadsorption provides an alternative therapy. European Atherosclerosis Society Consensus Panel also suggests considering IA therapy in young or middle-aged patients with progressive coronary disease and significantly raised plasma lipoprotein(a) levels [115]. In the US, apheresis is approved for use by the FDA in heterozygous FH patients unresponsive to medical therapy after 6 months with an LDL-cholesterol level of above 200 mg/dL and lipoprotein(a) above 50 mg/dL [114].

Homozygous FH is a category I condition whilst heterozygous FH is a category II condition with both having a grade 1A recommendation as per the American Society for Apheresis (ASFA) guidelines on the use of therapeutic apheresis in clinical practice. Lipoprotein(a) hyperproteinaemia is a category II condition with a 1B grade recommendation. A category I condition is a disorder in which apheresis is the accepted first line therapy and a category II condition is one in which apheresis is the accepted second line therapy, as a stand-alone modality or as an adjunct to other treatment. A grade 1A recommendation is defined as a strong recommendation based on high quality evidence and applicable to most patients without reservation. A grade 1B recommendation is a strong recommendation based on moderate quality evidence and can be applied to the majority of patients in most circumstances [98].

5.2.2. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a progressive disease that is a major cause of heart failure worldwide with a high mortality and morbidity. Despite treatment it remains one of the main precipitants to heart transplants in adults [116, 117]. In most patients the cause is unknown, but for a significant proportion it is an autoimmune disease. After years of speculation that there was an autoimmune component to condition, a number of autoantibodies have now been discovered. Evidence now suggests that these autoantibodies, particularly β 1-adreno-receptor autoantibodies (β 1-AAB), are pathogenic in nature [118, 119]. Given they are generally of the IgG class, removal of the antibody is particularly amenable to IA and it has now been used successfully in DCM for over 2 decades with a significant body of evidence supporting its use. The first reported case series from 1996 used the Ig-TheraSorb (Baxter, Germany) column to treat eight patients with severe DCM and NYHA class II-IV [120].

Since that time a number of studies have reported on the benefits of IA in DCM both short and long term, with a reduction in circulating antibodies and with clinical improvement [121–128].

Dörffel et al. treated nine patients with NYHA class III or IV and ejection fraction <25%, on 5 consecutive days with the Ig-TheraSorb (Baxter). Here there was a marked reduction in circulating antibody level and an improvement in the patients' dyspnoea. There was no improvement in LVEF in this study although this is likely due to the very short follow up [129]. A longer prospective case control study with a 1-year follow-up expanded on this earlier work. Here 34 patients with an NYHA class II or above significant LV dysfunction and considered candidates for heart transplantation were enrolled. 17 patients received standard medical treatment whilst 17 received adjunctive IA for 5 consecutive days. β 1-AAB levels had a highly significant mean reduction of 93.2% at month three with no significant increase within the 1 year follow up. Antibody levels remained unchanged in the control group [123].

At 1 year follow up there was also a marked improvement in the cardiac performance of patients in the control group with a significant increase in their LVEF and a reduction in the left ventricular internal diameter in diastole (LVIDd). At 5 years post-IA there was also a statistically significant improvement in survival for those patients in the treatment group compared to the control group [123].

Long-term data also suggests that the antibodies are slow to reappear. In a study of 108 patients, only 16 (14.6%) had detectable antibodies 3 years post-IA and a further nine (8.3%) had detectable antibodies after 3 years post-IA. In the majority of these patients (76%), the reappearance of the antibody correlated with a deterioration in their clinical symptoms. With this continued antibody remission there continues to be long-term clinical improvement. Some studies show a mortality rate similar to post-transplantation, although with a lower LVEF [119, 121, 128].

Many of these studies have utilised replacement intravenous immunoglobulins at the end of the IA treatment. There has been some suggestion that much of the benefits seen are due to this although there does appear to be clinical and biochemical improvement without IVIg replacement [130].

IA use in dilated cardiomyopathy has a level II category and 1B grade recommendation as per the American Society for Apheresis (ASFA) guidelines on the use of therapeutic apheresis in clinical practice. A level II category is defined as a disorder in which apheresis is the accepted second line therapy or first line in conjunction with other treatments. A grade 1B recommendation is defined as a strong recommendation with moderate quality of evidence and can be applied to the majority of patients without reservation [98].

5.2.3. Myocardial infarction

Despite ever increasing survival following acute MI, post-MI morbidity continues to present patients with a modest prognosis. Interest in the inflammatory response following an MI has gained traction in recent years and in particular the role C-reactive protein (CRP) plays in ongoing myocardial damage. Along with this, elevated CRP is a poor risk factor for all-cause

mortality, major adverse cardiac events and recurrent MIs [131, 132]. Experimental animal models have shown that inhibition of CRP following induced MI results in a smaller infarct area although this therapeutic molecule is still in early development and not yet humanised [133, 134]. Immunoadsorption now offers the ability to remove CRP with specific adsorbents in early animal models suggesting a benefit. In a study of 10 pigs (five receiving IA and five controls) with induced MI, those pigs who underwent IA had a reduction in the post-MI infarct size and preservation of their cardiac output as measured by LVEF [135]. Given these promising results a clinical trial is now underway in Germany to investigate the benefit of using CRP-specific immunoadsorption in acute ST-elevation MI (STEMI). Unpublished interim analysis suggests that the therapy is safe and well tolerated post-STEMI with promising results on infarct size in relation to CRP reduction. The results of this study have the potential to change management following an MI and subsequent PCI with an improvement in patient morbidity and mortality long-term.

5.2.4. Chagas cardiomyopathy

Chagas disease, caused by *Trypanosoma cruzi* (*T. cruzi*), affects ~10 million people per year, predominantly in South America where it is endemic. Of those affected, many have no long-term sequelae but up to 40% can develop Chagas Cardiomyopathy with arrhythmias, heart failure and an increased mortality [136, 137]. The vast majority of patients with Chagas cardiomyopathy are known to possess IgG autoantibodies suggesting an autoimmune component to the disease with the potential to respond to IA therapy. A clinical trial is currently underway to investigate this.

5.3. Neurology

5.3.1. Multiple sclerosis

Multiple sclerosis (MS) is the most common chronic inflammatory condition of the central nervous system (CNS) worldwide. It is characterised by demyelination of differing parts of the CNS (space) with different lesions appearing over time. A majority of patients present with visual loss due to optic neuritis although depending on where the lesion is can also present with symptoms such as limb weakness, sensory loss, ataxia or cognitive impairment [138–140]. It is estimated to affect 50–300 per 100,000 with ~2 million people diagnosed worldwide. It is generally a disease of early adulthood and given the impact on mobility and quality of life the disease confers, it represents a significant healthcare burden [141]. There are currently four recognised phenotypes of the condition. Many patients present with a single episode that resolves over time known as a clinically isolated syndrome. Patients who then go on to have further episodes (relapses) are described as having relapsing-relapsing MS. Approximately 15% of patients will present with a progressive disease course from onset known as primary progressive MS. The fourth category is the development over time of secondary progressive MS in a proportion of patients with relapsing-relapsing MS. The pathogenesis of MS is still not clearly defined although genetic, lifestyle and autoimmune factors are all understood to play a role in the disease [139, 140, 142].

There are now a large number of approved disease modifying medications for the treatment of MS with apheresis reserved for non-responders. In many national guidelines for the treatment of MS, TPE is considered a second line therapy for steroid resistant relapsing-remitting MS [143]. The American Society for Apheresis (ASFA) gives TPE for MS a category II (Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment) based on grade 1B evidence (Strong recommendation, moderate quality evidence) [98]. As early as 1989, IA has been shown to be as effective as TPE in the treatment of MS with an ever-growing body of evidence to support its role [144–149]. However, given the lack of RCTs there has been limited uptake of the therapy. This has led relapsing-remitting MS to be an indication for IA by the ASFA although the lack of RCTs has resulted in it being designated a category III disease with Grade 2C evidence (optimum role of apheresis therapy is not established. Decision making should be individualized. Weak recommendation with low-quality or very low-quality evidence) [98].

5.3.2. Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is one of the most common causes of acute polyneuropathy worldwide with an incidence of ~1 per 100,000. It is considered an autoimmune disease generally found in association with a preceding infection, initiating an immune cascade that results in an inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy [150]. TPE has been used for a number of years with robust evidence. The ASFA have designated GBS a category I condition with grade 1A evidence (disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. Strong recommendation, high-quality evidence) [98]. This has inevitably led researchers to consider IA in GBS.

Evidence for IA suggests that it is a treatment that should be considered as a viable alternative to TPE. Most published studies comparing IA to the standard of therapy, be it TPE, double filtration plasma exchange or IVIG has shown that not only is safety comparable or better, but also efficacy is as comparable. This has led a number of researchers to suggest, given its safety record, that it should be considered instead of TPE as a first line treatment [151–154].

5.3.3. Autoimmune encephalitis

Autoimmune encephalitis is an acute neurological inflammatory condition now known to be caused by a variety of antibodies. Treatment therefore generally takes the form of immunomodulation using steroids, IVIG and TPE. As yet there are no randomly controlled trials investigating the efficacy of IA in autoimmune encephalitis and only retrospective trials.

Dogan Onugoren et al. treated 14 patients with autoimmune encephalitis caused by leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-2 (CASPR2), N-methyl-D-aspartate receptor (NMDAR) and intracellular glutamic acid decarboxylase (GAD) antibodies using either tryptophan and protein A adsorbers. Directly after follow up, nine patients (64%) had improved their Modified Rankin Scale (mRS) score by one or more point and five (35%)

became seizure free. At late follow up, several months after IA therapy, 12 (86%) patients had improved mRS scores [155].

Köhler et al. treated 13 patients with antibodies to NMDAR, GAD, Lgl1 and γ -amino-butyric-acid (GABA) using tryptophan IA. Eleven patients (85%) were noted to have a clinical improvement following IA with a good side effect profile [156].

In a prospective observational case control study treating 10 patients with tryptophan IA and 11 with TPE. 60% of patients in the IA group compared to 67% in the TPE showed a clinical improvement with a reduction of their mRS score of one or more points. There were more adverse events in the TPE group (three in the TPE group and zero in the IA group) [157].

A recent review analysed the published studies comparing IA (25 patients in total) to TPE therapy (57 patients), used alone or in combination with steroids. Here they found that 88% of patients improved following IA treatment with 77% of patients improving with TPE treatment. The effect seemed to be more pronounced for antibodies against the neuronal cell surface compared to intracellular antigens. It was also found to be the safer option with fewer side-effects [158].

Despite the lack of RCTs, the evidence for IA in autoimmune encephalitis is encouraging and would suggest that it should be considered as a therapy.

5.3.4. *Chronic inflammatory demyelinating polyradiculoneuropathy*

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is among the most common chronic neuropathies worldwide. Although the exact pathogenesis remains unknown, it is considered an autoimmune disorder directed against, and causing demyelination of, the myelin sheath. This results in progressive or relapsing distal and peripheral weakness. The condition has a multitude of phenotypes, and with this heterogeneity many consider it a spectrum of disease, as opposed to a single disease [159]. Current treatment aims at immunomodulation with IVIG and steroids the first line therapy with consideration of TPE in non-responders. ASFA guidelines consider CIDP as a category I disorder for treatment with TPE (disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment) with grade 1B evidence (strong recommendation, moderate quality evidence) [98]. Given the efficacy of TPE, a number of studies have investigated the use of IA in CIDP.

Galldiks et al. treated 10 patients with CIDP unresponsive to standard therapy using a tryptophan-linked polyvinyl alcohol adsorber. Response as measured by the inflammatory neuropathy cause and treatment disability (INCAT) score and improvements in strength, sensation and performance of activities of daily living. Improvements in the INCAT was seen in all but one of the patients. Four of the patients received long-term IA in an outpatient setting with clinical improvement. In three of these four patients, they had previously been treated with TPE and noted no clinical decline on switching to IA [160].

Zinman et al. conducted a randomised, single-blinded study investigating the efficacy of protein A immunoadsorption versus IVIG. Here they treated nine patients with high dose IVIG,

four with low IVIG and five with IA. One patient in the high dose IVIG withdrew consent prior to treatment and two patients in the low dose IVIG group died of illness not thought to be related to treatment. Six-month data was not available for one patient in the IA group and two in the IVIG arm. Two months following treatment, four patients (80%) in the IA group were considered responders compared to four out of eight (50%) in the IVIG arm. At 6 months, all four of the patients in the IA group were considered responders compared with three out of six in the IVIG group (100 versus 50%) [161].

More recently a prospective randomly controlled study investigating the efficacy and safety of IA versus TPE, again using the tryptophan-linked polyvinylalcohol adsorber. There were nine patients in each group with no significant differences in baseline characteristics. Clinical improvement was assessed using the INCAT score and the Medical Research Council (MRC) sum score. It was found that four patients (44.4%) in the TPE group responded to treatment compared to six patients (66.7%) in the IA group. In the IA group, 100% of the patients had an improvement in their MRC sum scores and four patients out of six patients (66.7%) [162].

Despite these small numbers, IA has shown promising results especially when considering the majority of the patients included in the studies were patients who had already failed standard therapy. The safety profile was comparable to TPE and IVIG and albeit with limited study populations, appeared to be as, if not more, efficacious than the current standard therapy.

5.3.5. Dementia

Dementia represents an increasing problem for healthcare systems worldwide, exacerbated by an aging problem. The most common form, Alzheimer's disease, is characterised by the deposition of β -amyloid plaques and neurofibrillary tangles. The exact cause of the disease remains unknown and given the heterogenous nature of the condition it is likely to be multifactorial. There can also be some overlap in patients with both Alzheimer's disease and Vascular dementia, a disease resulting from damage to the vasculature of the brain. Research has suggested there can be an autoimmune component to some dementia patients with the discovery of autoantibodies against the β_1 -adrenergic receptor (β_1 -AR) and the β_2 -adrenergic receptor (β_2 -AR) present in up to 59% of dementia patients [163, 164].

Hempel et al. treated eight patients with immunoadsorption; all patients were anti- β_1 -AR positive and five were also anti- β_2 -AR positive. Patients treated for 4 consecutive days saw a reduction in anti- β_1 -AR levels of 96% compared to only 78% in those treated for 2–3 consecutive days. Those patients treated with 4 days of IA also saw a sustained elimination of antibody over the course of the study but in those treated for a shorter time period saw a rebound of the antibody level. Cognitive function was assessed using a range of tests including the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment scale (ADAS; cognitive and non-cognitive), Bayer Activities of Daily Living (Bayer-ADL), Clinical Global Impression Scale (CGI), Geriatric Depression Scale (GDS) and the Short Cognitive Performance Test (SKT). They found that over the course of the study, those treated for 4 days had stabilisation of their cognitive function. Those treated for only 2–3 days suffered from declining cognition [165].

This is a limited study with a small number of patients but its promise has led to a number of current ongoing studies to investigate further.

5.3.6. *Lambert-Eaton myasthenic syndrome*

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease resulting in muscle weakness, autonomic dysfunction and areflexia. Up to 60% of patients with LEMS will also be found to have a carcinoma, with small cell lung cancer (SCLC) making up the vast majority of these patients. Pathogenic antibodies to voltage-gated calcium channels (VGCC) have been found in 80–90% of patients and up to 100% in patients with SCLC. Current therapy consists of 3,4-diaminopyridine as first line and treatment of any underlying malignancy. Second line treatment involves the addition of pyridostigmine to the 3,4-diaminopyridine or converting to azathioprine and prednisolone. In the case of severe weakness TPE or IVIG can also be considered [166]. There are also a number of very small case series describing the use of IA in refractory LEMS.

Sauter et al. describe the case of a young man with rapidly progressive weakness, muscular atrophy and cerebellar dysfunction initially treated with thymectomy for presumed malignancy and pulsed prednisolone with some resolution of symptoms and a reduction in anti-VGCC antibodies titres. Further treatment with Azathioprine and IVIG was initiated with some improvement clinically although this was not sustained and corresponded with a rise in his antibody titre. IA was performed on 3 consecutive days every 6 weeks with a decrease in antibody level over this time and an improvement symptomatically, especially in regards to gait [167]. Baggi et al. treated three patients unresponsive to immunosuppression and plasma exchange with IA. All patient showed clinical improvement with one patient regaining the ability to walk and one reaching pharmacological remission [168]. Batchelor et al. treated 13 paraneoplastic patients one of whom had LEMS characterised as bilateral ptosis and proximal limb weakness. They received a total of six IA sessions (two per week for 3 weeks) with a protein A adsorber. In the patient with LEMS, clinical improvement was seen with resolution of the ptosis and the recovery of muscle strength allowing her to climb stairs and walk unaided again. There was also a significant reduction in the anti-VGCC antibody titre from 458 to 25 pmol/L [169]. Ishikawa et al. treated a 75 year-old man with gait disturbance and somnolence diagnosed as LEMS. Anti-VGCC titre was initially over 11,000 pmol/L but the use of a phenylalanine adsorber column along with concomitant prednisolone resulted in a significant reduction in his antibody titre and subsequent clinical improvement [170].

There are currently no RCT or prospective trial data for the use of IA in LEMS. However, in patients who are non-responsive to standard therapy or in whom immunosuppression or TPE are contraindicated, there is limited data to suggest that IA can be considered an alternative.

5.4. Dermatology

5.4.1. *Pemphigoid vulgaris*

Pemphigoid vulgaris (PV) is a potentially fatal autoimmune blistering condition of the skin and mucous membranes. It is associated with pathogenic IgG autoantibodies to the desmosomal

cadherins; desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) [171–173]. Treatment and management of PV can be challenging. Currently treatment consists of oral steroids alone or in combination with dapsone and immunosuppression such as azathioprine, methotrexate or cyclophosphamide. This has dramatically improved survival but there is significant morbidity as a result of the side-effects from these therapies [174].

A number of groups have now used IA with differing adsorbers and protocols. A tryptophan-linked polyvinylalcohol adsorber was used to treat seven patients with severe PV. There was a significant reduction in circulating antibodies and clinical improvement seen in the pemphigoid lesions and a reduction in steroid and immunosuppression required [175]. Protein A immunoadsorption has also been used with the first study describing its use in 2003. Here four patients were treated using IA as an additional treatment to steroids. All patients saw an improvement in their pemphigoid lesions and significant reduction in their antibody titres [176]. Further, nine patients were treated with a modified protocol by Shimanovich et al. with a higher dose of adjunctive steroids and either azathioprine or mycophenolate mofetil. All patients showed a significant reduction in antibody levels and clinically, with remission reported up to 26 months after treatment [177]. Protein A immunoadsorption has also been used in combination with Rituximab and IVIg with positive results [178] and in patients with longstanding disease resistant to multiple therapies [179]. In the largest trial for IA in PV, IA was used in combination with Rituximab in 23 patients. Seventeen patients using protein A IA (Immunosorba) and six patients using polyclonal anti-human IgG sheep antibodies coupled to sepharose (Thera-Sorb). IA was given more frequently than previous protocols with 1000 mg Rituximab given on days 4 and 24. This resulted in a significant reduction in antibody titres in all patients. At 6 months, 16 (70%) of the patients were in complete remission and five (22%) were in partial remission. A relatively low relapse rate of six patients was seen over the follow up period requiring either retreatment with IA, Rituximab or immunosuppression [180].

Given the antibodies to Dsg1 and Dsg3 are IgG, Eming et al. used the Globaffin (Fresenius, Germany), an IgG specific column to treat PV in four patients. All patients experienced a reduction in antibody levels of up to 70% and a marked improvement clinically [181]. Behzad et al. used the Globaffin column in combination with Rituximab in 10 difficult to control PV patients in a retrospective study. Six months after treatment, 8 out of the 10 patients were in remission, one had a partial response and one patient did not respond at all [182]. In one study comparing adjunctive IA versus Rituximab therapy, antibody levels, clinical improvement as assessed by the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and oral steroid doses all reduced faster in the IA group compared to the Rituximab group. However, there were more relapses in the IA group requiring further treatment [183].

Despite the evidence for IA in PV, an autoimmune disease with well-defined pathogenic IgG autoantibodies, its widespread adoption has been limited. This has been hampered by the small study numbers, lack of RCTs and multiple treatment protocols. Given this PV is a recommended indication for the use of IA by the ASFA where it is classified as a category III disease (optimum role of apheresis therapy is not established) with 2C evidence (weak recommendation, low-quality or very low-quality evidence) [98]. The British Association of

Dermatologists guidelines for the treatment of pemphigus vulgaris also state that IA could be considered in patients unresponsive or intolerant to standard treatment [174].

5.4.2. Bullous pemphigoid

Bullous pemphigoid (BP) is an autoimmune condition resulting in the development of sub-epidermal blisters or bullae and is the most common of the autoimmune blistering conditions. It is caused by IgG autoantibodies directed against the BP180 and the BP230 antigens found in the hemidesmosomes. The mainstay of treatment is the use of topical or systemic steroids with or without oral immunosuppression [184, 185]. In patients refractory to this, IA has been used with varying success.

Herrero-González et al. used tryptophan IA to treat two patients with BP initially unresponsive to methylprednisolone, dapsone and in one patient, additional azathioprine and topical clobetasol propionate. Both patients saw dramatic improvement in their skin lesions after 2 weeks with all active lesions disappearing by 6 weeks [186]. Kasperkiewicz et al. treated seven patients with severe disease using protein A immunoadsorption. Here four patients had previously failed treatment with oral steroids, topical clobetasol propionate and either dapsone or mycophenolate mofetil and three were immunosuppression naïve. All patients saw a significant reduction in circulating antibodies and had no active lesions 1–3 months after therapy. Six of the seven patients remained in clinical remission at the end of follow up with two of the patients requiring no adjuvant medication [187]. Ino et al. used dextran sulfate conjugated cellulose columns to treat two patients who had not responded to steroids or dapsone. In one patient the lesions disappeared 2 weeks after treatment however in the second patient the skin lesions returned after 6 weeks and despite a second course of IA continued to have active blistering [188].

Given the pathogenicity of the IgG antibodies involved in BP and the positive results, albeit from very limited published data, IA has the potential to provide adjunctive therapy in refractory BP.

5.4.3. Atopic dermatitis

Atopic dermatitis (AD) is a chronic inflammatory condition affecting up to 20% of the population [189]. It is characterised by recurrent pruritic eczematous lesions and generally presents in childhood. Its pathogenesis is not completely understood, exacerbated by the heterogeneous nature of the disease, but genetic, environmental and humoral factors are all associated with its development. The disease itself can be associated with other atopic and inflammatory conditions such as asthma, allergic rhinitis and inflammatory bowel disease. Far from being a typical type I hypersensitivity reaction as initially thought it now appears to be a complex combination of epidermal barrier dysfunction, T helper 2 (Th2) cell-mediated and IgE immune regulated pathways. The majority of patients show a raised serum IgE titre with some circumstantial evidence suggesting it plays a pathogenic role [190, 191].

The first published study used IA in 12 patients with severe AD and total serum IgE levels of >4500 kU/L. Patients saw a significant improvement in their mean Scoring Atopic Dermatitis

(SCORAD), reducing from 78.6 ± 3.9 to 32.4 ± 3.5 at the end of the study at week 13. There were also significant improvements seen in the mean Eczema Area and Severity Index (EASI) and the pruritus score by the end of the study [192]. Since that time there has been a large number of patients treated in clinical trials with promising results [193–196]. Reich et al. treated 26 severe AD patients with IgE specific IA and 24 patients with a Pan-immunoglobulin IA. Both groups reported an equal improvement in their EASI scores with almost 50% of patients reporting a >50% improvement. There were also improvements seen in the Dermatology Life Quality Index (DLQI), the SCORAD and the Patient-Oriented Eczema Measure (POEM). In this study the IgE specific adsorber was better tolerated with less adverse events than the pan-immunoglobulin adsorber with similar clinical outcomes [196].

Given the weight of evidence now accumulating and the safety profile of the IgE specific adsorbers, IA should be considered in the case of AD unresponsive to standard care or in those in whom it is contraindicated.

5.5. Respiratory

5.5.1. Asthma

Asthma is one of the world's most prevalent chronic diseases affecting an estimated 300 million people worldwide and rising. A variant of asthma, allergic asthma is classified as a type 1 hypersensitivity reaction. Here IgE binds to high-affinity FcεRI receptors on Mast cells and Basophils leading to degranulation and the release of inflammatory mediators. There is now increasing evidence that the incidence of IgE-mediated allergies is on the rise. In allergic asthma, as in other allergen related disease, the severity is progressive as patients come into contact with the allergen over time [197–199].

The IgEnio is a single use IgE specific adsorber developed by Fresenius Medical Care. The ESPIRA trial (Extracorporeal IgE Immunoabsorption in Allergic Asthma: Safety and Efficacy) is a randomized controlled trial investigating the efficacy of IA in 14 adult patients with allergic asthma and raised IgE titres. Patients were treated for three cycles with each cycle consisting of three sessions. Mean IgE levels reduced by 87% per cycle for total IgE with similar reductions in IgE specific for seasonal and perennial allergens. A steady improvement in peak flow levels, overall allergy symptoms as assessed by the Visual Analogue Scale (VAS) and lung specific symptoms were also seen. In the US, omalizumab is only indicated in patients with an IgE titre of below 700 U/ml and in the EU below 1500 U/ml. Along with the clinical and biochemical improvements seen with the treatment, interestingly it also allowed three of the patients, who were previously ineligible for omalizumab due to their high titres, to qualify for omalizumab treatment. Further work is needed given this is the first reported use of IA in allergic asthma but the initial findings are promising [199].

6. Conclusion

Despite recent healthcare advances, sepsis remains a significant cause of morbidity, mortality and admission to ICU. However, new technologies with the ability to remove damaging factors

in the pathogenesis of sepsis may help to improve patient outcomes. Since its development over 2 decades ago, immunoadsorption therapy has proven to be a highly efficient method of removing antibodies with a remarkably safe side effect profile. As our understanding of not only sepsis but also autoimmune disease increases, the range of conditions that are amenable to IA will also increase. With the development of columns for more specific antibodies and molecules such as those for sepsis, its use can reasonably be expected to become more ubiquitous.

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