Current topics**Potential for plasma exchange in children**

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Plasmapheresis and plasma exchange are terms that are often used synonymously in today's literature. However plasma exchange has become possible only since the introduction of efficient cell separation techniques. A cell separator machine can remove large volumes of plasma, necessitating replacement with whole or fractionated plasma or a plasma substitute, to maintain intravascular colloid osmotic pressure. Plasmapheresis is the removal of plasma only, with the return of the cellular blood components, as first described in 1914.¹ The original term being derived from the Greek *apheresis* meaning a withdrawal.

Technique

Plasma exchange is the continuous or discontinuous flow of anticoagulated blood into some form of centrifugal device which enables plasma separation to occur. Plasma is removed and an equivalent volume of replacement material is recombined with the patient's cells and returned to the patient. An example of the continuous flow system is the IBM 2997, and of the discontinuous flow system is the Haemonetics Model 30 or V50. Each has its own particular advantage, but in a discontinuous flow system fluid balance requires more careful management and it takes longer for a set volume because of the intermittent nature of the procedure. The volume of an exchange and the frequency and duration of treatment depends entirely on the individual disorder. At present treatment programmes vary enormously between different centres and there is a need for controlled studies to establish rational protocols and therapeutic efficacy in the variety of different disorders for which therapeutic plasma exchange has been used.

Rationale of plasma exchange

The aims of plasma exchange are (1) Removal of plasma factors responsible for the causation or progression of disease. (2) Replacement of deficient plasma factors if the deficiency is causing the

disease. (3) Specific enrichment of plasma factors necessary for control of the disease.

The majority of current usage falls into category (1); however recent reports suggest that disorders falling into category (2) are under investigation,² but as yet there is little information on category (3) usage.

Clinical uses

The Table gives a list of diseases together with references to cases in which plasma exchange has been used and for which there may be a paediatric application. Most of these studies were undertaken in adults, and reports of therapeutic plasma exchange undertaken in childhood are few.

It is not the purpose of this review to deal in depth with each disease but rather to select examples of the principles concerned from each group, together with any reports of usage in children.

Table *List of diseases with references to cases in which plasma exchange has been used*

Immunological disorders
<i>Antibody mediated</i>
Goodpasture's syndrome ³
Acquired myasthenia gravis ⁴⁻⁶
Dermatitis herpetiformis ⁷
Idiopathic thrombocytopenic purpura ^{8 13}
Autoimmune haemolytic anaemia ^{9 10}
Haemophilia with inhibitors ¹¹⁻¹³
Rh haemolytic disease of the newborn (maternal treatment) ¹⁴⁻¹⁶
Bone marrow transplantation across an ABO incompatible barrier ^{17 18}
Insulin-resistant diabetes with insulin receptor antibodies ¹⁹
<i>Immune complex mediated</i>
Systemic lupus erythematosus ^{20 21}
Immune complex type of rapidly progressive glomerulonephritis ²²
Cutaneous vasculitis ^{23 24}
<i>Presumed immunological</i>
Transplantation rejection ²⁵
Disseminated cancer with 'blocking factors' ^{26 27}
Rheumatoid arthritis ^{28 29}
Dermatomyositis ³⁰
Guillain-Barré syndrome and the Miller-Fisher variant ³¹⁻³³
Miscellaneous disorders
Familial hypercholesterolaemia ³⁴
Poisoning ^{35 36}
Reifsum's disease ³⁷
Asthma ³⁸
Uncontrollable hypertension ³⁹
Haemolytic uraemic syndrome ^{2 40 41}
Thrombotic thrombocytopenic purpura ^{42 43}
Hypogammaglobulinaemia ⁴⁴

Immunological disorders

Antibody mediated. The rationale for plasma exchange in these disorders is removal of the antibody implicated in the aetiology of the disease.

Goodpasture's syndrome (nephritis and lung haemorrhage)

The first major application of plasma exchange in autoimmune disorders was the removal of anti-glomerular basement membrane antibodies found circulating in patients with Goodpasture's syndrome.³ This is a rare form of rapidly progressive glomerulonephritis in which the underlying pathogenetic mechanism is partly understood. Anti-glomerular basement membrane antibodies have been shown to fix on to glomerular basement membrane and to crossreact with lung basement membrane; this antibody when eluted from kidneys of patients with the disease can produce a severe nephritis in experimental animals.⁴⁵

Since the introduction of a treatment regimen with intensive daily plasma exchange combined with immunosuppressive drug therapy (azathioprine or cyclophosphamide, or both, plus prednisolone) the mortality for this disease has been reduced from over 90 to 25%.⁴⁶ Immunosuppressive therapy must be used to inhibit further antibody synthesis and to suppress inflammation. Further suppression of inflammation is thought to result from using plasma protein fraction as the replacement fluid, as this is devoid of non-specific inflammatory mediators such as fibrinogen and complement.³ The clinical response to this regimen appears to correlate well with changes in anti-glomerular basement membrane antibody concentration²¹ and it is recommended that any patient with this disease showing rapid deterioration of renal function accompanied by pulmonary haemorrhage should have immediate plasma exchange, for the prognosis worsens once anuria has occurred. Although the disease is rare in childhood, cases do occur and a combination of plasma exchange and immunosuppression can be successful.⁴⁷

Idiopathic thrombocytopenic purpura

Several workers have claimed remission of disease after plasma exchange in fulminant idiopathic thrombocytopenic purpura with demonstrable anti-platelet antibodies. A prompt rise in platelets has been achieved after a minimum of one and a maximum of four plasma exchanges. Novak and Williams⁴⁸ described an 8-year-old girl whose platelet count responded to one exchange but who died 48 hours later. In contrast Weir *et al.*⁴⁹ reported a patient who failed to respond; they suggested that a controlled trial should be carried out. However

fulminant idiopathic thrombocytopenic purpura is fairly rare and if a child presents with catastrophic complications, unresponsive to conventional treatment, and with demonstrable anti-platelet antibodies, a trial of plasma exchange is not unreasonable.

Haemophilia with circulating inhibitors

The development of autoantibodies to factor VIII or IX in haemophiliacs can present a major problem in management, particularly if operative procedures are necessary. Cobcroft *et al.*¹² showed that pre-operative plasma exchange for the removal of antibody and replacement with fresh frozen plasma and factor VIII concentrate enabled restoration of normal factor VIII levels, thus permitting an operative procedure to be undertaken safely. This is an example not only of the removal of the offending material but also of specific enrichment of the needed plasma factor. A new approach to this problem has been developed by Nilsson *et al.*⁵⁰ which may have much broader applications. Factor IX antibodies were removed by extracorporeal adsorption of plasma (separated intermittently in a Haemonetics Model 30) on columns of sterile protein-A-Sepharose, with retransfusion of the treated plasma. A total of 6 litres of the patient's plasma was depleted of antibodies in this manner enabling adequate factor IX substitution therapy and subsequent surgery to be undertaken safely. The patient's total immunoglobulin content and specific antibody level decreased to one-fifth of the original values, and in principle this form of treatment could be used in patients with other forms of antibodies.

Rh haemolytic disease of the newborn

In this situation it is the maternal circulation which must be cleared of the causative IgG red cell antibody to protect the fetus from haemolysis. It was Graham-Pole *et al.*¹⁵ who first demonstrated that an intensive plasma exchange regimen could reduce the maternal anti-D level and the degree of fetal haemolysis, thereby saving affected infants without resort to intrauterine transfusion even if the mother had had previous stillbirths. This work has been extended in other centres and has produced a success rate of 75% in a series in which the expected stillbirth rate was 62%.¹⁶ As a result plasma exchange started early in pregnancy can be recommended as a non-hazardous form of treatment in the management of severe Rh haemolytic disease.

As no concomitant immunosuppressive therapy is advisable to help control further antibody production, plasma exchange has to be done about twice a week for a mean period of 13½ weeks to maintain low antibody levels.¹⁶ However, should restimulation of the antibody occur by release of fetal Rh

D-positive cells into the maternal circulation, and should the rise in anti-D become impossible to control by plasma exchange alone, the only alternative is to use intrauterine transfusion. This problem may soon be overcome by the development of immunoadsorption columns in which specific removal of anti-D⁵¹ may prove possible.

Immune complex mediated. The logic of using plasma exchange for the treatment of immune complex disease is based on the following concepts: removal of the immune complex load, removal of antigen or antibody or both of these, alteration of the size and lattice formation of the immune complex and thereby possibly its pathogenicity, unblocking of the reticuloendothelial system, and the removal of non-specific inflammatory mediators.

Although the potential role of plasma exchange in immune complex disease appears greater than in antibody-mediated disease, the results are difficult to assess as many of these diseases are known to have spontaneous fluctuations in activity and most patients have been subjected to treatment with multiple drugs before the use of plasma exchange.

Systemic lupus erythematosus

The removal of immune complexes by plasma exchange in severe unresponsive systemic lupus erythematosus has been shown to be beneficial.^{20 21} Furthermore, studies on the levels of immune complexes in such cases have shown significant reductions in concentrations after plasma exchange. These levels continue to fall beyond the end of the plasma exchange period, supporting the concept that clearance of the reticuloendothelial system blockade is also achieved.^{52 53} Most workers have used plasma protein fraction as the replacement fluid but Moran *et al.*⁵⁴ suggested that patients with systemic lupus erythematosus respond better if fresh frozen plasma is used. They argue that in their 2 patients a more prolonged relief of symptoms and a better clearance of immune complexes was achieved by specific enrichment of complement present in fresh frozen plasma and often deficient in systemic lupus erythematosus. Further data are necessary before proper evaluation can be made, particularly as fresh frozen plasma carries the risk of further enhancing the inflammatory response by enrichment with non-specific inflammatory mediators. Few cases in children have been reported as systemic lupus erythematosus is rare in them. However, plasma exchange certainly has a place in rapidly progressive disease states that are not controlled by conventional drugs, and a course of plasma exchange combined with immunosuppressive therapy is a

logical step to take in the management of childhood systemic lupus erythematosus.

Presumed immunological. The problem with this group of disorders is that the underlying pathogenesis is poorly understood and the use of plasma exchange is often empirical. Plasma exchange should be regarded as a research procedure until properly controlled studies have shown a benefit.

Transplantation rejection

It is thought that acute vascular rejection may be mediated by humoral antibodies and the removal of such antibodies and other humoral factors by plasma exchange may help to prevent graft failure. Uncontrolled studies have been reported recently suggesting a favourable response to plasma exchange but none shows a statistically significant improvement in the overall graft survival.⁵⁵⁻⁵⁷ However, two recently reported controlled studies^{58 59} suggest that plasma exchange exerts no beneficial effect in transplantation rejection episodes and as a result of negative findings, it is no longer used in one unit.

Juvenile rheumatoid arthritis

As a result of earlier successes in 2 children with severe connective tissue disease^{30 60} Brewer *et al.*⁶¹ used plasma exchange to treat 4 children with severe juvenile rheumatoid arthritis, based on the belief that circulatory immune complexes and reticuloendothelial system blockade may be the pathogenetic factors in this disorder. Plasma exchange was associated with partial remission in 2 patients, and a corticosteroid sparing effect permitted normal pubertal growth in one patient who was steroid dependent and dwarfed.

There was no improvement in the characteristic eye lesions and no evidence that progression of erosive arthritis was prevented. One sudden death occurred during plasma exchange with fresh frozen plasma, the cause of death appeared related to microemboli of unknown nature found in the lungs at necropsy. In view of this episode these workers conclude that plasma exchange in children should be treated as a research procedure and should be performed only under conditions of intensive care.

Miscellaneous disorders

This group of disorders includes those in which known noxious agents are present in excess—for example cholesterol, poisons, phytanic acid; or those in which unknown noxious agents may be responsible for rapid disease progression—for example asthma and hypertension; or those in which certain specific factors are lacking—for example the

haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, or hypogammaglobulinaemia. The aim of plasma exchange is therefore removal of excess components or specific enrichment, or both.

Hypercholesterolaemia

Repeated plasma exchange at weekly or monthly intervals for periods of up to five years in 22 patients with severe hypercholesterolaemia has been shown safely and effectively to control cholesterol levels inducing regression of xanthomata and arrest or retardation of atheroma.³⁴

Although these results are striking the cost of the plasma protein fraction used in commercial terms is about £150 000 (1000 litres). Recently Borberg has described the use of specific sepharose adsorption columns for the removal of low density lipoproteins in plasma.⁶² This new technology could considerably reduce the cost and may well be more efficient than the present method of management.

Poisoning

Plasma exchange can be of benefit in the management of poisoning if the ingested material is protein bound and hence non-dialysable—for example methyl parathion (a pesticide)³⁵ or mushroom poisoning.³⁶ It has also been used effectively in sodium chlorate poisoning (weedkiller) for the removal of methaemoglobin and the degenerate cell debris produced by this powerful oxidant.⁶³

Mild accidental poisoning in children is common; however severe poisoning is rare and accounts for only about 15 deaths a year in England and Wales. Many of these fatal cases are due to the tricyclic antidepressants (for example amitriptyline and imipramine), iron, and digoxin, for which the potential use of plasma exchange in management has yet to be exploited.

Ninety-six per cent of circulating amitriptyline is reversibly bound to plasma protein and its half-life is between 44 and 75 hours; both these facts suggest that provided plasma exchange is technically feasible, it could prove invaluable in the management of this type of poisoning. The half-life of imipramine is much shorter (3½ hours), hence plasma exchange would be of benefit only if used within 3 hours of ingestion.

The problems of iron intoxication are created by the direct toxic effect of iron on the gastrointestinal tract leading to direct access to the portal circulation without transport across the intestinal mucosa.

This results in toxic levels of unbound serum iron, and although this is chelatable, continued release of free iron from its protein bound state necessitates repeated doses of desferrioxamine. If a combined therapeutic approach of chelation therapy and

plasma exchange were used, more rapid control might be achieved and previously unsalvageable cases be rescued.

The potential use of plasma exchange in digoxin intoxication is more difficult to predict as it is rapidly distributed to the tissues and is preferentially bound to the myocardium at a ratio of 200:1 compared with the amount circulating. Although only 25% of circulating digoxin is protein bound, its half-life is between 34 and 51 hours and plasma exchange could therefore provide a useful means of removing any remaining circulating digoxin before it becomes irreversibly tissue bound and thereby serve as a useful adjunct to more conventional therapy.

Refsum's disease (heredopathia atactica polyneuritis-formis)

This is an autosomal recessive lipid storage disorder characterised by chronic polyneuropathy, retinitis pigmentosa, and ichthyosis with raised blood levels of phytanic acid due to failure of α -oxidation of this fatty acid. Exacerbation of the disease correlates with a rise in blood level of phytanic acid, and improvement with a fall. Treatment in the past has been mainly by diet, but Gibberd *et al.*³⁷ recently achieved a good response in one patient by using large volume plasma exchange combined with a diet low in phytanic acid but of a high calorific value, thereby preventing mobilisation of phytanic acid from fat stores.

Early diagnosis and treatment of this disease by diet, and if necessary by plasma exchange, could lead to good long-term survival provided retinitis pigmentosa has not developed as this is irreversible.

Haemolytic uraemic syndrome

Recent hypotheses concerning the pathogenesis of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura suggest the absence of a plasma factor needed for prostacyclin production by vascular endothelium, or the presence of a circulating inhibitor to its production, or both of these.^{2 64} The belief being that defective prostacyclin activity favours the formation of platelet thrombi in the microcirculation, a finding typical of haemolytic uraemic syndrome and allied disorders. Two recently reported cases in which therapeutic plasma exchange with fresh frozen plasma as the replacement fluid was used in the management of childhood haemolytic uraemic syndrome appear to support this hypothesis.^{40 41} However the use of therapeutic plasma exchange for haemolytic uraemic syndrome should be reserved for children in whom the prognosis is poor, as our experience in the Leeds paediatric nephrology unit during the last 10 years

has been a mortality rate of less than 5% for children aged under 5 years. In both cases reported, plasma exchange was used during a recurrent phase of the disease, a recognised poor prognostic factor, although both children were under 5 at their initial presentation.^{40 41} If conventional forms of treatment fail to resolve the life threatening situation of severe thrombocytopenia, haemolytic anaemia, and hypertension, rapid resort to therapeutic plasma exchange may prove to be a rational and life-saving alternative in the management of severe haemolytic uraemic syndrome.

Problems

Plasma exchange is a fairly safe procedure with few adverse effects provided it is undertaken in an experienced unit. The most commonly encountered problems are citrate toxicity, management of fluid and electrolyte balance, hazards associated with the replacement fluids, and vascular access.

Anticoagulant. Citrate is the most commonly used anticoagulant in all cell separation techniques and temporary hypocalcaemia can be a recurring problem unless measures are taken to avoid it.⁶⁵

Fluid and electrolyte balance. If there is impaired renal function exact fluid and electrolyte balance are of paramount importance. As most of these patients are incapable of responding to any fluid or electrolyte imbalance during plasma exchange, care must be taken to ensure that the colloid osmotic pressure and the electrolyte content of any replacement fluid are within physiological limits. In childhood, volume changes pose a particular problem as the extracorporeal circulatory volume must be kept within the toleration limits of the child—that is less than 15% of the total blood volume to avoid hypotensive episodes. To minimise blood volume changes special paediatric equipment or the addition of red cell and fluid supplements to the extracorporeal circuit may be necessary.

Replacement fluids. Plasma protein fraction and fresh frozen plasma are the main replacement fluids used. Fresh frozen plasma has the advantage of being cheap; it is readily obtainable and helps to maintain normal immunoglobulins, coagulation factors, and complement components but it has the disadvantage that it can cause allergic reactions, citrate load, and can transmit hepatitis and sensitisation to proteins. Allergic reactions to fresh frozen plasma are not uncommon and other workers as well as ourselves have found a higher incidence in alloimmunised individuals and in patients with

autoimmune disorders than in the general hospital population.²⁶

Anaphylaxis is a serious hazard and unless fresh frozen plasma has been shown to have a therapeutic advantage over plasma protein fraction its use is not recommended. Plasma protein fraction does not appear to be allergenic and is free from the risk of transmitting hepatitis and sensitisation to protein; it is also devoid of inflammatory mediators. It has the disadvantage of being expensive and in short supply and when used in large volume exchanges it can give rise to a transient coagulopathy. It is also deficient in pseudocholinesterase which could give rise to a prolonged episode of suxamethonium-induced apnoea during anaesthesia unless fresh frozen plasma replacement is used before any anaesthetic procedure.⁶⁶ Hypotension in response to the rapid infusion of plasma protein fraction is seen occasionally in the USA and Australia, but this has not been reported in Europe and slight variations in methods of production must be responsible for these differences.

Occasionally combinations of commercial plasma expanders and plasma protein fraction or fresh frozen plasma have been used, but this generally gives rise to protein depletion and transient coagulopathy; some allergic reactions have also been reported.

Vascular access. A major problem encountered in childhood is adequate vascular access. This is essential to ensure a reasonable blood flow into the cell separator machine, otherwise plasma exchange cannot be undertaken. In the majority of cases intra-arterial or central venous lines or arteriovenous shunts have to be inserted with all their attendant risks.

From the foregoing list of problems it can be seen that plasma exchange in childhood is a more difficult and hazardous procedure than in adults. This may account for its fairly limited usage to date in paediatric practice. However its potential is exciting provided a rational approach is taken and its limitations are realised.

Limitations

Transient effect. Unless plasma exchange is used to remove short-lived non-recurring specific noxious agents—for example poisons—it can be regarded only as an emergency therapeutic measure used to interrupt a disease process whether mediated by antibodies, immune complexes, non-specific inflammatory mediators, or by other as yet unspecified humoral agents—either a lack of them or an excess. The rationale being the prevention of further

irreversible tissue damage occurring before more conventional treatment—such as drug immunosuppression—has become effective or before the damaged tissue or organ has had time to recover. Occasionally long-term treatment is indicated—for example in hypercholesteraemia—but this is a practicable proposition only if the interval between exchanges can be lengthened while still maintaining therapeutic benefit. At present plasma exchange is a fairly crude form of treatment, but with the advent of adsorption columns future prospects are brighter making the method more specific and obviating the need for any substitution fluid. The whole procedure then becomes cheaper, safer, and more satisfactory.

Cost

As therapeutic effectiveness is difficult to ascertain, the cost of the procedure must be taken into consideration. The current cost of undertaking one plasma exchange in childhood in terms of disposable equipment and plasma protein fraction used, is in the region of £150. This figure does not take into account the capital and revenue expenditure incurred by the running of an efficient cell separator unit; without experienced staff the procedure is impossible to carry out. It is foolhardy and potentially hazardous to attempt therapeutic cell separation procedures only occasionally with an inexperienced team, but the costs of running such units are high.

Conclusion

Plasma exchange is an exciting field which has given a new therapeutic approach to a variety of different disorders. Furthermore it has opened up the possibility of a combined approach using adsorption columns for the removal of the specific unwanted substance. By enabling the enrichment or depletion of a particular substance in the circulation it can be used as an investigative tool in the study of that substance's role in the disease process.

It is important that such studies are undertaken in units in which full laboratory assessment is possible and that controlled trials are undertaken in diseases where the therapeutic efficacy of plasma exchange is in doubt. To quote from a recently written article on plasma exchange, 'Its excessive use beyond its natural limitations could overshadow its intrinsic merits and hasten its decline.'⁴⁴

References

- Abel J J, Rowntree L G, Turner B B. Plasma removal with return of corpuscles (plasmapheresis). *J Pharmacol Exp Ther* 1914; **5**: 625–41.
- Remuzzi G, Marchesi D, Mecca G, *et al.* Haemolytic uraemic syndrome: deficiency of plasma factor(s) regulating prostacyclin activity? *Lancet* 1978; **ii**: 871–2.
- Lockwood C M, Rees A J, Pearson T A, Evans D J, Peters D K, Wilson C B. Immunosuppression and plasma exchange in the treatment of Goodpasture's syndrome. *Lancet* 1976; **i**: 711–5.
- Pinching A J, Peters D K, Newsom Davis J. Remission of myasthenia gravis following plasma exchange. *Lancet* 1976; **ii**: 1373–6.
- Dau P C, Lindstrom J M, Cassel C K, Denys E H, Shev E E, Spittler L E. Plasmapheresis and immunosuppressive drug therapy in myasthenia gravis. *N Engl J Med* 1977; **297**: 1134–40.
- Newsom Davis J, Wilson S G, Vincent A, Ward C D. Long term effects of repeated plasma exchange in myasthenia gravis. *Lancet* 1979; **i**: 464–8.
- Carruthers J A, Ewins A R. Herpes gestationis: studies on the binding characteristics, activity, and pathogenetic significance of the complement fixing factor. *Clin Exp Immunol* 1978; **31**: 38–44.
- Branda R F, Tate D Y, McCullough J J, Jacob H S. Plasma exchange in the treatment of fulminant idiopathic (autoimmune) thrombocytopenic purpura. *Lancet* 1978; **i**: 688–90.
- Branda R F, Moldow C F, McCullough J J, Jacob H S. Plasma exchange in the treatment of immune disease. *Transfusion* 1975; **15**: 570–6.
- Patten E, Reuter F P. Evans' syndrome: possible benefit from plasma exchange. *Transfusion* 1980; **20**: 589–93.
- Pintado T, Taswell H F, Bowie E J W. Treatment of life threatening hemorrhage due to acquired factor VIII inhibitor. *Blood* 1975; **46**: 535–41.
- Cobcroft R, Tamagnini G, Dormandy K M. Serial plasmapheresis in a haemophiliac with antibodies F VIII. *J Clin Pathol* 1977; **30**: 763–5.
- Isbister J P, Biggs J C, Penny R. Experience with large volume plasmapheresis in malignant paraproteinaemia and immune disorders. *Aust NZ J Med* 1978; **8**: 154–64.
- Clarke C A, Bradley J, Elson C J, Donohoe W T A, Lehane D, Hughes-Jones N C. Intensive plasmapheresis as a therapeutic measure in rhesus-immunised women. *Lancet* 1970; **i**: 793–8.
- Graham-Pole J, Barr W, Willoughby M L N. Continuous flow plasmapheresis in management of severe rhesus disease. *Br Med J* 1977; **i**: 1185–8.
- Robinson E A E, Tovey L A D. Intensive plasma exchange in the management of severe Rh disease. *Br J Haematol* 1980; **45**: 621–31.
- Gale R P, Feig S, Ho W, Falk P, Rippee C, Sparkes R. ABO blood group system and bone marrow transplantation. *Blood* 1977; **50**: 185–94.
- West N C, Clink H M, Powles R. Plasma exchange before marrow transplant. In the proceedings of the IBM Symposium on the Clinical Aspects of Cell Separation, London 1981.
- Muggeo M, Flier J S, Abrams R A, Harrison L C, Deisseroth A B, Kahn C R. Treatment by plasma exchange of a patient with auto-antibodies to the insulin receptor. *N Engl J Med* 1979; **300**: 477–80.
- Verrier Jones J, Cumming R H, Bucknall R C, *et al.* Plasmapheresis in the management of acute systemic lupus erythematosus? *Lancet* 1976; **i**: 709–11.
- Lockwood C M, Pussell B, Wilson C B, Peters D K. Plasma exchange in nephritis. *Adv Nephrology* 1979; **8**: 383–418.
- Lockwood C M, Rees A J, Pussell B A, Peters D K. Experience of the use of plasma exchange in the management of potentially fulminating glomerulonephritis and SLE. *Exp Hematol* 1977; **5**: Supplement, 117–36.

- 23 Pussell B A, Lockwood C M, Scott D M, Pinching A J, Peters D K. Value of immune complex assays in diagnosis and management. *Lancet* 1978; **ii**: 359-65.
- 24 Valbonesi M, Garelli S, Mosconi L, Camerone G, Bedarida G, Di Guardo G. Plasma exchange in the management of a patient with diffuse necrotizing cutaneous vasculitis. *Vox Sang* 1980; **39**: 241-5.
- 25 Cardella C J, Sutton D M C, Falk J A, Katz A, Uldall P R, de Veber G A. Effect of intensive plasma-exchange on renal transplant rejection and serum cytotoxic antibody. *Transplant Proc* 1978; **10**: 617-9.
- 26 Israel L, Edelstein R, Mannoni P, Radot E, Greenspan E M. Plasmapheresis in patients with disseminated cancer: clinical results and correlation with changes in serum protein. The concept of 'non-specific' blocking factors. *Cancer* 1977; **40**: 3146-54.
- 27 Hobbs J R, Byrom N, Elliot P, Oon C J, Retsas S. Cell separators in cancer immunotherapy. *Exp Hematol* 1977; **5**: Supplement, 95-103.
- 28 Wallace D J, Goldfinger D, Gatti R, *et al.* Plasmapheresis and lymphoplasmapheresis in the management of rheumatoid arthritis. *Arthritis Rheum* 1979; **22**: 703-10.
- 29 Rothwell R S, Davis P, Gordon P A, *et al.* A controlled study of plasma exchange in the treatment of severe rheumatoid arthritis. *Arthritis Rheum* 1980; **23**: 785-90.
- 30 Brewer E J, Jr, Giannini E H, Rossen R D, Patten B, Barkley E. Plasma exchange therapy of a childhood onset dermatomyositis patient. *Arthritis Rheum* 1980; **23**: 509-13.
- 31 Brettell R P, Gross M, Legg N J, Lockwood M, Pallis C. Letter: Treatment of acute polyneuropathy by plasma exchange. *Lancet* 1978; **ii**: 1100.
- 32 Littlewood R, Bajada S. Successful plasmapheresis in the Miller Fisher syndrome. *Br Med J* 1981; **282**: 778.
- 33 Valbonesi M, Garelli S, Mosconi L, Zerbi D, Celano I. Plasma exchange as a therapy for Guillain-Barré syndrome with immune complexes. *Vox Sang* 1981; **41**: 74-8.
- 34 Thompson G R. Plasma exchange for hypercholesterolemia. *Lancet* 1981; **i**: 1246-8.
- 35 Luzhnikov E A, Yaroslavsky A A, Molodenkov M N, Shurkalin B K, Evseev N G, Barsukov U F. Letter: Plasma perfusion through charcoal in methylparathion poisoning. *Lancet* 1977; **i**: 38-9.
- 36 Lembeck F, Beubler E, Lepuschütz H J, Stolze A. Plasmaphorese zur Elimination toxischer Stoffe mit hoher Plasmaproteinbindung. *Wien Klin Wochenschr* 1976; **89**: 257-60.
- 37 Gibberd F B, Page N G R, Billimoria J D, Retsas S. Heredopathia atactica polyneuritiformis (Refsum's disease) treated by diet and plasma exchange. *Lancet* 1979; **i**: 575-8.
- 38 Gartmann J, Grob P, Frey M. Letter: Plasmapheresis in severe asthma. *Lancet* 1978; **ii**: 40.
- 39 Whitworth J A, d'Apice A J F, Kincaid-Smith P, Shulkes A A, Skinner S L. Letter: Antihypertensive effect of plasma exchange. *Lancet* 1978; **i**: 1205.
- 40 Beattie T J, Murphy A V, Willoughby M L N, Machin S J, Defreyn G. Plasmapheresis in the haemolytic-uraemic syndrome in children. *Br Med J* 1981; **282**: 1667-8.
- 41 Sweny P, Winning A, Gross M L P, Moorhead J F. Letter: Plasmapheresis in the haemolytic-uraemic syndrome in children. *Br Med J* 1981; **282**: 2137.
- 42 Bukowski R M, King J W, Hewlett J S. Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. *Blood* 1977; **50**: 413-7.
- 43 Okuno T. Letter: Plasmapheresis for thrombocytopenia. *Lancet* 1978; **i**: 1095.
- 44 Pussell B A, Lockwood C M. Plasma exchange in immunological disorders. *IBM Medical Review* 1980; **2**: 22-9.
- 45 Dixon F J, Feldman J D, Vazquez J J. Experimental glomerulonephritis: the pathogenesis of a laboratory model resembling the spectrum of human glomerulonephritis. *J Exp Med* 1961; **113**: 899-920.
- 46 Kincaid-Smith P, d'Apice A J F. Plasmapheresis in rapidly progressive glomerulonephritis. *Am J Med* 1978; **65**: 564-6.
- 47 Siegler R L, Bond R E, Morris A H. Treatment of Goodpasture's syndrome with plasma exchange and immunosuppression. *Clin Pediatr (Phila)* 1980; **19**: 488-91.
- 48 Novak R, Williams J. Plasmapheresis in catastrophic complications of idiopathic thrombocytopenic purpura. *J Pediatr* 1978; **92**: 434-6.
- 49 Weir A B, Poon M C, McGowan E I. Letter: Plasma exchange for idiopathic thrombocytopenic purpura. *Lancet* 1978; **ii**: 689.
- 50 Nilsson Inga M, Jonsson S, Sundqvist S-B, Ahlberg Å, Bergentz S-E. A procedure for removing high titer antibodies by extracorporeal protein-A-Sepharose adsorption in hemophilia: substitution therapy and surgery in a patient with hemophilia B and antibodies. *Blood* 1981; **58**: 38-44.
- 51 Jonsson S, Håkansson L. Extracorporeal affinity chromatography of blood plasma over agarose beads. In the proceedings of the Fourth International Conference on Applied Affinity Chromatography and Allied Techniques, Sweden 1981.
- 52 Verrier Jones J. Plasmapheresis: great economy in the use of horses. *N Engl J Med* 1977; **297**: 1173-5.
- 53 Pussell B A, Lockwood C M, Bartolotti S R, Peters D K. Plasma exchange in immune-complex disease and Goodpasture's syndrome. In the proceedings of a Workshop on Plasma Cytapheresis, Mayo Clinic, April 1979.
- 54 Moran C J, Parry H F, Mowbray J, Richards J D M, Goldstone A H. Plasmapheresis in systemic lupus erythematosus. *Br Med J* 1977; **i**: 1573-4.
- 55 Riffe G, Chalopin J M, Turc J H, *et al.* Plasmapheresis in the treatment of renal allograft rejections. *Transplant Proc* 1979; **11**: 20-6.
- 56 Adams M B, Kauffman H M, Herbert L A, Hussey C V, Duquesnoy R J, Tomasulo P A. Plasmapheresis in the treatment of renal allograft rejection. *Proc Clin Dial Transplant Forum* 1979; **9**: 252-3.
- 57 Cardella C J, Sutton D M C, Falk J A, Katz A, Uldall P R, deVeber G A. Intensive plasma exchange, complement dependent microcytotoxicity, and renal transplant rejection. *Proc Eur Dial Transplant Assoc* 1977; **14**: 328-35.
- 58 Kirubakaran M G, Disney A P S, Norman J, Pugsley D J, Mathew T H. A controlled trial of plasmapheresis in the treatment of renal allograft rejection. *Transplantation* 1981; **32**: 164-5.
- 59 Power D, Nicholls A, Muirhead N, *et al.* Plasma exchange in acute renal allograft rejection: is a controlled trial really necessary? *Transplantation* 1981; **32**: 162-3.
- 60 Birdsall H H, Brewer E J, Rossen R D, Moake J L. Clinical improvement associated with hypocomplementemia following plasmapheresis. In: Dau P C, ed. *Plasmapheresis and the immunobiology of myasthenia gravis*. Boston: Houghton Mifflin, 1978: 191-8.
- 61 Brewer E J, Jr, Nickeson R W, Jr, Rossen R D, Person D A, Giannini E H, Milam J D. Plasma exchange in selected patients with juvenile rheumatoid arthritis. *J Pediatr* 1981; **98**: 194-200.
- 62 Borberg H. New perspectives in plasma exchange therapy. In the proceedings of the Advanced Blood Component Seminar. Haemonetics Research Institute European Meeting, Montreux, July 1981.

- ⁶³ Davison A M, Mascie-Taylor B H, Robinson A, Barnard D L. The use of plasma exchange, transfusion, and haemodialysis in the management of sodium chlorate intoxication. In: Sieberth H G, ed. *Proceedings of the International Symposium on Plasma Exchange, Cologne, June 1980*. Stuttgart: Schattauer, 1980: 373-4.
- ⁶⁴ Anonymous. Platelets, endothelium, and renal disease. *Lancet* 1979; ii: 890-1.
- ⁶⁵ Watson D K, Penny A F, Marshall R W, Robinson E A E. Citrate induced hypocalcaemia during cell separation. *Br J Haematol* 1980; 44: 503-7.

- ⁶⁶ Evans R T, Macdonald Rosemary, Robinson Angela. Suxamethonium apnoea associated with plasmapheresis. *Anaesthesia* 1980; 35: 198-201.

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