

GUIDELINES FOR THE USE OF THERAPEUTIC PLASMA EXCHANGE (TPE) IN RENAL DISEASE

REASON FOR ISSUE: Update and revision of Terminology to align with ASFA.

BACKGROUND

For a majority of renal diseases, there are few prospective controlled clinical trials with adequate statistical power to allow definitive conclusions to be reached regarding the efficacy of therapeutic plasma exchange (TPE). The clinical application of TPE is still largely based on anecdotal or uncontrolled studies. In many diseases where TPE is used, it is difficult to evaluate whether any improvement can be attributed to the TPE. National registries have been founded to compensate for this lack of evidence. More recently there has been concerted reexamination of the efficacy of therapeutic plasma exchange in renal diseases. These guidelines specify plasma exchange regimens for diseases in which there is some evidence to support its use. The criteria for initiating and stopping apheresis and the frequency of apheresis and number of procedures are important components of the guidelines. Supportive evidence has assigned each potential indication into 1 of 4 categories which is in line with the American Society of Apheresis Guidelines:

- I. TPE is standard and acceptable.
- II. TPE is generally accepted but considered to be supportive or adjunctive to other more definitive treatments.
- III. TPE has a suggestion of benefit but existing evidence is insufficient.
- IV. TPE shows no demonstrated value in controlled trials or anecdotal reports have been discouraging.

PROTOCOLS

1. Transplantation-Renal: Antibody Mediated Rejection and HLA Desensitization-Category II Indication.

There is no good evidence to suggest a role for TPE in hyperacute and chronic rejection. The results of a few uncontrolled series have been disappointing in chronic rejection. For patients with **acute graft rejection** results of a few randomised controlled trials indicate a trend towards superior graft survival in patients receiving TPE. However, the evidence remains weak. The use of **C4d staining** in peritubular capillaries as a correlate of acute humoral rejection may be useful. Some centres require biopsy-proven humoral rejection prior to accepting patients for the procedure. However, The Johns Hopkins protocol is probably the most pragmatic. Recently published data suggest that donor-directed HLA antibodies often develop well before the biopsies become positive by C4d staining. This is probably the first important test to do to diagnose humoral rejection.

- **TPE should be considered** a therapeutic option when a diagnosis of antibody mediated rejection has been confirmed by a renal biopsy and/or donor-directed HLA antibodies have been demonstrated and treatment with immunosuppressive treatment has not made any difference.
- It is **recommended that** 1-1.5 total plasma volume TPE be performed daily or every other day. and after a certain number of procedures, usually 5 to 6, this is **followed by maintenance** TPE. Albumin is the usual replacement fluid. Although creatinine levels can be used to monitor graft function, biopsy proven response to treatment will be required in some cases.

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- TPE can also be used prior to transplant to remove HLA antibodies. The desensitization protocols should be used in highly selected cases.
- The decision to discontinue plasmapheresis should be based on one of the following:
 - 1) elimination of donor-directed HLA antibody
 - 2) establishment of good graft function
 - 3) graft failure

2. Focal Segmental Glomerulosclerosis FSGS – Recurrent in Transplanted Kidney – Category 1 Indication

Although several renal diseases can be successfully treated with post transplant TPE, the **end points in terminating the treatments are not well defined**. Several authors have reported on the successful use of apheresis in patients with Recurrent Focal and Segmental Glomerulosclerosis (FSGS) in the transplanted kidney. Evidence suggests that treatment should be initiated promptly after the appearance of proteinuria. It must be noted that similar results have not been obtained in patients with primary disease

- It is recommended that therapeutic plasma exchange be initiated soon after diagnosis in cases of recurrent disease especially so in patients with Focal and Segmental Glomerulosclerosis. One accepted protocol is to perform 1-1.5 total plasma volume exchanges with albumin replacement daily or every other day. Usually a minimum of nine to 10 procedures is followed by tapering which is determined on a case by case basis.
- Improvement or normalisation in clinical status, proteinuria, haematocrit, LDH, peripheral blood picture, and haptoglobin may all be used as criteria for successful treatment. Control of proteinuria can take several weeks to months. Some patients have received long-term monthly exchanges as maintenance therapy.
- Return of **renal function should not be used as a sole criterion** for the termination of the procedure.

3. Anti- Glomerular Basement Membrane Disease - Anti-GBM (Goodpasture Syndrome)- Category I Indication.

Results of a single randomized, controlled study and that of other non-randomized and case controlled studies suggest that TPE does provide a more rapid decline in the serum levels of the anti-GBM antibody, a lower post-treatment serum creatinine level and a decreased incidence of end-stage renal disease. The degree of renal impairment has a bearing on the effectiveness of apheresis. It is critical that TPE be implemented early in the course of anti-GBM Disease. It has been suggested that patients who are dialysis dependent at presentation do not benefit from TPE and it should not be performed unless pulmonary haemorrhage is present. However, ASFA Guidelines maintains a Category 1 indication for this category of patients. Reviews suggest that avoidance of End Stage Renal Disease can be achieved in 40-45% of patients.

- The usual **recommendation is for daily or every other day TPE for a minimum of 14 days** with continued apheresis required if antibody titres are still elevated. Albumin and/or plasma can be used as replacement fluid.

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4. Vasculitis, ANCA – Associated AAV)

Much of the published experience with TPE includes all forms of Rapidly Progressive Glomerulonephritis(RPGN), not just exclusively Wegener's disease or ANCA-associated RPGN. This has complicated interpretation of results. However, subset analysis reveals that apheresis was found to be beneficial for those patients presenting **with severe disease or are dialysis dependent**. A controlled trial of ANCA associated RPGN suggests TPE may improve prognosis even in nondialysis dependent patients. A retrospective case series reported effective management of pulmonary haemorrhage in ANCA vasculitis.

- Daily or every other day 1 to 1.5 total plasma volume TPE is recommended with albumin as replacement fluid. Consider daily procedures in fulminant cases or with pulmonary haemorrhage. Plasma should be used as replacement fluid in diffuse alveolar haemorrhage (DAH).
- A total 7 over a median period of 14 days is usually recommended. Up to 12 procedures has reported further improvement in patients with severe renal failure or DAH.

5. Vasculitis, IgA(Henoch-Schönlein Purpura)- Category III Indication

A percentage of patients with IgA nephropathy will progress to end stage renal disease. There are a smaller percentage who present with Rapidly Progressive Glomerulonephritis. The removal of circulating IgA by plasmapheresis has been shown to be successful in the amelioration of both acute and chronically progressive disease. Presently chronic disease is treated with fish oil and angiotensin converting enzyme inhibitors and apheresis maintains a role in acute disease.

- It is recommended that patients with rapidly progressive glomerulonephritis related to Henoch-Schönlein purpura should be considered as candidates for apheresis. The recommended schedule is **thrice weekly for 2 weeks and then weekly for 6 weeks. In severe manifestations, the course of therapy has ranged from 1-11 daily plasma exchanges with discontinuation of TPE upon resolution of symptoms.**

6. Systemic Lupus Erythematosus- Category III-IV Indication.

Randomised, controlled trials have not been able to document a generalised benefit to apheresis when added to standard immunosuppressive therapy. However, in a subgroup of patients, particularly those with nephrotic syndrome resistant to cyclophosphamide, during pregnancy when cytotoxic agents are undesirable and in lupus associated conditions such as hyperviscosity, cryoglobulinaemia, pulmonary haemorrhage, CNS involvement and thrombotic microangiopathy, plasma exchange may be considered. No specific protocol can be recommended, although thrice weekly 1-1.5 total plasma volume exchanges with albumin and/or plasma as replacement fluid is suggested with evaluation at the end of seven procedures.

7. Catastrophic Antiphospholipid Syndrome (CAPS)-Category I Indication.

Optimal therapy is still debatable since there have been no prospective studies due to the rarity of the condition. There have been reports describing the use of apheresis for the removal of anti-phospholipid antibodies in order to avoid spontaneous abortion as well as to treat catastrophic anti-phospholipid syndrome. However, experience with apheresis in the removal of these antibodies in renal disease is limited. A minimum of 3 to 5 1-1.5 total plasma volume procedures is recommended

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with plasma alone or in combination with albumin as replacement fluid. Discontinuation is based on clinical response. Some patients have been treated for weeks.

8. Cryoglobulinaemia- Category I Indication.

TPE removes cryoglobulins efficiently and has been used in active moderate to severe disease with renal disease (membranoproliferative glomerulonephritis), neuropathy, vasculitis, and/or ulcerating purpura. Despite a lack of high level evidence, there have been many case reports and uncontrolled studies indicating the successful use of apheresis as adjunctive treatment of severe, active disease as manifested by progressive renal failure. 1-1.5 total plasma volume exchanges with albumin as replacement fluid is recommended. For acute symptoms 5-6 procedures are recommended with re-evaluation for clinical benefit. Weekly to monthly maintenance treatments may be necessary in responsive patients to prevent recurrent symptoms.

9. Myeloma with Acute Renal Failure- Category III Indication.

A case can be made in patients with suspected cast nephropathy since apheresis can lower the serum levels of toxic light chains more rapidly than can be achieved with chemotherapy alone. All studies combine TPE with chemotherapy and other forms of supportive care. Controlled trials have employed TPE as short-term adjunct to chemotherapy and fluid resuscitation over the period of 2-4 weeks. Procedure- 1-1.5 total plasma volume exchange daily or every other day with albumin replacement.

10. Thrombotic microangiopathy (TMA), complement mediated and Thrombotic Microangiopathy, Thrombotic Thrombocytopenic Purpura (TTP) – Category I Indication

Two types of HUS have been described: diarrhoea-associated HUS (d+ HUS or typical HUS) and non-diarrhoea-associated HUS (d- HUS) or atypical HUS (aHUS) now called complement-mediated thrombotic microangiopathy. In children with d+HUS, supportive care is the mainstay of therapy. TPE has no proven role in d+HUS in children. For aHUS in children TPE seems to be a reasonable option considering the poor prognosis of aHUS. In patients with non-idiopathic thrombotic microangiopathy, aHUS, or TMA, TPE may be appropriate under certain circumstances particularly where suspicion for TTP remains high. Alternatively, for aHUS and TMA conditions TPE should be abandoned if no response to an initial therapeutic trial. TPE is no longer considered a standard care for TMA following HPC transplant.

Eculizumab, a humanized anti-C5 monoclonal antibody is recommended by several guidelines as the front-line therapy for aHUS. Empiric TPE is recommended while investigations for TTP and other forms of TMA are in progress or if eculizumab is not available. Decisions on duration or to discontinue TPE should be made based on patient response and condition.

For TTP initially daily therapy is recommended with tapering of frequency based on response. 1-1.5 volume plasma exchange with plasma as replacement fluid is standard protocol. The aim is to achieve a durable remission (e.g. platelet count $> 150 \times 10^9/L$, LDH near normal and no neurologic deficit, if initially present). A therapeutic trial using a limited number of procedures is appropriate for selected cases. For responding patients, TPE is continued from less than a week to extended period to maintain a remission. The decision to taper or stop abruptly is an empirical decision. Daily TPE should be reinitiated with exacerbation (recurrent disease less than 30 days of TPE) or relapse (recurrent disease greater than 30 days of complete remission) among responding patients.

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11. Transplantation, Renal, ABO incompatible

Isoagglutinins (ABO- antibodies) represent a major barrier in optimizing living kidney donation. Transplantation across the blood group barrier can result in hyperacute antibody-mediated allograft rejection. TPE before and after transplantation in conjunction with immunosuppressive treatment is the current commonly used desensitization protocol used in these patients.

TPE can reduce high titre antibodies, which are responsible for humoral rejection of the solid organ. Replacement fluid is 4% Albumin with or without plasma compatible with both recipient and donor or group AB depending on presence or absence of coagulopathy or imminent surgery. 1-1.5 daily or alternate day TPE with the aim to reduce isoagglutinin titres. This could range from 4-16 in renal transplantation. This titre can be achieved in usually 2-5 days, depending on baseline titres. The antibody titre may increase 3-7 days posttransplantation; therefore, daily or alternate day antibody titre for the first 2 weeks posttransplantation is necessary. If the antibody titre is high with or without humoral rejection, plasma exchange should be performed again in the posttransplantation period. If the antibody titre can be maintained at less than 1:8 in the first week and posttransplant and 1:16 in the second week, the risk of humoral rejection is decreased.

12. Transplantation, Renal, ABO Compatible: Antibody mediated rejection (AMR), Desensitization, living donor – Category I Indications

In AMR TPE is performed in conjunction with other immunosuppressive drugs. Controlled studies since 1985 have shown improvement when TPE is used patients with acute vascular rejection in combination with a variety of anti-rejection medications.

For desensitization prior to transplant patients TPE is useful in carefully selected patients. The aim is to achieve a negative crossmatch.

For AMR TPE is performed daily or every other day.