Category IV Indications for Therapeutic Apheresis—ASFA Fourth Special Issue

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The American Society for Apheresis (ASFA) Committee on Clinical Applications systematically and critically reviews published information on the use of therapeutic apheresis in clinical practice. On the basis of this review, selected diseases are assigned one of five categories (category I, II, III, IV, and P). The diseases, which were classified as category IV indications, and the rationale for such assignment are reviewed in this article. The diseases assigned to category I, II, III, and newly created category P are discussed in a separate article in this issue. 

INTRODUCTION

The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. This elaborate process had been undertaken every 7 years resulting in three prior publications in 1986, 1993, and 2000 of “The ASFA Special Issues” [1–3]. The Fourth ASFA Special Issue is significantly modified in comparison with the previous editions. A new concept of a fact sheet has been introduced. The fact sheet succinctly summarizes the evidence for the use of therapeutic apheresis. All diseases assigned category I–III as well as category P (pending) are discussed in a separate article in this issue [4].

The category IV indication is used for diseases that therapeutic apheresis has shown no benefit in randomized controlled trials or where there is a consistent lack of efficacy among multiple case series/case reports [1–3,5]. Therapeutic apheresis should not be used to treat diseases in category IV except within the context of an IRB-approved research protocol. Some diseases listed herein were specified as category IV indications in the 2000 ASFA Clinical Applications guidelines [2]. Others have been added to provide a more complete list of diseases for which existing data fail to support the use of a therapeutic apheresis modality. In one case, the use of plasma exchange for acute humoral (vascular) rejection of a renal allograft, new data have resulted in a change from a category IV indication in 2000 to a category III indication in 2007 [4]. Diseases may have some presentations or apheresis treatment modalities which are category IV and others which are category I–III. Those presentations and apheresis treatment modalities that are category I–III are discussed in the accompanying article [4] with only the category IV indications discussed here. An example of different categories based upon disease presentation is systemic lupus erythematosus (SLE). The

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use of therapeutic plasma exchange (TPE) to treat lupus nephritis is a category IV while the use to other disease treat manifestations is a category III. An example of different categories for different apheresis treatment modalities in the same disease is idiopathic thrombocytopenic purpura (ITP). The use of TPE to treat ITP is a category IV while treatment of this disorder with immunoadsorption (IA) is a category II. All diseases assigned category IV are listed in Table I.

### Amyloidosis, Systemic

**Procedure:** Therapeutic plasma exchange.

**Rationale for category IV:** The most common forms of acquired systemic amyloidosis involve the deposition of protein aggregates and amyloid fibrils composed of immunoglobulin light chain (AL amyloidosis), serum amyloid A protein (AA amyloidosis), or β2-microglobulin (dialysis-related amyloidosis; DRA). Case reports and small case series have described the use of specialized adsorption columns or membrane filters to remove β2-microglobulin, serum amyloid A, or light chains. Anecdotally, TPE has been used in combination with hemodialysis in two patients with AL amyloidosis and renal failure, one of whom had amyloid arthropathy. However, no positive data exist, supporting the use of TPE for neuropathy or other complications associated with AL, DRA, or AA amyloidosis [6–8].

### Amyotrophic Lateral Sclerosis

**Procedure:** Therapeutic plasma exchange and leukocytapheresis.

**Rationale for category IV:** Multiple small series and a small controlled trial in the late 1970s and early 1980s failed to show any benefit for TPE alone or TPE in combination with immunosuppressive therapy for patients with ALS [9–11].

### Cutaneous T-Cell Lymphoma, Nonerythrodermic

**Procedure:** Extracorporeal photopheresis.

**Rationale for category IV:** The most effective treatment for erythrodermic (stage T4) mycosis fungoides (see Cutaneous T Cell Lymphoma; Mycosis Fungoides fact sheet) and should be considered as first-line therapy for patients at that stage of disease, therefore it is a category I in this setting [4,12,13].

### Dermatomyositis or Polymyositis

**Procedure:** Therapeutic plasma exchange and leukocytapheresis.

**Rationale for category IV:** The benefit of TPE was initially suggested by early anecdotal reports in pediatric patients and two large retrospective case series that described improvement following prolonged courses of TPE in conjunction with oral immunosuppressives. In a prospective, randomized, sham-controlled trial, 39 corticosteroid refractory patients with inflammatory myopathies were assigned to treatment with TPE, leukocytapheresis, or sham apheresis in double-blind fashion. All patients were maintained on prednisone. Although serum levels of muscle enzymes decreased significantly with TPE and lymphocytes decreased with leukocytapheresis, no significant differences were seen among the three

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**TABLE I. Category IV Indications for Therapeutic Apheresis**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Procedure</th>
<th>ASFA 2007</th>
<th>ASFA 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis, systemic</td>
<td>TPE</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Cutaneous T-cell lymphoma, nonerythrodermic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ECP</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Dermatomyositis or polymyositis</td>
<td>TPE</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>Diarrhea associated pediatric hemolytic uremic syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>TPE</td>
<td>IV</td>
<td>III</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>TPE</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Rheumatoid arthritis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TPE</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Scleroderma/progressive systemic scleosis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ECP</td>
<td>IV</td>
<td>NC</td>
</tr>
<tr>
<td>Systemic lupus erythematosus, nephritis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TPE</td>
<td>IV</td>
<td>NC</td>
</tr>
</tbody>
</table>

ECP, extracorporeal photopheresis; LCP, leukocytapheresis; NC, not categorized; TPE, therapeutic plasma exchange.

<sup>a</sup>These diseases are also discussed in the fact sheet format in the main article of this Special Issue as noted in the text [4].
Diarrhea-Associated Pediatric Hemolytic Uremic Syndrome

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TMA) predominantly affecting the kidneys. HUS is characterized by the triad of microangiopathic hemolytic anemia (MAHA, schistocytes on peripheral blood smear), thrombocytopenia, and acute renal failure. Two types of HUS have been described: diarrhea-associated HUS (d+ HUS) and nondiarrhea-associated HUS (d− HUS). d+ HUS is the most common form and occurs about a week after onset of bloody diarrhea caused by Shiga toxin-producing bacteria, predominantly Escherichia coli O157:H7, in about 6% of patients (9–30% of children). In children with d+ HUS, acute renal failure predominates but the majority recovers spontaneously with a mortality rate of 3–5%. In d+ HUS, Shiga toxins may attach to glomerular capillary endothelial cells and stimulate endothelial cells to release “unusually large” von Willebrand factor (UL-vWF) multimers from the Weibel–Palade bodies. In addition, Shiga toxin may activate platelets and promote adhesion and aggregation of platelets onto UL-vWF multimers. In children with d+ HUS, supportive care is the mainstay of therapy, including RBC transfusion, dialysis, and renal transplantation if indicated. Corticosteroids, plasma infusion, or plasma exchange have no proven role in d+ HUS in children, and therefore this disorder is a category IV indication for TPE. By comparison, atypical HUS (including d− HUS), d+ HUS in adults, and TMA are category III indications and thrombotic thrombocytopenic purpura (TTP) is a category I indication for TPE (see Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome: Thrombotic Microangiopathy; and Transplant Associated Microangiopathy fact sheets) [4,16,17].

Idiopathic Thrombocytopenic Purpura

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Anecdotal case reports and small case series of patients with chronic idiopathic thrombocytopenic purpura (ITP) have described a potential benefit for TPE when combined with other salvage therapies, such as prednisone, splenectomy, intravenous immunoglobulin (IVIG), and cytotoxic agents. Responses with combination therapy were often transient. No improvement was reported among five patients who underwent TPE for refractory ITP after splenectomy. In one controlled trial, the 6-month response rate and rate of splenectomy were no different among 12 patients who received TPE plus prednisone compared to seven patients treated with prednisone alone. In contrast to the category IV, indication for TPE, chronic, refractory ITP is a category II indication for extracorporeal IA with protein A (see Idiopathic Thrombocytopenic Purpura fact sheet) [4,18–20].

Inclusion Body Myositis

Procedure: Therapeutic plasma exchange and leukocytapheresis.

Rationale for category IV: A single case report described a patient with biopsy confirmed inclusion body myositis (IBM) who received 22 leukocytapheresis procedures combined with prednisone and azathioprine. After improvement, during the early induction phase with frequent cytaphereses, the clinical response was subsequently lost during a maintenance course with less frequent procedures. One uncontrolled study reported improved muscle strength in 32 of 35 patients with treatment-resistant idiopathic inflammatory myopathy after weekly TPE was performed for up to 10 weeks together with either cyclophosphamide or chlorambucil. However, the diagnosis of IBM was not specified and the potential role of TPE in these responses could not be determined. The lack of benefit for TPE and leukocytapheresis in patients with other inflammatory myopathies casts further doubt on the utility of these modalities for IBM [15,21,22].

POEMS Syndrome

Procedure: Therapeutic plasma exchange.

Rationale for category IV: POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes) is a rare multisystem paraneoplastic syndrome usually associated with an underlying plasma cell proliferative disorder. Patients with POEMS have undergone TPE because they were initially thought to have chronic inflammatory demyelinating polyneuropathy (CIDP). A few reported cases have described benefit for double filtration plasmapheresis and IA. Among 30 patients with POEMS treated with TPE, no responses were seen among the 16 who received TPE alone. The response rate was 20% among 14 patients who received TPE with concurrent corticosteroids, but this rate was similar to the response rate with steroid therapy alone. Thus, TPE is likely to be ineffective for this disorder [23,24].

Psoriasis

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Psoriasis is a chronic skin disorder with a high genetic predisposition. The plaques and papules are a result of hyperproliferation and abnormal differentiation of the epidermis. One small controlled trial and one small series showed that TPE provides no benefit in the treatment of psoriasis [25,26].
Rheumatoid Arthritis

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease of unknown etiology with a high genetic predisposition. The most characteristic feature is an inflammatory synovitis (relapsing or persistent), usually involving peripheral joints in a symmetric distribution. Two small controlled trials did not show benefit with TPE in patients with refractory RA, and therefore this disorder is a category IV indication for TPE. By comparison, benefit has been shown with extracorporeal IA with protein A in patients with RA refractory to other therapies; thus, refractory RA is a category II indication for this apheresis modality (see Rheumatoid Arthritis fact sheet) [4,27,28].

Schizophrenia

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Schizophrenia is a chronic psychiatric disorder with psychosis and deterioration in function. A double-blind, randomized trial of TPE versus sham-apheresis demonstrated no benefit [29].

Scleroderma/Progressive Systemic Sclerosis

Procedure: Extracorporeal photopheresis.

Rationale for category IV: Systemic sclerosis, or scleroderma, is characterized by the accumulation of connective tissue in skin and viscera. Three randomized trials have been performed using ECP on patients with scleroderma. An early multicenter study of 79 patients with recent onset and progressive scleroderma showed improvement in skin and joint parameters at 6 months among those receiving ECP compared to a lack of improvement among those treated with D-penicillamine. A more recent crossover trial of 19 patients with progressive systemic sclerosis of less than 5 years’ duration revealed no benefit of ECP with regard to skin score or quality of life after 1 year of treatment. The latest multicenter trial randomized 64 patients with a diagnosis of scleroderma of less than 2 years’ duration to either active or sham photopheresis on two consecutive days every month without concomitant treatments. At the end of 12 months, improvements were observed in the skin scores and mean joint involvement in both groups. Although the improvements in the cohort receiving ECP were greater than those among sham-treated patients, the difference did not reach statistical significance. Confirmatory evidence for a benefit of ECP in a randomized clinical trial setting is therefore still lacking. By comparison, scleroderma is a category III indication for TPE (see Scleroderma/Progressive Systemic Sclerosis fact sheet) [4,12,30–32].

Systemic Lupus Erythematosus, Nephritis

Procedure: Therapeutic plasma exchange.

Rationale for category IV: Lupus nephritis is a common complication of systemic lupus erythematosus (SLE). SLE is a chronic autoimmune disorder caused by autoantibodies leading to complement-mediated tissue injury. A controlled trial of TPE plus prednisone and cyclophosphamide versus prednisone and cyclophosphamide in patients with severe lupus nephritis showed no benefit of TPE. Smaller later trials have supported these data. By comparison, some other presentations of SLE are a category III indication for TPE (see Systemic Lupus Erythematosus fact sheet) [4,33–35].

REFERENCES


