Therapeutic Plasma Exchange in Renal Diseases

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ABSTRACT

Plasma exchange has been used extensively for over 2½ decades to treat a variety of renal diseases. In this article, the scientific rationale for therapeutic plasma exchange in primary and secondary glomerulonephritis, thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome, myeloma cast nephropathy, and allograft rejection are reviewed. The clinical studies that evaluate its efficacy are summarized, with special emphasis on the results of randomized controlled trials, when available. Consensus plasma exchange regimens are presented for diseases in which there is evidence to support its use.

Key Words: Plasmapheresis, glomerulonephritis, vasculitis, multiple myeloma, HUS/TTP

"Plasma exchange" refers to the removal of large quantities of plasma (usually 2 to 5 L) from a patient and replacement by either fresh-frozen or stored plasma. The procedure is frequently referred to as "plasmapheresis" when a solution other than plasma (e.g., isotonic saline) is used as replacement fluid ("apheresis" from the Greek for "to remove" or "to take away"). Apheresis technology was initially developed in the 1950s to harvest peripheral blood cells from healthy donors for transfusion into patients (1,2). Subsequently, the techniques were introduced widely, usually based on anecdotal or uncontrolled studies, as primary or adjunctive treatment for an array of human conditions in which "circulating factors" were believed to contribute to disease pathophysiology. The 1980s and 1990s have witnessed a more rigorous re-examination of the efficacy of therapeutic plasma exchange (2-6).

SCIENTIFIC RATIONALE

Table 1 summarizes some potentially beneficial actions of plasma exchange. The technique is used most frequently to modulate humoral components of the immune response and rapidly lower circulating titers of autoantibodies (e.g., anti-glomerular basement membrane disease) or immune complexes (e.g., cryoglobulinemia), while immunosuppressive therapy suppresses de novo antibody production (1). Plasma exchange has also been proposed as a useful adjunct to chemotherapy for the removal of circulating immunoglobulin (lg) or Ig components in multiple myeloma and other dysproteinemias (7). In addition, plasma exchange is utilized for the removal of components other than lg, such as thrombotic factors (e.g., in thrombotic thrombocytopenic purpura) (8) or other putative toxic mediators (e.g., focal segmental glomerulosclerosis) (9). Infusion of normal plasma may itself have beneficial effects, independent of removal of abnormal circulating factors. Indeed, there is compelling evidence that replacement of a deficient plasma component contributes to, and may be the principal mechanism of action of plasma exchange in thrombotic thrombocytopenic purpura (TTP) (10). Finally, many other theoretical effects on immune function have been proposed. These include depletion of complement products, fibrinogen, and possibly cytokines, improvement in reticuloendothelial system function (11,12) and immunomodulatory actions such as alterations in idiotypic/anti-idiotypic antibody balance (13,14). The influence of plasma exchange on cellular immune mechanisms, if any, are poorly defined.

TECHNICAL CONSIDERATIONS

The technical aspects of plasma exchange are discussed extensively in most major textbooks of dialysis (e.g., References 15,16). The basic components of any modality of plasma exchange are withdrawal of venous blood, separation of plasma from cellular components, and reinfusion of cellular elements plus either autologous plasma or an alternate replacement solution. Plasma is separated from blood cells by either centrifugation or membrane filtration (Figure 1). At present, there are two types of centrifugation devices: intermittent and continuous. With intermittent devices, blood is drawn in successive batches and separated into its components. These cycles are repeated as often as necessary to obtain the desired volume of plasma to be removed (usually, the equivalent of one plasma volume or 2.5 to 4.0 L is removed during a session). Advantages of intermittent devices are the simplicity of operation, the portability of the machines, and the possibility of a single-needle pe-
TABLE 1. Possible mechanisms of action of plasma exchange in kidney diseases

| Removal of an abnormal circulating factor or a physiologic factor produced in excess: |
|-----------------------------------|------------------------------|
| Antibody (anti-GBM disease)       |
| Immune complexes (lupus nephritis, cryoglobulinemia) |
| Myeloma protein (myeloma cast nephropathy) |
| Toxic factor ? (TP/HUS, FSG\(^a\)) |
| Replacement of a deficient plasma factor: |
| Thrombotic thrombocytopenic purpura |
| Other effects on the immune system: |
| Removal of inflammatory mediators |
| Improvement in reticuloendothelial system function |
| Effects on immune regulation |

\(^a\) TP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; FSG, focal segmental glomerulosclerosis.

Membrane technology provides an alternative to centrifugal devices. The patient’s blood is pumped through a parallel-plate or hollow-fiber filter at a continuous blood-flow rate, typically of 50 to 200 mL/min (Figure 1B). The membranes usually have pore diameters of 0.2 to 0.6 μm, sufficient to allow passage of plasma while retaining cellular elements. The separated plasma is collected and weighed at regular intervals (every 15 to 30 min) and the infusion rate of the replacement fluid is adjusted manually or automatically to maintain a stable circulating intravascular volume. Compared with centrifugal devices, membrane filtration has several advantages. Equipment requirements are relatively minimal; only a blood pump and pressure monitors are required. Membrane filtration can thus be performed by using standard hemodialysis-delivery equipment and patients with acute renal failure who require hemodialysis and plasmapheresis can receive both sequentially, using the same dialysis machine. The procedure time depends on the blood-flow rate through the device and the patient’s hematocrit value. In general, a plasma removal rate of 30 to 50 mL/min can be expected with a blood-flow rate of 100 mL/min. Thus, the average time required to perform a typical membrane filtration is less than 2 h. On the other hand, membrane filters have potential problems related to the exposure of circulating blood to an artificial surface, such as cell damage and complement activation (although the clinical significance of the latter has yet to be determined). Also, insertion of a large vein catheter is always required to obtain adequate blood-flow rates.

In terms of efficacy, membrane filtration has been shown to be as safe and efficient as centrifugal plasmapheresis (17). The primary difference between the techniques in economic terms is the cost of equip-
The typical replacement fluids are fresh-frozen or stored plasma, 5% albumin, or other plasma derivatives (e.g., purified protein fraction), and crystalloids (e.g., 0.9% saline, Ringer's lactate solution) (15). The choice of replacement fluid has major implications for the efficacy of the procedure, oncotic pressure, coagulation, and potential side-effects. Albumin or purified protein fraction is usually preferred to plasma, given the potential risks of hypersensitivity reactions and transmission of viral infections with the latter. In this regard, albumin (5%) is generally combined with 0.9% saline on a 50%/50% (vol/vol) basis. The precise composition of replacement fluids should be tailored to the needs of individual patients and diseases. For example, plasma may be more prudent in patients at high risk of bleeding (e.g., severe liver disease, disseminated intravascular coagulation, hemolytic uremic syndrome [HUS]/TTP, etc.) or requiring intensive therapy (e.g., daily exchanges for weeks) (6).

INTERPRETATION OF CLINICAL TRIALS EVALUATING THE EFFICACY OF PLASMA EXCHANGE: GENERAL COMMENTS

Before examining the published studies on the efficacy of plasma exchange in renal diseases, several general considerations that may complicate data interpretation deserve mention. First, there are few prospective controlled clinical trials of adequate statistical power to allow definitive conclusions to be reached regarding the therapeutic value of plasma exchange. This drawback reflects, in part, the relative rarity of most of the disorders under investigation. To compensate, many investigators have understandably grouped heterogeneous diseases, often retrospectively, and utilized historical controls. The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care over time may be misconstrued as a benefit of plasma exchange. Second, the natural history of many diseases commonly treated by plasma exchange (e.g., cryoglobulinemia, systemic lupus erythematosus [SLE]) is characterized by episodes of exacerbation and remission, further underscoring the importance of adequate concurrent controls. Third, the threshold for intervention and the details of treatment protocols may vary widely between centers, rendering it difficult to compare studies. Fourth, plasma exchange is primarily utilized in the treatment of inflammatory renal diseases as an adjunct to conventional immunosuppressive therapy and might be expected a priori to confer only a small additional benefit that would require large sample size for its detection. Finally, negative studies are inevitably less likely to be published and estimations of efficacy made on the basis of published reports may be biased in favor of plasma exchange.

EFFICACY OF PLASMA EXCHANGE IN SPECIFIC RENAL DISEASES

The efficacy of plasma exchange has been assessed most extensively in primary and secondary forms of rapidly progressive glomerulonephritis (RPGN), including anti-glomerular basement membrane (anti-GBM) antibody disease, immune complex-mediated glomerulonephritis, and pauci-immune RPGN. Other disorders in which the technique is often advocated include TTP, acute renal failure associated with myeloma, and allotransplant rejection.

Anti-Glomerular Basement Membrane Antibody Nephritis

Anti-GBM antibody disease typically presents as RPGN without or with pulmonary hemorrhage (Goodpasture's syndrome). Renal biopsy characteristically reveals crescentic glomerulonephritis with deposition of immunoglobulin G (IgG) and C3 along the glomerular basement membrane (18). Greater than 90% of patients have anti-GBM antibodies in their circulation. The latter are directed against the 28-kd noncollagenous C-terminus of the α3 chain of the Type IV collagen, an epitope that is relatively restricted to glomerular and alveolar basement membrane. In general, disease activity correlates with the titer of circulating antibodies, and passive transfer experiments have provided compelling evidence that circulating anti-GBM antibodies are nephrotoxic. The latter observation provided an attractive rationale for therapeutic removal of anti-GBM antibodies by plasma exchange.

Before 1975, anti-GBM-induced nephritis was associated with very poor prognosis. In a study by Wilson and Dixon in 1973, 89% of patients with anti-GBM nephritis who had been treated with various combinations of steroids and cytotoxic drugs progressed to ESRD or death within 5 yr of diagnosis (19). Similar conclusions were reported in a review by Rees, with
more than 85% of patients treated with conventional therapy progressing to ESRD (20). Against this background, only two controlled studies evaluated the efficacy of plasma exchange as an adjunct to conventional immunosuppressive therapy in anti-GBM nephritis (21,22). Although these studies were small (17 and 20 patients, respectively), both suggested a beneficial effect, as evidenced by more rapid decline in anti-GBM antibody titers, lower mean serum creatinine values at end of therapy, and fewer patients progressing to renal failure (Table 2). Johnson et al. compared the influence of plasma exchange (4 L every 3 days) plus immunosuppression (prednisone and cyclophosphamide) to immunosuppression alone on the clinical course and rate of disappearance of antibodies in a randomized controlled trial of 17 patients with anti-GBM disease (21). Patients treated with plasma exchange had a more rapid disappearance of anti-GBM antibodies and a mean serum creatinine value that was less than 50% that of patients receiving immunosuppression alone at the end of the study (9.5 ± 0.7 mg/dL [840 ± 62 μmol/L] versus 4.4 ± 0.6 mg/dL [390 ± 53 μmol/L]; $P < 0.05$). In a nonrandomized study, Simpson et al. compared the clinical course and levels of anti-GBM antibodies in eight patients treated with immunosuppression and plasma exchange (at least 10 sessions, 3 L each), four patients treated with immunosuppression alone, and eight patients who did not receive specific therapy (22). There was a more rapid fall in the level of anti-GBM antibodies in the eight patients treated with immunosuppression and plasma exchange. In this group, only three patients progressed to ESRD, compared with two of four patients treated with immunosuppression alone and six of eight patients with no specific therapy. It should be noted, however, that at study entry, patients that received plasma exchange had milder disease than patients in the control groups. Indeed, Johnson et al. reported that the percent of crescents on the initial biopsy and the initial serum creatinine values correlated better with outcome than did the therapeutic modalities employed.

The results of more than 20 uncontrolled studies on almost 250 patients, published over the past 20 yr, also suggest a favorable effect on renal outcome in about 40% of patients (reviewed in Reference 23). The largest published series comes from the Hammersmith Hospital, a pioneer in this field. More than 59 patients have been treated with plasma exchange and immunosuppression at this center since 1974 (20,24–29). When using daily 4-L plasma exchanges for at least 14 days, 85% of patients were alive after 2 months of follow-up, 41% progressed to ESRD and required chronic dialysis, and 44% retained independent renal function. These results compare favorably with historical controls used before 1975 (survival, 47%; ESRD, 87%). Despite plasma exchange, significant recovery of renal function was infrequent in patients who were either oliguric, had a serum creatinine value above 600 μmol/L (6.8 mg/dL), or required dialysis at presentation, even though anti-GBM antibody titers were reduced effectively.

In light of these studies, it seems reasonable to conclude that plasma exchange, when used as an adjunct to conventional immunosuppressive drugs, accelerates the disappearance of anti-GBM antibody from the circulation and may improve renal function if instituted promptly in patients with milder forms of anti-GBM nephritis. In patients with severe disease (oliguria, dialysis, or serum creatinine value > 600 μmol/L [6.8 mg/dL]), plasma exchange should probably be reserved for treatment of lung hemorrhage.

### Table 2: Major clinical trials evaluating the efficacy of plasma exchange in treatment of anti-glomerular basement membrane antibody nephritis

<table>
<thead>
<tr>
<th>Authors (Reference)</th>
<th>Study Design</th>
<th>N</th>
<th>Patients on Dialysis at Presentation</th>
<th>Number of Plasma Exchanges</th>
<th>Concomitant Therapy</th>
<th>Benefit of Plasma Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. (21)</td>
<td>Randomized controlled trial</td>
<td>17</td>
<td>2 of 17</td>
<td>4 to 17</td>
<td>Steroids Cyclo</td>
<td>25%&lt;sup&gt;a&lt;/sup&gt; 67%&lt;sup&gt;a&lt;/sup&gt; 25% 11%</td>
</tr>
<tr>
<td>Simpson et al. (22)</td>
<td>Nonrandomized controlled study</td>
<td>20</td>
<td>7 of 20</td>
<td>10 to 25</td>
<td>Steroids Cyclo</td>
<td>38%&lt;sup&gt;a&lt;/sup&gt; 50%&lt;sup&gt;a&lt;/sup&gt; 13% 25%</td>
</tr>
<tr>
<td>Hammersmith Group* (20)</td>
<td>Uncontrolled case series</td>
<td>59</td>
<td>30 of 59</td>
<td>&gt;14</td>
<td>Steroids Cyclo Aza</td>
<td>41%&lt;sup&lt;f&gt;1&lt;/sup&gt; 87%&lt;sup&gt;1&lt;/sup&gt; 15%&lt;sup&gt;1&lt;/sup&gt; 47%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> PE, plasma exchange; Cyclo, cyclophosphamide; Aza, azathioprine; ESRD, end-stage renal disease.

<sup>1</sup> All concomitant methods of therapy were administered by mouth.

<sup>b</sup> Expressed as incidence of ESRD.

<sup>c</sup> Significant benefit, but patients receiving plasma exchange had milder disease.


<sup>d</sup> Benefit when patients treated with plasma exchange are compared with historical controls.
because renal function is unlikely to recover even with aggressive treatment. As an initial regimen, most authorities recommend daily plasma exchange for 14 days, using 4-L exchanges and albumin solution as replacement fluid, in addition to steroids and cytotoxic drugs. Response to therapy should be monitored by repeated assessments of urine output, serum creatinine values, and plasma anti-GBM levels.

Pauci-Immune Rapidly Progressive Glomerulonephritis

Approximately 40% of patients with RPGN present with crescentic glomerulonephritis characterized by few or absent immune deposits (pauci-immune RPGN), as determined by direct immunofluorescence (23). Patients with this clinicopathologic presentation usually have either Wegener’s granulomatosis, polyarteritis nodosa, or “renal-limited” pauci-immune GN. These diagnoses may represent a spectrum of manifestations of a single disease because there is marked overlap of clinical and histopathologic features, and many patients have anti-neutrophil cytoplasmic antibodies (ANCA) in their circulation. In some, although not all, studies, circulating ANCA titers correlate with disease activity, and ANCA may contribute to the pathophysiology of pauci-immune RPGN through reactivity with neutrophils and/or endothelial cells, and other inflammatory mechanisms (30–32). The prognosis of pauci-immune RPGN in general has been poor. Precise figures are difficult to obtain from the literature, because most series consist of patients with several types of RPGN. However, available data would indicate that 80% of such patients progress to ESRD without therapy with high dose immunosuppression or cytotoxic drugs (see the review by Couser, Reference 23).

Five randomized controlled trials have evaluated the efficacy of plasma exchange as an adjunct to conventional immunosuppressive therapy in patients with pauci-immune RPGN (Table 3) (33-37). Glöckner et al. randomized 26 patients with RPGN to immunosuppressive agents (steroids, cyclophosphamide, azathioprine) with or without plasma exchange (14 and 12 patients, respectively) (33). The plasma exchange regimen consisted of 3.5-L exchanges performed over 4 wk: three sessions in the first week and at least two sessions weekly thereafter. No statistically significant difference was found in renal outcome between groups. After 8 wk, 73% of patients receiving conventional therapy and 69% undergoing adjunctive plasma exchange showed an improvement of > 20 mL/min in creatinine clearance values compared with pretreatment values, or attained a clearance value of greater than 10 mL/min (for patients who required dialysis at presentation). Cole et al. randomly assigned 32 patients with renal-limited RPGN to receive immunosuppressive therapy (steroids and azathioprine) with or without plasma exchange (16 patients in each group) (34). Patients underwent at least 10 plasma exchanges, with removal of 1 plasma volume at each session. At 1, 3, 6, or 12 months following randomization, there was no significant difference between the two groups in mean serum creatinine values, change in serum creatinine value, or with regard to dialysis dependency.

Although the aforementioned two studies suggested that routine plasma exchange affords little benefit in the majority of patients who present with pauci-immune RPGN, Pusey et al. (35) provided evidence for a benefit in a subgroup of patients who presented with severe (dialysis-dependent) disease. Specifically, they compared the influence of plasma exchange plus immunosuppression (steroids, azathioprine, and cyclophosphamide) to immunosuppression alone on renal outcome in 48 patients with pauci-immune RPGN. The plasma exchange regimen consisted of at least five 4-L exchanges within the first week. The total number of exchanges was then determined by the clinical response. A mean of nine procedures was performed (range, 5 to 25). Of the 11 dialysis-dependent patients who were treated with plasma exchange, ten recovered sufficient renal function to stop dialysis (mean follow-up of 4 months), compared with only three of eight conventionally treated patients (P = 0.041).

A similar trend was noted in two other trials. Riffel and Dechelette randomized 14 patients with idiopathic RPGN, many pauci-immune, to receive pulse methylprednisolone, immunosuppressive drugs, and heparin with (six patients) or without (eight patients) plasma exchange (36). Recovery of renal function, measured as discontinuation of dialysis or decrease of at least 50% in serum creatinine value, was better in the plasma exchange group at 2 months after randomization (P = 0.02); however, this difference was no longer significant at the end of follow-up (22 months). Mauri et al. prospectively compared the efficacy of an immunosuppressive regimen of steroids and cyclophosphamide with or without plasma exchange in a heterogeneous group of 22 patients with RPGN, most of whom had pauci-immune disease (37). Among the 11 patients who presented with a serum creatinine value above 800 μmol/L, renal function improved in five of six patients treated with adjunctive plasma exchange, compared with only one of five patients treated with immunosuppressive drugs alone (at 4 months after randomization, serum creatinine value was 728 μmol/L with plasma exchange versus 1163 μmol/L in control patients; P = 0.016). Importantly, none of the randomized controlled trials listed in Table 3 reported improvement in patient survival when this parameter was specifically addressed.

In aggregate, the results of five randomized trials argue against a role for plasma exchange in milder forms of pauci-immune RPGN, but suggest a potential benefit when the technique is used as an adjunct to conventional immunosuppressive therapy in patients with severe disease. This relative lack of efficacy probably reflects the efficiency of conventional immunosuppressive agents in halting inflammation and preserving renal function in most patients. The latter
<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Study Design</th>
<th>N</th>
<th>Presentation</th>
<th>Initial Renal Function</th>
<th>ANCA</th>
<th>Number of Plasma Exchanges</th>
<th>Concomitant Therapy (method)</th>
<th>Benefit of Plasma Exchange</th>
<th>Renal Outcome</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glöckner et al. (33)</td>
<td>Randomized controlled trial</td>
<td>26</td>
<td>RPGN-systemic diseases included</td>
<td>46% dialysis-dependent</td>
<td>NR</td>
<td>11.3 (mean)</td>
<td>Steroids (po) Aza (po) Cyclo (po)</td>
<td>Improved creat. clearance: PE: 69% Controls: 73%</td>
<td>Mortality: PE: 7% Controls: 8%</td>
<td></td>
</tr>
<tr>
<td>Cole et al. (34)</td>
<td>Randomized controlled trial</td>
<td>32</td>
<td>RPGN-systemic diseases excluded</td>
<td>34% dialysis-dependent (+) in 71%</td>
<td>&gt;10</td>
<td>Steroids (iv + po) Aza (po)</td>
<td>Dialysis requirement: PE: 75% Controls: 71%</td>
<td>Mortality: PE: 13% Controls: 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pusey et al. (35)</td>
<td>Randomized controlled trial</td>
<td>48</td>
<td>RPGN-systemic diseases included</td>
<td>39% dialysis-dependent</td>
<td>NR</td>
<td>9 (mean)</td>
<td>Steroids (po) Aza (po) Cyclo (po)</td>
<td>No benefit for entire group. For dialysis patients, discontinuation of dialysis: PE: 91% Controls: 37%</td>
<td>Mortality: PE: 48% Controls: 35%</td>
<td></td>
</tr>
<tr>
<td>Rifier and Dechelette (36)</td>
<td>Randomized controlled trial</td>
<td>14</td>
<td>RPGN-systemic diseases included</td>
<td>79% dialysis-dependent</td>
<td>NR</td>
<td>19 (mean)</td>
<td>Steroids (iv + po) Cyclo (po) Hep (sc)</td>
<td>Benefit for entire group. For dialysis patients, discontinuation of dialysis: PE: 75% Controls: 0%</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Mauri et al. (37)</td>
<td>Randomized controlled trial</td>
<td>22</td>
<td>RPGN-systemic diseases included</td>
<td>50% with s. creatinine &gt;800 μmol/L</td>
<td>NR</td>
<td>&gt;6</td>
<td>Steroids (po) Cyclo (po)</td>
<td>No benefit for entire group. For patients with initial s. creat. &gt;800 μmol/L, mean s. creat.: PE: 728 μmol/L Controls: 1163 μmol/L</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

RPGN, rapidly progressive glomerulonephritis; PE, plasma exchange; s. creat., serum creatinine; creat. clearance, creatinine clearance; Discont. of dialysis, discontinuation of dialysis; NR, not reported; Aza, azathioprine; Hep, calcium heparinate; Cyclo, cyclophosphamide.

Some studies (33,34,36) included patients with immune complex deposits.

Defined as an increase of >20 ml/min in creatinine clearance compared with pretreatment values or a clearance >10 ml/min for patients who required dialysis at presentation.

No statistically significant difference between plasma exchange group and control group.

Added benefit of plasma exchange versus control group (P < 0.05).
conclusions are further supported by the combined results of 12 uncontrolled case series (reviewed in Reference 23), suggesting a response rate of 70% in patients with RPGN treated with plasma exchange similar to that of patients treated with conventional therapy (response rate, 60%). Given the paucity of convincing data, it is impossible to give firm recommendations regarding the specifics of therapy. If utilized, it would seem prudent to perform at least four plasma exchange sessions during the first week of immunosuppressive therapy, using 4-L exchanges and albumin solution as replacement fluid. Response to therapy should be monitored with repeated assessments of urine output, serum creatinine values, and possibly ANCA titers.

Lupus Nephritis

Clinically overt nephritis complicates 38 to 90% of cases of SLE. Clinical manifestations of lupus nephritis range from mild abnormalities of the urinary sediment to fulminant inflammation and renal failure. These diverse clinical presentations, in turn, reflect the array of renal histopathologic entities encountered in SLE, classified by the World Health Organization as follows: Class I, normal or minimal disease; Class II, mesangial injury; Class III, focal and segmental proliferative GN; Class IV, diffuse proliferative GN; and Class V, membranous GN (reviewed in Reference 18). Typical serologic abnormalities in lupus nephritis include the presence of anti-nuclear (ANA), anti-doubled-stranded DNA (anti-dsDNA) and other autoantibodies, circulating immune complexes, and evidence of complement activation. Formation of immune complexes within glomeruli appears to be a central event in the pathophysiology of lupus nephritis. Plasma exchange has been advocated as an adjunct to conventional immunosuppressive regimens to remove immune complexes, auto-antibodies, and other inflammatory mediators, and to improve reticuloendothelial function (11,12,38–40).

Early case reports and uncontrolled case series suggested a benefit of plasma exchange in lupus nephritis (40–45), however, a recent large multicenter prospective randomized controlled trial provided strong evidence against its use (46). The Lupus Nephritis Collaborative Study Group assessed the efficacy of plasma exchange as an adjunct to prednisone and cyclophosphamide in 86 patients with severe lupus nephritis (mean duration of disease > 13 months; serum creatinine value > 2.0 mg/dL [180 μmol/L]). Patients underwent plasma exchange three times weekly for 4 wk and were then followed for an average of 136 wk. Plasma exchange induced a more rapid reduction of serum anti-dsDNA and cryoglobulin, but did not influence renal function or mortality. A similar percentage of patients (28% in the standard therapy group versus 30% in the plasma exchange group) underwent remission of their renal disease, as judged by a return of serum creatinine to ≤ 106 μmol/L (1.2 mg/dL) and remission of 24-h urinary protein excretion to ≤ 0.2 g per day (P = 0.86). Six patients (13%) in the standard therapy group and eight patients (20%) in the plasma exchange group died (P = 0.39). Indeed, there was a tendency for patients treated with plasma exchange to have a worse outcome, which ultimately led the External Data Monitoring Board to recommend early termination of the trial.

Four other randomized controlled trials of plasma exchange in lupus nephritis have been reported over the last 15 yr (Table 4) (47–50). Wei et al. randomized 20 patients to receive either six 4-L plasma exchanges or sham procedures over a 2-wk period (47). Only patients with mild disease were included (creatinine clearance value > 20 mL/min, prednisone dose < 1.0 mg/kg, no cytotoxic drugs). Throughout the study, all nonsteroidal anti-inflammatory drugs and corticosteroids were maintained at constant dosage. Plasma exchange produced significant reduction in circulating immune complexes and anti-DNA antibodies, but the frequency and degree of partial or complete remission was the same in both plasma exchange and control groups. Clinical outcome was evaluated by using physician assessment and a clinical activity index designed on the basis of 21 separate clinical manifestations of active SLE. Among the 18 patients who completed the trial, the proportion of patients with at least 50% improvement in physician assessment and clinical activity index was 55% in the plasma exchange group versus 33% in the control group at 6 wk after entry into the study, a difference that did not reach statistical significance. Derksen et al. conducted a trial that compared a 3-wk course of plasma exchange versus cytotoxic drugs (cyclophosphamide or azathioprine) in 20 patients with proliferative lupus nephritis who had not responded within 3 wk to high doses of prednisone (≥ 1 mg/kg) (48). Five of 20 patients had a significant increase in creatinine clearance values (three in the PE group; two in the cytotoxic drugs group). Of the six patients with a creatinine clearance below 20 mL/min (two in the PE group, four in the cytotoxic drugs group), none had a significant change in clearance. No beneficial effect of plasma exchange on extrarenal manifestations was observed. The French Cooperative Group randomized five patients to corticosteroids and plasma exchange and seven patients to corticosteroids alone. All patients received 1.5 mg/kg per day of prednisone for 60 days, with subsequent tapering to reach 1 mg/kg per day at Day 90. The plasma exchange regimen consisted of 23 sessions over a 2-month period, with removal of at least 60 mL of plasma/kg per exchange. Clinical outcome was evaluated by using physician assessment and a clinical activity index obtained at Day 90. Outcome was similar in both treatment groups (activity scores: 34 in the PE group, 39 in the control group; P > 0.05).

In contrast to these studies with short-term intensive therapy, Clark et al. suggested a possible role for
TABLE 4. Randomized controlled trials evaluating the efficacy of plasma exchange in treatment of lupus nephritis

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Study Design</th>
<th>N</th>
<th>Disease Severity</th>
<th>Initial Renal Function</th>
<th>Number of Plasma Exchanges</th>
<th>Concomitant Therapy</th>
<th>Benefit of Plasma Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al. (46)</td>
<td>Randomized controlled trial</td>
<td>86</td>
<td>Severe disease</td>
<td>Mean s. creat. of 180 μmol/L</td>
<td>12</td>
<td>Steroids Cyclo</td>
<td>ESRD: a</td>
</tr>
<tr>
<td>Wei et al. (47)</td>
<td>Randomized controlled trial</td>
<td>20</td>
<td>Mild disease</td>
<td>CrCl &gt;20 mL/min</td>
<td>6</td>
<td>Steroids Anti-malarials NSAID</td>
<td>PE: 25% Controls: 17%</td>
</tr>
<tr>
<td>Derksen et al. (48)</td>
<td>Randomized controlled trial</td>
<td>20</td>
<td>Unresponsive to conventional therapy</td>
<td>Mean CrCl of 30 mL/min</td>
<td>9</td>
<td>Steroids</td>
<td>PE: 55% Controls: 33%</td>
</tr>
<tr>
<td>French Group a, (49)</td>
<td>Randomized controlled trial</td>
<td>12</td>
<td>Active disease</td>
<td>Patients with &lt;50% crescents*</td>
<td>23</td>
<td>Steroids</td>
<td>Remission rate: a</td>
</tr>
<tr>
<td>Clark et al. (50)</td>
<td>Randomized controlled trial</td>
<td>39</td>
<td>Mild disease</td>
<td>CrCl &gt;30 mL/min</td>
<td>NR</td>
<td>Steroids Aza</td>
<td>PE: 97 μmol/L Controls: 124 μmol/L</td>
</tr>
</tbody>
</table>

a PE, plasma exchange; s. creat., serum creatinine; CrCl, creatinine clearance; NR, not reported; Aza, azathioprine; Cyclo, cyclophosphamide; NSAID, nonsteroidal anti-inflammatory drug; ESRD, end-stage renal disease.
b All concomitant methods of therapy were administered by mouth.
c No statistically significant difference between plasma exchange group and control group.
d French Cooperative Study Group on Systemic Lupus Erythematosus.
* Patients with rapidly progressive glomerulonephritis or >50% crescents on renal biopsy were excluded.

Prolonged plasma exchange therapy in lupus nephritis (50). In a controlled study, 39 patients with diffuse proliferative GN were randomized to conventional immunosuppressive therapy (steroids ± azathioprine) with or without 4-L plasma exchange every 3 to 4 wk. A trend toward better preservation of renal function was identified in the plasma exchange group. Specifically, the mean serum creatinine value was 33% lower in patients treated with plasma exchange versus the control group at the end of the study, a difference that did not reach statistical significance (plasma exchange, 1.1 mg/dL [97 μmol/L]; conventional therapy, 1.4 mg/dL [124 μmol/L]; P = 0.085).

In summary, the results of multiple prospective randomized controlled trials do not support a role for plasma exchange in the routine treatment of lupus nephritis. There is experimental and clinical evidence that rapid removal of circulating antibody by plasma exchange triggers a rebound B-cell clonal proliferation and enhanced antibody synthesis (13,14, 51,52). Because proliferating cells have increased vulnerability to cytotoxic agents, it has been suggested that plasma exchange may be useful in patients with lupus nephritis if synchronized with pulse cyclophosphamide (the latter administered shortly after plasma exchange) (53). Initial studies supported this contention (54–56); however, this approach requires validation in larger trials before it is employed as routine therapy.

Cryoglobulinemia

Cryoglobulins are Ig that precipitate in the cold. Three types of cryoglobulinemia have been described (57,58). In Type I, the cryoglobulin is a single monoclonal Ig and is usually found in association with multiple myeloma, Waldenström’s macroglobulinemia, or other lymphoproliferative malignancies. Types II and III are "mixed cryoglobulins" that contain at least two Ig. Type II cryoglobulins are usually composed of polyclonal IgG directed against an antigen and a monoclonal IgM with rheumatoid factor activity directed against the polyclonal IgG. In Type III cryoglobulins, both Ig components are polyclonal. Most mixed cryoglobulins are found in association with connective tissue diseases, infections, lymphoproliferative malignancies or autoimmune disorders and are therefore referred to as "secondary mixed cryoglobulinemias". Until recently, no precise etiology could be found in approximately 30% of cases of mixed cryoglobulins and these were termed "essential mixed cryoglobulinemia" (58). Recent studies suggest that most cases of mixed essential cryoglobulinemia cases are triggered by hepatitis C (HCV) infection (58).

Precipitation of cryoglobulins within the glomerular capillary lumen can induce a spectrum of nephritides, depending on the rate and magnitude of deposition. Renal symptoms usually appear several years after
the onset of the extrarenal manifestations. Fifty percent of cases present with proteinuria, microscopic hematuria, or mild to moderate renal insufficiency. Another 25% of cases present with nephrotic syndrome, whereas 20 to 25% present with nephritic syndrome. The characteristic morphologic glomerular lesion is membranoproliferative GN with subendothelial deposits (58). GN is triggered by cryoglobulin-induced complement activation, leukocyte infiltration, and induction of other mediator systems. Regarding relevance to plasma exchange therapy, most investigators report poor correlation between the cryocrit and disease activity (59,60). In addition, mixed essential cryoglobulinemia has a variable and often unpredictable natural history. In one third of patients, the renal disease has an indolent course and does not progress to renal failure despite persistent urinary abnormalities. Other patients have either a waxing and waning course characterized by exacerbations and remissions, or slowly progressive renal injury that culminates in end-stage renal failure (58). Progression to ESRD was initially reported in 30 to 50% of patients who had been treated with various combinations of nonsteroidal anti-inflammatory drugs, steroids, and cytotoxic drugs (61). Gorevic et al., reported a 55% mortality rate at 7.4 yr in patients who had been treated with conventional immunosuppression (60). Considering these poor results, plasma exchange was proposed as a means of rapidly reducing the circulating cryocrit and limiting deposition in tissues (62). In addition, removal of large quantities of cryoglobulins could potentially restore the clearing function of an overloaded reticuloendothelial system (11).

Plasma exchange has been utilized for the treatment of cryoglobulinemia for over 20 yr, unfortunately without being subjected to prospective randomized controlled clinical trials. Table 5 summarizes the results of uncontrolled studies in which greater than five patients were evaluated (59,63-68). Ferri et al. reported nine patients with mixed cryoglobulinemia and severe membranoproliferative GN who were treated with plasma exchange alone or in combination with corticosteroids (methylprednisolone, 40 to 60 mg/kg) (63). Five of nine patients had significant improvement in renal function and/or proteinuria after a mean of 54 plasma exchanges over a 10-month interval (from a

| Authors (Ref.) | Study Design | N | Patients with Renal Involvement | Diagnosis | Number of Plasma Exchanges | Concomitant Therapy (method) | Response to Therapy | Mortality | Renal Function | Renal Function
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<tbody>
<tr>
<td>Ferri et al. (63)</td>
<td>Uncontrolled case series</td>
<td>9</td>
<td>9 of 9</td>
<td>Mixed cryo</td>
<td>15 to 113</td>
<td>Steroids (po)</td>
<td>Improved s. creat. in 55%</td>
<td>NR</td>
<td></td>
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<tr>
<td>Singer et al. (64)</td>
<td>Uncontrolled case series</td>
<td>16</td>
<td>10 of 16</td>
<td>Mixed cryo (mostly Type II)</td>
<td>3 to 12</td>
<td>Steroids (po)</td>
<td>Improved or stable CrCl in 80%</td>
<td>25%</td>
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<td></td>
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<td>Sinico et al. (65)</td>
<td>Uncontrolled case series</td>
<td>20</td>
<td>16 of 20</td>
<td>Mixed cryo</td>
<td>3 to 34</td>
<td>Steroids (iv+po)</td>
<td>Improved s. creat. in 87%</td>
<td>5%</td>
<td></td>
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</tr>
<tr>
<td>Valtbonesi et al. (66)</td>
<td>Uncontrolled case series</td>
<td>15</td>
<td>8 of 15</td>
<td>Mixed cryo</td>
<td>3 to 5</td>
<td>Steroids (po) Aza (po)</td>
<td>Improved clinical score in 75%</td>
<td>13%</td>
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<tr>
<td>Frankel et al. (59)</td>
<td>Uncontrolled case series</td>
<td>13</td>
<td>10 of 13</td>
<td>Mixed cryo (Type II)</td>
<td>4 to 238</td>
<td>Steroids (po)</td>
<td>Improved or stable s. creat. in 67%</td>
<td>62%</td>
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<tr>
<td>L'Abbate et al. (67)</td>
<td>Uncontrolled case series</td>
<td>11</td>
<td>11 of 11</td>
<td>Mixed cryo</td>
<td>4 to 28</td>
<td>Steroids (iv+po)</td>
<td>Improved or stable CrCl in 73%</td>
<td>9%</td>
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<tr>
<td>Schena et al. (68)</td>
<td>Uncontrolled case series</td>
<td>10</td>
<td>7 of 10</td>
<td>Mixed cryo</td>
<td>12 to 17</td>
<td>Steroids (iv+po) Aza (po)</td>
<td>Clinical improvement in 75%</td>
<td>NR</td>
<td></td>
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</table>

a cryo. cryoglobulinemia; Aza. azathioprine; Cyclo. cyclophosphamide; NR. not reported; s. creat.. serum creatinine; CrCl. creatinine clearance.
b Includes studies published before 1995 that involved more than 5 patients.
c Most studies focused on mixed essential cryoglobulinemia and excluded cases with secondary disease.
d Expressed as percent of patients with renal involvement at presentation.
e Expressed as percent of patients from the entire group.

* Estimated value (not precisely reported).
pretreatment serum creatinine value of 4.6 ± 2.1 mg/dL (406 ± 185 μmol/L) to a posttreatment value of 2.1 ± 1.0 mg/dL (185 ± 88 μmol/L). Improvement was almost exclusively observed in those patients who had presented with a rapid worsening of renal function in the weeks before plasma exchange and/or in the presence of histologically active lesions and minimal renal scarring. Singer et al. retrospectively reported on 16 patients who were treated with either immunosuppressive therapy alone (three patients), plasma exchange plus immunosuppression (ten patients), or plasma exchange alone (three patients) (64). Ten of the 16 patients had proteinuria, with a range of 0.2 to 12.8 g/day, and the GFR was reduced in nine of these ten patients. Fourteen of the 16 patients experienced a fall in circulating cryoglobulin levels and renal function stabilized or improved in eight of ten patients who had renal impairment over the course of the study; however, neither the degree of improvement nor the duration of the follow-up was reported. Sindico et al. reviewed the clinical and laboratory data of 20 patients with mixed cryoglobulinemia who were treated with immunosuppressive drugs and an average of 18 plasma exchanges (65). Sixteen patients had renal involvement. Serum creatinine values and proteinuria decreased significantly with therapy in all but two patients (serum creatinine value, from 2.9 to 1.6 mg/dL [256 to 141 μmol/L]; proteinuria, from 3.5 to 1.6 g/24-h). Similar results were reported in several other series (Table 5) (59,66–68). Overall, plasma exchange has been reported to lower serum cryoglobulin levels and is associated with improved renal function in 55 to 87% of patients. It is claimed to be most effective if used in patients with active inflammation and in the first few weeks of an acute flare-up. Plasma exchange is also associated with improved survival (an approximate 25% mortality rate) when compared with historical data (an approximate 55% mortality rate).

Because of the uncontrolled nature of all of the studies reported to date, it is impossible to determine if the improvement in renal outcome and in survival is attributable to plasma exchange or to other factors such as patient selection, earlier diagnosis, wide variability in presentation and natural history, advances in general medical management or other aspects of immunosuppressive therapy. It is probably advisable to limit plasma exchange to patients with clinical or renal biopsy evidence of acute active and severe disease. If employed, most investigators advocate combining plasma exchange with conventional immunosuppression and performing the procedure thrice weekly for the first 2 wk, using 4-L exchanges and albumin solution as replacement fluid. Therapy should be tailored subsequently, according to the clinical and biochemical response. Measurement of circulating cryoglobulins is a poor index of efficacy because, as mentioned above, there is a poor correlation between the cryocrit and disease activity. The role of plasma exchange in the therapy of mixed essential cryoglobulinemia is undergoing constant reevaluation with the realization that hepatitis C is the etiologic agent in most cases and that interferon-alpha frequently induces remission (58).

IgA Nephropathy

IgA nephropathy is the most common form of GN worldwide (69). Whereas the majority of patients present with hematuria and normal renal function, up to 50% of patients suffer progressive deterioration in GFR over 20 yr (69,70). Furthermore, as many as 10% of patients with IgA nephropathy present with nephritic syndrome or RPGN. The latter presentation is almost identical morphologically and functionally to the typical renal presentation of Henoch-Schönlein purpura, and many investigators consider Henoch-Schönlein purpura and IgA nephropathy as a spectrum of presentations of the same pathogenic process. The pathognomonic feature of both diseases on renal biopsy is mesangial deposition of IgA. Serum total IgA concentration is elevated in 33 to 55% of adults with IgA nephropathy (71), although circulating levels of IgA do not usually correlate with the severity or activity of the disease. The precise mechanism(s) of glomerular IgA deposition and role of deposited IgA in disease pathophysiology have not been defined. Nevertheless, plasma exchange has been advocated as an adjunct to immunosuppressive drugs in patients with aggressive disease to remove circulating antibodies and other putative inflammatory mediators, and to augment reticuloendothelial system function (72).

The published worldwide experience of therapeutic plasma exchange in IgA nephropathy or Henoch-Schönlein purpura is limited to approximately 50 patients, all reported as case reports or small uncontrolled series (72–79). Nicholls et al. evaluated the efficacy of plasma exchange in 13 patients who had progressive IgA nephropathy (79). The plasma exchange regimen consisted of daily 3 to 4-L treatment for 4 days, followed by thrice-weekly treatment for 2 wk, twice-weekly treatment for 2 wk, then weekly treatment until the completion of 3 months of total plasma exchange. Comparison of the rate of deterioration in renal function before, during, and after plasma exchange suggested a possible beneficial effect. In seven of 13 patients, the rate of decline in GFR was significantly slower during treatment with plasma exchange than before (P < 0.001). However, the benefit was transient, as the rate of decline returned to pretreatment values after cessation of plasma exchange. There was also a suggestion that plasma exchange was more likely to be beneficial in patients with a rapidly progressive course. Coppo et al. studied the effect of plasma exchange combined with prednisolone and cyclophosphamide on renal function in five patients with IgA nephropathy (74). Two of the three patients with a rapidly progressive course had substantial improvement after plasma exchange, whereas two other patients presenting with a more slowly evolving course had no substantial benefit.
Despite these claims of efficacy in patients with a rapidly progressive course, no firm conclusion can be drawn regarding the role of plasma exchange in IgA nephropathy because of the lack of adequate concurrent controls, small number of subjects, and marked variability in the plasma exchange regimens. Given the encouraging preliminary results, however, the role of plasma exchange deserves to be assessed further in IgA nephropathy in larger randomized controlled trials.

**Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome**

TTP and HUS probably represent a spectrum of manifestations of the same disease and are characterized by thrombotic microangiopathy with consumptive thrombocytopenia, microangiopathic hemolytic anemia, and renal failure (80,81). Patients with the HUS variant tend to be younger and have more prominent renal involvement, whereas TTP is more common in adulthood and frequently associated with fever and neurologic abnormalities. Postulated pathogenetic mechanisms in HUS/TTP include (1) deficiency of anti-thrombotic or fibrinolytic activity, and (2) the presence of circulating factors that provoke endothelial injury and/or platelet aggregation, and promote microthrombi formation. Bacterial-derived toxins (e.g., *Escherichia coli*-derived verotoxin), anti-endothelial antibodies, immune complexes, abnormal von Willebrand multimers, and various toxic agents have been incriminated in the latter regard (see the review by Shepard and Bukowski, Reference 82). Therapeutic plasma exchange could potentially benefit patients with HUS/TTP by replacing a deficient plasma factor and/or removing circulating toxins.

In a review of TTP in 1966, Amorosi and Ultmann concluded that the disease is usually rapidly progressive and almost uniformly fatal (93% fatality rate; 79% within 90 days), and that there was no effective therapy (83). Since the mid-1960s, numerous treatment modalities have been attempted, such as steroids, antiplatelets, heparin, vincristine, and splenectomy. With the introduction of plasma infusion or exchange to the therapeutic regimen, remission rates of greater than 75% have been consistently reported (84–86). These data and the scientific rationale summarized above led to widespread utilization of plasma infusion or exchange in patients with HUS/TTP. Since the early 1980s, an overall survival rate of 84% has been reported in more than 20 uncontrolled studies that used plasma exchange as the primary therapy (reviewed in Reference 87). Two controlled trials compared plasma exchange with either plasma infusion or drug therapy alone (steroids, antiplatelet drugs) (Table 6) (88,89). Both suggested that plasma exchange improves the remission rate, renal outcome, and mortality rate. The French Cooperative Group retrospectively studied 53 patients with HUS/TTP, who had been followed for an average of 38.1 months (88). Improved actuarial patient survival was observed with plasma exchange as compared with the other therapies (100% versus 77% respectively, \( P = 0.03 \)). However, actuarial renal survival was similar in both groups (overall renal survival, approximately 50%) even though, in the subgroup of patients presenting with severe (dialysis-dependent) disease, plasma exchange was shown to improve renal survival (14 of 19 treated with plasma exchange versus 4 of 11 in the control group were able to discontinue dialysis for \( \geq 2 \) months, \( P = 0.05 \)). The Italian Cooperative Group retrospectively studied 29 patients with HUS/TTP, followed-up for an average of 36.5 months (89). Complete remission was achieved in 19 of 22 patients (86%) who had been treated with plasma exchange, as compared with four of seven patients (57%) who had been treated with plasma infusion and/or drug therapy.

One study conducted in children with HUS compared plasma exchange with supportive symptomatic therapy but failed to find any significant beneficial effect of plasma exchange (nine of 11 [82%] patients treated with plasma exchange and 12 of 22 [55%] patients treated with supportive care alone had a creatinine clearance value greater than 80 mL/min per 1.73 m² at 1 yr of follow-up; \( P > 0.05 \)) (90). However, cases with creatinine clearance values lower than 60 mL/min/ per 1.73 m² and cases with end-stage renal failure 1 yr after the acute phase were found exclusively in patients who had not been treated with plasma exchange.

A key question in the aforementioned studies is whether the beneficial effect of plasma exchange is actually the result of the exchange procedure or of plasma infusion alone. Two randomized controlled trials compared plasma exchange with plasma infusion in patients with HUS/TTP (Table 6) (91,92). Rock et al. randomized 102 adults with TTP to either plasma exchange or plasma infusion with fresh-frozen plasma (91). In addition, all patients received aspirin and dipyridamole. The outcomes in the two groups were compared 9 days and 6 months after entry into the trial. Response to therapy was defined as an improvement in the platelet count to more than 150 \( \times 10^9 \) for 2 consecutive days. At both 9 days and 6 months, patients who had received plasma exchange had a higher response rate and a better survival rate than those who had received plasma infusion (survival at 6 months: plasma exchange group, 78%; plasma infusion group, 63%). Although the authors concluded that plasma exchange is preferable to plasma infusion, interpretation should be guarded, because patients who underwent plasma exchange received three times as much plasma as patients who underwent plasma infusion. Indeed, Henon did not observe a difference in outcome between plasma infusion and plasma exchange in a smaller multicenter controlled trial in which 40 adults were randomized to receive either daily infusions of 15 mL/kg of fresh-frozen plasma or plasma exchange with a mixture of 15
<table>
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<tr>
<th>Authors (Ref.)</th>
<th>Study Design</th>
<th>N</th>
<th>Diagnosis</th>
<th>Number of Plasma Exchanges</th>
<th>Other Therapies (method)</th>
<th>Benefit of Plasma Exchange</th>
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<td>PE versus other therapies</td>
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<tr>
<td>French Group (88)</td>
<td>Retrospective controlled study</td>
<td>53</td>
<td>HUS (adults)</td>
<td>Mean s. creat. 1022 μmol/L</td>
<td>2 to 21</td>
<td>Plasma infusion Steroids (po)</td>
</tr>
<tr>
<td>Iaconi et al.* (89)</td>
<td>Retrospective controlled study</td>
<td>29</td>
<td>TTP (adults)</td>
<td>Mean s. creat. 1.1 mg/dl</td>
<td>3 to 15</td>
<td>Plasma infusion Steroids (po) Anti-platelets (po)</td>
</tr>
<tr>
<td>Gianvitti et al. (90)</td>
<td>Retrospective controlled study</td>
<td>33</td>
<td>HUS (children)</td>
<td>ARF in all patients</td>
<td>3 to 10</td>
<td>None</td>
</tr>
<tr>
<td>PE versus plasma Infusion</td>
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<tr>
<td>Rock et al. (91)</td>
<td>Randomized controlled trial</td>
<td>102</td>
<td>TTP (adults)</td>
<td>Mean s. creat. 138 μmol/L</td>
<td>3 to 36</td>
<td>ASA (po) Dipyridamole (po)</td>
</tr>
<tr>
<td>Henon (92)</td>
<td>Randomized controlled trial</td>
<td>40</td>
<td>TTP (adults)</td>
<td>Mean s. creat. 278 μmol/L</td>
<td>3 to 35</td>
<td>ASA (po) Dipyridamole (iv)</td>
</tr>
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a PE, plasma exchange; TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic-uremic syndrome; s. creat., serum creatinine; CrCl, creatinine clearance; Discont. of dialysis, discontinuation of dialysis; NR, not reported; ARF, acute renal failure; ASA, aspirin.
b Remission defined as >150,000 platelets.
c French Cooperative Study Group for Adult HUS.
d Data suggest benefit of plasma exchange but study design prevents definitive conclusions.
e Italian Cooperative Group for the study of Thrombotic Thrombocytopenic Purpura.
f No statistically significant difference between plasma exchange group and control group.
g Statistically significant benefit of plasma exchange versus control group (P < 0.05).
mL/kg of fresh-frozen plasma and 45 mL/kg of 5% albumin as replacement fluid (92).

In summary, there is evidence, albeit largely based on historical controls, that plasma exchange improves renal outcome and mortality in adult patients with HUS/TTP. It is unclear whether this benefit occurs as a result of plasma infusion alone with replacement of a deficient plasma factor or as a result of plasma exchange with removal of a circulating toxic mediator. From a practical viewpoint, it is often necessary to perform plasma exchange to administer the desired amount of plasma as these patients are often oligoanuric and prone to develop hypervolemia and pulmonary edema. Thus, it seems reasonable to begin plasma infusion promptly upon making the diagnosis and to commence plasma exchange as early as possible thereafter. The following plasma exchange protocol was reported by Rock et al. (91): daily plasma exchange is performed for 7 to 14 days, using 4-L exchanges and fresh-frozen plasma as replacement fluid. The results of recent reports suggest that cryosupernatant may be an alternative replacement fluid in some patients, because it does not contain large von Willebrand multimers that have been implicated in the pathogenesis of TTP (93-95). Response to therapy is monitored with repeated assessments of platelet counts, lactate dehydrogenase, urine output, and serum creatinine values. Concomitant adjuvant therapy remains highly controversial. Aspirin, dipyridamole, corticosteroids, vincristine, and splenectomy have been suggested, but their efficacy has never been demonstrated conclusively.

Renal Failure Associated with Multiple Myeloma

Renal failure complicates 3 to 9% of cases of multiple myeloma and is associated with poor prognosis. Renal impairment is caused by toxicity of myeloma light chains to renal tubules, although other factors can also contribute, including hypercalcemia, hyperuricemia, cryoglobulinemia, amyloidosis, light-chain deposition, hyperviscosity, infections, and chemotherapeutic agents (96,97). Response to chemotherapy is the major factor that conditions patient survival. Individuals with tumors unresponsive to chemotherapy fare poorly no matter what treatment is utilized (98). Serum levels of myeloma protein, and type and severity of renal lesions are the major factors that condition the recovery of renal function (99). Patients with advanced irreparable renal damage (such as severe cast nephropathy with interstitial fibrosis and tubular atrophy) are not likely to respond to any form of therapy. Plasma exchange combined with chemotherapy has been advocated as a means of rapidly reducing the plasma concentration of myeloma proteins and, hence, reducing the filtered load and nephrotoxicity of these proteins (7).

Two randomized controlled trials of plasma exchange in multiple myeloma have been reported (Table 7) (100,101). Johnson et al. (100) randomized 21 patients to either chemotherapy plus forced diuresis or to a similar protocol plus plasma exchange and could detect only a small and nonsignificant benefit despite rapid lowering of plasma myeloma protein. Recovery of renal function (sufficient to discontinue dialysis) was noted in three of seven patients treated with plasma exchange who required hemodialysis at onset, but in none of the five dialysis-dependent patients in the control group. However, there was no difference in survival between the two groups (25% survival in both groups at 30 months). In contrast, Zucchelli et al. randomized 29 patients to receive steroids and cyclophosphamide with or without plasma exchange (15 and 14 patients, respectively) (101). All patients had severe acute renal failure (creatinine values > 5 mg/dL [442 μmol/L]) and 24 required dialysis. Thirteen of 15 patients who had been treated with plasma exchange recovered renal function (creatinine values < 2.5 mg/dL [221 μmol/L]). In contrast, only two of 14 patients in the control

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<th>Authors (Ref.)</th>
<th>Study Design</th>
<th>N</th>
<th>Patients on Dialysis at Presentation</th>
<th>Number of Plasma Exchanges</th>
<th>Concomitant Therapy (method)</th>
<th>Benefit of Plasma Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. (100)</td>
<td>Randomized controlled trial</td>
<td>21</td>
<td>12 of 21</td>
<td>3 to 12</td>
<td>Forced diuresis Steroids (po)</td>
<td>PE:43% Controls:0%</td>
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<tr>
<td>Zucchelli et al. (101)</td>
<td>Randomized controlled trial</td>
<td>29</td>
<td>24 of 29</td>
<td>5</td>
<td>Forced diuresis Steroids (IV+po)</td>
<td>PE:84% Controls:18%</td>
</tr>
</tbody>
</table>

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<tr>
<th>Renal Outcome&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mortality&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>PE:43% Controls:0%</td>
<td>PE:43% Controls:25%</td>
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<tr>
<td>PE:84% Controls:18%</td>
<td>PE:84% Controls:72%</td>
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</tbody>
</table>

<sup>a</sup> All studies focused on acute or progressive renal failure associated with multiple myeloma and excluded patients with chronic renal impairment.

<sup>b</sup> PE: plasma exchange; Cyclo, cyclophosphamide; Discont. of dialysis, discontinuation of dialysis.

<sup>c</sup> Expressed as percent of patients on dialysis at presentation.

<sup>d</sup> Expressed as percent of patients from the entire group.

<sup>e</sup> No statistically significant difference between plasma exchange group and control group.

<sup>f</sup> Statistically significant benefit of plasma exchange versus control group (P < 0.05).
group had a similar outcome. In the subgroup of patients who required dialysis at presentation, 84% in the plasma exchange group and 18% in the control group recovered enough renal function to stop dialysis \( (P < 0.05) \). After a mean follow-up period of 23 months, none of the improved patients treated with plasma exchange had to resume dialysis. The 1-yr survival rate was 66% in the plasma exchange group versus 28% in the control group \( (P < 0.01) \). These results suggested that plasma exchange improves both renal outcome and patient survival. A similar trend was noted in additional nonrandomized studies and case series by Wahlin et al., Misiani et al., and Pozzi et al. These studies supported the notion that plasma exchange promotes recovery of renal function and lessens the need for chronic dialysis in certain patients with myeloma-related renal failure \( (7,98,99) \).

Thus, whereas the role of plasma exchange in multiple myeloma remains controversial, there is sufficient, albeit limited, data to justify the use of plasma exchange as adjunctive therapy in some patients with myeloma cast nephropathy. However, given the paucity of data, it is impossible to give firm recommendations regarding the specifics of therapy. If utilized, it would seem reasonable to perform at least five plasma exchange sessions, using 4-L exchanges and albumin solution as replacement fluid. Response to therapy should be monitored with repeated assessments of urine output, serum creatinine, and possibly plasma myeloma protein levels.

### Renal Transplantation

Over the past 20 yr, plasma exchange has been used in experimental protocols to prevent or treat renal allograft rejection by removing cytotoxic antibodies and other inflammatory mediators. In addition, plasma exchange has been utilized for the prevention and treatment of recurrence of primary renal disease in allografts.

Approximately 20% of patients on waiting lists for cadaveric transplantation have high levels of preformed cytotoxic antibodies that render them at high risk for hyperacute and acute allograft rejection \( (102) \). In an attempt to solve this problem, plasma exchange and immunoabsorption have been assessed before transplantation as a means of removing cytotoxic antibodies. In uncontrolled but compelling studies, plasma exchange significantly reduced the titers of preformed cytotoxic antibodies. However, this benefit was usually transient and antibody titers rebounded to pretreatment levels over the ensuing weeks \( (103-105) \). In a representative study, Hakim et al. treated 14 transplant candidates with an immunoabsorption system that used Protein A, which selectively removes Ig from plasma \( (104) \). Three to six procedures were performed on consecutive days. At the end of the treatment course, plasma IgG levels were reduced by 90% ± 8% and cytotoxic anti-HLA antibodies were reduced 18-fold when compared with pretreatment values \( (P < 0.01) \). Unfortunately, anti-HLA antibody titers returned to baseline levels during the subsequent 4-wk follow-up period. The effect of transient antibody removal on allograft survival was not assessed in this study.

In other trials, transplantation was attempted after prophylactic removal of cytotoxic antibodies by using plasma exchange, with encouraging results \( (105-107) \). Taube et al. treated 17 highly sensitized patients with immunoabsorption to remove anti-HLA antibodies before transplantation \( (107) \). Fifteen of the 17 patients had positive cross-matches with their donor when using pre-exchange sera, whereas cross-matches were negative immediately pretransplant after plasma exchange. Only one patient lost his graft because of rejection \( (108) \). Blake, Cardella et al. randomized 17 highly sensitized patients to either standard triple therapy alone \( (107) \), prednisone and azathioprine, and 1.4 episodes per patient in those treated with prednisone, cyclosporine, and antithymocyte globulin \( (ATG) \). Despite these encouraging results, large trials that evaluate the influence of pretransplant removal of anti-HLA antibodies by plasma exchange will be required before firm conclusions can be drawn about the efficacy of this practice.

Prophylactic plasma exchange has also been evaluated as induction therapy in highly sensitized patients in the immediate postoperative period, again in an effort to prevent early humoral rejection \( (103,108) \). The results did not show a major benefit of plasma exchange over conventional antirejection prophylaxis.

In a controlled trial, Reisaeter et al. randomized 17 highly sensitized patients to either standard triple therapy alone \( (prednisolone, cyclophosphamide, cyclosporine, and antithymocyte globulin \( (ALG) \)) or standard therapy plus plasma exchange \( (6 exchanges over a 2-wk period) \( (108) \). There was no difference in the number of early rejection episodes and in graft survival. In the plasma exchange group, seven of nine patients experienced rejections within 4 wk and five lost their grafts, whereas in the control group, all eight had early rejections but no grafts were lost. Frasca et al. reported similar results in a study in which 13 patients who had undergone prophylactic plasma exchange in the immediate postoperative period as an adjunct to a standard immunosuppressive protocol \( (immunosuppressive drugs plus antilymphocyte globulin \( (ALG) \)) were compared with 11 patients treated with the standard protocol \( (103) \). Six rejection episodes were noted in the plasma exchange group compared with eight in the control group. It is disconcerting to note that incidence of severe infections was slightly higher in patients treated with plasma exchange \( (eight versus six severe infection episodes) \).

Four randomized controlled trials have been reported on the efficacy of plasma exchange in the treatment of established biopsy-proven acute allograft rejection \( (Table 8) \( (109-112) \). Blake, Cardella et al. randomized 85 patients to receive conventional antirejection therapy with or without plasma exchange for...
treatment of all episodes of acute rejection occurring within the first 3 months of transplantation (109,113,114). No statistically significant difference in 5-yr actuarial graft survival was observed between groups, although there was a trend toward superior graft survival in patients who had undergone plasma exchange (plasma exchange group, 64%; conventional therapy group, 51%; P > 0.05). Three smaller trials focused on the efficacy of plasma exchange in acute rejection with prominent vascular inflammation on the basis that this process is mediated in large part by circulating antendothelial-cell antibodies (110-112). Allen et al. and Kirubakaran et al. randomized 27 and 24 patients, respectively, to conventional antirejection therapy (iv methylprednisolone) with or without plasma exchange (110,111). Renal biopsy was performed in all cases and histological examination confirmed severe vascular rejection. Analysis of short-term benefit, as evidenced by a reduction in serum creatinine values (6 days and 1 month after entry) and by subsequent graft survival revealed no statistically significant difference between treatment groups. Only one randomized trial suggested a statistically significant benefit of plasma exchange in acute vascular rejection. Bonomini et al. studied 44 patients with acute rejection and predominantly vascular lesions that had not responded to a 3-day course of iv methylprednisolone (112). Patients were randomized to either a second course of 3 daily doses of iv methylprednisolone or to plasma exchange. All patients were maintained on cytotoxic drugs (azathioprine or cyclophosphamide) during the entire course of the study. Those who had been treated with plasma exchange had a lower incidence of graft failure and a higher actuarial graft survival than patients who had received pharmacological antirejection therapy alone (graft failure: 7 of 23 [30%] in the plasma exchange group compared with 17 of 21 [81%] in the control group; P < 0.02). It should be noted, however, that these episodes were not typical of acute rejection; the mean interval between transplantation and the onset of rejection being 11 months. Thus, the sum of data published to date do not support the use of therapeutic plasma exchange for the prevention or treatment of acute rejection.

The published experience with therapeutic plasma exchange in chronic rejection is limited to a few uncontrolled series and case reports (103,115,116). The results reported by Frasca et al. suggest a potential benefit of plasma exchange (103). Six patients with progressive deterioration of renal function and detectable circulating cytotoxic antibodies were treated with plasma exchange. Improvement in renal function was noted in one patient (the degree and the duration of the improvement is not reported in the paper, however). In three cases, stabilization of the renal function was noted, and in the remaining two cases, the treatment had no effect on the rate of deterioration in renal function. In general, the results of other smaller studies have also been disappointing, with improvement in graft function being, at best, modest and usually transient (115,116).

A few uncontrolled studies suggest a role for plasma exchange in the prevention and treatment of recurrent glomerular disease, particularly primary focal segmental glomerulosclerosis, after transplantation (9,117,118). In a representative study by Dantal et al., eight patients with recurrent nephrotic syndrome....
were treated with plasma immunoadsorption that used Protein A (9). This technique induced a fall in urinary protein excretion values in all patients by an average of 82% (P < 0.001), however, the effect of therapy was transient in all but one patient, with a return to the preadsorption level within 2 months. Thus, to date, there is insufficient data to recommend routine use of plasma exchange in recurrent glomerular disease.

COMPLICATIONS OF PLASMA EXCHANGE

Risk:benefit ratio is an important consideration when discussing the merits of any therapeutic intervention, and the perception that plasma exchange is a benign procedure has undoubtedly contributed to its widespread use for unproven indications. Although plasma exchange is relatively safe when performed by skilled clinicians, complications related to either vascular access or the composition of replacement fluids are frequent. Table 9 summarizes the results from several major studies that specifically assessed the type and the incidence of complications related to therapeutic plasma exchange (adapted from Mokrzycki et al. with permission) (119–127). The overall incidence of adverse reactions ranges from 1.6% to 25%, with severe reactions occurring in 0.5% to 3.1%. Hematomas, pneumothorax and catheter infections are the most frequent complications of vascular access, occurring in 0.02 to 4% of treatments. Complications related to the replacement fluids include anaphylactoid reactions to fresh-frozen plasma, coagulopathies induced by inadequate replacement of clotting factors, transmission of viral hepatitis, and other infections. Symptomatic hypocalcemia resulting from citrate infusion, either as the treatment’s anticoagulant or in fresh-frozen plasma, complicates 1.5 to 9% of treatments. Hypotensive episodes occur in 0.4 to 4% of patients and can be triggered by vasovagal episodes, delayed or inadequate volume replacement, hypo-oncotic fluid replacement, or anaphylaxis. A recent report suggests that patients who undergo plasma exchange with membrane filtration can suffer anaphylactoid reactions when on angiotensin-converting enzyme inhibitors, similar to those described with hemodialysis (128). Repeated plasma exchange has been proposed to be immunosuppressive and may increase the risk of life-threatening infections in patients who are receiving conventional immunosuppressive agents. Although this postulate is supported by the results of numerous uncontrolled studies (25,129–132), it is noteworthy that an increase in infectious complications was not observed in the largest randomized controlled trial of plasmapheresis treatment of an inflammatory disease (133). As alluded to previously, the potential complications have been highlighted recently, with the observation that patients treated with plasma exchange for lupus nephritis tended to have a worse outcome than those treated with conventional therapy.

CONCLUSION

In summary, there is some evidence, albeit for the most part uncontrolled, that plasma exchange is a useful adjunct to conventional immunosuppression in the treatment of anti-GBM nephritis, particularly if instituted early before patients are dialysis-dependent. In contrast, the results of several randomized controlled trials suggest that plasma exchange is of little additional benefit to standard immunosuppressive regimens in the treatment of pauci-immune

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Number of Treatments</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td><strong>Centrifugal System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borberg (120)</td>
<td>205</td>
<td>13%</td>
</tr>
<tr>
<td>Autefuivre et al. (121)</td>
<td>3086</td>
<td>22%</td>
</tr>
<tr>
<td>Ziselman et al. (122)</td>
<td>1389</td>
<td>1.6%</td>
</tr>
<tr>
<td>Fabre et al. (123)</td>
<td>578</td>
<td>25%</td>
</tr>
<tr>
<td>Rossi et al. (124)</td>
<td>926</td>
<td>17.3%</td>
</tr>
<tr>
<td><strong>Membrane-Based System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sprenger et al. (125)</td>
<td>306</td>
<td>4.2%</td>
</tr>
<tr>
<td>Samtleben et al. (126)</td>
<td>120</td>
<td>17.5%</td>
</tr>
<tr>
<td>Mokrzycki and Kaplan (119)</td>
<td>699</td>
<td>9.7%</td>
</tr>
<tr>
<td><strong>Both Types of System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutton et al. (127)</td>
<td>5235</td>
<td>12%</td>
</tr>
</tbody>
</table>

\(^{a}\) Mild adverse reactions defined as symptoms of little clinical significance.

\(^{b}\) Moderate adverse reactions defined as easily treatable and without prolonged consequence.

\(^{c}\) Severe adverse reactions defined as potentially life-threatening.

\(^{d}\) Mild and moderate reactions were grouped together in this study.
RPON, except in severe dialysis-dependent patients. Although therapeutic plasma exchange is used extensively in mixed essential cryoglobulinemia, the case for its use in this disorder is largely unproven and warrants further investigation. Data from controlled trials do not support a role for therapeutic plasma exchange in other forms of immune complex-mediated GN such as lupus nephritis, and suggest that plasma exchange may adversely affect outcome in some patients. The introduction of plasma exchange appears to have dramatically improved renal outcome and mortality in patients with HUS/TTP. It remains to be determined definitively whether this benefit reflects the removal of a circulating toxic factor or infusion of normal plasma components. The role of plasma exchange in myeloma cast nephropathy remains controversial, but further clinical trials are justified, given the actual data. Most controlled studies argue against the use of plasma exchange as a means of preventing or treating allograft rejection, although its potential role in preparing highly sensitized patients for transplantation has not been adequately evaluated. The more widespread application of prospective randomized controlled clinical trials should help to better define the true value of plasma exchange in our armamentarium of treatments for renal diseases.

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384

Plasma Exchange and Kidney Diseases


