Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

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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.” This article is the integral part of the Fourth ASFA Special Issue. The Fourth ASFA Special Issue is significantly modified in comparison to 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. A detailed description of the fact sheet is provided. The article consists of 53 fact sheets devoted to each disease entity currently categorized by the ASFA. Categories I, II, and III are defined as previously in the Third Special Issue. However, a few new therapeutic apheresis modalities, not yet approved in the United States or are currently in clinical trials, have been assigned category P (pending) by the ASFA Clinical Categories Subcommittee. The diseases assigned to category IV are discussed in a separate article in this issue. J. Clin. Apheresis. 22:106–175, 2007 ©2007 Wiley-Liss, Inc.

Key words: apheresis; plasma exchange; immunoadsorption; leukocytapheresis; photopheresis; categories; indications; evidence based

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INTRODUCTION

The American Society for Apheresis (ASFA) Apheresis Applications Committee is charged with a review and categorization of indications for therapeutic apheresis. The customary name for these publications has been “The ASFA Special Issue.” This process has been undertaken every 7 years resulting in three prior publications in 1986, 1993, and 2000 [1–3]. In 2006, a new approach to category assignment was proposed and is thoroughly discussed in the accompanying publication in this issue of the Journal of Clinical Apheresis [4].

This new approach is designed to achieve several objectives. First, it provides uniformity to category assignment and disease discussion while minimizing personal bias; second, it is as much evidence based as possible, though the authors recognize some inevitable shortcomings of this approach; and last, it provides comprehensive, yet condensed, information which could be shared with patients and clinical services requesting the use of therapeutic apheresis.

This article is a compilation of all fact sheets for disease entities which were assigned ASFA categories I, II, III, and P. The addition of category P for pending was necessary to recognize new apheresis modalities which are not yet approved for clinical use in the US. A thorough description of these categories as well as description of the process we used for categorization can be found in the introductory article to this Special Issue [4]. The diseases which were assigned category IV are briefly discussed in the subsequent article, and are not included in the fact sheet format [5].

Therapeutic apheresis procedures considered in this publication and included in the fact sheets are therapeutic plasma exchange (TPE), erythrocytapheresis, thrombocytapheresis, leukocytapheresis, extracorporeal photopheresis (ECP), immunadsorption (IA), selective removal methods, adoptive cytapheresis, and membrane differential filtration [4].

DESIGN OF THE FACT SHEET

With the support of the ASFA Board of Directors, the ASFA Clinical Categories Subcommittee has decided to significantly change the presentation of diseases and indications for therapeutic apheresis. The information, provided in the fact sheet format, is comprehensive but limited in length to facilitate its use as a quick reference. The design of the fact sheet and explanation of information contained is included in Figure 1. The authors encourage the reader to use this figure as a guide to interpretation of all entries in the fact sheets since substantial condensing of available information was required to achieve this user friendly format. The references provided are not meant to be exhaustive but rather serve as a starting point in a search for more information. With very few exceptions the World Wide Web resources that were utilized by the committee members were excluded from the reference section and are available on the ASFA web site (www.apheresis.org). This decision was made to minimize the risk of sending a reader to resources which may not be available any longer while at the same time allowing the subcommittee to periodically review the content of the websites.
The name of the disease as well as its eponym when appropriate.

Each disease entity was assigned a disease group. The disease groups are primarily based on the ASFA Special Issue 2000 with minor modifications. The following are the disease groups used in the ASFA Special Issue 2007: autoimmune, hematologic, metabolic, miscellaneous, neurological, renal, rheumatic, and transplantation. The subcommittee recognizes that some of the diseases can be assigned to multiple groups, in such situations a primary and secondary group was used. However, only the primary assigned group was used in the Tables.

This section lists the incidence and/or prevalence of the disease in the US and other selected geographic region, when appropriate. In some instances when the incidence varies between genders, ethnicity or race, this information was noted as well. For certain diseases with insufficient data on either incidence or prevalence, other terms such as rare or unknown were used. The reader is cautioned to use this information only as an indicator of disease prevalence. It is possible prevalence may vary by geographical area.

The type of therapeutic apheresis procedure is listed here. Only diseases which were categorized are listed. More information on category IV indications can be found in a separate publication in this Special Issue. For certain diseases there are several apheresis based modalities available. In such instances (e.g., hypercholesterolemia) all types of therapeutic apheresis procedures are listed.

The ASFA category is listed for each therapeutic apheresis modality discussed. See the article in this Special Issue discussing the process of category assignment. Some categories have additional information to further specify a subgroup of patients for whom the category was assigned. It is important to recognize that an ASFA category was assigned only in this particular subset of patients. More information is always available in the text of the fact sheet.

Journal of Clinical Apheresis DOI 10.1002/jca
This section lists the number of patients reported in the literature who were treated with therapeutic apheresis. The committee used three categories: fewer than 100, between 100 and 300, and more than 300. This entry will help readers in judging how often this entity was reported to be treated with TA. However, the number of patients treated is less important than the quality of the scientific reports and sometimes can be misleading as negative results tend to be published less frequently.

Randomized controlled trials (RCT). The number of randomized controlled trials and the total number of patients studied. For example, 4 (250) indicates that there were 4 randomized controlled trials with 250 enrolled patients. The 250 patients include all patients irrespectively of randomization to either treatment group with TA or control arm. Some trials have more than two arms and therefore simplification was necessary. The minimum requirement for these studies was randomization to a control arm and a test arm the quality of the study is not reflected here. Example: Two randomized studies with 50 patients in each arm and one randomized study with 75 patients in each arm will be denoted as 3 (350).

Controlled trials (CT): the notation is similar to randomized controlled trials. Studies listed here were not randomized. The control group could be historical or concurrent to the treatment group.

Case series (CS). Number of case series (with total number of patients reported). We required that the case series described at least 3 patients. Case series with two patients were included in case reports. Example: 4 (56) implies that there were 4 case series with the total number of reported patients of 56.

Case reports (CR). Number of case reports (with total number of patients reported) – this information was derived also from abstract reports. Due to limitations of space, only up to 14 of the most germane references were cited for each fact sheet. For interested readers additional information can be obtained after perusing the cited references. All references are combined and printed at the end of this article.

This section provides basic criteria for discontinuation of apheresis procedures (i.e. end points, outcomes both clinical and laboratory). In some instances a general statement referring to the introductory article is provided.

This section is used when there are several different TA procedures used and it was necessary to subdivide available scientific reports. Not all entries will have this section.

This section briefly describes technical suggestions relevant to the treated disease, which the committee believed were important to improve quality of care or increase chances of positive clinical outcome. Not all diseases have specific technical notes, in such instances a general statement referring to the introductory article is provided.

The proposed frequency of treatment is listed here. The frequency is based on the data from the published reports however, due to variability of such reports; the committee suggested what is believed to be the clinically most appropriate frequency. When used, “every other day” generally indicates 3 procedures per week. Application of this information is left to discussion between the treating physician and the apheresis physician.

The strength of evidence was assigned based on the grading system used by the University HealthSystem Consortium as discussed in the introductory article in this Special Issue. If there were multiple TA modalities used the attempt was made to assign strength of evidence to each modality.

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This section briefly describes technical suggestions relevant to the treated disease, which the committee believed were important to improve quality of care or increase chances of positive clinical outcome. Not all diseases have specific technical notes, in such instances a general statement referring to the introductory article is provided.
Description of the disease
Major incompatibility refers to the presence of natural antibodies in the recipient against the donor’s ABO blood group, which may cause hemolysis of red cells present in the transplanted product. In peripheral hematopoietic progenitor cells (HPC) that are collected by apheresis, there is a lower risk of hemolysis due to reduced red cell contamination (2–5%) as compared to HPCs derived from the bone marrow, which comprise about 25–35% of the component volume. Either the product needs to be red cell reduced or the patient’s antibody titer needs to be lowered to prevent an acute hemolytic reaction. If the recipient has a high titer of antibodies (especially a group O patient receiving a group A transplant), a delayed erythroid engraftment or even pure red cell aplasia may result (PRCA) (see aplastic anemia; pure red cell aplasia fact sheet).

In minor incompatibility, the donor HPC product has antibodies against the recipient’s ABO blood type. The product should be plasma reduced to prevent an acute hemolytic transfusion reaction. Donor lymphocytes (passenger B lymphocytes) are capable of mounting an antibody response against the recipient’s A or B antigens, which can result in severe and rarely fatal hemolysis (generally occurring 7–10 days post transplantation). The use of HPCs collected through apheresis has greater risk of this complication than the use of HPCs collected through bone marrow harvest, since there are 16-fold more CD3+ T lymphocytes and 11-fold more CD19+ B lymphocytes. T cell depletion and cyclosporine-A increase the risk for a delayed hemolytic reaction, whereas methotrexate reduces this risk, since it suppresses the proliferation of donor lymphocytes.

Current management/treatment
In major incompatibility, red cell depletion of the product can be used to prevent acute hemolytic transfusion reaction. In minor incompatibility, plasma depletion of the product should be performed to prevent acute hemolytic transfusion reaction. For delayed erythroid engraftment or PRCA, posttransplantation various management strategies have been reported including high-dose erythropoietin, plasma exchange, immunadsorption, rituximab, donor lymphocyte infusions, discontinuation of cyclosporine, and antithymocyte globulin. The optimal treatment is currently not well defined.

Rationale for therapeutic apheresis
TPE can reduce ABO antibodies, which are responsible for hemolysis and PRCA. There are conflicting data about the correlation between pretransplant isoaglutinin titers and development of PRCA. In major ABO incompatibility, removal of the high titer antibody from the recipient’s circulation can prevent hemolysis, if unable to red cell deplete the product. TPE is more effective in the removal of IgM antibodies than IgG antibodies due to distribution of IgG in both intravascular and extravascular compartments.

In minor ABO incompatibility with passenger lymphocytes making antibody 7–12 days after infusion, prophylactic red cell exchange with group O red cells can be performed to deplete recipient type red cells.

Technical notes
If unable to red cell deplete the HPC product, TPE should be performed before infusion of HPCs and replacement fluid is combination of albumin and plasma (50:50) compatible with both donor and recipient.

Volume treated: 1–1.5 TPV
Replacement fluid: albumin; plasma
Frequency: daily

Duration and discontinuation/number of procedures
The goal should be to reduce the IgM or IgG antibody titers to ≤1:16 immediately before HPC transplantation. Generally, 2–4 TPEs are sufficient. If the antibody titer is high in the case of delayed red cell recovery or PRCA, TPE may be performed in the posttransplantation period.

References [6–11]
*As of March 1, 2006, using PubMed and the MeSH search terms ABO incompatible stem cell and bone marrow transplantation, plasmapheresis, plasma exchange, pure red cell aplasia for articles published in the English language. References of the identified articles were searched for additional cases and trials.
ABO INCOMPATIBLE SOLID ORGAN TRANSPLANTATION

**Disease Group:** Transplantation

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Procedure</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>TPE</td>
<td>II (kidney; heart (infants))</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th># of reported patients*; &gt;300</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0</td>
<td>22 (550)</td>
<td>10 (10)</td>
<td>Type II-3</td>
</tr>
<tr>
<td>Heart</td>
<td>0</td>
<td>0</td>
<td>6 (55)</td>
<td>8 (9)</td>
<td>Type II-3</td>
</tr>
<tr>
<td>Liver</td>
<td>0</td>
<td>0</td>
<td>10 (85)</td>
<td>3 (5)</td>
<td>Type II-3</td>
</tr>
</tbody>
</table>

**Description of the disease**

Major incompatibility refers to the presence of natural antibodies in the recipient against the donor’s ABO blood group; these antibodies may cause hyperacute/acute humoral rejection of the organ due to endothelial damage as ABO antigens are expressed on the vascular endothelium. The A2 blood group has reduced expression of A antigen on their RBCs and, therefore, group A2 donors are preferred over group A1 donors for group O recipients in kidney transplantation. In liver transplantation, there is not sufficient evidence regarding better graft survival in group A2 versus group A1 donors in ABO incompatible transplants. Generally, ABO identical transplantations are performed in liver transplantation; however, in emergent situations, ABO incompatible transplants are occasionally utilized. In this situation, TPE may be performed to prevent hyperacute rejection by removal of the preformed anti-A and/or anti-B antibodies. Recent case reports have used rituximab in ABO incompatible transplantation, both prophylactically and to treat rejection. ABO incompatible heart transplantation should be avoided if possible because of the risk of hyperacute rejection even though there is less ABO antigen expression in the heart than other tissues. When this has been performed, there is a high incidence of early graft failure in adults. In infants, ABO incompatible heart transplantation results are much better, since they have very low titers (<1:4) of anti-A or anti-B antibodies due to a relatively immature immune system.

Minor incompatibility occurs where the donor has naturally occurring ABO antibodies against the recipient. Donor lymphocytes present within the graft (known as passenger lymphocytes) may produce antibodies against the recipient RBC’s resulting in severe hemolysis.

**Current management/treatment**

The current immunosuppressive treatment (e.g., tacrolimus, mycophenolate mofetil, rituximab) is effective in B cell ablation; however, it does not affect plasma cells. Other immunotherapy modalities include intravenous immunoglobulins (IVIG) and antithymocyte globulins (ATG).

**Rationale for therapeutic apheresis**

TPE can reduce high titer antibodies, which are responsible for humoral rejection of the solid organ. For ABO mismatched solid organ transplant, the antibody titer can be lowered by peri-transplant TPE, thus preventing hyperacute rejection to improve graft survival. This should be performed in conjunction with immunosuppression and/or IVIG. The category III is assigned to liver transplantation based on paucity of data.

**Technical notes**

The replacement fluid for TPE is 5% albumin with or without plasma (compatible with both the recipient and donor or group AB), depending upon presence or absence of coagulopathy. Thus, in liver transplantation TPE can be performed with (1) 100% plasma for moderate to severe coagulopathy or (2) half 5% albumin and half plasma for antibody removal with mild coagulopathy. For heart and kidney cases generally 5% albumin is sufficient.

**Volume treated:** 1–1.5 TPV

**Replacement fluid:** albumin; plasma

**Frequency:** daily or every other day

**Duration and discontinuation/number of procedures**

The goal should be to reduce the antibody titer (IgM and IgG) in liver transplantation and in renal transplantation. A range of titers have been used in case series (ranging 4–16 for kidney transplantation and 8–64 in liver transplantation) using a variety of different techniques to measure the titer. This titer can be achieved usually in 2–5 days, depending upon the baseline titers. The antibody titers may increase 3–7 days after transplantation; therefore, daily antibody titer for the first 2 weeks posttransplantation is necessary. In kidney transplantation, during the following 2 weeks antibody titer measurement every second day helps to prevent immunologic graft events. If the antibody titer is high with or without humoral rejection, plasma exchange should be performed again in the posttransplantation period. Usually three more plasma exchanges are performed postoperatively (every second or third day followed by IVIG). If the antibody titer can be maintained at less than 1:8 in the first week posttransplant and 1:16 in second week, the risk of humoral rejection is decreased. In liver transplantation TPE for elevated titer are performed for only for the first 2 weeks and then there is evidence for accommodation.

Since plasma has citrate as an anticoagulant, ACD-A can be used in a ratio of 1:25–50 to prevent citrate reactions in liver transplantation cases. Simultaneous calcium infusion can be administered to patients with citrate toxicity.

**References [6, 12–17]**

*As of March 1, 2006 (kidney), and February 17, 2007 (heart and liver), using PubMed and the MeSH search terms ABO incompatible liver, heart and kidney transplantation, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease
Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory monophasic demyelinating disease that affects the brain and spinal cord, which typically occurs after a febrile (often presumed to be viral) prodrome or vaccination. The pathogenesis is thought to be disseminated multifocal inflammation and patchy demyelination associated with a transient autoimmune response against myelin or other autoantigens. The typical presentation is that of multifocal neurological deficits (ataxia, weakness, dysarthria, and dysphagia) accompanied by change in mental status. Most commonly it is a monophasic illness that lasts from 2 to 4 weeks. Predominantly children and young adults are affected. MRI is the diagnostic imaging modality of choice for the demyelinating lesions of ADEM. Characteristic lesions seen on MRI appear as patchy areas of increased signal intensity with typical involvement of deep cerebral hemispheric and subcortical white matter, as well as lesions in the basal ganglia, gray-white junction, brain stem, cerebellum, and spinal cord. The differentiation of ADEM from a first attack of multiple sclerosis has prognostic and therapeutic implications. ADEM has these features which help to distinguish it from MS: florid polysymptomatic presentation, lack of oligoclonal band in CSF, predominance of MRI lesions in the subcortical region with relative sparing of the periventricular area, and complete or partial resolution of MRI lesions during convalescence. New lesions should not appear unless a clinical relapse has occurred.

Current management/treatment
Corticosteroids are the mainstay of therapy, which hasten recovery and result in clinical improvement in up to 60% of patients. Intravenous immunoglobulin (IVIG) is reserved for patients who do not respond to corticosteroids.

Rationale for therapeutic apheresis
Therapeutic plasma exchange is used and has a clearly defined role in other neurological conditions that are presumed to be immunologically mediated. TPE works by removing presumed offending antibodies as well as through immunomodulation. The category III is assigned based on paucity of data.

Technical notes
See the introductory article in this issue.

Volume treated: 1–1.5 TPV  
Replacement fluid: albumin  
Frequency: every other day

Duration and discontinuation/number of procedures
There is no clear standard based upon which to make recommendations as to the optimum use of TPE in ADEM. However, in most published literature, response was noticeable within days, usually after two to three plasma exchanges. If improvement is not observed early in treatment, then it is unlikely a response will occur. TPE therapy consists most commonly of five treatments, but three to six treatments have been used in the literature.

References [18–24]
*As of September 23, 2005, using PubMed and the MeSH search terms acute disseminated encephalomyelitis, acute CNS demyelination, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease
Acute liver failure (ALF) can develop in a normal liver (known as fulminant hepatic failure; FHF) or in chronic liver disease. The most common cause of ALF is viral hepatitis in the United States, and acetaminophen toxicity in Great Britain. Other causes include drugs, ingestion of hepatotoxins, autoimmune hepatitis, and Wilson’s disease. The mortality rate in FHF is 50–90% due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy; however, following transplantation, the survival rate is >60%. Spontaneous recovery from FHF depends on the cause: high recovery rates are observed in fatty liver of pregnancy, acetaminophen ingestion, and hepatitis A; hepatitis B has intermediate prognosis; other drugs and unknown etiologies have less than 20% recovery rate; and patients with FHF due to Wilson’s disease rarely recover spontaneously. Without spontaneous recovery, the standard treatment of ALF is supportive care as a bridge to liver transplantation. Transplantation is performed for acute or chronic liver failure due to a variety of causes. About 30% of liver transplantation recipients have ALF. Generally ABO identical transplantations are performed except in emergent situations (see ABO incompatible solid organ transplantation fact sheet).

Current management/treatment
Currently there are no FDA approved cell based liver support systems available in the United States and, therefore, these therapies are still considered experimental. Some of these therapies include: Bioartificial liver (BAL), Extracorporeal Whole Liver Perfusion (ECLP), and Extracorporeal Liver Assist Device (ELAD). The non cell based therapies include: therapeutic plasma exchange, albumin dialysis, MARS (Molecular Adsorbents Recirculation System), and SPAD (Single Pass Albumin Dialysis). The supportive therapies consist of blood pressure support, prophylactic antibiotics, regulation of blood glucose, prevention of gastroduodenal hemorrhage, treatment of coma, correction of coagulopathy with blood products, and conventional continuous veno-venous hemofiltration.

Rationale for therapeutic apheresis
In FHF, TPE can remove albumin bound and large molecular weight toxins, including aromatic amino acids, ammonia, endotoxin, indols, mercaptans, phenols, and other factors which may be responsible for hepatic coma, hyperkinetic syndrome, decreased systemic vascular resistance, and cerebral blood flow. Most studies show improved cerebral blood flow, mean arterial pressure, cerebral perfusion pressure and cerebral metabolic rate, increased hepatic blood flow, improvements in other laboratory parameters such as cholinesterase activity, or galactose elimination capacity after TPE. TPE also restores hemostasis by supplying the coagulation factors and removing activated clotting factors, tissue plasminogen activator, fibrin, and fibrinogen degradation products. In some patients, the liver may regenerate during TPE and in other patients TPE can bridge to liver transplantation. The category III is assigned based on conflicting data.

Technical notes
Since plasma has citrate as an anticoagulant, ACD-A can be used in a ratio of 1:25–50 to prevent severe hypocalcemia in FHF. Simultaneous calcium infusion can be used if necessary. There is a preference for plasma as a replacement fluid due to moderate to severe coagulopathy; however, addition of albumin is acceptable. TPE will lower laboratory values such as bilirubin and hepatic enzymes, but do not necessarily reflect a change in the patient’s clinical status. Their rate of increase after TPE needs to be followed.

Volume treated: 1–1.5 TPV
Replacement fluid: plasma; plasma and albumin
Frequency: daily

Duration and discontinuation/number of procedures
In FHF, daily TPE is performed until transplantation or self-regeneration occurs. Because TPE removes liver enzymes and improves coagulopathy, the response to TPE should be evaluated in following morning’s laboratory levels.

References [16, 25–33]
*As of March 1, 2006, using PubMed and the MeSH search terms acute hepatic failure, fulminant liver failure, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease

Acute Inflammatory Demyelinating Polyneuropathy (AIDP) or the Guillain-Barre Syndrome is an acute progressive paralyzing illness affecting both motor and sensory peripheral nerves. Typically the disease begins with symmetrical muscle weakness and paresthesias that spread proximally. Progression, which can occur briskly over several weeks, may involve respiratory and oropharyngeal muscles in more severe cases. Thus, mechanical ventilation is required for approximately 25% of patients. Autonomic dysfunction can cause variability in blood pressure and heart rate. Spontaneous recovery may occur; however, up to 75% of patients develop long-term neurologic deficits. Mortality is estimated at 5%. The Miller–Fisher variant is characterized by ophthalmoplegia, ataxia, and areflexia. AIDP is distinguished from chronic inflammatory demyelinating polyneuropathy (CIDP) based on length of illness (see Chronic Inflammatory Demyelinating Polyneuropathy fact sheet). An autoimmune pathogenesis is strongly suggested due to the presence of antibodies to the myelin sheath constituents in the majority of patients as well as in animal models of the disease. The observation of a preceding infectious illness in many patients suggest cross-reactive antibodies may be a component in disease pathogenesis.

Current management/treatment

Since spontaneous recovery is anticipated in most patients, supportive care is the mainstay of treatment including intensive care, mechanical ventilation, and assistance through the paralysis and necessary rehabilitation over several months to a year or more. Corticosteroids have not been shown helpful when used alone. TPE was the first therapeutic modality to impact the disease favorably and several major randomized controlled clinical trials have confirmed its efficacy. Another controlled trial comparing intravenous immunoglobulin (IVIG) to TPE showed superiority of IVIG in the treatment of AIDP. However, the results of this IVIG trial were the target of skepticism since the TPE treatment group did not perform equivalently in comparison to prior reports and, both IVIG treatment failures and disease relapses responsive to subsequent TPE have been reported. A subsequent international randomized trial compared TPE, IVIG, and TPE followed by IVIG in 383 adult patients with severe AIDP and found all three modalities to be equivalent. There were no differences in the three treatment groups in mean disability improvement at 4 weeks nor the time to be able to walk without assistance (TPE group 49 days, IVIG group 51 days, and TPE/IVIG group 40 days). Since IVIG is readily available, it is frequently used as initial therapy. Other therapeutic modalities studied include immunoadsorption apheresis, CSF filtration, and double filtration plasmapheresis.

Rationale for therapeutic apheresis

The favored etiology of AIDP is autoimmune antibody-mediated damage to the peripheral nerve myelin. The results of several controlled trials comparing TPE to supportive care alone indicate TPE treatment can accelerate motor recovery, decrease time on the ventilator, and speed attainment of other clinical milestones. While recovery with TPE is improved, the duration of disability from AIDP remains significant. For example in the French Cooperative Study, median time to wean from mechanical ventilation was 18 days versus 31 days for TPE compared to control, respectively. In the North American Trial the median time to walk without assistance was 53 days versus 85 days. Of note, the Cochrane Neuromuscular Disease Group review of TPE in AIDP found that TPE is most effective when initiated within 7 days of disease onset.

Technical notes

The typical TPE strategy is to exchange 250 mL of patient plasma per kg body weight over 10–14 days. This will generally require five to six TPE procedures with albumin replacement and one plasma volume exchange. The clinical effects of disease may progress despite the initiation of therapy. Plasma is not routinely used for replacement. Since autonomic dysfunction is present, affected patients may be more susceptible to volume shifts, blood pressure, and heart rate changes during extracorporeal treatment. When IVIG is used for treatment, the typical dose is 0.4 g/kg for 5 consecutive days. Relapses may occur in approximately 10% of patients 2–3 weeks following either treatment. Additional therapy, usually TPE, can be helpful. In AIDP patients with axonal involvement, TPE has been reported to be of greater potential benefit than IVIG.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1–1.5 TPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement fluid:</td>
<td>albumin</td>
</tr>
<tr>
<td>Frequency:</td>
<td>every other day</td>
</tr>
</tbody>
</table>

Duration and discontinuation/number of procedures

See Technical Notes above

References [34–43]

*As of March 20, 2006, using PubMed and the MeSH search terms Guillain-Barré, AIDP, plasma exchange, TPE, apheresis, and IVIG for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease

Rapidly progressive glomerulonephritis (RPGN) is a clinicopathologic entity consisting of rapid loss of renal function, usually a 50% decline in glomerular filtration rate within 3 months, and the principle histologic finding of crescents involving over 50% of glomeruli. RPGN is a clinical syndrome that can result from a number of etiologies, which have been divided into three main groups based on renal biopsy immunofluorescence. Anti-glomerular basement membrane GN (anti-GBM) accounts for 15% of cases, immune-complex GN accounts for 24% of cases, and pauci-immune GN for 60% of cases. (See fact sheets for Rapidly Progressive Glomerulonephritis and Anti-Glomerular Basement Membrane Disease.)

Pauci-immune GN is characterized by minimal immune deposits in the glomeruli and the presence of anti-neutrophil cytoplasmic antibodies (P-ANCA, C-ANCA in the serum). ANCA associated small vessel vasculitis encompasses a clinical spectrum of disease which ranges from renal-limited vasculitis to systemic involvement, including microscopic polyangiitis (MP), Wegener’s granulomatous, and the Churg-Strauss syndrome. The presentation of the pulmonary-renal syndrome associated with ANCA is clinically similar to anti-glomerular basement membrane disease (Goodpasture’s Syndrome). Diffuse alveolar hemorrhage (DAH) associated with ANCA vasculitis poses significant risk of mortality.

Current management/treatment

The current standard approach to management of ANCA small vessel vasculitis is combination therapy consisting of high-dose corticosteroids and cytotoxic immunosuppressive drugs. In fulminant cases, including DAH, TPE has been added. Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors (mycophenolate mofetil, cyclosporin), and antibodies against T-cells.

Rationale for therapeutic apheresis

The presence of ANCA autoantibodies indicates a humoral component to disease pathogenesis and has fueled interest in TPE for management. Much of the published experience with TPE includes all forms of RPGN, not just exclusively Wegener’s disease or ANCA-associated RPGN, which complicates interpretation of results. Six trials have examined the role of TPE in pauci-immune and immune-complex GNs. Of these three consisting of a total 87 patients, found no benefit of TPE over standard therapy. Two trials consisting of 62 patients found benefit in patients who were dialysis dependent at presentation but not those mildly affected. One trial consisting of 14 patients found benefit in all. These trials suggest that TPE is most beneficial in patients with dialysis dependency (at presentation) and offers no benefit over immunosuppression in milder disease. A controlled trial of ANCA associated RPGN of 26 patients suggests TPE may improve prognosis even in nondialysis dependent patients. A retrospective case series reported effective management of pulmonary hemorrhage in ANCA vasculitis. In a European prospective study of 100 patients presenting with an initial diagnosis of ANCA-associated vasculitis with severe renal involvement, patients received standard therapy of oral corticosteroids and cyclophosphamide and were randomly assigned adjunctive therapy of either TPE or pulse methylprednisolone (1,000 mg/d × 3 days). Randomization to the treatment arm which included plasma exchange (7 treatments over 14 days) was predictive of dialysis independence at 12 months (54% compared to 29%). Inclusion in this study required serum Cr > 500 µmol/L (>5.7 mg/dL), intention to initiate dialysis within 48 hours, ANCA positivity, and histologic confirmation to exclude other causes of glomerulopathy.

Technical notes

In patients with pulmonary hemorrhage, replacement with plasma is recommended to avoid dilutional coagulopathy resulting from non-plasma replacement.

| Volume treated: | 1–1.5 TPV | Frequency: daily or every other day |
| Replacement fluid: | albumin, plasma when DAH present |

Duration and discontinuation/number of procedures

Consider daily procedures in fulminant cases or with pulmonary hemorrhage then continuing every 2–3 days for total of six to nine procedures.

References [44–54]

*As of November 1, 2006, using PubMed and the MeSH search terms rapidly progressive glomerulonephritis or ANCA and apheresis or plasma exchange or TPE or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Rapidly progressive glomerulonephritis (RPGN) is a clinicopathologic entity consisting of rapid loss of renal function, usually a 50% decline in glomerular filtration rate within 3 months, and a principle histologic finding of crescent formation, usually involving over 50% of glomeruli. Crescent formation consists of an extracapillary proliferation of cells within Bowman’s space of the glomerulus due to the extravasation of proteins into the space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes. RPGN does NOT represent a single disease entity but is a clinical syndrome that can result from a number of etiologies. (See Rapidly Progressive Glomerulonephritis fact sheet.)

Anti-glomerular basement membrane glomerulonephritis (anti-GBM), also called Goodpasture’s syndrome, accounts for 15% of cases of RPGN. Clinically, anti-GBM consists of RPGN and lung hemorrhage, though 30–40% of patients will have only renal involvement. The pulmonary symptoms include breathlessness to overt hemoptysis. Chest radiographs are nonspecific. Predisposing factors for anti-GBM included the presence of HLA DRB1*1501 allele, exposure to hydrocarbons, and cigarette smoking.

Almost all patients have anti-GBM antibodies detectable in their blood. This antibody is directed toward the α3 chain of type IV collagen, which is found in renal and alveolar basement membrane. In addition, 30% of patients will also have detectable ANCA. Patients exhibiting both antibodies behave more like anti-GBM than ANCA-vasculitis in the short-term but more like ANCA-vasculitis in the long-term. Anti-GBM is characterized by linear deposits of IgG and complement on renal biopsy.

Current management/treatment
In anti-GBM GN, the current treatment is the combination of TPE, cyclophosphamide, and corticosteroids. In general, the disease does not relapse and therefore patients do not need chronic immunosuppression. The exception to this is those patients with ANCA. These patients respond rapidly to treatment, like anti-GBM, but can relapse, like ANCA-vasculitis. These patients require long-term immunosuppression.

Rationale for therapeutic apheresis
Because of the knowledge that the disorder was associated with the presence of autoantibodies and the poor prognosis of the disorder with current treatment, TPE was applied to the disorder in the mid 1970s. A large number of case reports as well as a significant number of case series involving a large number of patients have appeared. A single randomized prospective trial involving a small number of patients has been reported and demonstrated improved survival of both the patients and their kidneys.

Technical notes
It is critical that TPE be implemented early in the course of anti-GBM. Several series have demonstrated that most patients with creatinine levels less than 6.6 mg/dL recover renal function while it is rare for those with an initial creatinine above 6.6 mg/dL to recover renal function. It has been suggested that patients who are dialysis dependent at presentation do not benefit from TPE and it should not be performed unless pulmonary hemorrhage is present. Pulmonary hemorrhage can be rapidly fatal, may have relatively mild manifestations, and responds to TPE in 90% of affected patients. Therefore, a low threshold for implementing TPE is warranted in the presence of pulmonary hemorrhage where the final portion of the replacement fluid should be plasma.

**Volume treated:** 1–1.5 TPV  
**Replacement fluid:** albumin, plasma  
**Frequency:** daily or every other day

Duration and discontinuation/number of procedures
In most patients undergoing TPE and immunosuppression, anti-GBM antibodies fall to undetectable levels within 2 weeks and the minimum course of TPE should be 14 days. The presence or absence of antibody itself should not be used to initiate or terminate therapy, because antibody is not demonstrable in a small percentage of people with the disease and the antibody may be present in patients without active disease. In those patients with active disease and anti-GBM present, TPE should be continued until antibodies fall to undetectable levels.

References [55–59]
*As of November 1, 2005, using PubMed and the MeSH search terms Goodpasture’s syndrome and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
APLASTIC ANEMIA; PURE RED CELL APLASIA

<table>
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<th>Disease Group: Hematologic</th>
<th>Procedure</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA: 2 per 1,000,000/year; PRCA: Rare</td>
<td>TPE</td>
<td>III</td>
</tr>
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</table>

# of reported patients*: <100

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
<th>Incidence</th>
<th>Strength of evidence</th>
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<tr>
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<td>TPE</td>
<td>AA</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Type III</td>
<td>TPE</td>
<td>PRCA</td>
<td>0</td>
</tr>
</tbody>
</table>

Description of the disease

Aplastic anemia (AA) and pure red cell aplasia (PRCA) are rare hematopoietic stem cell disorders. AA involves all cell lines and is defined as marked pancytopenia in the peripheral blood with hypocellular bone marrow in the absence of clonal hematopoiesis, abnormal cellular infiltration, or increased reticulin fibrosis. PRCA selectively involves erythroid precursors and is characterized by normochromic normocytic anemia, reticulopenia (reticulocyte count <1%), and an almost complete absence of marrow erythroblasts with normal platelet and leukocyte counts. Most cases of AA and PRCA are acquired; however, unusual inherited forms exist. Acquired disease can be primary (idiopathic) or secondary to a variety of neoplastic, autoimmune, infectious diseases, or certain drugs. Chronic infection and lysis of erythroid progenitors by parvovirus B19 may cause PRCA in immunocompromised individuals (e.g., AIDS patients).

Acquired PRCA may also result from injury of erythroid progenitor cells by IgG antibodies or cytotoxic T lymphocytes, by IgG against mature erythroblasts, or by anti-erythropoietin antibody. PRCA occurs in ≤20% of patients after a major ABO mismatched hematopoietic progenitor cell transplant, and is usually related to persistent host anti-donor isohemagglutinins that suppress erythroid progenitors/precursors (see also fact sheet on ABO Incompatible Hematopoietic Progenitor Cell Transplantation). Immune-mediated mechanisms of acquired AA involve cytotoxic T cells and marrow-suppressive cytokitones. Primary acquired PRCA may present at any age with symptoms of severe anemia. Acquired AA occurs most commonly between the ages of 15 and 25 with a second smaller peak after age 60. Certain HLA loci (e.g., HLA DR2) are associated with AA. The disease can develop abruptly over days or insidiously over weeks to months. AA is classified according to the degree of peripheral blood pancytopenia. Severe AA is defined as bone marrow cellularity <20%, two of three peripheral blood criteria of ANC < 500 x 10^9/L, platelet count < 20 x 10^11/L or reticulocyte < 4 x 10^11/L, and no other hematologic disease. Most patients with AA present with symptoms related to bleeding (most frequent), anemia, and/or infection.

Current management/treatment

For both AA and PRCA, underlying triggering etiologies, such as malignancies or infections, should be sought and treated and possible offending drugs (including erythropoietin in PRCA) should be discontinued. Intravenous immunoglobulin (IVIG) is indicated for chronic active parvovirus B19 virus infection in immunocompromised patients with PRCA and surgical resection may be curative for PRCA associated with thymoma. For other etiologies, the current approach to therapy includes replacement of defective hematopoiesis by hematopoietic progenitor cell (HPC) transplantation, or suppression of an apparent autoimmune process.

Allogeneic HPC transplant is the treatment of choice for severe AA in newly diagnosed patients <40 years old. Young patients with mild disease or without a matched donor and older patients with AA are treated with anti-thymocyte globulin (ATG) and cyclosporine A. Hematopoietic growth factors and androgens are often used as adjunctive therapies.

Primary acquired PRCA is usually responsive to immunosuppressive therapy until remission is obtained. Corticosteroids (prednisone at 1 mg/kg/day) are used as first line therapy. Alternative treatment is required if no response is achieved after 2–3 months. Salvage agents include cyclophosphamide, azathioprine, cyclosporine, ATG, and high-dose IVIG. No data exist favoring one salvage agent over the other.

Rationale for therapeutic apheresis

Because these diseases may be immunologically mediated, TPE may be helpful by removing serum antibody and/or inhibitory activity. Case reports of benefit with TPE for AA consisted of patients who had concomitant autoimmune diseases. TPE is therefore reasonable to consider for such patients with severe AA who do not have a HPC transplant option and have failed to respond to conventional immunosuppressive therapy, TPE may also improve PRCA developing after major ABO-mismatched HPC transplant or in the setting of erythropoietin therapy with anti-erythropoietin antibodies. In the setting of PRCA after major ABO-mismatched HPC transplant, there are three reports, which suggest benefit for using immunoadsorption. The category III is assigned based on paucity of data.

Technical notes

See the introductory article in this issue.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1–1.5 TPV</th>
<th>Frequency: daily or every other day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement fluid:</td>
<td>albumin, plasma</td>
<td></td>
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</table>

Duration and discontinuation/number of procedures

TPE was performed until recovery of hematopoiesis or adequate red cell production. No well-defined treatment schedules exist; however, 1–24 treatments were reported in the literature.

In patients with PRCA, TPE is used usually for a minimum of 2–3 weeks and occasionally for much longer until a response occurs.

References [60–66]

*As of November 28, 2005, using PubMed and the MeSH search terms aplastic anemia, pure red cell aplasia, major ABO-incompatibility bone marrow transplant, plasma exchange, and plasmapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
Cold agglutinin disease (CAD) consists of IgM autoantibodies that react optimally at 0–5°C and can be directed against the red cell I/i antigens. It usually arises in reaction to an infection (polyclonal autoantibodies) or to a lymphoproliferative disorder (monoclonal autoantibodies). The laboratory findings are of hemolysis (anemia, hyperbilirubinemia, elevated serum LDH, reticulocytosis), as well as a positive direct antiglobulin (Coombs) test. AIHA can be classified into two major types, warm autoimmune hemolytic anemia (WAIHA) and cold agglutinin disease (CAD).

Warm autoantibodies consist of IgG hemolysins that react optimally at 37°C and are directed primarily against the red cell Rh antigens. Causes of WAIHA include: idiopathic (30% of cases), secondary (associated with underlying autoimmune diseases, lymphoproliferative disorders, cancer, or infections), and drug-induced (e.g., methyl-dopa, cephalosporins). In WAIHA, the direct antiglobulin test is positive with anti-IgG and may additionally be positive with anti-C3d/b.

Cold agglutinin disease (CAD) consists of IgM autoantibodies that react optimally at 0–5°C and can be directed against the red cell I/i antigens. It usually arises in reaction to an infection (polyclonal autoantibodies) or to a lymphoproliferative disorder (monoclonal autoantibodies). The cold-reactive IgM autoantibody produced after Mycoplasma pneumoniae infection usually has anti-I specificity, whereas the autoantibody associated with Epstein-Barr virus infection (infectious mononucleosis) frequently has anti-i specificity. In CAD, the direct antiglobulin test is positive with anti-C3d/b only. Pathologic cold autoantibodies characteristically have titers greater than or equal to 1:1,000.

The degree of hemolysis in AIHA is affected by the titer of the autoantibody, its avidity for the relevant red blood cell (RBC) autoantigens, and, for cold autoantibodies, its ability to fix complement, and its thermal amplitude. The thermal amplitude is defined as the highest temperature at which the antibody is reactive. Cold autoantibodies with high thermal amplitude could, therefore, be active within in vivo temperature ranges (i.e., 30–37°C), and in these cases the thermal amplitude most accurately predicts the severity of the disease.

Current management/treatment
Therapy for WAIHA initially involves prednisone at 1–2 mg/kg/day, until response becomes evident. Prednisone suppresses antibody production and down-regulates Fc-receptor-mediated red cell destruction in the spleen. Second-line therapy includes splenectomy, intravenous immunoglobulin (IVIG), rituximab, danazol, and immunomodulatory agents (e.g., cyclophosphamide, azathioprine, cyclosporine A).

Treatment for CAD is often not necessary due to the relatively ineffective mechanisms of cellular destruction initiated by the cold agglutinins (particularly true in infection-related CAD). If indicated by more severe hemolysis/anemia, treatment primarily involves avoiding exposure to cold. Antibody removal by TPE is also effective. Prednisone is usually ineffective, as is splenectomy, because the liver is the dominant site of destruction of C3b-sensitized red cells.

Rationale for therapeutic apheresis
TPE may remove pathogenic immune complexes, activated complement components, and autoantibodies. TPE is most useful in AIHA to reduce/eliminate autoantibody in severe situations (i.e., anemia not responding to transfusion) until immunosuppressive therapy takes effect or if other treatments have failed. IgG is mostly extravascular and at body temperature is absorbed to the RBC and thus not efficiently removed when plasma is removed. Anecdotal evidence of favorable results has been described in some cases of IgG hemolysis. IgM, on the other hand, is mostly extravascular and binds poorly to RBC at body temperature thus TPE may significantly reduce antibody titer in CAD. In either case, improvement of AIHA after TPE is usually temporary, depending on the autoantibody, and its rate of production.

Case reports have claimed success using TPE as a “primer” for IVIG or cyclophosphamide treatment (e.g., synchronization of three daily sessions of TPE followed by pulse treatments with cyclophosphamide and prednisone). The category III is assigned based on paucity of data.

Technical notes
If the thermal amplitude of an IgM cold autoantibody is such that agglutination occurs at room temperature, red cell agglutination may occur within the cell separator and tubing. In these situations, therapy may require a controlled, high temperature setting of 37°C both in the room and within the extracorporeal circuit. In cases of IgG AIHA, patient anemia may require priming of the extracorporeal circuit with RBCs to safely perform the procedure. RBC units may require careful selection due to problematic serology and autologous incompatibility.

References [67–73]
*As of February 2, 2006, using PubMed and the MeSH search terms autoimmune hemolytic anemia, cold agglutinin disease, plasma exchange, and plasmapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
**Description of the disease**

Babesiosis is a protozal disease transmitted from an animal reservoir to humans by the bites of hardticks, or, more rarely, by transfusion. Ixodes dammini, the deer tick, is usually responsible for transmission of the disease from animal reservoirs to human hosts. Three out of 70 species of babesia (B. bovis, B. divergens, and B. microti) have been positively implicated in causing human infection and diseases. In the U.S., B. microti appears to be the predominant human pathogen. Endemic areas are the coastal and inland regions of the northeast, as well as Wisconsin and Minnesota.

The incubation period is usually 1–3 weeks, with longer incubation period (6–9 weeks) reported with transfusion transmission. Most cases are subclinical or result in a mild flu like illness. In clinical apparent cases, symptoms are usually nonspecific and include fever, anorexia, shaking chills, headaches, myalgia, vomiting, abdominal pain, and emotional lability. However, immunocompromised patients, especially asplenic patients, patients with HIV, simultaneous infection with Lyme disease, and elderly patients may have much more serious clinical course. In these patients, symptoms may include hemolytic anemia, acute renal failure, disseminated intravascular coagulation (DIC), congestive heart failure, and pulmonary disease. Specific diagnosis is made through examination of a Giemsa-stained blood smear, DNA amplification using polymerase chain reaction, or detection of specific antibody. Usually 1–10% of the red blood cells (RBCs) are parasitized in normal hosts. In immunocompromised host, parasitemia up to 85% has been described.

**Current management/treatment**

Primary therapy includes a combination of antibiotics, most commonly quinine sulfate and clindamycin. However, in patients who cannot tolerate those antibiotics because of toxicities or adverse events, atovaquone suspension plus azithromycin was recently reported as equally effective and less toxic.

**Rationale for therapeutic apheresis**

The mechanism of action of exchange transfusion is twofold. First, it helps to lower the level of parasitemia by physically removing the infected RBC from the blood stream and replacing them with noninfected RBC. Because babesia organisms do not have an exo-erythrocytic phase, removal of RBC-associated parasites is potentially curative. Second, the hemolytic process produces vasoactive compounds, including a variety of cytokines (including TNF-α, IL-6, IL-10) and thromboplastin substances, which can promote renal failure and disseminated intravascular coagulation. RBC exchange may help to curtail the production of these substances. The greatest advantage of RBC exchange over antibiotic therapy is its rapid therapeutic effectiveness. In severe cases, the benefits seem to clearly outweigh the risks of the procedure, mainly, exposure to multiple red cell transfusions. The specific level of parasitemia to guide when to perform RBC exchange is not clear. Greater than 10% parasitemia is the most commonly used guideline. Patients with symptomatic disease and significant comorbidites may benefit from early intervention with RBC exchange in addition to antibiotics even if the parasitemia level is below 10%.

**Technical notes**

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired postprocedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume red cell exchange can reduce the fraction of remaining patient red cells to roughly 10–15% of the original.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1–2 total RBC volume</th>
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</thead>
<tbody>
<tr>
<td>Replacement fluid:</td>
<td>leukoreduced RBCs</td>
</tr>
<tr>
<td>Frequency:</td>
<td>single procedure but can be repeated</td>
</tr>
</tbody>
</table>

**Duration and discontinuation/number of procedures**

The specific level to which parasitemia must be reduced to elicit the maximum therapeutic effect is not clear. Treatment is usually discontinued after achieving <5% residual parasitemia. Decision to repeat the exchange depends on the level of parasitemia post exchange as well as the clinical condition (ongoing signs and symptoms).

**References [74–78]**

*As of November 8, 2005, using PubMed and the MeSH search terms babesiosis, erythrocytapheresis, and red cell exchange for reports published in the English language. References of the identified articles were searched for additional cases and trials.*
**Description of the disease**

CAPS was first described in 1992 by Asherson, as an unusual variant of antiphospholipid syndrome (APS). Catastrophic Antiphospholipid Syndrome (CAPS) is defined as the acute onset of multiple thrombosis in at least three organ systems over a period of days or weeks, in patients with serologic evidence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, and/or anti-β2 glycoprotein I). The most commonly affected sites are small vessels of kidneys, lungs, brain, heart, and skin, although large vessel thrombosis can also be present. Common manifestations include renal failure, acute respiratory distress syndrome, pulmonary embolism, livedo reticularis, purpura, skin necrosis, cerebral infarcts, encephalopathy, seizures, and cerebral venous occlusion. In addition, the systemic inflammatory response syndrome (SIRS) is a component of the acute phase of CAPS. Thrombocytopenia can be marked, over 33% of patients have hemolysis, and 20% present with disseminated intravascular coagulation. However, schistocytes are only rarely seen, and help differentiate CAPS from other thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). CAPS may be the first manifestation of APS (“de novo”) or complicate the course of patients known to have the syndrome. Mortality approaches 50% and is mainly due to myocardial thrombosis with or without respiratory failure.

**Current management/treatment**

The optimal treatment of CAPS is still debatable since there have been no prospective studies due to the rarity of the condition. However, the therapeutic approach has to have three clear aims: to treat any precipitating factors (e.g., infection, necrotic organ), to prevent and to control ongoing thrombosis, and to suppress the excessive cytokine production. Full anticoagulation with heparin, high dose corticosteroids, therapeutic plasma exchange (TPE), and intravenous immunoglobulin are the most commonly employed therapies. If CAPS is associated with a flare of systemic lupus erythematosus, cyclophosphamide is also used. Parenteral antibiotics should be administered early if infection is suspected. A review of the outcomes of the first 220 patients entered into the CAPS Registry (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) demonstrated that the combination of TPE or intravenous immunoglobulin, anticoagulants, and steroids had the best survival rate of 63% of all treatment approaches.

**Rationale for therapeutic apheresis**

The exact mechanism of TPE in CAPS is not known, but the removal of pathologic antiphospholipid antibodies as well as cytokines, tumor necrosis factor alpha, and complement is thought to play an important role. Furthermore, since plasma has been the replacement in most reported cases, transfusion of natural anticoagulants such as protein C, protein S, and antithrombin may contribute to the overall benefit of the procedure. However, it has not been established if plasma transfusion alone would have a similar benefits as this option has not been tested. The category III is assigned based on paucity of data.

**Technical notes**

See the introductory article in this issue.

**Volume treated:** 1–1.5 TPV  
**Frequency:** daily

**Duration and discontinuation/number of procedures**

Minimum of three to five exchanges. Discontinuation is based on the patient’s clinical response. Some patients have been treated for weeks.

**References [78–84]**

*As of March 1, 2006, using PubMed and the MeSH search terms catastrophic antiphospholipid syndrome (CAPS), antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, therapeutic plasma exchange, plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.  
# Data include all patients entered into the CAPS registry. Most cases have been published and the references are available at the web site as well.
**Description of the disease**

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by proximal and distal symmetrical muscle weakness either with or without numbness that progresses and relapses for over two or more months. Neurologic impairment includes decreased sensation, diminished or absent reflexes, elevated cerebrospinal fluid protein level, and evidence of demyelination is present. CIDP can occur in conjunction with other disorders such as HIV and diabetes. Patients with monoclonal gammopathies can present with similar findings (see fact sheet on polyneuropathy in monoclonal gammopathy). CIDP is distinct from Guillain-Barre syndrome (acute inflammatory demyelinating polyneuropathy; AIDP) by being chronic rather than acute disorder (see Acute Inflammatory Demyelinating Polyneuropathy fact sheet). Other disorders with similar clinical presentations include inherited, paraneoplastic, toxic, nutritional deficiency, porphyria, and critical illness neuropathies.

**Current management/treatment**

Corticosteroids, TPE, and intravenous immunoglobulin (IVIG) all have similar treatment outcomes based on controlled trials. Decision to use one over another is based on cost, availability, and side effects. Individuals may differ in response to any one of these agents. Therapeutic response is measured by improvement or stabilization, at which point treatment can be tapered or discontinued. Sixty percent to 80% respond to initial therapy but long-term prognosis varies. Maintenance therapy, including continuing steroids, periodic TPE, or infusion of IVIG, is usually required because discontinuation of therapy may be followed by relapse. Maintenance therapy is dictated based on the patient’s symptoms and clinical exam. Secondary therapies include cyclosporine, interferon alpha, azathioprine, and cyclophosphamide.

**Rationale for therapeutic apheresis**

The presumed etiology of CIDP is autoimmune attack on the peripheral nerves. The sera or purified IgG of CIDP patients causes demyelination or peripheral nerve deficits following intramuscular or intraneural injection into rats. Therapies are aimed at modulation of the abnormal immune response. 

Case series and case reports have described the treatment of CIDP using Staphylococcal protein A silica Immunoadsorption** and double filtration plasmapheresis.

**Technical notes**

See the introductory article in this issue.

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**Volume treated:** 1–1.5 TPV  
**Frequency:** 2–3 TPE/week until improvement, then taper as tolerated

**Replacement fluid:** albumin

**Duration and discontinuation/number of procedures**

TPE provides short-term benefit but rapid deterioration may occur afterwards. This may necessitate maintenance treatment with TPE, which should be tailored to the individual patient. The frequency of maintenance TPE may range from weekly to monthly as needed to control symptoms.

**References [42, 85–88]**

*As of October 3, 2005, using PubMed and the MeSH search terms chronic inflammatory demyelinating polyneuropathy, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.  
**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.*

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*Journal of Clinical Apheresis DOI 10.1002/jca*
COAGULATION FACTOR INHIBITORS

Disease Group: Hematologic
Incidence: 20–30% in Hemophilia A patients; 3–5% in Hemophilia B patients; 0.2–1 per 1,000,000/year for spontaneous FVIII inhibitor; rare FV inhibitor

<table>
<thead>
<tr>
<th># of reported patients*</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
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Description of the disease
Factor deficiencies can either be congenital or acquired; the majority of acquired deficiencies result from autoimmune. In addition congenital factor deficient patients can develop inhibitors, alloantibodies, to the factors. Twenty percent to 30% of patients with severe hemophilia A, factor VIII deficiency, develop inhibitors while 3–5% of hemophilia B, factor IX deficiency, patients develop inhibitors. Acquired hemophilia due to an autoimmune against FVIII is rare with a biphasic age distribution in the elderly and in the post partum period. It is associated with autoimmune disorders, infections, and malignancy. Allo- or auto-antibodies bind to coagulation factors and cause clearance by reticuloendothelial system or inhibit their functions, both of which result in bleeding tendency. These inhibitors are quantified and expressed as Bethesda units (BUs). A titer of <5 BU is considered a low titer antibody. The incidence of antibodies against FV and prothrombin has increased with frequent use of topical bovine thrombin in fibrin glue. The bovine thrombin preparation contains FV. Once exposed to these bovine factors, patients can make antibodies that in turn cross react with human factors causing their deficiencies. Patients with lupus anticoagulant occasionally have selective prothrombin deficiency due to an antibody against FII. Acquired FX deficiency is frequently associated with systemic amyloidosis due to selective binding of FX to amyloid fibrils. Acquired von Willebrand’s disease is frequently associated with monoclonal gammopathies, lymphoproliferative, myeloproliferative, and autoimmune disorders. Other congenital factor deficiencies are rare. Some of these deficiencies place patients at risk for bleeding while other place patients at risk for thrombosis.

Current management/treatment
In patients with factor inhibitors, the therapy should be individualized, depending on the clinical setting, the presence or absence of bleeding, and the inhibitor titer. The goals of therapy include cessation of bleeding and suppression of inhibitor production. The current treatment options for bleeding or preoperatively is to replace the factor or bypass it. For example in factor VIII deficient patients include high doses of FVIII for low titer inhibitor (>5 BU) and FVIII bypassing products for high titer inhibitors (>5 BU), which include activated prothrombin complex concentrates, such as FEIBA, Autoplex, and recombinant factor VIIa (Novoseven).

The treatment options for inhibitor suppression include high dose corticosteroids, cyclophosphamide, cyclosporine, rituximab, and high dose IVIG.

Rationale for therapeutic apheresis
For coagulation factor inhibitors, the extracorporeal removal by immunoadsorption is more effective than plasma exchange. There are currently two immunoadsorption techniques in practice, one of them is Staphylococcal protein A agarose** (SPA); the other is sepharose-bound polyclonal sheep antibodies against human Ig. Polyclonal sheep antibodies bind all classes of immunoglobulin, whereas, SPA binding of IgG subclasses 1, 2, 4 are stronger than IgG1, IgM, and IgA. Because antibodies against coagulation factors are mostly IgG4, SPA immunoadsorption is more effective in removal of antibodies and improvement of the clinical condition. SPA can also interact with the immune system, which may result in immunomodulation. These effects include a decrease in activated monocytes and cytotoxic T cells, a change in T cell population, and a decrease in autoantibody. Hence, SPA can remove a large amount of IgG. The reduction in inhibitor titer is temporary. Postprocedure antibody titer may be elevated due to the re-equilibration of antibodies from extravascular to intravascular compartments.

Plasma infusion is the main stay of the treatment for rare congenital factor (V, X, XI) deficiencies when factor concentrates are not available. However, when there is a concern for volume overload or when surgery is scheduled that requires 80–100% factor level that cannot be obtained by simple plasma infusion, TPE with plasma as replacement fluid may be used.

The category III assignment is based on paucity of data.

Technical notes
To remove inhibitors, plasma flow rates are 35–40 mL/minute in SPA; a three plasma-volume treatment (10 L) requires 20–30 adsorption cycles. Anticoagulant should be used at the lowest amount possible. TPE for rare factor deficiencies requires careful adjustment of anticoagulation with ACD.

Volume treated: 1–1.5 TPV TPE; 3 TPV IA
Replacement fluid: TPE: plasma; IA: none
Frequency: TPE for congenital, rare factor deficiencies: as needed; IA for inhibitors: daily

Duration and discontinuation/number of procedures
For rare congenital factor deficiency, before and after surgery to maintain 80% and 50% factor level, respectively. For inhibitors, daily until antibody titer decreases and bleeding can be easily controlled with other therapeutic modalities.

References [73, 89–94]
*As of March 1, 2006 (IA), and February 20, 2007 (TPE), using PubMed and the MeSH search terms coagulation factor deficiency, coagulation factor inhibitors, factor VIII inhibitors, immunoadsorption, plasmapheresis, and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.
**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.
**Description of the disease**

Cryoglobulins comprised immunoglobulins that reversibly precipitate below body temperature. The aggregates of cryoglobulins can deposit on small vessels and cause damage by activating complement followed by recruiting leukocytes. This most likely occurs on the skin of lower extremities because of exposure to lower temperatures. The symptoms secondary to cryoglobulinemia range from none to severe. Cryoglobulinemia is associated with a wide variety of diseases including lymphoproliferative disorders, autoimmune disorders, and viral infections (e.g., hepatitis B and C). Mild symptoms include purpura, arthralgia, and mild sensory neuropathy. Severe symptoms include glomerulonephritis, motor neuropathy, and systemic vasculitis. Cryoglobulins are classified into three types: type I consist of monoclonal immunoglobulins, usually due to multiple myeloma or Waldenström’s macroglobulinemia, type II contain polyclonal IgG and monoclonal IgM rheumatoid factor usually due to hepatitis C infection, and type III contain polyclonal IgG and IgM usually due to inflammatory disorders, autoimmune disease, or hepatitis C infection. About 80% of individuals with mixed cryoglobulinemia (types II and III) have hepatitis C. The diagnosis of cryoglobulinemia is made by history, physical findings, low complement levels, and detection of cryoglobulins (cryocrit).

**Current management/treatment**

Management is based on treating the underlying disorder and the severity of symptoms. There is no correlation between the severity of disease and cryocrit. Individuals with type I have a higher cryocrit than individuals with type II or III. Asymptomatic individuals do not require treatment of their cryoglobulinemia. Mild symptoms can be treated with cold avoidance and analgesics. More severe disease warrants the use of immunosuppressive therapy such as steroids and cytoxan. There are reports of good clinical response following the use of rituximab (anti-CD20). Interferon and ribavirin are the treatment of choice in cases related to hepatitis C infection.

**Rationale for therapeutic apheresis**

Plasma exchange (TPE) removes cryoglobulins efficiently. It is used in all types of cryoglobulinemia for a wide variety of clinical manifestations. TPE has been most used in active moderate to severe cryoglobulinemia with renal impairment (membranoproliferative glomerulonephritis), neuropathy, vasculitis, and/or ulcerating purpura. TPE may be performed in conjunction with steroids or cytotoxic agents or by itself. It has been used in both the short and long term management. Case series and case reports suggest 70–80% improvement with TPE. Double cascade filtration, which separates plasma out of whole blood in the first filter and removes high molecular weight proteins in the second filter (such as IgM), has also been used to treat cryoglobulinemia.

**Technical notes**

There is a single case report of a patient receiving plasma exchange who had acute oliguric renal failure due to precipitation of cryoglobulin within glomerular capillary loops, which was thought to be the result of the infusion of cold plasma. Other cases have reported cryoglobulin precipitation in the extracorporeal circuit. Therefore, it is prudent to warm the room, use blood warmers to warm the draw and return lines, and/or warm the replacement fluid.

**Volume treated:** 1–1.5 TPV  
**Replacement fluid:** albumin  
**Frequency:** every other day

**Duration and discontinuation/number of procedures**

The reports use a variety of number of treatments and frequencies. For acute symptoms, performance of five or six procedures, and re-evaluation for clinical benefit should be considered. TPE allows for resolution of acute symptoms prior to the ability to treat the underlying disease and to suppress immunoglobulin production by immunosuppressive drugs. Weekly to monthly maintenance treatments may be necessary in patients who initially responded to prevent recurrent symptoms. Because the cryocrit is not a marker of disease activity, it should not be used as a criterion for initiating or discontinuing TPE.

**References [95–99]**

*As of September 21, 2005, using PubMed and the MeSH search terms cryoglobulinemia and plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease
Mycosis fungoides (MF) and Sézary syndrome are the most common types of cutaneous T cell lymphomas and are the only ones treated with extracorporal photopheresis (ECP). Their etiology and pathogenesis are unknown. MF is an indolent disease that progresses from an erythematous phase, the classical plaque stage, to skin tumors or erythroderma. Sézary syndrome is defined by erythroderma, generalized lymphadenopathy and malignant T cells (Sézary cells) in skin, lymph nodes, and blood. The latter is a highly characteristic feature of the syndrome, but not pathognomonic. Throughout all phases, itching can be debilitating and demands therapeutic intervention. Survival is typically 10 years from presentation and has not improved despite various treatment modalities, including ECP. However, prognosis depends on the type and extent of skin and deep tissues involvement. Most patients with extracutaneous disease will die of CTCL. Bacteremia from infected skin lesions and subsequent sepsis is the most common cause of death.

Current management/treatment
Treatment can be topical or systemic. In the early stages, it aims at preventing spread to extracutaneous sites. Topical options are used in the early stages of MF and include emollients, steroids, ultraviolet B, psoralen photochemotherapy (PUVA), chemotherapy or retinoids, external beam radiotherapy, and total skin electron beam therapy. Systemic treatment is added to patients with widespread disease at any stage and may consist of single-agent or combination chemotherapy. Regimens with multiple agents have yielded response rates of up to 80% with complete responses of 30% lasting for up to 1 year. Additional systemic treatments include interferon alpha, interleukin-12, retinoids, oral bexarotene, and immunologic approaches such as monoclonal antibodies. ECP has been approved for MF since 1987 based on data that demonstrated an overall combined response rate for advanced disease (erythrodermic stage) of 58%, including 15% with complete remission of lesions. ECP for the nonerythrodermic stage is not indicated (see the publication on category IV indications in this Special Issue).

Rationale for therapeutic apheresis
Although the mechanism of action of ECP is still unknown, it is currently accepted that it induces immunomodulation through lymphocyte apoptosis and monocyte transformation into dendritic cells (DCs). In turn, mature DCs loaded with pathogenic T cell peptides mediate a cytotoxic response towards the malignant clones. More than 20 published studies have shown clinical benefit of ECP. Clinical response varies from control of itching to clearing of skin lesions. Furthermore, ECP is well tolerated and has a very low toxicity profile. The literature suggests that ECP may potentially be the most effective treatment for erythrodermic MF and should be considered as first-line therapy for patients at that stage. The following characteristics appear to be associated with response to ECP: short duration of disease, absence of bulky lymphadenopathy or internal organ involvement, white blood cell count <20 × 10^9/L, Sézary cells comprising only 10–20% of mononuclear cells, normal or close to normal natural killer cell activity, CD8+ T cells above 15%, lack of prior intensive chemotherapy and plaque-stage disease involving only 10–15% of the skin surface.

Technical notes
Since ECP is an intermittent (discontinuous) procedure, it is crucial to ensure that the extracorporeal volume does not reach or exceed 15% any time during the collection or processing of the blood. Constant monitoring of vital signs help diagnose hemodynamic compromise. If hypovolemia occurs, blood collection should be paused and saline boluses can be given through the vascular access for ECP. Lipemic plasmas may prevent the instrument’s ability to detect the buffy coat layer in the centrifuge bowl. In severe cases, the treatment has to be aborted and the patient should be told to avoid a high fat meal prior to undergoing ECP. At the end of a successful treatment, patients should be instructed to wear eye and skin protection against ultraviolet radiation for the next 24 hours due to the infusion of free psoralen with the buffy coat suspension.

Duration and discontinuation/number of procedures
Response to ECP is not usually seen before 6–8 months of treatments in the frequency mentioned above. While some patients may undergo a tapering schedule and remain well, others require long-term ECP for control of the disease and its symptoms. A percentage of Sézary cells in the circulation greater than 20% may be associated with the need for chronic photopheresis. Since there is no standardized approach, itching is often used to gauge the need for more intense treatment. Improvement of the skin lesions is not always achieved. The decision to discontinue ECP has to be made in conjunction with the patient and the healthcare team. Important factors to be considered include treatment response, tolerability and availability, as well as patient prognosis.

References [100–106]
*As of March 25, 2006, using PubMed and the MeSH search terms cutaneous T-cell lymphoma, Sézary syndrome, extracorporeal photochemotherapy (ECP), and photopheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
ERYTHROCYTOSIS AND POLYCYTHEMIA VERA

Prevalence: 0.3% (erythrocytosis)
Incidence: 2.3 per 100,000/year (polycythemia vera)

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<tr>
<td>Strength of evidence</td>
<td>Type II-3</td>
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Description of the disease
Absolute erythrocytosis is defined as a red cell mass of at least 25% above the gender-specific mean predicted value. Hematocrit (Hct) values >60% for males and >56% for females are always indicative of absolute erythrocytosis, as these levels cannot be achieved with plasma volume contraction alone or other causes of “apparent” or “relative” erythrocytosis. Primary erythrocytosis refers to the myeloproliferative disorder polycythemia vera (PV), in which an abnormal hematopoietic stem cell clone autonomously overproduces red cells. Additional features of PV include splenomegaly, granulocytosis, thrombocytosis and a point mutation in the tyrosine kinase JAK2 gene. Secondary erythrocytosis refers to isolated red cell overproduction due to a congenital erythropoietic or hemoglobin defect, chronic hypoxia related to a respiratory or cardiac disorder, ectopic erythropoietin (Epo) production (e.g., from renal cell carcinoma, uterine leiomyoma, or Epo augmentation (e.g., post-renal transplantation). Idiopathic erythrocytosis refers to erythrocytosis in the absence of a primary disorder or features of PV. Whole blood viscosity increases significantly as the Hct level exceeds 50%. Patients with PV may experience hyperviscosity-related symptoms with modestly elevated Hct, whereas patients with secondary erythrocytosis are usually asymptomatic until Hct levels exceed 55–60%. Hyperviscosity complications include headache, dizziness, slow mentation, confusion, fatigue, myalgia, angina, dyspnea and thrombosis. Roughly 15–40% of patients with PV develop arterial or venous thrombosis. Thrombotic risk factors with PV include uncontrolled erythrocytosis, age >60 years, history of prior thrombosis, cardiovascular comorbidities, immobilization, pregnancy and surgery. PV may also induce microvascular ischemia of the digits or in the central nervous system.

Current management/treatment
Erythrocytosis and hyperviscosity symptoms due to pulmonary hypoxia resolve with long-term supplemental oxygen and/or continuous positive airway pressure maneuvers. Surgical interventions may correct secondary erythrocytosis due to a cardiopulmonary shunt, renal hypoxia or an Epo-producing tumor. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists are beneficial for postrenal transplantation erythrocytosis. When the primary disorder cannot be reversed, symptomatic hyperviscosity can be treated by isovolemic phlebotomy. The therapeutic endpoint for phlebotomy varies according to the underlying etiology and the need for an increased oxygen-carrying capacity (especially with cyanotic congenital heart disease). Patients with PV require regular phlebotomies to maintain a normal Hct (i.e., <45%). Low-dose aspirin is useful for thromboprophylaxis. Cytoreductive agents may be indicated to control the Hct and/or platelet count.

Rationale for therapeutic apheresis
Red cell reduction by automated apheresis, like isovolemic phlebotomy, corrects hyperviscosity by lowering the hematocrit, which reduces capillary shear rates, increases microcirculatory flow and improves tissue perfusion. Optimal tissue oxygenation minimizes the release of prothrombotic factors induced by ischemia. For PV patients with acute thromboembolism, severe microvascular complications or bleeding, therapeutic erythrocytapheresis may be a useful alternative to emergent large-volume phlebotomy; particularly if the patient is hemodynamically unstable. Erythrocytapheresis may also be appropriate prior to surgery to reduce the high risk of perioperative thrombohemorrhagic complications in a PV patient with uncontrolled Hct. Thrombocytapheresis, “plateletapheresis”, as well as erythrocytapheresis may be indicated for patients with PV and an acute complication associated with uncontrolled thrombocytosis and erythrocytosis. With secondary erythrocytosis and symptomatic hyperviscosity or thrombosis, red cell reduction by apheresis may, in selected cases, be a safer and more effective approach than simple phlebotomy.

Technical notes
Automated apheresis instruments can calculate the volume of blood removal necessary to achieve the desired postprocedure hematocrit. Saline boluses may be required during the procedure to reduce blood viscosity in the circuit and avoid pressure alarms.

Duration and discontinuation/number of procedure
In patients with PV, the goal is normalization of the Hct (i.e., <45%). For secondary erythrocytosis, the goal is to relieve symptoms but retain a residual red cell mass that is optimal for tissue perfusion and oxygen delivery. A postprocedure Hct of 50–52% might be adequate for pulmonary hypoxia or high oxygen affinity hemoglobins, whereas Hct values of 55–60% might be optimal for patients with cyanotic congenital heart disease. A single procedure should be designed to achieve the desired postprocedure Hct.

References [107–112]
*As of March 15, 2006, using PubMed and the MeSH search terms erythrocytosis, polycythemia vera, erythrocytapheresis, apheresis, hyperviscosity, red cell exchange, and myeloproliferative disorder for reports published in the English language. References of the identified articles were searched for additional cases and trials.
**FAMILIAL HYPERCHOLESTEROLEMIA**

**Disease Group:** Metabolic

**Incidence:** Heterozygotes 200 per 100,000/year; Selective Removal I (homozygotes) Homozygotes 1 in 1,000,000/year Selective Removal II (heterozygotes)

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**# of reported patients*: >300**

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<td>II (heterozygotes)</td>
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<td>TPE</td>
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**Description of the disease**

Familial hypercholesterolemia (FH) is an autosomal dominant disorder associated with well-characterized mutations of hepatocyte apolipoprotein-B (apo-B) receptors resulting in decreased LDL removal by the liver. FH exhibits a gene dosage effect: Homozygotes may have cholesterol in the range of 650–1,000 mg/dL, xanthomata by age 4 years, and death from coronary heart disease by age 20. Heterozygotes may have cholesterol in the range of 250–550 mg/dL, xanthomata by age 20 years, and atherosclerosis by age 30.

**Current management/treatment**

HMG-CoA reductase inhibitors, bile acid binding resins, nicotinic acid, and dietary modification can result in significant reductions of cholesterol in heterozygotes, but homozygotes and some heterozygotes are unresponsive to (or intolerant of) medical management. Other therapies of last resort include distal ileal bypass, portacaval shunts, and liver transplantation. In the late 1970s therapeutic plasma exchange (TPE) was employed to lower serum cholesterol in patients with FH. More recently, selective removal systems have been used.

**Rationale for therapeutic apheresis**

Trials have examined the effect of apheresis on hypercholesterolemia. At first, TPE was used as it showed effective reduction in cholesterol levels. The nonselective nature of TPE with the removal of beneficial substances, e.g., HDL and immunoglobulins, prompted the development of systems for the selective removal of apo-B containing lipoproteins (LDL, Lp(a)).

Studies have demonstrated a number of beneficial effects of LDL removal. A single treatment, regardless of the system used, reduces LDL cholesterol levels by 50–60%. Short-term effects of this include improved myocardial and peripheral blood flow as well as enhanced endothelial function. LDL apheresis also alters LDL cholesterol subclass distribution with reduction of atherogenic LDL 4 and 5 subclasses. Decreased expression of adhesion molecules such as VCAM-1, E-selectin, and ICAM-1 on granulocytes, monocytes, and endothelial cells occurs following treatment.

Because of the slow rise in LDL and Lp(a) levels following treatment (1–2 weeks), the time-averaged cholesterol levels are reduced with repeated treatments. Long-term angiographic, ultrasonic, and CT studies have demonstrated stabilization or regression of coronary stenoses, widening of coronary artery diameter, decrease in plaque area, and decrease in plaque calcification. Long-term outcomes studies have demonstrated significant reductions in the number of coronary events.

**Technical notes**

Five selective removal systems are available world-wide. These are: (1) immunoadsorption: columns containing anti-apo-B antibodies bound to a matrix, (2) dextran sulphate columns: columns that bind apo-B containing lipoproteins by an electrostatic interaction, (3) heparin extracorporeal LDL precipitation (H.E.L.P.): precipitates apo-B molecules in the presence of heparin and low pH, (4) direct adsorption of lipoprotein using hemoperfusion: removes apo-B lipoproteins from whole blood through electrostatic interactions with polyacrylate coated polyacrylamide beads, and (5) membrane differential filtration: filters LDL from plasma based upon size.

All of these are equivalent with regard to cholesterol reduction and side-effects. Currently, only the dextran sulphate and H.E.L.P. systems are approved for use in the United States by the Food and Drug Administration (FDA). Both techniques require heparinization.

The use of angiotensin converting enzyme (ACE) inhibitors is contraindicated in patients undergoing LDL apheresis. Some negatively charged columns (e.g., dextran sulphate) convert kininogen to bradykinin. The inhibition of the normal metabolic pathway of bradykinin by the ACE inhibitors produces unopposed bradykinin effects including profound hypotension and flushing.

The goal of LDL apheresis is to reduce the time-averaged total cholesterol levels by 45–55%, the LDL levels by 40–60%, and the Lp(a) by 40–60%. FDA approved indications for patients with FH unresponsive to pharmacologic and dietary management are: (1) functional homozygotes with an LDL cholesterol >500 mg/dL, (2) functional heterozygotes with no known cardiovascular disease but an LDL cholesterol >300 mg/dL, (3) functional heterozygotes with known cardiovascular disease and LDL cholesterol >200 mg/dL.

Patients without FH but with very high LDL or Lp(a) cholesterol who cannot tolerate or whose condition is unresponsive to conventional therapy can also be treated.

During pregnancy, LDL cholesterol levels in individuals affected by FH can rise to extreme levels that can compromise uteroplacental perfusion. There have been case reports of the use of LDL apheresis in this setting to allow for the successful completion of pregnancy.

TPE can be effective but because of the availability of the selective removal systems and their enhanced efficiency of cholesterol removal, the use of TPE to treat FH is uncommon. It may, however, be the only option in small children.

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**Volume treated:** 1–1.5 TPV

**Replacement fluid:** selective removal: not applicable; TPE: albumin

**Frequency:** once every 2–3 weeks

**Duration and discontinuation/number of procedures**

Treatment is continued indefinitely with the frequency adjusted to maintain the time-averaged lipoprotein levels as described above.

**References [113–117]**

*As of November 30, 2005, using PubMed and the MeSH search terms hypercholesterolemia and apheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

*Journal of Clinical Apheresis* DOI 10.1002/jca
FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Disease Group: Renal

Incidence: Unknown—FSGS accounts for 5–15% of patients with nephrotic syndrome

Procedure Category

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Strength of evidence

Type II-3

Description of the disease

FSGS is more precisely a glomerular lesion than a specific diagnosis, with the common feature of steroid-resistant nephrotic syndrome. On kidney biopsy, the lesion is characterized by focal areas of sclerosis of some glomeruli while others appear normal. However, there are several histological variants such as cellular, collapsing, tip lesion, and perihilar, which are associated with different clinical manifestations at presentation and renal outcomes following treatment.

FSGS can be primary or secondary to a variety of entities such as obesity, reflux nephropathy, HIV infection, and heroin use. Since at least 50% of patients with FSGS progress to renal failure within 5 years, many undergo renal transplants. Unfortunately, ~20% of patients will experience a recurrence in the renal allograft, especially children. Recurrent disease is diagnosed by new onset of proteinuria, which should be aggressively treated to slow or arrest progression to renal insufficiency and graft loss. Patients who lost grafts due to recurrent FSGS have >80% chance of developing the same lesion in subsequently transplanted kidneys.

Current management/treatment

FSGS in native kidneys is treated primarily with corticosteroids for at least 6 months prior to trying second-line agents such as cyclophosphamide, chlorambucil, or azathioprine. For resistant cases, paucity of data on the role of TPE precludes it from being currently an option. On the other hand, several investigators worldwide have used TPE in the management of patients with FSGS in transplanted organs, in an attempt to save the graft. Although there is no standardized treatment for recurrent FSGS post-transplant, the majority of regimens use a combination of an immunosuppressant such as cyclophosphamide and TPE. While the optimal use of TPE has not been established, published data suggest that TPE should be initiated soon after the diagnosis of recurrence in order to induce quick remission and improve graft survival. However, the number of treatments needed to control proteinuria, a surrogate marker of FSGS, is quite variable and can reach dozens. Other therapeutic options for such cases include high-dose cyclosporine, angiotensin converting enzyme inhibitors, and indomethacin. Another approach to prevent recurrent FSGS is several sessions of preemptive TPE immediately prior to and following the transplant. Although some success has been obtained with such regimens, the number of treated patients is quite small and conclusions cannot be drawn at this point.

Rationale for therapeutic apheresis

Serum from FSGS patients appears to contain an ill defined “permeability factor,” probably a glycoprotein of molecular weight of 30–50 kDa that induces profound leakage of albumin when incubated with isolated rat glomeruli. Such factor is removed by TPE and its decrease in serum concentration coincides with improvement in proteinuria. Since it is thought that the immediate onset of proteinuria following transplant is mediated by this factor, prophylactic TPE may be instituted in high risk patients. A few case reports describe the use of Staphylococcal protein A silica** adsorption columns in recurrent FSGS, but the literature was not sufficient to allow any conclusions. The category III for primary FSGS and secondary FSGS was assigned to this disease based on limited and conflicting data available in the literature.

Technical notes

See the introductory article in this issue.

Volume treated: 1–1.5 TPV

Replacement fluid: albumin

Frequency: daily or every other day

Duration and discontinuation/number of procedures

One approach is to begin with three daily exchanges followed by at least six more TPEs in the subsequent 2 weeks, for a minimum of nine procedures. Tapering should be decided on a case by case basis and is guided by the degree of proteinuria. Timing of clinical response is quite variable and control of proteinuria may take several weeks to months. Some patients have received long-term monthly exchanges as maintenance therapy. There are no clinical or laboratory characteristics that predict the likelihood of success with TPE.

References [118–126]

*As of April 30, 2006, using PubMed and the MeSH search terms FSGS, recurrent FSGS, and therapeutic plasma exchange for reports published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Imunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.
GRAFT-VERSUS-HOST DISEASE

Description of the disease

Graft-versus-host disease (GVHD) following allogeneic hematopoietic progenitor cell transplantation (HPCt) is typically characterized as either acute (aGVHD) or chronic (cGVHD). Acute GVHD usually occurs within 3 months after HPCt and results from activation of donor T-cells by host antigen-presenting cells, leading to immune and cytokine-mediated tissue injury. The skin, gastrointestinal (GI) tract, and liver are major targets of aGVHD. Chronic GVHD often evolves from aGVHD and is mediated by donor allo- or autoreactive T cells that activate inflammatory cytokines, B-cells, autoantibody production, and cytolytic processes. End-organ complications of cGVHD include progressive fibrosis and/or dysfunction of the skin, eyes, mouth, lungs, gastrointestinal tract, liver, joints, and vagina. Classification of GVHD as acute or chronic relies on the disease manifestations, rather than strictly the time of onset, and clinical assessment scores have been developed to grade the severity of disease.

Current management/treatment

Acute GVHD of grades II to IV severity is treated with systemic corticosteroids plus a calcineurin inhibitor. Those patients who fail to respond adequately to corticosteroids (roughly 50%) suffer high rates of morbidity and mortality due to steroid side effects, infection, and organ dysfunction. Salvage therapies include antithymocyte globulin, monoclonal antibodies against T cells or inflammatory cytokines, mycophenolate mofetil, sirolimus, pentostatin, and extracorporeal photopheresis (ECP). Moderate to severe cGVHD is usually treated with high-dose systemic corticosteroids. Steroid-refractory or steroid-dependent cGVHD also carries a poor prognosis because of steroid side effects, infections, permanent organ/tissue injury, and disability. Treatment options include local/topical measures for the skin, eyes, mouth, and GI tract along with systemic therapies such as calcineurin inhibitors, mycophenolate mofetil, rapamycin, thalidomide, hydroxychloroquine, pentostatin, monoclonal antibodies against T cells, B cells or cytokines, and ECP.

Rationale for therapeutic apheresis

ECP involves three steps: (1) collection of peripheral blood leukocytes by apheresis; (2) extracorporeal exposure of the leukocytes to 8-methoxypsoralen (8-MOP) followed by irradiation with ultraviolet A (UVA) light; and (3) reinfusion of the photoactivated cells. The therapeutic effect of ECP for GVHD appears to involve induction of apoptosis in treated lymphocytes, modulation of monocyte-derived dendritic cell (DC) differentiation, increased production of anti-inflammatory cytokines by monocytes and T cells, decreased DC antigen-presenting function, restoration of normal T helper cell and DC subsets and endogenous regulatory T cells that establish immune tolerance. Response rates for steroid-refractory aGVHD range from 35 to 60% for GI and liver involvement to roughly 80% for skin disease, with complete responses outnumbering partial responses. For cGVHD, ECP improves skin or oral manifestations in 60–80% of steroid-dependent patients. Liver or GI complications respond in roughly 35–75% of cases, with the highest rates reported in children. Most responses with cGVHD are partial. Because ECP does not induce general immunosuppression, the greatest benefit may be in facilitating a rapid corticosteroid taper. A number of retrospective and prospective cohort studies using ECP for GVHD have been reported, including many within the last few years. No randomized controlled trial data are yet available. The British photodermatology group and the UK skin lymphoma group published their evidence-based practice guidelines in early 2006; however, those were based on study data only through 2001. The category III indication for non-skin GVHD was assigned because of the still limited data available in the literature.

Technical notes

ECP in individuals >40 kg can be performed using an intermittent-flow system and 8-MOP approved for the treatment of cutaneous T cell lymphoma. Heparin is utilized as anticoagulant but ACD-A can be substituted if necessary. An alternative two-process method is commonly used in Europe and for smaller body weight patients (i.e., weight <40 kg or when the extracorporeal volume exceeds 15% at any time during the collection or processing of the blood). This involves collecting mononuclear cells (MNC) by standard continuous-flow apheresis, photoactivating the MNC, and reinfusing the treated cells.

Duration and discontinuation/number of procedures

ECP is often performed one series weekly for aGVHD until disease response (usually within 4 weeks) and then tapered to every-other-week before discontinuation. For cGVHD, one series weekly ECP treatments are continued every week or biweekly until either a response or for 8–12 weeks, followed by a taper to every 2–4 weeks until maximal response.

References [127–135]

*As of March 15, 2006, using PubMed and the MeSH search terms graft-versus-host disease, extracorporeal photochemotherapy, extracorporeal photopheresis, and photopheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

**Varies greatly depending on age, conditioning regimen, graft manipulation, and HLA matching.
### HEART TRANSPLANT REJECTION

<table>
<thead>
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<tbody>
<tr>
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<td>I (prophylaxis of rejection)</td>
</tr>
<tr>
<td>ECP (treatment of rejection)</td>
<td>II (treatment of rejection)</td>
</tr>
<tr>
<td>TPE</td>
<td>III</td>
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### # of reported patients*: 100–300

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<tr>
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<td>0</td>
<td>8 (120)</td>
<td>4 (8)</td>
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</tbody>
</table>

### Description of the disease

Thousands of heart transplants are performed in the world each year. While outcomes have gradually improved since the first successful transplant in 1967, long-term survival is still threatened by infection, malignancy, and allograft rejection or vasculopathy. Cellular rejection mediated by T cells and diagnosed histopathologically, is the most common form of rejection. Humoral rejection is less frequent but is associated with increased graft loss, mortality, and vasculopathy. It is suspected when severe allograft dysfunction is accompanied by no histological signs of cellular rejection. Allograft vasculopathy is an accelerated form of atherosclerosis that occurs in up to 60% of transplanted recipients within 5 years posttransplantation.

### Current management/treatment

Prevention and treatment of rejection employ cyclosporine, mycophenolate mofetil, and corticosteroids with or without antilymphocyte antibodies. In addition, extracorporeal photopheresis (ECP) has been used to prevent or treat cellular rejection episodes and allograft vasculopathy and plasma exchange (TPE) has been used in episodes of acute humoral rejection.

### Rationale for therapeutic apheresis

The benefits of ECP in transplant management were initially shown in animals receiving skin or heart allografts. The first human studies were published in 1992 when patients were randomized to receive either ECP or corticosteroids to reverse cellular rejection. Their results demonstrated that both therapies were equally efficient and ECP had very low toxicity. In 1998, a multicenter study on prophylaxis after heart transplant showed that patients treated with ECP in addition to triple-drug immunosuppression had fewer rejection episodes after 24 ECP procedures compared with controls who received drugs alone. In 2000, a pilot, randomized, prophylactic study of 23 patients demonstrated a significant reduction in HLA antibodies in those treated with ECP plus immunosuppressive drugs at two time-points in the first 6 months of therapy. Furthermore, the ECP group had significantly reduced coronary artery intimal thickness compared with the control group. Although the mechanism of action of ECP remains unclear, two possible explanations for the beneficial effect are: (1) Stimulation of the immune system to destroy clone-specific T cells causing allograft rejection (“transimmunization”); and (2) Induction of antigen-specific immunotolerance via expansion of regulatory T cells (Tregs). TPE, on the other hand, is used in an attempt to remove antibodies and/or inflammatory mediators implicated in humoral rejection. Although there are reports of success with TPE, no control trials are available. The category III for TPE was assigned to this disease based on limited data available in the literature.

### Technical notes

ECP in heart transplant recipients is commonly performed in the outpatient setting and requires long-term vascular access. One option is a subcutaneous port which is easy to maintain and has less risk of infection. As with ECP for any indication, extracorporeal volume during blood processing may require technical adjustments such as saline boluses to avoid hypovolemia. Since patients are also receiving immuno-suppressive agents, they may have leukopenia and, especially, lymphopenia. Although there is no conclusive data that a minimum concentration of circulating lymphocytes is needed to mediate the benefits of ECP, it is advisable to check a complete blood cell count prior to the procedure to ensure that the count is not extremely low.

#### Volume treated:
- mononuclear cell product of approximately 270 mL consisting of mononuclear cells, plasma and saline ECP
- 1–1.5 TPV TPE

#### Replacement fluid:
- ECP: not applicable; TPE: albumin, plasma

#### Frequency:
- ECP: 2 procedures on consecutive days (one series) weekly or every 2–8 weeks for several months; TPE: daily to every other day

### Duration and discontinuation/number of procedures

ECP: The largest randomized clinical trial of ECP treated patients with 24 series during the first 6 months following transplantation and demonstrated decreased risk of cardiac rejection. The second largest study showed significant reduction of vasculopathy with one series of ECP every 4–8 weeks for 2 years. There are no defined criteria for duration or discontinuation of ECP or TPE.

### References [102,136–142]

*As of April 30, 2006, using PubMed and the MeSH search terms heart transplant, cellular rejection, humoral rejection, transplant vasculopathy, ECP, photopheresis, plasmapheresis, and therapeutic plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.*
Description of the disease

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that predominantly affects the kidneys. HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Two types of HUS have been described: diarrhea-associated HUS (d+ HUS or typical HUS) and non-diarrhea-associated HUS (d- HUS or atypical HUS (aHUS)). 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 6% of infected children (9-30% of children). In children with d+ HUS, acute renal failure predominates but most individuals recover spontaneously with a mortality rate of 3–5%. In adults with HUS, regardless of the presence of diarrhea, clinical manifestations are often severe and the mortality rate is high. aHUS may cluster in a family or occur sporadically with high mortality and morbidity. Familial HUS, accounting for 5–10% of all HUS, is associated with frequent relapses, end stage renal disease (ESRD), and a mortality rate of 54%. In familial HUS, 20–30% of patients have deficiency of factor H, membrane cofactor protein (MCP) or factor I due to mutations of complement regulator genes. Sporadic HUS is often associated with drugs (cyclosporine, quinine, mitomycin C, ticlopidine, oral contraceptives, etc), pregnancy, autoimmune diseases, infections, including HIV, or allogeneic hematopoietic progenitor cell (HPC), or solid organ transplantation. These disorders are now categorized into non-idiopathic thrombotic thrombocytopenic purpura (TTP) or thrombotic microangiopathy (TMA), particularly in adults. Clinical and laboratory features of aHUS are often indistinguishable from those of TTP, especially in adults, and therefore this syndrome has also been described as TTP-HUS (see TTP fact sheet). Assays for ADAMTS13 activity and its inhibitor can identify patients with congenital or acquired (idiopathic) TTP, which are characterized by severe deficiency of ADAMTS13 protease activity, but ADAMTS13 assays may not specifically differentiate HUS from TTP. Multiple factors may play a role in the development of aHUS and TMA, with direct insults to microvascular endothelial cells being the dominant hypothetical mechanism. 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-parade bodies. In addition, Shiga toxin may activate platelets and promote adhesion and aggregation of platelets onto UL-vWF multimers. In familial aHUS, the lack of functional factor H, MCP, or factor I in plasma results in over activation of the alternate complement pathway resulting in excessive consumption of complement C3, which may potentiate autoantibody- or immune complex-mediated glomerular injury.

Current management/treatment

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 has no proven role in d+ HUS in children (see the publication on category IV indications in this issue). Despite conflicting reports of the effectiveness of TPE in children with aHUS, TPE seems a reasonable option considering the poor prognosis of aHUS. In patients with non-idiopathic TTP, aHUS, or TMA, the role of TPE is uncertain but this treatment may be appropriate under certain circumstances and with a defined therapeutic trial endpoint because of the high mortality with idiopathic TTP and the inability to differentiate between the two. If response to initial treatment is poor, corticosteroids may be added and the volume or frequency of plasma exchange increased if the suspicion for TTP remains high. Alternatively, for aHUS and TMA conditions TPE should be abandoned if no response to an initial therapeutic trial. TPE is no longer considered a standard of care for TMA following HPC transplantation (transplant associated microangiopathy (TAM)), since effectiveness has not been proven. In familial HUS due to factor H, MCP, or factor I deficiency, benefits of transfusion of plasma would be expected but have not yet been shown to prevent relapse or progression to ESRD. The category III indication for aHUS, D+ adult HUS, D-pediatric HUS, TAM, and TMA was assigned because of the limited and/or conflicting data available in the literature.

Rationale for therapeutic apheresis

The rationale for TPE in HUS and TMA is undefined. However, TPE using replacement with plasma products can effectively replace the missing or defective factor H or factor I in familial HUS. ADAMTS13 protease or other unidentified factors that may be deficient in some cases of aHUS may be replenished by plasma replacement during TPE.

Technical notes

See the introductory article in this issue.

**Volume treated:** 1–1.5 TPV  
**Replacement fluid:** plasma; plasma cryoprecipitate reduced  
**Frequency:** daily then may taper frequency

Duration and discontinuation/number of procedures

Duration of daily TPE to achieve a durable remission (e.g., platelet count greater than 150 × 10^9/L, LDH near normal and no neurologic deficit, if initially present) is extremely variable, depending on the condition. A therapeutic trial using a limited number of procedures is appropriate for selected patients. For responding patients, continued TPE may be indicated for less than a week to an extended period in order to maintain a remission. Whether to stop abruptly or to taper after a clinical response is an empirical decision. Daily TPE should be reintiated with exacerbation (recurrent disease <30 days of TPE) or relapse (recurrent disease >30 days of complete remission) among responding patients.

References [143–148]

*As of April 30, 2006, using PubMed and the MeSH search terms hemolytic uremic syndrome, transplant associated microangiopathy, microangiopathy, plasmapheresis, and therapeutic plasma exchange for articles published in the English language. References of the identified articles were searched for additional cases and trials.

*Journal of Clinical Apheresis* DOI 10.1002/jca
HYPERLEUKOCYTOSIS

Disease Group: Hematologic

Incidence: AML with WBC > 100 × 10^9/L: 5–13% in adults and 12–25% in children; ALL with WBC > 400 × 10^9/L: ≤ 3%

Procedure

Leukocytapheresis

Category

I (leukostasis)

III (prophylaxis)

# of reported patients*: >300

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<td>I (leukostasis)</td>
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<tr>
<td>Leukocytapheresis</td>
<td>III (prophylaxis)</td>
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</tbody>
</table>

Description of the disease

Hyperleukocytosis is conventionally defined as a circulating white blood cell (WBC) or leukemic blast cell count >100 × 10^9/L. Leukostasis complications associated with hyperleukocytosis include organ or tissue dysfunctions directly attributable to the high burden of circulating leukemic myeloid or lymphoid blast cells in the absence of infection, thromboembolism, or other underlying etiology. In general, leukostasis is observed in acute myeloid leukemia (AML) when the WBC is >100 × 10^9/L and in acute lymphoblastic leukemia (ALL) when the WBC is >400 × 10^9/L. Patients with AML and an initial WBC count >100 × 10^9/L (predominantly consisting of blasts) have a twofold to threefold higher early mortality rate, primarily because of leukostasis and bleeding complications. However, the onset and severity of clinical complications is not predicted by the degree of hyperleukocytosis. Myeloid blasts are physically larger and more rigid than lymphoid blasts, and their cytokine products may upregulate endothelial cell adhesion molecule expression and activate inflammation. These processes can lead to microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction, and hemorrhage. The monoblastic/monocytic subtypes of AML appear particularly pathogenic, as pulmonary complications are reported at blast counts <50 × 10^9/L. Central nervous system (CNS) manifestations include confusion, somnolence, delirium, coma, and parenchymal hemorrhage with focal neurological deficits. Pulmonary complications include dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure, and radiographic findings of interstitial and/or alveolar infiltrates.

Current management/treatment

Definitive treatment is with induction chemotherapy. Hydroxyurea may be a useful temporizing cytoreductive agent. Associated tumor lysis syndrome and hyperuricemia are treated with intravenous fluids, electrolyte replacement, allopurinol or rasburicase, alkalization of the urine, and dialysis. Plasma, cryoprecipitate, and/or platelets are treated, as indicated, for bleeding or coagulopathy. Because of concerns of adding more cell mass to the circulation, RBC transfusions are generally avoided prior to cytoreduction. Adjunctive radiation therapy may be considered in individual cases with parenchymal brain lesions.

Rationale for therapeutic apheresis

Uncontrolled, retrospective data suggest that prophylactic leukocytapheresis can reduce early mortality but does not improve overall or long-term survival in patients with AML and hyperleukocytosis. One cohort study of patients with AML and hyperleukocytosis showed that a post-leukocytapheresis WBC count of around 90 × 10^9/L was not predictive of survival at one-week, suggesting that either a lower therapeutic endpoint is necessary and/or that associated comorbidities are more important determinants of outcome. Despite the inability to accurately predict leukostasis complications and the lack of a clear treatment goal, prophylactic leukocytapheresis should be considered for AML patients with a blast count >100 × 10^9/L and especially for those with a monocytic/monoblastic subtype. Among children and adults with ALL, clinical leukostasis occurs in <10% of those with WBC counts <400 × 10^9/L. Prophylactic leukocytapheresis offers no advantage over aggressive induction chemotherapy and supportive care, including those with tumor lysis syndrome. By comparison, pulmonary and CNS complications develop in over 50% of children with ALL and a WBC count ≥400 × 10^9/L. Prophylactic leukocytapheresis should, therefore, be considered in those patients. The category III indication for prophylaxis of hyperleukocytosis was assigned because of the limited and conflicting data available in the literature. By comparison, a number of uncontrolled studies report that cytoreduction with leukocytapheresis can rapidly reverse the pulmonary and CNS manifestations of leukostasis with either AML or ALL. Severe end-organ injury or hemorrhage may not improve, however, in patients with extensive and/or severe pre-existing tissue damage. Leukocytapheresis should be repeated in persistently symptomatic patients until clinical manifestations resolve or a maximum benefit is achieved. Concurrent chemotherapy is also required in order to prevent rapid reaccumulation of circulating blasts.

Technical notes

A single leukocytapheresis can reduce the WBC count by 30–60%. Erythrocyte sedimenting agents (e.g., hydroxyethyl starch) are not required but can enhance the efficiency of WBC removal. Red cell priming of the apheresis circuit can be employed for selected adults with severe anemia; however, undiluted packed red blood cells should be avoided in small children as this may increase viscosity. Utilize replacement fluid to ensure at least a net even ending fluid balance.

Volume treated: 1.5–2 TBV

Replacement fluid: crystalloid; albumin; plasma

Duration and discontinuation/number of procedures

For prophylaxis of asymptomatic AML patients, discontinue treatments when the blast cell count is <100 × 10^9/L (monitor patients with monocytic subtypes closely). For AML patients with leukostasis complications, discontinue when the blast cell count is ≤50–100 × 10^9/L and clinical manifestations are resolved. For prophylaxis of asymptomatic ALL patients, discontinue treatment when the blast cell count is <400 × 10^9/L. For ALL patients with leukostasis complications, discontinue treatment when the blast cell count is <400 × 10^9/L and clinical manifestations are resolved.

References [149–155]

*As of March 15, 2006, using PubMed and the MeSH search terms hyperleukocytosis, leukostasis, apheresis, leukapheresis, leukocytapheresis, and leukemia for reports published in the English language. References of the identified articles were searched for additional cases and trials.
HYPERTRIGLYCERIDEMIC PANCREATITIS

Disease Group: Metabolic

Incidence: 18 per 100,000/year

<table>
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<th>Procedure</th>
<th>Category</th>
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<tr>
<td>TPE</td>
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# of reported patients*: 100–300

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<td>7</td>
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</table>

Description of the disease

Hypertriglyceridemia (HTG) results from elevations in the lipoproteins responsible for triglyceride (TG) transport. Primary causes include mutations in genes such as those encoding lipoprotein lipase (LPL) and its activator apo C-II. Secondary causes include diabetes mellitus (DM), hypothyroidism, pregnancy, and medications. Extreme TG elevations are seen in homozygotes due to mutations as well as when secondary causes are superimposed upon underlying genetic defects. Complications occur when TG levels are >2,000 mg/dL. These include acute pancreatitis, chronic abdominal pain, hepatosplenomegaly, eruptive xanthomas, lipemia retinialis, peripheral neuropathy, memory loss/dementia, and dyspnea. Endothelial damage due to chemical irritation by fatty acids and lyssolecithin is felt to cause pancreatitis while hyperviscosity and tissue deposition produce the other complications.

Lipoatrophy is a rare case of HTG, which is characterized by adipose tissue loss, diabetes mellitus, and HTG. HTG leads to organomegaly, pancreatitis, and rarely cutaneous xanthomas. The cause of this disorder is unknown.

Current management/treatment

Treatment includes dietary restriction and lipid lowering agent administration (e.g., fibrates and nicotinic acid derivatives). With acute pancreatitis due to HTG, additional treatments include total parenteral nutrition (TPN), complete avoidance of oral intake, and moderate caloric restriction. If DM is present, insulin is also administered. Heparin has also been administered as it releases LPL from endothelial stores enhancing TG clearance. Heparin may exacerbate hemorrhage into the pancreatic bed in the setting of pancreatitis and, therefore, its use is controversial.

Rationale for therapeutic apheresis

Reports, series, and a single nonrandomized controlled trial have examined the use of TPE to treat acute pancreatitis due to HTG. Reductions in TG levels of 70–80% have been reported with improvement in symptoms of pancreatitis following one to two TPE. The single trial, however, found no difference with regard to mortality, systemic complications, and local complications in patients with severe pancreatitis (10 treated with standard therapy and TPE versus 19 treated with standard therapy). Adequate information was not provided to ascertain the comparability of the two groups. While the authors felt that these negative findings were due to delayed initiation of TPE and recommended earlier intervention, the time from diagnosis to start of TPE was not provided.

Five case reports examined TPE use in pregnant women with HTG-induced pancreatitis. In four cases, a single treatment was administered following delivery. In one case, monthly TPE was used to control HTG until fetal viability had been reached. The child was delivered by c-section and the HTG resolved.

Two case reports have examined TPE in generalized lipoatrophy. In both, serial TPE was used to control HTG and avoid pancreatitis. One report found benefit while one did not. In the latter, a variety of metabolic abnormalities were noted following TPE that were attributed to the treatment and TPE was not recommended based upon patient safety. It should be noted that the abnormalities attributed to TPE were amenorrhea, galactorrhea, proliferative retinopathy, and hypertension, complications that otherwise have not been reported to occur due to TPE and are of questionable association.

Other causes of HTG pancreatitis have been reportedly treated by TPE. One case report of lipid emulsion over-dose complicated by HTG and pancreatitis in a patient on TPN has been published. Reports of TPE treatment of HTG due to isotretinoin, proteinase inhibitors, and cyclosporin have been published. In all of these cases, treatment has been reported to be beneficial. One series reported chronic TPE treatment of two patients with recurring pancreatitis who were noncompliant with medical management. TPE prevented further episodes of pancreatitis. The category III for TPE was assigned to this disease based on limited data available in the literature.

Technical notes

Both centrifugal and double membrane filtration TPE have been used to treat pancreatitis due to HTG. A comparison of these two methods found greater removal with centrifugal methods because of the tendency of the TG to clog the pores of the filters.

Reports have suggested that heparin be used as the anticoagulant for these procedures because of its ability to release LPL which should enhance TG reduction. Many reports have used ACD-A with similar TG reductions. Most reports have used albumin as the replacement fluid. Some have used plasma as it contains LPL and could enhance TG removal. No direct comparisons of anticoagulants or replacement fluids have been reported.

Treatment has usually been implemented early in the course of the pancreatitis secondary to HTG.

Volume treated: 1–1.5 TPV

Replacement fluid: albumin; plasma

Frequency: one procedure may be repeated

Duration and discontinuation/number of procedures

For patients with acute pancreatitis, one TPE has been sufficient to improve the patient’s clinical condition and lower their TG levels with a second treatment if necessary.

References [156–162]

*As of January 7, 2006, using PubMed and the MeSH search terms hypertriglyceridemia and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease

Whole blood viscosity varies as a function of hematocrit, red blood cell aggregation, plasma proteins, and interactions with the vasculature. As blood viscosity rises, a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates, produces damage to fragile venular endothelium of the eye and other mucosal surfaces. The term “hyperviscosity syndrome” refers to the clinical sequelae of mucous membrane bleeding, retinopathy, and neurological impairment. Specific signs and symptoms include headache, dizziness, vertigo, nystagmus, hearing loss, visual impairment, somnolence, coma, and seizures. Other manifestations include congestive heart failure (related to plasma volume overexpansion), respiratory compromise, fatigue (perhaps related to anemia), peripheral polyneuropathy (depending on specific properties of the immunoglobulin), and anorexia. This syndrome occurs most typically in Waldenström’s macroglobulinemia, a lymphoplasmacytic lymphoma associated with the elaboration of ≥3 g/dL of monoclonal IgM immunoglobulin (M-protein) in the plasma. It also occurs in multiple myeloma, a plasma cell dyscrasia, when there is ≥6–7 g/dL of monoclonal IgA or ≥4 g/dL of monoclonal IgG3 in the plasma. In vivo whole blood viscosity is not necessarily identical to in vitro serum viscosity (relative to water: normal range being 1.4–1.8 Ostwald units). Therefore, serum viscosity measurement does not consistently correlate with clinical symptoms among individual patients. Almost all patients will be symptomatic when their serum viscosity rises to between 6 and 7. Some may be symptomatic at a viscosity as low as 3–4, others not until their viscosity reaches 8–10.

Current management/treatment

Plasma removal has been successfully employed in the treatment of hyperviscosity syndrome in Waldenström’s macroglobulinemia since 1959. Manual plasma exchange techniques have been supplanted by automated plasma exchange. Because Waldenström’s macroglobulinemia and multiple myeloma are lymphoproliferative disorders, they are not curable by TPE alone. Alkylating agents, corticosteroids, targeted therapies, and transplant approaches are used to affect long-term clinical control of the disease.

Rationale for therapeutic apheresis

Early reports demonstrated that manual removal of up to 8 units of plasma per day (8 L in the first 1–2 weeks) could relieve symptoms of acute hyperviscosity syndrome, and that lowered viscosity could be maintained by a maintenance schedule of 2–4 units of plasma removed weekly. Today, removal of 8 L of plasma can be accomplished in two consecutive daily treatments using automated equipment. As the M-protein level rises in the blood, its effect on viscosity increases logarithmically. At some point an individual patient reaches his/her symptomatic threshold. By the same token, at the symptomatic threshold, a relatively modest removal of M-protein from the plasma (by plasma exchange) will have a logarithmic viscosity-lowering effect. Thus TPE is both rapid and efficient in relieving hyperviscosity.

Technical notes

There is no uniform consensus regarding the preferred exchange volume for treatment of hyperviscosity. It is understood that viscosity falls rapidly as M-protein is removed, thus relatively small exchange volumes are effective. Conventional calculations of plasma volume based on weight and hematocrit are inaccurate in M-protein disorders because of the expansion of plasma volume that is known to occur. Therefore, an empirical exchange volume of one plasma volume per procedure seems reasonable. Centrifugation, cascade filtration, and membrane filtration techniques have been described in case reports, most U.S. institutions employ continuous centrifugation plasma exchange.

<table>
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<th>Volume treated: 1–1.5 TPV</th>
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<tbody>
<tr>
<td>Replacement fluid: albumin</td>
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</table>

Duration and discontinuation/number of procedures

Patients can be treated daily until acute symptoms abate (generally 1–3 TPEs). At that point, serum viscosity measurement can be repeated to determine the patient’s symptomatic viscosity threshold. An empirical maintenance schedule of one plasma volume exchange every 1–4 weeks based on clinical symptoms may be employed to maintain clinical stability pending a salutary effect of medical therapy (e.g., chemotherapy).

References [163–170]

*As of January 23, 2006, using PubMed and MeSH search terms apheresis and hyperviscosity, for articles published in the English language. References of the identified articles were searched for additional cases and trials.
IDIOPATHIC THROMBOCYTOPENIC PURPURA

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# of reported patients*: >300

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<td>0</td>
<td>0</td>
<td>&gt;17 (520)</td>
<td>8 (9)</td>
<td>Type II-3</td>
</tr>
</tbody>
</table>

Description of the disease

Idiopathic (or autoimmune) thrombocytopenic purpura (ITP) is the most common autoimmune hematologic disorder. Autoantibodies or immune complexes are bound to platelet surface antigens, primarily GPIIb/IIIa and/or GPIb/IX, causing accelerated platelet destruction. ITP, which is a diagnosis of exclusion, is characterized by isolated thrombocytopenia without known cause in otherwise healthy individuals. Childhood ITP is generally acute, benign, self-limited, and typically presents with abrupt onset of petechiae, bruising and/or epistaxis following viral infection. Peak age is 2–5 years old with both sexes affected equally. Of 1,597 affected children reviewed, ITP resolved in 76% within 6 months (referred to as acute ITP), with the remainder having thrombocytopenia for >6 mo (referred to as chronic ITP). Remission occurred in 37% of chronic cases. Adult ITP generally has an insidious onset with 40–50% becoming chronically refractory and primarily affects women aged 18–40 years old. Up to 10% of adult ITP is associated with secondary disease (such as systemic lupus erythematosus, lymphoproliferative disorders, drug ingestion, and immunodeficiency disease like HIV). ITP in adults is more serious than in children, because the risk of fatal bleeding increases with age. At platelet counts <30 × 10^9/L, in patients younger than 40, 40–60, and >60 years old, this risk is 0.4%, 1.2%, and 13% per patient year, respectively.

Current management/treatment

Therapy is generally not indicated when platelet count is >20–30 × 10^9/L unless bleeding occurs. First-line therapies are oral corticosteroids (1–2 mg of prednisone/kg/day), intravenous immunoglobulin (IVIG) at 1 g/kg/day for 1–2 days, and IV anti-Rh (D) (50–75 µg/kg). In adults, corticosteroids remain the standard therapy. In children, IVIG or anti-Rh (D) may be substituted for prednisone for rapid response. If thrombocytopenia persists or recurs, splenectomy is recommended in adults but is deferred in children to prevent overwhelming postsplenectomy infection or to allow for spontaneous remission. In patients refractory to conventional therapy, other treatments include danazol, vinca alkaloids, cyclophosphamide, azathioprine, cyclosporine, interferon alpha, anti-CD20 (rituximab), and TPE (see the publication on category IV indications in this issue). Extracorporeal immunoadsorption with Staphylococcal protein A silica** (IA) may be considered in patients with refractory ITP, with life-threatening bleeding or in whom splenectomy is contraindicated.

Rationale for therapeutic apheresis

Staphylococcal protein A has a high affinity for the Fc portion of IgG and also for aggregated IgG. IgG antibodies and IgG-containing circulating immune complexes (CICs) can be selectively removed by extracorporeal exposure of patient’s plasma to protein A immobilized on a matrix. Although the mechanism of action remains poorly understood, the clinical effect may not derive from antibody removal per se, as response is not directly related to the quantitative removal of antibodies but may result indirectly from immunomodulation by the release of protein A into the patient, which induces targeted B-cell depletion. Previous studies of IA have demonstrated a range of outcomes from no improvement to complete remission for longer than 6 years. In 72 patients, including 4 with HIV-associated thrombocytopenia, 33 (46%) achieved a platelet count of >50 × 10^9/L with 18 having an acute increase to >100 × 10^9/L; 10 of the 18 achieved this increase during the first week of treatment. Median time to response was 2 weeks. In a trial in 5 children, aged 2.3–9.5 y, with chronic refractory ITP, 3 responded to IA with a rise in platelet count >50 × 10^9/L that persisted for >6 months. To reduce or prevent life-threatening complications, use of this column is contraindicated when the patient is on angiotensin converting enzyme (ACE) inhibitors, has a history of hypercoagulability or thromboembolic events.

Technical notes

Using Staphylococcal protein A silica**, the procedure can be done either on-line after separation of plasma by continuous-flow cell separator or off-line using phlebotomized blood. Plasma is treated by perfusion through the column and then reinfused with the flow rate not exceeding 20 mL/min. No significant difference between the two methods has been demonstrated in either safety or effectiveness. In children, extra care must be given to maintain isovolemia because of the large extracorporeal volumeinvolved with the procedure.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1,000–2,000 mL plasma On-line; 250–500 mL of plasma off-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency:</td>
<td>once a week or every 2–3 days</td>
</tr>
<tr>
<td>Replacement fluid:</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

Duration and discontinuation/number of procedures

There are no clear guidelines concerning treatment schedule and duration of treatment. Procedure is generally discontinued when either the patient shows improvement in platelet count >50 × 10^9/L or no improvement after about 6 treatments.

References [171–178]

*As of December 31, 2005, using PubMed and the MeSH search terms immune thrombocytopenia, immunoadsorption, and plasma exchange or plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.

Journal of Clinical Apheresis DOI 10.1002/jca
Description of the disease
The Lambert-Eaton myasthenic syndrome (LEMS) is a myasthenia gravis-like disorder of neuromuscular transmission that is caused by an immune attack on the neuromuscular junction. The salient feature of the disease is muscle weakness, most prominent in proximal muscles of the lower extremities, hyporeflexia, and autonomic dysfunction which may include dry mouth, constipation, and male impotence. Muscle weakness, hyporeflexia, and autonomic dysfunction constitute a characteristic triad of the syndrome. In contrast to myasthenia gravis, brain stem symptoms such as diplopia and dysarthria are uncommon. LEMS typically presents in mid to late life (age 40–79 years) and should be suspected in patients, particularly smokers, with typical symptoms and in patients with unexplained ventilatory failure or prolonged apnea after anesthesia. Approximately 60% of patients have small cell lung cancer that may not become radiologically apparent for 2–5 years after the onset of the neurological syndrome. Lymphoma, malignant thymoma, and carcinoma of breast, stomach, colon, prostate, bladder, kidney, and gallbladder have been reported in association with the syndrome. LEMS is estimated to occur in 3–6% of patients with small cell lung cancer, but as many as 44% may have neuromuscular or autonomic deficits that are not sufficient to make the diagnosis of LEMS. Rapid onset and progression of symptoms over weeks or months should heighten suspicion of underlying malignancy. A diagnostic hallmark of LEMS is the presence of autobody directed at the voltage-gated calcium channel (VGCC) of the nerve terminal in upwards of 75% of LEMS with primary lung cancer, in up to 25% of LEMS with other forms of cancer, in up to 50% of LEMS patients without cancer, and in up to 10% of lung cancer patients without LEMS. Antibody levels do not correlate with severity but may fall as the disease improves in response to immunosuppressive therapy. These antibodies are believed to cause insufficient release of acetylcholine quanta by action potentials arriving at motor nerve terminals. Unlike myasthenia gravis, which is characterized by antibodies to the postsynaptic acetylcholine receptor, VGCC antibodies target a presynaptic structure.

Current management/treatment
Apart from a search for, and treatment of, underlying malignancy, management of LEMS is directed toward support of acetylcholine-mediated neurotransmission and immunosuppression. Cholinesterase inhibitors such as pyridostigmine (Mestinon) tend to be less effective given alone than they are in myasthenia gravis but can be combined with agents that act to enhance release of acetylcholine from the presynaptic nerve terminal. Guanidine hydrochloride is such an agent and is taken orally in divided doses up to 1,000 mg/day in combination with pyridostigmine. Higher doses result in serious side effects including bone marrow suppression, renal tubular acidosis, interstitial nephritis, pancreatic dysfunction, cardiac arrhythmias, and neuropsychiatric changes. 4-aminopyridine which prolongs stimulation of the voltage-gated calcium channel thus producing an increase in neurotransmitter (acetylcholine) release may cause seizures in clinically useful doses and therefore is not widely used. 3,4-diaminopyridine, is less prone to cause seizures, is effective therapy in LEMS and may be combined pyridostigmine. When approved for use by the FDA, 3,4-diaminopyridine may become first line therapy for many patients. Immunosuppression with prednisone or prednisolone starting at 1–1.5 mg/kg on alternate days, or azathioprine starting at 50 mg/day and increased over several weeks to 2–2.5 mg/kg/day in divided doses (with careful monitoring for hematological and other toxicities), is also useful. The immunosuppressants cyclosporine and cyclophosphamide have also been used. Intravenous immunoglobulin (IVIG) has been shown effective in LEMS in a randomized, double-blind, placebo-controlled crossover trial involving 9 patients. IVIG may be useful in repeated monthly infusion of 2 g/kg given over 2–5 days for even up to 2 years.

Rationale for therapeutic apheresis
The identification of LEMS as an autoantibody-mediated syndrome has led to several attempts to use therapeutic plasma exchange in its treatment. Reports of benefit were tempered by the observation that the benefit accrued more slowly than was typical in patients with classical myasthenia gravis. In addition, patients tended to worsen after completion of TPE if additional immunosuppressive therapy was not employed. TPE may be a useful adjunct to management of patients with LEMS whose neurological deficit is severe or rapidly developing, or in the case of patients who are too uncomfortable to wait for immunosuppressive or aminopyridine drugs to take effect.

Technical notes
The reported TPE regimens vary from 5 to 15 daily TPE over 5–19 days to 8–10 TPE carried out at 5–7 day intervals. Most reports indicate an exchange volume of 1.25 plasma volume. Of note: improvement may not be seen for the first 2 weeks or more after initiation. This may be due to the slower turnover of the presynaptic voltage gated calcium channel compared to the postsynaptic acetylcholine receptor.

Duration and discontinuation/number of procedures
Treatment should continue until a clear clinical and EMG response is obtained or at least to a 2- to 3-week course of TPE. Repeated courses may be applied if necessary, but the effect can be expected to last only 2–4 weeks in the absence of immunosuppressive drug.

References [42, 179–184]
*As of November 16, 2005, using PubMed and the MeSH search terms Lambert-Eaton and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease
Lung transplantation has become an accepted and definite therapy for patients with end-stage lung disease. Acute lung allograft rejection occurs in 50–70% of lung transplant recipients and typically occurs in the first 6–12 months after lung transplantation. Chronic rejection of the lung allograft remains the most common cause of death in lung transplant recipients after the first year of transplant. Bronchiolitis obliterans syndrome (BOS) is a pathological process that affects small airways of the lung and is recognized as a significant etiology of chronic dysfunction in the lung allograft. BOS represents chronic allograft rejection, and it occurs in approximately 60–80% of lung transplant survivors 5–10 years after the transplant. BOS is a major factor limiting long-term survival after lung transplantation. Because it can be difficult to diagnose by transbronchial biopsy, BOS does not require histologic confirmation and merely refers to graft deterioration secondary to persistent airflow obstruction. A staging system for BOS was developed by the International Society for Heart and Lung Transplantation, which is based on the forced expiratory volume in 1 second (FEV1). In this staging system BOS is graded between 0 and 3. Stage 0 refers to no significant abnormality, FEV1 is below 80%, while stage 3 refers to severe BOS with FEV1 < 50%. Each staging category has a subcategory, which reflects pathological evidence of BOS: “a” and “b” designate without or with pathological evidence, respectively.

There are multiple reasons for the increased incidence of acute rejection after lung transplant. First, no HLA matching is or can be performed. Second, the lung graft is in permanent contact with the external environment and is thus exposed to various inhaled agents, such as fumes, toxins and infectious agents, which may potentially cause local inflammation and trigger acute rejection. Furthermore, the lung graft contains abundant donor antigen-presenting cells constantly processing and presenting HLA alloantigens to recipient lymphocytes that initiate a process of immune recognition.

Current management/treatment
Maintenance immunosuppressive therapy after lung transplant typically consists of a three-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), azathioprine or mycophenolate mofetil, and steroids. The initial treatment of BOS usually consists of repeated pulses of high-dose methylprednisolone. For patients with unresponsive BOS, alternative immunosuppressive therapies were attempted including tacrolimus, methotrexate, antithymocyte globulin (ATG), and monoclonal murine anti-C3 antibody (OKT3). Chronic rejection refractory to medical therapy occurs in 60–80% of lung transplant patients.

Rationale for therapeutic apheresis
The first use of extracorporeal photopheresis (ECP) in lung transplant patient was published in 1995. At first, ECP was used in the context of refractory BOS (stages 2–3) in which beneficial effect was demonstrated by initial stabilization or improvement in FEV1. Since then, case studies suggest that ECP may be an effective therapeutic modality to stabilize the lung function in patients with persistent acute rejection and early BOS (stages 0–“b1–1), thus preventing further loss of pulmonary function. Although the mechanism of action remains unclear, possible explanations for the beneficial effects include: stimulation of production of clone-specific suppressor T cells, induction of lymphocyte apoptosis and alterations in the T-cell receptor, release of inflammatory mediators (IL-1, IL-6 and TNF-α) by ECP-treated monocytes and, induction of antigen-specific immunomodulation via regulatory T cells which suppresses immune reactions in an antigen-specific fashion.

Overall, the reinforcement of the treated leukocytes mediates a specific suppression of both the humoral and cellular rejection response, prolonging the survival of transplanted tissues and organs. Importantly, ECP is not associated with increase risk of infection, common with immunosuppressant drugs. The category III for ECP was assigned to this disease based on limited data available in the literature.

Technical notes
Vascular access should be suitable for an extended treatment duration.

Duration and discontinuation/number of procedures
A common regimen includes one series every 2 weeks for the first 2 months, followed by once monthly for the next 2 months (total of six series). Another option is one series weekly for 5 weeks, then every 2 weeks for 2 months, and monthly thereafter. The optimal duration remains unclear. The median number of series in the published case studies was 6 (range 3–13).

References [140, 141, 185–190]
*As of May 1, 2006, using PubMed and the MeSH search terms lung transplantation and extracorporeal photopherotherapy or photopheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
MALARIA

**Disease Group:** Hematologic

**Incidence:** 400 million cases worldwide; 1.320 cases (4 deaths) of imported malaria in the U.S. in 2004

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytapheresis (RBC exchange)</td>
<td>II (severe)</td>
</tr>
</tbody>
</table>

**# of reported patients*: >300**

<table>
<thead>
<tr>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>279</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>32</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Description of the disease**

Malaria is a vector-borne protozoal infection caused by *Plasmodium vivax*, *P. ovale*, *P. malariae*, or *P. falciparum*. Transmission rates in endemic regions range from 14 to 53%. Malaria accounts for an estimated 700,000 to 2.7 million deaths each year. The *Plasmodia* life cycle includes an intra-erythrocytic stage of reproduction, which is responsible for many of the pathological manifestations of the disease and the vehicle for transmission by mosquitoes or blood transfusion. The major diagnostic test for malaria involves identification of typical intraerythrocytic organisms on thick blood smears. Infectious symptoms usually begin within 10 days to 4 weeks after inoculation by an infected mosquito. Parasitemia leads to hemolysis and activation of inflammatory cells and cytokines that cause fever, malaise, chills, headache, myalgia, nausea, vomiting and, in some cases, anemia, jaundice, hepatosplenomegaly, and thrombocytopenia. *P. falciparum* is responsible for most of the severe and fatal malaria cases, usually in the setting of high-grade parasitemia, disseminated microcirculatory occlusion and multisystem dysfunction. Poor prognostic features include coma, seizures, pulmonary edema, shock, disseminated intravascular coagulation, renal failure, acidosis, and other metabolic derangements. Nonimmune hosts (i.e., travelers with inadequate chemoprophylaxis), children, and pregnant women with parasitemia >10% are at greatest risk. *P. falciparum* is now the most common etiology of “imported” malaria in non endemic countries. Because severe complications can develop in up to 10% of cases, symptomatic patients with a positive travel history should be promptly evaluated and treated.

**Current management/treatment**

Malaria treatment is based on the clinical status of the patient, the *Plasmodium* species involved and the drug-resistance pattern predicted by the geographic region of acquisition. Imported, uncomplicated malaria in the U.S. is treated with single or combination oral agents, including chloroquine, quinine (alone or with doxycycline, tetracycline, or clindamycin), atovaquone, mefloquine, and primaquine. Alternative agents are available outside of the U.S. and for drug-resistant strains. Severe malaria often requires aggressive support in an intensive care unit with intravenous quinidine (or parenteral quinine) plus doxycycline, tetracycline, or clindamycin. Falciparum malaria with more severe anemia, hypoxemia, hyperparasitemia, neurologic manifestations (i.e., cerebral malaria) or metabolic derangements, particularly in children, asplenic or immunocompromised individuals, should be managed with parenteral antimalarials and aggressive supportive care. Severely ill patients often require aggressive volume resuscitation, electrolyte replacement, antiseizure medications, airway control, and/or ventilatory maintenance.

**Rationale for therapeutic apheresis**

Erythrocytapheresis or manual red cell exchange in severely ill patients with hyperparasitemia (i.e., >10%) is believed to improve blood rheological properties (especially with cerebral malaria) and to reduce pathogenic mediators such as parasite-derived toxins, hemolytic metabolites, and cytokines. A number of reports have described rapid clinical improvement of severe *P. falciparum* malaria after manual or automated red cell exchange, when used in conjunction with antimalarial therapy. Of note, a meta-analysis of 279 patients from eight case-controlled trials found no survival benefit of red cell exchange compared to antimalarials and aggressive supportive care alone. However, the exchange transfusion methods in those trials were not comparable: the patients in the transfusion groups were more ill, additional differences in treatment populations and confounding variables were not adjusted in the analysis and other important outcomes, such as duration of coma and severe end-organ complications (i.e., severe malaria), were not assessed. Despite these observations and the lack of randomized controlled trials, the Centers for Disease Control (CDC) recommends consideration of adjunctive erythrocytapheresis if parasitemia is >10% or if the patient has severe malaria manifested by altered mental status, nonvolume overload pulmonary edema, or renal complications. Quinidine administration should not be delayed for an exchange transfusion and can be given concurrently. Proposed guidelines in the U.K. for treatment of severe malaria in children also suggest consideration of erythrocytapheresis for severely ill patients who are unresponsive to resuscitation treatments.

**Technical notes**

Automated apheresis instruments calculate the amount of RBCs required to achieve the desired postprocedure hematocrit, fraction of red cells remaining and, by inference, the estimated final parasite load. A single two-volume red cell exchange can reduce the fraction of remaining patient red cells to roughly 10–15% of the original. The risks of automated erythrocytapheresis include fluid overload, febrile and allergic transfusion reactions, blood-borne infection (especially in developing countries), hypocalcemia, red blood cell allosensitization, and secondary infections.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1–2 total RBC volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement fluid:</td>
<td>leukoreduced RBCs, plasma</td>
</tr>
<tr>
<td>Frequency:</td>
<td>daily</td>
</tr>
</tbody>
</table>

**Duration and discontinuation/number of procedure**

Treatment is discontinued after achieving <5% residual parasitemia, usually after 1–2 treatments. Treatment should be continued for higher parasite levels with ongoing signs and symptoms of infection.

**References [75, 191–195]**

*As of November 26, 2005, using PubMed and the MeSH search terms malaria, falciparum, apheresis, erythrocytapheresis, red cell exchange, and hyperparasitemia for reports published in the English language. References of the identified articles were searched for additional cases and trials.*
Description of the disease

Multiple sclerosis (MS) is a relapsing and often progressive disorder of central nervous system white matter demyelination. It presents in early adulthood and has variable prognosis. The relapsing-remitting form, 80% of MS patients, is when symptoms and signs evolve over days, stabilize, and then improve within weeks. Corticosteroids speed recovery, but this effect decreases over time. Persistent symptoms may develop and the disease may progress between relapses, referred to as secondary progressive multiple sclerosis. Alternatively, 20% of MS patients have a primary progressive form with continuous progression without improvement. Clinical symptoms include sensory disturbances, unilateral optic neuritis, diplopia, limb weakness, gait ataxia, neurogenic bladder, and bowel symptoms. MRI shows multiple lesions of different ages involving the white matter, brain stem, cerebellum, and spinal cord white matter. A more severe clinical course can be predicted by frequent relapses in the first 2 years, primary progressive form, men, and early permanent symptoms. Acute central nervous system inflammatory demyelinating disease is usually secondary to multiple sclerosis, but includes cases of acute transverse myelitis and neuromyelitis optica (Devic’s syndrome).

Current management/treatment

There are genetic and environmental factors that play a role in the pathogenesis of MS. It is believed to be an autoimmune disorder, with involvement of both the humoral and cellular components. In acute, severe attacks of multiple sclerosis in patients who fail initial treatment with high-dose steroids, TPE may be of benefit.

Interferon beta-1a, glatiramer acetate, and immunoglobulin may delay the development of relapse in the relapsing-remitting form. Interferon beta-1b and mitoxantrone hydrochloride may reduce rate of relapse and delay progression in secondary progressive MS. TPE has not been specifically studied in relapsing-remitting MS.

No adequate treatment yet exists for primary progressive MS. The data demonstrate a small benefit or no benefit with TPE in conjunction with other immunosuppressive drugs in patients with chronic progressive MS in multiple randomized controlled trials. It is not clear whether the cost and potential adverse effects of TPE outweigh the small benefit.

Rationale for therapeutic apheresis

MS is an autoimmune disease with not clearly understood pathogenesis. TPE may benefit MS patients by removing an autoantibody, such as anti-myelin antibody, or by modulating immune response. There have been four immunopathological patterns of demyelination in early MS lesions. The characteristics of demyelination for each pattern are I T-cell/macrophage-associated, II antibody/complement-associated, III distal oligodendroglialopathy, and IV is oligodendrocyte degeneration. A recent study of patients with fulminant CNS inflammatory demyelinating disease demonstrated that all 10 patients with pattern II but none of the 3 with patterns I or 6 with pattern III had substantial improvement with TPE.

The category III for TPE was assigned to Devic’s syndrome and chronic progressive MS based on limited and/or conflicting data available in the literature.

Technical notes

See the introductory article in this issue.

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**Volume treated:** 1–1.5 TPV  
**Replacement fluid:** albumin  
**Frequency:** acute: 5–7 over 14 days; chronic progressive: weekly

Duration and discontinuation/number of procedures

In acute MS, 2–3 weeks of TPE had a response rate of 50%. In chronic progressive MS, TPE would be a long-term therapy to be continued, if shown to be a benefit and tapered off as tolerated.

References [196–201]

*As of December 5, 2005, using PubMed and the MeSH search terms multiple sclerosis, plasma exchange, and plasmapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
Myasthenia gravis (MG) is an autoimmune disease characterized by weakness and fatigability with repetitive physical activity, which usually improves with rest. Common presentation includes ptosis and diplopia with more severe cases having facial, bulbar, and limb muscle involvement. The disease is more prevalent in women in their 20s and 30s. The causative antibody is usually against the acetylcholine receptor (anti-AChR). At the neuromuscular junction the nerve releases acetylcholine across the synaptic space to the muscle surface. When it reaches the muscle and the acetylcholine binds the acetylcholine receptor, which generates the electrical potential and muscle contraction. Anti-AChR results in decrease in the number of acetylcholine receptors, which decreases the action potential achieved with stimulation. About 80–90% of MG patients have detectable anti-AChR. Likely other factors play a role in the disease because antibody level does not correlate with disease severity and severe disease can occur without detection of this antibody. Antibodies to the muscle specific receptor tyrosine kinase (MusK) are present in about 50% in patients without anti-AChR. MuSK mediates formation of the neuromuscular junction and induction of the AChR. The remainder of seronegative individuals may have these antibodies but they are unable to be detected by current laboratory methods or have other autoantibodies acting at the neuromuscular junction.

Myasthenic crisis is characterized by acute respiratory failure requiring intubation, prolonged intubation following thymectomy, or bulbar weakness causing dysphasia and high risk of aspiration.

Current management/treatment

With modern treatment regimens the mortality from MG has greatly decreased, 30% to less than 5%. The four treatment modalities include cholesterase inhibitors, thymectomy, immunosuppression, and plasma exchange or intravenous immunoglobulin (IVIG). Cholesterase inhibitors (pyridostigmine bromide) delay the breakdown of acetylcholine and lead to variable improvement in strength. The cholinergic side affects can be dose limiting and lead to non-compliance. These effects include diarrhea, abdominal cramping, increased salivation, sweating, and bradycardia. Thymic abnormalities, hyperplasia or thymoma, are commonly associated with MG. Thymectomy leads to clinical improvement in many patients under the age of 65 but may take years for the benefits to show. Immunosuppressive drugs (corticosteroids, azathioprine, cyclosporine, and tacrolimus) have a delayed effect and, therefore, they play an important role in the longer term rather than the short term treatment.

Rationale for therapeutic apheresis

Plasma exchange (TPE) is used to remove circulating autoantibodies. Both seropositive and seronegative patients respond to TPE. TPE is especially used in myasthenic crisis, peroperatively for thymectomy, or as an adjunct to other therapies to maintain optimal clinical status. TPE works rapidly; clinical effect can be apparent within 24 hours but may take a week. The benefits will likely subside in 2–4 weeks, if immunosuppressive therapies are not initiated to keep antibody levels from reforming.

Two randomized controlled trials compared IVIG and TPE. One trial randomized 87 patients with major exacerbations to 3 every other day 1.5 volume TPE, 0.4 g/kg × 3 days of IVIG, or 0.4 g/kg × 5 days of IVIG. All 3 arms were equivalent at day 15. A second trial included 12 stable patients with moderate to severe disease, which found TPE to be better at 1 week, equivalent improvement at 4 weeks, and neither to show improvement at 16 weeks. A retrospective multicenter chart review of 54 episodes compared the two treatment modalities for myasthenic crisis. Patients received either 5 or 6 of 25–45 mL/kg plasma exchange on alternate days or 0.4 g/kg × 5 days of IVIG. TPE had significantly more improvement than IVIG in ventilatory status at 2 weeks and outcome at 1 month. In the two larger studies adverse effects of TPE were more frequent (hypotension, bleeding/hematoma, thrombosis, nausea/vomiting) versus IVIG (headache, renal failure, nausea/vomiting).

Technical notes

See the introductory article in this issue.

Volume treated: 1–1.5 TPV
Replacement fluid: albumin
Frequency: daily or every other day

Duration and discontinuation/number of procedures

Usually a series of five procedures are performed; as few as two procedures can be beneficial. The number and frequency of procedures depends upon the clinical scenario. Some patients may require long-term maintenance plasma exchange.

References [202–204]

*As of March 28, 2006, using PubMed and the MeSH search terms myasthenia gravis and apheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
**Description of the disease**

Renal failure develops in up to 50% of patients with multiple myeloma and shortens their survival. Myeloma kidney (cast nephropathy) accounts for approximately 30–80% of such cases, depending on the class of M-protein. Autopsy studies show distal renal tubules obstructed by laminated casts composed of light chains (Bence-Jones protein), albumin, Tamm-Horsfall protein, and others. As tubular obstruction progresses the decline in renal function becomes irreversible. Hypotheses regarding the mechanism of distal tubule cast formation leading myeloma kidney focus on an increase in light chain concentration in the distal tubular urine. This can result from an overwhelming of the proximal tubule clearance of light chain when light chain production is rising due to tumor progression. Other contributing factors may include hypercalcemia, hyperuricemia, dehydration, and intravenous contrast media for imaging studies.

**Current management/treatment**

Therapeutic approaches rely on inducing an alkaline diuresis through intravenous administration of normal saline and sodium bicarbonate with or without loop diuretics (e.g., furosemide or equivalent). Anti-myeloma chemotherapy consisting of an alkylating agent (e.g., cyclophosphamide or melphalan) with a corticosteroid (prednisone, methylprednisolone, or dexamethasone) is used to diminish M-protein production. Autologous bone marrow transplant has been found to increase survival compared with conventional chemotherapy and is now incorporated routinely in the treatment of the disease. More recently, immune modulation (thalidomide, lenalidomide) and proteosome inhibition (bortezomib) have emerged as effective therapy. Supportive care with hemodialysis or peritoneal dialysis is employed as needed.

**Rationale for therapeutic apheresis**

Chemotherapy, to diminish the production of the M-protein, and alkaline intravenous fluid, for the purpose of lowering the urinary concentration and pH of the light chains, are the primary modes of therapy. TPE has been used to acutely decrease the delivery of light chains delivered to the renal glomerulus for filtration. Peritoneal dialysis (but not hemodialysis) can also remove light chains but with lower efficiency than TPE. A recently reported study from the Canadian Apheresis Group, in which almost half of the study subjects received the VAD chemotherapy regimen, failed to demonstrate conclusive evidence that 5–7 plasma exchanges over 10 days substantially reduces a composite outcome of death, dialysis dependence, or severe renal insufficiency at 6 months. There are no studies that compare one apheresis treatment schedule with another, but the randomized trials referenced above rely on short periods of daily treatment. Smaller trials have demonstrated improved 1-year survival in the groups whose treatment included TPE, the largest, randomized trial did not demonstrate improved survival at six months. In all cases ultimate survival depends on a satisfactory response to chemotherapy. The category III for TPE was assigned to myeloma kidney based on conflicting data available in the literature.

**Technical notes**

Initial management in nonoliguric patients should focus on fluid resuscitation (2.5–4 L/day), alkalinization of the urine, and initiation of chemotherapy. If serum creatinine continues to rise, or remains elevated after up to several days, consider addition of TPE to the patient’s management. For patients who are oliguric, who excrete ≥10 grams of light chains per 24 hours, or whose serum creatinine is ≥6 mg/dl, TPE may be considered in initial management. Published studies vary with respect to treatment schedules and replacement fluids employed for plasma exchange. All studies combine TPE with chemotherapy and other forms of supportive care described above. If TPE and hemodialysis are to be performed on the same day, they can be performed in tandem (simultaneously) without compromising the efficiency of the hemodialysis procedure.

**Volume treated:** 1–1.5 TPV

**Replacement fluid:** albumin

**Frequency:** daily or every other day

**Duration and discontinuation/number of procedures**

Controlled trials have employed TPE as a short-term adjunct to chemotherapy and fluid resuscitation over the period of 2–4 weeks.

**References [62, 205–214]**

*As of December 31, 2005, using PubMed and MeSH search terms multiple myeloma, renal disease, and plasma exchange, for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease

Drug overdose and poisoning, whether accidental, intentional, or iatrogenic, result from excessive exposure to an agent capable of producing tissue injury and/or organ dysfunction. Ingestion, inhalation, and injection are common routes of exposure. The list of agents potentially toxic to humans is enormous and diverse. It is difficult to quantify the morbidity and mortality attributable to these problems. The majority of incidents is accidental and occur at home, most often involving children under the age of 6. Fortunately, serious injury is the exception to the rule. The mechanism of tissue damage varies with the nature of the offending substance and the mode of entrance into the body. Agents may be directly toxic to human tissue or may require enzymatic conversion to an active, injurious metabolite. Local effects at the site of entry into the body may accompany systemic effects, and the onset of symptoms may be rapid or delayed. Initial treatment focuses on supportive care and the removal of the toxic agent.

Current management/treatment

Evaluation and stabilization of the airway, breathing, circulation, and neurologic status are primary concerns. Toxin-specific antidotes, when available, are promptly administered. The physician can choose from a vast array of methods to enhance removal of the toxin, depending on specific characteristics of the agent and the route of exposure. Induced emesis, gastric lavage, and oral administration of activated charcoal may be used to minimize gastrointestinal absorption of ingested substances. Whole-bowel irrigation, another technique available for gastro-intestinal decontamination, is particularly useful for removing poorly absorbed agents that are not adsorbed to charcoal. Forced acid or alkaline diuresis is used to promote the renal elimination of ionized agents that are not strongly bound to proteins. Extracorporeal elimination techniques are also used. Hemodialysis is an effective technique for removing drugs that are not tightly bound to plasma proteins and that readily diffuse through a semipermeable membrane. Hemoperfusion, a procedure in which blood is passed directly over sorbent particles, can be more effective than dialysis for protein-bound drugs and large molecules. Comprehensive lists of drugs and chemicals removed with dialysis and hemoperfusion have been compiled. Less than 0.04% of poisoned patients were treated with extracorporeal procedures such as hemodialysis, hemoperfusion and others.

Rationale for therapeutic apheresis

TPE is an alternative technique for the removal of protein-bound toxins that are not readily removed with dialysis or hemoperfusion. TPE is effective in removing highly protein-bound toxins from the blood but not from other fluid compartments. Efficiency is limited by the unique characteristics of the toxic substance. Agents that are most amenable to removal by TPE are not lipid soluble or bound to tissue, and do not have a large volume of distribution outside the bloodstream. The clinical benefit can be achieved only if toxin levels can be reduced to concentrations below the threshold for tissue damage. Reports of the successful use of apheresis in the treatment of various drug overdoses and poisonings are generally anecdotal. Interestingly, there is no correlation between protein binding and a volume of distribution among substances which were successfully treated with TPE. This may indicate that other factors played more important role in patients’ recovery. There are also case reports of the failure of plasma exchange to remove substances bound to proteins and lipids such as barbiturates, chlordecone, aluminum, tricyclic antidepressants, benzodiazepines, quinine, and phenytoin. Agents known to be highly protein bound or those with delayed metabolic effects are the best candidates for removal by TPE. Indications for TPE include progressive clinical deterioration, coma, and compromised excretory functions.

Amanita poisoning is the most frequent clinical diagnosis where TPE has been utilized. Large case series showed decreased mortality among patients, mostly children, treated with TPE when compared with historical controls. Very early initiation of the treatment (less than 30 hours) resulted in the best outcomes. There are anecdotal reports on the use of immunadsorption to treat poisoning with toxins such as botulin toxin.

Technical notes

The replacement fluid chosen should be one that contains enough protein to draw toxin into the blood compartment for elimination; albumin is such an agent and generally acts as an effective replacement fluid. However, some toxic substances may bind to other plasma constituents preferentially over albumin. For example, dipyridamole, quinidine, imipramine, propranolol, and chlorpromazine are known to have strong affinity for alpha-1-acid glycoprotein; for overdoses of these agents, plasma may be a more appropriate choice.

Duration and discontinuation/number of procedures

TPEs are usually performed and continued on a daily basis until the clinical symptoms have abated and delayed release of toxin from tissues is no longer problematic.

References [33, 52, 215, 216]

*As of March 23, 2006, using PubMed and the MeSH search terms plasmapheresis/poisoning; plasmapheresis/overdose; apheresis/poisoning; apheresis/overdose; apheresis/poisoning, for articles published in the English language. References of the identified articles were searched for additional cases and trials.
PARANEOPLASTIC NEUROLOGIC SYNDROMES

<table>
<thead>
<tr>
<th>Description of the disease</th>
<th>Current management/treatment</th>
<th>Rationale for therapeutic apheresis</th>
<th>Technical notes</th>
</tr>
</thead>
</table>
| These syndromes affect approximately 1% of cancer patients and may precede the diagnosis of cancer in 50% of cases. Major syndromes are classified according to the affected central nervous system anatomy but an international workshop consensus statement called for a combination of immunohistochemistry and Western immunoblotting for proper diagnosis. (1) Paraneoplastic cerebellar degeneration (PCD) may present with symptoms developing over several days in patients with small cell lung cancer, breast, ovarian or other gynecological cancer, and Hodgkin’s lymphoma. Autoantibodies reactive against Purkinje cell cytoplasm react on Western blot analysis with 34-kDa and 62-kDa Purkinje cell proteins and are referred to as “anti-Yo” antibodies. The onset of symptoms, including truncal and limb ataxia, dysarthria (which may be severe), and downbeating nystagmus may precede the diagnosis of cancer by months to years. (2) Paraneoplastic encephalomyelitis (PEM) in patients with small cell lung cancer presents with seizures, subacute dementia and personality change (limbic encephalitis), subacute cerebellar signs, and autonomic nervous system dysfunction. Autonomic (e.g., cardiac dysrhythmias) and respiratory failure, of central origin or due to neuromuscular weakness, are principal causes of death. Most patients have polyclonal IgG anti-neuronal nuclear antibodies (ANNA-1 or anti-Hu antibodies) which react with a group of proteins with apparent molecular weights of 35–40 kDa on immunoblots of human neuronal extracts. A serum anti-Hu antibody and rapidly developing symptoms of encephalomyelitis will likely lead to a diagnosis of small cell lung cancer within several months. (3) Paraneoplastic opsoclonus/myoclonus (POM) is characterized by involuntary, jerky rapid vertical, and horizontal eye movements (saccades), sometimes associated with ataxia or other cerebellar signs. POM occurs mostly with breast or small cell lung cancer, but a similar syndrome occurs in children with neuroblastoma. The onset is often abrupt in adults and may be accompanied by nausea and vomiting, and then progress to truncal ataxia, generalized myoclonus, altered mental status, and sometimes to stupor and coma. Patients with POM and breast or gynecological cancer demonstrate a serum and CSF antibody called anti-Ri, also referred to as ANNA-2, that recognizes neuronal proteins of 55 and 80 kDa on Western blots. (4) Paraneoplastic stiff-person syndrome, associated with antibodies to the 128 kDa synaptic vesicle-associated protein amphiphysin, is reviewed in the fact sheet on Stiff-Person Syndrome. (5) Cancer-associated retinopathy (CAR) consists of subacute vision loss, photosensitivity, night blindness, and impaired color vision. It is associated with small cell lung cancer, cervix cancer, and malignant melanoma. Most patients have serum autoantibodies to the retinal photoreceptor protein recoverin.
| Although considered autoimmune phenomena, neither immunosuppressive therapy nor anti-tumor therapy is beneficial in most cases of CNS paraneoplastic neurological syndromes, in particular PEM and POM. Adults with POM may improve spontaneously or following corticosteroid or specific anticancer treatment. Neurological improvement or worsening may correlate with tumor response or relapse. Some patients with CAR may improve or stabilize with corticosteroid treatment. Intravenous immunoglobulin (0.5 g/kg/day for 5 days every 4 weeks for 3 months, followed by 0.5 g/kg one day per month for another 3 months) may result in improvement in patients with anti-Hu or anti-Yo, mostly in patients whose symptoms are restricted to the peripheral nervous system.
| The presumed autoimmune nature of PCD and POM and their association with specific CSF and serum antibodies (anti-Yo and anti-Hu, respectively) led to the use of immunosuppressive therapy, including therapeutic plasma exchange (TPE), in their management. In general patients who have been treated with TPE have also received corticosteroids or other immunosuppressive drugs as well as specific anticancer therapy. TPE often lowers serum anti-Hu or anti-Yo antibodies but not CSF antibodies and few patients have had convincing improvement after TPE. An occasional patient is described as improving with respect to lethargy, vertigo, or ataxia but other aspects of neurological deficit persist. Improvements are short-lived. Three patients with POM were treated with Staphylococcal protein A silica** immunoadsorption of plasma and experienced complete remission of their neurological syndrome. An additional two patients with POM had substantial improvement. All patients subsequently relapsed. The category III for TPE and IA was assigned to this disease based on limited data available in the literature.
| TPE cannot be considered standard therapy for autoimmune paraneoplastic neurologic syndromes. If a patient presents prior to development of severe neurological impairment but with a rapidly developing syndrome, aggressive immunosuppression, including TPE may be reasonable in an attempt to halt the process. Staphylococcal protein A silica immunoadsorption **, either “on-line” or “off-line” may be employed, particularly for POM, although there is very little published experience.

### Volume treated

**Type I: 1.0–1.5 TPV**

- **IA Off-line:** 500–1,000 mL of plasma from whole blood collected and separated for off-line Staphylococcal protein A silica column treatment;
- **IA On-line:** treatment of 1,000 mL of plasma at a plasma flow rate of up to 20 ml/min may be an alternative approach.

**Type II:**

- **TPE:** albumin; **IA:** not applicable

### Frequency

**TPE:** daily or every other day;

**IA:** twice weekly

### Duration and discontinuation/number of procedures

Five to six procedures over up to 2 weeks for patients undergoing plasma exchange. If there is no response no additional treatments are recommended. The course of treatment for IA consists of six treatments performed twice weekly for 3 weeks.

### References [217–226]

*As of November 15, 2005, using PubMed and the MeSH search terms paraneoplastic cerebellar syndromes and plasmapheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.

DOI 10.1002/jca
PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDERS ASSOCIATED WITH STREPTOCOCCAL INFECTIONS AND SYDENHAM'S CHOREA

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<th>Disease Group</th>
<th>Neurological</th>
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<tbody>
<tr>
<td>Incidence</td>
<td>PANDAS: Rare; SC: Rare; 1–2% of school aged children and adolescents have obsessive compulsive disorders and tic disorders</td>
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<table>
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<td>I (severe exacerbation)</td>
</tr>
<tr>
<td>TPE (SC)</td>
<td>I (severe exacerbation)</td>
</tr>
</tbody>
</table>

Description of the diseases

PANDAS and SC are postinfectious autoimmune neuropsychiatric disorders. Both share an array of neuropsychiatric symptoms, which typically follow Group-A beta-hemolytic streptococcus (GABHS) infection, and may have a shared etiopathogenesis. Postulated pathogenesis suggests that streptococcal antigens induce antineuronal antibodies by an abnormal immune response. Some investigators have reported that antibodies produced against streptococcal M proteins crossreact with neuronal tissue of basal ganglia. GABHS infection has been associated with childhood-onset neuropsychiatric disorders such as obsessive compulsive disorder (OCD) and tic disorders. The subgroup shares a unique clinical course and is identified by the acronym PANDAS which is characterized by five criteria: presence of OCD and/or a tic disorder, prepubertal presentation, abrupt onset and/or relapsing-remitting course of symptom severity, neurological abnormalities during periods of exacerbation, and a temporal association between GABHS infection and worsening of symptoms. The onset of PANDAS is acute and dramatic, presenting with emotional/mood lability, attention deficit, deterioration of handwriting, separation anxiety, tactile/sensory defensiveness, enuresis, cognitive deficits, and motor hyperactivity. Severe symptoms often last several weeks or longer and then gradually subside in severity, often remitting completely until the patient is again infected with GABHS. SC is the most common acquired chorea of childhood, with major clinical manifestations including chorea, hypotonia, and emotional lability. SC may persist for several months with a recurrence rate of about 20%. Choreatic movements are rapid, jerky, and involuntary and affect the face, trunk, and extremities. During the choreic episode, approximately 65% of SC patients have OCD. The mean ages of onset for PANDAS and SC are 6.8 years old (3–12) and 8.4 years old (5–15), respectively. SC is diagnosed exclusively by clinical presentations and a history of rheumatic fever. Although PANDAS is temporally associated with GABHS, it is not associated with rheumatic fever. Laboratory tests show an elevated or increasing streptococcal antibody titers [(e.g., anti-streptolysin O (ASO), anti-deoxyribonuclease-B (anti-DNase B)], but an elevated titer does not necessarily indicate a recent streptococcal infection. In PANDAS, the presence of streptococcal infection is associated with at least two episodes of neuropsychiatric symptoms as well as a negative throat culture or stable titers during times of remission. Elevated levels of antineuronal antibodies have been reported in a subgroup of patients with PANDAS and SC.

Current management/treatment

Initial treatments for PANDAS include antibiotics and cognitive behavioral therapy. Severe form of SC is treated with diazepam, valproic acid, phenothiazines, or haloperidol. If these fail, corticosteroids may be tried. While children with SC require long-term penicillin prophylaxis to reduce the risk of rheumatic carditis, the efficacy of penicillin prophylaxis in preventing symptom exacerbations in children with PANDAS remains doubtful. Since recurrence of OCD has been associated with acute GABHS infection, prompt antibiotic administration to treat or eradicate GABHS or tonsillectomy may represent an effective treatment option in PANDAS patients. In severely symptomatic or refractory patients with PANDAS or SC, intravenous immunoglobulin (IVIG at 1 g/kg/day for 2 days) or TPE has been shown to reduce symptom severity or shorten the course.

Rationale for therapeutic apheresis

Because of the possible role of antineuronal antibodies in the pathogenesis, antibody removal by TPE may be effective. However, the mechanism for the benefit of TPE is not clear, as there is a lack of relationship between therapeutic response and the rate of antibody removal. A randomized controlled study on 18 patients with SC showed that the mean chorea severity scores decreased by 72%, 50%, and 29% in the IVIG, TPE, and the prednisone groups, respectively. Another randomized placebo-controlled trial of IVIG and TPE on 29 children with PANDAS showed that both therapies at 1 month after treatment produced striking improvements in OCD, with mean improvement of 45% and 58%, respectively. More than 80% of the patients who received IVIG or TPE remained much or very much improved at 1 year. The TPE group appeared to have greater OCD symptom relief than did the IVIG group.

Technical notes

In uncooperative children, sedation is recommended.

Volume treated: 1–1.5 TPV
Replacement fluid: albumin
Frequency: daily or every other day

Duration and discontinuation/number of procedures

Five or six procedures over 7–14 days were utilized in the randomized controlled trial. There are no data on any benefit of repeated treatment.

References [204, 227–234]

*As of January 31, 2006, using PubMed and the MeSH search terms PANDAS, Sydenham’s chorea, neuropsychiatric disorder, obsessive-compulsive disorder, tics, basal ganglia disease, streptococcal infection, plasma exchange, plasmapheresis, for articles published in the English language. References in identified articles were searched for additional cases and trials.
PEMPHIGUS VULGARIS

**Disease Group:** Autoimmune
**Incidence:** 0.42 per 100,000/year (US)

<table>
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<td>ECP</td>
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<th>CS</th>
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<tr>
<td>ECP</td>
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<td>0</td>
<td>1 (4)</td>
<td>5 (9)</td>
<td>Type III</td>
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</tbody>
</table>

**Description of the disease**

Pemphigus vulgaris is a rare, potentially fatal, autoimmune mucocutaneous blistering disease. Both genders are equally affected with the mean age of onset in the sixth and seventh decade of life. The patients present with skin lesions typically flaccid blisters which can be recurrent and relapsing. The blisters can be located on the entire body surface as well as on the mucous membranes of the mouth. The lesions tend to peel superficially or detach easily. A large surface of skin can be affected at any given point leading to situations akin to severe burn. Pathology of Pemphigus vulgaris is characterized by the in vivo deposition of an autoantibody on the keratinocyte cell surface. This antibody, which is also present in the circulation, is typically directed against a 130-kDa protein (desmoglein 3). Additional autoantibodies against desmoglein 1 have been detected. Histology reveals the presence of a suprabasilar intraepidermal split with acantholysis. There are deposits of IgG and C3 on the corticokeratinocyte cell surface in the mid and lower or entire epidermis of perilesional skin or mucosa.

**Current management/treatment**

The treatment of pemphigus vulgaris, especially in its severe form, is challenging. Historically, this disease was associated with a high morbidity and mortality. Introduction of corticosteroids reduced the mortality rate from 70 to 100% to a mean of 30%. However, long-term administration of high doses of corticosteroids can be associated with severe adverse effects (e.g., hypertension, osteoporosis, atherosclerosis, peptic ulcer disease, aseptic necrosis, diabetes mellitus/glucose intolerance, and immunosuppression). Other therapeutic options include dapsone, gold, and systemic antibiotics. They are often used in combination with other immunosuppressant agents such as azathioprine, methotrexate, and cyclophosphamide. Recently newer therapeutic modalities such as mycophenolate mofetil, chlorambucil, dexamethasone-cyclophosphamide pulse therapy, cyclophosphamide, TPE, extracorporeal photo-chemotherapy (ECP), intravenous immunoglobulin (IVIG) therapy, and rituximab, anti-CD20 monoclonal antibody, have been investigated.

**Rationale for therapeutic apheresis**

The rationale for using TPE in the treatment of pemphigus vulgaris is based on the presence of circulating pathogenic autoantibodies. TPE has been utilized in patients with severe symptoms who either received high doses of conventional agents and/or had an aggressive and rapidly progressive disease. TPE was used in patients in all age groups (13–80 years old). The duration of disease prior to using TPE ranged between 1 month and 25 years. All reported patients have received high-dose systemic corticosteroids and immunosuppressive agents which either produced life-threatening adverse effects or failed to control the disease. The goal of TPE was to reduce the level of autoantibodies with subsequent improvement in clinical symptoms. The decline in autoantibody titers, anti-keratinocyte cell surface antibodies and anti-desmoglein 3, correlated with clinical response in a number of patients. In published reports a clinical response has been observed as early as the first few days after TPE but also several months after discontinuation of TPE. The latter observation questions clinical efficacy of TPE in some patients.

The rationale for using ECP in this disease is more questionable but could involve inhibition of pathogenic autoantibody production by B lymphocytes. This issue has not yet been well addressed. The category III for TPE and ECP was assigned to this disease based on limited data available in the literature.

**Technical notes**

The TPE protocols used in pemphigus vulgaris vary widely and have been usually based on the observed clinical response after each treatment. The reported volume processed was as low as 400 mL and as high as 4,000 mL and the reported frequency of treatments varied widely as well. Though, more recent reports noted that one plasma volume exchanges are preferable in patients who are resistant to conventional therapy. The levels of autoantibody have been noted to rebound in the reported patient within 1–2 weeks after discontinuation of treatment which necessitates continuation of immunosuppression.

The clinical response in patients who underwent ECP was observed after two to seven cycles (two daily procedures per cycle). The total number of cycles received varied from 2 to 48. In one report 100% clinical response with decreased autoantibody titer was reported. The follow up ranged between 4 and 48 months. The disease was controlled in most patients, but only two patients were able to discontinue all oral systemic agents.

**Volume treated:** 1–1.5 TPV TPE; A mononuclear cell product of approximately 270 mL consisting of mononuclear cells, plasma and saline ECP

**Frequency:** TPE: daily or every other day; ECP: two consecutive days (one series) every 2 or 4 weeks

**Replacement fluid:** ECP: not applicable; TPE: albumin; plasma

**Duration and discontinuation/number of procedures**

For plasma exchange, as noted above, the treatment protocols are highly variable. The rational approach should include monitoring of autoantibody titers and clinical symptoms. The lack of clinical response after a trial period with concomitant adequate immunosuppression should be sufficient to discontinue treatment.

For ECP the treatments were continued until clinical response was noted. The rational discontinuation criteria should be similar as those for TPE.

**References [132,235–243]**

*As of December 1, 2005, using PubMed and the MeSH search terms plasmapheresis, pemphigus vulgaris, and photopheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.

*Journal of Clinical Apheresis* DOI 10.1002/jca
**PHYTANIC ACID STORAGE DISEASE (REFSUM'S DISEASE)**

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<td>CS</td>
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<td>CR</td>
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**Strength of evidence**
- Type III

**Description of the disease**

Phytanic Acid Storage disease (Refsum’s Disease), also known as heredopathia atactica polyneuritiformis, is an autosomal recessive disorder. Patients have significant defects in the metabolism of phytanic acid (PA) due to deficiency in alpha-oxidase. This branched chain fatty acid is derived exogenously from dietary sources. The inability to degrade PA results in its accumulation in fatty tissues, liver, kidney, myelin, serum lipoproteins, and the plasma. Clinical consequences are largely neurologic including retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, sensorineural deafness, and anosmia. Other manifestations include skeletal abnormalities, cardiac arrhythmia, and ichthyosis. The clinical progression is typically slow and gradual with onset of signs and symptoms during the second or third decades of life.

**Current management/treatment**

Limiting intake of PA by dietary restriction to 10 mg daily is the cornerstone of therapy. Food rich in PA are dairy, butter, cheeses, meats, and some fish. Diet alone can benefit many patients and lead to reversal of neuropathy, weakness, and ichthyosis. Care is taken to maintain overall general nutrition and caloric intake to rapid weight loss which has precipitated clinical relapse due to sudden mobilization of PA from liver and adipose tissue stores. The relative unpalatability of diets low in PA limits compliance and the effectiveness of dietary management of this disorder. Even with adequate dietary compliance, there can be a delay in the fall of PA levels presumably because of its release from adipose tissue stores.

**Rationale for therapeutic apheresis**

Plasma exchange rapidly reduces plasma PA from elevated levels. This can be useful in the setting of acute attacks or exacerbation of the disease as well as for maintenance therapy. The normal plasma PA level in humans is <33 μmol/L. Symptomatic levels of Refsum’s Disease range from 700 to 8,000 μmol/L. A number of small case series and isolated reports have described clinical improvements in patient signs and symptoms with plasma exchange in conjunction with dietary control. Since PA is also bound to plasma lipoproteins and triglycerides, lipoapheresis using cascade filtration been used to successfully manage these patients.

**Technical notes**

Although approaches to therapeutic apheresis for Refsum’s Disease vary, a typical course consists of 1–2 plasma exchange treatments per week for several weeks to months. In some cases maintenance plasma exchanges continue with decreasing frequency over subsequent weeks to months. Therapeutic strategy is ultimately determined by monitoring the patient’s PA level, clinical signs and symptoms, and the need to control or prevent exacerbations of the disease.

**Volume treated:** 1–1.5 TPV
**Replacement fluid:** albumin

**Frequency:** one or two per week

**Duration and discontinuation/number of procedures**

Due to limited number of patients and rarity of this disease treatment should be decided on a case by case basis. The treatment may take as long as several weeks to months.

**References [244–252]**

*As of March 20, 2006, using PubMed and the MeSH search terms Refsum’s disease, phytanic acid, apheresis, plasma exchange, plasmapheresis, and apheresis for articles published in the English language. References in identified articles were searched for additional cases and trials.
PARAPROTEINEMIC POLYNEUROPATHIES

Disease Group: Neurological

Incidence: MGUS: up to 3% of general population over 50 y
Multiple myeloma: 4–6 per 100,000/year

Procedure Category

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Category</th>
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<tbody>
<tr>
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<tr>
<td>TPE</td>
<td>III (c)</td>
</tr>
<tr>
<td>IA</td>
<td>III (a, b)</td>
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</tbody>
</table>

(a) Demyelinating polyneuropathy with IgG/IgA; (b) Polyneuropathy with IgM (±Waldenström’s); (c) Multiple myeloma with polyneuropathy; # the same trial (see text).

Description of the disease

Polyneuropathy can present as acute, subacute, or chronic process with initial sensory symptoms of tingling, prickling, burning, or bandlike dysesthesias in the balls of the feet or tips of the toes. These are usually symmetric and graded distally. Nerve fibers are affected according to axon length, without regard to root or nerve trunk distribution (e.g., stocking-glove distribution). The polyneuropathies are diverse in timing, severity, mix of sensory and motor features, and presence or absence of positive symptoms.

Polyneuropathy can be associated and/or caused by the presence of monoclonal proteins in conditions such as amyloidosis (see the publication on category IV indications in this issue), POEMS syndrome (see the publication on category IV indications in this issue indications), Castleman’s disease, type II cryoglobulinemia (see Cryoglobulinemia fact sheet), multiple myeloma (MM), B-cell lymphoma, chronic lymphocytic leukemia (CLL), Waldenström’s macroglobulinemia (WM) and with IgA, IgG or IgM monoclonal gammopathy of undetermined significance (MGUS). MGUS is defined as serum monoclonal protein <3 g/dL, bone marrow plasma cells <10%, and absence of end-organ damage (e.g., lytic lesions, anemia, hypercalcemia, or renal failure).

The paraproteinemic polyneuropathies (PP) are chronic progressive illnesses and resemble chronic inflammatory demyelinating polyneuropathy (CIDP). The diagnosis can be established based on electrophysiological studies and the presence of monoclonal proteins. PP are most commonly seen in the setting of MGUS, with IgA-MUGUS. Symptoms tend to progress more rapidly in patients with IgM compared to IgA- or IgG-MGUS. The pathologic activity of anti-MAG can be transferred to laboratory animals. The monoclonal proteins damage peripheral nerves causing vasculitis (i.e., cryoglobulinemia) or protein deposition (i.e., amyloidosis).

Current management/treatment

Response to immunosuppressive drugs varies. Corticosteroids alone tend to be more effective in IgG- and IgA- polyneuropathies with a response rate of 40–60%. Combination therapy with low dose cyclophosphamide and prednisone given monthly over 6 months improves clinical outcome irrespective of antibody specificity or class. Polyneuropathies with IgG monoclonal protein resistant to this treatment have been successfully treated with cyclosporine A and carbamustine. Intravenous immunoglobulin at 0.4 g/kg/day for 5 days has shown clinical benefit in approximately one third of the patients. However, this was not confirmed in a small randomized trial and when compared to interferon alpha. Polyneuropathies associated with MM or POEMS syndrome are difficult to treat and may respond to alkylating agents. Response, if it occurs, is typically slow. Recent reports with limited number of patients showed that anti-CD20 antibody (rituximab) has been successful in IgM PP with anti-MAG. Some patients with anti-MAG neuropathy also have benefited from fludarabine or cladribine. These new therapies are likely to change the therapeutic approach if the benefits are confirmed in larger trials.

Rationale for therapeutic apheresis

A randomized, double-blind trial compared plasma exchange to sham plasma exchange in 39 patients with stable or worsening MGUS-associated polyneuropathy. TPE was performed twice a week for three consecutive weeks. In the IgG and IgA MGUS group there was a neurological improvement as measured by electrophysiological studies and the presence of monoclonal proteins. The clinical response lasted from 7 to 20 days without any additional treatment. The IgM MGUS group did not appear to respond to TPE in this trial. The heterogeneity of the IgG group, which included patients with more treatment refractory axonal neuropathy, may have adversely affected the observed results. A retrospective analysis of 19 patients with IgM and 15 patients with IgG PP concluded that the two groups were equally likely to respond to plasma exchange or other therapies. Patients with CIDP and MGUS respond well to TPE. In a small study, patients with PP and IgM paraproteins with anti-MAG activity responded to five to seven monthly courses of TPE combined with IV cyclophosphamide. Similar results were observed in patients with anti-GMI antibodies.

Other TA modalities such as double filtration plasmapheresis and Staphylococcal protein A silica** immunoadsorption may be effective alternatives to conventional TPE in PP though clinical experience is limited.

Technical notes

Patients with demyelinating PP may be treated at any time in their course (including patients referred up to 4 years after onset of symptoms).

Volume treated: 1–1.5 TPV
Replacement fluid: albumin; plasma
Frequency: every other day

Duration and discontinuation/number of procedures

The typical course is 5–6 treatments over the course of 10–14 days. Long-term TPE or slow tapering off TPE can be considered. The patient may continue to improve over weeks following cessation of plasma exchange. If the level of paraprotein is correlated to the polyneuropathy then it can be monitored to evaluate the frequency of treatment. However, the titer of the paraprotein may not correlate with the clinical disease state.

References [42, 253–262]

*As of March 1, 2006, using PubMed and the MeSH search terms polyneuropathy, apheresis, plasma exchange, plasmapheresis, anti-MAG, paraproteinemic polyneuropathy, and MGUS for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba*) and Staphylococcal A silica (Prosorba*) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.
Description of the disease

PTP is characterized by severe and abrupt onset of profound thrombocytopenia (often \( < 10^3 \times 10^9/L \)) 5–10 days after transfusion of any blood component. PTP occurs generally in patients who have preformed alloantibodies against HPA-1a antigen due to immunization during pregnancy or multiple blood transfusions. It is not clearly understood why patients who have normal platelet counts before transfusion of red cells suddenly develop thrombocytopenia. The most plausible explanation is that the soluble HPA-1a antigen present in transfused blood component gets adsorbed to the patient’s HPA-1a negative platelets on GPIIIa. The HPA-1a antigen also induces an anamnestic response, and these alloantibodies then destroy the patient’s own platelets that have adsorbed the antigen. Immune-mediated destruction of antigen negative platelets can be described as bystander immune cytolysis. Other hypotheses include immune complex mediated destruction of platelets and autoantibody phenomenon, both are poorly explained. The detection of antibodies (generally high titer) against HPA-1a antigen in the serum of a patient, who lacks this antigen, is necessary for the diagnosis of PTP. The high titer antibody can be detected for up to 1 year after the PTP episode. PTP is self-limited, with complete recovery in even untreated patients in about 20 days. The mortality of PTP is 10–20%. Sometimes, especially after cardiac surgery, PTP patients can be falsely diagnosed as Heparin-induced Thrombocytopenia (HIT) in the early stages, however, a platelet count of \( < 20 \times 10^9/L \) is uncommon in HIT and patients usually do not bleed.

Current management/treatment

The current mainstay of the treatment is high dose intravenous immunoglobulin (IVIG) (0.4 g/kg/day for 2–5 day or 1 g/kg/day for 2 days). It possibly acts by Fc receptor blockade of reticuloendothelial system. All nonessential transfusions of blood components should be immediately discontinued. In a bleeding patient transfuse HPA-1a negative platelets, if available. HPA-1a positive platelet transfusion is generally ineffective and likely to stimulate more antibody production. Patients are also given high dose of corticosteroids. The TPE is indicated only if IVIG is not effective and severe thrombocytopenia persists. Recombinant FVIIa may be considered in a bleeding patient when HPA-1a negative platelets are not available.

Rationale for therapeutic apheresis

Removal of HPA-1a alloantibodies by plasma exchange results in a decrease of antibody titer, removal of any unattached HPA-1a antigen, and an increase in platelet count and cessation of bleeding. TPE should be considered as the urgent treatment of hemorrhage and severe thrombocytopenia if IVIG therapy is not effective. The category III for TPE was assigned to this disease based on limited data available in the literature.

Technical notes

Due to severe thrombocytopenia, the AC ratio should be adjusted to 25:1 to 50:1. Typically the replacement fluid is albumin to avoid further exposure to HPA-1a antigen. However, in bleeding patient plasma supplement can be given toward the end of procedure (e.g., albumin:plasma volume ratio of 75:25).

References [62, 263–268]

*As of March 1, 2006, using PubMed and the MeSH search terms post transfusion purpura and apheresis for articles published in the English language. References in identified articles were searched for additional cases and trials.
RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Disease Group: Renal
Incidence: 0.7 per 100,000/year TPE III

# of reported patients*: >300

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Category</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Strength of evidence</th>
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</thead>
<tbody>
<tr>
<td>TPE</td>
<td>III</td>
<td>7</td>
<td>196</td>
<td>20</td>
<td>273</td>
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</tbody>
</table>

Description of the disease
RPNGN is a clinicopathologic entity consisting of rapid loss of renal function, usually a 50% decline in glomerular filtration rate within 3 months, and a principle histologic finding of crescent formation, usually involving over 50% of glomeruli. Crescent formation consists of an extracapillary proliferation of cells within Bowman’s space of the glomerulus due to the extravasation of proteins into the space. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes. RPGN does NOT represent a single disease entity but is a clinical syndrome that can result from a number of etiologies. Causes of RPGN have been divided into three main groups based upon the immunofluorescence pattern on renal biopsy. Anti-gglomerular basement membrane GN (anti-GBM) accounts for 15% of cases, immune-complex GN accounts for 24% of cases, and pauci-immune GN for 60% of cases. Anti-GBM is characterized by linear deposits of IgG and complement and the presence of autoantibodies to type IV collagen. Immune-complex GN is characterized by granular immune deposits and caused by a number of immune GNs including post-streptococcal GN, Henoch-Schönlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis. Pauci-immune GN is characterized by minimal immune deposits in the glomerulus and the presence of anti-neutrophil antibodies (either C-ANCA or P-ANCA) and typically seen in Wegner’s granulomatosis (WG) and microscopic polyangiitis (MP).

Importantly, when discussing RPGN, a number of entities are frequently included in case series and trials, thus confounding results. In this special issue, anti-GBM and WG, the major causes of RPGN, are discussed as separate fact sheet.

Current management/treatment
Therapy consists of administration of high-dose corticosteroid (e.g., methylprednisolone) and cytotoxic immunosuppressive drug (e.g., cyclophosphamide or azathioprine). Other drugs that have been used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, and antibodies against T-cells.

Rationale for therapeutic apheresis
Because of the benefit of plasma exchange in the crescentic GN of anti-GBM, plasma exchange was applied to all causes of RPGN. While early trials and series included all causes of RPGN, subsequent trials have excluded anti-GBM. The role of TPE has been examined in six trials in pauci-immune and immune-complex GNs and in a single trial in the treatment of pauci-immune GN. There are no trials for immune-complex GN.

In three out of six trials examining immune-complex GN and pauci-immune GN there was no benefit of TPE over standard therapy in a total of 87 patients. Two trials showed benefit in 62 patients who were dialysis dependent at the time of presentation; there was no benefit to those who had mild disease. Therapy proved beneficial in all 14 patients in a single trial. These trials indicate that TPE may be beneficial for dialysis-dependent patients presenting with severe renal dysfunction; however, there is no therapeutic benefit over immunosuppression in milder disease. The predominance of pauci-immune GN cases in these series may account for these results.

Because so many disorders can produce RPGN, appropriate indications for TPE are difficult to determine. TPE appears not to be beneficial in most immune-complex GN cases. However, there are some reports of TPE efficacy in RPGN due to IgA nephropathy; these include short-term improvement in renal function and delay in dialysis dependency. Randomized trials of TPE in lupus nephritis have shown no benefit. TPE in cryoglobulinemia has proven successful in several series. The category III for TPE was assigned to this disease based on limited data available in the literature.

A single trial involving 44 patients that compared TPE to immunoadsorption using a Staphylococcal protein A agarose** column found no difference in outcome between the two.

Technical notes
As stated above, TPE may be beneficial in dialysis-dependent patients at presentation.

Duration and discontinuation/number of procedures
Treatment for 1–2 weeks followed by tapering with less frequent treatments. The duration of therapy is not well defined in the literature. Some trials have stopped plasma exchange if there is no response after 4 weeks of therapy as outlined above.

References [45, 48–50, 269]
*As of November 1, 2005, using PubMed and the MeSH search terms rapidly progressive glomerulonephritis and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.
**Rasmussen’s Encephalitis**

**Disease Group:** Neurological

**Incidence:** Rare

**Procedure:** TPE

**Category:** II

<table>
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</tr>
<tr>
<td>CR</td>
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</tr>
</tbody>
</table>

**Strength of evidence:** Type II-3

**Description of the disease**

This syndrome of chronic encephalitis characterized by intractable focal seizures and slowly progressive neurological deterioration was originally described in three patients by Theodore Rasmussen in 1958. Onset is typically in childhood (mean age 6.8 \pm 5.1 years) but a similar syndrome has been described in adults. The etiology is unknown, but antecedent infection with Epstein-Barr virus, herpes simplex, enterovirus, or cytomegalovirus has been implicated. Cytomegalovirus genome has been found in resected cortical tissue of three adult patients with Rasmussen’s encephalitis. Cerebrospinal fluid analysis is typically normal, although mild lymphocytic pleocytosis and elevated protein may be found. The hallmark of Rasmussen’s encephalitis is epilepsy uncontrollable with anticonvulsant drugs, progressive hemiparesis, and progressive unilateral cerebral atrophy. There is progressive loss of function in the affected cerebral hemisphere and cognitive decline.

**Current management/treatment**

Anticonvulsants are necessary but are not always effective in controlling the disease nor do they arrest its progression. Subtotal, functionally complete hemispherectomy may markedly reduce seizure activity in a majority of patients but results in permanent contralateral hemiplegia. Corticosteroids given for up to 24 months in a tapering schedule may help to diminish episodic partialis continua and motor deficits during the first year of onset and before hemiplegia develops. Intravenous immunoglobulin (IVIG 0.4 g/kg/day for 3 days, then 0.4 g/kg monthly if there is a response) may be tried prior to a trial of corticosteroids in patients with established disease and may produce modest improvement in hemiparesis. Some authors recommend intravenous methylprednisolone (400 mg/m² every other day for 3 infusions followed by monthly infusions for the first year) and prednisone (2 mg/kg/day tapered over 1–2 years) if further treatment is needed. Intraventricular interferon alpha given via Omaya reservoir has been used to control epileptic and neurological complications.

**Rationale for therapeutic apheresis**

Patients with Rasmussen’s encephalitis may have autoantibodies against several neural molecules, and these autoantibodies may be produced in the CNS after cytotoxic T cell-mediated neuronal damage. The demonstration of serum immunoreactivity to the glutamate receptor GluR3 in 3 individuals with histologically confirmed Rasmussen’s encephalitis led to the use of therapeutic plasma exchange (TPE) in a 9-year-old girl. An initial 7 single-volume TPE procedures over 3 weeks followed by weekly TPE for 4 weeks resulted in marked reduction in GluR3 immunoreactivity and significant clinical improvement (decreased frequency of seizures, resumption of playing with dolls, and riding a bicycle) during the first 7 weeks of treatment. Serum GluR3 immunoreactivity spontaneously rose over the subsequent 4 weeks and she deteriorated clinically but had transient responses to repeat course of therapy. Clinical and EEG parameters of epileptogenesis were transiently diminished by TPE in two other patients treated with TPE. Monthly courses of plasma immunoadsorption using Staphylococcal protein A silica** diminished seizure frequency and halted cognitive deterioration in a 16-year-old girl with IgG anti-GluR3 antibodies over a 2-year period.

**Technical notes**

Neuropsychological assessment may be helpful in evaluating patients with slowly progressive disease to determine whether TPE is effective in postponing surgical therapy. Monthly staphylococcal protein A immunoadsorption apheresis of 1.5–2 plasma volumes per treatment has been reported effective in one patient. Protein A column treatment has not been directly compared to TPE. An initial course of TPE may be followed by 2 days of IVIG 1 g/kg/day. Confirmation of anti-GluR3 antibodies may support the use of apheresis in patients with Rasmussen’s encephalitis.

**Volume treated:** 1–1.5 TPV

**Replacement fluid:** albumin

**Frequency:** every other day

**Duration and discontinuation/number of procedures**

After an initial course of treatment of 5–6 TPE over 10–12 days, subsequent courses of TPE (with or without IVIG) may be performed at 2–3 month intervals as empirically needed. Immunosuppressive medications may increase the interval between courses. Surgical treatment is offered in case of neurocognitive decline or intractable seizure activity.

**References [42, 270–275]**

*As of November 13, 2005, using PubMed and the MeSH search terms Rasmussen’s encephalitis and apheresis, for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Imunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.
RED CELL ALLOIMMUNIZATION IN PREGNANCY

Description of the disease
Hemolytic disease of the fetus and newborn (HDFN) occurs when maternal plasma contains an alloantibody against a red cell antigen carried by the fetus. The maternal IgG crosses the placenta and causes hemolysis of the fetal red cells. This leads to fetal anemia and when severe enough, fetal death (hydrops fetalis). Most frequently HDFN is secondary to anti-D (previously termed, Rh disease), but it can be caused by a variety of red cell alloantibodies (anti-K, anti-c, anti-PP1Pk, and anti-E, for instance). Sensitization to red cell antigens usually occurs after fetal-maternal hemorrhage during pregnancy or delivery, or through previous red cell transfusion. Only 0.1 mL of fetal cells can result in Rh sensitization. Due to the use of Rhesus immunoglobulin during pregnancy and post-partum, the incidence of HDFN secondary to anti-D has greatly decreased. The severity of HDFN usually increases with subsequent pregnancies.

Current management/treatment
The flow of management of a newly identified clinically significant alloantibody is as follows. First, take a history to help identify the source of exposure, such as previous pregnancy or transfusion. Second, phenotype the father to assess for risk of HDFN, if paternity is assured. If the father does not carry the antigen, then no further work up needs to be performed. If the father is heterozygous for the antigen, then the fetus has a 50% chance of being at risk. If the father is homozygous for the antigen, the fetus will be at risk. Third, maternal antibody titer should be performed. Higher titers predict for more severe HDFN. Titers should be repeated with every scheduled prenatal obstetrics visit (approximately monthly until 24 weeks then every 2 weeks). Fourth, if titers, performed in the same laboratory, are above 1:16 or have increased fourfold, then ultrasound and/or amniocentesis should be performed to evaluate the fetus. Ultrasound can detect signs of anemia (middle cerebral artery velocity) or hydrops (ascites). Ultrasound is a noninvasive way of following the severity of HDFN. Amniocentesis provides samples for fetal genotype (if needed), amniotic fluid spectral analysis, and fetal lung maturity. Spectral analysis at 450 OD measures amniotic bilirubin; the results are plotted on the Liley’s correlative graph for predicting the severity of HDFN after 26 weeks gestation. Results in the severe zone or high moderate zone indicate need for fetal blood sampling, delivery, or close follow up. Fetal lung maturity testing predicts if the fetus can be safely delivered. Fetal blood sampling allows for the measurement of fetal hematocrit and, if needed, an intrauterine transfusion (IUT), which cannot occur until about 20 weeks gestational age. The fetus is transfused with RBCs negative for the antigen against which maternal antibody is directed. Fetal mortality related to IUT is 1–2%. IUT can be repeated, approximately every 1–2 weeks, until the fetus is ready for delivery. HDFN can result in neonatal hyperbilirubinemia which can cause kernicterus and permanent brain damage.

Anti-K deserves to be mentioned separately. Unfortunately, the use of antibody titers and amniocentesis for delta 450 OD measurements are not as predictive as with other antibodies. Anti-K suppresses red cell production as well as causes hemolysis. Therefore, monitoring the middle cerebral artery velocity by ultrasound is important.

If the fetus is known to be at high risk for hydrops fetalis, based on ultrasound or previous prenatal loss, then a more aggressive approach early during pregnancy is needed. The current mainstay of treatment is IUT, but if there is a high risk of fetal demise or signs of hydrops prior to 20 weeks, then intravenous immunoglobulin (IVIG) and/or TPE may be indicated.

Rationale for therapeutic apheresis
TPE removes the maternal red cell alloantibody that causes HDFN. Therefore, it is thought that TPE will decrease the maternal antibody titer and, in turn, the amount transferred to the fetus, thereby protecting it from HDFN. Survival in severe cases of HDFN with the use of TPE and/or IVIG prior to IUT is about 70%. Category II is assigned for patients when there is a previous history of a severely affected pregnancy and the fetus is less than 20 weeks gestational age. Typically, IUT can be performed after the fetus reaches 20 weeks of gestation.

Technical notes
Plasma exchange can safely be performed during pregnancy. During pregnancy blood volume especially the plasma volume increases. In the second or third trimester, it is preferable to place the patient on her left side to avoid compression of the inferior vena cava by the gravid uterus. Hypotension should be avoided as it may result in decrease perfusion to the fetus.

Duration and discontinuation/number of procedures
TPE should be considered early in pregnancy (from 7th to 20th week) and continued until IUT can safely be administered (about 20th week of gestation). Close monitoring of the fetus for signs of hydrops will aid in guiding treatment. One approach is to use TPE for the first week (three procedures) followed by IVIG at 1 g/kg weekly.

References [276–281]
*As of December 15, 2005, using PubMed and the MeSH search terms maternal alloimmunization and plasmapheresis, hemolytic disease of the newborn and apheresis for articles published in the English language. References in identified articles were searched for additional cases and trials.

Journal of Clinical Apheresis DOI 10.1002/jca
RENA L TRANSPLANTATION: ANTIBODY MEDIATED REJECTION AND HLA DESENSITIZATION

**Disease Group:** Renal

**Incidence:** renal transplantation: 7 per 100,000/year

### # of reported patients*

<table>
<thead>
<tr>
<th>Disease Group</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Strength of evidence</th>
</tr>
</thead>
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<td>24 (396)</td>
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<td>18 (219)</td>
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<td>Type II-3</td>
</tr>
</tbody>
</table>

### Description of the disease

Kidney transplantation is performed to allow individuals with end stage renal disease to discontinue dialysis. Transplantation increases the life span of these individuals. Barriers to transplantation include antibodies to human leukocyte antigens (HLA) and ABO incompatibility with the donor because there is an increased risk for graft loss secondary to hyperacute rejection. Patients with an elevated HLA antibody screen have difficulty finding an HLA compatible donor and remain on the transplantation list significantly longer than unsensitized patients. The goal of desensitization protocols is to allow these individuals to be transplanted using a donor kidney that would otherwise not be usable due to the high likelihood of graft loss.

Allograft rejection has traditionally focused on T cell mediated process causing cellular rejection. Acute vascular rejection (also termed acute humoral rejection or antibody-mediated rejection) has been thought of as antibody mediated based on correlating histological findings with the identification of donor specific antibody. Recently a clear histological diagnosis of antibody-mediated rejection (AMR) can be made based on the Sixth Banff Conference on Allograft pathology in 2001. The diagnosis is based on (1) documentation of donor specific antibody (DSA); (2) histologic evidence of acute tissue injury, such as acute tubular injury, neutrophils in peritubular capillaries and/or glomeruli, and/ or capillary thrombosis, or intimal arteritis/ fibrinoid necrosis/ intramural or transmural inflammation in arteries; and (3) C4d in peritubular capillaries or immunoglobulin and complement in arterial fibrinoid necrotic areas by immunohistology.

AMR affects less than 10% of renal allografts. Recipients at increased risk include those with previous transplant and high panel-reactive antibodies.

Information about the use of plasma exchange (TPE) in ABO incompatible renal transplantation can be found in a separate fact sheet focusing on ABO incompatibility and solid organ transplantation.

### Current management/treatment

New immunosuppressive drugs are continually being developed to prevent and treat acute allograft rejection. All transplant recipients are placed on immunosuppressive therapy but individuals with a high likelihood of acute rejection, including those with HLA antibodies and recipients of cadaveric organs, receive more intense regimens. The optimal regimen has yet to be defined but include the use of cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, and antithymocyte globulin.

The two published desensitization protocols use either high dose intravenous immunoglobulin (IVIG) or plasma exchange (TPE) with low dose IVIG to convert a positive crossmatch to a negative crossmatch and allow for transplantation. The TPE/IVIG regimen has been used for potential living donors while the high dose IVIG regimen has been used for both living and deceased donors. Immunosuppressive drugs, such as rituximab, glucocorticosteroids, mycophenolate mofetil, and tacrolimus, are initiated at the start of the protocol. Rapid post transplantation diagnosis and treatment of AMR is essential.

### Rationale for therapeutic apheresis

In antibody-mediated rejection, DSA are generated after transplantation. These antibodies can be removed with plasma exchange, double filtration plasmapheresis, lymphoplasmapheresis, and immunoabsorption. Therapeutic apheresis is always used in combination with other immunosuppressive drugs, such as antithymocyte globulin glucocorticosteroids, rituximab, and intravenous immunoglobulin. Randomized controlled trials in the early 1980s did not show plasma exchange to be beneficial when used in combinations with corticosteroids for either acute rejection with DSA detected or acute vascular rejection. Case series published since 1985 have shown improvement when plasma exchange is used in patients with acute vascular rejection in combination with a variety of anti-rejection medications. This is likely due to improved anti-rejection medications, improved detection of DSA, and improved definition of AMR using the Banff criteria. Previously there was a high graft loss rate with acute vascular rejection, current regimens which include plasma exchange have a graft survival rate of 70-80%.

Therapeutic apheresis can also be used prior to transplant to remove HLA antibodies. TPE (some series have used double filtration plasmapheresis and one small series used Staphylococcal protein A silica column**) is used in combination with immunosuppressive drugs pre transplant until crossmatch is negative. TPE is usually continued postoperatively and re-initiated in cases where AMR occurs. The ability to obtain a negative crossmatch depends on the DSA titer. Using approximately 5 TPE preoperatively, will allow the titer of <32 to become negative based on both the John Hopkins and Mayo Clinic experience. The risk of AMR is approximately 30% with a small number of graft losses. The desensitization protocols should be used only in highly selected patients.

### Technical notes

Patients should be started on immunosuppressive drugs prior to initiating plasma exchange to limit antibody resynthesis. For desensitization protocols, there appears to be a correlation between the number of TPEs needed pre-operatively to obtain a negative crossmatch and the antibody titer.

<table>
<thead>
<tr>
<th>Volume treated:</th>
<th>1–1.5 TPV</th>
<th>Frequency: daily or every other day</th>
</tr>
</thead>
</table>
| Replacement fluid: | albumin | **Duration and discontinuation/number of procedures**

For AMR, some protocols use a set number of procedures, usually 5 or 6, daily or every other day. Other protocols guide the number of treatments based on improvement in renal function and decrease in DSA titers. It is also undecided if low dose intravenous immunoglobulin should be used after every procedure, at the end of the series or, not at all.

For desensitization protocols, TPE is performed daily or every other day per protocol until crossmatch becomes negative. TPE is also performed post-operatively for a minimum of three procedures. Further treatment is determined by risk of AMR, DSA titers, or the occurrence of AMR.

### References [282–288]

*As of April 11, 2006, using PubMed and the MeSH search terms kidney transplantation and apheresis for articles published in the English language. References in identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agrose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.

*Journal of Clinical Apheresis DOI 10.1002/jca*
Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease of unknown etiology. The most characteristic feature is an inflammatory synovitis (relapsing or persistent), usually involving peripheral joints in a symmetric distribution. RA most commonly affects women between the fourth and sixth decades, although it may affect people of all ages and ethnic origins. The primary joint lesion involves the synovium. Synovial hypertrophy is due to inflammatory changes caused mainly by macrophages and T lymphocytes. Synovitis is often progressive and leads to structural damage and disability. In about 20% of the patients, there are extra-articular features. These may include involvement of skin, eyes, lungs, heart, blood, and blood vessels. About 80% of patients are seropositive for rheumatoid factor. More recently, there has been increasing attention to the role of antibodies to cyclic citrulinated peptides (anti-CCP) in the pathogenesis and diagnosis of RA.

Current management/treatment
The goals of therapy of RA are (1) relief of pain, (2) reduction of inflammation, (3) protection of articular structures, (4) maintenance of function, (5) control of systemic involvement, and (6) healing of bone erosions. None of the current therapeutic interventions is curative, and must be viewed as palliative, aimed primarily at relieving the signs and symptoms of the disease.

Medical management of RA can conveniently be divided into five groups of medications: (1) aspirin, other nonsteroidal anti-inflammatory drugs, and simple analgesics to control the symptoms and signs of the local inflammatory process; (2) low-dose oral glucocorticoids to suppress inflammatory signs and symptoms, and may retard the development and progression of bone erosions; (3) disease-modifying anti-rheumatic drugs (DMARDs) (e.g., methotrexate), which have the capacity to decrease elevated levels of acute phase reactants, and thus modify the inflammatory component and its destructive capacity; (4) cytokine-neutralizing agents (i.e. anti-TNF, anti-IL1) to improve signs and symptoms and slow progressive damage to articular structures; and (5) immunosuppressive and cytotoxic drugs. Recently, several novel and effective biologic agents like anti-CD20 (rituximab) and CTLA4-Ig, were approved for treatment of RA.

Rheumatoid arthritis: 500–1,000 per 100,000/year

**Rationale for therapeutic apheresis**

The rationale for using the Staphylococcal protein A silica column was the observation that protein A has a high affinity for Fc portion of IgG and for high molecular weight IgG and IgM complexes, such as rheumatoid factors and circulating immune complexes (CIC). Thus, IgG antibodies and CICs can be selectively removed from the circulation by extracorporeal exposure of patient’s plasma to Staphylococcal protein A silica (SPA) immobilized on a solid matrix. Animal studies and clinical observations support an immunosuppressive role for CICs in autoimmune diseases. Their removal or alteration by immunoadsorption, could be immunomodulatory and potentially beneficial for patients with RA. It was shown though that only relatively small amounts of immunoglobulins are removed from plasma by immunoadsorption (1–3% of total serum immunoglobulins) and their concentrations are unchanged as well as plasma levels of CICs. Thus, the precise mechanism of action remains unclear and is probably multifactorial. The slow onset and sustained duration of immunoadsorption-induced therapeutic responses in RA suggest an indirect immunomodulatory mechanism. There are several possible indirect immunomodulation mechanisms: (1) the release of protein A into the circulation, which induces development of SPA inhibitory activity, presumably antibody-mediated (responsive patients have significantly higher levels of SPA antibodies than those who are not responsive) (2) the activation of complement components which solubilize previously formed immune precipitates and prevent immune precipitation (3) the remodeling of CICs into larger immune complexes that can be cleared by the reticuloendothelial system and (4) the potential for SPA to function as a superantigen to modify the B cell repertoire.

**Technical notes**

Using Staphylococcal protein A silica column ** for RA, the procedure can be done after separation of plasma by continuous-flow cell separator. Plasma is treated by perfusion through the column and then reinfused with the flow rate not exceeding 20 mL/min. Common adverse effects include chills, low-grade fever, musculoskeletal pain, hypotension, nausea, vomiting, and short-term flare in joint pain and swelling following treatment. Concomitant use of angiotensin converting enzyme inhibitor is a contraindication to immunoadsorption.

**Volume treated:** 1,200 mL of plasma  
**Replacement fluid:** not applicable  
**Frequency:** once a week
Systemic sclerosis (SSc), or scleroderma, is a chronic multisystem disorder of unknown etiology with worldwide distribution characterized clinically by thickening of the skin cause by accumulation of connective tissue and by involvement of visceral organs, including the gastrointestinal tract, lungs, heart, and kidneys. Abnormalities in microvasculature are typical and prominent features of SSc. SSc patients present with either with diffuse cutaneous scleroderma (i.e., symmetric skin thickening of proximal and distal extremities, face and trunk) or with limited cutaneous scleroderma (i.e., symmetric skin thickening limited to distal extremities and face). The latter group usually presents with features of CREST (Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangectasia). Raynaud’s phenomenon is an initial symptom of SSc in the majority of patients. The severity of visceral disease determines survival as it affects critical organs (e.g., lungs (interstitial fibrosis), heart, liver (biliary cirrhosis), and/or kidneys (renovascular hypertensive crisis]). Antinuclear antibodies are present in more than 95% of patients with SSc. Antinuclear and anti-nucleolar antibodies are directed against topoisomerase 1 (Scl 70/40%), centromere (60–80%), RNA polymerase I, II, and III (5–40%), Th RNP (14%), and/or kidneys (renovascular hypertensive crisis]. Antinuclear antibodies are present in more than 95% of patients with SSc. Antinuclear and anti-nucleolar antibodies are directed against topoisomerase 1 (Scl 70/40%), centromere (60–80%), RNA polymerase I, II, and III (5–40%), Th RNP (14%), U1 RNP (5–10%), and PM/Scl (25%).

Accumulation of collagen and other extracellular matrix proteins including fibronectin, tenasin, and glycosaminoglycans, in skin and other organs is characteristic for SSc. A state of chronic ischemia caused by an injury to endothelial cells in small arteries, arterioles, and capillaries precedes fibrosis. The current understanding of pathophysiology implicates cell mediated immunity involving activated T cells and IL-2, increased ratio of circulating CD4+ to CD8+ cells, and by involvement of activated T cells and IL-2, increased ratio of circulating CD4+ to CD8+ cells, and significant involvement of macrophages and their products IL-1, IL-6, TNFa, TGFb, PDGF, and fibronectin.

Current management/treatment
Treatment of involved organ systems can relieve symptoms and improve function, though SSc is not curable at this time. D-Penicillamine is the most widely used drug and has been shown in a retrospective study to improve the skin thickening and survival of patients, when compared to no treatment. In rapidly progressive disease, corticosteroids, azathioprine, methotrexate, cyclophosphamide, and other immunosuppressants have been used. Symptomatic treatment of Raynaud’s phenomenon with calcium channel blockers may provide symptomatic relief, but can be associated with aggravation of GI symptoms. Raynaud’s phenomenon complicated by digital ulcers and pulmonary hypertension may respond to intravenous prostacyclin. ACE inhibitors have dramatically improved the typically poor outcome of renal hypertensive crisis. The newer treatment modalities include the use of minocycline, psoralen-UV-A, lung transplantation, etanercept, and thalidomide. However, no medications appear to be truly effective in patients with aggressive disease. A clinical benefit was observed in total of 46 patients who underwent high dose chemotherapy followed by autologous hematopoietic cell salvage.

Rationale for therapeutic apheresis
Pathophysiology of SSc is not fully elucidated but, as presently understood, lends little support to the use of plasma exchange as a treatment option. There is no known circulating factor, pivotal in pathogenesis of this disease, which could be easily identified and removed. Nevertheless, there are several controlled trials as well as case series spanning over the last 20 years. A controlled trial of 23 patients randomized to no apheresis, plasma exchange, or lymphoplasmapheresis was reported in 1987 as an abstract. Both treatment groups showed statistically significant improvement in skin score, physical therapy assessment, and patient and physician global assessment. The study has never been published in the peer-reviewed literature. An effect of long term TPE was evaluated in a controlled trial. The TPE were scheduled as 2–3 weekly for 2 week, 1 TPE weekly for 3 months, and 1 TPE every other week as a maintenance therapy. One volume exchange was used with 4% albumin in a replacement fluid. All serological markers improved in comparison to the control group; however, there was no difference in clinical outcomes between the groups. In a case series reporting on 15 patients who received TPE in combination with prednisone and cyclophosphamide, 14 patients had clinical improvement. Severe gastrointestinal symptoms were ameliorated in 4 patients, severe polymyositis was largely reversed in 2 patients, and pulmonary and cardiac function was improved in others. The category III was assigned to this disease based on conflicting data available in the literature.

Involvement of activated T lymphocytes could lead to the use of other apheresis modalities such as extracorporeal photopheresis (ECP). There were three randomized controlled trials using ECP in SSc (see the publication on category IV indications in this Special Issue).
Incidence:

750,000 cases per year in the US based on limited and conflicting data available in the literature.

TPE the next day if there was no improvement or development of hemodynamic instability. The category III for TPE was assigned to this disease.

tic regression, the significance of the treatment variable on mortality was compared to 53.8% in the control group (P < 0.07). In this study, patients received a single TPE with one additional TPE performed in the presence of severe coagulopathy. The larger randomized trial found 28-day mortality rates of 33% in the TPE group compared to 53.8% in the control group (P < 0.05). When differences between the control and experimental groups were considered using multiple logistic regression, the significance of the treatment variable on mortality was P = 0.07. In this study, patients received a single TPE with one additional TPE the next day if there was no improvement of development of hemodynamic instability. The category III for TPE was assigned to this disease based on limited and conflicting data available in the literature.

Description of the disease

Sepsis, a systemic inflammatory response to infection, is the most common cause of death in non-coronary intensive care units and the 10th most common cause of death in the United States. It accounts for 2–3% of all hospital admissions. The incidence of sepsis has increased over the last two decades with an unchanged mortality rate of 28–50%.

Signs and symptoms consist of fever or hypothermia, tachycardia, hyperventilation, and leukocytosis or leukopenia. Organ dysfunction, hypoperfusion, and hypotension can be seen. Risk factors include age extremes, chronic medical conditions, immune compromise, indwelling catheters and devices, and disruption of natural defense barriers. Sepsis is a complex process consisting of activation of a variety of host defense systems. Production of a wide variety of inflammatory molecules can lead to organ dysfunction or an anti-inflammatory response resulting in an immunocompromised state. Cytokines and other mediators in sepsis include TNF, IL-1, IL-2, IL-6, IL-8, leukotrienes, prostaglandins, endotoxin, and TGF-β.

Current management/treatment

Management includes antimicrobial agents and control of the source of the infection, hemodynamic support including volume and pressors, oxygenation and ventilatory support, and avoidance of complications. Additional innovative treatments have included the administration of corticosteroids, monoclonal antibodies to TNF, soluble TNF receptor, antithrombin, activated protein C, and tissue factor pathway inhibitor. These therapies seek to interrupt the cascade of inflammation and anti-inflammatory response.

Rationale for therapeutic apheresis

Attempts to block or remove single mediators of sepsis have been somewhat successful. Plasma exchange, due to its non-selective nature, has the potential to remove multiple toxic mediators of the syndrome and may therefore be more effective than blocking single components of the process.

Nonrandomized clinical trials and case series of plasma exchange in the treatment of sepsis have found survivals of 66–82% compared to either predicted survivals or survival of historical controls of 20%. Two randomized trials of 43 and 160 patients have been published. In the smaller trial, TPE and continuous venous hemofiltration versus continuous venovenous hemofiltration alone were examined. The number of TPE performed is not clear. Mortality rates were similar, 42.1 versus 45.8%. However, significant differences were seen in some APACHE II subgroups. In patients with single or double organ failure, significantly lower mortality was seen with TPE (25% vs 0% and 42% vs 17%, P < 0.0001 for both). TPE was associated with a significant improvement in cardiac index. The larger randomized trial found 28-day mortality rates of 33% in the TPE group compared to 53.8% in the control group (P < 0.05). When differences between the control and experimental groups were considered using multiple logistic regression, the significance of the treatment variable on mortality was P = 0.07. In this study, patients received a single TPE with one additional TPE the next day if there was no improvement of development of hemodynamic instability. The category III for TPE was assigned to this disease based on limited and conflicting data available in the literature.

Technical notes

Both centrifugal based and filtration based apheresis instruments have been used in the trials of TPE. There has also been suggestion by some authors that early performance of TPE may be more beneficial than waiting and may explain discrepancies in some series and trials. In the presence of severe coagulopathy, plasma alone is indicated as a replacement fluid.

The trials, case series, and case report numbers given above refer to reports of the use of TPE in the treatment of sepsis. In addition to TPE, a number of selective removal columns have also been examined.

The polymyxin B columns consist of polymyxin B bound to polystyrene fibers. Whole blood is perfused through the column which binds endotoxin. A randomized trial of 70 patients found a 54% survival in the treatment arm compared to a 36% survival in the control arm. A case series of 99 patients, survival of 66% was seen compared to an expected survival of 20%. These patients received treatments lasting two hours though the frequency and total volume treated were not given.

The Matisse column contains human albumin bound to polymethacrylate. Whole blood is passed through this column which binds endotoxin. A randomized trial involving 145 patients found a trend towards improvement or morbidity and organ dysfunction. These columns used to treat 1–1.5 blood volumes daily for four days. Neither of these devices have been approved for use in the United States.

Duration and discontinuation/number of procedures

The randomized trials have limited treatment to one to two TPEs. Case series have treated patients daily until improvement. In many, “improvement” has not been defined while in other series it has been variably defined as resolution of DIC, decrease in hemodynamic support, reversal of multisystem organ dysfunction, and improvement in laboratory values.

References [301–307]
*As of November 1, 2005, using PubMed and the MeSH search terms sepsis and apheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.

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SICKLE CELL DISEASE

Description of the disease
Sickle cell disease (SCD) is an inherited disorder caused by an abnormal hemoglobin (Hb) due to substitution of valine for glutamic acid at β 6 (Hb S). The most common type of SCD is sickle cell anemia, in which the individual is homozygous for the β gene (Hb SS). Variants of SCD include Hb SC, Hb Sβ-thalassemia, Hb SD, etc. Morbidity and mortality are significantly higher in Hb SS than in SCD variants. Diagnosis is most commonly made by isoelectric focusing and cellulose acetate electrophoresis. Hb S polymerizes upon deoxygenation, causing red blood cells (RBCs) to become rigid and deformed (sickled RBCs). Sickled RBCs have a shortened lifespan, producing hemolytic anemia and occluding the microvasculature leading to tissue hypoxia and infarction. Major manifestations are vaso-occlusive events (VOE), splenic sequestration, and transient red cell aplasia (TRCA). Among VOE, painful episodes are the most common. Other serious VOE include acute chest syndrome (ACS), stroke, priapism, and splenic, hepatic, and renal dysfunction. Leading causes of death are sepsis, ACS, stroke, and acute multiorgan failure. Infection is the most common cause of death in children, primarily due to autosplenectomy. Overall mortality rate for SCD is 2.6% (0.5 deaths/100 person years) with the peak at 1–3 years of age. Median ages of death in males and females with Hb SS in the mid 1990s were 42 and 48 years old, respectively.

Current management/treatment
Standard therapies include penicillin prophylaxis, folic acid, pneumococcal and *Haemophilus influenzae* vaccinations, analgesics for painful episodes, and antibiotics for infections. Hydroxyurea may be used to reduce frequency of severe pain and ACS. RBC Transfusion (Tx) can be a primary or a first-line adjunct therapy. Methods include simple RBC Tx (S-Tx) or RBC exchange Tx (Ex-Tx). Ex-Tx can be accomplished manually or by erythrocytapheresis using an automated cell separator. Manual Ex-Tx is a labor intensive and longer procedure and may be less efficient. Acute S-Tx is indicated for severe anemia due to TRCA, splenic sequestration, or hyperhemolysis, ACS with hypoxia, stroke, acute multiorgan failure. Infection is the most common cause of death in children, primarily due to autosplenectomy. Overall mortality rate for SCD is 2.6% (0.5 deaths/100 person years) with the peak at 1–3 years of age. Median ages of death in males and females with Hb SS in the mid 1990s were 42 and 48 years old, respectively.

Rationale for therapeutic apheresis
In severe anemia, S-Tx is the best transfusion method to improve oxygen-carrying capacity of blood by increasing RBC mass. In acute ischemic stroke, ACS, or acute life- or organ-threatening complications, erythrocytapheresis is preferred over S-Tx since the Hb S concentration is reduced rapidly by removing and replacing sickled RBCs with normal RBCs without increasing blood viscosity and volume overload. However, advantages of erythrocytapheresis over S-Tx through randomized controlled clinical trials have not been documented. Long-term erythrocytapheresis has the distinctive advantage of preventing or markedly reducing transfusion associated iron accumulation, but is associated with significantly higher (1.5–3 times higher) blood requirements than S-Tx. Increased blood donor exposure can potentially increase rates of viral transmission and RBC alloimmunization. Strategies to reduce the risk of alloimmunization include the use of phenotypically-matched RBC.

Technical notes
Automated apheresis equipment provides calculations to achieve the desired target Hb S and Hb levels and the replacement packed-RBC volume. Guidelines to calculate replacement volume using COBE Spectra are: (1) END Hct at 30 ± 3% (<36% to avoid hyperviscosity) and (2) FCR (desired fraction of patient’s RBCs remaining at end of procedure) at 25–30%. In previously transfused patients, calculate the FCR by dividing the desired Hb S level by pre-apheresis Hb S level multiplied by 100. To maintain isovolemia, primed saline is not diverted and RINSEBACK is skipped at the end of the run. In children, clinically unstable or severely anemic patients, the RBC priming is advisable. Modification of erythrocytapheresis utilizing isosmolemic hemodilution, which consists of RBC depletion with 0.9% NaCl replacement followed by standard RBC exchange, reduces replacement packed-RBC volume.

Volume treated: 1–2 total RBC volume
Replacement fluid: Hb S negative leukoreduced
RBCs and, if available, antigen-matched for E, C, and Kell

Frequency: acute: one procedure; chronic: at required intervals to maintain the desired Hb S level <30–50%

Duration and discontinuation/number of procedures
For some clinical indications such as stroke prevention lifelong transfusion therapy is indicated. One procedure is typically sufficient to treat the acute complications of SCD resulting in a FCR of less than 40% (one RBC volume) or less than 20% (two RBC volumes). For chronic transfusion therapy, erythrocytapheresis is typically performed at patient specific intervals to maintain the desired Hb S level <30–50%.

References [308–317]
*As of January 31, 2006, using PubMed and the MeSH search terms sickle cell disease, red blood cell exchange transfusion, and erythrocytapheresis for reports published in the English language. References of the identified articles were searched for additional cases and trials.*
Description of the disease
Stiff-person syndrome is a rare chronic disorder characterized by involuntary stiffness, painful muscle spasms, and rigidity, predominantly in the axial (truncal) muscles. Seven criteria were used by Lorish et al. for confirmation of the diagnosis: (1) prodrome of stiffness and rigidity in axial muscles; (2) slow progression of stiffness to include proximal limb muscles, making volitional movements and ambulation difficult; (3) fixed deformity of the spine (most often a pronounced lordosis); (4) presence of superimposed episodic spasms precipitated by sudden movement, jarring, noise, and emotional upsets; (5) normal findings on motor and sensory nerve examinations; (6) normal intellect; (7) typical electromyographic findings of continuous motor activity abolished by the intravenous administration of diazepam or a positive response to a therapeutic trial of orally administered diazepam. The onset is insidious, symptoms progress slowly, and men and women are equally affected. Stiff-person syndrome is associated with autoimmune endocrinopathies such as Graves’ disease, Hashimoto’s thyroiditis, diabetes mellitus, and others, in patients and their families. The rigidity and spasm improve with benzodiazepines suggesting a loss of inhibition of motor neurons, due to an imbalance between gamma-aminobutyric acid-(GABA)-ergic and catecholaminergic neurons. Autoantibodies reactive to a 65 kDa glutamic acid decarboxylase (GAD65, the enzyme responsible for the synthesis of GABA) in brain and pancreatic islet cells was found in the serum and cerebrospinal fluid of approximately 60% of patients with stiff-person syndrome and insulin-dependent diabetes mellitus. A paraneoplastic form of the syndrome, associated with autoantibodies to the 128 kDa synaptic protein amphiphysin, has been described in breast, colon and small cell lung cancer, and in Hodgkin’s lymphoma.

Current management/treatment
Diazepam, a benzodiazepine that diminishes continuous motor unit activity through inhibition of central catecholamine neurons and activation of GABA-ergic neurons, is given in total daily doses ranging from 20 mg to as much as 300 mg to decrease rigidity and spasms. Baclofen, a GABA-B agonist, valproate, and clonazepam are also used. Intrathecal baclofen administered via constant-infusion pump has shown efficacy. High-dose intravenous immunoglobulin (IVIG; 2 g/kg given over 2 consecutive days per month) is effective in relieving symptoms of stiffness and spasticity, and in reducing the titer of anti-GAD65 antibodies.

Rationale for therapeutic apheresis
The association of specific autoantibodies with stiff-person syndrome has led to scattered case reports, both with positive and negative results, and a few small case series describing responses to TPE in conjunction with other immunosuppressive therapies. There are no randomized trial data. Relatively small exchange volumes (e.g., 2–3 L) have been employed, possibly compromising the potential effectiveness of treatment. TPE can effectively deplete antibodies of the IgG class when sufficient plasma volumes are exchanged in a brief period of time. If TPE is to be offered to a patient with stiff-person syndrome, the patient should be made aware of the paucity of clinical data to support its use and also of the availability of IVIG as an alternative. If IVIG is not available then it may be reasonable to proceed with TPE. TPE may also be considered if the patient does not respond to conventional therapy. TPE should be used as an adjunct with standard pharmacological therapy. The category III for TPE was assigned to this disease based on limited data available in the literature.

Technical notes
TPE can effectively deplete antibodies of the IgG class when sufficient plasma volumes are exchanged in a brief period of time.

Volume treated: 1–1.5 TPV
Replacement fluid: albumin
Frequency: every other day

Duration and discontinuation/number of procedures
A series of 4–5 plasma exchanges over 8–14 days should effectively deplete IgG. Repeat series of TPE can be employed empirically if there is an objective clinical improvement that is followed by a relapse of symptoms.

References [318–324]
*As of November 14, 2005, using PubMed and the MeSH search terms Stiff-person syndrome, plasma exchange, and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Incidence: 15–50 per 100,000/year. TPE III and high titers of autoantibodies suggest active disease. While the more specific antibodies to double-stranded DNA (anti-dsDNA) and Sm antibodies are used as confirmatory tests. Low complement levels in autoimmune disease. Laboratory testing is helpful in establishing diagnosis. Screening tests for antinuclear antibodies (ANA) are commonly positive. PLEXES. Recent observations point toward nucleosomes and possibly complement factor C1q as major factors in SLE pathogenesis. The nucleosome serves as an autoantigen in SLE and is presented to pathogenic T helper and B cells. A defect in apoptosis is also postulated to be an important factor in autoimmunity. Laboratory testing is helpful in establishing diagnosis. Screening tests for antinuclear antibodies (ANA) are commonly positive while the more specific antibodies to double-stranded DNA (anti-dsDNA) and Sm antibodies are used as confirmatory tests. Low complement levels and high titers of autoantibodies suggest active disease.

Current management/treatment
SLE is an incurable chronic, remitting, and relapsing illness. Therapy entails immunosuppressive agents such as cyclophosphamide, azathioprine, prednisone, methotrexate, cyclosporine, and mycophenolate mofetil. Newer agents directly target abnormal immune cells and include rituximab (anti-CD20), epratuzumab (anti-CD22), and the anti-dsDNA tolerogen LJP394. Other promising approaches include inhibition of the CD40-CD40 ligand pathway (anti-CD40 ligand monoclonal antibody), inhibition of the B7 pathway (CTLA-4 antibody), blockade of IL-10, and anti-tumor necrosis factor therapy but controlled trials of these agents have not been performed. Patients with end-stage nephritis are treated with dialysis and renal transplantation. In addition, there are ongoing Phase III trials using autologous hematopoietic progenitor cell (HPC) transplantation with high dose chemotherapy in SLE.

The SLE Disease Activity Index (SLEDAI) and the SLE Activity Measure (SLAM) are used to determine disease activity. The SLEDAI consists of 19 items representing nine organ systems. Each item is rated as present or absent. The SLEDAI score above 5.0 defines active disease. The SLAM includes 24 clinical manifestations for nine organ systems and eight laboratory variables to evaluate organs that cannot otherwise be assessed. All items are scored as 0–2 or 0–3 according to their severity. Evaluation of therapy efficacy in SLE typically includes one or both scores. The relationship between clinical impression and SLEDAI score has been recently evaluated with the following proposed: flare (increase in SLEDAI by >3), improvement (reduction of SLEDAI by >3), persistently active disease (change in SLEDAI ±3), and remission (SLEDAI of 0).

Rationale for therapeutic apheresis
TPE was initially used to treat SLE under the assumption that reduction in autoantibody concentration would change the rate of disease progression. This rationale has not translated into a clear clinical response. In the early 1980s it was reported that more than 50% of patients with various manifestations of SLE improved after TPE. However, the first RCT in mild SLE, where the patients underwent six 4 liter exchanges within 2 weeks with expected autoantibody and immune complex reductions, showed no clinical improvement. More recently, the use of cyclosporine A and TPE to control symptomatic disease in a prospective trial of 26 patients with flares resulted in quicker resolution of symptoms and decreased doses of cytotoxic drugs. Multiple well documented case reports of beneficial effect of TPE in SLE associated TTP (see TTP fact sheet), pulmonary hemorrhage, myasthenia gravis (see MG fact sheet), hyperviscosity (see hyperviscosity fact sheet), and cryoglobulinemia (see cryoglobulinemia fact sheet) have been published. A recent review of 26 patients with SLE and CNS involvement who were treated with TPE or combination TPE/cyclophosphamide revealed that 74% of patients improved, 13% stabilized, and 13% progressed. These results highlighted a potential benefit for refractory or critically ill patients. The category III for TPE was assigned to SLE based on conflicting data available in the literature. TPE in lupus nephritis is classified as Category IV as controlled trials have shown no benefit (see the publication on category IV indications in this issue).
THROMBOCYTOSIS

Description of the disease
Thrombocytosis, defined as a circulating platelet count ≥ 500 × 10^9/L, is most commonly a secondary phenomenon related to acute bleeding, hemolysis, infection, inflammation, asplenia, cancer, or iron deficiency. The increased normal platelets in these cases do not predispose to thrombosis or bleeding. By comparison, myeloproliferative disorders (MPD) are associated with thrombocytosis and functionally abnormal platelets that are causally linked to vascular complications. Patients with polycythemia vera (PV) and essential thrombocythemia (ET) are at significant risk of arterial and, less commonly, venous thromboembolic events. These occur either spontaneously or during situational hypercoagulability, such as surgery, immobilization, and pregnancy. Additional risk factors include age > 60 years, history of prior thrombosis, cardiovascular comorbidities and, for PV, uncontrolled erythrocytosis. Thromboembolism with ET occurs in 11–25% at diagnosis and in 11–27% during follow-up. Similarly, thrombosis has affected 12–39% of patients with PV at diagnosis and develops in 10–25% during follow-up. Microvascular ischemia of the digits or central nervous system can also occur. “Rebound” thrombocytosis after splenectomy can also lead to thromboembolic complications in patients with MPD, especially among those with chronic idiopathic myelofibrosis (IMF). Although the thrombotic risk with MPDs is not directly related to the circulating platelet number, most events occur when the count is > 600 × 10^9/L. Bleeding, usually in mucocutaneous sites, is less common than thrombosis. Major bleeding with ET occurs in 4–37% at diagnosis and in 1–7% during follow-up, and in 2–20% with PV at diagnosis and in 2% during follow-up. Hemorrhagic risk is greatest with platelet counts > 1,500 × 10^9/L (occurring in roughly 12% and 23% of patients with ET and PV, respectively) with associated acquired von Willebrand syndrome (AVWS).

Current management/treatment
Low-dose aspirin is indicated for thromboprophylaxis in patients with ET or PV who do not have a bleeding tendency. Phlebotomy is required to maintain a normal hematocrit with PV. Platelet-lowering therapy, to maintain a normal platelet count, is indicated for patients older than 60 years, those with thrombotic risk factors and/or those with a platelet count > 1,500 × 10^9/L. The platelet count should also be normalized before general anesthesia and surgery. Postplenectomy patients may require treatment to avoid bleeding and thrombotic complications associated with “rebound” thrombocytosis. Hydroxyurea is the preferred platelet-lowering agent. Alternatives include anagrelide and interferon alpha (the treatment of choice during pregnancy). Thromboembolic complications are treated acutely with unfractionated or low-molecular-weight heparin followed by transition to therapeutic warfarin. Thrombocytapheresis (plateletapheresis) is an exceptional treatment modality for thrombotic or bleeding complications in patients with MPD and uncontrolled thrombocytosis.

Rationale for therapeutic apheresis
Thrombocytapheresis “Plateletapheresis” is indicated to prevent recurrent or progressive thromboembolism or hemorrhage in a patient with a MPD and uncontrolled thrombocytosis. Although the therapeutic mechanisms are not well defined, rapid cytoreduction is believed to ameliorate prothrombotic factors associated with the dysfunctional platelets. In patients with AVWS and > 1,500 × 10^9/L platelets, restoration of a normal platelet count rapidly corrects in vitro plasma hemostatic defects. Thrombocytapheresis “Plateletapheresis” can also improve severe microvascular ischemic complications that are unresponsive to anti-platelet agents and may be useful to prevent thrombotic events in patients with extreme “rebound” thrombocytosis after splenectomy. In all cases, platelet-lowering agents must also be given to prevent rapid reaccumulation of circulating platelets. Thrombocytapheresis “Plateletapheresis” may be appropriate for selected high-risk patients with ET, PV, or IMF when cytoreductive agents are contraindicated or intolerable (e.g., during pregnancy) or when the onset of pharmacologic therapy would be too slow (e.g., before urgent surgery). Prophylactic thrombocytapheresis “plateletapheresis” is not indicated or beneficial for standard-risk pregnant women with PV or ET. Similarly, although anecdotal case reports and small series have described a possible benefit of thrombocytapheresis “plateletapheresis” with secondary thrombocytosis due to infection or postsplenectomy, the rationale is undefined and efficacy unproven; therefore, a category III indication is assigned based on conflicting and limited data available in the literature.

Technical notes
Each procedure lowers the platelet count by 30–60%. A central venous catheter may be required for multiple treatments or long-term therapy. Anticoagulant ratio of whole blood: anticoagulant should be 1:8–12, and heparin should be avoided to prevent ex vivo platelet clumping.

Volume treated: 1.5–2 TBV
Replacement fluid: none, crystalloid
Frequency: daily or as indicated for chronic management

Duration and discontinuation/number of procedures
With acute thromboembolism or hemorrhage, the goal is normalization of the platelet count and maintenance of a normal count until cytoreductive therapy takes effect. With very high pretreatment counts more than one procedure may be required to achieve a normal count. The goal for prophylaxis of high-risk patients who are pregnant, undergoing surgery or postplenectomy should be determined on a case-by-case basis (e.g., considering the patient’s history of thrombosis or bleeding at a specific platelet count). Without an informative clinical history, a platelet count of < 600 × 10^9/L may be sufficient in these patients.

References [336–341]
*As of March 15, 2006, using PubMed and the MeSH search terms thrombocytapheresis, platelet(apheresis, essential thrombocythemia, polycythemia vera, and thrombocytosis for reports published in the English language. References of the identified articles were searched for additional cases and trials.
Therapeutic Apheresis—Guidelines

**Description of the disease**

TTP is a systemic thrombotic illness that is characterized by the only consistent abnormalities of microangiopathic hemolytic anemia (MAHA; fragmented red cells on blood smear and elevated lactate dehydrogenase) and thrombocytopenia. When initially described, TTP was defined by a pentad of clinical findings: thrombocytopenia, MAHA, mental status changes, renal failure, and fever. In current practice, however, the clinical findings of thrombocytopenia and MAHA are sufficient to consider TTP and initiate treatment. The differential diagnosis includes other causes of systemic thrombotic microangiopathy (TMA) such as disseminated intravascular coagulopathy or severe (malignant) hypertension and these therefore should be ruled out prior to initiating therapy. Recently, TTP has been shown to be associated with a severe (<5%) deficiency of ADAMTS13 enzyme, which is a protease that cleaves multimers of von Willebrand Factor (vWF). Idiopathic acquired TTP is associated with autoantibodies that bind ADAMTS13 and neutralize the protease activity. Congenital TTP is associated with somatic mutations resulting in severely deficient ADAMTS13 function. Severe ADAMTS13 deficiency appears to be an important proximal step in the pathophysiology of TTP. However, some patients with idiopathic TTP have no defect in ADAMTS13 function. The role of laboratory assays that measure anti-ADAMTS13 antibody level and protease activity in medical decision-making in TTP is still unknown. At this time TTP remains a clinical diagnosis. Because TTP is potentially fatal if left untreated, there should be a low threshold to treat presumed TTP. Work to differentiate TTP from hemolytic uremic syndrome (HUS: TMA, thrombocytopenia, and renal failure) is currently underway. Better understanding of which individuals suffer from HUS or TTP may result in improved treatment by identification of patients who would benefit from emergent TPE. Pregnancy, connective tissue disease (e.g., SLE), medications, infection, cancer, and transplantation are all associated with TTP and HUS syndrome (see Hemolytic Uremic Syndrome; Thrombotic Microangiopathy; Transplant Associated Microangiopathy fact sheet).

**Current management/treatment**

TPE is life-saving therapy for TTP. TPE decreased the overall mortality from uniformly fatal to <10%. TPE should be initiated emergently once TTP is recognized. If TPE is not immediately available, plasma infusions should be started at approximately 30–40 mL/kg patient body weight per day, with care not to induce volume overload, until TPE can be initiated. Both plasma and plasma cryoprecipitate reduced (PCR) have been used as replacement fluid for TPE, with similar results in patient outcome. Corticosteroids are often used as an adjunct at 1 mg/kg/d; however, no definitive trials to prove their efficacy have been performed. Other adjuncts include rituximab, vincristine, and splenectomy. Although platelet counts can be very low, patients with TTP have thrombotic rather than hemorrhagic tendency. Bleeding, if present, is typically limited to skin and mucous membranes. Platelets should not be transfused unless clinically indicated. Because congenital TTP is characterized by constitutive deficiency of ADAMTS13 activity without an inhibitor, simple infusions of plasma (10–15 mL/kg) or cryoprecipitate (which contains ADAMTS 13) are used.

**Rationale for therapeutic apheresis**

TPE with plasma replacement has significantly improved patients’ clinical outcomes. No other intervention has had as significant of an impact on the treatment of TTP. A hypothesis is that TPE removes the anti-ADAMTS13 autoantibody, while restoring ADAMTS 13 protease activity.

**Technical notes**

Transfusion of RBC, when medically necessary, may be given emergently during TPE. Clinical response usually correlates with recovery of platelet count and normalization of LDH with clearing of mental status. The median number of TPE procedures to establish hematologic recovery is 7–8 days. The pattern of platelet response is variable and platelet count may fluctuate during treatment. Allergic reactions and citrate reactions are more frequent due to the large volumes of plasma required. Since plasma has citrate as an anticoagulant, ACD-A can be used in a higher ratio to minimize citrate reactions, especially with moderate to severe thrombocytopenia. Fibrinogen levels may decrease following serial TPE procedures with PCR as replacement fluid. In patients with severe allergic reactions to plasma proteins or limited supply of ABO compatible plasma, 5% albumin may be substituted for the initial portion (<50%) of replacement. Albumin alone however has never shown efficacy.

**References [342–348]**

*As of February 1, 2006, using PubMed and the MeSH search terms thrombotic thrombocytopenic purpura, plasma exchange, plasmapheresis, and rituximab for reports published in the English language. References of the identified articles were searched for additional cases and trials.

**Volume treated:** 1–1.5 TPV

**Replacement fluid:** plasma; plasma cryoprecipitate removed

**Frequency:** daily

**Duration and discontinuation/number of procedures**

TPE is generally performed daily until the platelet count is above 150 × 10⁹/L, and LDH near normal for 2–3 consecutive days. LDH and bilirubin are removed during TPE; therefore, normalization of these values may be seen post-TPE, but these values will continue to rise if TMA is ongoing. The role of tapering TPE over longer duration has not been studied prospectively. Persistence of schistocytes alone on peripheral blood smear, in the absence of other clinical features of TTP, does not preclude discontinuation of treatment.
**THYROTOXICOSIS**

**Disease Group:** Metabolic  
**Incidence:** Rare  
**Procedure**  
**Category**  

<table>
<thead>
<tr>
<th># of reported patients*</th>
<th>RCT</th>
<th>CT</th>
<th>CS</th>
<th>CR</th>
<th>Strength of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>0</td>
<td>0</td>
<td>2 (9)</td>
<td>10 (14)</td>
<td>Type III</td>
</tr>
</tbody>
</table>

**Description of the disease**

Thyrotoxicosis is the state of thyroid hormone excess. It may result from increased thyroid function (hyperthyroidism), drugs such as amiodarone, or overdose of thyroxine. However, hyperthyroidism caused by Graves’ disease, toxic multinodular goiter or toxic adenomas, are the most frequent causes of thyrotoxicosis. As a medical emergency, patients with thyrotoxicosis present with decompensation of one or more organ systems. Their clinical manifestations vary depending on hormone concentration, duration of the disease, age of the patient, and individual susceptibility to excess of thyroid hormone. Early diagnosis and aggressive approach are essential to limit the morbidity and mortality associated with thyrotoxicosis. The crisis starts abruptly and is usually preceded by a precipitating factor such as infection, ketoacidosis, acute trauma, thyroidal surgery, $^{131}$I radio-metabolic treatment, administration of iodine-containing materials (amiodarone), and parturition. Signs and symptoms of thyrotoxicosis include hyperactivity, irritability, dysphoria, heat intolerance and sweating, palpitations, fatigue and weakness, weight loss despite increased appetite, diarrhea, polyuria, oligomenorrhea, loss of libido, tachycardia, tremor, goiter, warm and moist skin, proximal myopathy, lid retraction or lag, and gynecomastia. Such findings should suggest the diagnosis of a thyrotoxic crisis, which can be confirmed by the demonstration of a suppressed level of serum thyroid-stimulating hormone (TSH) and increased levels of total and free thyroid hormones (T3 and T4). Thyroid storm is an exaggerated and life-threatening form of thyrotoxicosis with a mortality rate of up to 30% even with treatment. The most common causes of death are cardiac failure, arrhythmia, and hyperthermia.

**Current management/treatment**

The treatment regimen of thyrotoxicosis requires intensive monitoring, supportive care, and various specific approaches such as (a) Propylthiouracil to inhibit thyroid hormone synthesis and peripheral conversion of thyroxine to triiodothyronine (T3); (b) Iodine to block the glandular release of thyroid hormones; and (c) Propranolol to reduce tachycardia and other adrenergic manifestations. In addition, dexamethasone, antibiotics if infection is present or suspected, cooling, oxygen, intravenous fluid and TPE can be added. In uncontrolled life-threatening thyrotoxicosis, thyroidectomy should also be considered.

**Rationale for therapeutic apheresis**

Since a portion of T3 and T4 is firmly bound to plasma proteins, TPE should, in theory, efficiently reduce their circulating pool. While the literature exhibits mixed results, most reported cases note a decrease in the concentration of the total levels of these hormones. In one report, TPE increased the elimination of total T4 approximately 30-fold more than standard medical treatment. This effect was dependent on the serum level of T4, suggesting that TPE is more efficient if done early. In patients with amiodarone-associated thyrotoxicosis, TPE has also been used to reduce the plasma concentration of the drug, which has a half-life of months in patients on chronic therapy. The category III for TPE was assigned to this disease based on conflicting and limited data available in the literature.

**Technical notes**

Almost all (99%) T3 and T4 is plasma bound; half life of T4 is 5–7 days and of T3 is 1 day. Since T3 is 4 times as active as T4, it may help explain why apheresis may not have such an active role in thyrotoxicosis. Also, cholestyramine binds T4 and T3, which disrupts the enterohepatic circulation. Plasma can be used as a replacement fluid with added benefit of having thyroglobulin to improve binding of free hormones. This benefit should be weighted against inherent risks of using plasma.

**Volume treated:** 1–1.5 TPV  
**Frequency:** daily or every other day  
**Replacement fluid:** albumin; plasma

**Duration and discontinuation/number of procedures**

TPE should be reserved for life-threatening situations when rapid amelioration of symptoms resistant to drug therapy is mandatory. Reported cases suggest that clinical improvement precedes changes in measured hormone levels in serum. TPE should be discontinued once improvement is noted.

**References [349–355]**

*As of March 2, 2006, using PubMed and the MeSH search terms thyrotoxicosis, thyroid storm, hyperthyroidism, therapeutic plasma exchange (TPE), and plasmapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.*
The next group of diseases was assigned pending category status denoted by P [4]. This category was created to recognize diseases which can be treated by therapeutic apheresis using devices that are not available in the US and/or do not have FDA clearance. Some of these devices are being studied in Phase III trials in the US.

The authors of this publication strongly believe that review of these new indications is necessary to broaden general knowledge on technologies and clinical indications which may soon enter the market in the US. At the same time due to the fact that these devices are not available in the US the assignment of permanent ASFA category was deemed premature. Presently these diseases can be treated using the described devices only in the research setting.

The ASFA Apheresis Applications Committee will be pro-active in reviewing new devices utilized in apheresis based treatments and will seek to assign category P indications whenever appropriate.
Dilated cardiomyopathy (DCM) is a myocardial disorder characterized by enlargement of the heart with impaired ventricular systolic function of one or both ventricles. DCM is an uncommon cause of congestive heart failure but is the second most common cause of heart transplantation. There is a 10% per year risk of either death or heart transplantation for patients with DCM. The pathogenesis of DCM involves viral infection of the myocardium as well as inherited susceptibility factors, environmental variables (e.g., selenium and other heavy metal exposure), and immune variables. Twenty-five percent of patients with DCM have viral genome detectable on endomyocardial biopsy and most have one or more cardiac autoantibodies.

**Rationale for therapeutic apheresis**

Eighty percent of patients with chronic dilated cardiomyopathy have detectable antibodies to myocardial antigens such as to myosin heavy chain, β1-adrenergic receptor, mitochondrial antigens, adenosine diphosphate carrier protein, and adenosine triphosphate carrier protein. These antibodies have been found to lyse and decrease contractility of isolated rat myocytes and impair calcium transport. Rabbits immunized with peptides from the extracellular loops of the β1-adrenergic receptor develop macroscopic and microscopic changes of DCM. Attempts to modify the course of DCM with immunosuppression and/or intravenous immunoglobulin have had mixed results. Treatment of acute myocarditis has not been successful but subsets of patients with chronic DCM treated with steroids and immunosuppressive medications have demonstrated benefit.

Trials and case series involving the use of immunoadsorption (sheep anti-human polyclonal antibody columns, Staphylococcal protein A agarose column**, columns containing recombinant β1-adrenergic receptor extracellular domains) have demonstrated both short-term and long-term improvement of cardiac function as measured by echocardiography, invasive monitoring, and reported symptoms as measured by standardized instruments. In addition, histologic improvement including decreased expression of HLA and decreased myocardial inflammation have been demonstrated following treatment. While most studies have examined patients with demonstrable cardiac antibodies, at least one case series found improvement in cardiac function even in patients without detectable antibodies.

The mechanism of action of immunoadsorption is unknown. Whether the effects are the result of antibody removal or other alterations in cytokines has not been determined. To date, there have been no reports of the use of plasma exchange in the treatment of this disorder.

Despite strong supportive data, due to the lack of availability of the instrument in the United States, this is categorized as a category P.

**Technical notes**

Trials and case series have focused on the treatment of chronic DCM. Treatment of the acute stage of the disorder has not been examined. Most patients had at least 6 months of symptoms and were receiving optimal medical treatment.

The majority of trials have used columns containing sheep anti-human immunoglobulin. These columns remove all immunoglobulin classes including all IgG subclasses. When one column becomes saturated, plasma flow is switched to the other column while the first is regenerated with an elution buffer. Limited trials with staphylococcal protein A agarose columns capable of regeneration have also been performed. IgG3 antibodies appear to be critical in the pathogenesis of the disorder and must be removed meaning that staphylococcal protein A columns are not as effective as other immunoadsorption techniques which have a higher affinity for IgG3. Modifications to the protocols have resulted in enhanced removal of IgG3, however. Finally, a small number of patients have been treated with a column consisting of recombinant β1-adrenergic receptor epitopes that remove antibodies directed toward this cardiac component. This column is also capable of regeneration.

In some trials, polyclonal immunoglobulin replacement has been given at a dose of 0.5 g/kg following the last apheresis treatment.

**Volume treated:** Most trials have not reported the volume of plasma treated. One trial had a target of 5 L

**Replacement fluid:** not applicable

**Frequency:** trials have involved one of two schedules:

- 5 treatments over five consecutive days or
- 3 treatments over three consecutive days followed by two consecutive treatments a month for three months

**References [356–366]**

*As of October 12, 2005, using PubMed and the MeSH search terms dilated cardiomyopathy and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.

**In December 2006 the production of Staphylococcal protein A agarose (Immunosorba®) and Staphylococcal A silica (Prosorba®) columns was discontinued in the United States. These devices are no longer available in the United States but may be available in other countries.

Journal of Clinical Apheresis DOI 10.1002/jca
Description of the disease

Ulcerative colitis (UC) and Crohn’s Disease (CD) are chronic inflammatory diseases of the gastrointestinal tract and are collectively known as Inflammatory Bowel Disease (IBD). The incidence of IBD is highest in North America, Europe and Scandinavia however it has a world wide distribution. Dysfunction of the immune system, in addition to genetic, environmental, and physiologic factors contributes to the pathogenesis of IBD. Histological abundance of leukocytes and monocytes in the mucosa of the bowel incriminate these cells, along with accompanying cytokines and proinflammatory mediators, in the disease process. The phenotype of these disorders is variable affecting predominately individuals in the third decade of life. Because of the progressive and debilitating natural history of IBD, long-term therapy to induce and maintain clinical remission is desirable. A disease activity index (DAI) has been used to standardize and quantify clinical parameters present during active illness in order to monitor response to treatment.

Current management/treatment

In order to target inflammatory process, aminosalicylates are typically the first-line therapy. For moderate to severe IBD, corticosteroids are frequently required to control the disease. Unfortunately, complications from chronic administration include steroid resistance, dependency and the sequelae of long-term steroid use. For those patients who become steroid resistant, immunosuppressive drugs such as azathioprine and 6-mercaptopurine are used. In CD, infliximab, monoclonal antibody to anti-tumor necrosis factor, may induce remission and has been FDA cleared for this purpose. Surgical intervention may be necessary in some patients. Selective apheresis is emerging as a useful adjunct for the management of IBD.

Rationale for therapeutic apheresis

Because of mounting evidence that granulocytes and monocytes (GM) are pathogenic and the degree of GM infiltration correlates with severity of disease, therapy targeting GM and accompanying inflammatory mediators offer promise. While centrifugation can remove leukocytes from the circulation, selective apheresis is more efficient at their depletion. Randomized controlled clinical trials of selective apheresis have illustrated clinical improvement in IBD patients, including those who are steroid resistant. Clinical benefits have included a higher percentage of patients responding compared to placebo controls, more rapid remission of disease than controls, greater measurable improvement in disease activity index (DAI) and fewer adverse reactions than with steroid treatment alone. Endoscopic evidence of healing and diminished leukocyte infiltrates in bowel mucosa by histology has also been documented. Selective apheresis may also be useful as a steroid sparing adjunct. Immunomodulatory effects including reduction in levels of a variety of cytokines (TNF-alpha, IL-6, IL-8, and IL-1B) suggest selective apheresis may mitigate IBD pathogenesis. Adverse reactions have been infrequently reported and include headache, fatigue, nausea, arm pain, hematoma, and light-headedness. Results of Placebo-controlled trials are which are currently being performed in North America may provide more definitive evidence for selective apheresis in IBD.

Technical notes

Two types of selective apheresis devices are the Cellsorba (Asashi Medical, Tokyo, Japan) which is a column containing cylindrical non-woven polyester fibers and, the Adacolumn (JIMRO, Japan) which contains cellulose acetate beads. Both require anticoagulation (heparin/ACD-A and heparin alone, respectively) to remove granulocytes and monocytes from venous whole blood by filtration/adhesion. For Cellsorba, venous whole blood is processed at 50 mL/min through the column for 60 minutes. Some platelets and lymphocytes are also removed by this column. For Adacolumn, venous whole blood is processed at 30 mL/min for 60 minutes. The Adacolumn is relatively selective for removing activated granulocytes and monocytes. Patients taking ACE inhibitors should not undergo treatment with Adacolumn. Cellsorba and Adacolumn are currently available in Europe and Japan.

Volume treated: 1,800 mL (Adacolumn) or 3,000 mL (Cellsorba) Replacement fluid: not applicable

Frequency: once per week, more intensive therapy may include 2 per week

Duration and discontinuation/number of procedures

The typical length of treatment is 5–10 weeks for Adacolumn and 5 weeks for Cellsorba. Some published reports indicate more intensive therapy offers greater proportion of patients experiencing clinical improvement or remission of disease.

References [367–375]

*As of March 2, 2006, using PubMed and the MeSH search terms Crohn’s disease, ulcerative colitis, apheresis, and adoptive cytapheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
Description of the disease

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the Western world in those over 60 years of age. It affects the macula and is a progressive condition with loss of central vision. This affects the ability of the patient to read, recognize faces, and drive. AMD is characterized by the collection of debris (drusen) beneath the retinal pigment epithelium. This stage is called “dry AMD.” Over 10 years, 12.5% of those with the dry form will progress to “wet AMD.” This is characterized by the growth of blood vessels into the choroid (choroidal neovascularization). Risk factors for AMD include smoking, hypertension, elevated body mass index, as well as a direct correlation with cholesterol, fibrinogen, and \( \alpha_2 \)-macroglobulin levels.

The pathogenesis of AMD has not been completely elucidated. With age, lipids are deposited within the sclera which becomes increasingly rigid. This compromises blood flow in the choroidal layer of the eye, diminishing nutrient and oxygen supply to the retinal pigmented epithelium (RPE). The resulting hypoxia leads to a loss of the ability of the RPE to phagocytize cellular debris generated by normal turnover. This leads to deposition of extracellular debris (drusen) and dry AMD. These deposits lead to an increase in the distance that oxygen must diffuse leading to more hypoxia and greater RPE dysfunction. Increasing hypoxia eventually leads to RPE production of vascular growth factors resulting in the in-growth of blood vessels (choroidal neovascularization) and wet AMD.

Current management/treatment

The current treatment for dry AMD is limited and consists of high dose supplementation of vitamins C and E, beta carotene, and zinc. Wet AMD is treated by ablating the choroidal neovascularization with laser photocoagulation, transpupillary thermotherapy, photodynamic therapy, external beam irradiation, surgical removal of the neovascular membrane, or macular rotation.

Rationale for therapeutic apheresis

The rationale behind the use of membrane differential filtration (also called double filtration apheresis or cascade filtration apheresis) is that high-molecular weight molecules that have been associated with risk of AMD development (e.g., fibrinogen, LDL-cholesterol, fibronectin, von Willebrand factor) are removed from the patient’s plasma. This results in a reduction in blood and plasma viscosity, platelet and red cell aggregation, and enhanced red cell membrane flexibility. This improves RPE perfusion, decreasing hypoxia, and allowing improved RPE function.

Numerous case series and two completed randomized controlled trials have reported efficacy of membrane differential filtration in treating AMD. These studies have shown improvement in the number of lines that can be read on ETDRS charts, improvement in the Pepper Visual Skills for reading test, decrease in a number of viscosity parameters, shortening of arteriovenous passage time, and improvement on electroretinogram. These studies have shown improvement shortly after completion of treatment which has lasted up to four years following the course of therapy. The results of the MIRA-1 trial, a large randomized double-blinded placebo (sham procedure) controlled trial failed to demonstrate a significant difference between controls and treatment groups due to the controls doing better than predicted. Analysis excluding protocol violators and patients with vision loss due to other causes demonstrated a significant improvement with treatment but resulted in the trial being under-powered to address the study’s primary goals.

Due to conflicting data and the lack of availability of the instrument in the United States, this is categorized as a category P.

Technical notes

The majority of series and trials have been performed using membrane differential filtration. In this technique, plasma is separated from whole blood, either by centrifugation or filtration, and then passed through a second filter. Low-molecular weight substances such as albumin pass through the filter while high-molecular weight substances are removed. One case series did indicate that plasma exchange with albumin replacement was used to treat AMD but the trial included the use of other treatment modalities (e.g., tryptophan polyvinyl alcohol columns and membrane differential apheresis) and the authors provide inadequate information to determine whether there was a benefit with plasma exchange.

Studies have suggested that those with elevations in high-molecular weight plasma components have a better response and that patients with dry AMD respond better than those with wet AMD.

For membrane differential apheresis, either heparin or ACD has been used as an anticoagulant.

Duration and discontinuation/number of procedures

Treatments performed as part of clinical trials have been per protocol. Efficacy has been reported to last for up to 4 years. One case series has suggested that after 12 months, two to four booster treatments could be considered depending upon the patient’s course.

References [376–387]

*As of October 1, 2005, using PubMed and the MeSH search terms macular degeneration and apheresis for articles published in the English language. References of the identified articles were searched for additional cases and trials.
REFERENCES


187. Szczepiorkowski et al.


